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Treatment of Cognitive Impairment in Schizophrenia: Potential Value of Phosphodiesterase Inhibitors in Prefrontal Dysfunction

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Abstract: No pharmacological treatment is available to date that shows satisfactory effects on cognitive symptoms in patients diagnosed with schizophrenia. Phosphodiesterase inhibitors (PDE-Is) improve neurotransmitter signaling by interfering in intracellular second messenger cascades. By preventing the breakdown of cAMP and/or cGMP, central neurotransmitter activity is maintained. Different PDE families exist with distinct characteristics among which substrate specificity and regional distribution.

Preclinical data is promising especially with regard to inhibition of PDE2, PDE4, PDE5 and PDE10. In addition, cognitive improvement has been reported in both elderly and/or non-impaired young human subjects after PDE1 or PDE4 inhibition. Moreover, some of these studies show effects on cognitive domains relevant to schizophrenia, in particular memory. The current review incorporates an overview of the distinct molecular characteristics of the different PDE families and their relationship to the neurobiological mechanisms related to cognitive dysfunction in schizophrenia. So far, procognitive effects of only three types of PDE-Is have been assessed in patients diagnosed with schizophrenia inhibiting PDE3, PDE5 and PDE10. However, the limited data available do not allow to draw firm conclusions on the value of PDE-Is as cognitive enhancers in schizophrenia yet. The field is still in its infancy, but nevertheless different PDE-Is seem promising as candidate to optimise neural communication in the prefrontal cortex favouring cognitive functioning in patients diagnosed with schizophrenia, in particular dual inhibitors including PDE1-Is, PDE3-Is and PDE10A-Is.

Keywords: Schizophrenia, phosphodiesterase inhibitor, cognition, memory, pharmacological treatment.

INTRODUCTION

One century ago, the syndrome now called schizophrenia was referred to as ‘dementia praecox’. This implies that back then, cognitive symptoms were acknowledged as a hallmark of the disorder. In the years thereafter, attention shifted towards positive symptomatology. However, during the past twenty years, a renewed interest in cognitive impairment in schizophrenia has evolved. Not only is it recognized as a prominent feature and symptom domain impacting on course and outcome [1-5], cognitive alterations also represent a stable trait, independent of positive symptoms, that precedes the onset of schizophrenia [6-10]. Pharmacological interventions in schizophrenia are targeting positive symptoms, and an effective treatment of cognitive symptoms in patients with a diagnosis of schizophrenia is presently still lacking. Considering the impact of cognitive impairment, and the associated costs, the need for development of pharmacological interventions specifically targeting this domain is undeniable. Despite a strong increase in activity within this field, to date no cognition enhancer is available specifically targeting those cognitive problems that constitute a core feature of schizophrenia.

This review will describe the potential of phosphodiesterase inhibitors (PDE-Is) as cognitive enhancers in schizophrenia. The working mechanism of PDE-Is is intrinsically different from drugs currently in use as antipsychotics. Instead of stimulating or inhibiting receptor activity, PDE-Is affect intracellular second messenger systems downstream of the receptor. Since different neurotransmit-

ter systems can have similar second messengers [11], the effect of PDE-Is is not limited to a single neurotransmitter system. In addition, due to the distinct spatial organization of the different PDE families and their isoforms, it might be possible to specifically stimulate the activity of neurotransmitter systems in restricted brain areas. This allows targeting those areas that are critically involved in the execution of cognitive tasks. For this reason, PDE-Is might be superior to drugs currently in use for schizophrenia, in particular with regard to treating cognitive symptoms.

COGNITIVE DEFICITS IN SCHIZOPHRENIA

In schizophrenia, a broad spectrum of cognitive alterations is present in an array of functions [5, 8, 10, 12]. Cognitive impairment is present in many patients suffering from schizophrenia and results in significant disabilities in social, occupational and economic functioning [13]. All tested functions are included in the domains of cognitive functions identified by MATRICS (Measurements and Treatment Research to Improve Cognition in Schizophrenia; <http://www.matrics.ucla.edu>). These domains include attention and vigilance, processing of speed, memory (working memory, verbal learning and memory, visual learning and memory), reasoning and problem solving (executive function), and social cognition.

