Histaminergic manipulations of human cognition: studies of pharmacological effects on evoked potentials and performance tests

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HISTAMINERGIC
MANIPULATIONS OF
HUMAN COGNITION:
STUDIES OF PHARMACOLOGICAL
EFFECTS ON EVOKED POTENTIALS
AND PERFORMANCE TESTS

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HISTAMINERGIC MANIPULATIONS OF HUMAN COGNITION: STUDIES OF PHARMACOLOGICAL EFFECTS ON EVOKED POTENTIALS AND PERFORMANCE TESTS

Proefschrift

Ter verkrijgen van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. Mr. G.P.M.F. Mols, volgens het
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Peter van Ruitenbeek

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Promotor

Prof. dr. W.J. Riedel

Copromotor

Dr. A. Vermeeren

Beoordelingscommissie

Dr. J.G. Ramaekers (voorzitter)

Prof. dr. B. Leonard (University of Galway, Ireland)

Dr. M.A. Mehta (University of London, United Kingdom)

Prof. dr. F.R.J. Verhey

Prof. dr. P. de Weerd

TABLE OF CONTENTS

PROLOGUE	7
GENERAL INTRODUCTION	
CHAPTER 1	21
COGNITIVE DOMAINS AFFECTED BY HISTAMINE H ₁ ANTAGONISM IN HUMANS: A LITERATURE REVIEW	
CHAPTER 2	57
HISTAMINE H ₁ -RECEPTOR BLOCKADE IN HUMANS AFFECTS PSYCHOMOTOR PERFORMANCE BUT NOT MEMORY	
CHAPTER 3	81
MEMORY IN HUMANS IS UNAFFECTED BY CENTRAL H ₁ - ANTAGONISM WHILE OBJECTIVELY AND SUBJECTIVELY MEASURED SEDATION IS INCREASED	
CHAPTER 4	103
SPECIFIC ANTIHISTAMINERGIC EFFECTS ON COGNITION: IMPAIRED CENTRAL PROCESSING SPEED AND UNAFFECTED ATTENTION AND WORD LEARNING	
CHAPTER 5	121
HISTAMINE H ₁ RECEPTOR BLOCKADE PREDOMINANTLY IMPAIRS SENSORY PROCESSES IN HUMAN SENSORIMOTOR PERFORMANCE	
CHAPTER 6	147
EFFECTS OF L-HISTIDINE DEPLETION AND L-TYROSINE/L- PHENYLALANINE DEPLETION ON SENSORY AND MOTOR PROCESSES IN HEALTHY VOLUNTEERS	

CHAPTER 7	177
GENERAL DISCUSSION	
SUMMARY	191
SAMENVATTING	199
DANKWOORD	207
CURRICULUM VITAE	211

PROLOGUE

GENERAL INTRODUCTION

PROLOGUE

PROLOGUE

GENERAL INTRODUCTION

There is a great need to treat cognitive impairments such as age related forgetfulness and dementia. Pharmacological treatments have been investigated for over 30 years now and results have been far from successful [e.g. (Courtney, et al., 2004)]. For example, worldwide there are five drugs registered for the treatment of Alzheimer's disease with cognitive symptoms as core target. Neither of these drugs attenuates the progress of the disease, indicating that they are not fully successful. The unsuccessful pharmacological treatment also partially indicates that we do not fully understand the pathology of the disorders. For example, Alzheimer's disease is associated with decreased activity of the neurotransmitter acetylcholine. Theoretically, returning the activity of the neurotransmitter system to a normal level should decrease the symptoms characteristic cognitive disorders. However, Alzheimer's disease is characterized by a decline across a whole spectrum of cognitive functions (Riedel, 1995) and besides brain atrophy functional decline of several neurotransmitter systems are involved in symptomatology of the disorder. In order to understand the pathology attempts have been made to model these impairments in healthy subjects. However, these attempts have been relatively unsuccessful, possibly because just one transmitter system is pharmacologically manipulated as opposed to multiple. For example, muscarinic receptors in the brain, through which acetylcholine functions, can be blocked using the drug scopolamine. As scopolamine induces impaired memory functioning, it does not cause the large variety of impairments typical for Alzheimer's disease and is therefore not a sufficient model for the disorder. In addition, stimulating the muscarinic receptors has little effect on the whole range of cognitive complaints seen in Alzheimer's patients (Kelly, 1999). Therefore, the view that only the cholinergic system is affected appears to be too reductionistic (Bacciottini, Passani, Mannaioni, & Blandina, 2001). Hence, cognition enhancing drugs used in clinical disorders and Alzheimer's disease in particular should be based on more neurotransmitter systems.

Histamine and clinical disorders

In respect of developing new treatments that can be given additional to or that can replace the current treatment the histamine neurotransmitter system may be a promising target. This transmitter system has been associated with some clinical disorders like Alzheimer's disease [e.g. (Higuchi, 2000)], schizophrenia [e.g. (Nakai, et al., 1991)], Attention Deficit Hyperactivity Disorder (Komater, et al., 2005; Peled, Carraso, Globman, & Yehuda, 1997), depression (Akhtar, Pillai, & Vohora, 2005; Kano, et al., 2004), Parkinson's disease [e.g. (Anichtchik, Rinne, Kalimo, & Panula, 2000; Rinne, et al., 2002)]

PROLOGUE

and Wernicke-Korsakoff's syndrome [for review see: (Onodera, Yamatodani, Watanabe, & Wada, 1994)].

Of these disorders, the relationship between Alzheimer's disease and histamine has been studied the most. Using Positron Emission Tomography imaging Higuchi et al. (2000) found a decrease in histamine receptors in Alzheimer's disease patients and a relationship between the cognitive impairment and the absence of these histamine receptors. The decrease in number of receptors seemed particularly to be the case in areas of the brain involved in memory functioning. In addition, Panula et al. (1998) found a decrease in histamine concentration in deceased Alzheimer's disease patients in the same areas as Higuchi and colleagues. More so, Airaksinen, Paetau, et al. (1991) and Airaksinen, Reinikainen, Riekkinen, & Panula (1991) found that the characteristic neurofibrillary tangles to be present in the histaminergic cells in Alzheimer's disease patients brains. Taken together, these studies strongly suggest a relationship between histamine and Alzheimer's disease.

Another example of histamine being involved in clinical disorders regards schizophrenia. Nakai et al. (1991) found a decreased number of histamine receptors in brains of schizophrenic patients and Prell et al. (1995) found increased breakdown products of histamine in the cerebrospinal fluid of schizophrenic patients.

More so, in patients suffering from Parkinson's disease it has been shown that density of histamine nerves to areas of the brain particularly deteriorated in Parkinson's disease and the density of certain histamine receptors are altered (Anichtchik, Peitsaro, Rinne, Kalimo, & Panula, 2001; Anichtchik, et al., 2000). In addition, these patients exhibit increased histamine levels in the brain (Rinne, et al., 2002). These studies show that the deficits in the histaminergic system may contribute to the impairment seen in these patients. The histamine neurotransmitter system, therefore, might be a good candidate to base new drugs on in order to pharmacologically treat such clinical disorders.

Histamine system in the brain

Before embarking on determining how histamine based drugs may contribute to the treatment of clinical disorders, some background knowledge about the histamine system may be useful.

Histamine has been known to be a neurotransmitter for little more than 30 years. Schwartz in 1975 suggested that histamine is a neurotransmitter in the mammalian brain and that it may play a role in sleep and wakefulness. Around that time Garbarg, Barbin, Feger, & Schwartz (1974) actually showed that histaminergic neurons were present in the mammalian brain. Later Watanabe, et al. (1983) and Panula, Yang, & Costa

PROLOGUE

(1984) more specifically showed that histaminergic neurons were located in a structure called the tuberomammillary nucleus of the posterior hypothalamus in the rat brain. Panula, Airaksinen, Pirvola, & Kotilainen (1990) finally showed that such a histamine system is also present in the human brain. The histaminergic cells in the tuberomammillary nucleus project to all areas of the brain and such a structure resembles that of other monoamine systems. This suggests that histamine may play a large role in many functions including cognition.

It is known that histamine exerts its functions in the brain through interactions with four types of receptors i.e. the H₁, H₂, H₃ and H₄ receptors located throughout the brain [for a comprehensive review see: (Haas, Sergeeva, & Selbach, 2008)]. As the H₄ receptor has only recently been discovered little is known about its functional role, but it seems to closely resemble the H₃ receptor in structure (Gbahou, et al., 2006; Nakamura, Itadani, Hidaka, Ohta, & Tanaka, 2000). The other receptors have been extensively studied. Activation of the H₁ and H₂ receptors leads to excitatory signal transmission or increased firing of neurons. In contrast, the H₃ receptor functions as an autoreceptor and activation leads to decreased histamine release from neurons (Arrang, Garbarg, & Schwartz, 1983). The H₃ receptor also functions as a heteroreceptor whereby it decreases the release of other neurotransmitters (e.g. norepinephrine, serotonin and acetylcholine). As many clinical disorders coincide with deficits in multiple transmitter systems and drug treatments are based on increasing neurotransmitter activity (e.g., Alzheimer's disease, Attention Deficit Hyperactivity Disorder, Parkinson's disease, depression) blocking the H₃ receptor and increasing not only histamine activity, but at the same time also that of other neurotransmitters, is a very promising concept for pharmacological treatments.

New histamine based drug treatments

There are now histamine based drugs under development, which show very promising preliminary results. Many pharmaceutical companies are developing H₃-antagonists and these have proven effective in animal models for cognitive deficits, which occur in clinical disorders. Blocking the H₃ receptor in animal brains leads to increased performance on many tasks assessing cognitive functioning [for reviews see: (Bonaventure, et al., 2007; Esbenshade, Fox, & Cowart, 2006; Leurs, Blandina, Tedford, & Timmerman, 1998; Vohora, 2004; Wijtmans, Leurs, & de Esch, 2007; Witkin & Nelson, 2004)]. Especially performance on learning and memory tasks was improved in animals that otherwise show impaired performance. For example, mice that showed early signs of senescence improved their performance on tasks assessing memory consolidation after being treated with the H₃ antagonist

PROLOGUE

thioperamide (Meguro, et al., 1995). This drug was also able to reverse scopolamine induced spatial orientation, working memory and passive avoidance impairments in animals (Komater, et al., 2005; Medhurst, et al., 2007). In addition, H₃-antagonists have shown to attenuate deficits in animal models for impairments seen in schizophrenia to the same degree as antipsychotics (Akhtar, Uma Devi, Ali, Pillai, & Vohora, 2006; Browman, et al., 2004; Fox, et al., 2005). This is only a small selection of the evidence derived from studies done in animals that suggest that H₃-antagonists may be effective in cognitive disturbances in clinical disorders in humans. When taken all the research done together, the evidence is quite overwhelming.

Aim

In spite of all the evidence from animal studies direct evidence that histamine H₃ receptor antagonists are effective as treatments in humans is still very scarce, because these drugs are still hardly available for use and testing in humans. However, these drugs will be available before long and, when suitable to be used in humans, need to be tested. Testing the many compounds that will be available in long-term patient studies is very time consuming. Alternatively, if cognitive deficits associated with histaminergic dysfunction can be modelled in healthy humans, the screening of the new treatments can be speeded up significantly. In order to be able to effectively test the efficacy of these new drugs knowledge about the role of histamine in human cognition is very useful. First, we need to know in which cognitive functions histamine is involved to determine which functions can be targeted with H₃ antagonists. Second, with this knowledge a model of cognitive impairments associated with histaminergic dysfunction can be constructed in order to rapidly test new H₃ drugs. Therefore, the aim of this dissertation is to determine what role histamine plays in cognitive functioning i.e. what cognitive functions highly depend on histaminergic activity. Second, to determine what manipulation of the histamine system can be used to model cognitive deficits associated with histamine dysfunction.

Methodology

There are different approaches that can be taken to evaluate the involvement of a neurotransmitter system in human cognition. First, the neurotransmitter system can be manipulated in different ways and, second, the subsequent functional impairments can be measured using different methods.

In this dissertation, the histamine neurotransmitter system is manipulated in two ways. The first is by blocking the histamine H₁ receptor in the central nervous system by administering 'first generation' antihistamines to healthy subjects. The drawback of using the 'first generation' antihistamine is that they are mostly unselective in their ability

PROLOGUE

to block receptors for neurotransmitters. The later developed 'second generation' are more selective, but may be less suitable as they penetrate the central nervous system to a lesser extent. Both types of substances are investigated in this dissertation.

Another way to manipulate the histamine system is by depleting the central nervous system of the histamine precursor L-histidine. Histamine is synthesized by decarboxylation of L-histidine by the enzyme histidine-decarboxylase (Schwartz, Arrang, Garbarg, Pollard, & Ruat, 1991). The primary source of L-histidine is every day food. Taking L-histidine out of the consumed food leads to decreased levels of L-histidine in the body. It is hypothesised that consequently to the decrease in L-histidine histamine levels are decreased in the central nervous system, which affect cognitive performance.

To assess the effects of these different treatments on cognitive performance several approaches will be taken. The first consists of applying a test battery, which can be called the multiple-tasks one-factor approach (Riedel, Mehta, & Unema, 2006). The one factor is the treatment of which the effects are measured on a variety of neuropsychological and other behavioural tests. The result is profile of cognitive impairments as measured with these different tasks.

The second approach is the multi-factor one-task approach in which task manipulations are combined with drug treatments in order to determine their interacting effects on specific cognitive processes. The basic logic underlying this method has been developed by Sternberg in 1969 who showed that if factors interacted with each other they affect at least the same cognitive process. The method applying this basic principle was called the 'Additive Factor Method'. For example, in studying the effects of drugs a choice reaction time task can be used in which the difficulty of recognizing a stimulus, the difficulty of response choice and/or the complexity of the response itself can be varied. If a treatment interacts with one of these factors, it is concluded that the treatment affects the cognitive process that is also affected by that particular factor. For instance, it is known that visual degradation of a stimulus affects the cognitive process of stimulus identification. If a certain treatment enlarges the effect of stimulus degradation, it is concluded that the treatment affects stimulus identification.

In this dissertation, different outcome measures are used to evaluate treatment effects on cognitive functioning. Next to measures like reaction time and number of correct answers as outcome measures, psychophysiological measures are also used. These psychophysiological measures consist of measuring evoked brain potentials using electrodes placed on the scalp of a subject. The signals derived following an event e.g. stimulus presentation and/or response execution, are called Event Related Potentials. The duration between the event and occurrence of such potentials

PROLOGUE

are indicative of the duration of certain cognitive brain processes. For instance, a certain potential occurs X ms after the presentation of a visual stimulus which is easily recognizable. If this same potential occurs X + Y ms after the presentation of a stimulus difficult to recognize, the process of recognizing that stimulus is said to take Y ms longer. Using these Event Related Potentials and measures of their properties effects of treatments on specific cognitive processes will be presented in this dissertation.

Outline of this thesis

Chapter 1

The main question attempted to be answered in chapter 1 is: What cognitive processes and domains are affected by histamine H₁ blockade? Therefore, papers are reviewed in which the effects of first generation H₁ antagonists on cognitive performance in healthy volunteers are described.

Chapter 2

The open questions revealed by the review are attempted to be answered by the study described in chapter 2. An experimental study is described that assessed the effects of a first generation antihistamine on psychomotor performance, memory and attention.

Chapter 3

It is unclear whether H₁ antagonists affect memory performance and whether this is secondary to the sedative effects of these drugs. An experiment is described which specifically investigates the effects of the first generation H₁ antagonist dexchlorpheniramine on memory and arousal. The effects are contrasted with the effects of the benzodiazepine lorazepam on memory and arousal.

Chapter 4

The second generation antihistamines are more selective for the histamine H₁ receptor than the first generation drugs. It is also claimed in general that the 2nd generation antihistamine drugs penetrate the brain to a much lesser extent. However, this general claim is highly disputed. An example of the evidence may be provided by studying the cognitive effects of the 2nd generation antihistamine cetirizine. This chapter describes an experimental study in which the effects of cetirizine on psychomotor performance, memory and attention were investigated.

Chapter 5

Psychomotor performance seems to be very sensitive to the effects of H₁ antagonists. It is, however, unclear what underlying processes are affected

PROLOGUE

resulting in impaired performance. In chapter 5, a study is reported in which behavioural and electrophysiological measures are used to determine the effects of a first generation antihistamine on specific cognitive processes. To this end task manipulations and the Additive Factor Method are employed.

Chapter 6

An alternative method to decrease histaminergic activity is by depleting subjects from the histamine precursor L-histidine. As opposed to H₁ blockade, L-histidine depletion may affect the histaminergic system differently and may be a good method to model histaminergic dysfunction. L-histidine depletion has hardly been studied and the effects of L-histidine depletion on cognitive performance have never been studied. Chapter 6 describes an experimental study in which blood-plasma levels of the histamine precursor L-histidine and other amino acids and cognitive performance after L-histidine depletion are evaluated.

Chapter 7

The final chapter provides a general discussion of the previous chapters. The role histamine plays in cognition is discussed and the attempts to answer which manipulations may be used to model histaminergic dysfunction are made.

PROLOGUE

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CHAPTER 1

COGNITIVE DOMAINS AFFECTED BY HISTAMINE H₁ ANTAGONISM IN HUMANS: A LITERATURE REVIEW

Van Ruitenbeek, P., Vermeeren, A., Riedel, W. J. (*submitted*). Cognitive domains affected by histamine H₁ antagonism in humans: a literature review.

CHAPTER 1

CHAPTER 1

INTRODUCTION

Some 30 years ago Schwartz (Schwartz, 1975, 1977; Schwartz, Pollard, & Quach, 1980) suggested that histamine is a neurotransmitter in the mammalian central nervous system and that it plays a role in arousal. The histaminergic cells in the tuberomammillary nucleus project to all areas of the brain. Activation of the H₁ and H₂ receptors leads to excitatory transmission or increased neuronal firing. In contrast, the H₃ receptor functions as an autoreceptor and activation leads to decreased histamine release (Arrang, Garbarg, & Schwartz, 1983). The widespread presence of histaminergic projections and receptors suggest a role in various central nervous system functions, which may be affected in clinical disorders, including cognitive performance.

The histamine system has been shown to be affected in Parkinson's disease, epilepsy, dementia and schizophrenia (Onodera, Yamatodani, Watanabe, & Wada, 1994; Vohora, 2004). For example, Higuchi et al. (2000) found decreased H₁ receptor binding potential in the frontal and temporal cortex in Alzheimer's disease patients as compared with normal age matched subjects. In addition, Panula et al. (1998) found a decrease in histamine content in the hypothalamus, hippocampus and temporal cortex of post mortem Alzheimer brains. Regarding schizophrenia, Nakai et al. (1991) found a decreased number of H₁ receptors in brains of schizophrenic patients and Prell et al. (1995) found increased histamine metabolites in the cerebrospinal fluid of schizophrenic patients. These studies suggest a histamine dysfunction in these disorders.

Development of new treatments that increase histamine activity include H₃-receptor antagonists. Results from animal studies have already shown that administration of H₃-antagonists leads to increased histaminergic activity and to improved cognitive performance on many cognitive tasks, especially learning and memory in impaired animals [e.g. (Bernaerts, Lamberty, & Tirelli, 2004; Komater, et al., 2005; Medhurst, et al., 2007; Orsetti, Ghi, & Di Carlo, 2001) for review see: (Esbenshade, Fox, & Cowart, 2006; Witkin & Nelson, 2004)]. Therefore, these H₃-antagonists may have therapeutic potential in humans for treatment of disorders associated with histaminergic dysfunction (Leurs, Blandina, Tedford, & Timmerman, 1998; Passani, Lin, Hancock, Crochet, & Blandina, 2004).

In order to assess the efficacy of the H₃-antagonists for treatment of cognitive dysfunction in patients a pharmacological model of histaminergic dysfunction in healthy volunteers would be very useful. Such a model may provide a method to quickly obtain indications for efficacy of H₃-antagonists, before initiation of long term clinical trials in patients.

CHAPTER 1

One way to decrease histaminergic activity is by blocking H₁ receptors in the central nervous system using antihistamines. Due to their sedative effects and impairment of motor vehicle control, the behavioural effects of antihistamines have been extensively studied in the context of traffic safety [for reviews see: (McDonald, Trick, & Boyle, 2008; O'Hanlon & Ramaekers, 1995; Shamsi & Hindmarch, 2000; Theunissen, Vermeeren, Vuurman, & Ramaekers, In prep)]. These studies clearly indicate that the so called 'first generation' antihistamines exert much larger sedative effects compared to the newer 'second generation'. Therefore, a first generation antihistamine may be a useful tool drug to model histaminergic dysfunction in healthy volunteers. Since the aim of previous research and consecutive reviews was mainly to establish whether particular drugs or doses are likely to impair driving performance the differential effects of antihistamines on cognitive domains, such as memory and learning received relatively little attention.

The suitability of H₁-antagonism as a model for low histamine functioning depends on the magnitude and specificity of the effects. Too few effects results in too many false negatives when testing H₃ drugs. For example, if H₁-antagonists do not impair a certain cognitive function, which an H₃-antagonist is capable of improving, the cognition enhancing effect may not be detected. In contrast, if a drug is highly sedative through which performance on many tasks deteriorates it is not specific for the cognitive domains sensitive for histaminergic dysfunction. In order to determine which cognitive processes are affected by H₁-antagonism, the aim of this review is to investigate the impairments of different cognitive domains after administration of a 'first generation' antihistamine.

METHODS

Literature search

A computer assisted literature search was conducted in the PsychInfo, Medline, PubMed and EMbase databases to identify placebo controlled studies, which reported the acute effects of orally administered first generation H₁-antagonists on cognitive performance in healthy young human volunteers. To be included papers should have a sound methodology (e.g. suitable number of subjects and time of testing around T_{max}) and be published in peer reviewed journals until August 2008. Studies in which the antihistamine was administered only in combination with other treatments were excluded. Search terms were 'antihistamines', 'H₁-antagonists', 'psychometric', 'sedation', 'cognitive function', 'psychomotor', 'learning', 'memory', 'attention', 'event related potentials' and specific antihistamine names.

CHAPTER 1

Data collection

The tests used in studies to evaluate treatment induced impairment were categorized by clustering tasks that measure aspects of the same cognitive domain (see table 1). The clustering was mainly based on that of the 'Theoretical Framework for Substance Effects on Safe Driving', a programme for a project funded by the European Union to investigate the effects of drugs on driving performance. The clustering was extended where tasks were not mentioned in the original clustering and changed where we judged the task to measure a different domain/aspect of cognitive performance. In case a test measures more than one aspect of cognitive performance, the test was categorized according to the function it most saliently measures. Performance on most tasks is a resultant of many cognitive subprocesses, e.g. sensory, central and motor information processing. As the large majority of the studies do not investigate the effects on these specific subprocesses, the tasks were clustered such that the cognitive domains consist of tasks in which the emphasis is on measuring particular processes, as opposed to measuring the processes themselves.

The effects of treatments at all doses were listed as 'impairment' or 'no impairment'. When an impairing effect was significantly different from placebo with $p < 0.05$ the effect was considered as an example of impairment on a certain cognitive domain according to a liberal criterion (LC). An effect was considered to be an impairment according to a more strict criterion (SC) if $p < 0.01$. The strict criterion was used to control for type I errors. However, performance differences in 15 papers were not tested for significance at a 0.01 level, e.g. only with a 95% confidence interval. Non-significant effects were noted as such in the 'no impairment' column of the tables. The impairing acute effects of treatments were determined for all studies and all treatments (See table 2 for abbreviations).

RESULTS AND DISCUSSION

The literature search resulted in 70 papers from January 1966 until August 2008. The papers described the effects of a total of 16 different sedative first generation H_1 -antagonists in different dosages (table 2) on 531 assessments. Of these assessments 292 (55%) indicated impaired performance according to the LC ($p < 0.05$). There were 101 (19%) assessments that indicated an impairment according to the SC ($p < 0.01$). The results indicate that not all cognitive domains have been equally studied nor are equally impaired by the H_1 -antagonists.

CHAPTER 1

Table 1: Tasks assessing functions within cognitive domains.

Cognitive domain	Task
<i>Driving</i>	
Simulated driving	Driving simulator tests
Actual driving	Weaving, Speed consistency
<i>Psychomotor skills</i>	
Eye-hand coordination	Pursuit rotor, Spiral maze, Visuomotor coordination, Fine motoric test, Word typing, Compensatory tracking, Critical tracking
Postural stability	Body sway
Motor speed	Symbol copying, Finger tapping
<i>Speed of discrete responding</i>	
Simple reaction time	Simple reaction time
Choice reaction time	Choice reaction time
<i>Perception</i>	
Pattern matching	Speeded inference, Letter matching
Visual threshold	Visual discrimination
Perceptual processing speed	Critical Flicker/Fusion Frequency
Complex perceptual functions	Speed anticipation, Temporal estimation
<i>Sensory visual function</i>	
Physiology of the eye	Pupillary functions
Eye movements	Eye saccades
<i>Attention</i>	
Spatial attention	Visual attention, , Covert attention, D2 cancellation, Alphabetical cross-out, Visual search
Alertness	Sustained attention, Vigilance, Rapid Visual Information Processing
Selective attention	Auditory selective attention, Focussed attention, Stroop
Divided attention	Divided attention
Categorization tasks	Trial making, Digit symbol substitution, Card sorting, Attention shift rule finding
<i>Memory</i>	
Working memory	ANAM running memory, Digit memory recall/Digit span, N-back, Sternberg's memory scanning, Logical reasoning, Syntactic reasoning, Arithmetic
Semantic memory	Semantic verification
Episodic memory	Word association, Spatial paired associates learning, Word learning, Pattern recognition, Information recall, Source memory

CHAPTER 1

Table 2: Treatments and their respective abbreviations.

Treatment	Dose	Abbreviation
Astemizole	10 mg	A10
Azatadine	2 mg, 4 mg, 8 mg	AZ2, AZ4, AZ8
Brompheniramine	10 mg, 12 mg, 20 mg	B10, B12
	12 mg extended release	B12er
Carbinoxamine	12 mg	CA12
Cinnarizine	15 mg, 30 mg, 45 mg	CI15, CI30, CI45
Chlorpheniramine	4 mg, 8 mg, 10 mg, 12 mg,	C4
	12 mg extended release	C12er
Clemastine	1 mg, 2 mg	CL1, CL2
Cyclizine	25 mg, 50 mg, 100 mg	CY25, CY50, CY100
Dexchlorpheniramine	2 mg 4 mg	DC2, DC4
	1 mg (i.v.), 2 mg (i.v.),	DC1iv, DC2iv
	6 mg extended release	DC6er
Diphenhydramine	25 mg, 50 mg, 75 mg, 100 mg,	DH25, DH50, DH75, DH100,
	1mg/kg, 50 mg (i.v.)	DH1mg/kg, DH50iv
Emedastine	2 mg, 4 mg	E2, E4
Hydroxyzine	20 mg, 25 mg, 30 mg, 50 mg	H20, H25, H30, H50
Ketotifen	1 mg, 2 mg	K1, K2
Olopatadine	5 mg	O5
Promethazine	10 mg, 20 mg, 25 mg, 30 mg, 50 mg	P10, P20, P25, P30, P50
Triprolidine	2.5 mg, 5 mg, 7.5 mg, 10 mg, 25 mg	T2.5, T5, T7.5, T10
	10 mg extended release	T10er

The drug most studied is diphenhydramine in oral doses ranging between 25 mg and 100 mg. The effects of the 50 mg dose have been assessed using tests in all cognitive domains discussed in the present paper. Therefore, in addition to the impairment ratio of all drugs studied within a domain, the effects of diphenhydramine will be used as the prototypical drug to determine which domains are sensitive to its impairing effects

Sedation

Sleepiness

Histamine has been known to be involved in sleep wake regulation (Saper, Chou, & Scammell, 2001; Saper, Scammell, & Lu, 2005). During sleep histaminergic activity is decreased while in a waking state histaminergic neurons in the tuberomammillary nucleus are most active. Therefore, blockade of the excitatory H₁-receptor leads to decreased wakefulness (table 3).

This is reflected in the measures of sleepiness, which was assessed 20 times by the sleep onset latency. In 95% (LC) the latency was shortened by the H₁-antagonist as compared with placebo. Applying the SC resulted in 45% of the measurements indicating shorter sleep onset latencies. A study using wrist actigraphy showed a significant reduction in daytime behavioural activity following the use of a sedative antihistamine.

CHAPTER 1

Effects of diphenhydramine on sleep latency were assessed 6 times after doses between 50 and 100 mg. All doses had significant effects according to the LC and once according to the SC. These results show that diphenhydramine is capable of inducing clear sedation and sleepiness in doses of 50 mg and higher.

Subjective alertness

Subjective sedation (table 4) has been assessed most frequently of all assessments i.e. 107 times and has been most frequently assessed using visual analogue scales.

The sedative effects were clearly shown by the 80% rate of subjective sedation as determined by the LC. When applying the SC subjects felt less alert in 25% of the assessments. Diphenhydramine was studied 36 times and almost all found significant effects on subjective alertness (LC: 97%; SC: 33%). The lowest dose studied (25 mg) already induced subjective sedation in 80% of the cases.

Cognition

Driving

The impairing effects of H₁-antagonists are highly relevant for traffic safety as assessed with tests of car driving performance (table 5).

As car driving is a highly complex task involving many cognitive functions it may be expected that performance is sensitive to the sedative effects of H₁-antagonists. An impairment on any function incorporated in car driving may result in impaired driving performance. Effects on driving performance have been assessed 13 times. Overall, performance was impaired on 11 occasions (85%) of which 2 times (15%) according to the SC. On 3 occasions a simulator was used and on 10 occasions actual driving performance was assessed in an 'on the road driving test'. All 3 simulated driving tests indicated impaired performance after the administration of the H₁-antagonist as determined using the LC (100%), but once according to the SC. Actual driving performance was impaired in 8 out of the 10 assessments (LC: 80%) of which 2 (20%) as determined by the SC.

Diphenhydramine 50 mg was studied 6 times and consistently impaired performance on all occasions. The effects of 25 mg have not been studied using tests of actual driving.

Table 3: Effects of first generation H₁-antagonists on measures of sleepiness

Cognitive domain/task	No impairment	Impairment		References
		p<0.05	p<0.01	
<i>Sleepiness (n=21)</i>		95% (20/21)	43% (9/21)	
Sleep onset latency (n=20)	CI30 ⁷	95% (19/20) CI15 ⁷ , CI45 ⁷ DH50 ^{1,20,104,112} , DH75 ¹ DH100 ¹ H25 ^{79,80,111} , H50 ¹¹¹ P10 ^{7,8,74} , P25 ⁵ T2.5 ²⁹ , T5 ^{29,31}	45% (9/20) CI15 ⁷ , CI45 ⁷ DH50 ^{20,104} , DH75 ¹ DH100 ¹ P25 ⁵ , P10 ⁷ , T5 ²⁹	¹ Turner, et al., 2006; ⁵ Nicholson, et al., 2003; ⁷ Nicholson, et al., 2000; ⁸ Nicholson, et al., 2002; ²⁰ Roth, Roehrs, Koshorek, Sicklesteel, & Zorick, 1987; ²² Nicholson, Pascoe, & Stone, 1985; ²⁹ Nicholson & Stone, 1986; ³¹ Volkerts, Van Willigenburg, Van Laar, & Maes, 1992; ⁷⁴ Nicholson & Turner, 1998; ⁷⁹ Seidel, et al., 1990; ⁸⁰ Seidel, Cohen, Bliwise, & Dement, 1987; ¹⁰⁴ Richardson, et al., 2002; ¹¹¹ Alford, Rombout, Jones, Foley, & Aldzikowski, 1992; ¹¹² Roehrs, Tietz, Zorick, & Roth, 1984
Motoric activity (n=1)		100.0% (1/1) DC4 ³²	0.0% (0/1)	³² Kamei, et al., 2003;

Table 4: Effects of first generation H₁-antagonists on measures of subjective alertness

Cognitive domain/task	No impairment	Impairment	References
		p<0.05	p<0.01
<i>Subjective alertness (n=107)</i>		80% (86/107)	25% (27/107)
Subjective ratings (n=107)	A10 ⁶⁴ ,	80% (86/107)	25% (27/107)
	CA12 ⁷¹	B12 ⁷¹ ,	
	CI30 ⁷	C4 ^{14,14,53,82} , C12er(increase) ¹⁸	
	CL1 ⁶⁵	CI15 ⁷ , CI45 ⁷	CI15 ⁷ , CI45 ⁷
	CY50 ^{25,26}	CL1 ⁷¹ , CL2 ⁶³	
	DC4 ^{32,104,106}	CY25(increase) ²⁶ , CY100 ^{25,26} ,	
	DC1iv ³⁴ ,	DC2 ^{35,45} ,	
	DC2iv ³⁴	DC4 ⁴⁵ , DC6er ^{35,58,76} ,	DC4 ⁴⁵
	DH25 ⁹	DH25 ^{4,14,14,105} ,	
		DH50 ^{1,1,3,9,13,13,14,14,15,17,21,44,47,50,72} ,	
		DH50 ^{72,77,81,90,95,100,104,113} ,	DH50 ^{1,1,21,47,72,72,104} ,
		DH75 ^{1,1,110} , DH100 ^{1,1,108} ,	
		DH1mg/kg ⁴¹ , DH50iv ⁴⁴	DH75 ^{1,1} , DH100 ^{1,1,108}
	E2 ⁹³	E4 ⁹³ ,	
		H20 ⁴⁰ ,	
	H25 ^{38,79} , H50 ⁹	H25 ⁷⁹ , H30 ^{37,89,89} , H50 ^{59,91,99}	H30 ^{89,89,89} , H50 ^{59,91,99}
		K1 ¹⁰³ , K2 ⁴⁸ ,	K1 ¹⁰³
	P10 ^{7,82} , P20 ² ,	O5 ⁸⁸ ,	O5 ⁸⁸
	P30 ⁵⁷	P10 ^{8,8,74,74} ,	P10 ^{8,8} ,
		P25 ^{5,5,60,68,78} , P30 ^{2,56} , P50 ⁷⁸	P25 ^{5,5,68}
	T2.5 ²⁵	T2.5 ³⁹ , T5 ³⁹ , T7.5 ¹⁶ , T10 ^{19,29,55,61,84}	

¹Turner, Handford, & Nicholson, 2006; ²Acons, Chan, Drummond, & Tiplady, 2006; ³Vuurman, Rikken, Muntjewerff, de Halleux, & Ramaekers, 2004; ⁴Gupta, Kapoor, Gillani, Kapoor, & Gupta, 2004; ⁵Nicholson, Handford, Turner, & Stone, 2003; ⁷Nicholson, Stone, Turner, & Mills, 2000; ⁸Nicholson, Stone, Turner, & Mills, 2002; ⁹Curran, Pooviboonsuk, Dalton, & Lader, 1998; ¹³Witek, Canestrari, Miller, Yang, & Riker, 1992; ¹⁴Witek, Canestrari, Miller, Yang, & Riker, 1995; ¹⁵Gengo, Gabos, & Mechtler, 1990; ⁹⁹De Brabander, 1990; ¹⁶Swire, Marsden, Barber, & Birmingham, 1989; ¹⁷Gengo, Gabos, & Miller, 1989; ¹⁸Lee, Lader, & Kitler, 1988; ¹⁹Bradley & Nicholson, 1987; ²¹Mattila, Mattila, & Konno, 1986; ²⁵Hamilton, Bush, Bye, & Peck, 1982; ²⁶Clubley, Bye, Henson, Peck, & Riddington, 1979; ²⁹Nicholson & Stone, 1986; ³²Kamei, et al., 2003; ³³Barbanoj, et al., 2006; ³⁴Okamura, et al., 2000; ³⁵Tagawa, et al., 2002; ³⁷Tashiro, et al., 2004; ³⁹Cohen, Hamilton, Liao, Findlay, & Peck, 1985; ⁴⁰Levander, Stahle-Backdahl, & Hagermark, 1991; ⁴¹Oken, Kishiyama, & Salinsky, 1995; ⁴⁴Carruthers, Shoeman, Hignite, & Azarnoff, 1978; ⁴⁵Van Ruitenbeek et al., 2008; ⁴⁶Goetz, Jacobson, Apaliski, Repperger, & Martin, 1991; ⁴⁷Grunberger, Saletu, Linzmayer, & Barbanoj, 1988; ⁴⁸Adamus, Oldigs-Kerber, & Lohmann, 1987; ⁵⁰Cohen, Hamilton, & Peck, 1987; ⁵³Kulshrestha, Gupta, Turner, & Wadsworth, 1978; ⁵⁵Hindmarch & Shamsi, 2001; ⁵⁶Hindmarch, Shamsi, & Kimber, 2002; ⁵⁷Hindmarch, Shamsi, Stanley, & Fairweather, 1999; ⁵⁸Mochizuki, et al., 2002; ⁵⁹Ridout, Shamsi, Meadows, Johnson, & Hindmarch, 2003; ⁶⁰Shamsi, Kimber, & Hindmarch, 2001; ⁶¹Kerr, Dunmore, & Hindmarch, 1994; ⁶³Vuurman, Uiterwijk, Rosenzweig, & O'Hanlon, 1994;

⁶⁴Dhorranintra, Limsuvan, & Bunnag, 1986; ⁶⁵Gaillard, et al., 1988; ⁶⁶Gaillard & Verduin, 1983; ⁶⁸Levin, Barbat, Hedges, & Turner, 1984; ⁷⁰Millar & Standen, 1982; ⁷¹Seppala, Nuotto, & Korttila, 1981; ⁷²Kay, et al., 1997; ⁷⁴Nicholson & Turner, 1998; ⁷⁶Theunissen, Vermeeren, van Oers, van Maris, & Ramaekers, 2004; ⁷⁷Verster, Volkerts, et al., 2003; ⁷⁸Schroeder, Collins, & Elam, 1985; ⁷⁹Seidel, Cohen, Bliwise, & Dement, 1990; ⁸¹Simons, Fraser, Reggin, & Simons, 1996; ⁸²Clarke & Nicholson, 1978; ⁸⁴Nicholson & Stone, 1982; ⁸⁸Takahashi, Ishida-Yamamoto, & Iizuka, 2004; ⁸⁹Tashiro, et al., 2005; ⁹⁰Verster, de Weert, et al., 2003; ⁹¹Vuurman, Theunissen, van Oers, van Leeuwen, & Jolles, 2007; ⁹³Vermeeren, Ramaekers, & O'Hanlon, 2002; ⁹⁵Gengo & Gabos, 1987; ¹⁰⁰Gandon & Allain, 2002; ¹⁰³Tsujii, Yamamoto, Ohira, Saito, & Watanabe, 2007; ¹⁰⁴Richardson, Roehrs, Rosenthal, Koshorek, & Roth, 2002; ¹⁰⁵Fine, et al., 1994; ¹⁰⁶Serra-Grabulosa, Grau, Escera, & Sanchez-Turet, 2001; ¹⁰⁸Moser, Huther, Koch-Weser, & Lundt, 1978; ¹¹⁰Hou, Langley, Szabadi, & Bradshaw, 2007; ¹¹³Simons, Fraser, Reggin, & Simons, 1995

CHAPTER 1

Psychomotor skills

The effects on psychomotor skills (table 6) were measured on 96 occasions of which 50 (LC: 52%) indicated impaired performance of which 21 (22%) according to the SC.

