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Histamine H_1-receptor blockade in humans affects psychomotor performance but not memory

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Abstract

Results from recent animal studies suggest an important role for histamine in memory functioning. Histaminergic drugs might prove beneficial for people suffering from memory impairment. To determine if histamine is involved in memory functioning this study evaluates the effects of histaminergic dysfunction on memory performance by administrating a H_1-antagonist to humans. The study was conducted according to a 4-way, double-blind, crossover design in 20 healthy female volunteers, aged 18–45 years. On each test day subjects completed three test sessions: before and around 2 and 4 h after administration of single oral doses of dexchlorpheniramine 2 mg or 4 mg, scopolamine 1 mg or placebo. Drug effects were assessed using tests of memory, psychomotor and attention performance, and subjective alertness. Results showed that dexchlorpheniramine impaired performance in tests of spatial learning, reaction time, tracking and divided attention but showed no effects on working memory, visual memory, word learning or memory scanning. Scopolamine induced a similar pattern of effects. In addition, both drugs decreased subjective alertness. In conclusion results show that dexchlorpheniramine and scopolamine clearly impaired performance on psychomotor and attention tasks but do not suggest a specific role of the histaminergic system in learning and memory in humans.

Keywords

cognition, memory, psychomotor performance, histamine, acetylcholine, H_1-antagonist, muscarinic antagonist

Introduction

Recently interest in the 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 on the basis of 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 H_1-antagonists in humans, they provide little support for the hypothesis that decreased histaminergic functioning is associated with impaired memory functions. This is largely because of 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 anti-histamines 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)]. As 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 H_1 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

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healthy elderly subjects. Vuurman *et al.,* (1994; 1996) found 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 because of the anti-muscarinic effects of the anti-histamines used.

The aim of the present study was therefore, to assess the effects of the relatively selective H_1-antagonist dexchlorpheniramine (2 and 4 mg) on 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 H_1-antagonists than males (Ramaekers and O'Hanlon, 1994; Robbe, 1990; Vermeeren *et al.*, 2002; Vuurman *et al.*, 1994). The effects were to be compared with 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; Rubinsztein *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 H_1-antagonists; that is 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 H_1-antagonist having a moderately high-binding affinity for the H_1-receptors, but relatively low affinities for muscarinic, alpha-1, alpha-2 and beta-receptors. The affinity for the muscarinic receptor is especially low (Kd = 3300 for chlorpheniramine) as compared with scopolamine (Kd = 0.1) (Wiech and Martin, 1982). The half-life of chlorpheniramine is approximately 28 h (range 19–43 h) and maximum plasma concentrations are reached at 2.8 h (range 2–4 h) 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 h after drug administration (Clarke and Nicholson, 1978). On the basis of these results it was decided to measure the effects of dexchlorpheniramine at both times reported for peak impairment that is between 1.5 and 2.5 h and between 3.5 and 4.5 h after administration.

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 h after oral intake and scopolamine has an average elimination half-life of 4.3 h (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 anti-depressants 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 (BMI) value outside 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 units per week or more than five 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 h 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 ± SD age of the 20 subjects who completed the study was 23.7 ± 7.3 years. Their mean ± SD BMI was 21.6 ± 3.0 kg/m^2. Five subjects were smokers, who on average (±SD) smoked 4.6 (±2.1) cigarettes and no more that 10 per day. Eighty percent of the subjects were in college or had a similar level of education. The remaining 20% 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 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, four-way crossover design. Treatments were single oral doses of dexchlorpheniramine 2 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 2 weeks prior to their first treatment day. On treatment days they arrived at the University around 9:00 h. Between 9:45 and 10:45 h, a battery of psychometric tests was completed to obtain baseline performance scores. At 11:00 h, subjects ingested the study medication. Thereafter the test battery was repeated at 12:30 and 14:30 h that is between 1.5 and 2.5 h, and 3.5 and 4.5 h after ingestion, henceforth indicated as t_2 and t_4.