Cognitive control is known to rely on coordination processes of several brain regions. The most important regions are the dorso-lateral prefrontal cortex (DLPFC), medial frontal cortex, including the anterior cingulate cortex (ACC), and parietal regions. Damage to these regions results in deficits in context maintenance and response inhibition. These brain regions interact in a complex network manner to fulfil multiple purposes and act in several different executive processes. The DLPFC maintains rules for action and response selection, parietal regions are important to shift attention

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and focus, and the ACC detects response conflicts and activates the DLPFC to improve performance. In addition, networks including the ACC have also been implicated in social cognition [14]. The frontal lobes are crucial to problem solving, insight and other high level reasoning. In particular, functional consequences of impaired PFC signalling in general, ranges from impaired judgement, organisation, planning and decision-making, to behavioural disinhibition and impaired intellectual abilities, resulting in diminished abilities with regard to coordinational processes [15]. Indeed, perturbations in patients with a diagnosis of schizophrenia result in difficulties in planning and organization. Therefore cognitive control must be seen as the activation of a complex interconnected cortical network [16]. In patients with a diagnosis of schizophrenia, the DLPFC shows task-related reduced activity [17, 18]. Reduced DLPFC activity results in impaired task performance and behavioural disorganization as well as in impaired prefrontal control mechanisms [16]. In addition, decreased activation of DLPFC and ventrolateral PFC has been related to impaired episodic memory, both encoding and retrieval processes [19]. Episodic memory is required for a wide range of cognitive functions and impairments in schizophrenia have also been associated with structural abnormalities in medial temporal regions, including the hippocampal region which mediates learning and memory formation and the amygdala [20, 21].

Evidence from neuroimaging studies in patients with schizophrenia suggests marked structural changes within the brain that can be related to the cognitive deficits mentioned above. Reduced whole brain volume together with increased volume of the lateral ventricles has been confirmed by a recent meta-analysis [22]. In addition, impairments in cognitive domains may be associated with alterations in grey and white matter density in relevant brain areas [16, 23, 24]. However, the causality of this relationship has been disputed [25]. White matter deficits have been found in the right deep frontal lobe and left deep temporal lobe in first episode patients [26], and seem to occur to a similar degree in medicated and unmedicated patients [27]. A meta-analysis of diffusion tensor imaging studies revealed that the tracts involved suggest a lack of connectivity within the fronto-limbic circuitry [26]. Another recent meta-analysis did not find differences in white matter volume in patients naive to antipsychotic medication [22]. The same authors described a negative correlation between gray matter loss and cumulative exposure to antipsychotic treatment. This is in line with the finding that gray matter deficits are less extensive in medication naive patients [27]. Gray matter loss has been described for frontal, temporal and parietal regions [28]. Meta-analyses have shown pronounced decrease in the insula, caudate, uncus regions and superior temporal gyri [24, 29-31]. Gray matter volume loss in the superior temporal gyri and left insula correlate with the severity of auditory hallucinations, possibly related to disturbed language processing [24, 32].

NEUROTRANSMITTER AND RECEPTOR THEORIES OF SCHIZOPHRENIA

Signal Transduction

PDE-Is affect neuronal communication by interfering in intracellular second messenger pathways, i.e. pathways activated after extracellular neurotransmitter binding. Neurotransmitter receptors can be divided into groups according to the way in which receptor and effector function are coupled. One group is the ionotropic or ion channel receptors and the other is the metabotropic or GTP-binding protein (G-protein) coupled receptors.

G-protein activation engages second messenger cascades [33]. Second messengers translate an extracellular signal, such as the binding of a neurotransmitter to its receptor, into a non-structural (increased neurotransmitter release) or structural (receptor and/or synapse formation) cellular responses [34, 35]. Traditionally, the cAMP second messenger system (Gs and Gi linked) and the phos-

phoinositol second messenger system (Gq linked) received the most attention. The second messenger complex inositol-1, 4, 5, triphosphate/diacylglycerol (IP₃/DAG) is formed out of the hydrolysis of phosphatidylinositol 4, 5-bisphosphate (PIP₂) by phospholipase C (PLC) after activation by Gq. The second messenger cAMP is synthesised by adenylate cyclase (AC), which is stimulated or inhibited by Gs or Gi, respectively, and degraded by different phosphodiesterases (PDEs)

cAMP activates cAMP-dependent protein kinase (PKA), which phosphorylates cAMP response element binding protein (CREB). P-CREB is an activated transcription factor, which initiates transcription of specific genes which can include neurotransmitter receptors such as ionotropic AMPA receptors or growth factors as brain-derived neurotrophic factor (BDNF) [36]. DAG activates calcium-dependent protein kinase (PKC) in the presence of calcium (Ca²⁺), which is mobilized by IP₃. PKC activates CREB via the MAP kinase pathway.

Postsynaptic Ca²⁺, either after mobilization by IP₃ or after entering via the ionotropic NMDA receptor, can also bind to calmodulin. This so-called Ca²⁺/CaM complex activates Ca²⁺/CaM protein kinase (CaMK), which can stimulate the insertion of AMPA receptors in the postsynaptic membrane [37]. In addition, CaMK can activate PKC, but also PKA via activation of AC and subsequent production of cAMP. On the other hand, PKA can also activate the MAP kinase pathway. Thus, there is interplay between the cAMP second messenger system and the phosphoinositol second messenger system.