Similar to the driving performance, psychomotor skills involve many cognitive operations. Eye-hand coordination – typically assessed by tracking tests- was most frequently assessed (67 times) and 39 (LC) and 20 (SC) times H₁-antagonists induced impaired performance (LC: 58% and SC: 30%, respectively). In contrast, motor speed as assessed by symbol copying and finger tapping tests, involves less cognitive operations and was slowed less frequently i.e. in 29% (LC) of the 24 measurements and only once as determined by the SC (4%). Postural stability was impaired in 3 out of 4 measurements (CL: 75%). However, postural stability was assessed only 4 times.

Table 5: Effects of first generation H₁-antagonists on measures of driving performance.

Cognitive domain/task	No impairment	Impairment		References
		p<0.05	p<0.01	
<i>Driving (n=13)</i>		85% (11/13)	15% (2/13)	
Simulated driving (n=3)		100% (3/3) DH50 ^{15,17,95}	0% (0/3)	⁹⁵ Gengo & Gabos, 1987; ¹⁷ Gengo, et al., 1989; ¹⁵ Gengo, et al., 1990;
Actual driving (n=10)		80% (8/10) DC6er ^{75,76} DH50 ^{3,90} E2 ⁹³ , E4 ⁹³	20% (2/10) DH50 ³	³ Vuurman, et al., 2004; ³¹ Volkerts, et al., 1992; ⁵⁹ Ridout, et al., 2003; ⁷⁵ Theunissen, Vermeeren, & Ramaekers, 2006; ⁷⁶ Theunissen, et al., 2004;
	H30 ⁸⁹ , H50 ⁵⁹	H50 ⁹¹ T5 ³¹	H50 ⁹¹	⁸⁹ Tashiro, et al., 2005; ⁹⁰ Verster, de Weert, et al., 2003; ⁹¹ Vuurman, et al., 2007; ⁹³ Vermeeren, et al., 2002

Table 6: Effects of first generation H₁-antagonists on measures of psychomotor skills

Cognitive domain/task		No impairment	Impairment	References
			p<0.05	p<0.01
<i>Psychomotor</i>	<i>skills</i>		52% (50/96)	22% (21/96)
(n=96)				
Eye-hand coordination			58% (39/67)	30% (20/67)
(n=67)	A10 ⁶⁴ , AZ2 ⁴³ , AZ4 ⁴³ B12 ⁷¹ C4 ^{14,53} CA12 ⁷¹ CI15 ⁷ , CI45 ⁷ CL1 ^{30,71} , CL2 ³⁰ , DC4 ⁵² , DC6 ^{er75,76} DH25 ^{30,69} DH50 ^{30,69} H20 ⁴⁰ , H25 ³⁸ P10 ⁷ , P20 ^{2,2} , P25 ^{60,86} , P30 ^{2,2}	AZ8 ⁴³ B12 ^{er83} , B4 ⁸³ C4 ^{82,83} , C12 ^{er114} CI30 ⁷ CL1 ⁶⁵ , CL2 ⁶³ DC2 ⁴⁵ , DC4 ^{32,43,45} DH25 ¹⁴ , DH50 ^{3,13,14,21,50,72,73,77} DH75 ²⁷ O5 ⁸⁸ P10 ^{8,74,82} , P25 ^{5,78} , P30 ⁵⁶ , P50 ^{78,87} T2.5 ⁸³ , T10 ^{19,24,29,61,84} , T10 ^{er83}	AZ8 ⁴³ , B12 ^{er83} , C4 ⁸² , CL1 ⁶⁵ , CL2 ⁶³ , DC2 ⁴⁵ , DC4 ^{32,43,45} DH50 ³ , P25 ^{5,78} P10 ⁸ , P10 ⁸² T2.5 ⁸³ , T10 ^{19,24,29,83,84}	² Acons, et al., 2006; ³ Vuurman, et al., 2004; ⁵ Nicholson, et al., 2003; ⁷ Nicholson, et al., 2000; ⁸ Nicholson, et al., 2002; ¹³ Witek, et al., 1992; ¹⁴ Witek, et al., 1995; ¹⁹ Bradley & Nicholson, 1987; ²¹ Mattila, et al., 1986; ²⁴ Nicholson & Stone, 1983; ²⁷ Baugh & Calvert, 1977; ²⁹ Nicholson & Stone, 1986; ³⁰ Pishkin, Sengel, Lovallo, & Shurley, 1983; ³² Kamei, et al., 2003; ³⁸ Barbanoj, et al., 2004; ⁴⁰ Levander, et al., 1991; ⁴³ Biehl, 1979; ⁴⁵ Van Ruitenbeek, 2008; ⁵⁰ Cohen, et al., 1987; ⁵² Franks, Hensley, Hensley, Starmer, & Teo, 1978; ⁵³ Kulshrestha, et al., 1978; ⁵⁶ Hindmarch, et al., 2002; ⁶⁰ Shamsi, et al., 2001; ⁶¹ Kerr, et al., 1994; ⁶³ Vuurman, et al., 1994; ⁶⁴ Dhorranintra, et al., 1986; ⁶⁵ Gaillard, et al., 1988; ⁶⁹ Linnoila, 1973; ⁷¹ Seppala, et al., 1981; ⁷² Kay, et al., 1997; ⁷³ Moskowitz & Burns, 1988; ⁷⁴ Nicholson & Turner, 1998; ⁷⁵ Theunissen, et al., 2006; ⁷⁶ Theunissen, et al., 2004; ⁷⁷ Verster, Volkerts, et al., 2003; ⁷⁸ Schroeder, et al., 1985; ⁸² Clarke & Nicholson, 1978; ⁸³ Nicholson, 1979; ⁸⁴ Nicholson & Stone, 1982; ⁸⁵ Seppala & Savolainen, 1982; ⁸⁶ Hedges, Maclay, Newman-Taylor, & Turner, 1971; ⁸⁷ Molson, Mackey, Smart, & Turner, 1966; ⁸⁸ Takahashi, et al., 2004; ¹¹⁴ Hindmarch & Bhatti, 1987;

Postural stability (n=4)		75% (3/4)	0% (0/4)	³ Vuurman, et al., 2004; ⁵⁰ Cohen, et al., 1987; ⁵² Franks, et al., 1978; ¹⁰⁰ Gandon & Allain, 2002
	DH50 ³	DC4 ⁵²		
		DH50 ^{50,100}		
Motor speed (n=24)	AZ4 ⁴³ , AZ2 ⁴³	29% (7/24)	4% (1/24)	⁹ Curran, et al., 1998; ¹⁸ Lee, et al., 1988; ²⁰ Roth, et al., 1987; ²⁵ Hamilton, et al., 1982; ²⁶ Clubley, et al., 1979; ²⁹ Nicholson & Stone, 1986; ³⁸ Barbanøj, et al., 2004; ³⁹ Cohen, et al., 1985; ⁴⁰ Levander, et al., 1991; ⁴¹ Oken, et al., 1995; ⁴³ Biehl, 1979; ⁴⁴ Carruthers, et al., 1978;
	CY25 ²⁶ CY50 ^{25,26}	AZ8 ⁴³		
	CY100 ^{25,26}	C12er ^{18,18}		
	DH25 ^{9,9} , DH50 ^{9,44}	DC4 ⁴³		
	DH1mg/kg ⁴¹ , DH50iv ⁴⁴	DH50 ^{9,20}		
	H20 ⁴⁰ , H25 ³⁸			
	T2.5 ^{25,39} , T5 ³⁹	T10 ²⁹	T10 ²⁹	

CHAPTER 1

Diphenhydramine 50 mg impaired performance on eye-hand coordination on 8 out of 10 occasions (LC: 80%), postural stability 2 out of the 3 times (LC: 67%) and motor speed 2 out of 4 times (LC: 50%). The lower dose impaired eye-hand once out of 3 (33%), but did not slow motor speed

The results suggest that H₁-antagonists affect psychomotor performance to a large extent. The tasks that were used do not discriminate between different cognitive processes underlying performance. The affected processes that cause the impairment may be motor related processes as these are also affected. However, these are affected to a lesser extent than eye-hand coordination, which suggests that other processes are impaired as well.

Speed of discrete responding

Performance on reaction time tasks (table 7) depends less on central cognitive processes as compared with psychomotor skills e.g. compensatory tracking. Performance on reaction time tasks does depend greatly on sensory and motor processes. Slowing of any of those process, results in a decrease in performance.

Of the 78 measurements assessing reaction time 40 (LC: 51%) and 9 (SC: 12%) indicated slowed performance. Simple reaction time was slowed on 14 and 2 of the 35 measurements (LC: 40%, SC: 6%, respectively). In comparison, performance on the choice reaction time task was slowed on 26 occasions of the 43 assessments (LC: 61%) and on 7 occasions using the SC (16%). Assuming pure insertion, the choice reaction time task includes the additional process of 'response choice' as compared with the simple reaction time task. It may be that antihistamines affect the choice of the response in addition to slowed sensory and motor processes.

This pattern was also seen after diphenhydramine administration, albeit to a lesser extend. Two doses of diphenhydramine (25 and 50mg) were used in both simple and choice reaction time tasks. Simple reaction time speed was slowed in 4 cases of the 8 measurements (LC: 50%). Choice reaction time was slowed 6 times of the 11 times measured (LC: 55%). Performance after administration of lowest dose of diphenhydramine (25 mg) was impaired on both tasks, indicating that both measures are sensitive to the impairing effects.

Apart from 'response choice', the simple- and choice reaction time tasks mostly do not discriminate between different processes in cognitive functioning (e.g. sensory and motor processes). However, some authors have assessed specific processes involved in performance on the choice reaction time task. In two studies of Gaillard et al. (Gaillard & Verduin, 1983; Gaillard, Gruisen, & De Jong, 1988) the interaction between the effect of an antihistamine and the presentation of visually degraded stimuli was studied. One of these studies found that the antihistamine tended to interact with the task manipulation i.e. stimulus degradation (Gaillard & Verduin, 1983).

CHAPTER 1

Stimulus degradation is known to affect the processing of sensory information. The interaction indicates the effect of antihistamines on at least that same process (Sanders, 1980; Sternberg, 1969). In contrast, in their second study (Gaillard, et al., 1988) they concluded that the antihistamine mainly affected motoric processes. Next to these two studies there are no studies examining the specificity of the effects of antihistamines.

Perception

Tasks in which the emphasis is on perceptual functions (visual and temporal) (table 8) were used on 49 occasions of which 24 showed an impairment according to the LC (49%) and on 6 occasions using the SC (12%).

Within this domain perceptual processing speed (Critical Flicker/Fusion Frequency) has been assessed most frequently (i.e. 34 times). These measurements indicated slowed perceptual speed 18 times (LC: 53%) and 4 times (SC: 12%). Visual threshold was measured only 6 times, but was impaired on 5 occasions (LC: 83%) and twice using the SC (33%). These results suggest that perceptual processes are sensitive to the effects of antihistamines. In contrast, pattern matching was assessed 5 times of which an impairment was detected only once (LC: 20%)

Finally, temporal processing (time and speed perception) was assessed 4 times and showed no impairment. Processing of complex patterns, time and speed appear to be less affected by the H₁-antagonists than processing of visual information.

The conclusion that visual processing speed is affected is supported when considering the impairments induced by diphenhydramine. Diphenhydramine 25 mg, 50 mg and 75 mg together impaired perceptual processing speed in a total of 44% of the cases (LC), diphenhydramine could not impair pattern recognition on the 2 occasions measured (LC: 0%). However, the effect of this drug on visual threshold and complex perceptual functions were not assessed.

More sensory visual functions have only been assessed 4 times of which 2 (LC: 50%) indicated an impairment (table 9). Pupillary function was impaired in 1 of 3 assessments (LC 33%), due to effects of diphenhydramine 75 mg. Effects of diphenhydramine 50 mg on pupillary functions were not significant, but this dose did impair saccadic eye movements. No other H₁-antagonists were studied using saccadic eye movements. These four assessments indicate that visual sensory functions can be affected by H₁-antagonists, but data are limited as to few studies have been done.

Table 7: Effects of first generation H₁-antagonists on measures of speed of discrete responding

Cognitive domain/task	No impairment	Impairment p<0.05	p<0.01	References
<i>Speed of discrete responding</i> (n=78)		51% (40/78)	12% (9/78)	
Simple reaction time (n=35)	AZ2 ⁴³ , AZ4 ⁴³ C4 ⁵³ CL1 ³⁰ , CL2 ³⁰ , CY25 ²⁶ , CY50 ^{25,26} CY100 ²⁶ , DC2 ³⁵ , DC4 ⁵² DC6 ^{er35} DH50 ^{3,20,30,50} H20 ⁴⁰ , H25 ³⁰ K2 ⁴⁸ T2.5 ^{25,39}	40% (14/35) AZ8 ⁴³ C12 ^{er18} , CY100 ²⁵ DC2 ⁴⁵ , DC4 ^{43,45} DH25 ⁴ , DH50 ^{44,47} DH50 ^{iv44} H25 ³⁸ , H30 ^{36,37} T5 ³⁹	6% (2/35) DC4 ⁴⁵ , DH50 ⁴⁷	³ Vuurman, et al., 2004; ⁴ Gupta, et al., 2004; ¹⁸ Lee, et al., 1988; ²⁰ Roth, et al., 1987; ²⁵ Hamilton, et al., 1982; ²⁶ Clubley, et al., 1979; ³⁰ Pishkin, et al., 1983; ³⁵ Tagawa, et al., 2002; ³⁶ Tashiro, et al., 2002; ³⁷ Tashiro, et al., 2004; ³⁸ Barbanoj, et al., 2004; ³⁹ Cohen, et al., 1985; ⁴⁰ Levander, et al., 1991; ⁴³ Biehl, 1979; ⁴⁴ Carruthers, et al., 1978; ⁴⁵ Van Ruitenbeek et al., 2008; ⁴⁶ Goetz, et al., 1991; ⁴⁷ Grunberger, et al., 1988; ⁴⁸ Adamus, et al., 1987; ⁵⁰ Cohen, et al., 1987; ⁵² Franks, et al., 1978; ⁵³ Kulshrestha, et al., 1978; ⁵⁴ Roberts, 1971
Choice reaction time (n=43)	A10 ⁶⁴ AZ2 ⁴³ , AZ4 ⁴³ , AZ8 ⁴³ B12 ⁷¹ CL1 ⁷¹ DC4 ^{32,43,52} DH25 ⁶⁹ , DH50 ^{1,21,47,69} H25 ³⁸ P20 ² T10 ⁵⁵	61% (26/43) B10 ⁷⁰ C4 ¹⁴ CA12 ⁷¹ CL1 ⁶⁵ DC2 ^{35,45} , DC4 ⁴⁵ DC6 ^{er35,58} DH25 ^{4,14} , DH50 ^{13,14} , DH75 ¹ , DH100 ¹ H30 ^{36,37,57} , H50 ⁵⁹ , P25 ^{5,60,68} , P30 ^{2,56} T5 ³¹ , T10 ⁶¹	16% (7/43) B10 ⁷⁰ DC6 ^{er35} DH100 ¹ H50 ⁵⁹ P25 ⁵ , P30 ^{2,56}	¹ Turner, et al., 2006; ² Acons, et al., 2006; ⁴ Gupta, et al., 2004; ⁵ Nicholson, et al., 2003; ¹⁴ Witek, et al., 1995; ²¹ Mattila, et al., 1986; ³¹ Volkerts, et al., 1992; ³² Kamei, et al., 2003; ³⁵ Tagawa, et al., 2002; ³⁶ Tashiro, et al., 2002; ³⁷ Tashiro, et al., 2004; ³⁸ Barbanoj, et al., 2004; ⁴³ Biehl, 1979; ⁴⁵ Van Ruitenbeek, 2008; ⁴⁶ Goetz, et al., 1991; ⁴⁷ Grunberger, et al., 1988; ⁵² Franks, et al., 1978; ⁵⁵ Hindmarch & Shamsi, 2001; ⁵⁷ Hindmarch, et al., 1999; ⁵⁸ Mochizuki, et al., 2002; ⁵⁹ Ridout, et al., 2003; ⁶⁰ Shamsi, et al., 2001; ⁶¹ Kerr, et al., 1994; ⁶³ Vuurman, et al., 1994; ⁶⁴ Dhorranintra, et al., 1986; ⁶⁵ Gaillard, et al., 1988; ⁶⁶ Gaillard & Verduin, 1983; ⁶⁸ Levin, et al., 1984; ⁶⁹ Linnoila, 1973; ⁷⁰ Millar & Standen, 1982; ⁷¹ Seppala, et al., 1981

Table 8: Effects of first generation H₁-antagonists on measures of perception

Cognitive domain/task	No impairment	Impairment		References
		p<0.05	p<0.01	
<i>Perception (n=49)</i>		49% (24/49)	12% (6/49)	
Pattern recognition (n=5)	CL1 ³⁰ , CL2 ³⁰ DH25 ³⁰ , DH50 ³⁰	20% (1/5)	0% (0/5)	³⁰ Pishkin, et al., 1983; ³¹ Volkerts, et al., 1992
Visual threshold (n=6)	DC1iv ³⁴	T5 ³¹ 83% (5/6) DC2 ³⁵ , DC6er ³⁵ , DC2iv ³⁴ H30 ^{36,37}	33% (2/6) DC2 ³⁵ DC6er ³⁵	³⁴ Okamura, et al., 2000; ³⁵ Tagawa, et al., 2002; ³⁶ Tashiro, et al., 2002; ³⁷ Tashiro, et al., 2004
Perceptual processing speed (n=34)	B12 ⁷¹ C4 ⁵³ , C12er ¹⁸ CA12 ⁷¹ CL1 ^{30,71} DC4 ³² , DC6er ⁷⁶ , DH25 ⁹ , DH50 ^{3,9,30,47} H25 ³⁰ K2 ⁴⁸ T10 ⁵⁵	CL2 ^{30,63} DH25 ⁴ , DH50 ^{21,100} DH75 ¹¹⁰ H25 ³⁸ , H50 ⁵⁹ K1 ¹⁰³ P25 ^{60,68,86} , P30 ^{56,57} T7.5 ¹⁶ , T10 ^{24,29,61}	12% (4/34) K1 ¹⁰³ P25 ⁸⁶ T7.5 ¹⁶ , T10 ²⁹	³ Vuurman, et al., 2004; ⁴ Gupta, et al., 2004; ⁹ Curran, et al., 1998; ¹⁶ Swire, et al., 1989; ¹⁸ Lee, et al., 1988; ²¹ Mattila, et al., 1986; ²⁴ Nicholson & Stone, 1983; ²⁹ Nicholson & Stone, 1986; ³⁰ Pishkin, et al., 1983; ³² Kamei, et al., 2003; ³⁸ Barbanoj, et al., 2004; ⁴⁷ Grunberger, et al., 1988; ⁴⁸ Adamus, et al., 1987; ⁵³ Kulshrestha, et al., 1978; ⁵⁵ Hindmarch & Shamsi, 2001; ⁵⁶ Hindmarch, et al., 2002; ⁵⁷ Hindmarch, et al., 1999; ⁵⁹ Ridout, et al., 2003; ⁶¹ Kerr, et al., 1994; ⁶³ Vuurman, et al., 1994; ⁶⁸ Levin, et al., 1984; ⁷¹ Seppala, et al., 1981; ⁷⁶ Theunissen, et al., 2004; ⁸⁶ Hedges, et al., 1971; ¹⁰⁰ Gandon & Allain, 2002; ¹⁰³ Tsujii, et al., 2007; ¹¹⁰ Hou, et al., 2007
Complex perceptual functions (n=4)	B12 ⁷¹ CA12 ⁷¹ CL1 ⁷¹ H25 ³⁸	0% (0/4)	0% (0/4)	³⁸ Barbanoj, et al., 2004; ⁷¹ Seppala, et al., 1981

CHAPTER 1

Table 9: Effects of first generation H₁-antagonists on measures of sensory visual functions

Cognitive domain/task	No impairment	Impairment		References
		p<0.05	p<0.01	
<i>Sensory Visual function (n=4)</i>		50% (2/4)	0% (0/4)	
Physiology of the eye (n=3)	DC6er ⁷⁶ DH50 ⁴⁷	33% (1/3)	0% (0/3)	⁴⁷ Grunberger, et al., 1988; ⁷⁶ Theunissen, et al., 2004;
Eye movements (n=1)		DH75 ¹¹⁰ 100% (1/1) DH50 ⁵⁰	0% (0/1)	¹¹⁰ Hou, et al., 2007 ⁵⁰ Cohen, et al., 1987

Attention

The effects of the H₁-antagonists on tasks assessing attention have been assessed extensively and often lead to impaired performance (table 10).

Effects on attention have been assessed 91 times of which 40 assessments (44%) indicated impaired performance using the LC. Using the SC, 17 assessments (19%) indicated impaired performance.

Of these measures divided attention was most frequently impaired as determined using both the LC (58%) and SC (26%). However, divided attention tasks often include tracking as one of two tasks and as shown earlier, eye-hand coordination is very sensitive to H₁-antagonism. This may therefore have confounded the results.

Performance on categorization tasks (e.g. Digit Symbol Substitution Tasks, Card Sorting Task), which also include considerable eye-hand coordination in addition to executive processes, was impaired 14 of the 37 assessments (LC: 38%) and 9 times using the SC (24%). The impairment on these tasks is of similar magnitude as found in divided attention tasks as judged by the SC (i.e. 24 and 26%). Nevertheless, tasks including less eye-hand coordination and executive functions like sustained attention and vigilance were also impaired on 11 out of 23 times (LC: 48%) but only once (4%) using the SC.

Spatial attention was found to be impaired 3 out of 8 times and was impaired as determined by the LC (38%) of which 2 times according to the SC (25%). Selective attention was impaired only once (LC) out of 4 times. So, even though impaired performance on some tasks may not result purely from impaired attentional processes, other tasks do suggest that attention is impaired after the administration of H₁-antagonists

Diphenhydramine impaired performance on divided attention and categorization tasks the most. Effects of doses ranging between 25 and 100 mg were assessed. Impaired performance was found on all assessments of divided attention (100%) and on 7 of the 16 assessments using categorization tasks (LC: 44%). Similar to the impairment ratio from all drugs, the divided attention task appears to be a very sensitive task. Tasks in which the

CHAPTER 1

psychomotor component is smaller, like measures of spatial attention, are reasonably sensitive as performance was impaired twice of the 6 assessments and twice of the 4 assessments for spatial attention and alertness, respectively.

Memory

The effects of H₁ blockade on memory performance (table 11) has been assessed 73 times of which 19 (26%) showed impaired performance as determined using the LC and 10 times (14%) using the SC.

Within this domain, working memory has been assessed most frequently (i.e. 50 times). In 36% (LC) subjects showed impaired performance, which was the case in 18% when SC was applied. In contrast, episodic memory performance was assessed 23 times and an impairment was indicated only once (4%) using both LC and SC. Semantic memory was measured once and was not impaired.

Working memory was clearly more frequently impaired compared with explicit and semantic memory. Performance on tasks assessing working memory frequently relies on response speed. For example, overall response speed is often the dependent outcome measure of the Sternberg's memory scanning task and N-back task and, therefore, resembles a choice reaction time task. In such cases antihistamines impair performance in 60% (LC) of the assessments, which resembles the 61% (LC) impaired choice reaction time task performance. In contrast to the working memory tasks, explicit and semantic memory is frequently measured using word learning tasks or recall of information, which is largely irrespective of speed and show impaired performance in only 4% (LC and SC) of the cases. In addition, Performance on working memory tasks not dependent on response speed, e.g. digit recall, was impaired in only 27% (LC) of the assessments. It may be that information processing speed is affected, but not the functional integrity e.g. correctly recalled words.

The effects of diphenhydramine were only assessed on working memory. In correspondence with the impairment ratio of all drugs, working memory was impaired in 26% (LC) of the cases. The 25 mg dose was capable of impairing the performance on one occasion. However, in several studies the 50, 75 and 100 mg doses were able to impair performance. Therefore, in contrast to all the impairment ratio of all drugs working memory seems to be rather insensitive to the effects of diphenhydramine

Table 10: Effects of first generation H₁-antagonists on measures of attention

Cognitive domain/task	No impairment	Impairment p<0.05	p<0.01	References
<i>Attention (n=91)</i>		44% (40/91)	19% (17/91)	
Spatial Attention (n=8)	DH25 ⁹ , DH50 ^{9,47} , DH1mg/kg ⁴¹ H25 ³⁸	DH25 ⁴ DH1mg/kg ⁴¹ H25 ³⁸	DH1mg/kg ⁴¹ H25 ³⁸	⁴ Gupta, et al., 2004; ⁹ Curran, et al., 1998; ³³ Barbanoj, et al., 2006; ³⁸ Barbanoj, et al., 2004; ⁴¹ Oken, et al., 1995; ⁴⁷ Grunberger, et al., 1988
Alertness (n=23)	CI15 ⁷ , CI45 ⁷ CL2 ⁶³ CY25 ²⁶ , CY50 ²⁶ , CY100 ²⁶ DC4 ³² DH50 ^{1,20} , DH75 ¹ , DH100 ¹	CI30 ⁷ DH25 ¹⁰⁵ , DH50 ^{72,73}	DH50 ⁷²	¹ Turner, et al., 2006; ⁵ Nicholson, et al., 2003; ⁷ Nicholson, et al., 2000; ⁸ Nicholson, et al., 2002; ²⁰ Roth, et al., 1987; ²⁶ Clubley, et al., 1979; ³² Kamei, et al., 2003; ³⁹ Cohen, et al., 1985; ⁶³ Vuurman, et al., 1994; ⁷¹ Seppala, et al., 1981; ⁷² Kay, et al., 1997; ⁷³ Moskowitz & Burns, 1988; ⁷⁴ Nicholson & Turner, 1998; ⁷⁹ Seidel, et al., 1990; ⁸⁰ Seidel, et al., 1987; ¹⁰⁵ Fine, et al., 1994
Selective attention (n=4)	P10 ⁷ P20 ² , P30 ² T10 ⁶¹	H25 ^{79,80} , P10 ^{8,74} , P25 ⁵ T2.5 ³⁹ , T5 ³⁹ 25% (1/4) DC4 ¹⁰⁶	0% (0/4)	² Acons, et al., 2006; ⁶¹ Kerr, et al., 1994; ¹⁰⁶ Serra-Grabulosa, et al., 2001
Divided attention (n=19)	B12 ⁷¹ CA12 ⁷¹ C4 ¹⁴ CL1 ^{65,71} DC2 ⁴⁵ , DC6 ^{er75,76}	58% (11/19) CL2 ⁶³ DC4 ⁴⁵ DH25 ¹⁴ , DH50 ^{13,14,21,72,73,77,104}	26% (5/19) CL2 ⁶³ DC4 ⁴⁵ DH50 ^{21,72}	¹³ Witek, et al., 1992; ¹⁴ Witek, et al., 1995; ²¹ Mattila, et al., 1986; ⁴⁵ Van Ruitenbeek, 2008; ⁵⁵ Hindmarch & Shamsi, 2001; ⁶³ Vuurman, et al., 1994; ⁶⁵ Gaillard, et al., 1988; ⁷¹ Seppala, et al., 1981; ⁷² Kay, et al., 1997; ⁷³ Moskowitz & Burns, 1988; ⁷⁵ Theunissen, et al., 2006; ⁷⁶ Theunissen, et al., 2004; ⁷⁷ Verster, Volkerts, et al., 2003; ¹⁰⁴ Richardson, et al., 2002

Categorization tasks (n=37)		T10 ⁵⁵	P10 ⁸	¹ Turner, et al., 2006; ² Acons, et al., 2006; ³ Vuurman, et al., 2004; ⁴ Gupta, et al., 2004; ⁵ Nicholson, et al., 2003; ⁷ Nicholson, et al., 2002; ⁸ Nicholson, et al., 2000; ⁹ Curran, et al., 1998; ¹³ Witek, et al., 1992; ¹⁴ Witek, et al., 1995; ¹⁵ Gengo, et al., 1990; ¹⁶ Swire, et al., 1989; ¹⁷ Gengo, et al., 1989; ¹⁸ Lee, et al., 1988; ¹⁹ Bradley & Nicholson, 1987; ²⁰ Roth, et al., 1987; ²¹ Mattila, et al., 1986; ²⁴ Nicholson & Stone, 1983; ²⁵ Hamilton, et al., 1982; ²⁶ Clubley, et al., 1979; ²⁷ Baugh & Calvert, 1977; ²⁹ Nicholson & Stone, 1986; ⁴⁴ Carruthers, et al., 1978; ⁶⁴ Dhorrnintra, et al., 1986; ⁹⁹ De Brabander, 1990
		38% (14/37)	24% (9/37)	
	C4 ¹⁴ C12 ^{er18}		A10 ⁶⁴	
	CI15 ⁷ , CI45 ⁷	CI30 ⁷ ,	CI30 ⁷ ,	
	CY25 ²⁶ ,			
	CY50 ^{25,26} ,			
	CY100 ^{25,26} ,	DH25 ⁴ ,	DH50 ^{17,44} ,	
	DH25 ^{9,14} ,	DH50 ^{1,15,17,20,21} ,	DH50iv ⁴⁴	
	DH50 ^{3,13,14,15,9} ,	DH100 ¹ ,		
	DH75 ^{1,27}			
	H50 ⁹⁹ ,	P25 ⁵ , P10 ⁸	P25 ⁵	
	P10 ⁷ , P20 ² , P30 ²	T7.5 ¹⁶ , T10 ^{24,19,299}	T7.5 ¹⁶ , T10 ^{24,29}	
	T2.5 ²⁵			

CHAPTER 1

CONCLUSION

Taken together, if the LC is applied driving (85%) is most sensitive to the effects of centrally active H₁-antagonists followed by psychomotor skills (52%, in particular tracking), speed of discrete responding (51%, in particular choice reaction time), perception (49%, in particular CFF) and attention (44%, in particular divided attention). Finally, memory performance was impaired in 26% of the assessments (in particular working memory). When applying the SC driving was only impaired in 15% of the assessments. In accordance with the LC psychomotor skills (22%) and attention (19%) were highly sensitive to H₁-antagonism. Speed of discrete responding (12%), perception (12%) and memory (14%) were affected less frequently.

There are some limitations to these numbers that need to be considered. First of all, the effects on memory may be related to effects on working memory task performance. As most tasks assess a product of cognitive processes as opposed to a single process, also working memory performance frequently depends on psychomotor speed e.g. as measured with reaction time. It should also be taken into account that only 12 studies assessed episodic memory. Compared to, for example, eye-hand coordination (45 studies), choice reaction time (31 studies), perceptual processing speed (27 studies) and simple reaction time (23 studies) it may be suggested that future studies need to further test the effects of H₁-antagonists on episodic memory.

Furthermore, sensory visual functions were affected in 50% as judged using the LC, but were only investigated 4 times. Regarding the use of the SC it should also be taken into account that 15 studies did not test for significance at a 0.01 level. These studies provided only information about whether the p value was smaller than 0.05 or not. However, the above stated profile is not expected to be greatly affected by results from these studies.

Effects of diphenhydramine show a similar pattern of results compared with the impairment ratio of all drugs (table 12). The 50 mg dose has been used most frequently and the effects of this dose on all domains have been assessed. Driving (100%), psychomotor skills (71%), attention (61%) and sensory visual function (50%) (i.e. saccadic eye movements and papillary functions) seem to be the most sensitive cognitive domains to the effects of diphenhydramine. However, sensory visual function has been very scarcely studied and therefore further research is needed before it can be determined whether the function is sensitive. Speed of responding and perception are also frequently affected by diphenhydramine 50 mg (33% and 29%, respectively). Finally, memory appears to be least sensitive (17%), especially when considering episodic memory.

Table 11: Effects of first generation H₁-antagonists on measures of memory

Cognitive domain/task	No impairment	Impairment		References
		p<0.05	p<0.01	
<i>Memory (n=83)</i>		23% (19/83)	12% (10/83)	
Working memory (n=51)	AZ2 ⁴³ , AZ4 ⁴³ , AZ8 ⁴³ , CY25 ^{26,26} , CY50 ^{26,26} , CY100 ²⁶ DC2 ^{45,45} , DC4 ^{43,45} , DC6er ⁷⁶ , DH50 ^{1,1,3,13,13,21,47,47,77} DH75 ^{1,1} , DH100 ^{1,1} , DH1mg/kg ⁴¹	CL2 ⁶³ , CY100 ²⁶ , DC2 ⁴⁵ , DC4 ⁵² DH25 ⁴ , DH50 ^{72,72,102} , DH75 ²⁷ H25 ^{38,38} K1 ^{103,103} P25 ^{5,5} T5 ³¹ , T10 ^{19,55}	DC2 ⁴⁵ , DC4 ⁵² DH50 ^{72,72,102} K1 ¹⁰³ K1 ¹⁰³ , P25 ^{5,5}	¹ Turner, et al., 2006; ² Acons, et al., 2006; ³ Vuurman, et al., 2004; ⁴ Gupta, et al., 2004; ⁵ Nicholson, et al., 2003; ¹³ Witek, et al., 1992; ¹⁶ Swire, et al., 1989; ¹⁹ Bradley & Nicholson, 1987; ²¹ Mattila, et al., 1986; ²⁶ Clubley, et al., 1979; ²⁶ Clubley, et al., 1979; ²⁷ Baugh & Calvert, 1977; ³¹ Volkerts, et al., 1992; ³⁸ Barbanoj, et al., 2004; ⁴¹ Oken, et al., 1995; ⁴³ Biehl, 1979; ⁴⁵ Van Ruitenbeek, 2008; ⁴⁷ Grunberger, et al., 1988; ⁵² Franks, et al., 1978; ⁵⁵ Hindmarch & Shamsi, 2001; ⁶¹ Kerr, et al., 1994; ⁶³ Vuurman, et al., 1994; ⁷² Kay, et al., 1997; ⁷⁶ Theunissen, et al., 2004; ⁷⁷ Verster, Volkerts, et al., 2003; ⁹⁷ Higgins, et al., 1979; ¹⁰² Gevens, Smith, & McEvoy, 2002; ¹⁰³ Tsujii, et al., 2007
Semantic memory (n=1)	DH50 ³	0.0% (0/1)	0.0% (0/1)	³ Vuurman, et al., 2004
Episodic memory (n=23)	C4 ^{98,98,98} , C12er ¹⁸ DC2 ^{45,45} , DC4 ^{45,45} , DC6er ⁷⁶ DH25 ⁹ , DH50 ^{1,3,9,47,77,100} DH75 ¹ , DH100 ¹ H50 ⁹⁹ , P20 ² , P30 ²	4% (1/23) P25 ⁵	4% (1/23) P25 ⁵	¹ Turner, et al., 2006; ² Acons, et al., 2006; ⁵ Nicholson, et al., 2003; ⁹ Curran, et al., 1998; ¹⁸ Lee, et al., 1988, ⁴⁵ Van Ruitenbeek, 2008; ⁴⁷ Grunberger, et al., 1988; ⁷⁶ Theunissen, et al., 2004; ⁷⁷ Verster, Volkerts, et al., 2003; ⁹⁸ Carter & Cassaday, 1998; ⁹⁹ De Brabander, 1990; ¹⁰⁰ Gandon & Allain, 2002

CHAPTER 1

Table 12: The typical H₁-antagonist diphenhydramine used to indicate cognitive domains sensitive to H₁-antagonism. Percentages indicate the proportion of the treatments that impaired performance on tasks assessing a certain cognitive domain.