The duration of the test battery was approximately 1 h 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 t_4 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 associate learning test. At 0.5 h 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 test (Klaassen *et al.*, 2002; Rey, 1964; Riedel *et al.*, 1999) assesses short- and long-term verbal memory. Thirty Dutch monosyllabic meaningful nouns and adjectives are presented for 1000 ms at a rate of 1 per 2 s 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 min 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 with 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 6×4 grid, at a rate of 1 pattern per 3 sec. 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 min 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 nontargets. 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 six blocks of 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 associate 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 eight 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 nonrepeated items. The dependent variables are the median reaction times (ms) for repeated and nonrepeated 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 extend 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 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 'lambda$_c$' (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 s. 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. Secondly, 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 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 t_2 and t_4 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) $\times$ 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) $\times$ 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 t_2 and t_4 separately. This is a legitimate procedure as 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 ($\pm$SE) 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 with placebo were observed after administration of

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)

	Overall analyses of changes from baseline		Mean (±SEM) scores				
	Main effect of Treatment $P =$	Interaction of Treatment × Time $P =$	Test Session	Treatment PLA	D2	D4	S1
Syntactic reasoning task							
Number correct (#)	0.620	0.253	Baseline	28.4 ± 1.0	28.1 ± 1.0	28.2 ± 1.0	29.2 ± 1.1
			t_2	28.4 ± 1.0	27.8 ± 1.0	28.4 ± 1.1	28.3 ± 1.0
			t_4	29.2 ± 1.0	29.0 ± 1.0	28.9 ± 0.0	29.3 ± 1.0
Mean reaction time (ms)	0.865	0.509	Baseline	1651 ± 169	1591 ± 163	1652 ± 118	1614 ± 121
			t_2	1594 ± 138	1546 ± 155	1654 ± 124	1544 ± 105
			t_4	1582 ± 141	1464 ± 139	1629 ± 115	1556 ± 120
Spatial paired associate learning task							
Median reaction time (ms)	0.008	0.176	Baseline	509 ± 15	495 ± 15	503 ± 18	481 ± 13
repeated items			t_2	501 ± 16	520 ± 20*	512 ± 17	504 ± 16*
			t_4	479 ± 12	485 ± 16	488 ± 17	497 ± 17*
Median reaction time (ms)	0.097	0.432	Baseline	521 ± 22	501 ± 16	494 ± 16	487 ± 15
non-repeated items			t_2	504 ± 19	502 ± 20	514 ± 22	503 ± 14
			t_4	472 ± 15	489 ± 19	481 ± 16	495 ± 18
Word learning task							
Immediate recall (# words correct)			t_4	45.3 ± 1.8	42.9 ± 1.9	46.9 ± 1.7	44.7 ± 1.5
Delayed recall (# words correct)			t_4	15.1 ± 1.0	14.6 ± 0.8	15.6 ± 0.9	14.6 ± 0.8
Recognition (ms)			t_4	647 ± 20	644 ± 17	652 ± 17	643 ± 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
			t_2	26.6 ± 0.7	26.5 ± 0.7	25.5 ± 0.8	25.2 ± 1.0
			t_4	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
			t_2	916 ± 42	905 ± 46	936 ± 57	871 ± 43
			t_4	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
			t_2	24.8 ± 0.7	24.5 ± 0.8	23.8 ± 0.8	23.3 ± 0.9
			t_4	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
			t_2	1004 ± 63	1039 ± 78	1022 ± 70	1022 ± 82
			t_4	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
			t_2	47 ± 3	50 ± 4	56 ± 5	53 ± 5
			t_4	44 ± 3	50 ± 4	49 ± 5	50 ± 4
Intercept (ms)	0.379	0.340	Baseline	345 ± 11	334 ± 9	331 ± 10	332 ± 11
			t_2	338 ± 9	338 ± 1	336 ± 12	338 ± 8
			t_4	333 ± 10	317 ± 9	328 ± 10	329 ± 9

Significant ($P < 0.05$) a-priori drug-placebo contrasts are indicated as asterisk.

dexchlorpheniramine 2 mg at t_2 ($F_{1,19} = 14.5$, $P < 0.001$), and after administration of scopolamine 1 mg at t_2 ($F_{1,19} = 12.7$, $P < 0.002$) and t_4 ($F_{1,19} = 13.6$, $P < 0.002$).

Psychomotor performance and attention

A summary of mean (±SE) 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 t_2 ($F_{1,19} = 5.3$, $P < 0.032$; $F_{1,19} = 8.4$, $P < 0.009$; $F_{1,19} = 15.5$, $P < 0.001$, respectively). These differences were no longer significant at t_4.

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 t_2 showed significantly longer reaction times after administration of dexchlorpheniramine 2 mg ($F_{1,19} = 6.3$, $P < 0.021$), dexchlorpheniramine 4 mg ($F_{1,19} = 5.9$, $P < 0.025$) and scopolamine 1 mg ($F_{1,19} = 10.4$, $P < 0.004$).

A main effect of Treatment was also found on critical tracking performance ($F_{3,17} = 3.3$, $P < 0.044$). Tracking was impaired at both 1.5 h as 2.5 h 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 h after administration (Figure 1).