The enzyme AC is also present presynaptically and elevation of cAMP has been found to result in the synthesis and/or release of several neurotransmitters including glutamate and dopamine (DA) [38-40]. This might be mediated via a presynaptic CaMK/cAMP/PKA cascade and hence signal transduction is influenced.

Ca²⁺ is also known to activate the enzyme nitric oxide synthase (NOS) which produces NO [41]. The latter stimulates the enzyme guanylate cyclase (GC) which produces the second messenger cGMP, which is also degraded by PDEs. cGMP activates cGMP-dependent protein kinase (PKG), which can also induce CREB phosphorylation [42]. NO is also known to act as a retrograde messenger and can thus stimulate presynaptic GC. Linked to this, via a cGMP/PKG cascade the synthesis and/or release of neurotransmitters including glutamate and DA can be influenced [43, 44], and thus signal transduction. Fig. 1 provides a schematic overview of the pre- and postsynaptic cellular processes related to the second messengers cAMP and cGMP involved in signal transduction.

Different neurotransmitter systems have been suggested to be involved in the pathogenesis of schizophrenia, including DA, glutamate, γ -Aminobutyric acid (GABA), serotonin (5-HT), and acetylcholine. All of these systems may be potential targets to, directly or indirectly, ameliorate cognitive functioning in schizophrenia. As described above, the cascade of intracellular events that follows neurotransmitter binding depends on the type of receptor being stimulated. Since PDE-Is potentiate neurotransmitter signalling by interfering within intracellular cascades, a brief overview is given on the supposed role of the different neurotransmitter systems in schizophrenia. This provides the framework from which more specific targets for treatment of cognitive deficits in schizophrenia can be inferred.

Dopamine

Historically, the dopaminergic theory of schizophrenia received most attention. In essence, hyperactivity of the dopaminergic system was supposed to be the primary cause of this disorder [45]. Later, this theory was refined and hyperactivity was proposed to be confined to the mesolimbic areas [46].

Fig. (1). Ca^{2+} entry through the postsynaptic ionotropic glutamatergic NMDA receptor results in the activation of CaMK. Activated CaMK stimulates the insertion into the membrane of the ionotropic AMPA receptor which is involved in baseline signal transduction. In addition, CaMK activates AC resulting in the production of the second messenger cAMP. The latter activates PKA, which has a positive effect on the transcription factor CREB. CREB activation is known to result in an increased gene expression, including the genes for AMPA receptors and brain BDNF and thus future signal transduction is enhanced. Ca^{2+} is also known to activate NOS, which produces NO. The latter can activate GC, which produces the second messenger cGMP. Postsynaptically cGMP has similar effects as cAMP, but via activation of PKG. NO is also known to act as a retrograde messenger and can thus stimulate presynaptic GC. It has been found that cGMP stimulates the synthesis and/or release of glutamate and DA via PKG. Presynaptic AC produces cAMP which is known to increase the synthesis and/or release of glutamate and DA. This is likely mediated via a CaMK/cAMP/PKA cascade.

DA exerts its function by different central pathways and different receptor subtypes. The mesolimbic and mesocortical pathway are critically involved in the pathogenesis of schizophrenia [47, 48]. Both pathways arise from the ventral tegmental area. The mesolimbic pathway projects to the ventral striatum (the nucleus accumbens) and the amygdala. The mesocortical pathway projects to cortex including the medial and prefrontal cortex, the cingulate and the entorhinal cortex. In addition, five DA receptor subtypes have been identified (D_{1-5}), of which both pre-synaptic and post-synaptic receptors may play a role in schizophrenia. In particular D_1 and D_2 receptors have been described in the dopaminergic theory of schizophrenia [49]. D_1 receptors are most widely distributed throughout the brain as compared to the other dopaminergic receptors. In the nucleus accumbens the D_1 receptor is situated post-synaptically, whereas the D_2 receptor is situated both pre- and post-synaptically. Overstimulation of the postsynaptic D_2 receptors in the nucleus accumbens is thought to contribute to the positive symptoms of schizophrenia [48, 50].

In the PFC, the D_1 receptor is situated post-synaptically (Gs-coupled) as well, but other than in the nucleus accumbens, D_2 receptors are located pre-synaptically (Gi -coupled) only. The impact of negative feedback on signal transduction by pre-synaptic D_2 stimulation is probably limited, since D_2 numbers within the PFC are low. It has been suggested that pre-synaptic D_3 receptors, which have functional and pharmacological similarities to D_2 receptors, are the primary pre-synaptic target for DA in this area. Under normal circumstances, DA modulates the excitability of glutamatergic and GABA-ergic neurons. DA stabilizes cortical network activity by decreasing the level of cortical noise and as such, enhancing cortical signal-to-noise ratio [48].