<i>Cognitive domain</i>	<i>Diphenhydramine dose</i>			
	100 mg	75 mg	50 mg	25 mg
Driving	n.a.	n.a.	100%	n.a.
Psychomotor skills	n.a.	100%	71%	20%
Attention	50%	0%	61%	57%
Sensory visual function	n.a.	100%	50%	n.a.
Speed of discrete responding	100%	100%	33%	75%
Perception	n.a.	100%	29%	50%
Memory	0%	25%	17%	50%

In conclusion, this review indicates that H₁-blockade impairs speed of cognitive information processing, which makes performance on tasks that rely on speed (e.g. critical tracking) most sensitive to H₁-blockade and tasks that rely little on speed least sensitive (e.g. episodic memory). In accordance, driving performance and psychomotor skills have shown to be most sensitive. We suggest that deficits in these functions may be modelled using H₁-antagonists and used for screening new H₃-antagonists for their potential to improve such deficits. The results suggest that perceptual functions are impaired by H₁-antagonism, which may partly underlie the psychomotor impairments. As discussed above, driving and psychomotor functions include multiple cognitive processes related to stimulus perception, decision making and response preparation and execution. However, so far, only a few studies have assessed effects of H₁ antagonists on separate underlying processes and came to contradictory conclusions. The specificity of the effects of centrally active H₁-antagonists therefore deserves further study.

In contrast to results from animal studies results from this review suggests that memory in healthy human volunteers is not likely to be impaired after H₁-antagonist administration. Therefore, deficits in this domain do not seem to be modelled adequately using H₁ antagonists. Data are limited however, as memory and episodic memory in particular, have been investigated by only a few authors when compared to functions like divided attention and psychomotor performance. Effects of H₁ antagonist on memory therefore also deserve further study.

CHAPTER 1

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CHAPTER 1

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CHAPTER 2

HISTAMINE H₁-RECEPTOR BLOCKADE IN HUMANS AFFECTS PSYCHOMOTOR PERFORMANCE BUT NOT MEMORY

Van Ruitenbeek, P., Vermeeren, A., & Riedel, W. J. (2008). Histamine H₁-receptor blockade in humans affects psychomotor performance but not memory. *J Psychopharmacol*, 22(6), 663-672.

CHAPTER 2

CHAPTER 2

INTRODUCTION

Recently interest in role that histamine might play in cognition has increased (Bacciottini et al. 2001; Blandina et al. 2004). Especially the cognitive domain of learning and memory is of interest. Animal studies have shown that increases in histaminergic functioning improve memory performance and decreases impair it [c.f.(Giovannini et al., 1999; Hancock and Fox, 2004; Komater et al., 2005; Meguro et al., 1995; Orsetti et al., 2001; Witkin and Nelson, 2004)].

Currently, evidence supporting a role of histamine in learning and memory is mainly based on studies in animals. So far there are hardly any studies specifically addressing this subject in humans. Although there are many studies assessing the behavioural effects of histaminergic blockade by centrally acting H₁-antagonists in humans, they provide little support for the hypothesis that decreased histaminergic functioning is associated with impaired memory functions. This is largely due to the fact that most of these studies simply did not include tests for memory functioning. Most of them have been conducted in the context of behavioural safety of antihistamines with an emphasis on car-driving (for reviews see: (Hindmarch and Shamsi, 1999; O'Hanlon and Ramaekers, 1995; Shamsi and Hindmarch, 2000; White and Rumbold, 1988). Since driving performance is more strongly dependent on perceptual-motor and attentional functions than on memory, only a few studies included memory tests.

The studies that did assess the effects of H₁ blockade on memory, show inconsistent results. The majority found no significant effects on memory (Acons et al., 2006; Bower et al., 2003; Curran et al., 1998; De Brabander, 1990; Kerr et al., 1994; Lee et al., 1988; Turner et al., 2006), whereas others did (Hindmarch et al., 2001; Katz et al., 1998, Sands et al., 1997; Vuurman et al., 1994). Two studies (Katz et al., 1998; Sands et al., 1997) found significant effects of diphenhydramine 50 mg on memory performance in healthy elderly subjects. Vuurman et al. (1994, 1996) found a significant learning impairment in children and adolescents after the use of diphenhydramine, and Hindmarch and Shamsi (2001) found a significant effect of triprolidine 10 mg on performance of healthy young volunteers in a memory-scanning task.

The contradictory results may be partly explained by the methods used. The use of insensitive memory tests and assessing memory functions before or after the time of peak behavioural impairments might explain the absence of effects. Alternatively, the significant effects found in some studies might be due to the antimuscarinic effects of the antihistamines used.

The aim of the present study was therefore to assess the effects of the relatively selective H₁-antagonist dexchlorpheniramine (2 and 4 mg) on

CHAPTER 2

performance of healthy female volunteers. The decision to select only female subjects was based on results from a number of previous studies suggesting that females are more sensitive to effects of H₁-antagonists than males (Ramaekers and O'Hanlon, 1994; Robbe, 1990; Vermeeren et al., 2002; Vuurman et al., 1994). The effects were to be compared to those of the muscarinic antagonist scopolamine that was included as a verum.

To detect potential effects of the dexchlorpheniramine on memory, a number of tests were selected that had previously been shown sensitive to detect drug induced impairments, and together covered a range of important aspects of memory function, such as short-term or working memory, long term memory, memory for verbal and visual material, and implicit and explicit (declarative) memory (Ramaekers et al., 1992; Riedel et al., 1990; Rubensztein et al. 2001; Vermeeren et al. 1995; Vuurman et al., 1994). A word learning test and a pattern recognition test were included to assess effects on short and long term memory for verbal and visual material, respectively; a memory scanning task and a syntactic reasoning task were included to assess integrity of working memory functions; and a spatial paired associate learning test was included to assess effects on implicit memory and learning. A simple reaction time test and a choice reaction test were added to the battery for the purpose of measuring effects on response speed without the cognitive components of the memory tests. To assess time of peak impairment of dexchlorpheniramine two tasks were included that have repeatedly been shown to be among the most sensitive tests to assess the impairing effects of H₁-antagonists; i.e., a critical tracking test, and a divided attention test (Burns and Moskowitz, 1980; Hindmarch and Shamsi, 1999; Meltzer, 1991; Theunissen et al., 2004; Vermeeren and O'Hanlon, 1998; Verster et al., 2003).

Dexchlorpheniramine was selected as a tool drug, because it is a first generation H₁-antagonist having a moderately high binding affinity for the H₁-receptors, but relatively low affinities for muscarinic, alpha-1, alpha-2 and beta receptors. The affinity for the muscarinic receptor is especially low ($K_d=3300$ for chlorpheniramine) as compared to scopolamine ($K_d=0.1$) (Wiech and Martin, 1982). The half-life of chlorpheniramine is approximately 28 hours (range 19-43 hours) and maximum plasma concentrations are reached at 2.8 hours (range 2-4 hours) after oral doses (Huang et al., 1982; Paton and Webster, 1985). Two studies have shown that single oral doses of 4 mg chlorpheniramine produced significant performance impairment which was most pronounced shortly after t_{max} (Kamei et al., 2003; Witek et al., 1995). Yet, in a third study performance was significantly impaired only at 1.5 hours after drug administration (Clarke and Nicholson, 1978). Based on these results it was decided to measure the effects of dexchlorpheniramine at both times reported for peak impairment i.e. between 1.5 and 2.5 hours and between 3.5 and 4.5 hours after administration.

CHAPTER 2

Scopolamine 1 mg in oral doses (p.o.) was included as an active control because the drug is well known for its impairing effects on learning and memory (Bartus et al., 1985). Oral doses of 1 mg or above have been reported to impair cognitive functioning (Kennedy et al., 1990; Rammsayer et al., 2000). Peak plasma concentrations are reached at approximately 0.8 hours after oral intake and scopolamine has an average elimination half-life of 4.3 hours (Golding et al., 1991).

METHODS

Subjects

Twenty healthy female volunteers aged between 18 and 45 years were recruited as subjects for the study by means of advertisements in local newspapers and paid for their participation. Subjects were screened using a medical history questionnaire and a physical examination, including a 12-lead electrocardiogram, blood chemistry and haematology, and urinary tests for pregnancy and drugs of abuse (opiates, benzodiazepines, cocaine, tricyclic antidepressants and cannabis). Exclusion criteria were pregnancy or lactation, a history or presence of any mental or physical disorder; gastrointestinal, hepatic, renal, cardiovascular or neurological. Also, drug abuse, a body-mass index value outside the limits of 18 and 28 kg/m², blood pressure outside the limits of 100 and 150 Hg systolic and 60 and 90 Hg diastolic and drinking more than 20 standard alcoholic units per week or more than 5 beverages containing caffeine per day, were regarded as exclusion criteria. No drugs or medication except oral contraceptives, aspirin and acetaminophen, were allowed to be taken from a week before the first test-day until the end of the study. Smoking and use of caffeine was prohibited on test-days and the use of alcohol from 24 hours before and during each test-day.

Three volunteers did not complete the study for reasons unrelated to treatment. Two of them withdrew before the second treatment session and the third subject was excluded for smoking on the first test-day as determined by measurement of carbon monoxide in expired air, using a Smokerlyzer Micro® (Bedfont Scientific Ltd.). These subjects were replaced. Mean $\pm$ SD age of the 20 subjects who completed the study was 23.7 $\pm$ 7.3 years. Their mean $\pm$ SD body mass index was 21.6 $\pm$ 3.0 kg/m². Five subjects were smokers, who on average ($\pm$ SD) smoked 4.6 ($\pm$ 2.1) cigarettes and no more than 10 per day. Eighty percent of the subjects were in college or had a similar level of education. The remaining twenty percent had all at least finished high school at an average level of education.

All subjects received written information about the study procedures and were able to ask questions. They signed an informed consent form prior

CHAPTER 2

to enrolment. The study was approved by the Ethics committee of Maastricht University and University Hospital Maastricht and carried out in accordance with the World Medical Association Declaration of Helsinki (Edinburgh, 2000).

Study design and treatments

The study was conducted according to a double blind, placebo-controlled, 4-way crossover design. Treatments were single oral doses of dexchlorpheniramine 2 mg and 4 mg, scopolamine 1 mg (all immediate release formulations) and placebo. Treatments were spaced apart by a washout period of at least 7 days.

Procedure

Subjects were individually trained to perform all psychomotor and memory tests within two weeks prior to their first treatment day. On treatment days they arrived at the University around 9:00 hours. Between 9:45 and 10:45 hours a battery of psychometric tests was completed to obtain baseline performance scores. At 11:00 hours subjects ingested the study medication. Thereafter the test battery was repeated at 12:30 hours and 14:30 hours, i.e. between 1.5 and 2.5 hours, and 3.5 and 4.5 hours after ingestion, henceforth indicated as t2 and t4.

The duration of the test battery was approximately one hour and consisted of the tasks and assessments in the following sequence: critical tracking, divided attention, subjective alertness, syntactic reasoning, immediate pattern recognition, memory scanning, simple reaction time, choice reaction time, spatial paired associate learning, delayed pattern recognition and critical tracking. The t4 test battery included a 30-words learning task, that was completed only once per test day to prevent interference of the previously learned words that same day. The immediate recall part was done following the syntactic reasoning test and delayed recall part was done following the spatial paired associated learning test. At 0.5 hours after drug intake an additional critical tracking task was performed, with performance on this test then assessed at hourly intervals after drug administration. This allowed better monitoring of the time of peak impairment induced by both drugs.

Assessments

Memory performance

30-Words learning task - The 30-words learning task (Klaassen et al., 2002; Rey, 1964; Riedel et al., 1999) assesses short and long term verbal memory. Thirty Dutch mono-syllabic meaningful nouns and adjectives are presented

CHAPTER 2

for 1000 ms at a rate of 1 per 2 seconds and subjects are required to read them aloud. When the presentation ends, subjects are required to verbally recall as many words as possible (immediate recall). This procedure is repeated three times, with the same words presented in the same sequence. After a 45 minutes delay subjects are requested again to recall as many words as possible (delayed recall). Finally, subjects are presented a series of 30 words on a computer screen that include 15 words from the original list and 15 comparable but new words. Subjects are asked to indicate as quickly as possible whether the presented words are from the original list or not by pressing one of two buttons (delayed recognition). Dependent variables were the total number of words correctly recalled over the three immediate recall trials, the number of correctly recalled words after the delay and median reaction time (ms) of correct answers during recognition. Since the distribution of reaction times is generally skewed to the right, the median RT was selected as dependent variable in all tasks except when indicated otherwise. The median is less sensitive to the presence of one sided outliers as compared to the mean.

Pattern recognition task - The pattern recognition task assesses short and long term memory for visual information. In this test subjects are presented a series of 15 randomly generated black and white block patterns of a 6x4 grid, at a rate of 1 pattern per 3 seconds. Subjects are asked to memorize the patterns. The same series of patterns is presented three times in the same order. Immediately thereafter a series of 30 patterns is presented, including 15 patterns from the original set and 15 new patterns. Subjects are asked to indicate as quickly as possible whether the presented patterns are from the original list or not by pressing one of two buttons. After approximately 30 minutes this recognition procedure is repeated. The dependent measures are the median reaction time and the number of patterns correctly recognized in the immediate and delayed recognition tests.

Memory scanning task - The memory scanning task (Sternberg, 1969) measures the time it takes to scan items held in memory as part of working memory integrity, separating it from other processes required to respond. When subjects judge whether a test symbol is contained in a short memorized sequence of symbols, their mean reaction time increases linearly with the length of the sequence. The linearity and slope of the function imply the existence of an internal serial comparison process whose average rate is between 20 and 30 items per second. In this test the subjects are presented with a set of 1, 2 or 4 consonants, which they are asked to memorize. Hereafter a series of 48 consonants is presented on a computer screen of which 24 are targets and 24 are non-targets. The subjects' task is to indicate as fast as possible whether or not the presented letter was one from the memory set by pressing one of two buttons. The task consists of 6 blocks of

CHAPTER 2

48 stimuli with different memory sets. The order of the blocks is 1, 2, 4, 4, 2 and 1 letters, respectively. The median reaction time for correct responses is recorded and used to calculate individual linear regression lines between reaction time and memory set size. The slope of this line is a measure of speed of scanning short term memory, whereas the intercept is a measure of psychomotor speed. Both slope (ms/letter) and intercept (ms) are outcome measures.

Spatial paired associate learning - Spatial memory and learning is assessed by the spatial paired learning task. In this task the subject is presented with two highly discriminative pictures flanking a central crosshair on a computer screen for 1000 ms. Hereafter, one of the two original stimuli (target) or a third (new picture) is presented in the centre of the screen and subjects were asked to indicate the original location (left or right) of the stimulus by pressing a corresponding button as fast as possible. Targets appear either left or right with a 50% probability. In total there are 32 different targets of which 16 targets are presented only once and 16 targets are presented 8 times at the same location with random intervals over the test. Reaction time following repeated presentation of a target is hypothesized to diminish during the test as a result of implicit learning of the location associated with each target picture. Therefore, the median reaction time following the repeated items should be lower than that following the non-repeated items. The dependent variables are the median reaction times (ms) for repeated and non-repeated targets.

Syntactic reasoning task - The syntactic reasoning task (Baddeley, 1968) assesses speed and accuracy of logical reasoning processes in working memory (Repovs and Baddeley, 2006). The task consists of 32 short sentences each describing the order of the letters 'A' and 'B' and belonged to one of four categories: active positive, active negative, passive positive and passive negative (e.g. A follows B, A does not follow B, A is followed by B, A is not followed by B, respectively). The sentence is immediately followed by a letter-pair ('A-B' or 'B-A') in the same or opposite order as in the sentence. The required response is to indicate as quickly as possible whether or not the letters are in the same order as in the sentence. Dependent variables are the number of correct responses and the mean reaction time (ms). The mean reaction time was chosen, because the categories differed to a large extent in terms of difficulty and the median is very sensitive to fluctuations in performance on the different categories.

Psychomotor performance and attention

Simple and choice reaction time tasks - The simple and choice reaction time tasks assess the speed of perceptual-motor processing without the cognitive components of the other tests. The simple reaction time test consists of a white square that appears on a computer screen and turns red after a

CHAPTER 2

variable interval. The subject has to press a single button as fast as possible. The choice reaction time task is similar to the simple reaction time task, with the exception that two squares are presented and the subject should press one of two buttons corresponding to the left or right square turning red. Both tasks consist of 48 trials and the dependent measure is the median reaction time (ms).

Critical tracking task - The critical tracking task measures the ability to control an unstable triangle, which is displayed on a horizontal axis on a computer screen, using a joystick (Jex et al., 1966). An error signal causes the triangle to become increasingly unstable and therefore it tends to diverge from the centre of the axis. The subject has to make compensatory movements to null the error in order to keep the triangle in the middle. As the correction frequency of the cursor deviations increases as a stochastic function of time, the subject is required to make compensatory movements with an increasingly higher frequency to the limit of her ability, whereupon control is lost. This frequency decreases under the influence of sedating drugs. The dependent measure is the average frequency at which control is lost of five trials after removing the lowest and highest score. This is called the 'critical frequency' or ' λ_c ' (rad/s).

Divided attention task - The divided attention task (Moskowitz, 1973) assesses the ability to perform two tasks simultaneously and evaluates cognitive processing resources. The primary task is similar to the critical tracking task described above, with the exception that the level of difficulty is held constant at 50% of that, which is just controllable by the subject. Tracking error is measured by the absolute distance (in mm) between the cursors position and the centre. The secondary task involves the monitoring of 24 digits (0-9) that are arranged around the display's periphery. The digits change asynchronously every 5 seconds. The requirement is to respond as rapidly as possible by lifting her foot from a pedal anytime the digit "2" appears. Because relative long reaction times are recorded, outliers are expected to be present at both ends of the distribution. Therefore, average reaction time to targets is recorded as the response measure in this task. Performance scores in the subtasks were combined to overall performance scores before analysis, because performance in the two subtasks is related within subjects and tests. First, average reaction times and tracking error of each test were transformed to z-scores using data from all subjects, test days and test sessions. Second, the standardized scores of the subtasks were summed to yield an overall performance score for each subject, test day and test session. Overall scores were used for further analysis.

Subjective alertness

Subjective alertness was assessed using a mood rating scale consisting of 16 visual analogue scales (i.e. 100 mm lines) each representing a continuum

CHAPTER 2

between two extremes of a certain mood (e.g. alert and drowsy; (Bond and Lader, 1974)). Subjects are required to indicate how they feel by placing a vertical line on the scale corresponding to their mood at that moment. Together these scales provide three factor-analytically defined summary scores- "alertness", "contentedness" and "calmness", of which the factor 'alertness' was of primary interest.

Statistical analysis

After unblinding treatments turned out to be not completely balanced over periods, due to errors in the ordering of replacement medication. Since baseline scores of some tasks showed significant Period effects in spite of prior training, assessments at t2 and t4 were analysed as changes from baseline at the same day. This is a valid method of analysing the data (Van Breukelen, 2006). Changes from baseline were screened for normality of the distributions. No significant deviations were found.

Dependent variables expressed as differences from baseline were analysed in repeated measures multivariate analysis of variance, according to a 2 (Time) x 4 (Treatment) factorial model to test the main effect of Treatment and the interaction of Treatment and Time. The data from the critical tracking task were analysed according to a 5 (Time) x 4 (Treatment) factorial model, but otherwise in a similar fashion. Regardless of the outcome of the overall F-tests, three planned univariate comparisons were carried out between the treatments and placebo for t2 and t4 separately. This is a legitimate procedure since the comparisons are suggested by the theoretical basis of the experiment (Winer, 1971). All data were analysed using SPSS for Windows (version 12.0.1).

RESULTS

Memory

A summary of mean ($\pm$ SEM) performance scores of tasks assessing memory performance is presented in table 1.

No significant main effects of Treatment or interactions between Treatment and Time were found in any memory test except for the simplified spatial paired associate learning task. Analysis showed that there was a main effect of Treatment on speed of responses to repeated stimuli. ($F_{3,17} = 5.5$, $p < 0.008$). Longer reaction times as compared to placebo were observed after administration of dexchlorpheniramine 2 mg at t2 ($F_{1,19} = 14.5$, $p < 0.001$), and after administration of scopolamine 1 mg at t2 ($F_{1,19} = 12.7$, $p < 0.002$) and t4 ($F_{1,19} = 13.6$, $p < 0.002$).

CHAPTER 2

Psychomotor performance and attention

A summary of mean ($\pm$ SEM) performance scores of tasks assessing psychomotor functioning and attention is presented in table 2.

Analysis of variance of simple reaction time showed a significant main effect of Treatment and a significant interaction between Treatment and Time ($F_{3,17}= 5.2$, $p < 0.010$, $F_{3,17}= 4.9$, $p < 0.012$, respectively). Drug-placebo comparisons showed that dexchlorpheniramine 2 mg, dexchlorpheniramine 4 mg and scopolamine 1 mg all significantly increased reaction times at t2 ($F_{1,19}= 5.3$, $p < 0.032$; $F_{1,19}= 8.4$, $p < 0.009$; $F_{1,19}= 15.5$, $p < 0.001$, respectively). These differences were no longer significant at t4.

Similar results were obtained from the choice reaction time task. The main effect of Treatment on response speed was nearly significant ($F_{3,17}= 2.7$, $p < 0.078$) and drug-placebo comparisons at t2 showed significantly longer reaction times after administration of dexchlorpheniramine 2 mg ($F_{1,19}= 6.3$, $p < 0.021$), dexchlorpheniramine 4 mg ($F_{1,19}= .9$, $p < 0.025$) and scopolamine 1 mg ($F_{1,19}= 10.4$, $p < 0.004$).

A main effect of Treatment was also found on critical tracking performance at ($F_{3,17}= 3.3$, $p < 0.044$). Tracking was impaired at both 1.5 hours as 2.5 hours following the administration of dexchlorpheniramine 2 mg ($F_{1,19}= 7.6$, $p < 0.012$, $F_{1,19}= 5.5$, $p < 0.030$), dexchlorpheniramine 4 mg ($F_{1,19}= 14.7$, $p < 0.001$, $F_{1,19}= 7.8$, $p < 0.012$) and scopolamine 1 mg ($F_{1,19}= 13.7$, $p < 0.001$, $F_{1,19}= 12.3$, $p < 0.002$). The effects were no longer significant at 3.5 and 4.5 hours after administration (figure 1).

Due to a technical error, reaction times in the visual search task of the divided attention test were not recorded for one subject during baseline measurements before administration of dexchlorpheniramine 4 mg. Her data were excluded from all analyses of performance in this task.

A significant main effect of Treatment was found on the overall performance measure ($F_{3,16}= 7.7$, $p < 0.002$). Dexchlorpheniramine 4 mg produced a significant impairment at t2 ($F_{1,18}= 9.9$, $p < 0.006$) and at t4 ($F_{1,18}= 7.4$, $p < 0.014$). Similarly, scopolamine 1 mg impaired performance at both times of assessment ($F_{1,19}= 19.9$, $p < 0.001$ and $F_{1,19}= 15.6$, $p < 0.001$).

Subjective alertness

There were significant main effects of Treatment and a significant interaction between Treatment and Time on subjective ratings of alertness ($F_{3,17}= 8.6$, $p < 0.001$ and $F_{3,17}= 3.3$, $p < 0.045$, respectively). Table 2 shows that subjects judged themselves to be less alert at t2 after intake of dexchlorpheniramine 2 mg ($F_{1,19}= 5.6$, $p < 0.029$), and at t2 and t4 after intake of dexchlorpheniramine 4 mg ($F_{1,19}= 9.5$, $p < 0.006$, $F_{1,19}= 5.0$, $p < 0.037$) and scopolamine 1 mg ($F_{1,19}= 33.0$, $p < 0.001$, $F_{1,19}= 8.8$, $p < 0.008$).

CHAPTER 2

Figure 1. Mean changes ($\pm$ SEM) from baseline of the critical frequency in the critical tracking task at 0.5, 1.5, 2.5, 3.5 and 4.5 hours after administration of placebo (PLA), dexchlorpheniramine 2 mg (D2), dexchlorpheniramine 4 mg (D4) and scopolamine 1 mg (S1). Significant ($p < 0.05$) a-priori drug-placebo contrasts at each time are indicated as *.

Table 1. Summary of data obtained from tests assessing memory performance after administration of placebo (PLA) dexchlorpheniramine 2 mg (D2), dexchlorpheniramine 4 mg (D4), and scopolamine 1 mg (S1). Significant ($p < 0.05$) a-priori drug-placebo contrasts are indicated as *.

	Overall analyses of changes from baseline		Mean ($\pm$ SEM) scores				
	Main Effect of Treatment p =	Interaction of Treatment X Time p =	Test Session	Treatment PLA	D2	D4	S1
<i>Syntactic reasoning task</i>							
number correct (#)	0.620	0.253	Baseline	28.4 $\pm$ 1.0	28.1 $\pm$ 1.0	28.2 $\pm$ 1.0	29.2 $\pm$ 1.1
			t2	28.4 $\pm$ 1.0	27.8 $\pm$ 1.0	28.4 $\pm$ 1.1	28.3 $\pm$ 1.0
			t4	29.2 $\pm$ 1.0	29.0 $\pm$ 1.0	28.9 $\pm$ 0.0	29.3 $\pm$ 1.0
Mean reaction time (ms)	0.487	0.500	Baseline	1651 $\pm$ 169	1591 $\pm$ 163	1652 $\pm$ 118	1614 $\pm$ 121
			t2	1594 $\pm$ 138	1546 $\pm$ 155	1654 $\pm$ 124	1544 $\pm$ 105
			t4	1582 $\pm$ 141	1464 $\pm$ 139	1629 $\pm$ 115	1556 $\pm$ 120
<i>Spatial paired associate learning task</i>							
Median reaction time (ms)	0.008	0.176	Baseline	509 $\pm$ 15	495 $\pm$ 15	503 $\pm$ 18	481 $\pm$ 13
repeated items			t2	501 $\pm$ 16	520 $\pm$ 20*	512 $\pm$ 17	504 $\pm$ 16*
			t4	479 $\pm$ 12	485 $\pm$ 16	488 $\pm$ 17	497 $\pm$ 17*
Median reaction time (ms)	0.097	0.432	Baseline	521 $\pm$ 22	501 $\pm$ 16	494 $\pm$ 16	487 $\pm$ 15
non-repeated items			t2	504 $\pm$ 19	502 $\pm$ 20	514 $\pm$ 22	503 $\pm$ 14
			t4	472 $\pm$ 15	489 $\pm$ 19	481 $\pm$ 16	495 $\pm$ 18
<i>Word learning task</i>							
Immediate recall (# words correct)			t4	45.3 $\pm$ 1.8	42.9 $\pm$ 1.9	46.9 $\pm$ 1.7	44.7 $\pm$ 1.5
Delayed recall (# words correct)			t4	15.1 $\pm$ 1.0	14.6 $\pm$ 0.8	15.6 $\pm$ 0.9	14.6 $\pm$ 0.8
Recognition (ms)			t4	647 $\pm$ 20	644 $\pm$ 17	652 $\pm$ 17	643 $\pm$ 13

Pattern recognition task

Immediate recognition

Patterns correct (#)	0.075	0.767	Baseline	26.5 ± 0.5	26.9 ± 0.5	26.7 ± 0.5	27.4 ± 0.5
			t2	26.6 ± 0.7	26.5 ± 0.7	25.5 ± 0.8	25.2 ± 1.0
			t4	27.1 ± 0.5	27.3 ± 0.5	26.8 ± 0.6	26.7 ± 0.5
Median reaction time (ms)	0.056	0.663	Baseline	972 ± 59	904 ± 51	928 ± 70	945 ± 46
			t2	916 ± 42	905 ± 46	936 ± 57	871 ± 43
			t4	880 ± 50	858 ± 60	886 ± 68	891 ± 48

Delayed recognition

Patterns correct (#)	0.760	0.308	Baseline	25.8 ± 0.5	25.7 ± 0.9	25.5 ± 0.8	25.9 ± 0.6
			t2	24.8 ± 0.7	24.5 ± 0.8	23.8 ± 0.8	23.3 ± 0.9
			t4	24.5 ± 0.7	24.4 ± 0.9	24.3 ± 0.7	24.2 ± 0.9
Median reaction time (ms)	0.135	0.370	Baseline	1033 ± 74	995 ± 65	970 ± 74	961 ± 47
			t2	1004 ± 63	1039 ± 78	1022 ± 70	1022 ± 82
			t4	986 ± 59	965 ± 67	993 ± 63	978 ± 64

Sternberg memory scanning task

Slope (ms/letter)	0.880	0.337	Baseline	44 ± 4	49 ± 3	52 ± 5	47 ± 4
			t2	47 ± 3	50 ± 4	56 ± 5	53 ± 5
			t4	44 ± 3	50 ± 4	49 ± 5	50 ± 4
Intercept (ms)	0.379	0.340	Baseline	345 ± 11	334 ± 9	331 ± 10	332 ± 11
			t2	338 ± 9	338 ± 1	336 ± 12	338 ± 8
			t4	333 ± 10	317 ± 9	328 ± 10	329 ± 9

Table 2. Summary of data obtained from tests assessing psychomotor performance and subjective alertness after administration of placebo (PLA) dexchlorpheniramine 2 mg (D2), dexchlorpheniramine 4 mg (D4), and scopolamine 1 mg (S1). Significant ($p < 0.05$) a-priori drug-placebo contrasts are indicated as *.

	Overall analyses of changes from baseline		Mean ($\pm$ SEM) scores				
	Main Effect of Treatment	Interaction of Treatment X Time	Test Session	Treatment			
	p =	p =		PLA	D2	D4	S1
<i>Simple reaction time task</i>							
Median reaction time (ms)	0.010	0.012	Baseline	246 $\pm$ 8	249 $\pm$ 7	258 $\pm$ 12	246 $\pm$ 7
			t2	258 $\pm$ 10	283 $\pm$ 11*	294 $\pm$ 11*	288 $\pm$ 12*
			t4	257 $\pm$ 11	261 $\pm$ 10	257 $\pm$ 10	271 $\pm$ 11
<i>Choice reaction time task</i>							
Median reaction time (ms)	0.078	0.174	Baseline	308 $\pm$ 9	312 $\pm$ 7	314 $\pm$ 10	309 $\pm$ 8
			t2	322 $\pm$ 10	346 $\pm$ 11*	355 $\pm$ 12*	356 $\pm$ 14*
			t4	312 $\pm$ 8	317 $\pm$ 10	325 $\pm$ 10	333 $\pm$ 12
<i>Divided attention task</i>							
Overall performance (z-score)	0.002	0.400	Baseline	-0.31 $\pm$ 0.30	-0.33 $\pm$ 0.31	-0.54 $\pm$ 0.30	-0.63 $\pm$ 0.25
			t2	-0.31 $\pm$ 0.31	0.25 $\pm$ 0.28	0.60 $\pm$ 0.32*	0.97 $\pm$ 0.40*
			t4	-0.43 $\pm$ 0.26	-0.02 $\pm$ 0.33	0.32 $\pm$ 0.38*	0.30 $\pm$ 0.32*
<i>Subjective alertness scale</i>							
	0.001	0.045	Baseline	25.6 $\pm$ 3.1	27.4 $\pm$ 3.8	26.8 $\pm$ 4.0	28.1 $\pm$ 3.5
			t2	32.0 $\pm$ 4.3	41.2 $\pm$ 3.4*	44.1 $\pm$ 4.8*	53.3 $\pm$ 4.0*
			t4	31.6 $\pm$ 3.5	37.9 $\pm$ 4.9	41.0 $\pm$ 4.5*	41.3 $\pm$ 4.4*

CHAPTER 2

DISCUSSION

This study assessed the effects of the H₁-antagonist dexchlorpheniramine on memory and psychomotor performance in humans. Based on results from animal studies it was hypothesized that the drug would impair performance in humans in one or more memory tests, in addition to its well known effect on psychomotor performance. Results failed to confirm this hypothesis however - no significant effects of dexchlorpheniramine were found on memory. At the same time dexchlorpheniramine did impair performance in psychomotor tasks in both doses, indicating that the drug reached sufficient concentrations in the central nervous system to have behavioural effects. Significant impairing effects were found on simple and choice reaction time, critical tracking and divided attention. In addition subjects reported significant decreases in subjective feelings of alertness after dexchlorpheniramine. These results are in line with findings from several studies showing that centrally active antihistamines produce sedation and impair psychomotor performance (Hindmarch and Shamsi, 1999; White and Rumbold, 1988; Witek et al., 1995).

There was only one parameter in a memory related task that was impaired by dexchlorpheniramine - reaction time to repeated targets in the spatial paired associate learning task. This response was significantly slowed at t2 by dexchlorpheniramine 2 mg and scopolamine in comparison to placebo. Since the effects were only found for repeated and not for novel items it could be argued that it reflects an effect on implicit learning. Implicit learning in this test was hypothesized to decrease reaction times to repeated items relative to non-repeated items. However, comparison of reaction times to repeated and non-repeated items within the baseline and placebo conditions did not reveal any difference. This does not support the hypothesis that implicit learning took place. Consequently, it is difficult to conclude that learning was impaired by the drugs. Alternatively, the effects may be related to speed of psychomotor processing, similar to that found in the simple and choice reaction time tasks.

Surprisingly, the active control scopolamine also failed to impair memory performance in the present study, which is in contrast with most other studies using similar or slightly higher oral doses. For example, Parrott et al. (1986) found that 1.2 mg scopolamine (p.o.) impaired performance on memory storage. Similarly, Rammsayer et al. (2000) found that 1 mg scopolamine (p.o.) impaired recall performance on a word list learning task. Performance on the Word Learning Task and Memory Scanning Task has also been shown to be affected by scopolamine (Ebert et al., 1998; Riedel et al., 1995). Both studies showed that 0.6 mg (s.c.) and 0.5 mg scopolamine (s.c.), respectively decreased the number of recalled words and increased

CHAPTER 2

memory search time. Considering this it might be argued that the memory tests or procedures in the present study were not sufficiently sensitive to detect impairing effects of drugs on memory. We do not believe this was the case, however. Most importantly, all the memory tests have shown to be sensitive to the effects of drugs in previous studies (Riedel et al., 1995; Riedel et al., 1999; Rubinsztein et al., 2001; Schmitt et al., 2000; Vermeeren et al., 1995). In addition, there are pharmacokinetic factors related to the oral dose of scopolamine that could explain its lack of effects on memory in the present study and are mentioned below.

First of all, the second test battery after drug administration might have been too late to detect behavioural impairment of scopolamine. This could have resulted in a failure of this drug to show significant effects on the Word Learning Task, which was only administered at t4. Scopolamine has a relatively short half-life ($t_{1/2} = 4.3$ hours) and it rapidly reaches peak plasma concentrations after oral administration ($t_{\max} = 0.8$ hours), indicating that it has a rapid onset and fast decline of action (Golding et al., 1991). Results from the critical tracking task support that the effect of scopolamine peaked between 1.5 and 2.5 hours and had rapidly returned to baseline at 3.5 hours after drug intake. It can therefore be assumed that only very few effects could have been found 4 hours after its intake. Furthermore, it has been reported that compared to subcutaneous, intravenous and intramuscular administration oral doses of scopolamine result in relatively low and variable blood plasma concentrations, which are associated with small and relatively inconsistent effects found on behaviour (Kennedy et al., 1990; Renner et al., 2005; Wesnes, 1988). In line with this, the data show that average performance generally decreases on memory related tasks after administration of scopolamine as compared to placebo. The effects were probably too weak and variable to be statistically significant. In this respect, the selection of an oral dose of scopolamine instead of using a more intrusive method seems to have been an unfortunate choice.