Owing 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 t_2 ($F_{1,18} = 9.9$, $P < 0.006$) and at t_4 ($F_{1,18} = 7.4$, $P < 0.014$). 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

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)

	Overall analyses of changes from baseline		Mean (±SEM) scores				
	Main effect of Treatment $P =$	Interaction of Treatment × Time $P =$	Test Session	Treatment PLA	D2	D4	S1
Simple reaction time task							
Median reaction time (ms)	0.010	0.012	Baseline	246 ± 8	249 ± 7	258 ± 12	246 ± 7
			t_2	258 ± 10	283 ± 11*	294 ± 11*	288 ± 12*
			t_4	257 ± 11	261 ± 10	257 ± 10	271 ± 11
Choice reaction time task							
Median reaction time (ms)	0.078	0.174	Baseline	308 ± 9	312 ± 7	314 ± 10	309 ± 8
			t_2	322 ± 10	346 ± 11*	355 ± 12*	356 ± 14*
			t_4	312 ± 8	317 ± 10	325 ± 10	333 ± 12
Divided attention task							
Overall performance (*z*-score)	0.002	0.400	Baseline	−0.31 ± 0.30	−0.33 ± 0.31	−0.54 ± 0.30	−0.63 ± 0.25
			t_2	−0.31 ± 0.31	0.25 ± 0.28	0.60 ± 0.32*	0.97 ± 0.40*
			t_4	−0.43 ± 0.26	−0.02 ± 0.33	0.32 ± 0.38*	0.30 ± 0.32*
Subjective alertness scale	0.001	0.045	Baseline	25.6 ± 3.1	27.4 ± 3.8	26.8 ± 4.0	28.1 ± 3.5
			t_2	32.0 ± 4.3	41.2 ± 3.4*	44.1 ± 4.8*	53.3 ± 4.0*
			t_4	31.6 ± 3.5	37.9 ± 4.9	41.0 ± 4.5*	41.3 ± 4.4*

Significant ($P < 0.05$) a-priori drug-placebo contrasts are indicated as asterisk.

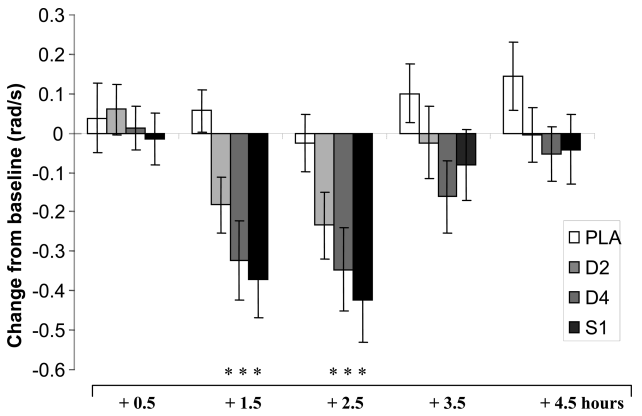

Figure 1 Mean changes (±SEM) from baseline of the critical frequency in the critical tracking task at 0.5, 1.5, 2.5, 3.5 and 4.5 h after administration of placebo (PLA), dexchlorpheniramine 2 mg (D2), dexchlorpheniramine 4 mg (D4) and scopolamine 1 mg (S1) Significant ($P < 0.05$) a-priori drug-placebo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

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 t_2 after intake of dexchlorpheniramine 2 mg ($F_{1,19} = 5.6$, $P < 0.029$), and at t_2 and t_4 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 ($F_{1,19} = 33.0$, $P < 0.001$, $F_{1,19} = 8.8$, $P < 0.008$).

Discussion

This study assessed the effects of the H_1-antagonist dexchlorpheniramine on memory and psychomotor performance in humans. On the basis of the 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 anti-histamines 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 t_2 by dexchlorpheniramine 2 mg and scopolamine in comparison with placebo. As 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 nonrepeated items. However, comparison of reaction times to repeated and nonrepeated 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 with 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 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 with 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 t_4. Scopolamine has a relatively short half-life ($t_{1/2} = 4.3$ h) and it rapidly reaches peak plasma concentrations after oral administration ($t_{max} = 0.8$ h), 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 at peaked between 1.5 and 2.5 h and had rapidly returned to baseline at 3.5 h after drug intake. It can therefore, be assumed that only very few effects could have been found 4 h after its intake. Furthermore, it has been reported that compared with 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 with 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 (baseline versus t_2; Rosnow and Rosenthal, 1996) showed that scopolamine's effects on memory were almost twice as strong as those of dexchlorpheniramine 4 mg (ES 0.41 versus 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 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.

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, whereas 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 anti-histamines 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 with 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 H_1-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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