Negative and cognitive symptoms of schizophrenia, are associated with reduced DA function in the PFC, also referred to as hypofrontality. The reduced prefrontal DA function disturbs the balance of excitatory-inhibitory synaptic interactions in this area [51]. Thus, the decreased ratio of D_1/D_2 signalling in schizophrenia would favour unstable cortical representation of internal and external stimuli [52] and as such, affect cognition.

Glutamate

A second major theory of schizophrenia concerns glutamatergic neurotransmission. An early report by Kim *et al.* (1980; [53]) showed low CSF glutamate levels in patients with a diagnosis of schizophrenia, suggestive of a hypofunctional glutamatergic system. Further indication came from the observation that psychotic symptoms could be evoked in healthy individuals by antagonising the NMDA receptor, one of the ionotropic (calcium channel) glutamate receptors, using ketamine and phencyclidine [54, 55]. Subsequent clinical evidence pointed to dysfunctional receptors as an important mediator of reduced glutamatergic functioning. Post-mortem brain tissue from patients with a diagnosis of schizophrenia showed an altered expression of NMDA receptor subunits, primarily in the PFC [56]. This theory is referred to as the NMDA Receptor Hypofunction Hypothesis. The shift in subunits of the NMDA receptors in GABAergic interneurons results in diminished NMDA activity leading to reduced GABAergic tone on other GABAergic interneurons which synapse on the dopaminergic mesocortical pathway neurons [57]. The increased inhibition of the GABAergic interneurons results in hypofrontality. In other words, the observed abnormalities in DA signalling as described in the dopaminergic theory of schizophrenia, might be secondary to NMDA dysfunction.

GABA

In addition to a reduced GABAergic tone due to NMDA receptor hypofunction, primary abnormalities in this major inhibitory neurotransmitter system, in particular within the DLPFC, have been reported in schizophrenia. Both the synthesis and reuptake of GABA may be significantly reduced in a subset of DLPFC inhibitory neurons [58]. The reduced synthesis can be ascribed to locally reduced mRNA levels encoding glutamic acid decarboxylase, an enzyme that synthesizes GABA in about 30% of the GABAergic neurons in this area [59-61]. Moreover, a negative relationship has been described for glutamic acid decarboxylase mRNA and GABA membrane transporter expression in post-mortem material from patients with a diagnosis of schizophrenia [62]. This could well represent a compensatory mechanism, which makes it difficult to assess the magnitude of the alterations within the GABAergic system as a whole.

Serotonin

There is no established theory on the involvement of 5-HT in the pathophysiology of schizophrenia, but some observations suggest alterations within the serotonergic system. To draw conclusions on whether the serotonergic system is primarily involved in the pathophysiological mechanisms of schizophrenia is complicated by effects directly induced by medication use or related to comorbid conditions [63]. Especially in the case of post-mortem material, statements on the serotonergic status of patients with a diagnosis of schizophrenia who committed suicide are complicated due to the described relation between suicide and altered 5-HT homeostasis [64]. Most evidence in support of pro-cognitive effects induced by serotonergic manipulation comes from the comparison of typical and atypical antipsychotics. The last target the DA system, especially the D2 receptor, but as opposed to the classical typical antipsychotics, there is an additional, often stronger, effect on the serotonergic system. With regard to improving cognitive symptoms, atypical antipsychotics have shown their superiority as compared to the conventional antipsychotics, which has been ascribed to the antagonism of the 5HT_{2A} receptor (Gq-coupled, postsynaptically) which is thought to induce the release of glutamate in the PFC [65, 66], although the exact mechanism for this increase is not clear [67]. Moreover, stimulation of a second 5-HT receptor subtype, the 5HT_{1A} receptor, has been proposed as favourable target to specifically target cognitive problems related to schizophrenia [68]. Some atypical antipsychotics, like clozapine and quetiapine, are partial 5HT_{1A} agonists. It has been suggested that post-synaptic 5HT_{1A} agonism (Gi/o-coupled) stimulates DA release in the PFC, and that simultaneous 5HT_{2A} blockade strengthens this effect [69].

Acetylcholine

Theories on the role of cholinergic alterations in schizophrenia are less common, but considering the role of acetylcholine (ACh) in cognition, the cholinergic system should not be neglected as a potential target of cognition enhancement in schizophrenia. In fact, preventing the hydrolysis of ACh by giving acetylcholinesterase inhibitors as adjunctive therapy in patients with a diagnosis of schizophrenia, improved memory, motor speed and the attentional aspect of executive function [70]. The acetylcholinesterase inhibitor rivastigmine specifically recovered cognitive impairments in the NMDA antagonist ketamine-treated rats [71]. In other words, stimulating ACh signalling partly attenuates NMDA receptor antagonism.