Post-hoc inspection of average effect sizes (Rosnow & Rosenthal, 2000) (baseline versus t2) showed that scopolamine's effects on memory were almost twice as strong as those of dexchlorpheniramine 4 mg (ES 0.41 vs. 0.22, respectively). Effects of both drugs on psychomotor performance were more pronounced than those on memory, but the difference between the drugs was much smaller (ES 0.58 and 0.47, respectively). Although this may indicate that the memory tests are not as sensitive as the psychomotor tests, it seems consistent with the notion that scopolamine and dexchlorpheniramine have differential effects on memory and psychomotor performance. So assuming that the tests used were sufficiently sensitive to detect potential effects of dexchlorpheniramine on memory, we conclude that the blockade of central H_1 receptors does not produce clinically relevant effects on memory in humans.

CHAPTER 2

This conclusion was recently supported by results from another study addressing the same issue. Turner et al. (2006) recently published a study designed with comparable objectives as the present study. They assessed the effects of multiple doses of diphenhydramine and lorazepam on memory and psychomotor performance, and found impairing effects of both drugs in tasks without a memory component, whereas lorazepam, but not diphenhydramine, impaired performance in tasks with a memory component. Similarly, Curran et al (1998) conducted a study to dissociate the sedative and amnestic effects of lorazepam (2 mg p.o.), and therefore compared the effects with those of scopolamine (0.6 mg s.c.) and diphenhydramine (25, 50 mg p.o.). All drugs reduced levels of arousal, while only scopolamine and lorazepam caused impairments of memory. The doses of diphenhydramine were relatively low, however, as compared to those of lorazepam and scopolamine. Taken together, these studies indicate that antihistamines impair psychomotor performance and reduce levels of arousal but may not be able to disrupt memory functioning.

In summary, oral doses of 2 mg and 4 mg dexchlorpheniramine and of 1 mg scopolamine produced significant cognitive impairments compared to placebo shown by the effects on performance on psychomotor and attention related tasks. Clear effects on most memory related tasks were absent in this study. Supported by results from other studies it can be concluded that blockade of histaminergic function using an H₁ antagonist does not impair memory functions in man, as opposed to the findings in animals. This suggests that histamine does not play an obvious role in memory and learning in humans.

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CHAPTER 2

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CHAPTER 3

MEMORY IN HUMANS IS UNAFFECTED BY
CENTRAL H₁-ANTAGONISM WHILE
OBJECTIVELY AND SUBJECTIVELY
MEASURED SEDATION IS INCREASED

Van Ruitenbeek, P., Vermeeren, A., Riedel, W. J. (*submitted*). Memory in humans is unaffected by central H₁ antagonism while objectively and subjectively measured sedation is increased

CHAPTER 3

CHAPTER 3

INTRODUCTION

Animal studies indicate an important role for histamine in memory functioning. Decreasing histaminergic activity leads in most studies to impaired performance on tasks assessing memory. For example, H₁ knock-out animals were impaired on maze learning and showed a decrease in long-term potentiation (Dai, et al., 2007). Knock-out animals for the synthesizing enzyme histidine decarboxylase showed impaired performance on maze tasks, although no effects were found on object recognition (Acevedo, Ohtsu, Benice, Rizk-Jackson, & Raber, 2006). On the other hand, increasing histaminergic activity leads to improved performance on tasks assessing memory functioning. For example, administration of histamine improves retrieval of information (Zarrindast, Parsaei, & Ahmadi, 2008). Therefore, there especially is a large interest in H₃-antagonists which increase histamine levels and have shown to be able to reverse impaired memory performance in animals (Bacciottini, Passani, Mannaioni, & Blandina, 2001).

The role of histamine in human memory, however, is not clear. Increasing levels of histamine in man using H₃-antagonists is currently hardly possible as most compounds are unsuitable to be used in man. However, histaminergic activity can be lowered using H₁-antagonists. Studies to determine the behavioural effects of H₁-antagonists on cognitive performance have been conducted many times but mostly in the context of driving safety and not memory. These studies have therefore not assessed memory performance after the administration of an antihistamine in much detail. Results from studies that did include memory tests are somewhat conflicting. Whereas the majority found no significant effects of sedative H₁-antagonists on memory performance (De Brabander, 1990; Patat, et al., 1994; Theunissen, Vermeeren, van Oers, van Maris, & Ramaekers, 2004; Verster, et al., 2003; Vuurman, Rikken, Muntjewerff, de Halleux, & Ramaekers, 2004), a few studies (Hindmarch & Shamsi, 2001; Vuurman, Uiterwijk, Rosenzweig, & O'Hanlon, 1994; Volkerts, Van Willigenburg, Van Laar, & Maes, 1992) have reported impaired performance on measures of memory function. Yet, it is also possible that these effects are due to the sedative effects of antihistamines.

Three studies attempted to dissociate the effects of antihistamines on memory and sedation in humans, but none of them found effects on memory (Curran, Pooviboonsuk, Dalton, & Lader, 1998; Turner, Handford, & Nicholson, 2006; Van Ruitenbeek, Vermeeren, & Riedel, 2008). So, contrary to findings in animal studies, results from studies in humans do not support a specific role of histamine in human memory functioning. It is possible, however, that the failure to find any effects on memory in these studies was related to methodological issues.

CHAPTER 3

First, Curran et al. (1998) studied the effects of scopolamine (0.6 mg sc), lorazepam (2 mg oral) and diphenhydramine (25 and 50 mg oral) on memory and measures of sedation. As expected, they showed that these treatments all had some effects on measures of sedation and psychomotor performance. However, diphenhydramine only affected two of the six psychomotor performance measures that were used, while lorazepam and scopolamine all had an effect on performance on at least five tasks. Compared with the relative high dosages of scopolamine and lorazepam the effects of diphenhydramine may not have been pronounced enough to be measured. This is supported by studies that reported a larger increase in weaving in car driving after lorazepam 2 mg administration (increase of approximately 18 cm) (O'Hanlon, Vermeeren, Uiterwijk, van Veggel, & Swijgman, 1995) as compared with diphenhydramine 50 mg (increase of approximately 4 cm) (Vuurman, et al., 2004).

Second, Turner et al. (2006) have measured the effects of lorazepam (0.5 and 1.5 mg oral) and diphenhydramine (50, 75 and 100 mg oral) on tasks with and without a memory component and concluded that diphenhydramine affected only the performance on tasks without a memory component. However, to measure the effects on memory performance they used a word learning task, but presented the words before drug intake so the effects on encoding could not be measured.

Finally, Van Ruitenbeek et al. (2008) have studied the effects of dexchlorpheniramine (2 and 4 mg) on several measures of cognitive performance and compared these with the effects of scopolamine. Dexchlorpheniramine did not have any effect on memory performance. However, they also did not find an effect of scopolamine as the active control on their most sensitive test of memory performance. Their main task assessing memory was administered 4 hours after drug intake, which is most likely too late to pick up any effects. It can therefore be questioned whether the assessment was able to pick up the effects on memory.

Taken together the failure to find effects of histamine blockade on memory in these studies may have been due to the relatively low doses of antihistamines used and the time between drug intake and learning and memory testing. The present study was therefore designed to assess the effects of behaviourally effective dose of the selective H₁-antagonist dexchlorpheniramine (4 mg) on several measures of memory during time of peak impairment, i.e. between 1.5 and 2.5 hours after oral administration as established in a previous study (Van Ruitenbeek, et al., 2008). The benzodiazepine lorazepam 1 mg was included as an active control to demonstrate sensitivity of the tests and procedures. This drug-dose has been shown to impair memory performance in several studies (Bishop, 1996; Curran, et al., 1998; Hanks, O'Neill, Simpson, & Wesnes, 1995; Mintzer & Griffiths, 2003; Turner, et al., 2006).

CHAPTER 3

Drug effects on memory were assessed measuring performance and brain activity (Event Related Potentials i.e. P300) during a 30-Words Learning Task (WLT-30) and an n-back task. These memory tests were selected because previous studies show them to be sensitive to drug effects on memory. Performance on the WLT has been found highly sensitive to the effects of known memory reducing drugs like scopolamine (Riedel, 1995) and lorazepam (File & Lister, 1982). Speed and accuracy of performance on the n-back task have previously shown sensitive to the effects of the antihistamine diphenhydramine (50 mg oral) (Gevins, Smith, & McEvoy, 2002).

Brain activity was measured using EEG. The P300 was measured during encoding in the WLT and during performance on the n-back task. It has been found that the amplitude of the P300 component measured during encoding is larger for words that are later recalled than for words that are not recalled (Friedman & Johnson, 2000; Otten & Donchin, 2000) and has been shown to decrease with an increased memory load in the n-back task (Watter, Geffen, & Geffen, 2001). Drug effects on memory are therefore expected to decrease the P3 amplitude during encoding in the WLT and interact with memory load in the n-back task.

Finally, the EEG frequency spectrum was measured during the encoding phase of the WLT. The spectrum can be divided into delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and beta (12-30 Hz) frequency bands. Sedation is characterized by a decrease in beta power and an increase in theta and alpha power (Galliaud, et al., 2008) and, in case of more severe sedation also delta power (Borbely, 1982; Griffiths, Preece, & Green, 1991). The antihistamine induces mild sedation and it is therefore hypothesized that it will decrease the power of the beta frequency band and increase theta (Duschek, Meinhardt, & Schandry, 2006) and alpha (Sannita, Crimi, Riela, Rosadini, & Brusasco, 1996) frequency band power. Benzodiazepines and antihistamines have been shown to differentially affect the alpha and beta frequency bands. Benzodiazepines are able to decrease the alpha frequency band (Ebert, Oertel, & Kirch, 2000) and increase the beta frequency band (Greenblatt, et al., 2000; Saletu, Grunberger, & Sieghart, 1986). Therefore, it is hypothesized that lorazepam will increase the beta and decrease the alpha frequency bands. As a subjective measure of sedation the Mood Scale developed by Bond and Lader (1974) will be used and it is expected that alertness will decrease after the administration of both treatments.

METHODS

Subjects

Eighteen healthy right handed subjects (nine male) between 18 and 45 years (mean $\pm$ SE: 24.2 $\pm$ 1.7 years) were recruited by means of advertisements in local newspapers and were paid for their participation. Subject's health was

CHAPTER 3

screened using a medical history questionnaire and a physical examination, including a 12-lead electrocardiogram, blood chemistry and haematology, and urinary tests for pregnancy and drugs of abuse (amphetamine, benzodiazepine, cocaine, opiates, cannabis and methamphetamine). Exclusion criteria were a significant history or presence of any mental or physical disorder; gastrointestinal, hepatic, renal, cardiovascular or neurological. Also, drug abuse, a body-mass index outside the limits of 18 and 28 kg/m², blood pressure outside the limits of 100 and 150 Hg systolic and 60 and 90 Hg diastolic and drinking more than 20 standard alcoholic consumptions per week or 5 beverages containing caffeine per day were regarded as exclusion criteria. For women, pregnancy and lactation were also regarded as exclusion criteria. No drugs or medication, except oral contraceptives, aspirin and acetaminophen, were allowed to be taken from a week before the first test-day until the end of the study. Smoking and the use of caffeine were prohibited on test-days and the use of alcohol from 24 hours before and during each test-day. Subjects were allowed to have breakfast at home before 7:30am, i.e. at least 3 hours before drug intake.

All subjects received written information about the study procedures and were given the opportunity to ask questions. They signed an informed consent form prior to enrolment. The study was approved by the Ethics committee of Maastricht University and University Hospital Maastricht and carried out in accordance with the World Medical Association Declaration of Helsinki and its amendments (Edinburgh, 2000).

Study design and treatments

The study was conducted according to a double blind, placebo-controlled, 3-way crossover design. Treatments were single oral doses of dexchlorpheniramine 4 mg and lorazepam 1 mg (all immediate release formulations) and placebo and were spaced apart by a washout period of at least 4 days. The order of treatment was counterbalanced across subjects.

Procedure

Subjects were individually trained to perform all tasks on two separate occasions within two weeks prior to their first treatment day. On treatment days subjects arrived at the University at 9:00am. Between 9:00am and 9:30am the inclusion and exclusion criteria were checked. At 10:30am, the study medication was ingested and the tests were performed between 12:00am and 1:00pm. The battery consisted of the WLT-30, N-back task and subjective evaluations of drowsiness/alertness.

CHAPTER 3

Behavioural assessments

30-Words Learning Task

The WLT-30 is a verbal memory test for the assessment of immediate and delayed free recall, and recognition performance (Klaassen, Riedel, Deutz, & Van Praag, 2002; Rey, 1964; Riedel, Klaassen, Deutz, van Someren, & van Praag, 1999). Thirty monosyllabic nouns and adjectives were presented for 1000 ms at a rate of 1 per 2 seconds and subjects were instructed to memorize them. When the presentation ends, subjects were required to verbally recall as many words as possible (immediate recall). This procedure was repeated three times, with the same words presented in the same sequence.

After a 45 minutes delay subjects were requested again to recall as many words as possible (delayed recall). Finally, subjects were presented a series of 60 words on a computer screen that included 30 words from the original list and 30 comparable but new words. Subjects were asked to indicate as quickly as possible whether the presented words are from the original list or not by pressing one of two buttons (delayed recognition).

Dependent variables were the number of words correctly recalled on the three immediate recall trials, the number of correctly recalled words after the delay, the number of correctly recognized words and their average reaction time and the relative recall. The relative recall indicates how many of the initially remembered words are recalled after the delay. The relative recall is defined as the number of words recalled in the third trial of the immediate recall minus the number of words recalled in the delayed recall, which is divided by the number of words recalled in the third trial ($(IR3 - DR) / IR3$). In addition, during the word learning phase EEG was recorded as a measure of sedation and the P300 amplitude was measured as an indication of word encoding.

N-back Task

The N-back Task (Veltman, Rombouts, & Dolan, 2003) was used to assess working memory performance. In this task subjects were required to monitor a series of letters presented in the centre of a computer screen, and to respond whenever a letter was presented that is the same as the one presented one, two or three trials previously (i.e. 1-back, 2-back and 3-back, respectively). In the fourth (control) condition subjects had to press a button as fast as possible whenever they detected a pre-specified letter (e.g. X; 0-back). Letters were presented for 1000 ms or until the subjects responded and at a rate of 1 per 2 seconds.

In this study subjects completed four blocks consisting of 0-, 1-, 2-, or 3-back trials, each block was repeated three times in pseudorandom order. Within each block 21 stimuli were presented, including 3 or 4 targets, totalling 11 targets per n-back level. Number and speed of correct responses

CHAPTER 3

were averaged and were the dependent variables. In addition, the P300 amplitude was measured and is an indicator of processing capacity related to comparing stimuli (Watter, et al., 2001)

Subjective alertness

Subjective alertness is assessed using a series of 16 visual analogue scales of 100 mm. These provide three factors which are analytically defined summary scores for 'alertness', 'contentedness', and 'calmness' (Bond & Lader, 1974) of which alertness was of main interest.

EEG recordings

During performance on the WLT-30 and N-Back Task EEG activity was recorded by means of an electrocap from an array of 32 electrodes from the standard 10-20 system (Jasper, 1957). All electrodes were filled with electrode-gel and were referenced to the mastoid electrodes both left and right. The FPz electrode was used as ground electrode. Horizontal EOG was recorded using electrodes attached to the outer canthi of the eyes and vertical EOG was recorded from electrodes attached above and below the left or right eye and in line with the pupil when the subject looks straight ahead.

All electrode impedances were kept under below 5 k Ω . Signals were amplified using Neuroscan Synamps amplifiers and collected using neuroscan software. All signals were sampled at a 1000 Hz and filtered online using a 100 Hz low-pass filter and a 0.1 Hz high-pass filter.

Signal analysis

Continuous signals obtained during the performance on the WLT-30 were epoched in 1100 ms sweeps starting 100 ms before stimulus presentation. EEG was corrected for vertical and horizontal eye movements according to a procedure by Semlitsch et al. (1986). The interval between sweep onset and stimulus served as baseline. EEG and EOG epochs were filtered off-line using a 1.0 Hz high-pass filter and a 3.6 Hz low-pass filter for the WLT-30 and a 10.0 Hz low-pass filter for the N-Back Task. Sweeps containing artefacts exceeding +75 or -75 μ V were rejected.

For both the N-Back task and the WLT-30 the length of the interval between the stimulus and the P300 component was determined at the Cz electrode sites. The P300 signals were determined as the time between onset of the stimulus and the latency of the largest maximum in a window between 238 and 338 ms for the 30-WLT and between 290 and 490 for the N-Back task as determined by a visual inspection of the peak latency of the grand average of the P300 for both tasks separately.

The power of the delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and beta (12-30 Hz) frequency bands were measured during the presentation of

CHAPTER 3

the words in the WLT-30 and were calculated by means of a fast Fourier transformation of the means of the midline electrodes (Fz, Cz and Pz). These were taken as dependent variables and indicators of cortical activity and sedation.

Statistical analysis

All variables were screened for normality of the distributions. There were no indications of non-normal distributions.

The immediate recall data were analysed according to a 3x3 two-factorial model with Treatment (dexchlorpheniramine, lorazepam, placebo) and Trial (1, 2 and 3) as factors using Analysis of Variance for repeated measures. All other data derived from the WLT-30 were analysed for effects of Treatment using Analysis of Variance for repeated measures with Treatment as factor. For the N-Back task, the data were analysed using a 3x4 two-factorial model with Treatment and Memory Load (0, 1, 2 and 3 back) as factors. If overall F-tests indicate significant main effects or interactions ($p < 0.05$), the data were further analysed using two drug-placebo contrasts. In case of an effect of Trial or Memory load the data were further analysed using linear contrasts. All data were analysed using SPSS for Windows (version 12.0.1).

RESULTS

Missing data

Analyses of the EEG frequency band power were performed on 17 subjects because data from one subject showed extremely large delta frequency values and was therefore considered an outlier.

Behavioural assessments

30-Words Learning Task

Mean ($\pm$ SE) immediate and delayed recall scores for separate treatments are shown in figure 1. There were significant main effects of Trial and Treatment on the number of words recalled during the immediate recall ($F(2,16)=84.5$, $p < 0.01$ and $F(2,16)=7.7$, $p < 0.01$, respectively). Overall, the number of words recalled increased linearly in every consecutive trial as shown by the significant linear contrast ($F(1,17)=170.1$, $p < 0.01$). However, fewer words were recalled after lorazepam administration as compared with placebo ($F(1,17)=12.9$, $p < 0.01$). The difference between lorazepam and placebo was significant in all three immediate recall trials ($F(1,17)=6.0$, $p < 0.03$, $F(1,17)=8.7$, $p < 0.01$ and $F(1,17)=9.6$, $p < 0.01$, for trials 1, 2 and 3, respectively).

CHAPTER 3

There was no difference in immediate recall scores observed between the dexchlorpheniramine and placebo ($F(1,17)=2.7$, $p=0.12$).

There were also significant differences between treatments on the delayed recall scores ($F(2,16)=6.1$, $p<0.01$), but not in the relative recall ($F(2,16)=1.6$, $p=0.24$). Compared with placebo delayed recall was impaired after lorazepam administration ($F(1,17)=10.8$, $p<0.01$), but not after the administration of dexchlorpheniramine ($F<1$).

In line with the above there were significant differences between treatments in reaction time and accuracy during the recognition task ($F(2,16)=21.4$, $p<0.01$ and $F(2,16)=5.27$, $p<0.02$, respectively). Again the effect was due to the lorazepam induced impairment ($F(1,17)=23.6$, $p<0.01$ and $F(1,17)=10.0$, $p<0.01$, respectively).

Figure 1: Effects of treatments on immediate and delayed word recall. Subjects recalled fewer words on all trials after administration of lorazepam. * Indicates $p<.05$ when compared with placebo.

N-Back task

Accuracy in the N-Back task differed significantly between the number of trials back the subject had to recall the digit (Memory Load) ($F(3,15)=11.5$, $p<0.01$). Linear contrast showed that the number of errors increased when the Memory Load increased from 0 to 3 ($F(3,15)=8.1$, $p<0.01$). However, subjects made more errors in the 0-back condition as compared with the 1-back condition ($F(1,17)=4.4$, $p<0.05$). In addition, subjects responded slower

CHAPTER 3

when the Memory Load increased as indicated by the main effect of Memory Load ($F(3,15)=24.6$, $p<0.01$) and the linear contrasts ($F(1,17)=31.2$, $P<0.01$). However, the 2-back condition was not significantly different from the 3-back condition ($F<1$).

Treatment effects on performance in the N-Back task differed significantly as measured by reaction time ($F(2,16)=7.1$, $p<0.01$) and approached significance as measured by the accuracy ($F(2,16)=3.1$, $p<0.07$). Compared with placebo lorazepam increased reaction time ($F(1,17)=13.5$, $p<0.01$) and decreased the accuracy significantly ($F(1,17)=6.5$, $p<0.02$), while dexchlorpheniramine did not ($F_s(1,17)<1$). There was no significant interaction between Treatment and Memory Load ($F_s(2,16)<1$) (table 1).

Visual Analogue Scales

Subjective ratings of alertness were significantly different between treatments ($F(2,16)=7.8$, $p<0.01$). Dexchlorpheniramine decreased alertness scores from 65.5 (± 5.0) for placebo to 49.3 (± 4.3) ($F(1,17)=7.9$, $p<0.01$) and lorazepam to 40.6 (± 4.4) ($F(1,17)=16.6$, $p<0.01$).

EEG data

30-Words Learning Task

P300 amplitude during word learning differed significantly between treatments. ($F(16,2) = 6.2$, $p < 0.01$). Lorazepam decreased the amplitude ($F(1,17) = 13.0$, $p < 0.01$), but dexchlorpheniramine did not ($F < 1$) (figure 2).

Figure 2: Effects of treatments on the P300 amplitude. Lorazepam, but not dexchlorpheniramine, decreased the amplitude significantly, indicating reduced encoding.

CHAPTER 3

Table 1: Effects of treatments on working memory as measured using the N-Back task. Lorazepam increased reaction time and decreased accuracy as indicated by the main effects of Treatment and the respective drug-placebo contrasts. Treatment did not significantly affect P300 peak amplitude or interact with N-Back.

N-back task	Main effect of Treatment p =	PLC	D4 p = (D4 vs. PLC)	L1 p = (L1 vs. PLC)
Reaction Time ($\pm$ SEM) (ms)	0.006		0.456	0.002
0-back		342 (7.3)	351 (8.0)	378 (11.3)
1-back		362 (8.7)	372 (8.9)	395 (14.2)
2-back		396 (14.9)	401 (14.3)	444 (16.3)
3-back		403 (17.0)	416 (17.2)	431 (13.0)
Accuracy ($\pm$ SEM) (%)	0.071		0.474	0.021
0-back		95.3 (.01)	94.2 (.02)	93.8 (.01)
1-back		96.3 (.01)	96.4 (.01)	96.1 (.01)
2-back		95.2 (.01)	94.7 (.01)	91.4 (.02)
3-back		93.3 (.01)	92.7 (.01)	87.8 (.02)
P300 Amplitude ($\pm$ SEM) (μ V)	0.397		0.229	0.244
0-back		12.3 (3.8)	12.1 (4.6)	11.5 (6.6)
1-back		14.1 (5.0)	13.4 (5.0)	13.1 (3.9)
2-back		11.8 (3.9)	9.4 (3.5)	9.9 (4.9)
3-back		8.6 (4.2)	8.8 (3.5)	8.6 (4.6)

N-Back Task

P300 amplitude decreased with the number of trials back the subject has to recall the digit ($F(3,15) = 11.2$, $p = 0.01$). Contrast showed that the effect was linear ($F(1,17)=20.0$, $p<0.01$). P300 amplitude did not differ between treatments ($F<1$) and there was no significant interaction between Treatment and Memory Load ($F(6,12) = 1.3$, $p = 0.34$) (table 1).

Frequency band power

There were significant or nearly significant differences between treatments in alpha ($F(2,15)=11.6$, $p<0.01$) and theta ($F(2,15)=3.1$, $p<0.08$) power. Power in the alpha and theta frequency band was highest after dexchlorpheniramine and lowest after lorazepam. Compared to placebo alpha power was significantly increased following dexchlorpheniramine ($F(1,67)=11.4$, $p<0.01$), and decreased following lorazepam ($F(1,16)=17.1$, $p<0.01$). For theta power the differences from placebo were not significant. Post-hoc analysis showed that theta power was significantly lower after lorazepam as compared to dexchlorpheniramine ($F(1,16)=6.4$, $p<0.02$). Power in the beta and delta frequency bands did not differ significantly between treatments

CHAPTER 3

Table 2: Mean ($\pm$ SEM) absolute power of the delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and beta (13-30 Hz) frequency bands after the administration of placebo, dexchlorpheniramine and lorazepam. Dexchlorpheniramine significantly increased and lorazepam decreased the alpha power. * Indicates $p < 0.05$ when compared to placebo.

		PLC	D4	L1
delta power (μV^2)	Fz	9.7 (0.8)	9.3 (0.6)	10.7 (1.1)
	Cz	10.1 (0.6)	9.9 (0.7)	10.6 (0.9)
	Pz	9.6 (0.6)	9.3 (0.6)	9.1 (0.8)
theta power (μV^2)	Fz	7.1 (0.7)	7.5 (0.7)	7.0 (0.6)
	Cz	7.3 (0.7)	7.7 (0.7)	6.9 (0.6)
	Pz	5.8 (0.6)	6.2 (0.6)	5.3 (0.5)
alpha power (μV^2)	Fz	5.8 (0.8)	7.4 (1.2)*	4.4 (0.8)*
	Cz	6.9 (1.2)	8.7 (1.6)*	4.8 (1.0)*
	Pz	8.7 (2.1)	11.1 (2.8)*	5.4 (1.6)*
beta power (μV^2)	Fz	1.2 (0.1)	1.4 (0.1)	1.3 (0.1)
	Cz	1.3 (0.1)	1.6 (0.2)	1.5 (0.2)
	Pz	1.3 (0.1)	1.4 (0.1)	1.3 (0.1)

DISCUSSION

This study was designed to assess effects of an antihistamine on memory performance. Results clearly showed that the active control lorazepam impairs memory performance as measured by immediate and delayed word recall and speed and accuracy of working memory. In contrast, dexchlorpheniramine did not affect any of these measures. Both treatments increased feelings of drowsiness and affected cortical activity as measured with EEG indicating that treatments were effective. Although, dexchlorpheniramine induced sedation, it did not affect memory performance.

Memory

Lorazepam impaired memory functioning while dexchlorpheniramine did not. Benzodiazepines are known to produce anterograde amnesia as shown by the findings that recall of material learned after drug intake is impaired, but recall of material learned before drug intake is not. The latter also implies that retrieval processes are still intact (Turner, et al., 2006). The anterograde amnesia therefore seems to result from shallow encoding (Curran, et al., 1998), or impaired storage and consolidation.

In the present study lorazepam impaired immediate recall but not the relative recall as compared with the placebo condition suggesting encoding deficits. This is supported by psychophysiological data as the P300 was significantly reduced after lorazepam administration. The P300 is regarded as being involved in attentional processes and the updating of memory (Polich, 2007). It has been shown that information later not remembered coincides with a decreased P300 amplitude at the time when

CHAPTER 3

stimuli were learned, i.e. larger P300 amplitudes during encoding predicts better recall (Friedman & Johnson, 2000). The lack of effect of dexchlorpheniramine on the P300 amplitude is in line with the finding that dexchlorpheniramine did not affect immediate recall.

In contrast to the present study, anatomical studies suggest that the histamine system may be involved in memory processes. For example, H₁-receptors are found in many areas in the human brain, including prefrontal and temporal cortices in humans (Tashiro, et al., 2002; Yanai, et al., 1992) and in the CA3 and CA4 regions of the hippocampus in rats (Palacios, Wamsley, & Kuhar, 1981). These findings suggest that the H₁-receptor may be involved in memory processes. It may be that subjects who are treated with a centrally active antihistamine, which results in blockade of the central H₁-receptors, are able to compensate for the induced impairment. Subjects are often aware of the drug effects and increase effort or use alternative strategies in an attempt to counteract the drug induced impairment. In contrast, effects of lorazepam in this study may be slightly too large to be counteracted. Such hypotheses could be studied by measuring possible compensatory brain activity using imaging techniques such as fMRI. However, to the best of our knowledge there have been no imaging studies investigating the effects of H₁-antagonists on brain activity in areas related to memory. Further fMRI studies may elucidate the role of the histamine system in memory functioning.

Studies with H₃-receptor compounds in animals suggest that histamine is involved in memory functioning (Passani, Bacciottini, Mannaioni, & Blandina, 2000). For example, H₃-receptor agonists induce memory impairment (Garbarg, et al., 1992) and inverse agonists and antagonists improve memory performance in animals (Wijtmans, Leurs, & de Esch, 2007). Thus, there might be a discrepancy between the effects of manipulating the histaminergic system through H₁ and H₃-receptors. An explanation may be that the H₃-receptor plays a relatively large role as a heteroreceptor in memory functioning (Passani, Lin, Hancock, Crochet, & Blandina, 2004). It has been shown that H₃-receptor compounds are able to modulate cholinergic activity in the cortex (Blandina, Efofudebe, Cenni, Mannaioni, & Passani, 2004) and it has been suggested that cholinergic neurons may mediate these effects on memory (Passani, et al., 2000). This hypothesis is supported by the finding that bilateral lesions of the tuberomammillary nucleus, which leads to decreased tonic activation of H₃-heteroreceptor and thus less inhibition of other neurotransmitters (e.g. acetylcholine and norepinephrine), produced facilitation of learning (Klapdor, Hasenohrl, & Huston, 1994). In contrast to H₃-receptors, the H₁-receptor antagonism may not affect the cholinergic system, which is greatly involved in memory.

CHAPTER 3

An alternative explanation is that effects of H₃ compounds seen in animals may not be directly translated to man. For example, memory performance in rats is highly dependent on the hippocampus, while humans are able to use more strategies (e.g. use of language) and, therefore, brain structures. This may result in a higher sensitivity of rats for effects on memory. As H₃ compounds are still hardly available to be tested in man, the question whether the translation can be made is yet to be answered.

Effects on sedation

In accordance with our results many studies found increased subjective drowsiness after intake of lorazepam 1 mg [e.g. (Bond & Lader, 1988; Hanks, et al., 1995; Preston, et al., 1988)] and dexchlorpheniramine 4 mg (Van Ruitenbeek, et al., 2008). The shift of the power in the EEG frequency spectrum from an alert waking state to mild sedation is usually characterized by increased theta and alpha power (Galliaud, et al., 2008; Griffiths, et al., 1991) and a decrease in beta power. In accordance, the power of the alpha frequency band after dexchlorpheniramine administration was significantly increased in this study. Sannita and colleagues (1996) also observed chlorpheniramine 4 mg to increase the alpha power. However, we did not observe any significant differences between treatments on beta frequency power.

In contrast to the effects of dexchlorpheniramine, lorazepam decreased the power of the alpha frequency band which was also observed by Ebert et al. (2000) who administered midazolam (5 mg i.v.). It would be expected that lorazepam as a sedative agent would increase alpha power. The reduction in alpha frequency power after lorazepam administration has been explained by reductions in thalamic activity. Schreckenberger et al. (2004) in a PET study have found decreased alpha power to exclusively correlate with a decrease in thalamic metabolic activity. They argue that decreased occipital cortical input to the thalamus results in desynchronisation of thalamic output and, therefore, decreased oscillatory alpha activity. Lorazepam 1 mg also reduced the power of the theta frequency significantly as compared to dexchlorpheniramine 4 mg. However, the decrease in power was not significant as compared with placebo, possibly indicating that the effect is an incidental finding. Alternatively, as distinctions between frequency bands are sometimes arbitrary, theta frequency may be decreased for similar reasons as alpha frequency power decreases.

The effects on subjective alertness suggest that lorazepam induced more sedation than dexchlorpheniramine. This may be explained by the fact that an alert waking state is typically dependent on multiple transmitter systems like the cholinergic, noradrenergic, serotonergic, dopaminergic and orexinergic system and activity of the histaminergic neurons arising from the

CHAPTER 3

tuberomammillary nucleus (Espana & Scammell, 2004; Saper, Chou, & Scammell, 2001). In contrast, induction of sleep is largely orchestrated by GABA-ergic activity in the ventrolateral preoptic nucleus. Therefore, reductions in activity of a single system involved in actively maintaining a waking state may result in mild sedation, while increasing the GABA-ergic activity as a single modulator reduces activity in all waking systems and may thus induce more severe sedation.

Effects on memory may be partly secondary to the induced drowsiness, possibly explaining why the effects of lorazepam on memory were larger than those of dexchlorpheniramine. Brookhuis & de Waard (1993) have shown that increased sedation as measured with theta and alpha power significantly correlates with decreased performance on actual car driving, suggesting that performance impairment is secondary to sedation. To determine whether the memory performance is secondary to the sedative effects effect sizes (ES) of the treatments on measures of memory performance and sedation were calculated (Fredrickson, et al., 2008; Rosnow, 1996). Absolute ESs of lorazepam on immediate word recall on trials one, two, three, the delayed recall and P300 amplitude were larger than those of dexchlorpheniramine (0.61, 0.55, 0.62, 0.68 and 0.74 vs. 0.16, 0.09, 0.03, 0.01 and 0.16, respectively). Lorazepam also caused more sedation as measured by subjective drowsiness (lorazepam: ES=1.24, dexchlorpheniramine: ES=0.86). However, the difference in ES between lorazepam and dexchlorpheniramine on measures of memory performance was much bigger. It is, therefore concluded that the sedative effects are insufficient to explain the effects of the treatments on memory performance.

In conclusion, the hypothesis that antihistamines do not affect memory performance which was tested in studies attempting to dissociate the effects of different types of drugs on memory performance and arousal (Curran, et al., 1998; Turner, et al., 2006; Van Ruitenbeek, et al., 2008) is supported by our data. Both the EEG data and the subjective measure of drowsiness indicated that subjects were sedated after the administration of dexchlorpheniramine 4 mg. Effects on working memory, the recall of words presented around peak impairment and indications of impaired encoding were not observed, while the active control clearly affected performance on the memory tasks. It is concluded that H₁-receptor activation is not crucial for human memory functioning.

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CHAPTER 3

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CHAPTER 4

SPECIFIC ANTIHISTAMINERGIC EFFECTS ON COGNITION: IMPAIRED CENTRAL PROCESSING SPEED AND UNAFFECTED ATTENTION AND WORD LEARNING

Van Ruitenbeek, P., Vermeeren, A., Riedel, W. J. (*submitted*). Specific
antihistaminergic effects on cognition: impaired central processing speed
and unaffected attention and word learning

CHAPTER 4

CHAPTER 4

INTRODUCTION

The histamine neurotransmitter system has recently been discovered as a possible target for the pharmacological treatment of cognitive deficits in clinical disorders. Over the past years evidence has accumulated that histamine plays an important role in such disorders. The findings are mainly characterized by a histamine hypofunction. For example, Higuchi et al. (Higuchi, 2000) found decreased H₁-receptor binding in the frontal and temporal cortex in Alzheimer's disease patients as compared with age matched controls. Evidence for the histamine system as a possible drug target has also come from animal studies. These studies have shown that H₃-antagonists improve performance in models for many cognitive deficits and clinical disorders, like Alzheimer's disease, ADHD and schizophrenia [for review see: (Esbenshade, Fox, & Cowart, 2006)].

If histamine hypofunction is involved cognitive deficits seen in clinical disorders an artificial histaminergic hypofunction may reveal what cognitive functions are vulnerable in these disorders. Histamine H₁-receptor blockade decreases histaminergic activity and may be used as model for histamine hypofunction as seen in clinical disorders.

Recent studies attempted to investigate the specific effects of H₁ blockade in humans [e.g. (Turner, Handford, & Nicholson, 2006; Van Ruitenbeek, Vermeeren, & Riedel, 2008)]. Although some of the first generation antihistamines used in these studies are relatively selective (Van Ruitenbeek, et al., 2008), most antihistamines causing central effects are less specific in their receptor binding as compared with second generation antihistamines. However, second generation antihistamines cross the blood-brain barrier to a much lesser extend which make them less suitable as a tool drug. One possible exception may be cetirizine. Cetirizine is a selective second generation H₁-antagonist that has been shown to cross the blood-brain barrier. For example, Tashiro et al. (2002; 2004) have found that after a 20 mg dose cetirizine occupied 20 to 50% of the H₁ receptors in the brain.

There are also studies that show effects of cetirizine on behavioural performance measures and measures of alertness (Gengo & Gabos, 1987; Gupta, Kapoor, Gillani, Kapoor, & Gupta, 2004; Patat, et al., 1995; Nicholson & Turner, 1998; Ramaekers, Uiterwijk, & O'Hanlon, 1992; Sannita, Crimi, Riela, Rosadini, & Brusasco, 1996; Vermeeren, Ramaekers, & O'Hanlon, 2002). In contrast, Gupta, et al., (2004) found no effects on objective performance measures. In addition, several studies also did not find behavioural effects of cetirizine (Gengo, Gabos, & Mechtler, 1990; Seidel, Cohen, Bliwise, & Dement, 1987; Shamsi, Kimber, & Hindmarch, 2001; Theunissen, Vermeeren, van Oers, van Maris, & Ramaekers, 2004; Volkerts, Van Willigenburg, Van Laar, & Maes, 1992). So, despite the advantage of selectivity it is very unclear if cetirizine is suitable as a tool drug to model

CHAPTER 4

cognitive deficits secondary to histaminergic hypofunction. Therefore, the aim of this study was to investigate the behavioural effects of cetirizine.