Low binding to muscarinic postsynaptic (Gs-coupled) M1 and modulatory postsynaptic M4 (Gs-coupled) receptors in the PFC of patients with a diagnosis of schizophrenia has been found [72]. This suggests that ACh might directly modulate cortical DA release [73]. Also a decrease in presynaptic (sodium and calcium channel) nicotinic alpha7 receptors in the PFC of patients with a diagnosis of schizophrenia has been found [72]. As significant numbers of nico-

tinic receptors, in particular alpha7 and alpha4beta2 receptors are found on axon terminals, this suggests again a role in the modulation of neurotransmitter release [74, 75]. For instance, within the hippocampus, nicotine receptors may modulate the release of a number of neurotransmitters besides DA, including glutamate, GABA, noradrenalin, and ACh [76]. In the midbrain, nicotine receptors lie directly on DA neurons, modulating their firing rate and thereby, DA release in forebrain structures [77]. In rats, the presence of functional muscarinic receptors has been detected on dopaminergic neurons in the substantia nigra and ventral tegmental area [78]. Along similar lines, stimulation with muscarinic M1 agonists decreased DA release, while M2 antagonists stimulated DA release in the dorsal striatum respectively [79]. This is explained by their action on presynaptic inhibitor autoreceptors which are normally stimulated via M1 (Gq coupled) and inhibited via M2 (Gi coupled).

Indeed, *in vitro* and *in vivo* rat experiments showed that both alpha4beta2 and alpha7 nicotinic receptors can modulate DA release in the PFC [80]. Mice experiments showed that prefrontal alpha4beta2 and alpha7 nicotinic receptors are involved in the control of glutamatergic signalling [81]. Along similar lines, rodent studies showed that both nicotinic receptors are indeed involved in PFC related functions, i.e. attention, executive function and working memory [82]. Consequently, alpha7 receptor agonists are currently being developed as to enhance cognitive function in schizophrenia [83].

SIGNAL TRANSDUCTION AND IMPROVEMENT OF COGNITIVE FUNCTION IN SCHIZOPHRENIA

Although many different neurotransmitters appear to be involved in the observed 'hypofrontality' of the prefrontal cortex, it is clear that eventually the action of D1 receptors should be enhanced to attenuate cognitive impairment. This can be accomplished by increasing DA release in the PFC and/or to enhance downstream events that follow DA receptor binding. Fig. 2 illustrates how glutamate is mediating DA release in the PFC and which downstream second messenger signalling cascades are involved.

D1 receptors are stimulatory Gs coupled receptors which activate AC resulting in the increased synthesis of cAMP (Fig. 2). The action of cAMP and its related cellular response is terminated by specific PDEs, i.e. intracellular enzymes that degrade cAMP and/or cGMP. PDEs have been classified into 11 families (PDE1-PDE11) based on several criteria such as subcellular distributions, mechanisms of regulation, and enzymatic and kinetic properties. Most of these families have more than one gene product (e.g., PDE4A, PDE4B, PDE4C, PDE4D). In addition, each gene product may have multiple splice isoform variants (e.g., PDE4D1-PDE4D9). In total there are more than 100 specific PDEs [11].

Specific PDEs can be inhibited with selective PDE-Is. PDE-Is selective for PDEs that degrade cAMP could have potential as cognition enhancing drugs for schizophrenia as they stimulate the PFC D1 receptor-linked cAMP/PKA signalling cascade [84]. Interestingly, in contrast to the approved pro-cognitive drugs including acetylcholinesterase inhibitors, PDE-Is do not target a single neurotransmitter system since they exert their effects on the level of intracellular second messenger cascades that are shared by various transmitter systems. As a result, multiple neurotransmitter systems can be influenced, which might be preferable since optimal cognitive function relies on the action of different neurotransmitters [85, 86]. Of note, cAMP/PKA signalling is also important in the striatum in both direct and indirect pathway interneurons, with a preference for the latter [87, 88]. It is assumed that PDE-Is that act predominantly in indirect pathway GABAergic interneurons should work like DA D2 receptor antagonists and decrease in particular the positive symptoms. In detail, D2 receptors are inhibitory Gi-coupled receptors which decrease cAMP signalling in the indirect pathway. D2 receptor antagonists as well as cAMP-specific PDE-Is increase cAMP signalling.

Fig. (2). Intracellular signalling cascades mediating D1 receptor signalling that could be involved in PFC cognitive function. Glutamate release is mediated presynaptically via a cAMP/PKA as well as cGMP/PKG cascade (see also Fig. 1). Glutamate binds to the NMDA receptor on GABAergic interneurons which inhibit GABAergic interneurons synapsing on dopaminergic neurons. The latter release DA which, after binding to the D1 receptor, stimulate the cAMP/PKA/CREB pathway. Of note, glutamate release and DA release itself are also controlled by $\alpha 4\beta 2$ and $\alpha 7$ nicotinic receptors. Furthermore, metabotropic receptors for ACh (M1 and M4) or 5-HT (5-HT1A and 2-HT2A) can modulate DA release in the PFC although the exact mechanism of action is not clear. (D1: DA type 1; PFC: prefrontal cortex; GC: guanylyl cyclase; AC: Adenylyl cyclase; PKA: phosphokinase A; NMDA: N-Methyl-D-aspartate; GABA: γ -Aminobutyric acid; CREB: cyclic AMP response element-binding protein; M1: muscarinic type 1 receptor)