The recommended therapeutic dose of 10 mg may be insufficient to induce reliable behavioural effects. The effects of twice this dose (20 mg) have only been studied by some authors in the past and results are contradictory. Gengo & Gabos (1987) have shown that cetirizine 20 mg increases subjective drowsiness. In addition, Sannita et al. (1996) have shown that cetirizine 20 mg produced increased alpha frequency band power using electroencephalography as a sign of sedation. However, Seidel et al. (1987), Seidel, Cohen, Bliwise, & Dement (1990), Gengo, Dabronzo, Yurchak, Love, & Miller (1987), Gengo & Gabos (1987) and Gengo, et al. (1990) all found no effects of cetirizine 20 mg on behavioural performance. Therefore, the effects of two oral doses (10 and 20 mg) of cetirizine on cognitive performance were measured.

It is also unclear when the effects of cetirizine after administration occur. Peak blood-plasma concentrations (T_{max}) of cetirizine are shown at approximately 1 hour after oral dosing (Campoli-Richards, Buckley, & Fitton, 1990) and the elimination half life ($T_{1/2}$) is approximately 7 to 11 hours (Simons & Simons, 1991). However, there is some evidence that the behavioural effects occur after T_{max} . Volkerts et al. (1992) and Theunissen et al. (2004) failed to find effects of cetirizine 10 mg on driving performance 1 hour after acute dosing. In contrast, Ramaekers et al. (1992) and Vermeeren et al. (2002) found that 10 mg cetirizine impaired driving performance 3 to 4 hours after dosing. Therefore, in this study behavioural effects are assessed at both 1 hour and 3 hours after treatment.

To detect cognitive deficits tasks were used that have been shown to be sensitive to central H_1 blockade and that cover a range of important cognitive functions. The Critical Flicker/Fusion Frequency (CFF) is a sensitive measure to detect sedation which is caused by centrally active antihistamines [e.g. (Hou, Langley, Szabadi, & Bradshaw, 2007)]. The Visual Vigilance Test (VVT) (Nuechterlein, Parasuraman, & Jiang, 1983; O' Hanlon and Vermeeren, 1988) was added to the task battery as a measure of vigilance. Vigilance is known to be affected by sedating agents (Kay, 2000). The Critical Tracking Task and Divided Attention task are sensitive measures to detect slowing in sensorimotor performance and impaired attention (Van Ruitenbeek, et al., 2008). Explicit short term and long term memory was assessed using a Word Learning Task (Rey, 1964). Finally, to separate memory processes from the slowing of other processes the Sternberg's Memory Scanning Task was used (Sternberg, 1969).

CHAPTER 4

METHODS

Subjects

Eighteen (9 female) healthy volunteers were recruited for this study and were paid for their participation. One female subject withdrew from the study for reasons unrelated to treatments. The mean $\pm$ SD age of the 17 remaining subjects was 23 ± 2.6 years. Subject's health was screened using a medical history questionnaire and a physical examination. Exclusion criteria were hypertension, body mass index outside the limits of 18 and 28 kg m^{-2} , history of alcohol and drug abuse, history of psychiatric disorders, presence of cardiovascular, respiratory, renal, hepatic, metabolic or endocrine disorders, history of glaucoma, overt allergy, history of allergic reactions to antihistamine drug or any sensory or motor impairment. Subjects were not allowed to take any medication during or between treatments, except oral contraceptives, aspirin and acetaminophen.

All subjects received written information and were given the opportunity to ask questions. They signed a written informed consent prior to enrolment. The study was approved by the Ethics Committee of Maastricht University and University Hospital Maastricht and was carried out in accordance with the World Medical Association Declaration of Helsinki and its amendments (Edinburgh, 2000).

Study design and treatments

The study was conducted according to a 3×2 three-way, double blind, cross over design. The two factors were Treatment and Time of testing. Treatments were single oral doses of cetirizine 10 mg, cetirizine 20 mg and placebo. Subjects were tested twice on each testday, at 1 and 3 hours after drug administration. All test days were separated by a wash out period of one week. The order of treatments was counterbalanced using six independent 3×3 Latin squares.

Procedure

Subjects were trained on two separate occasions to perform the tasks until they reached a plateau level. On treatment days subjects arrived at the test facility well rested. Drugs administration occurred at 9:00 a.m., at least 3 hours after consuming a meal. Test sessions started 1 hour (T1) and 3 hours (T3) after drug administration. The duration of the battery was 1 hour and consisted of the 15-Words Learning Task (WLT), Critical Flicker/Fusion Frequency (CFF), Visual Vigilance Task (VVT), Critical Tracking Task (CTT), Divided Attention Task (DAT) and Sternberg's Memory Scanning (SMS) presented in the mentioned order. CFF was measured at both the beginning

CHAPTER 4

and end of the test battery. Ten minutes before the first test battery subjects consumed a light meal.

Assessments

15-Words Learning Task

The WLT (Rey, 1964; Riedel, et al., 1995) assesses short and long term verbal memory. Fifteen Dutch monosyllabic meaningful nouns and adjectives are presented for 1000 ms at a rate of 1 per 2 seconds and subjects are required to read them aloud. When the presentation ends, subjects are required to verbally recall as many words as possible (immediate recall). This procedure is repeated five times, with the same words presented in the same sequence. After a 20 minutes delay subjects are requested again to recall as many words as possible (delayed recall). Dependent variables were the sum of the number of words correctly recalled on the five immediate recall trials (IR), the number of correctly recalled words after the 20 minute delay (DR).

Sternberg's Memory Scanning Task

The SMS (Riedel, et al., 1995; Sternberg, 1969) measures the time it takes to scan items held in memory as part of working memory integrity, separating it from other processes required to respond. When subjects judge whether a test symbol is contained in a short memorized sequence of symbols, their mean reaction time increases linearly with the length of the sequence. The linearity and slope of the function imply the existence of an internal serial comparison process whose average rate is between 20 and 30 items per second. In this test the subjects are presented with a set of 1, 2 or 4 consonants, which they are asked to memorize. Hereafter a series of 90 consonants is presented on a computer screen of which 45 are targets and 45 are non-targets. The subjects' task is to indicate as fast as possible whether the presented letter was one from the memory set by pressing one of two buttons. The task consists of 3 blocks of 90 stimuli with memory sets of 1, 2 and 4 digits. The average reaction time for correct responses (detections and rejections) were recorded and used to calculate individual linear regression lines between reaction time and memory set size. The slope of this line is a measure of speed of scanning short term memory, whereas the intercept is a measure of psychomotor speed. Both slope (ms/letter) and intercept (ms) are outcome measures.

Critical Flicker/Fusion Frequency

The CFF measures the frequency threshold, which separates the perception of light flickering from fusion and light constancy. The threshold is fundamentally determined by the speed of information processing of the

CHAPTER 4

visual system, which can be influenced by sedative drugs. Subjects discriminated the flicker from fusion of a flickering of four light emitting diodes held at 0.75 m from the subject's eye using the Leeds Psychomotor Tester. The threshold (Hz) was determined by averaging three ascending and three descending frequency trials (Hindmarch, 1980).

Visual Vigilance Task

The VVT [(Nuechterlein, et al., 1983) and adjusted by (O'Hanlon and Vermeeren, 1988)] consists of rapidly presenting visual stimuli for 8 minutes and was used to assess sustained visual discrimination. The stimuli were presented for 34 ms at a rate of 1 per second and consisted of digits (0, 2, 3, 5, 6, 8 and 9) of which the '0' was considered the target and was presented at a 25% target rate. To visually degrade the stimuli a glass diffusion screen was positioned between the subject and the display. Upon appearance of the target subjects were instructed to press a response button as fast as possible. The reaction times of the false and correct detections were measured. From these measures the perceptual sensitivity index d' and the response criterion β were calculated to determine the effects on stimulus and response related processes, respectively.

Critical Tracking Task

The CTT measures the ability to control an unstable triangle, which is displayed on a horizontal axis on a computer screen, using a joystick (Jex, McDonnell, & Phatak, 1966). An error signal causes the triangle to become increasingly unstable and therefore it tends to diverge from the centre of the axis. The subject has to make compensatory movements to null the error in order to keep the triangle in the middle. As the correction frequency of the cursor deviations increases as a stochastic function of time, the subject is required to make compensatory movements with an increasingly higher frequency to the limit of her ability, whereupon control is lost. This frequency decreases under the influence of sedating drugs. The dependent measure is the average frequency at which control is lost of five trials after removing the lowest and highest score. This is called the 'critical frequency' or ' λ_c ' (rad s^{-1}).

Divided Attention Task

The DAT (Moskowitz, 1973) assesses the ability to perform two tasks simultaneously and evaluates cognitive processing resources. The primary task is similar to the critical tracking task described above, with the exception that the level of difficulty is held constant at 50% of that, which is just controllable, by the subject. Tracking error is measured by the absolute distance (in mm) between the cursors position and the centre. The secondary task involves the monitoring of 24 digits (0-9) that are arranged around the

CHAPTER 4

display's periphery. The digits change asynchronously every 5 seconds. Subjects were required to respond as rapidly as possible by lifting the foot from a pedal anytime the digit "2" appears. The average reaction time (in ms) to targets is recorded as the response measure in this task. Average reaction times and tracking error of each measure were transformed to z-scores using data from all subjects, test days and test sessions. Second, the standardized scores of the subtasks were summed to yield an overall performance score for each subject, test day and test session. Overall scores were used for further analysis.

Statistical analysis

All variables were screened for normality of the distribution. There were no signs of non-normal distributions. All dependent variables were analysed according to a 3x2 two factorial model with Treatment (cetirizine 10 mg, cetirizine 20 mg, placebo) and Time of testing (T1, T3) as factors using Analysis of Variance for repeated measures. The CFF data were analysed according to a 3x2x2 three factorial model with Treatment (3 levels), Time of testing (2 levels) and Time in battery (2 levels: begin, end). Time of testing comprised 4 levels as CFF was measured before and after each test battery. If overall F-tests indicate a significant ($p < 0.05$) main effect of Treatment, the data were further analysed using two drug-placebo contrasts. In case of a significant interaction ($p < 0.05$) between Treatment and Time of testing, the data were analysed post-hoc per level of Time of testing. All data were analysed using SPSS 15.0 for the Windows operating system.

RESULTS

A summary of mean ($\pm$ SEM) performance scores in tasks assessing critical flicker-fusion frequency, visual vigilance, critical tracking and divided attention is presented in Table 1.

15-Words Learning Task

There were no differences between the treatments and between the two test sessions. Thus, cetirizine did not affect immediate word recall on any of the trials at T1 or T3 after drug administration (figure 1).

There were also no differences between treatments on the number of words recalled during the delayed recall. Subjects tended to recall less words at T3 as compared with T1 ($F(2,15) = 3.2$, $p = 0.091$), but the difference was not affected by treatment ($F(2,15) = 1.2$, $p = 0.327$) (figure 1).

Table 1: Performance scores after treatment with cetirizine 10 mg, 20 mg or placebo. Bold p-values indicate significant or near significant main effects or interaction. Significant treatment placebo contrasts are indicated with an asterisk. In addition, at the end of each test battery (T1e and T3e) the CFF was significantly lower as compared with the beginning of the battery (T1b and T3b) as indicated by the main effect of Time in battery ($F(1,16)=14.1$, $p=0.002$).

	Overall analysis									Test session	Mean ($\pm$ SEM) scores		
	Main effect of Treatment			Main effect of Time of Testing			Interaction between Treatment x Time of Testing				Treatment		
	F =	df	p =	F =	df	p =	F =	df	p =		PLA	CET10	CET20
CFF													
Critical Frequency (Hz)	1.4	2,15	0.280	< 1	1,16	0.366	< 1	2,15	0.865	T1b	29.2 $\pm$ 0.8	28.7 $\pm$ 0.7	29.1 $\pm$ 0.8
										T1e	28.4 $\pm$ 0.8	28.3 $\pm$ 0.8	28.4 $\pm$ 0.8
										T3b	28.8 $\pm$ 0.9	28.9 $\pm$ 0.8	29.0 $\pm$ 0.8
										T3e	28.4 $\pm$ 0.9	27.9 $\pm$ 0.7	28.5 $\pm$ 0.8
VVT													
Hits (%)	1.5	2,15	0.262	3.1	1,16	0.096	< 1	2,15	0.800	T1	79.1 $\pm$ 3.5	75.1 $\pm$ 5.1	67.4 $\pm$ 5.4
										T3	75.5 $\pm$ 4.4	73.2 $\pm$ 5.4	65.9 $\pm$ 5.5
Reaction time (ms)	1.9	2,15	0.187	2.3	1,16	0.147	< 1	2,15	0.647	T1	503 $\pm$ 16	517 $\pm$ 9	522 $\pm$ 18
										T3	492 $\pm$ 11	502 $\pm$ 8	520 $\pm$ 24
d prime	2.2	2,15	0.150	< 1	1,16	0.393	< 1	2,15	0.590	T1	2.6 $\pm$ 0.3	2.8 $\pm$ 0.2	2.3 $\pm$ 0.3
										T3	2.8 $\pm$ 0.2	2.7 $\pm$ 0.2	2.1 $\pm$ 0.3
Beta	< 1	2,15	0.589	< 1	1,16	0.672	1.2	2,15	0.316	T1	5.0 $\pm$ 1.0	7.1 $\pm$ 2.0	6.8 $\pm$ 1.7
										T3	6.5 $\pm$ 1.3	5.9 $\pm$ 1.6	7.2 $\pm$ 2.2
CTT													
Lambda (rad/s)	4.2	2,15	0.035	< 1	1,16	0.752	1.1	2,15	0.363	T1	5.4 $\pm$ 0.2	5.1 $\pm$ 0.2*	5.4 $\pm$ 0.2
										T3	5.4 $\pm$ 0.3	5.2 $\pm$ 0.2	5.2 $\pm$ 0.3
DAT													
Overall performance (z-score)	< 1	2,15	0.664	2.6	1,16	0.129	< 1	2,15	0.416	T1	-0.12 $\pm$ 0.3	0.02 $\pm$ 0.4	-0.26 $\pm$ 0.4
										T3	-0.05 $\pm$ 0.4	0.32 $\pm$ 0.4	0.09 $\pm$ 0.4
Tracking error (mm)	1.8	2,15	0.199	2.4	1,16	0.144	2.4	2,15	0.124	T1	16.9 $\pm$ 1.3	19.3 $\pm$ 1.4	17.9 $\pm$ 1.6
										T3	17.9 $\pm$ 1.6	18.7 $\pm$ 1.5	19.2 $\pm$ 1.7
Reaction time (ms)	< 1	2,15	0.629	1.5	1,16	0.237	3.0	2,15	0.083	T1	1811 $\pm$ 81	1723 $\pm$ 102	1701 $\pm$ 76
										T3	1771 $\pm$ 102	1862 $\pm$ 86	1750 $\pm$ 78

CHAPTER 4

Word Learning - IR

Figure 1: Administration of cetirizine 10 or 20 mg did not affect the number of recalled word during the immediate recall.

Sternberg's Memory Scanning Task

The slope of the regression line of reaction time on memory load tended to differ between treatments ($F(2,15) = 3.1$, $p = 0.074$). Drug-placebo contrast indicated that both 10 and 20 mg cetirizine increased the slope significantly, indicating a slowing of memory scanning speed ($F(1,16)=5.2$, $p=0.037$ and $F(1,16)=4.8$, $p=0.044$, respectively). Although treatment effects did not differ significantly on T1 and T3 ($F(2,15)=1.7$, $p=0.223$), post hoc analysis indicated that cetirizine 10 mg increased the slope at T1 ($F(1,16)=6.7$, $p=0.020$) and cetirizine 20 mg tended to increase the slope at T3 ($F(1,16)=4.3$, $p=0.054$) (figure 2). There was no overall differences in slopes between T1 and T3 ($F(1,16) = 1.8$, $p=0.203$) (figure 2).

The intercept of the regression line of reaction time on memory load were not affected by Treatment or Time and these factors did not interact ($F_s < 1$) (figure 2).

CHAPTER 4

Figure 2: The slope of the regression line of reaction time on memory load increased after administration of cetirizine. The increase was significant at T1 for cetirizine 10 mg and at T3 for cetirizine 20 mg.

Critical Flicker/Fusion Frequency

The critical frequency was decreased at the end of every test battery as indicated by the significant effect of Time in battery ($F(1,16)=14.1$, $p=0.002$). However, this difference was not affected by Treatment ($F<1$). The differences between the treatments ($F(2,15)=1.4$, $p=0.280$) and times of testing ($F<1$) were not significant.

Visual Vigilance Task

The number of hits did not differ between the treatments. The number of hits tended to be less on T3 as compared with T1 ($F(1,16)=3.1$, $p=0.096$), but the difference was not affected by cetirizine treatment.

No differences between the treatments or between the times of testing on reaction time, the perceptual sensitivity index or response criterion were detected.

Critical Tracking Task

Tracking performance was significantly different between treatments ($F(2,15)=4.2$, $p=0.03$). Drug placebo contrasts showed that 10 mg cetirizine decreased tracking performance ($F(1,16)=7.1$, $p=0.017$). There were no differences between T1 and T3.

Divided Attention Task

The overall performance scores, tracking errors and reaction times did not differ between the treatments or times of testing. However, the interaction between Time of testing and Treatment approached significance ($F(2,15)=3.0$,

CHAPTER 4

$p=0.083$). Subjects tended to respond faster at T3 as compared with T1. However, after cetirizine 10 and 20 mg administration subjects responded slower at T3 as compared with placebo.

DISCUSSION AND CONCLUSIONS

The aim of the present study was to investigate if cetirizine would be a suitable tool drug to induce histamine hypofunction and the associated cognitive impairments. Histamine is known to be involved in attention, psychomotor functioning and possibly memory. It was, therefore, hypothesised that cetirizine would affect performance measures of these functions. In this study cetirizine tended to affect psychomotor performance and memory scanning speed. In contrast, cetirizine did not affect word learning, vigilance and divided attention.

Memory functioning as measured with the memory scanning task was impaired in this study. This is in accordance with results from a study by Ramakers et al. (1992) who found an increase in variability in memory scanning speed after administration of cetirizine 10 mg. In contrast, we did not observe effects on word learning and recall. Our results are consistent with those from another study, although these lack of effects may be explained by the fact that they only used 10 mg cetirizine (Theunissen, et al., 2004). Studies assessing the effects of other centrally active antihistamines usually also find no effects on word learning and recall [e.g. (Turner, et al., 2006; Van Ruitenbeek, et al., 2008)]. The difference between the word learning task and the memory scanning task is that performance on the former is characterized by the capability to store and retrieve new information mostly irrespective of speed. In contrast, performance on the memory scanning task depends largely on speed of information processing. It may be that cetirizine affects the speed, but not the integrity of information processing in working memory.

Slower information processing speed can also result in impaired tracking performance. The critical tracking task is a complex, sensitive and frequently used measure to assess drug induced psychomotor impairment [e.g. (Van Ruitenbeek, et al., 2008)]. Performance requires many cognitive processes like perceptual and motor processes, but also central executive processes like anticipation and inhibition of responses in case the anticipated response is not required to be executed. A delay in such central processes can result in impaired tracking performance. This study showed that tracking performance was impaired one hour after cetirizine 10 mg administration. In accordance, Nicholson & Turner (1998) and Patat et al. (1995) found impaired tracking performance after the administration of cetirizine. In contrast, Ramaekers et al. (1992), Theunissen, Vermeeren, &

CHAPTER 4

Ramaekers (2006), Theunissen, et al. (2004) and Shamsi et al. (2001) found no impairments. This may indicate that the effects of cetirizine are small and may not always be detected. Ramaekers et al. (1992) suggested that some subjects are very sensitive to effects of cetirizine, while others are not. Looking at the individual data did reveal that almost all subjects performed worse after cetirizine administration as compared with placebo. However, some subjects improved their performance after administration of both 10 mg and 20 mg of cetirizine, which indicates that some subjects may not have been sensitive to the effects of cetirizine.

Both sensory and motor related information processing were not affected by cetirizine. From the Visual Vigilance Task in this study the perceptual sensitivity index (d') and response criterion (β) were calculated, which are measures related to stimulus processing and response readiness, respectively. Neither measures indicated an impairment induced by cetirizine. In addition, the critical flicker/fusion frequency, which is a measure of information processing speed of the visual system i.e. sensory information, did not show any effects of cetirizine. In contrast, there was an effect on memory scanning speed, which is regarded as a central process, while all other processes as measured with the intercept in the Sternberg's Memory Scanning task remained unaffected. It may be concluded that the effects of cetirizine may not be located in sensory or response related processes, but may reside in a central processing speed.

It was expected that the effects of cetirizine would increase with increasing dosages. Surprisingly, the lower dose had more significantly impairing effects than the higher dose. Although both dosages impaired memory scanning speed, only the 10 mg dose impaired tracking performance. In addition, the effect of cetirizine 10 mg on memory scanning was also larger than that of cetirizine 20 mg, although the difference was not significant ($F(1,16)=1.2$, $p=0.281$). In contrast to our findings, three out of six previous studies that used both 10 and 20 mg cetirizine found effects of cetirizine 20 mg and not 10 mg (Gengo, et al., 1987; Gengo & Gabos, 1987; Gengo, et al., 1990; Sannita, et al., 1996; Seidel, et al., 1987, 1990). Taken together, cetirizine 20 mg seems to have larger effect than the 10 mg dose and our findings that cetirizine 20 mg has less effects than cetirizine 10 mg may have been incidental.

From the literature (Ramaekers, et al., 1992; Vermeeren, et al., 2002) it was suggested that the effects of cetirizine may not coincide with the T_{max} of approximately 1 hour and that the behavioural effects are delayed. This study assessed the effects both 1 and 3 hours after oral administration of cetirizine. The data did not suggest that performance after cetirizine was different at T3 as compared with T1. There was only one Treatment by Time of testing interaction as measured with the reaction time on the DAT. The interaction indicated that subjects responded slower at T3 after cetirizine 10

CHAPTER 4

mg or 20 mg as compared with T1 and after placebo the responded faster at T3 as compared with T1. However, taken together all other measures did not show such an interaction. Thus, our data did not suggest that effects of cetirizine are bigger after $T_{\max}$.

This study showed only marginal effects of cetirizine. Yanai, Okamura, Tagawa, Itoh, & Watanabe (1999) reported that H_1 -receptor occupancy in the brain is significantly correlated with the reported measures of sleepiness. Non-sedative antihistamines show receptor occupancy of approximately 30 percent, while sedative antihistamines occupy more than 70 percent of the central H_1 -receptors. Tashiro et al. (2004) reported a trend of cetirizine 20 mg to induce sedation while it occupied approximately 26 percent of the central H_1 -receptors. In addition, Tashiro et al. in an earlier study (2002) reported that cetirizine 20 mg slowed reaction times and occupied approximately 20 to 50 percent of the central H_1 -receptors. It may be concluded that cetirizine 20 mg occupies a moderate percentage of the central H_1 -receptors and induces marginal behavioural effects.

In conclusion, oral dosages of both cetirizine 10 mg and 20 mg enter the brain and cause slowing of central processes resulting in some behavioural effects. This study provides no evidence that these effects are delayed as compared with $T_{\max}$ and twice the recommended dose does not clearly increase the behavioural effects. The effects of cetirizine are not pronounced enough to be used as a model for histamine hypofunction.

CHAPTER 4

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CHAPTER 5

HISTAMINE H₁ RECEPTOR BLOCKADE PREDOMINANTLY IMPAIRS SENSORY PROCESSES IN HUMAN SENSORIMOTOR PERFORMANCE

Van Ruitenbeek, P., Vermeeren, A., Smulders, F. T. Y., Sambeth, A.,
Riedel, W. J. (*In press*). Histamine H₁ receptor blockade predominantly
impairs sensory processes in human sensorimotor performance. *British
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CHAPTER 5

INTRODUCTION

Several studies have shown that centrally active histamine H₁ receptor antagonists, frequently used for the treatment of Seasonal Allergic Rhinitis and Urticaria, produce sedation and impair cognitive performance, in particular complex sensorimotor performance such as tracking and car driving (Hindmarch & Shamsi, 1999; Theunissen, Vermeeren, van Oers, van Maris, & Ramaekers, 2004; Van Ruitenbeek, Vermeeren, & Riedel, 2008; Verster & Volkerts, 2004). However, little is known about the specific effects of H₁ receptor blockade on the cognitive subprocesses involved in performance on such tasks

Better knowledge about the cognitive deficits associated with reduced histamine activity (e.g. as induced by H₁-antagonists) can ultimately contribute to better diagnosis and treatment of clinical disorders in which histamine dysfunction seems one of the contributing factors. Degeneration or dysfunction of histamine neurons has been found in Alzheimer's disease, Parkinson's disease, epilepsy, ADHD and schizophrenia [For review see: (Esbenshade, Fox, & Cowart, 2006; Onodera, Yamatodani, Watanabe, & Wada, 1994; Passani, Bacciottini, Mannaioni, & Blandina, 2000; Witkin & Nelson, 2004; Yanai & Tashiro, 2007)]. So, drugs that increase histamine function, such as antagonists or inverse agonist for the H₃-receptor, are expected to be valuable new treatments for such disorders.

Better knowledge on the specific cognitive deficits associated with histamine dysfunction in humans can be derived from studies assessing the behavioural effect of centrally active H₁-antagonists in healthy volunteers. The aim of the present study was to clarify which subprocesses underlying sensorimotor performance are impaired by the representative antihistamine dexchlorpheniramine, which has been shown to affect sensorimotor performance (Van Ruitenbeek, et al., 2008). To this end, we adopted a behavioural and a psychophysiological approach.

The behavioural approach consists of the Additive Factor Method (AFM) (Sternberg, 1969). Within this framework human information processing between stimulus and response is dissected into a series of discrete stages, which represent distinct elementary cognitive operations such as perceptual encoding, decision making and response preparation (Bonin-Guillaume, Blin, & Hasbroucq, 2004). Roughly, these can be regarded as sensory, central and motor stages. Several task factors have been established that influence individual stages. For example, by decreasing Stimulus Quality (SQ) the perceptual process of feature extraction can be slowed resulting in a longer reaction time. Identifying the specific processing stages that are affected by drugs can be done using the AFM. The basic logic is that if two factors interact they affect at least one common stage (Sanders,

CHAPTER 5

1980; Smulders, Kenemans, Schmidt, & Kok, 1999; Sternberg, 1969). So, if a drug interacts with a task factor, which affects a specific stage, it is concluded that the drug affects at least that particular stage. [e.g. (Frowein, 1981; Frowein, Gaillard, & Varey, 1981)]. Only two studies investigated the effects of antihistamines using this framework, but with inconsistent results. According to the investigators results of the first study suggested that antihistamines might compromise perceptual processing (Gaillard and Verduin 1983), whereas results of a subsequent study were taken to indicate that they primarily affect motor processes (Gaillard et al. 1988). In the first study, results were not significant, however, probably due to a small sample size and low dose of the drug. In the second study, the antihistamine was found to interact with SQ in a reaction time task, but also to impair tracking performance. As the latter study did not include manipulations of task demands affecting motor processing, it remains unclear whether the antihistamine had generally sedating or specific effects on sensorimotor processing.

The second approach to identify the locus of effects of a drug is a psychophysiological approach, i.e. using event related potentials (ERPs) as markers to detect changes in specific stages of information processing. The latencies to the peak of the potentials are typically regarded as the time at which subprocesses occur after stimulus presentation. The P300 component is a central component and is thought to be associated with evaluation of a stimulus just before a decision takes place (Polich, 2007; Riedel, Mehta, & Unema, 2006). The amplitude of the P300 is thought to reflect the resources available for stimulus processing. For example, increased task demands to which attention is directed reduces the amplitude of the P300 (Beauducel, Brocke, & Leue, 2006). The latency of this component has been shown to increase after degradation of SQ (McCarthy & Donchin, 1981). In addition, the Lateralized Readiness Potential (LRP) is a response related component. Effects on response preparation, such as increasing response complexity (RC), increase the interval between the LRP-onset and the response. The locus of the drug effect can thus be determined using the P300 and LRP. Effects on stimulus related processes are identified by an increased interval between the stimulus and P300 (S-locked P300). Effects on response related processes are identified by an increased interval between the onset of the LRP and response (R-locked LRP).

A consistent finding is that antihistamines delay the P300 latency. For example, studies have found that chlorpheniramine or pheniramine increased the P300 latency during performance on an Odd-Ball task (Loring & Meador, 1989; Seidl, et al., 1997; Simons, Reggin, Roberts, & Simons, 1994). A delay in the duration of any process occurring before the P300 leads to a delay of the P300 peak amplitude. Therefore, these findings are in line with studies in which SQ was manipulated and suggest that H₁-blockade affects

CHAPTER 5

sensory stages of information processing (Gaillard, Gruisen, & De Jong, 1988; Gaillard & Verduin, 1983). However, the effects of antihistamines on motor processes and associated ERP components are largely unknown.

To demonstrate sensitivity of the tasks and procedures we included the benzodiazepine lorazepam (1 mg) as an active control drug. Similar to H₁-antagonists, benzodiazepines induce sedation and impair sensorimotor performance (Bond, Lader, & Shrotriya, 1983; Curran, 2000; Leufkens, Vermeeren, Smink, van Ruitenbeek, & Ramaekers, 2007; Turner, Handford, & Nicholson, 2006). Moreover, effects of benzodiazepines have been found to interact with SQ and motor processes (Pang & Fowler, 1994). In addition, they are known to affect latency and amplitude of several ERP components (Curran, Pooviboonsuk, Dalton, & Lader, 1998; Riba, Rodriguez-Fornells, Munte, & Barbanoj, 2005) including P300 (Pompeia, Manzano, Galduroz, Tufik, & Bueno, 2003) and motor-related evoked potentials (Riba, et al., 2005; Rockstroh, Elbert, Lutzenberger, & Altenmuller, 1991).

To summarize, the specificity of antihistamine induced psychomotor impairment is unknown and such knowledge may aid the search for treatments for disorders in which specific processes are affected. Using Sternberg's AFM and measuring ERPs, this study assessed the effects of dexchlorpheniramine as a representative centrally active and specific H₁-antagonist on sensory and motor stages of cognitive processing. Dexchlorpheniramine was expected to negatively affect sensory stages and therefore interact with SQ as measured by prolonged reaction time and S-locked P300 peak latency. In addition, this is the first study to assess the effects on response related processes as measured with the response locked LRP onset latency. This study shows that central H₁ blockade impairs the processing of sensory information.

METHODS

Subjects

Eighteen healthy right handed subjects (nine female) between 18 and 45 years (mean $\pm$ SD: 24.2 $\pm$ 7.3 years) were recruited by means of advertisements in local newspapers and were paid for their participation. Subject's health was screened using a medical history questionnaire and a physical examination, including a 12-lead electrocardiogram, blood chemistry and haematology, and urinary tests for pregnancy and drug abuse (amphetamine, benzodiazepine, cocaine, opiates, cannabis and methamphetamine). Exclusion criteria were a significant history or presence of any mental or physical disorder; gastrointestinal, hepatic, renal, cardiovascular or neurological. Also, drug abuse, a body-mass index outside

CHAPTER 5

the limits of 18 and 28 kg m⁻², blood pressure outside the limits of 100 and 150 Hg systolic and 60 and 90 Hg diastolic and drinking more than 20 standard alcoholic consumptions per week or 5 beverages containing caffeine per day were regarded as exclusion criteria. For women, pregnancy and lactation were also regarded as exclusion criteria. No drugs or medication, except oral contraceptives, aspirin and acetaminophen, were allowed to be taken from a week before the first test-day until the end of the study. Smoking and the use of caffeine were prohibited on test-days and the use of alcohol from 24 hours before and during each test-day. Subjects were allowed to have breakfast at home before 7:30am so that drug intake 3 hours later would be on a nearly empty stomach.

All subjects received written information about the study procedures and signed an informed consent form prior to enrolment. The study was approved by the ethics committee of Maastricht University and University Hospital Maastricht and carried out in accordance with the World Medical Association Declaration of Helsinki and its amendments (Edinburgh, 2000).

Study design and treatments

The study was conducted according to a double blind, placebo-controlled, 3-way crossover design. Treatments were single oral doses of dexchlorpheniramine 4 mg (Schering-Plough BV, Utrecht, The Netherlands) and lorazepam 1 mg (Hexal BV, Hillegom, The Netherlands) (all immediate release formulations) and placebo and were spaced apart by a washout period of at least 4 days. Within the choice reaction time task SQ and RC were varied and consisted of two levels each. The order of treatment and sequence of task conditions were counterbalanced between subjects.

Procedure

Subjects were individually trained to perform all tasks in two practice sessions within two weeks prior to their first treatment day. On treatment days subjects arrived at the University at 9:00am. Between 9:00am and 9:30am the inclusion and exclusion criteria were checked. At 10:00am subjects performed a short version of each task to remind them of the procedures. At 10:30am the study medication was ingested. The test-battery consisted of the Choice Reaction Time Task, Critical Tracking Task and Subjective Drowsiness and was performed between 12:00am and 1:00pm. A previous study (Van Ruitenbeek, et al., 2008) has shown that the peak impairment of dexchlorpheniramine is around 1.5 hours post treatment.

CHAPTER 5

Behavioural assessments

Choice reaction time task

The choice reaction time task (CRT) used in this study was based on Smulders, Kok, Kenemans, & Bashore (1995). The speed of information processing of the sensory and motor stages were assessed by manipulating the quality of the visual stimuli and complexity of the responses, respectively. Smulders et al. (1995) found additive effects of SQ and RC on reaction time. In addition, they found selective effects of SQ on the interval between the stimulus and P300 peak latency and selective effects of RC on the interval between the LRP-onset and the response.

The task consisted of a repeated presentation of the numbers 2 and 5 on a computer screen for 200 ms. The stimuli consisted of small squares surrounded by a frame of squares. The squares consisted of grids of 6 by 6 pixels. The time between offset of a stimulus and the presentation of the next stimulus was varied between 1500 and 2200 ms. Subjects had to respond as fast as possible by pressing a left or right hand button with their left or right index finger when a 2 or a 5 appeared, respectively. The task consisted of four blocks of 112 trials, which each lasted approximately 4 minutes and in which half of the stimuli were visually degraded and half of the stimuli were intact. Degradation was achieved by placing 20 squares (42%) from the frame at random positions in the field within the frame not occupied by the 26 squares of the digit. There were 7 degraded versions of each digit of comparable difficulty to prevent subjects from responding to learned features of the stimulus instead of recognizing the digit.

In two blocks (complex blocks; C) RC was increased by asking the subjects to press three buttons instead of one (simple blocks; S) in the following sequence; index, ring and middle finger. The pressing of the first button indicated the reaction time. The time (ms) between the first button press and the third was also recorded as 'motor time' (MT). The blocks were presented in the order SCCS to one half of the subjects and CSSC to the other half.

The primary performance variable in this task is the average reaction time of the correct responses for the four different task conditions, i.e. intact-simple, degraded-simple, intact-complex and degraded-complex and accuracy scores, which were logarithmically transformed due to the non-linear nature of a decrease in accuracy (Dickman & Meyer, 1988).

Critical tracking task.

The Critical Tracking Task (CTT) measures the ability to control an unstable error signal in a first-order compensatory tracking task (Jex, McDonnell, & Phatak, 1966). Error is displayed as a horizontal deviation of a yellow

CHAPTER 5

triangle from the midpoint on a horizontal scale. Compensatory movements null the error by returning the triangle to the centre. The frequency of the error gradually increases until the subject loses control. The frequency at which control is lost is the critical frequency or λ_c (rad s⁻¹). The CTT includes five trials of which the highest and lowest scores are removed. The average of the three remaining scores is the final score. A previous study has shown that the critical tracking task is sensitive to the effects of H₁-blockade between 1.5 and 2.5 hours after treatment (Van Ruitenbeek, et al., 2008).

Visual analogue scales

Subjective drowsiness is assessed using a series of 16 analogue scales of 100 mm. These provide three factor analytically defined summary scores for 'drowsiness', 'contentedness', and 'calmness' (Bond & Lader, 1974) of which drowsiness was of main interest. Visual analogue scales have been shown to be sensitive to the sedative effects of antihistamines (Van Ruitenbeek, et al., 2008).