Glutamate can also bind to G-protein (both Gs and Gi) coupled metabotropic receptors, but the ionotropic NMDA receptor is involved in dopaminergic cognitive function in the PFC. The release of glutamate itself can be stimulated by a presynaptic cAMP/PKA as well as cGMP/PKG cascade (Fig. 2). Inhibition of presynaptic cAMP- and/or cGMP-specific PDEs could therefore also have potential to improve cognitive function in schizophrenia.

PHOSPHODIESTERASE INHIBITION AND COGNITIVE IMPROVEMENT RELATED TO SCHIZOPHRENIA

Despite the recognition of the strong negative impact of cognitive symptoms in schizophrenia, and the proven pro-cognitive effects of PDE-Is in animals, there have been only few clinical trials testing the efficacy of PDE-Is in patients with schizophrenia [89-91]. Cognitive effects of PDE-Is mainly have been described in animal models not related to schizophrenia [92]. Generally, reliable modelling of cognitive deficits related to schizophrenia in animals has proven difficult. However, the use of NMDA antagonists, such as phenylcyclohexylpiperidine (PCP), MK-801 and ketamine, may be valid models with regard to the underlying neurobiological mechanism [93]. Moreover, the behavioural effects partly mimic the deficits as seen in schizophrenia, including some of the cognitive symptoms [94, 95].

Based on the current knowledge of the underlying mechanisms of cognitive impairment in schizophrenia, combined with knowledge on the localization of the different PDE's, assumptions can be made on the efficacy of PDE-Is in the treatment of cognitive deficits in patients with a diagnosis of schizophrenia (Table 1). The following paragraph describes relevant study outcomes in this respect for all PDE families with the exception of PDE6, since this specific family is highly expressed in the photoreceptors of the mammalian retina and not throughout the brain.

PDE1

PDE1 is a dual inhibitor, orchestrating the activity of both cAMP and cGMP [11]. The mechanism of PDE1 differs from other

PDEs in that it is the only PDE that is calcium/calmodulin-dependent. Optimal activity of PDE1 requires the binding of calcium ions. Consequently, PDE1 is a key enzyme in the complex interaction between the second messenger systems relying on cAMP on the one hand, and Ca^{2+} on the other hand. As a consequence, PDE1 inhibitors (PDE1-Is) have little effect on cyclic nucleotide levels in the resting state. They enhance cyclic nucleotide signalling in neurons under conditions that are associated with increased intracellular calcium levels, among which learning.

Within the CNS, PDE1 is present in the neocortex and the hippocampus [96, 97]. Moreover, the abundant expression of PDE1 in specific subsets of neurons in the striatum suggests it may correlate with cells having dopaminergic innervation and/or high levels of neuronal integration [96]. The PDE1-I vinpocetine was discovered in the late 1960's and has been used both in animal models and in humans for different indications. This PDE1-I finds its origin in the periwinkle plant, and as such, it is commonly referred to as herbal medicine. In rats, chronic treatment with vinpocetine improved streptozotocin-induced learning impairment and memory decline in Morris Water Maze and passive avoidance paradigms [98]. The authors suggested that the effect could partly be explained by the normalization of cholinergic function by inhibiting acetylcholinesterase activity. Whether the prevention of cAMP and cGMP breakdown contributes to this positive effect needs further research.

The pharmaceutical industry shows interest in PDE1-I as a specific treatment of cognitive symptoms in schizophrenia [99], but we found no evidence of initiation of clinical trials yet. The PDE1-I vinpocetine has been applied for cognitive symptoms related to other disorders, mainly dementia. Studies have been performed using vinpocetine in cognitive impairment and dementia with mixed results, not supportive for clinical application [100]. Nevertheless, a number of studies showed benefit of this compound in different disorders characterized by cognitive problems, including Mild Cognitive Impairment [101], organic psychosyndromes [102], elderly with chronic cerebral dysfunction [103] and in healthy female volunteers [104]. A more recent phase IV trial with Cognitex,

Table 1. PDE characteristics relevant for therapeutic use in schizophrenia. FC = frontal cortex