Event related potentials

During performance on the CRT subjects' EEG activity was recorded to measure the P300, LRP and P150 associated with correct responses. Dependent variables were duration of the interval (ms) between stimulus and P300 peak amplitude (S-locked P300) and between the response and the P300 peak amplitude (R-locked P300), and the interval between the stimulus onset and LRP onset (S-locked LRP) and between the response and LRP onset (R-locked LRP). In addition, the amplitude of the S-locked and R-locked P300 was determined as a measure of resource availability for stimulus processing.

Recordings and signal analysis

EEG activity was recorded from an array of 32 electrodes from the standard 10-20 system using an electrocap (Jasper, 1957). All electrodes were filled with electrode-gel and were line referenced to the right mastoid electrode. Offline they were referenced to both left and right mastoids. The FPz electrode was used as ground electrode. Horizontal EOG was recorded using electrodes attached to the outer canthi of the eyes and vertical EOG was recorded from electrodes attached above and below the left or right eye and in line with the pupil.

All electrode impedances were kept below 5 k Ω . Signals were amplified using Neuroscan Synamps amplifiers and collected using Neuroscan software. All signals were sampled at a 1000 Hz and filtered online using a 100 Hz low-pass filter and a 0.1 Hz high-pass filter.

CHAPTER 5

Continuous signals obtained during the performance on the CRT were filtered off-line using a 1 Hz high-pass filter after which EEG was corrected for vertical and horizontal eye movements according to a procedure by Semlitsch, Anderer, Schuster, & Presslich (1986). The S-locked sweeps were obtained by epoching from 100 ms before until 1000 ms after stimulus presentation and the interval between sweep onset and stimulus served as baseline. The R-locked sweeps were obtained by epoching from 475 ms before to 625 ms after the response. For the analysis of the P300 all sampled EEG and EOG epochs were low pass filtered using a 3.6 Hz low-pass filter and for the LRP the data were filtered using a 11.1 Hz low-pass filter. Sweeps containing artefacts exceeding $\pm 75 \mu\text{V}$ on the FZ, CZ, PZ, OZ, C3, or C4 electrodes were rejected. This resulted in an average acceptance of 92% of the epochs.

The length of the S-locked and R-locked intervals of the P300 were determined at the Cz electrode site. The S-locked P300 signals were determined as the time between onset of the stimulus and the latency of the largest maximum in a window between 333 and 463 ms as determined by the latency of the P300 of the grand average. The R-locked P300 intervals were determined as the time between the largest maximum of the P300 component and the given response in a window between 132 ms before and 68 ms after the response as determined by the latency of the grand average at the same site.

LRP's were computed by subtracting C4 from C3, point by point, for right and left hand trials and subtracting left hand from right hand trials. The onset latencies of the S-locked and R-locked LRP waveforms were determined using the jackknife scoring method with a fixed $1 \mu\text{V}$ criterium (Miller, Patterson, & Ulrich, 1998; Ulrich & Miller, 2001).

Statistical analysis

All dependent variables were screened for normality of their distributions and no non-normalities were detected. To determine whether task manipulations in the CRT were successful, performance scores and ERPs after placebo treatment were analyzed using repeated measures analysis of variance of a 2x2 factorial model. Within subject variables were SQ (intact, degraded) and RC (simple, complex).

Effects of Treatment (dexchlorpheniramine, lorazepam, placebo) and interactions with SQ and RC on performance measures and ERPs in the CRT were analysed in a 3x2x2 factorial model. F-values for differences in S-locked and R-locked LRP onset latencies were divided by $(n-1)^2$ to correct for the reduction of variance induced by the jackknife method (Ulrich & Miller, 2001). If overall multivariate F-tests indicated a significant difference ($p < 0.05$), data were further analysed using two univariate drug-placebo contrasts.

CHAPTER 5

Performance on the CTT and subjective drowsiness scores were analysed for Treatment effects using repeated measures Univariate Analysis of Variance. All data were analysed using SPSS for Windows (version 12.0.1).

RESULTS

Results of task manipulations and treatments on performance and ERPs are presented in table 1.

Choice reaction time task – task manipulations

Degraded stimuli prolonged reaction time (SQ, $F(1,17) = 153.7$, $p = 0.001$), S-locked P300 latency ($F(1,17) = 6.2$, $p = 0.023$) and the S-locked LRP-onset latency ($F(1,17) = 23.4$, $p = 0.001$). Stimulus degradation did not increase the interval between the R-locked P300 and the response and the R-locked LRP-onset and the response (SQ, $F_s(1,17) < 1$). Degraded stimuli also decreased the accuracy of the response ($F(1,17) = 20.9$, $p = 0.001$), decreased the amplitude of the S-locked P300 ($F(1,17) = 5.1$, $p = 0.038$) and the R-locked P300 amplitude ($F(1,17) = 5.0$, $p = 0.039$).

Increased response complexity prolonged reaction time (RC, $F(1,17) = 15.5$, $p = 0.001$), the interval between the R-locked P300 and the response ($F(1,17) = 17.4$, $p = 0.001$) and the interval between R-locked LRP-onset and the response ($F(1,17) = 8.5$, $p = 0.010$). Contrary to expectations, increased response complexity led to a decrease in S-locked P300 latency ($F(1,17) = 7.7$, $p = 0.013$) and tended to increase the S-locked LRP-onset latency ($F(1,17) = 3.1$, $p = 0.097$). Also, increased RC decreased the S-locked and R-locked P300 amplitude ($F(1,17) = 12.0$, $p = 0.003$ and $F(1,17) = 13.6$, $p = 0.002$, respectively).

There were no significant interactions between SQ and RC (RT: $F(1,17) < 1$, S-locked P300: $F(1,17) < 1$, R-locked P300: $F(1,17) = 1.5$, $p = 0.225$, S-locked LRP: $F(1,17) < 1$, R-locked LRP: $F(1,17) < 1$). Together these data indicate successful task manipulations.

Table 1: Effects of treatments and task manipulations on reaction time and ERPs. Lorazepam (L1) increased the effect of stimulus degradation on reaction time and dexchlorpheniramine (D4) increased the effect of stimulus degradation on P300 peak latency. Significant ($p < 0.05$) or near significant ($p < 0.10$) difference in effects of SQ after Treatment when compared with placebo are indicated with ** and *, respectively. Near significant ($p < 0.10$) difference in effects of RC after Treatment when compared with placebo is indicated with †

Choice Reaction Time task	Main effect Treatment p =	Treatment*SQ p =	Treatment *RC p =	Placebo Mean ($\pm$ SEM) Intact	Degraded	D4 Mean ($\pm$ SEM) Intact	Degraded	L1 Mean ($\pm$ SEM) Intact	Degraded
Reaction time (ms)	< 0.01	< 0.07	n.s.						**
Simple response				390 (10.6)	426 (12.6)	417 (14.7)	452 (17.3)	440 (14.8)	491 (17.8)
Complex response				420 (11.7)	455 (11.6)	436 (13.4)	478 (16.6)	472 (15.0)	517 (17.9)
S-Locked P300 latency (ms)	n.s.	< 0.02	n.s.				*		
Simple response				380 (5.2)	392 (8.3)	380 (7.1)	404 (7.7)	378 (8.7)	385 (9.7)
Complex response				370 (7.2)	384 (7.9)	375 (6.9)	395 (7.3)	373 (8.1)	381 (9.4)
R-Locked P300 latency (ms)	< 0.02	n.s.	n.s.						
Simple response				-14 (12.6)	-22 (10.8)	-20 (9.5)	-18 (8.6)	-35 (10.8)	-37 (10.7)
Complex response				-57 (10.3)	-55 (10.7)	-57 (12.2)	-55 (10.8)	-68 (8.2)	-80 (10.6)
S-Locked LRP-onset latency (ms)	< 0.01	n.s.	0.08				†		
Simple response				237 (0.7)	267 (0.7)	247 (0.7)	300 (0.7)	278 (1.6)	334 (1.6)
Complex response				239 (0.5)	285 (0.8)	239 (0.5)	280 (0.7)	305 (1.1)	368 (2.8)
R-Locked LRP-onset latency (ms)	n.s.	n.s.	n.s.						
Simple response				-137 (0.6)	-131 (0.4)	-142 (0.7)	-149 (0.7)	-130 (0.5)	-133 (0.6)
Complex response				-169 (0.7)	-166 (1.0)	-183 (1.1)	-202 (1.0)	-176 (1.2)	-162 (2.5)

CHAPTER 5

Figure 1: Effects of treatment and manipulations of stimulus quality and response complexity on the stimulus locked P300. Stimulus quality increased the peak latency ($p < 0.01$) and interacted with treatment ($p < 0.02$) which was caused by an increased effect of the degraded stimulus by dexchlorpheniramine ($p < 0.10$).

CHAPTER 5

Figure 2: Effects of treatment and manipulations of stimulus quality and response complexity on the interval between the R-locked P300 and the response. Response complexity and lorazepam increased the interval duration ($p < 0.05$), but did not interact.

CHAPTER 5

Choice reaction time task – Treatment effects

Reaction time, accuracy and motor time

Treatment had a significant main effect on overall reaction time ($F(2,16) = 15.5$, $p = 0.001$). Drug-placebo contrasts showed that both dexchlorpheniramine and lorazepam prolonged reaction time ($F(1,17) = 12.0$, $p = 0.003$; $F(1,17) = 29.8$, $p < 0.001$, respectively).

Treatment tended to interact non-significantly with SQ ($F(2,16) = 3.2$, $p < 0.069$) but not with RC ($F(2,16) < 1$). Lorazepam increased the effect of SQ as compared with placebo ($F(1,17) = 6.4$, $p = 0.022$), but dexchlorpheniramine did not ($F(1,17) < 1$).

S-locked and R-locked P300 latencies

Treatment did not have a significant main effect on the S-locked P300 latencies ($F(2,16) = 2.7$, $p = 0.099$). However, Treatment did interact with SQ ($F(2,16) = 5.4$, $p = 0.016$). Dexchlorpheniramine increased the effect of SQ on this interval nearly significant ($F(1,17) = 4.4$, $p = 0.052$), while lorazepam clearly did not ($F(1,17) = 1.4$, $p = 0.246$.) (figure 1).

Mean duration of the interval between the R-locked P300 and the response differed significantly between treatments ($F(2,16) = 5.5$, $p = 0.015$). Lorazepam increased the interval ($F(1,17) = 8.2$, $p = 0.011$), while dexchlorpheniramine did not ($F(1,17) < 1$). Treatment did not interact with RC or SQ ($F_s(2,16) < 1$) (figure 2).

R-locked and S-locked LRP

Treatment had no main effect on the onset of the R-locked LRP ($F(2,16) = 1.4$, $p = 0.283$) and did not interact with RC ($F(2,16) < 1$) and with SQ ($F(2,16) = 1.04$, $p = 0.376$) (figure 3).

Treatment did affect S-locked LRP-onset latency significantly ($F(2,16) = 6.2$, $p = 0.010$). Lorazepam increased the latency ($F(1,17) = 12.7$, $p = 0.002$), but overall dexchlorpheniramine did not ($F(1,17) = 1.5$, $p = 0.239$). However, RC tended to interact with Treatment ($F(2,16) = 2.9$, $p = 0.080$) and dexchlorpheniramine tended to decrease the S-locked LRP onset latency ($F(1,17) = 3.7$, $p = 0.070$) (figure 4).

S-locked and R-locked P300 amplitude

Treatment did not affect the S-locked P300 amplitude and did not interact with SQ ($F_s(2,16) < 1$). However, Treatment did interact with RC ($F(2,16) = 4.8$, $p = 0.023$). Lorazepam prevented a decrease of the amplitude of the P300 in the complex response condition compared with placebo ($F(1,17) = 10.2$, $p = 0.005$).

CHAPTER 5

Treatment also did not have a main effect on the R-locked P300 amplitude ($F(2,16) = 1.3$, $p = 0.298$). In contrast to the results above, Treatment did not interact with RC ($F(2,16) = 1.3$, $p = 0.296$).

Motor time

Treatment marginally significantly affected MT ($F(2,16) = 3.6$, $p = 0.052$). Lorazepam significantly increased MT with 31.6 ms on average ($F(1,17) = 7.2$, $p = 0.016$), while dexchlorpheniramine had no significant effect ($F(1,17) < 1$). SQ had no significant effect on MT ($F(1,17) < 1$) and did not interact with Treatment ($F(2,16) = 1.3$, $p = 0.296$).

Accuracy

Statistical tests on the Log transformed accuracy data revealed a similar pattern of effects as was shown by the reaction time data. Treatment had a main effect ($F(2,16) = 5.9$, $p = 0.012$); lorazepam tended to reduce the accuracy ($F(1,17) = 3.2$, $p = 0.093$). Treatment significantly interacted with SQ ($F(2,16) = 4.8$, $p = 0.023$), but not with RC ($F(2,16) < 1$). The accuracy reducing effect of degraded SQ ($F(1,17) = 45.0$, $p < 0.001$) was enlarged by lorazepam ($F(1,17) = 10.2$, $p = 0.005$) and near significantly by dexchlorpheniramine ($F(1,17) = 3.3$, $p = 0.085$).

CHAPTER 5

Figure 3: Effects of treatment and manipulations of stimulus quality and response complexity on the interval between the R-locked LRP and the response. Both treatments did not prolong the interval. Response complexity did increase the interval ($p < 0.01$), but did not interact with treatment.

CHAPTER 5

Figure 4: Effects of treatment and manipulations of stimulus quality and response complexity on the stimulus locked LRP onset latency. Lorazepam and degraded stimuli increased the onset latency (p 's < 0.01). Response complexity tended to interact with Treatment ($p < 0.10$) and dexchlorpheniramine tended to decrease the S-locked LRP onset when a complex response has to be given ($p < 0.10$).

CHAPTER 5

Critical Tracking Task

Treatment significantly impaired tracking performance ($F(2,16) = 11.6$, $p = 0.001$); lorazepam decreased the critical frequency from an average ($\pm$ SEM) lambda of 4.16 (± 0.14) after placebo administration to an average ($\pm$ SEM) lambda of 3.56 (± 0.17) ($F(1,17) = 24.4$, $p = 0.001$). Dexchlorpheniramine also decreased the critical frequency to an average lambda of 3.99 (± 0.12), but not significantly ($F(1,17) = 2.4$, $p = 0.141$).

Visual analogue scale

Treatment significantly affected subjective drowsiness ($F(2,16) = 7.8$, $p < 0.004$); lorazepam and dexchlorpheniramine increased drowsiness scores from 34.5 (± 5.0) to 51.7 (± 4.3) ($F(1,17) = 16.6$, $p = 0.001$) and 59.4 (± 4.5) ($F(1,17) = 7.9$, $p = 0.012$), respectively.

DISCUSSION AND CONCLUSIONS

This study aimed to determine the locus of effects of H_1 -blockade on sensorimotor processing in humans using the additive factor method and ERPs. Effects of the task manipulations in the placebo condition showed an additive pattern of effects of SQ and RC, confirming that the manipulations affected separate stages of information processing. Both treatments had significant sedative effects and impaired sensorimotor performance as measured by the CTT and CRT. The level of subjective drowsiness following dexchlorpheniramine administration was comparable to that in a former study (Van Ruitenbeek, et al., 2008).

Dexchlorpheniramine

In contrast to earlier studies, performance on the CTT was not significantly impaired by dexchlorpheniramine. A previous study by our group (Van Ruitenbeek, et al., 2008) used only female subjects, because they have been found to be more sensitive to the effects of antihistamines (Ramaekers & O'Hanlon, 1994; Robbe, 1990; Vermeeren, Ramaekers, & O'Hanlon, 2002; Vuurman, Uiterwijk, Rosenzweig, & O'Hanlon, 1994) whereas the present study used subjects of both sexes. Post-hoc analysis of Treatment effects in men and women in the present study revealed that in contrast to our expectations, the performance of women who received dexchlorpheniramine did not decrease, while the performance of men did. The interaction between Treatment and Gender was not significant, however. In contrast, lorazepam caused a marked decrease in performance in both sexes. Since lorazepam also increased MT in the CRT, the effects may partially be due to muscle relaxation (Olkkola & Ahonen, 2008).

CHAPTER 5

Both treatments slowed reaction times in the CRT. The effect of dexchlorpheniramine on the stimulus-locked P300 latency was enlarged if stimuli were degraded, which indicates that the location of the effect was before the P300 peak latency. The effects on processes occurring before 300 ms after stimulus presentation is supported by other studies in which antihistamines caused the P300 latencies to increase (Loring & Meador, 1989; Meador, Loring, Thompson, & Thompson, 1989; Seidl, et al., 1997). It needs some consideration that slowing of information processing may be related to impaired attention induced by antihistamines which has frequently been found [e.g. (Bower, et al., 2003; Fine, et al., 1994)]. Impaired attention processes are reflected by a decreased P300 amplitude (Polich, 2007). However, we did not observe an effect of dexchlorpheniramine on the P300 amplitude. Therefore, an attention deficit does not explain the effects of dexchlorpheniramine in this study.

To the best of our knowledge, there is no information on effects of antihistamines on response related processes. In the current study, dexchlorpheniramine did not have a main effect on the duration of the interval between the R-locked LRP-onset and the response nor did it interact with RC as measured by the duration of the interval. Taken together the results suggest that the effects of dexchlorpheniramine are located before the P300 peak amplitude and that it does not affect response related processes.

However, in terms of reaction time data an interaction with SQ was not found, but was expected if dexchlorpheniramine would affect the feature extraction stage. To explain this, the subjects may have compensated for the effects on feature extraction by decreasing the duration of a different stage following the P300. The question is what stage this would be. The increase in reaction time with regard to complex responses tended to be less after the administration of dexchlorpheniramine as compared with placebo. In addition, the interval between the stimulus and the onset of the LRP decreased when subjects were required to give a complex response after administration of dexchlorpheniramine, which suggests that subjects began with their response sooner. Therefore, an increased P300 peak latency might have been compensated for by speeding up a process before response programming (e.g. response choice) so that the effect of SQ was not increased by dexchlorpheniramine as measured with reaction time.

The Treatment by RC interaction as measured with the S-locked LRP is, however, problematic for the assumption of strictly serially ordered and discrete processing stages. Although not supported by some (de Jong, Wierda, Mulder, & Mulder, 1988), it has been suggested that information processing is not entirely serial and discrete (Miller & Hackley, 1992; Osman, Bashore, Coles, Donchin, & Meyer, 1992). Non-serial stages do not, however, invalidate the assumption of additivity (Miller, van der Ham, & Sanders, 1995) and partial information of the stimulus is sufficient to start the

CHAPTER 5

programming of the response. It is therefore possible that subjects started response programming before the stimulus had been identified.

The effects on sensory processing are supported by the post-hoc analysis of the P150 peak amplitude, which was increased after dexchlorpheniramine intake (drug-placebo contrast: $F(1,17) = 5.8$, $p = 0.028$). An increase in amplitude has been interpreted as increased mapping of visual features on higher order representations (Chauncey, Grainger, & Holcomb, 2008). It is suggested that visual information processing is impaired and that the increased P150 amplitude possibly reflects a compensatory mechanism.

This study has shown that histamine hypofunction impairs sensory information processing. This may be of relevance for the treatment of schizophrenic patients. Schizophrenia is characterized by changes in sensory processing and it has been found that the histamine system in these patients is affected (Onodera, et al., 1994; Witkin & Nelson, 2004). Our findings suggest that the affected histamine system may be involved in the sensory deficits in schizophrenia. Histamine based drugs may, therefore be useful as a treatment in this disorder (Geyer, Krebs-Thomson, Braff, & Swerdlow, 2001).

Lorazepam

Lorazepam increased the effect of SQ on reaction time and accuracy, which suggests that lorazepam affects the stage of feature extraction. In that case, however, lorazepam is expected to have a main effect on the S-locked P300 peak latency and interact with SQ. We did not observe these temporal effects. In contrast to our results, other studies found increased P300 latencies after the administration of lorazepam (Curran, et al., 1998; Pooviboonsuk, 1996). However, they all administered 2 mg orally which is twice the dose that was administered in this study. It is possible that only high dosages are able to increase the S-locked P300 latency and that a dose of 1 mg only has subtle effects on stimulus driven stages of information processing.

Similar to our results Pang & Fowler (1994) did not find triazolam to increase the effect of SQ on the S-locked P300 peak latency, while it did increase the effect of SQ on reaction time. Pang & Fowler (1994) argue that this dissociation between effects on the two measures may be due to the slowing of response related processes. This hypothesis is supported by the finding that lorazepam increased the interval between the R-locked P300 and the response. However, lorazepam did not affect the interval between R-locked LRP-onset and the response, which should be observed when response related processes are affected. Similarly, Riba, et al. (2005) did not observe effects of 1 mg lorazepam on the R-locked LRP-onset latencies.

CHAPTER 5

Therefore, it seems unlikely that response related processes within the central nervous system were affected.

If the effect of lorazepam is neither located before the P300 peak latency nor after the start of response programming, it may be located in the transition between feature extraction and response programming. In support, lorazepam did increase the S-locked LRP onset latency, indicating a later onset of the response programming. Riba, et al. (2005) also found increased S-locked LRP-onset latencies after the administration of 1 mg alprazolam and Northoff, et al. (2000) found that 1 mg lorazepam increased the latencies of late readiness potentials. Our results also show that lorazepam increased the interval between the R-locked P300 and response. These results suggest that the temporal locus of the effect is before the response programming and after identification of the stimulus.

To explain the difference between the temporal (ERP latency) and functional (functional stage) loci of effects, subjects may have shifted the speed-accuracy trade-off in favour of speed, such that subjects tended to guess the identity of the stimulus. If so, the effect on feature extraction is shifted such that subsequent stages of information processing (e.g. response choice) receive poor quality information on which the decision to respond left or right has to be based. Following such reasoning, the lorazepam induced delay in feature extraction may be located in central stages, i.e. in the interval between P300 and response onset.

In conclusion, this paper shows that both drugs affect at least sensory stages of information processing. However, the effects of the treatments differ qualitatively as shown by the ERPs. Therefore, caution needs to be taken when interpreting the data. The effects of lorazepam on feature extraction resulted in a delayed onset of response programming and increased reaction times. Nevertheless, lorazepam can be used as an active control in studies investigating effects of drugs on sensory stages. Central H₁-blockade leads to impaired sensory processing, but also to compensating response programming. Sensory disturbances in patients suffering from, for example schizophrenia, may be related to histamine dysfunction. Therefore, new histamine based drugs may be useful in treating sensory disturbances in such pathologies.

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CHAPTER 6

EFFECTS OF L-HISTIDINE DEPLETION AND L-TYROSINE/L-PHENYLALANINE DEPLETION ON SENSORY AND MOTOR PROCESSES IN HEALTHY VOLUNTEERS

Van Ruitenbeek, P., Sambeth, A., Vermeeren, A., Young, S. N., Riedel, W. J. (*In press*). Effects of L-histidine depletion and tyrosine/phenylalanine depletion on sensory and motor processes in healthy volunteers. *British Journal of Pharmacology*.

CHAPTER 6

INTRODUCTION

Histamine has been associated with a number of clinical disorders in which cognitive performance is impaired (Onodera, Yamatodani, Watanabe, & Wada, 1994). Animal models for cognitive deficits in disorders like Attention Deficit Hyperactivity Disorder, Parkinson's disease, schizophrenia and sleep disorders have been used to test the effects of histamine H₃-receptor antagonists as possible therapeutic agents (Esbenshade, Fox, & Cowart, 2006; Leurs, Blandina, Tedford, & Timmerman, 1998; Vohora, 2004). H₃-Receptor antagonists increase histamine function through presynaptic receptors. These studies have shown that performance on a plethora of tasks is improved and have therefore attracted the attention of many pharmaceutical companies (Esbenshade, et al., 2006; Leurs, et al., 1998; Wijtmans, Leurs, & de Esch, 2007).

To study the role of histamine in cognition histamine functioning can be manipulated. The main observation in such studies is that increasing histamine activity leads to improved cognitive performance and prolonged wakefulness, while decreasing histamine activity leads to diminished performance and increased sleepiness. More specifically, the role of histamine in human cognition has mostly been studied by looking at the effects of histamine H₁-receptor antagonists (i.e. antihistamines). The impairing effect of centrally active antihistamines in humans on sensorimotor performance has been well established and has often been attributed to its sedative effects (Hindmarch & Shamsi, 1999; Kay, 2000; O'Hanlon & Ramaekers, 1995; P. Van Ruitenbeek, Vermeeren, & Riedel, 2008). These effects are believed to be representative of low level of histamine functioning in the brain.

Next to histamine H₁-receptor blockade another way to decrease histamine functioning is by depleting the precursor L-histidine from the brain. Histamine is synthesized by decarboxylation of the essential amino acid L-histidine (Cho, Anderson, Wixom, Hanson, & Krause, 1984). Analogous to the depletion of L-L-tyrosine/L-phenylalanine to decrease dopamine levels in the brain, depletion of L-histidine may cause a decrease in brain histamine. In rodents histamine metabolism can be altered more by changes in precursor availability as compared with any other neurotransmitter (e.g. serotonin, catecholamines and acetylcholine) (Young, 1996). If the effects of low levels of histamine are H₁-receptor mediated, L-histidine depletion should exert the same effects as H₁-antagonists. The effects of L-histidine depletion on sensorimotor performance have never been assessed before. Therefore, the aim of the present study is to assess the effects of L-histidine depletion on sensory and motor related cognitive processes in healthy volunteers using a behavioural and psychophysiological

CHAPTER 6

approach as has been done before using an H₁-antagonist (Van Ruitenbeek, Vermeeren, Smulders, Sambeth, Riedel, *In press*).

The behavioural approach aims to find interactions between treatments and task manipulations in sensorimotor task performance. Sensorimotor functioning can be regarded as a result of information processing through serial stages from perception, through decision making to action. Treatments interacting with task manipulations specifically affecting individual stages consequently affect at least the same stage as the task manipulation (Sternberg, 1969). It has been shown that H₁-blockade increases the effect of the visual degradation of stimuli and therefore affects sensory stages of information processing (Gaillard, Gruisen, & De Jong, 1988; Van Ruitenbeek, Vermeeren, Smulders, Sambeth, A., Riedel, *In press*).

With the psychophysiological approach the effects of treatments on separate processes in cognitive functioning can be measured using Event Related Potentials (ERPs). The time interval between a peak and a stimulus or response is indicative of the duration of processes occurring during that interval. For example, the duration of the interval between a stimulus and the P300 peak latency is indicative of the duration of sensory processes (Polich, 2007; Riedel, Mehta, & Unema, 2006). The Lateralized Readiness Potential (LRP) is associated with motor programming and the interval between the onset of the LRP and the response is indicative for the duration of motor related processes (Hackley & Miller, 1995; Miller & Hackley, 1992). A former study has shown that H₁-blockade increases the duration of the P300 peak latency, but does not affect the interval between the LRP onset and the response (Van Ruitenbeek, Vermeeren, Smulders, Sambeth, Riedel, *In press*). Thus, H₁-blockade affects sensory, but not motor processes. L-histidine depletion is expected to have similar effects.

Since the behavioural effects of L-histidine depletion have never been assessed before an active control treatment is needed to demonstrate sensitivity of the tests and procedures. A known way to deplete a neurotransmitter from the brain is L-L-tyrosine/L-phenylalanine depletion (McTavish, Cowen, & Sharp, 1999). L-L-tyrosine is the precursor of dopamine and is synthesized from L-phenylalanine. A decrease in dopamine levels has been observed after L-tyrosine/L-phenylalanine depletion (Montgomery, McTavish, Cowen, & Grasby, 2003) and has been shown to impair cognitive performance (Harmer, McTavish, Clark, Goodwin, & Cowen, 2001), especially in tasks assessing working memory (Harrison, et al., 2004). In addition, an increase in dopamine levels by administration of levodopa has shown to have selective effects on sensory stages of information processing as it interacted with stimulus intensity and not with stimulus-response mapping or stimulus foreperiod duration (Rihet, Possamai, Micallef-Roll, Blin, & Hasbroucq, 2002). Therefore, L-tyrosine/L-phenylalanine depletion will act as an active control.

CHAPTER 6

In summary, if L-histidine depletion indeed causes brain histamine levels to decrease, and effects of H₁-antagonists are representative for those of low levels of histamine, similar behavioural effects as seen after administering H₁-antagonists are expected such as impaired psychomotor performance and increased sedation. Second, if L-histidine depletion affects sensorimotor performance the effects may be stage specific. This study shows that L-histidine depletion is effective in reducing L-histidine levels as measured in blood-plasma and that L-histidine depletion affects motor related processes, which is in contrast with the effects of H₁-blockade.

METHODS

Subjects

Twenty-two healthy volunteers (6 male) between 18 and 35 years (mean $\pm$ SD: 21 $\pm$ 2) were recruited by means of posters placed at Maastricht University locations. They were paid for their participation. Five subjects, all female, withdrew from the study due to side effects of the treatments i.e. nausea and vomiting after drinking the amino acid mixture. Data from another subject was lost due to a technical error. The remaining sixteen subjects out of the intended eighteen had a mean ($\pm$ SD) age of 21 ($\pm$ 2) years.

Subjects' health was screened using a medical history questionnaire. Exclusion criteria were a significant history or presence of any mental or physical disorder; gastrointestinal, hepatic, renal, cardiovascular or neurological. Also, drug abuse, a body-mass index outside the limits of 18.5 and 30.0 kg m⁻² and drinking more than 20 standard alcoholic consumptions per week or 5 beverages containing caffeine per day were regarded as exclusion criteria. For women, pregnancy and lactation were also regarded as exclusion criteria. No drugs or medication, except oral contraceptives, aspirin and acetaminophen, were allowed to be taken from a week before the first test-day until the end of the study. Smoking and the use of caffeine were prohibited on test-days, the use of alcohol from 24 hours before and during each test-day and the use of psychoactive drugs 2 weeks prior to the first test-day. On each test-day subjects received a low-protein, carbohydrate rich diet, which was similar to that given by Riedel, Klaassen, Deutz, van Someren, & van Praag (1999) and Sambeth et al. (2008)

All subjects received written information about the study procedures and signed an informed consent form prior to enrolment. The study was approved by the ethics committee of Maastricht University and University Hospital Maastricht and carried out in accordance with the World Medical Association Declaration of Helsinki and its amendments (Edinburgh, 2000).

CHAPTER 6

Study design and treatments

The study was conducted according to a double blind, placebo controlled, 3-way, cross-over design. Treatments were administration of L-histidine free (HID), L-tyrosine/L-phenylalanine free (TYD), or balanced (BAL) amino acid drinks (all treatments: Basic Pharma Manufacturing BV, Roermond, The Netherlands). L-histidine free treatment consisted of a mixture of 101.2 gram of amino acids mixed, but without the amino acid L-histidine. L-tyrosine/L-phenylalanine depletion treatment consisted of a mixture of 91.8 gram of amino, but without the amino acids L-tyrosine and L-phenylalanine. The balanced drink contained the entire range of 104.4 gram of amino acids. All mixtures were mixed with 200 ml tab water. Female subjects received 85% of the drink male subjects received to adjust for differences in bodyweight.

Treatment days were spaced apart by a washout period of at least 7 days. The order of treatments and sequence of task conditions were counterbalanced between subjects, however not completely due to the drop out of six subjects.

Table 1: Content of the amino acid mixtures (g). Histidine is lacking in the histidine depletion condition (HID), and L-tyrosine and L-phenylalanine are lacking in the L-tyrosine depletion condition (TPD).

	Balanced drink (BAL)	Histidine depletion (HID)	L-tyrosine depletion (TYD)
Isoleucine	8.0	8.0	8.0
Leucine	13.5	13.5	13.5
Lysine	11.0	11.0	11.0
Methionine	3.0	3.0	3.0
Valine	8.9	8.9	8.9
Threonine	6.5	6.5	6.5
Tryptophan	2.3	2.3	2.3
Alanine	5.5	5.5	5.5
Arginine	4.9	4.9	4.9
Cysteine	2.7	2.7	2.7
Glycine	3.2	3.2	3.2
Serine	6.9	6.9	6.9
Proline	12.2	12.2	12.2
Histidine	3.2	x	3.2
L-tyrosine	6.9	6.9	x
L-phenylalanine	5.7	5.7	x

Procedure

All subjects were trained to perform the tasks at a plateau level within two weeks prior to the first test day. On treatment days subjects arrived well rested at the test facility at 9:00 a.m. after refraining from eating from 9:00 p.m. the night before. One cup of tea or coffee (without milk or sugar) was allowed before 8:00 a.m. (6 hours before testing) to prevent possible caffeine

CHAPTER 6

withdrawal effects. Consumption of tea or coffee was held constant over the treatment days within subjects.

After arrival subjects completed visual analogue scales measuring subjective mood. A catheter was inserted into the inner bend of the elbow to take blood samples before and at 2, 4, 6 and 7 hours after treatment (T0, T2, T4, T6 and T7, respectively). At 9:15 a.m., subjects received the amino acid drink, which had to be consumed within 15 minutes. Three hours after treatment subjects received a small low-protein meal. After treatment, subjects could watch television and play board games in a specially equipped room. EEG electrodes were attached to the head of the subject four hours after treatment and cognitive assessments started 5 hours after treatment (14:15 p.m.) and lasted for 45 minutes. Assessments included a baseline EEG recording (2 minutes eyes open and 2 minutes eyes closed), followed by a critical tracking task. Thereafter, a choice reaction time task and a cued simple reaction time task were performed during which EEG was recorded. Finally, subjects completed visual analogue scales assessing subjective alertness.

Behavioural assessments

Choice Reaction Time Task

The choice reaction time task (CRT) used in this study was based on Smulders, Kok, Kenemans, & Bashore (1995) and was the same as to the task used by Van Ruitenbeek, Vermeeren, Smulders, Sambeth & Riedel (*In press*). The speed of information processing of the input and output stages are assessed by manipulating the quality of the visual stimuli and complexity of the motoric responses, respectively. Smulders et al. (1995) and Van Ruitenbeek, Vermeeren, Smulders, Sambeth & Riedel (*In press*) found selective effects of Stimulus Quality on the interval between the stimulus and P300 peak latency and selective effects of Response Complexity on the interval between the LRP-onset and the response.

The task consisted of a repeated presentation of the numbers 2 and 5 in random order on a computer screen. Stimuli consisted of small squares surrounded by a frame of squares. The squares consisted of grids of 6 by 6 pixels. Stimulus presentation time was 200 ms, and the time between offset of a stimulus and the presentation of the next stimulus was varied between 1500 and 2200 ms. Subjects had to respond as fast as possible by pressing a left or right hand button with their left or right index finger when a 2 or a 5 appeared, respectively. The task consisted of four blocks of 112 trials, which each lasted approximately 4 minutes. In all blocks half of the stimuli were visually degraded and half of the stimuli were intact. Degradation was achieved by placing 20 dots (42%) from the frame at random positions in the

CHAPTER 6

field within the frame not occupied by the 26 squares of the digit. There were 7 degraded versions of each digit to prevent subjects from responding to learned features of the stimulus instead of recognizing the digit.

In two blocks the complexity of the response was increased by asking the subjects to press three buttons instead of one in the following sequence; index, ring and middle finger. The pressing of the first button indicated the reaction time. The time between the first button press and the third was also recorded as 'motor time' (MT). Blocks requiring three button presses are indicated as complex (C) blocks and blocks requiring a single button press are indicated as simple (S) blocks. The blocks were presented in the orders SCCS and CSSC. Half of the subjects were presented with the SCCS order and the other half with the CSSC order.

The primary performance variables in this task were the average reaction times (ms) of the correct responses for the four different task conditions, i.e. intact-simple, degraded-simple, intact-complex and degraded-complex. Accuracy scores (%) were logarithmically transformed due to the non-linear nature of a decrease in accuracy (Dickman & Meyer, 1988).

Critical Tracking Task

The Critical Tracking Task (CTT) measures the ability to control an unstable error signal in a first-order compensatory tracking task (Jex, McDonnell, & Phatak, 1966). The task has been shown to be sensitive to effects of histamine manipulations (Van Ruitenbeek, et al., 2008). Error is displayed as a horizontal deviation of a yellow triangle from the midpoint on a horizontal scale. Compensatory movements null the error by returning the triangle to the centre. The frequency of the error gradually increases until the subject loses control. The frequency at which control is lost is the critical frequency or λ_c (rad s⁻¹). The CTT includes five trials of which the highest and lowest scores are removed. The average of the three remaining scores is the final score.

Cued Simple Reaction Time Task

A pre-cued simple reaction time task was used to assess treatment effects on the Contingent Negative Variation (CNV) (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). The CNV is a motoric process related slow potential which develops when there is a clear temporal relationship between a warning and an imperative signal (Rizzo, et al., 1985). In this task subjects started by focusing on a fixation cross presented in the centre of the screen for one second. Then a warning signal (red circle) appeared in the centre of the screen, which was followed by the imperative stimulus (green circle) after exactly 2 seconds. Subjects were asked to respond as fast as possible by pressing a button on a response box with their right index finger.