	Substrate	Inhibitors evaluated on human cognition	mRNA expression in		
			FC	N.Accumbens	Hippocampus
PDE1	cAMP / cGMP	vinpocetine	+ (1B, 1C)	++ + (1B) (1C)	+ (1B, 1C)
PDE2	cAMP / cGMP	-	++ (2A)	++ (2A)	++ (2A)
PDE3	cAMP / cGMP	cilostazol	~	~	~
PDE4	cAMP	MK-0952, HT-0712, MEM1414, roflumilast	+ (4A, 4B, 4D)	+ (4B)	+ (4B)
PDE5	cGMP	sildenafil, vardenafil, udenafil	~	~	~
PDE7	cAMP	-	~	~	~
PDE8	cAMP	-	+ (8B)	+ (8B)	+ (8B)
PDE9	cGMP	PF-04447943	~	~	~
PDE10	cAMP / cGMP	PF-2545920 (MP-10), papaverine	~	++ (10A)	~
PDE11	cAMP / cGMP	-	~	~	~

Relative expression values normalized with GPS1, RPOL2 and PSMB2 as reference genes, based on Lakics *et al.*, 2010 [109]. ++: 100%, +: 20-40%, ~: ↓20%

a dietary supplement including vinpocetine, was initiated. Cognitex significantly improved memory function in elderly with reported memory impairment [105]. However, this study was uncontrolled and Cognitex contains other ingredients that could have influenced memory function, which makes it hard to draw any conclusions on the specific effects of the PDE1-I. In Alzheimer's disease (AD), vinpocetine showed no cognitive improvement in an early open-label pilot study [106].

In addition to its function as PDE1-I, vinpocetine is a potent vasodilator, with strongest effect in the brain, which could potentially potentiate its suggested effects on memory [107]. Whether PDE1-Is can directly improve memory function in schizophrenia, and whether it will positively affect other cognitive symptoms within this syndrome, still needs to be investigated.

PDE2

PDE2 is part of the dual substrate PDE family, which shows affinity for both cAMP and cGMP, and is cGMP stimulated [11]. It has been demonstrated that PDE2 is observed in various brain regions including the hippocampus, cortex, nucleus accumbens and caudate putamen in healthy adults, people suffering from AD and age-matched controls [108, 109]. PDE2 mRNA is most prevalent of all PDEs in human hippocampus and all cortical regions, i.e. frontal, parietal, and temporal cortex.

With regard to cognitive effects, the most widely used PDE2-I is BAY 60-7550, but there are also other, less specific, inhibitors e.g. exisulind (Aptosyn). In addition to PDE2 inhibition, the latter also inhibits PDE5. Aptosyn has been used in clinical trials in the field of oncology. To our knowledge, cognitive parameters were not included in these trials.

Interestingly, several studies have shown that PDE2 inhibition with BAY 60-7550 reverses memory deficits induced by the NMDA receptor antagonist MK-801 as shown in the T-maze continuous alternation and the object recognition task [110, 111]. The

MK-801-induced memory deficit model is a commonly used model for preclinical research and disrupts particularly short-term memory and attention processes, thereby causing cognitive deficits affiliated to schizophrenia. Furthermore, positive effects of PDE2 inhibition on cognition have also been found in another animal model known to induce deficits related to schizophrenia: (sub)chronic PCP administration [112]. More specifically, BAY 60-7550 reversed PCP-induced attention deficits in the attention shifting task. Additionally, it has recently been found that BAY 60-7550 can affect specifically early information processing in rats [113].

More generally, it has been shown that BAY 60-7550 improved memory function in a variety of tasks in healthy rodents as well as in animals impaired by pharmacological or transgenic intervention (e.g. [114-116]). These findings suggest that PDE2 might be a potential therapeutic route to treat the cognitive deficits in people suffering from schizophrenia, especially since PDE2 is widely available in the relevant areas in the human brain including the frontal cortex, nucleus accumbens and hippocampus.

PDE3

Type 3 PDE-Is are dual inhibitors, preventing the break-down of both cAMP and cGMP. The effects of the PDE3-I cilostazol on cognition, have been assessed in patients with schizophrenia [90]. This clinical study was an open-label pilot study, describing the results of 6 patients. Patients were stable on second generation neuroleptics, combined with biperiden and in most cases, a benzodiazepine. Patients were treated for 8 weeks with cilostazol; 2 weeks 25 mg/d, and 6 weeks 50 mg/d. Six cognitive tasks assessing prefrontal functioning were performed and one memory task. The score on the Trial Making Test showed a significant decrease after 8 weeks of cilostazol treatment as compared to baseline values. This suggests improved visuo-motor search skills, simple attention and processing speed. Some of these cognitive functions were included in other tasks as well, in which no significant improvement was found. Of note, the patients were on drugs that are known to

have pro-cognitive effects. Since the PDE3-I promotes the effects of neurotransmitter systems affected by the drugs the patients were receiving, it might be possible that the resulting improvement is an interaction effect. On the other hand, in advance of the possible use of PDE-Is in the treatment of cognitive symptoms in schizophrenia, it is realistic to assume that PDE-Is will be used as add-on therapy in real-life as well.