CHAPTER 6

The average amplitude (μV) of a 500 ms time window of the CNV is a measure of response preparation and was a dependent variable in this study. A decrease in average amplitude indicates a decreased supply of preparatory potentiality (Rockstroh, Elbert, Lutzenberger, & Altenmüller, 1991). In addition, reaction time was measured as an indication of response slowing.

Subjective alertness scale

Subjects' mood was assessed using a series of 16 analogue scales of 100 mm. These provide three factor analytically defined summary scores for 'alertness', 'contentedness', and 'calmness' (Bond & Lader, 1974) of which alertness was of main interest. The scores on the 9 items associated with the factor drowsiness were added and taken as dependent measure.

Baseline EEG

Subjects sat still with their eyes open for a 2-minute period during which baseline EEG was recorded. Thereafter, baseline EEG was again recorded, but now subjects had their eyes closed. The power (μV^2) of the delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and beta (12-30 Hz) frequency bands were taken as objective indicators of sedation and cortical activity.

Plasma samples

After taking a blood sample the catheter was cleaned in order to keep it open during the test day. The blood sample was centrifuged for five minutes at 4°C at 4000 rpm and Next, 1 ml plasma was frozen and stored at -80°C until quantitative amino-acid analysis by high-performance liquid chromatography was performed (Van Eijk, Rooyakkers, & Deutz, 1993).

For the L-tyrosine/L-phenylalanine depletion we assessed changes in total L-tyrosine and L-phenylalanine levels from baseline at T7 (i.e. around testing). L-tyrosine and L-phenylalanine are transported across the blood-brain barrier by a transport system that is active towards all the large neutral amino acids (LNAA). As there is competition between the various LNAA for transport into the brain, the brain concentration is best approximated by the ratio of the plasma concentration of an amino acid to the sum of the plasma concentration of all other LNAA (ΣLNAA). Therefore, we also calculated the L-tyrosine and L-phenylalanine/ ΣLNAA ratio for these time points. Although L-histidine is weakly basic it is transported into the brain by the same transport system as the LNAA (Oldendorf & Szabo, 1976; Pardridge, 1983) Therefore, for the L-histidine depletion, we assessed the change from baseline in total L-histidine and in L-histidine/ ΣLNAA ratio for T2, T4, T6 and T7. The T2, T4 and T6 measurements were added due to the unknown decrease in L-histidine levels over time.

CHAPTER 6

Event related potentials

EEG recordings

During performance on the cued simple reaction time task and choice reaction time task EEG was recorded to measure the P300, LRP and CNV ERPs. Dependent variables were the stimulus locked and response locked P300 amplitude and peak latencies, stimulus locked and response locked LRP onset and the surface under the CNV. EEG activity was recorded by means of an electrocap from an array of 32 electrodes from the standard 10-20 system (Jasper, 1957). All electrodes were filled with electrode-gel and were line referenced to the right mastoid electrode. Offline they were referenced to both left and right mastoids. The FPz electrode was used as ground electrode. Horizontal EOG was recorded using electrodes attached to the outer canthi of the eyes and vertical EOG was recorded from electrodes attached above and below the left or right eye and in line with the pupil.

All electrode impedances were kept below 5 k Ω . Signals were amplified using Neuroscan Synamps amplifiers and collected using Neuroscan software. All signals were sampled at a 1000 Hz and filtered online using a 100 Hz low-pass filter and a 0.05 Hz high-pass filter.

Signal analysis

Continuous signals obtained during the performance on the choice reaction time task were filtered off-line using a 1 Hz high-pass filter after which EEG was corrected for vertical and horizontal eye movements according to a procedure by (Semlitsch, Anderer, Schuster, & Presslich, 1986). Dependent variables from the choice reaction time task were duration of the interval (ms) between stimulus and P300 peak amplitude (S-locked P300) and between the response and the P300 peak amplitude (R-locked P300), and the interval between the stimulus onset and LRP onset (S-locked LRP) and the interval between the response and LRP onset (R-locked LRP). In addition, the amplitude of the S-locked and R-locked P300 was determined as a measure of resource availability for stimulus processing. The S-locked data were epoched in 1100 ms sweeps starting 100 ms before stimulus presentation and the interval between sweep onset and stimulus served as baseline. The R-locked data were epoched from 475 ms before to 625 ms after the response. For the analysis of the P300 all sampled EEG and EOG epochs were low pass filtered using a 3.6 Hz low-pass filter (Smulders, et al., 1995) and for the analysis of the LRP the data were filtered using a 11.1 Hz low-pass filter (Miller & Hackley, 1992). Sweeps containing artefacts exceeding +75 or -75 μ V on the Fz, Cz, Pz, Oz, C3, or C4 electrodes were rejected. This resulted in an average acceptance of 93% of the epochs.

CHAPTER 6

The length of the S-locked and R-locked intervals of the P300 were determined at the Cz electrode sites. The S-locked P300 latencies were determined as the time between onset of the stimulus and the latency of the largest local maximum using the Jackknife method (Miller, Patterson, & Ulrich, 1998; Ulrich & Miller, 2001). The amplitude was determined as the amplitude of that local maximum. The R-locked P300 intervals were determined as the time between the largest local maximum of the P300 component and the given response, also using the Jackknife method. The amplitude was determined as the amplitude of that local maximum.

LRPs were computed by subtracting C4 from C3, point by point, for right and left hand trials and subtracting left hand from right hand trials. The onset latencies of the S-locked and R-locked LRP waveforms were determined using the Jackknife scoring method with a 1 μ V absolute criterium (Miller, et al., 1998; Ulrich & Miller, 2001).

For the cued simple reaction time task, the CNV was determined in a window of 500 ms as a measure of response preparation. The data were first epoched and then low-pass filtered using a 30 Hz low-pass filter. The area report 500 ms before the beginning of the imperative stimulus was the dependent variable.

The power of the delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and beta frequency (13-30 Hz) bands were calculated by means of a fast Fourier transformation of the means of the midline electrodes (Fz, Cz and Pz).

Statistical analysis

All dependent variables were screened for normality of their distributions and no non-normalities were detected.

Baseline differences in blood-plasma levels of L-histidine, L-histidine/ Σ LNAAs ratio, L-tyrosine/L-phenylalanine and L-tyrosine + L-phenylalanine/ Σ LNAAs ratio were analysed using Analysis of Variance (ANOVA) for repeated measures with Treatment as within subject factor (BAL, HID, TYD). The blood-plasma levels at T7 were further analysed as changes from baseline ($\Delta T = T7 - T0$) with Treatment as within subject factor with 3 levels (BAL, HID, TYD). All significant ($p < 0.05$) Treatment effects were followed by two treatment-placebo contrasts. Additionally, due to the unknown pattern of decrease in plasma levels over time, the L-histidine levels and the L-histidine/ Σ LNAAs ratio in the HID condition were analysed with Time as a within subject factor with 5 levels (T0, T2, T4, T6 and T7). Significant ($p < 0.05$) effect of Time was followed by 4 simple contrasts with baseline (T0).

Within subject factors in the CRT were Stimulus Quality (SQ: intact, degraded) and Response Complexity (RC: simple, complex). Performance and ERP data from the CRT were analysed for main effects of Treatment

CHAPTER 6

(BAL, HID, TYD) and interactions of Treatment with SQ and RC using a 3x2x2 within subjects factorial model. F-values for differences in S-locked and R-locked LRP onset latencies were divided by $(n-1)^2$ to correct for the reduction of variance induced by the jackknife method (Ulrich & Miller, 2001). If overall multivariate F-tests indicated a significant main effect or interaction ($p < 0.05$), data were further analysed using two univariate drug-placebo contrasts.

Performance on the CTT, CNV surface area, subjective drowsiness scores and plasma levels were analysed for Treatment (3 levels) effects using repeated measures ANOVA. The power of each frequency band was analysed separately for effects of the treatments using a 3x3 within subject model with Treatment and Electrode (Fz, Cz and Pz) as factors when subjects held their eyes open and when they held their eyes closed. All data were analysed using SPSS for Windows (version 12.0.1).

RESULTS

Missing data

One subject was removed from the CNV data set due to incomplete data collection. The analysis was done on complete data sets from 15 subjects. Due to difficulties during blood sample collection several blood samples could not be drawn, resulting in 14 complete data sets for the TYD condition. Therefore, Treatment effects were analysed using 14 data sets. Data sets for the BAL and HID conditions contained 16 subjects. The changes from baseline in the HID condition were analysed using 16 data sets.

Blood-plasma levels

Table 2 displays the average absolute values of L-histidine and L-tyrosine/L-phenylalanine blood-plasma levels and L-histidine/ Σ LNAA and L-tyrosine+L-phenylalanine/ Σ LNAA ratio over time and their changes from baseline.

Blood-plasma levels of L-histidine, L-histidine/ Σ LNAA ratio, L-tyrosine/L-phenylalanine, L-tyrosine+L-phenylalanine/ Σ LNAA ratio did not differ in the three conditions at baseline ($F(2,12) = 2.0$, $p = 0.181$ and $F_s < 1$, respectively).

Treatment had a marginally significant main effect on the change from baseline in absolute L-histidine levels ($F(2,12) = 3.5$, $p = 0.063$). Treatment-placebo contrasts showed that decrease from baseline of L-histidine levels at T7 in the HID condition (20%) was larger as compared with the change in the BAL condition ($F(1,13) = 7.6$, $p = 0.017$). L-histidine levels did not decrease after treatment in the TYD condition ($F < 1$) as compared with the BAL condition. Treatment also had a main effect on the

CHAPTER 6

L-histidine/ Σ LNAAs ratio in blood ($F(2,12) = 19.0$, $p < 0.001$). The decrease from baseline in the HID condition (48%) was larger than the decrease in the BAL condition (12%) ($F(1,13) = 33.3$, $p < 0.001$). There was no significant difference in L-histidine/ Σ LNAAs ratio change from baseline between the TYD and BAL conditions ($F < 1$).

Table 2: Effects of treatments on amino acid levels ($\mu\text{mol/L}$). Means ($\pm$ SEM) of absolute values of L-histidine levels, L-histidine/ Σ LNAAs ratio, L-tyrosine/L-phenylalanine levels and L-tyrosine + L-phenylalanine/ Σ LNAAs ratio at baseline (T0) and the change from baseline after 7 hours (ΔT) after a balanced drink (BAL), L-histidine depletion (HID) and L-tyrosine/L-phenylalanine depletion (TYD) conditions. ¹ Indicates significant ($p < 0.05$) change from baseline as compared with placebo.

<i>Treatment</i>	Baseline (T0)			ΔT (T7-T0)		
	BAL	HID	TYD	BAL	HID	TYD
L-histidine	93.8 (7.1)	85.7 (7.8)	92.1 (8.0)	2.5 (5.2)	-17.1 (5.5) ¹	8.6 (9.7)
L-histidine/ Σ LNAAs ratio	0.18 (0.009)	0.17 (0.014)	0.18 (0.016)	-0.021 (0.013)	-0.083 (0.011) ¹	-0.003 (0.021)
L-tyrosine/L- phenylalanine	107.3 (6.0)	112.2 (10.3)	111.7 (9.2)	59.8 (12.7)	71.1 (10.6)	-61.0 (5.3) ¹
L-tyrosine+L- phenylalanine/ Σ LNAAs ratio	0.28 (0.018)	0.28 (0.008)	0.27 (0.013)	0.120 (0.021)	0.088 (0.019)	-0.159 (0.015) ¹

A significant main effect of Time in the HID condition indicated successful reductions in plasma L-histidine levels ($F(4,12) = 9.0$, $p < 0.001$). Levels were decreased at T4 (22%: $F(1,15) = 15.1$, $p < 0.001$), T6 (26%: $F(1,15) = 21.5$, $p < 0.001$) and T7 (20%: $F(1,15) = 11.0$, $p < 0.005$). L-histidine levels were not significantly reduced at T2 as compared to T0 ($F(1,15) = 1.9$, $p = 0.186$). A main effect of Time also indicated a reduction of L-histidine / Σ LNAAs ratio ($F(4,12) = 45.0$, $p < 0.001$). The ratio was reduced at T2 (58%: $F(1,15) = 70.1$, $p < 0.001$), at T4 (59%: $F(1,15) = 62.0$, $p < 0.001$), at T6 (46%: $F(1,15) = 37.0$, $p < 0.001$) and at T7 (36%: $F(1,15) = 14.4$, $p = 0.002$) (figure 1).

Figure 1: L-histidine/ Σ LNAAs ratio in blood-plasma over time as a measure of L-histidine depletion. * indicates significant changes from baseline (T0).

Treatment had a significant main effect on the change from baseline of absolute L-tyrosine/L-phenylalanine levels ($F(2,12) = 62.4$, $p < 0.001$). Treatment-placebo contrasts showed that L-tyrosine/L-phenylalanine levels decreased (55%) after treatment in the TYD condition as compared with the BAL condition ($F(1,13) = 96.5$, $p < 0.001$). The change from baseline in L-tyrosine/L-phenylalanine levels did not differ between the HID and BAL conditions ($F < 1$). Treatment also affected the change from baseline in L-tyrosine/L-phenylalanine/ Σ LNAAs ratio ($F(2,12) = 58.7$, $p < 0.001$). Treatment-placebo contrasts showed that there was a decrease of the ratio in the TYD condition (59%) at T7 as compared with the change BAL condition ($F(1,13) = 125.6$, $p < 0.001$). The change from baseline of the L-tyrosine/L-

CHAPTER 6

phenylalanine/ Σ LNAAs ratio did not significantly differ between the HID and BAL conditions ($F(1,13) = 2.2$, $p = 0.163$).

Choice Reaction Time Task

Table 3 shows means and standard errors of performance measures and ERPs from the choice reaction time task.

Behavioural performance

Both SQ and RC affected response times ($F(1,15) = 53.8$, $p < 0.001$ and $F(1,15) = 5.9$, $p = 0.028$, respectively), but did not interact with each other ($F < 1$). Treatment did not affect reaction time and did not interact with SQ or RC ($F_s < 1$).

Accuracy of the responses was significantly decreased by stimulus degradation ($F(1,15) = 10.5$, $p = 0.006$), but RC had no effect ($F(1,15) = 1.6$, $p = 0.230$). Effects of SQ and RC did not interact ($F(1, 16) = 2.6$, $p = 0.130$). Treatment did not affect accuracy ($F(2, 14) = 1.8$, $p = 0.189$) and did not interact with SQ ($F < 1$) or RC ($F(2, 14) = 1.7$, $p = 0.222$).

P300

SQ significantly delayed the S-locked P300 peak latency ($F(1,15) = 8.0$, $p = 0.013$), whereas it tended to be shortened by RC ($F(1,15) = 4.1$, $p = 0.061$). Treatment did not affect the P300 peak latency ($F(2,14) = 1.7$, $p = 0.213$.) and did not interact with SQ or RC ($F_s < 1$). SQ, RC and Treatment did not affect the R-locked P300 peak latency ($F(1,15) = 2.3$, $p = 0.154$, $F(1,15) = 2.0$, $p = 0.176$ and $F(2,14) = 1.9$, $p = 0.182$, respectively).

Table 3: Summary of the data derived from the Choice Reaction Time Task after L-histidine depletion (HID), L-tyrosine/L-phenylalanine depletion (TYD) or the balanced (BAL) drink administration. Significant or near significant main effects or interaction are indicated with bold p value. Significant ($p < 0.05$) differences in effects of Response Complexity (RC) after HID or TYD as compared with BAL are indicated with ¹

[illegible]

latency (ms)	0.181	0.610	0.641						
Simple				-19 (0.7)	-29 (0.6)	-15 (0.8)	-34 (0.9)	-10 (0.7)	-20 (0.7)
Complex				-59 (-1.9)	-61 (1.4)	-42 (1.1)	-73 (3.5)	-34 (1.3)	-43 (2.4)
amplitude (μV)	0.965	0.025	0.8617						
Simple				5.0 (0.06)	4.5 (0.07)	5.2 (0.04)	3.9 (0.05)	4.6 (0.05)	4.8 (0.06)
Complex				2.6 (0.06)	2.1 (0.06)	2.6 (0.06)	2.1 (0.05)	2.7 (0.06)	2.2 (0.06)
<i>S-locked LRP</i>									
onset (ms)	0.336	0.218	0.286						
Simple				252 (0.5)	269 (0.8)	253 (1.0)	344 (3.5)	270 (0.5)	305 (2.0)
Complex				247 (0.7)	303 (0.7)	279 (0.7)	309 (1.2)	271 (0.5)	272 (0.5)
<i>R-locked LRP</i>									
onset (ms)	0.103	0.880	0.068						
Simple				-152 (0.9)	-152 (1.5)	-131 (0.7)	-118 (0.8)	-122 (0.7)	-124 (0.5)
Complex				-167 (1.2)	-172 (1.0)	-176 (1.2) ¹	-183 (1.6) ¹	-146 (0.5)	-152 (0.8)

CHAPTER 6

Figure 2: Effects of treatments of the R-locked LRP onset latency. L-tyrosine/L-phenylalanine depletion decreased the interval between the R-locked LRP and response. L-histidine depletion interacted with RC and increased the interval prolonging effect.

CHAPTER 6

S-locked P300 peak amplitude was significantly suppressed by RC ($F(1,15) = 25.2, p < 0.001$). Treatment tended to interact with RC ($F(2,14) = 3.4, p < 0.063$), which was due to an enhanced amplitude suppressing effect of RC after HID ($F(1,15) = 6.8, p < 0.002$) SQ and Treatment did not have main effects on the peak amplitude ($F(1,15) = 1.7, p = 0.213$. and $F < 1$, respectively) and did not interact ($F < 1$). The R-locked P300 amplitude was significantly suppressed by SQ and RC ($F(1,15) = 4.7, p = 0.046$ and $F(1,15) = 16.2, p < 0.001$, respectively), but Treatment did not decrease the amplitude ($F < 1$). However, Treatment interacted with SQ ($F(2,14) = 4.9, p = 0.025$). Drug-placebo contrasts did not reveal any differences with BAL, however (HID: $F(1,15) = 1.2, p = 0.285$, TYD: $F(1,15) = 1.7, p = 0.210$).

LRP

The interval between the stimulus and onset of the LRP (i.e. S-locked LRP onset latency) was delayed by decreased SQ ($F(2,14) = 7.9, p < 0.013$). Treatment and RC had no effect ($F(2,14) = 1.2, p = 0.336$ and $F < 1$, respectively) and Treatment did not interact with SQ ($F(2,14) = 1.7, p = 0.218$) or RC ($F(2,14) = 1.4, p = 0.286$). SQ and RC also did not interact ($F < 1$).

The interval between the response and LRP onset (i.e. R-locked LRP onset) was increased by increased RC ($F(1,15) = 13.8, p = 0.003$),. Treatment tended to interact with RC ($F(2,14) = 3.3, p = 0.068$), HID enhanced the effect of RC ($F(1,15) = 6.8, p = 0.020$) by increasing the interval between the LRP-onset and the response in case of a complex response (figure 2). Treatment ($F(2,14) = 2.68, p = 0.106$) did not have a main effect on the R-locked LRP onset. Nevertheless, drug-placebo contrasts showed that TYD decreased the interval between the R-locked LRP-onset and the response ($F(1,15) = 5.1, p = 0.039$). SQ had no effect on the R-locked LRP onset and did not interact with Treatment ($Fs < 1$).

Cued Simple Reaction Time Task

Simple reaction time and associated area under the Contingent Negative Variation did not differ between treatments ($F < 1$ and $F(2,13) = 1.3, p = 0.314$, respectively)(table 4).

Critical Tracking Task

Treatment had no significant main effect on the average tracking performance ($F(2,14) = 2.5, p = 0.115$) (table 4).

Drowsiness

Visual Analogue Scale

Treatment had no significant effect on subjective alertness ($F < 1$) (table 4).

CHAPTER 6

Table 4: Mean ($\pm$ SEM) performance scores on electrophysiological and behavioural measures. Simple Reaction Time task and Critical Tracking Task performance, and subjective alertness after the balanced drink (BAL), L-histidine depletion (HID) and L-tyrosine/L-phenylalanine depletion (TYD). There were no significant differences between the treatments.

	Treatment		
	BAL	HID	TYD
<i>Simple Reaction Time task</i>			
CNV surface area (μV^2)	4.4 (1.1)	3.3 (1.6)	5.2 (1.1)
Reaction time (ms)	260 (13.6)	272 (68.3)	250 (42.6)
<i>Critical Tracking Task</i>			
Lambda (rad/s)	3.7 (0.1)	3.8 (0.2)	3.6 (0.2)
<i>Visual Analogue Scale</i>			
Alertness (mm)	608 (39)	593 (41)	610 (38)

Frequency band power

Treatment did not affect the power of the delta ($F(2,14) = 1.9$, $p = 0.184$), theta and alpha ($F_s < 1$) and beta ($F(2,14) = 2.9$, $p = 0.091$) frequency bands when subjects held their eyes open. When subjects held their eyes closed Treatment also did not affect the power of the delta, theta, alpha ($F_s < 1$) and beta ($F(2,14) = 2.9$, $p = 0.092$) frequency bands (table 5).

Table 5: Mean ($\pm$ SEM) frequency band power (μV^2). Power for Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-12 Hz) and Beta (12-30 Hz) frequency bands at the Fz, Cz and Pz electrodes in eyes open closed conditions were not affected by L-histidine depletion (HID) and L-tyrosine/L-phenylalanine depletion (TYD) as compared with the balanced drink (BAL).

<i>Frequency</i>		Eyes open			Eyes closed		
		BAL	HID	TYD	BAL	HID	TYD
Delta power	Fz	12.2 (0.90)	12.3 (1.01)	14.1 (1.41)	18.6 (2.52)	17.0 (1.80)	20.3 (2.83)
	Cz	12.2 (0.78)	12.8 (0.99)	13.9 (1.02)	17.2 (2.05)	16.8 (1.61)	19.0 (1.74)
	Pz	12.0 (0.93)	12.8 (1.17)	13.6 (1.15)	15.9 (2.40)	14.7 (1.45)	16.6 (1.73)
Theta power	Fz	10.6 (1.07)	9.8 (1.14)	10.7 (1.40)	12.4 (0.90)	11.1 (1.13)	11.8 (1.35)
	Cz	9.5 (0.56)	9.8 (0.80)	10.0 (0.88)	12.9 (1.18)	11.8 (1.21)	12.7 (1.52)
	Pz	7.7 (0.55)	7.8 (0.63)	7.9 (0.69)	11.1 (1.38)	10.2 (1.11)	10.8 (1.39)
Alpha power	Fz	6.8 (0.95)	6.7 (1.22)	7.2 (1.29)	15.2 (2.66)	14.1 (2.99)	13.3 (2.40)
	Cz	8.2 (1.50)	8.0 (1.52)	8.5 (1.73)	19.4 (3.94)	18.6 (4.09)	17.0 (3.20)
	Pz	11.0 (2.14)	10.5 (2.48)	11.2 (2.56)	29.8 (6.71)	29.4 (7.51)	27.5 (5.88)
Beta power	Fz	1.3 (0.12)	1.2 (0.12)	1.4 (0.18)	1.7 (0.18)	1.5 (0.16)	1.7 (0.21)
	Cz	1.3 (0.13)	1.3 (0.12)	1.5 (0.18)	1.8 (0.19)	1.7 (0.17)	2.0 (0.21)
	Pz	1.5 (0.16)	1.3 (0.18)	1.5 (0.20)	2.3 (0.33)	2.1 (0.29)	2.2 (0.24)

DISCUSSION

The aim of the present study was to decrease histamine levels in the brain by depleting subjects of its precursor L-histidine. In order to observe that, we determined if HID would exert effects that are comparable to those seen in other methods of reduced histamine activity (e.g. H₁-blockade). To evaluate the hypothesised behavioural effects the neurophysiological consequences of precursor depletion needs to be considered. This can only be done based on observations concerning peripherally measured effects of the treatments. Results showed that, L-histidine levels in blood-plasma were successfully reduced by more than 20% from T4 to T7. The L-histidine/ Σ LNAAs ratio was maximally reduced by approximately 59% at T4 and by approximately 36% at T7. HID affected response related processes as shown with the significant interaction with RC as measured with the R-locked LRP onset latency and enhanced the amplitude suppressing effect of RC on the S-locked P300. However, L-histidine depletion did not significantly affect performance as measured with speed and accuracy in the CRT task, simple RT task or the CTT. In addition, HID did not significantly affect subjective and objective measures of alertness and arousal, such as mood and EEG power spectrum.

HID increased the duration of the interval between the LRP onset and response indicating increased time needed for more complex response programming. In addition, HID increased the effects of complex responses on the P300 amplitude indicating that increased response demands reduces resources available for stimulus processing (Beauducel, Brocke, & Leue, 2006; Kok, 1990). These effects were unexpected as a previous study (Van Ruitenbeek, Vermeeren, Smulders, Sambeth, Riedel, *In press*) showed that the H₁-antagonist dexchlorpheniramine enhanced the effect of stimulus degradation on S-locked P300 peak latency, whereas no effects on motor processes were found. The effects on processing of visual stimuli are in line with the observation that the visual cortex and other visual regions (e.g. LGN, superior colliculus) are densely innervated by histamine fibres (Manning, Wilson, & Uhlich, 1996). In contrast, less H₁-receptors are located in motor structures like the caudate putamen and globus pallidus of the basal ganglia of the guinea-pig brain (Bouthenet, Ruat, Sales, Garbarg, & Schwartz, 1988). However, we did not observe effects of HID on stimulus related processes in this study, suggesting that blocking the H₁-receptor and decreasing histamine availability and hence histamine release may have qualitatively different effects. A possible explanation is that L-histidine depletion affects the action of histamine on H₁, H₂, H₃ and H₄ receptors as opposed to solely H₁-blockade.

The involvement of histamine in motor processes is supported by animal studies in which the histamine synthesizing enzyme histidine

CHAPTER 6

decarboxylase (HDC) is depleted. For example, Brabant, et al. (2007) found that cocaine induced hyperactivity is reduced in HDC knock-out mice. In contrast, other authors found that the methamphetamine induced typical locomotor hyperactivity was facilitated in HDC knock-out mice (Iwabuchi, et al., 2004; Kubota, et al., 2002) and after administration of a H₁-antagonist (Ito, Onodera, Watanabe, & Sato, 1997). As methamphetamine and cocaine increase dopamine activity it may be suggested that histamine interacts with dopamine. Several mechanisms of interaction have been suggested, like interactions with the GABA neurotransmitter system (Kubota, et al., 2002), and dopamine transporter (Matsunaga, et al., 1998). However, a study assessing the latter hypothesis could not confirm this (Theunissen, van Kroonenburgh, van Deursen, Blom-Coenjaerts, & Ramaekers, 2006). Taken together it is suggested that histamine in the brain plays a role in motor processes, which may be mediated by dopamine. However, the exact mechanism is not clear.

The few significant effects on sensitive measures of psychomotor performance and sedation in this study call into question whether L-histidine depletion has effectively decreased histamine levels in the brain in this study. The analyses of the blood samples taken between T4 and T7 showed that L-histidine levels in the blood-plasma decreased by more than 20%. In comparison, the effects of TYD on L-tyrosine/L-phenylalanine level were more pronounced as shown by a reduction of approximately 55%. However, brain concentration of L-histidine is best approximated by the L-histidine/ Σ LNAA ratio as various LNAA are competitively transported across the blood brain barrier. Analyses showed that the maximal reduction in L-histidine/ Σ LNAA was 59%, which was similar to the maximal decrease in L-tyrosine + L-phenylalanine / Σ LNAA ratio. Compared with reductions in L-tyrosine/L-phenylalanine found in previous studies showing functional impairments (70-80%), reductions in L-histidine concentrations in the present study were only slightly lower (Leyton, et al., 2000; McTavish, et al., 1999; Montgomery, et al., 2003). The relationship between the decreased L-histidine availability in the brain and the decrease in histamine levels are yet unknown. It may be speculated that histamine stores were not yet fully depleted at time of testing and that the stored histamine was used during testing. Depletion of the stored histamine and the effect on behavioural measures may have occurred later. We suggest that in future studies behavioural performance should be assessed over a longer period of time to establish the time of maximal behavioural impairment.

It may be argued that the effects found in this study are due to a non-specific effect of amino imbalance. This is unlikely, however. A similar issue was raised concerning tryptophan depletion. It was shown that acute lysine depletion has no effect on mood and cognition in humans, unlike tryptophan depletion (Klaassen, Riedel, Deutz, van Someren, & van Praag,

CHAPTER 6

1999). In addition, in rodents histamine metabolism can be altered more by changes in precursor availability than can be done with any other neurotransmitter (Young, 1996). Therefore, the effects of HID found in this study might be attributed to small changes in histamine release. To account for the limited effect of HID that we found, it may be argued that a decrease in histamine release may not occur in all brain areas. Neurotransmitter release can be regulated differentially in different brain areas and small changes in histamine synthesis may lead to an inhomogeneous decrease of histamine release.

Surprisingly, TYD decreased the interval between the LRP and the response, indicating increased motor processing capacity. However, TYD did not affect the CNV and performance on the CTT and the CRT as measured with reaction time. Studies applying the L-tyrosine/L-phenylalanine depletion method are inconsistent regarding their results. Some studies showed impaired performance (Harmer, et al., 2001; Harrison, et al., 2004) and altered mood (Leyton, et al., 2000), while others did not observe such effects (Lythe, Anderson, Deakin, Elliott, & Strickland, 2005); (McLean, Rubinsztein, Robbins, & Sahakian, 2004). It has been suggested that the inconsistencies are due to large variability between subjects in brain dopamine availability. Mehta, Gumaste, Montgomery, McTavish, & Grasby (2005) showed that subjects who performed worse on a delayed response task and a planning task also showed the greatest reductions in dopamine levels in the striatum. It may be that there were many non-sensitive subjects in this study.

To conclude, this was the first study that attempted to decrease histamine levels in the brain by L-histidine depletion in order to study the role of histamine in cognitive performance. The importance of using different methods to study the involvement of histamine in cognitive deficits needs to be stressed. Moreover, to study the involvement of histamine in cognition the effects of L-histidine depletion are at least as important as studying the effects of H₁-blockade on cognitive performance. In this study, contrary to our expectations, HID had an impairing effect on motor related processes, suggesting that histamine is involved in more than sensory processing, which is affected by H₁-blockade. However, HID did not impair psychomotor performance as measured by the CTT and reaction times and did not cause sedation as indicated by subjective and objective measures. The absence of effects may be explained by the small changes in histamine release.

CHAPTER 6

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CHAPTER 6

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CHAPTER 6

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CHAPTER 6

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CHAPTER 7

GENERAL DISCUSSION

CHAPTER 7

CHAPTER 7

GENERAL DISCUSSION

The aim of the present dissertation was to gain knowledge about the role that the neurotransmitter histamine plays in human cognition. Studies described in this dissertation were done in order to discover which cognitive processes are affected when the histaminergic system is manipulated. The manipulations consisted of H₁-blockade using first and second generation antihistamines and depletion of the histamine precursor L-histidine. In this final chapter, an attempt is made to provide a coherent view on the role of histamine in cognition. Second, an attempt is made to relate the effects of different histaminergic manipulations to symptoms seen in clinical disorders in which histamine has shown to be involved and the possibility to model these impairments.

Histamine and cognition

Up until now evidence for the role of histamine in cognition is mainly derived from animal studies in which histaminergic activity is decreased by H₁-receptor blockade [e.g. (Kamei, Chung, & Tasaka, 1990)], H₁-receptor knock-out [e.g. (Yanai, Son, Endou, Sakurai, & Watanabe, 1998)] or knock-out for the histamine synthesizing enzyme histidine decarboxylase [e.g. (Brabant, et al., 2007; Iwabuchi, et al., 2004)]. Decrease in histaminergic activity leads to impaired performance on a plethora of cognitive tasks. In this dissertation, it is attempted to provide evidence for the role of histamine in human cognitive performance.

In the review of the literature on the effects of central H₁-receptor blockade on cognitive performance in humans is provided in chapter 1. It was concluded that alertness as measured either subjectively or objectively, psychomotor performance and driving performance were greatly affected by sedative first generation antihistamines. It seemed that tasks assessing more specific functions, or at least emphasizing specific functions, showed that both sensory and motor processes were affected after intake of the H₁-antagonist. Memory performance was also affected, but the effects seemed to be limited to those on working memory. Episodic and semantic memory functions were hardly affected by the drugs. The first experimental study described in this dissertation used a test battery to determine the pattern of the effects as described in the review. Indeed, it was established that psychomotor performance is impaired, alertness is decreased, but memory remained unaffected.

CHAPTER 7

Memory

From the review of the literature it was suggested that processing speed is decreased which leads to impaired working memory as measured using tasks like the N-back task and Sternberg's memory scanning task. The dependent measures often rely on speed of responses, which may be slowed due to impaired sensory and/or motor processes. This type of slowed information processing does not necessarily affect the functional integrity of human memory performance i.e. correctly recalling words which may be irrespective of speed, and therefore effects on episodic memory and semantic memory may have been hardly found. In addition, the results from the study investigating the effects of cetirizine showed impaired performance on Sternberg's memory scanning. The slope of the regression line of reaction time on memory load was increased after cetirizine administration. Therefore, cetirizine caused a slowing in mental scanning of digits held in memory, which does indicate impaired central processing speed.

In the first experimental study, it was hypothesized that the H₁-antagonist dexchlorpheniramine would affect memory performance. However, results showed a lack of effects on memory. The active control drug scopolamine also failed to affect memory performance. Formally, the possibility remained that the study was unable to show drug induced memory impairments. Secondly, although the evidence for a lack of effects of H₁-antagonists found on memory performance now seemed to pile up, there were still studies that reported such effects. Therefore, the presence of antihistaminergic effects on memory remained ambiguous.

To finally test whether antihistamine induced memory impairments and the effects are independent of sedation the study described in chapter 4 was conducted. In this study, the effects of H₁-antagonism on objective and subject alertness and memory performance were measured. This study clearly showed that the antihistamine dexchlorpheniramine decreased alertness, while memory was not affected. At the same time, the benzodiazepine affected both alertness and memory. However, the effect of the benzodiazepine on alertness was much larger than that of dexchlorpheniramine. Therefore, effects sizes were calculated which showed that the difference between the effects on alertness was much smaller than the difference between the effects on memory. Therefore, it was finally concluded that histamine H₁-antagonism does not affect memory.

The lack of impairments after histamine H₁-receptor blockade is in sharp contrast with the effects found of H₃-antagonist in animal studies. Many studies have shown that memory performance improves when animals are treated with these drugs. In addition to its function as an autoreceptor the H₃-receptor also functions as a heteroreceptor and blocking the receptor causes disinhibition of other monoamine transmitter release (Esbenshade et al., 2008). It has been suggested that there is a close interaction

CHAPTER 7

between acetylcholine and the H₃-receptor (Blandina 2004). Acetylcholine is known to be a very important mediator in memory functioning. Consequently, H₃-antagonism and not H₁-antagonism may lead to disinhibition of acetylcholine, which mediates the memory enhancing effects.

Alternatively, animal models for cognitive deficits may not accurately predict impaired functioning in humans. The organisms are not functionally similar. For example, when modelling memory impairments in rodents, memory in these animals is highly dependent on the hippocampus, while humans are able to use more strategies (e.g. use of language) and, therefore, brain structures. Humans may, therefore compensate for their impairment. This may result in a higher sensitivity of rats for effects on memory.

Sensory related processes

Our studies and those of others consistently show that psychomotor functioning is impaired by antihistamine drugs. In the study described in chapter 6 we attempted to determine what underlying cognitive processes are impaired following H₁-blockade. Using the additive factor method and psychophysiological measures, we found that the effects of visual degradation of a stimulus are enlarged by dexchlorpheniramine. This suggested that sensory, i.e. visual processes were affected by H₁-blockade. These findings may be explained by the observation that the visual cortex and other visual regions (e.g. LGN, superior colliculus) are densely innervated by histaminergic fibres (Manning, Wilson, & Uhlich, 1996). However, the study described in chapter 5 did not reveal effects on visual information processing as measured using a vigilance task. Using this task a stimulus discrimination index and response criterion were calculated. These measures are related to input and output processes, respectively. The previously observed effects on sensory processing suggested that the discrimination index would indicate impaired performance after H₁-blockade, while the response criterion would not. We did not observe any such effects, however. The lack of effects may be explained by the fact that a second generation antihistamine was used. Although these drugs have been shown to penetrate the blood brain barrier, they do so to a lesser extent than the first generation antihistamines and hence may only induce subtle effects.

Motor related processes

L-histidine depletion, described in chapter 7, caused the slowing of motor related processes. This effect was evidenced by the L-histidine depletion induced enlargement the response complexity effect as measured with the Lateralized Readiness Potential (LRP). The interval between this electrophysiological potential and the response indicates the duration of the processes needed for the preparation of the response. When subject are required to give a more complex response, i.e. pressing three buttons in a

CHAPTER 7

predefined sequence, the interval between the pressing of the first button and the LRP increases. More time is needed to program the more complex response. Treatments affecting the programming, therefore, cause an increase in the response complexity effect on the LRP-response interval. The effect of L-histidine depletion suggests that low level of histamine affects the response preparation process. This effect in contrast with that of H₁-antagonism and was unexpected. Compared with other brain areas less H₁-receptors are located in motor related structures of the guinea-pig brain like the caudate putamen and globus pallidus of the basal ganglia (Bouthenet, Ruat, Sales, Garbarg, & Schwartz, 1988), which possibly explains the lack of effects of H₁-blockade on motor related processes. A possible explanation for the effects of L-histidine depletion on motor related processes may be that the histaminergic system interacts with other transmitter systems. For example, the dopaminergic system is well known for its involvement in motor related functions. As the depletion of L-histidine likely affects more receptors than just the H₁ receptor i.e. H₃-receptor, it may be that dopamine is disinhibited by a decrease in H₃ activation.

Histamine based models

As has been discussed in the introduction, histamine is suggested to be involved in the cognitive impairments seen in clinical disorders like Alzheimer's disease [e.g. (Higuchi, 2000)], schizophrenia [e.g. (Nakai, et al., 1991)], Attention Deficit Hyperactivity Disorder (Komater, et al., 2005; Peled, Carraso, Globman, & Yehuda, 1997), depression (Akhtar, Pillai, & Vohora, 2005; Kano, et al., 2004), Parkinson's disease [e.g.(Anichtchik, Rinne, Kalimo, & Panula, 2000; Rinne, et al., 2002)] and Wernicke-Korsakoff's syndrome [for review see: (Onodera, Yamatodani, Watanabe, & Wada, 1994)]. Evidence for a possible treatment of these disorders comes from animal studies in which histamine functioning is increased using H₃-antagonists. Many studies show that cognitive performance is improved in animal models for these clinical disorders after the administration of H₃-antagonists [for reviews see: (Esbenshade, Fox, & Cowart, 2006; Leurs, Blandina, Tedford, & Timmerman, 1998; Vohora, 2004; Wijtmans, Leurs, & de Esch, 2007; Witkin & Nelson, 2004)]. It is therefore expected that increasing histaminergic activity in humans suffering from such disorders leads to improved cognitive functioning. In order to be able to quickly test the coming H₃-antagonist drugs a model for cognitive impairments following histaminergic dysfunction is highly useful.

Alzheimer's disease

Several studies have suggested that histamine plays an important role in Alzheimer's disease [e.g.(Airaksinen, Paetau, et al., 1991; Airaksinen,

CHAPTER 7

Reinikainen, Riekkinen, & Panula, 1991; Higuchi, 2000; Panula, et al., 1998) for a review see: (Onodera, et al., 1994)]. In addition, a large number of studies have shown that H₃-receptor blockade in animals leads to improved memory performance [e.g. (Bernaerts, Lamberty, & Tirelli, 2004; Medhurst, Atkins, et al., 2007; Medhurst, Briggs, et al., 2007; Miyazaki, Imaizumi, & Onodera, 1995; Molinengo, Di Carlo, & Ghi, 1999) for reviews see: (Esbenshade, et al., 2006; Leurs, et al., 1998; Vohora, 2004; Witkin & Nelson, 2004)]. Alzheimer's disease is characterized by cognitive impairments of which impaired memory is the most prominent. However, in this dissertation we were unable to show that central H₁-blockade affects memory performance. Therefore, H₁-blockade is not suitable as model for memory impairments as present in Alzheimer's disease.

Schizophrenia

Histamine has been suggested to be involved in the pathogenesis of schizophrenia (Onodera, et al., 1994). For example, Prell, et al. (1995) found increased levels of the histamine breakdown product, tele-methylhistamine, in the cerebrospinal fluid of schizophrenia patients suggesting increased histamine turn-over. They concluded that the increase could not be attributed to the medication taken, as patients who received antipsychotics and patients withdrawn from antipsychotic drugs displayed similar levels of the metabolite. Conventional antipsychotic medication has a high affinity for the H₁ receptor and blocks this receptor (Buckley, 2007), whereby it decreases histaminergic activity, which possibly explains some therapeutic effects. In addition, Nakai et al. (1991) and Iwabuchi et al. (2005) found decreased binding to the histamine H₁ receptor in the frontal cortex of schizophrenia patients, which indicates a decreased number of histamine H₁ receptors in these patients. Taken together, these findings suggest role for histamine in schizophrenia.

Patients suffering from schizophrenia show impaired sensory gating which holds that irrelevant information is not filtered out causing a sensory overload (Geyer, Krebs-Thomson, Braff, & Swerdlow, 2001). Impaired sensory gating can be modelled using the pre-pulse inhibition of the startle response. Normally the startle response is inhibited when the stimulus is preceded by a pre-pulse stimulus. Patients suffering schizophrenia show no, or less, inhibition of the startle response. In animal models increasing histamine release using H₃-antagonists attenuates the response to the same degree as antipsychotics (Browman, et al., 2004; Fox, et al., 2005; Ligneau, et al., 2007). In addition, H₁-knock-out mice and mice treated with an H₁-antagonist also showed attenuated prepulse inhibition behaviour (Dai, et al., 2005; Roegge, Perraut, Hao, & Levin, 2007), suggesting that histamine is involved in defective early sensory processing. The present dissertation has shown that histamine is involved in human sensory processing. More

CHAPTER 7

specifically, H₁-blockade leads to impaired feature extraction in sensory information processing. In the context of histamine possibly being involved in the sensory impairment as seen in schizophrenia, the effects of H₁-blockade and other histaminergic manipulations need to be tested in sensory gating paradigms like the pre-pulse inhibition paradigm. Nevertheless, the present results support the hypothesis that H₁-antagonism may be involved in schizophrenic symptomatology.

Parkinson's disease

Parkinson's disease is characterized by a neurodegeneration of the dopaminergic cells in the substantia nigra. The loss of cells leads to impaired motor control and cognitive disturbances (Feinberg & Farah, 1997). The histaminergic system densely interacts with the affected dopaminergic system (Anichtchik, et al., 2000). It has also been shown that Parkinson's disease patients exert high levels of histamine in the brain (Rinne, et al., 2002). In addition, the administration of L-histidine in rats (Maslinski, Lebrecht, Nowak, Pilc, & Wieczorek-Fila, 1973) and histamine in mice (Onodera, 1991) results in catalepsy like behaviour. Therefore, alterations in histamine lead to Parkinson's disease like motoric disturbances. Results from the experiment in which the effects of L-histidine depletion were studied showed that the programming of the response was affected by the treatment i.e. slowed by L-histidine depletion. The decreased levels of L-histidine presumably have led to low levels of histamine in the brain and may have exerted effects that resemble the symptoms in Parkinson's disease. It may be suggested that L-histidine depletion is a model for motoric disturbances in Parkinson's disease. However, the experiment described in chapter 7 was the first to apply this method and measure the effects on behaviour. Further studies need to confirm and elaborately study the effects of L-histidine depletion.

CONCLUSION

Taken together the histamine system appears to be involved in arousal regulating processes as evidenced by the effects of H₁-antagonism on objective and subjective measures of sedation. These studies also show that the histamine system is involved in psychomotor performance. Deficits in clinical disorders in which psychomotor performance is impaired or in which a decrease in arousal occurs can be modelled using H₁-antagonists. More specifically, H₁-antagonism may be a suitable model for disorders in which impaired sensory processes occur, like schizophrenia. H₁-antagonists do not affect memory performance. Therefore, H₁-antagonists are not suitable to be used as a model for histamine based memory impairment. Decreasing histamine levels centrally by L-histidine depletion slows motor

CHAPTER 7

related processes. Although further investigation is needed to study the effects of L-histidine depletion, it does appear to be promising as a model for disorders in which motor related processes are affected, like Parkinson's disease.

CHAPTER 7

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CHAPTER 7

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SUMMARY

SUMMARY

SUMMARY

SUMMARY

Pharmacological treatments of cognitive deficits across several clinical disorders are largely unsuccessful. Therefore, the search for new drugs continues. It has been suggested that histamine may play a large role in cognitive deficits seen in disorders like Alzheimer's disease, schizophrenia, Parkinson's disease and Attention Deficit Hyperactivity Disorder. Histamine is a monoamine neurotransmitter, which functions through its action at H₁, H₂, H₃ and H₄ receptors. Activation of the H₁-receptor leads to excitatory transmission, while activation of the H₃-receptor inhibits histaminergic activity.

Results from animal studies show that blocking the H₃-receptor improves performance on cognitive tasks, especially learning and memory. The so-called H₃-antagonists may be used as new treatments for cognitive impairments seen in clinical disorders. Before long-term patient studies are done to test the efficacy of these treatments, screening in human subjects in earlier stages of development may be very useful. Such a screening could be done in healthy volunteers using models of cognitive impairments such as induced by histamine dysfunction. The aim of this dissertation is to determine what role histamine plays in cognition and to determine which histaminergic manipulations in human subjects are suitable as tools to probe cognitive function.

An example of such a manipulation is pharmacological blocking of H₁-receptors, which may be used in healthy volunteers as a model for histaminergic dysfunction seen in clinical disorders. Many studies have tested the effects of H₁-antagonists on different cognitive domains.

In chapter 1, the literature is reviewed of papers describing the effects of centrally active H₁-antagonists. The review of 70 experimental studies on the performance effects of H₁-antagonists revealed that psychomotor performance is the most likely domain to be impaired. The affected cognitive processes underlying these impairments are largely unexplored. However, results from tasks assessing perceptual functions show that these are impaired and may at least contribute to the performance impairments such as those seen in psychomotor performance.

Performance on memory tasks after the administration of H₁-antagonists is frequently impaired when assessed using working memory tasks. However, results of such tasks may be confounded by slowed sensorimotor processing speed. Episodic memory relies less on sensorimotor speed and is less frequently impaired. However, episodic memory has only relatively scarcely been studied.

It is concluded in chapter 1, that H₁-antagonists may serve as a model for psychomotor impairment associated with reduced histaminergic

SUMMARY

activity. The underlying affected cognitive subprocesses and memory functions need to be investigated further.

In chapter 2, one of the main questions which emerged from the review discussed in chapter 1 was operationalized into an experiment in which H₁-antagonists were administered to healthy volunteers while cognitive functions, in particular memory, were assessed.

Twenty healthy young (aged 18-45 years) females participated as volunteers. Subjects received oral doses of the first generation antihistamine dexchlorpheniramine 2 mg, 4 mg, the muscarinic antagonist scopolamine 1 mg and placebo according to a double-blind, placebo-controlled, 4-way cross-over design. Treatment effects on cognition were assessed using tasks probing learning and memory, psychomotor performance, attention and subjective alertness. These were measured before-, 2 and 4 hours after drug intake

The centrally active antihistamine dexchlorpheniramine impaired performance on spatial learning, reaction time, tracking and divided attention but showed no effects on working memory, visual memory, word learning or memory scanning. However, scopolamine induced a similar pattern of effects, i.e. psychomotor impairment, but no effects on memory. As this was the active control drug a possible concern was that memory tasks were not sensitive in this study, even though the tasks shown to be sensitive to drug effects in other studies.

It was concluded that both dexchlorpheniramine and scopolamine clearly impaired performance on psychomotor and attention tasks. In contrast, learning and memory remained unaffected.

The question whether H₁-antagonists affect memory performance in humans was again put to the test in chapter 3. Animal studies suggest a role of histamine in memory, but studies in humans are scarce and produce conflicting results. Studies that have found effects of H₁-antagonists may have done so due to its sedative effects. Conversely, some studies that have not found effect on memory performance suffer from methodological issues. The aim of this study was to dissociate the effects of a centrally active antihistamine on memory performance and sedation.

Oral doses of dexchlorpheniramine 4 mg, lorazepam 1 mg or placebo were administered to eighteen healthy volunteers (9 male, 9 female) aged 18-45 years, according to a double-blind, placebo-controlled, 3-way cross-over design. The effects of the treatments on memory performance were assessed between 1.5 and 2.5 hours after drug administration using a 30-Words Learning Task, an N-Back task and Event Related Potentials (ERPs). Sedation was measured objectively and subjectively using visual analogue scales and electroencephalography (EEG).

The active control drug clearly showed effects on memory performance as indicated by both behaviour and ERPs. In contrast,

SUMMARY

dexchlorpheniramine did not affect memory performance, while both treatments clearly induced sedation. These results confirmed that H₁-blockade has a sedative effect, but does not affect memory in humans.

Previous chapters used the so-called first generation H₁-antagonists to investigate what role histamine plays in cognition. The drawback of these particular H₁-antagonists is that they are mostly non-selective for the H₁-receptor. The second-generation antihistamines are far more selective, but a general claim is that they do not, or to a lesser extent, cross the blood brain barrier. However, cetirizine has been shown to induce cognitive impairments and, therefore, may be capable to cross the blood brain barrier. Cetirizine may be used as a tool drug to model cognitive deficits associated with histamine hypofunction. However, there is inconsistency regarding dose and time after administration after which the behavioural effects occur.

In chapter 4, the effects of cetirizine on cognitive performance were measured by treating eighteen healthy volunteers (aged 18-45 years) with cetirizine 10 and 20 mg and placebo according to a double-blind, 3-way cross-over design. The effects of the treatments on word learning, memory scanning, vigilance, divided attention, tracking and visual information processing speed were assessed one hour and three hours after drug intake.

The results indicated that cetirizine 10 mg impaired tracking performance and memory scanning speed 1 hour after treatment. The 20 mg dose impaired memory-scanning speed 3 hours after drug intake. The other measures did not show any impairments, which suggested that the effects of cetirizine were not very pronounced. Therefore, it may not be suitable as a tool drug to model cognitive deficits following histamine dysfunction in clinical disorders.

A consistent finding regarding the effects of H₁-antagonists is that they impair sensorimotor performance. It is not clear, however, which underlying processes are affected by the H₁-antagonists, which results in the observed impairments. In chapter 5, a study is described which investigated the effects of H₁-antagonists on subprocesses involved in sensorimotor performance.

In order to gain more insight in which subprocesses are affected the interactions of dexchlorpheniramine with specific task manipulations in a choice reaction time task were studied. The task manipulations consisted of the visual degradation of stimuli and increased response complexity. The former affects stimulus processing and the latter affects the programming of the response. An interaction with these factors indicates which cognitive process is affected by the H₁-antagonist.

Healthy volunteers (9 female, 9 male) between 18 and 45 years of age were treated with single oral doses of 4 mg dexchlorpheniramine, 1 mg lorazepam as an active control drug and placebo according to a double-

SUMMARY

blind, placebo-controlled, 3-way cross-over design. Both behavioural measures (reaction times) and psychophysiological measures (ERPs) were used to assess the effects on cognitive processes between 1.5 hours and 3 hours after drug administration.

Dexchlorpheniramine significantly slowed reaction times, which indicated that the drug affected the performance. However, it did not significantly interact with task manipulations as measured with reaction times. Analyses of the ERP data showed that it did significantly interact with stimulus quality as measured by the prolonging effect of the antihistamine on the P300 component latency. Lorazepam also slowed reaction times and interacted with stimulus quality, but only shown by effects on reaction times. The results did not suggest any effects of the antihistamine on motor related processes.

Taken together, this study suggested that the H₁ receptor is involved in sensory information processing. In addition, this study showed that H₁ blockade does not affect response programming. It was suggested that clinical disorders in which histamine dysfunction plays a role may suffer from impaired sensory processing and that H₁-antagonists may suitable tools to model the deficit.

Chapters 2 to 5 have all described studies in which cognitive deficits have been attempted to be modelled using H₁ receptor blockade. However, this method may be limited as it mostly blocks just the H₁ receptor and, therefore, does not resemble low histamine levels. An alternative method to induce histamine hypofunction is to deplete the central nervous system from the histamine precursor, L-histidine. Histamine is synthesised from the essential amino acid L-histidine. Consumption of food containing other amino acids, but not L-histidine leads to a decrease in L-histidine levels in the body. Theoretically, histamine synthesis and, consequently, histamine levels in the central nervous system are lowered. In chapter 6, the method of L-histidine depletion was applied and the effects on cognitive measures were assessed. These effects were related to those of H₁-antagonism as seen in chapter 5.

Seventeen healthy volunteers (6 male, 11 female) aged between 18 and 35 years were treated with amino acid drinks containing all large amino acids but L-histidine, L-tyrosine/L-phenylalanine (active control) and all large amino acids (placebo) according to a double-blind, placebo-controlled, 3-way cross-over design. Similar as in chapter 5 the interactions with task manipulations in a choice reaction time task were studied. In addition, performance on a tracking task and subjective and objective sedation were measured. The effects were assessed 5 hours after drug administration

Analyses of the data showed that measures of sedation and critical tracking task performance were not affected by L-histidine depletion and L-tyrosine/L-phenylalanine depletion. In contrast to the effects of earlier

SUMMARY

studied H₁-antagonists, L-histidine depletion enlarged the effect of Response Complexity as measured with the response locked Lateralized Readiness Potential onset latency. This suggests that histamine is also involved in response related processes. Therefore, L-histidine depletion may be suitable as a model for histamine based motor impairments. As this was only the first study to investigate the effects of L-histidine on cognitive functions, future studies need to confirm the effects.

The final chapter provides an overview of the previous chapters and discusses the results and implications of the findings. The review of the literature from chapter 1 has shown that psychomotor performance is greatly sensitive to H₁-receptor blockade. In contrast, performance on episodic memory tasks does not seem to be affected. However, there are only a few authors who have investigated the effects of H₁-antagonism on episodic memory. Effects on working memory have been assessed frequently, but results may be confounded by effects of H₁-antagonism on sensorimotor performance. Subsequent chapters also described experiments in which the effects of H₁-antagonists on memory performance were assessed. These experiments all failed to find such effects. This is in sharp contrast with the effects of H₃-antagonists on memory in animals. It is suggested that this may be due to the fact the H₃-receptor also functions as a heteroreceptor, whereby it affects other transmitter systems. Alternatively, animal models of cognitive functions may not be generalized to human cognitive performance.

A more consistent finding is that H₁-antagonism impairs sensorimotor performance. It was shown that the impairment might be due to impaired sensory functioning, which is supported by anatomical data. Disorders like schizophrenia are also characterized by impaired sensory functioning. Although, further investigations are needed, H₁-antagonism is suggested as a model for histamine based sensory impairment.

In contrast to the effects of H₁-antagonists, depletion of the histamine precursor L-histidine leads to an impairment of motor related processes. It is well known that dopamine plays a large role in motor related processes. As the histaminergic system closely interacts with the dopaminergic system, it is suggested that the effect of L-histidine is mediated by the dopaminergic system.

Cognitive deficits as seen in Alzheimer's disease are characterized by memory impairments. Our findings showed that these may not be modelled using H₁-antagonists. In contrast, the effects of H₁-antagonism appear to be functionally located at the sensory processes. Therefore, these impairments may be modelled using H₁-antagonists. The effects of L-histidine depletion on motor related processes suggest a role for histamine in disorders like Parkinson's disease.

SAMENVATTING

SAMENVATTING

SAMENVATTING

SAMENVATTING

De farmacologische behandeling van cognitieve deficieten zoals die voorkomen in klinische stoornissen zijn in veel gevallen niet succesvol. Daarom gaat de zoektocht naar nieuwe medicatie onvermoeid door. De neurotransmitter histamine lijkt een belangrijke rol te spelen in de cognitieve deficieten zoals die te zien zijn in de ziekte van Alzheimer, schizofrenie, de ziekte van Parkinson en Attention Deficit Hyperactivity Disorder (ADHD). Histamine is een monoamine neurotransmitter en werkt in het brein door zich te binden aan de H₁, H₂, H₃ en H₄ receptoren. Activatie van de H₁-receptor leidt tot excitatoire neurotransmissie, terwijl de activatie van de H₃-receptor de activiteit van histamine remt.

Onderzoek in dieren heeft laten zien dat prestaties op cognitieve taken verbetert als de H₃-receptor wordt geblokkeerd, met name prestaties op taken die het geheugen meten. Deze zogenaamde H₃-antagonisten zouden gebruikt kunnen worden als nieuw middel tegen cognitieve deficieten zoals die voorkomen in klinische stoornissen, bijvoorbeeld bij de ziekte van Alzheimer. Voordat deze middelen kunnen worden getest in patiënt populaties is het nuttig om een snelle vroege screening van de middelen toe te passen in gezonde vrijwilligers, om zo het onderzoek naar geneesmiddelen te versnellen. Een dergelijke screening kan worden gedaan met behulp van modellen van cognitieve deficieten, die zijn te induceren door middel van histaminerge disfunctie in gezonde vrijwilligers. Het doel van dit proefschrift is het achterhalen welke rol histamine speelt in cognitie en welke histaminerge manipulatie in gezonde vrijwilligers kan dienen voor het creëren van een model voor cognitieve deficieten die voorkomen bij verschillende klinische stoornissen.

Een voorbeeld van een histaminerge manipulatie is het farmacologisch blokkeren van de H₁-receptor in het centraal zenuwstelsel. Deze manipulatie zou kunnen worden gebruikt om cognitieve deficieten op te roepen. H₁-antagonisten zijn middelen die de H₁-receptor blokkeren en zijn daarom misschien te gebruiken om de cognitieve deficieten te modeleren.

In het verleden is er al veelvuldig onderzoek gedaan naar de effecten van H₁-antagonisten op verschillende cognitieve functies. In **hoofdstuk 1** worden 70 experimentele onderzoeken beschreven waarin H₁-antagonisten zijn toegediend aan gezonde vrijwilligers en waarin de effecten op cognitieve functies zijn gemeten. In dit hoofdstuk komt naar voren dat het psychomotore functioneren het meest gevoelige cognitieve domein is voor de effecten van de H₁-antagonist. De cognitieve processen die onderdeel zijn van het psychomotore functioneren kunnen zijn aangetast door de H₁-antagonist en zo de oorzaak zijn van het verminderd functioneren. Deze

SAMENVATTING

onderliggende processen zijn helaas nog nauwelijks onderzocht. Tests die visuele processen meten, laten wel zien dat deze functie is aangetast. Dit suggereert dat de aangetaste visuele processen bijdragen aan de verslechterde prestaties op de psychomotore taken.

De prestaties op taken die het werkgeheugen meten zijn veelvuldig slechter na het toedienen van een H_1 -antagonist. Desalniettemin kan het zijn dat de oorzaak van deze verslechterde prestatie te vinden is in het feit dat het sensor-motorisch functioneren is vertraagd. Prestaties op de zogenaamde werkgeheugen taken zijn vaak in grote mate afhankelijk van sensor-motorisch functioneren. Het episodisch geheugen is, daarentegen, veel minder afhankelijk van deze functie en is dan ook minder vaak aangetast. Er dient wel te worden vermeld dat het episodisch geheugen niet vaak is gemeten na het toedienen van een H_1 -antagonist.

Uit hoofdstuk 1 wordt geconcludeerd dat H_1 -antagonisme zou kunnen dienen als model voor psychomotore deficieten dat wordt geassocieerd met verminderde histaminerge activiteit. De onderliggende processen die zijn aangetast en de geheugen functies dienen nog verder onderzocht te worden.

Eén van de vragen die voortkwam uit hoofdstuk 1 was de hoofdvraag van het in **hoofdstuk 2** beschreven onderzoek, namelijk: zijn geheugen deficieten te modeleren met H_1 -antagonisten? In dit onderzoek werd daarom een H_1 -antagonist toegediend aan gezonde vrijwilligers waarna verschillende cognitieve functies werden gemeten, met name geheugen. Twintig gezonde vrijwilligers tussen de 18 en 45 jaar oud namen deel aan het onderzoek. De vrijwilligers kregen 2 of 4 mg van het eerste generatie antihistaminicum dexchlorfeniramine of 1 mg van de muscarine antagonist scopolamine of placebo oraal toegediend volgens een dubbel blind, 4-wegs, cross-over design. De effecten van de middelen werden 2 en 4 uur na inname gemeten door gebruik te maken van taken die leren en geheugen, psychomotore functies, aandacht en subjectieve alertheid meten. Het antihistaminicum dexchlorfeniramine verslechterde de prestaties op spatieel geheugen, reactietijd, tracking en verdeelde aandacht taken, maar liet geen effect zien op werkgeheugen, visueel geheugen, woorden leren en geheugen scannen. De actieve controle scopolamine liet een soortgelijk patroon van effecten zien. Daardoor is een mogelijke verklaring dat de geheugentaken niet gevoelig genoeg waren om de effecten op te pikken, ondanks het feit dat vele andere onderzoeken hebben laten zien dat deze taken wel gevoelig zijn. Uit het onderzoek werd geconcludeerd dat dexchlorfeniramine een duidelijk effect had op psychomotore functies en niet op geheugen.

Het vraagstuk of H_1 -antagonisten een effect hebben op geheugen komt in het in **hoofdstuk 3** beschreven onderzoek opnieuw aan bod. Onderzoeken in dieren suggereren dat histamine een rol speelt in geheugen,

SAMENVATTING

maar onderzoeken in mensen zijn schaars en laten tegenstrijdige resultaten zien. De effecten op geheugen functies die door sommige onderzoeken worden aangetoond, kunnen het gevolg zijn van de versuffende werking van de antihistaminica. In tegenstelling tot deze onderzoeken laten andere onderzoeken geen effecten zien, maar dat zou het gevolg kunnen zijn van eventuele methodologische tekortkomingen. Het doel van het onderzoek beschreven in hoofdstuk 3 was daarom het dissociëren van de effecten van een H₁-antagonist op versuffing en geheugen. Achttien gezonde vrijwilligers tussen de 18 en 45 jaar oud kregen 4 mg dexchlorfeniramine, 1 mg lorazepam of een placebo oraal toegediend volgens een dubbel blind, 3-wegs, cross-over design. De effecten op geheugen functies zijn gemeten tussen 1.5 en 2.5 uur na inname van het middel door gebruik te maken van een 30-woorden leertaak, N-back taak en Event Related Potentials (ERPs). Versuftheid werd objectief gemeten door gebruik te maken van een electroencefalogram (EEG). Lorazepam, de actieve controle, liet duidelijke effecten op geheugen zien, zoals gemeten met zowel gedragsmaten als electrofysiologische maten. In tegenstelling tot deze effecten liet dexchlorfeniramine geen effecten op geheugen zien, terwijl beide middelen de vrijwilligers versufte. De resultaten ondersteunen de hypothese dat H₁-antagonisten wel een versuffende werking hebben, maar het geheugen niet verslechteren.

De voorgaande hoofdstukken beschreven onderzoeken naar de rol van histamine in cognitie die gebruik maakten van eerste generatie antihistaminica. Een nadeel van dit soort middelen is dat ze meestal erg onselectief zijn voor de H₁-receptor. Tweede generatie antihistaminica zijn veel selectiever, maar passeren in veel mindere mate de bloed-hersen-barrière. Het middel cetirizine is van de tweede generatie, maar kan een uitzondering zijn door wel de bloed-hersen-barrière te passeren en zo effecten uit te oefenen op cognitieve functies. Enkele voorgaande onderzoeken hebben effecten van cetirizine op cognitieve functies aangetoond. Door de inconsistente bevindingen is het nog een vraag of cetirizine kan worden ingezet als middel om cognitieve deficieten te modeleren. In **hoofdstuk 4** wordt een experiment beschreven waarin gezonde vrijwilligers tussen de 18 en 45 jaar een orale dosis van 10 of 20 mg cetirizine of een placebo toegediend kregen volgens een dubbel-blind, 3-wegs, cross-over design. De effecten van cetirizine op het leren van woorden, geheugen scannen, vigilantie, verdeelde aandacht, tracking en visuele informatie verwerking werden 1 en 3 uur na inname gemeten. De resultaten lieten zien dat cetirizine 10 mg de prestatie op de tracking taak en de snelheid van geheugen scannen 1 uur na inname verminderde. De 20 mg dosering verminderde de snelheid van het geheugen scannen 3 uur na inname. Alle andere zeer gevoelige maten lieten geen effecten van cetirizine zien. Dit toont aan dat de effecten van cetirizine niet erg groot zijn. Hierdoor

SAMENVATTING

is het op zijn minst twijfelachtig of cetirizine gebruikt kan worden om de cognitieve deficieten te modeleren.

Een consistente bevinding in het onderzoek naar de effecten van H₁-antagonisten is dat deze middelen het psychomotore functioneren verslechteren. Het is echter nog niet duidelijk welke onderliggende processen worden aangetast die leiden tot de geobserveerde verslechterde prestaties. In **hoofdstuk 5** wordt een onderzoek beschreven waarin de effecten van een H₁-antagonist op cognitieve subprocessen zijn onderzocht. Om meer inzicht te krijgen in welke cognitieve subprocessen worden aangetast door H₁-antagonisten, is er gebruik gemaakt van proces specifieke taak manipulaties in een keuze reactietijd taak. De manipulaties bestonden uit het visueel degraderen van de stimuli en het complexer maken van de respons. De eerste heeft invloed op de verwerking van de stimulus en de tweede beïnvloedt het programmeren van de respons. Een interactie-effect tussen de manipulatie en het antihistaminicum toont aan welke processen worden beïnvloed. Gezonde vrijwilligers (9 mannen en 9 vrouwen) tussen de 18 en 45 jaar kregen een orale dosis van 4 mg dexchlorfeniramine, 1 mg lorazepam of een placebo toegediend volgens een 3-wegs, dubbel-blind, cross-over design. Zowel maten van gedrag (reactietijd) als electrofysiologische maten (ERPs) zijn gebruikt om de effecten op cognitieve processen 1.5 en 3 uur na inname te bepalen. Dexchlorfeniramine vertraagde de reactietijd aanzienlijk, maar interacteerde niet met de taak manipulatie zoals gemeten met de reactietijd. Analyse van de ERP data liet zien dat dexchlorfeniramine interacteerde met stimulus kwaliteit zoals gemeten met de P300 latentie. Het middel bleek het effect van stimulus degradatie te vergroten. Lorazepam had hetzelfde effect, maar dan alleen zoals gemeten met reactietijd. De resultaten deden in geen enkel opzicht vermoeden dat de motorische processen door de middelen werden beïnvloed. Bij elkaar genomen kan worden geconcludeerd dat de H₁-receptor een rol speelt bij sensorische processen, maar niet bij motorische processen. Er kan nu worden gesuggereerd dat in stoornissen waarbij histamine een rol speelt vooral sensorische processen zijn aangetast en dat H₁-antagonisten deze deficieten mogelijk kunnen modeleren.

Hoofdstukken 2 tot en met 5 beschreven allemaal onderzoeken die H₁-antagonisten gebruikten om cognitieve deficieten te modeleren. Het kan zijn dat deze methode een onvolledig beeld geeft van de effecten van een verlaging van histaminerge activiteit, omdat het alleen de H₁-receptor direct beïnvloedt. Een alternatieve methode is om het lichaam te depletieren van de precursor van histamine, L-histidine, zodat de productie van histamine wordt verlaagd. Histamine wordt gesynthetiseerd door het omzetten van het essentiële aminozuur L-histidine. Consumptie van voedsel waar zich geen L-histidine in bevindt, leidt theoretisch tot een verlaging van de synthese van histamine en een verlaging van histamine in het brein. In **hoofdstuk 6** wordt

SAMENVATTING

een experiment beschreven waarin deze methode werd toegepast en de effecten op cognitieve processen zijn gemeten. De effecten werden vervolgens vergeleken met die van H_1 -antagonisme zoals beschreven in hoofdstuk 5. Zeventeen gezonde vrijwilligers (6 mannen, 11 vrouwen) tussen de 18 en 35 jaar namen deel aan het onderzoek waarin ze één van de drie aminozuurdrankjes dienden te drinken volgens een dubbel-blind, 3-wegs, cross-over design. De drankjes bevatten alle grote aminozuren behalve L-histidine of L-tyrosine/L-phenylalanine (actieve controle). De placebo-conditie bestond uit een drankje met alle aminozuren. Zoals ook het geval was in hoofdstuk 5 werden de interacties tussen taakmanipulaties in een keuze reactietijd taak en de farmacologische behandeling gemeten. Daarnaast werden de prestaties op de tracking taak en de versuffende effecten subjectief en objectief gemeten. Alle effecten werden 5 uur na inname van het drankje gemeten. De analyse van de data liet geen effecten van L-histidine depletie en L-tyrosine/L-phenylalanine zien op tracking prestatie en versuftheid. In tegenstelling tot de resultaten uit eerder onderzoek naar de effecten van de een H_1 -antagonist, vergrootte L-histidine depletie het effect van respons complexiteit zoals gemeten met de lengte van het interval tussen de respons en de 'Lateralized Readiness Potential'. Dit suggereert dat histamine ook een rol speelt bij respons gerelateerde processen. Dat zou kunnen betekenen dat L-histidine depletie een model kan vormen voor defecten van histamine gerelateerde motorische processen in het centraal zenuwstelsel. Echter, dit was het eerste onderzoek naar de effecten van L-histidine depletie op cognitieve processen. Vervolgonderzoeken dienen deze bevindingen te repliceren en uit te breiden.

Hoofdstuk 7 bevat een overzicht van de voorgaande hoofdstukken en bespreekt de implicaties van de bevindingen. Een overzicht van de literatuur zoals beschreven in hoofdstuk 1 wijst uit dat psychomotore functies erg gevoelig zijn voor de effecten van H_1 -antagonisten. In tegenstelling, prestaties op een taak die episodisch geheugen meet lijkt niet te worden aangetast. Echter, er zijn niet veel auteurs geweest die dit effect hebben onderzocht. Effecten van H_1 -antagonisten op het werkgeheugen zijn veel vaker onderzocht, maar de gevonden effecten kunnen het gevolg zijn van verstoorde sensor-motorische functies. In de vervolg hoofdstukken werden de effecten van H_1 -antagonisten op geheugen gemeten. Helaas werden er geen effecten gevonden wat in tegenstelling is met de onderzoeken die in dieren gedaan zijn. In de onderzoeken met dieren wordt vaak de H_3 -receptor geblokkeerd wat leidt tot geheugen verbeterende effecten. Een verklaring voor de discrepantie kan zijn dat de H_3 -receptor ook functioneert als heteroreceptor waardoor de blokkade invloed heeft op andere neurotransmitter systemen. Een andere verklaring is dat diersmodellen niet zomaar vertaald kunnen worden naar mensen.

SAMENVATTING

Een consistentere bevinding is dat H₁-antagonisten het psychomotore functioneren verslechteren. Het onderzoek beschreven in dit proefschrift toont aan dat het misschien de sensorische component is die wordt aangetast door H₁-antagonisten. Deze bevindingen worden ondersteund door de anatomie van het histaminerge systeem. Klinische stoornissen zoals schizofrenie worden gekenmerkt door een verslechterd sensorisch functioneren. Daarom wordt gesuggereerd dat H₁-antagonisme gebruikt kan worden voor het onderzoeken van enkele symptomen van deze stoornis.

In tegenstelling tot bovenstaande bevindingen, leidt L-histidine depletie tot een verstoring van de motorische processen. Het is bekend dat dopamine een rol speelt bij motorische processen. Het histaminerge systeem en het dopaminerge systeem staan in nauw verband met elkaar. Daarom wordt geopperd dat de effecten van L-histidine depletie mogelijk verlopen via het dopaminerge systeem.

Cognitieve deficieten in de ziekte van Alzheimer worden gekenmerkt door een verslechterd geheugen. Huidige bevindingen laten zien dat deze symptomen niet gemodelleerd kunnen worden door H₁-antagonisten. De effecten van deze middelen lijken te zijn gelokaliseerd in de sensorische processen, en dus zijn deze middelen mogelijk bruikbaar om defecten in sensorische processen te modelleren. De effecten van L-histidine depletie op motorisch gerelateerde processen suggereren een mogelijke rol voor histamine in onderzoek naar stoornissen waarin motorische symptomen een prominente rol spelen, bijvoorbeeld de ziekte van Parkinson.

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CURRICULUM VITAE

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Peter van Ruitenbeek werd op 4 mei 1980 te Amersfoort (Nederland) geboren. Na het behalen van zijn diploma Voorbereidend Wetenschappelijk Onderwijs in 1999 is hij psychologie gaan studeren aan de Universiteit van Maastricht. Hij studeerde in 2004 af in de biologische psychologie na een onderzoeksstage bij de Experimental Psychopharmacology Unit van de Faculteit der Psychologie met als onderwerp de rol van de neurotransmitter serotonine in geheugen. Vervolgens heeft hij als onderzoeksmedewerker gewerkt bij deze groep, waarna hij in 2005 is begonnen aan zijn promotie onderzoek naar de rol van histamine als neurotransmitter in menselijk cognitief functioneren. Tegenwoordig zet hij zijn onderzoek voort als post-doc onderzoeker.

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