In AD, three clinical trials have been performed with cilostazol. Sakurai *et al.* (2013; [117]) describe a sample of 11 patients with mild to moderate AD and cerebrovascular disease who received cilostazol 100 μ g for six months. Whereas the control group of AD patients on clopidogrel or aspirin showed cognitive decline over this period, the cilostazol treated subjects did not. This might indicate that cilostazol prevents AD progression. In addition to stable cognitive performance, cilostazol increased regional cerebral blood flow in the right anterior cingulate lobe. Hence, its effects on cognition might be the result of both PDE inhibition and increased supply of oxygen and brain specific nutrients. The cerebral blood flow increasing ability of cilostazol in humans has been confirmed before in different studies in chronically treated patient groups [118, 119]. Remarkably, this effect was not found in acute treatment in healthy volunteers [120], which suggests that longer term treatment is necessary to exert effects on cerebral blood flow.

A similar study had been initiated in 2011 by the Seoul National University Hospital (Lee (personal communication); ClinicalTrials.gov identifier: NCT01409564). A total number of 36 mild to moderate AD patients treated with donepezil was included in this trial. Subjects were equally divided over a cilostazol (100 mg BID) group and placebo group for 24 weeks. However, no difference between groups was found for cognitive measures which included the Mini-Mental State Exam (MMSE) and the cognitive scale of the cognitive portion of the Alzheimer's Disease Assessment Scale.

In a first pilot trial of Arai *et al.* (2009; [121]), 10 mild to moderate AD patients received 100 mg/day cilostazol as add-on to donepezil (5 mg/day) for a variable period of time, ranging between 1 and 13 months. This study was an open-label, uncontrolled trial. In this small group, a statistically significant improvement on the MMSE was reported during the first six months of follow up.

Taken together, the conflicting results of the AD studies do not allow drawing a clear conclusion on possible cognition enhancing effects of PDE3 inhibition yet. The results of PDE3-I treatment has also been tested on cognitive function in patients with a diagnosis of schizophrenia on antipsychotic treatment. However, its results were not uniform enough to be conclusive yet. More research is needed on PDE3 inhibition and its possible cognition enhancing effects in general and schizophrenia in particular.

PDE4

Different PDE4 inhibitors (PDE4-Is) are available for clinical use and have been tested in both humans and animals on pro-cognitive abilities. However, the focus has been in particular on memory and to our knowledge, there are no clinical trials with PDE4-Is in patients with schizophrenia. Concerning the localization of PDE4, PDE4-Is can provoke their effects in a large number of brain areas, including the cortex, striatum and hippocampus. In these areas mRNA of three of the four isoforms (PDE4A, B and D) have been shown to be present in the human brain [109].

Despite the absence of reports on the relationship between PDE4-I and cognitive symptoms in schizophrenia, PDE4 has been linked to schizophrenia. Different genetic studies have shown a positive relationship between PDE4B polymorphisms and schizophrenia, which seem to result in significantly decreased PDE4B levels as detected in postmortem brain tissue [122, 123]. Since PDE4 selectively degrades cAMP, cGMP levels are not affected [11]. In addition, low PDE4B levels do not necessarily result in increased cAMP levels. Several compensatory mechanisms can be

activated that counteract the decreased degradation of cAMP by PDE4B. Therefore, the functional meaning of this polymorphism remains to be elucidated.

In rats, PDE4A mRNA showed more than a twofold expression change in response to PCP. Following, the same authors found significant associations between the occurrence of schizophrenia and single nucleotide polymorphisms in PDE4A [124]. However, since those polymorphisms do not directly influence gene expression, its functional meaning, again, is unclear. Administration of rolipram, a selective PDE4-I, in rats treated with PCP significantly improved the selective impairment on extradimensional shift performance in an extradimensional-intradimensional test of cognitive flexibility [112].

A third genetic link is related to the gene Disrupted-in Schizophrenia-1 (DISC1). A chromosomal translocation disrupts this gene and increases susceptibility for major psychiatric disorders, including schizophrenia [125, 126]. Moreover, it has been linked to decreased cognitive functioning. HEP3, a haplotype of DISC1, was associated with decreased short-term visual memory in affected offspring of patients with schizophrenia and attention was decreased in both affected and unaffected offspring [127].

All PDE4 isoforms, A–D, directly bind to DISC1 which acts as a molecular scaffold that integrates the cAMP modulatory activity of PDE4 [128]. Mutations both in DISC1 and in particular in the PDE4B gene have been found to potentially alter the interactions within this co-complex. Loss of function of DISC1 increases PDE4D transcription [129], which should negatively impact cAMP levels. Moreover, in mice brain it was discovered that D1 receptor stimulation increased PDE4D9, indirectly regulated by DISC1. It was suggested that this pathway acts as a feedback mechanisms to control dopaminergic signalling [129]. Thus, considering the specific subcellular locations of DISC1 and the PDE4 isoforms, impaired DISC-PDE4 interactions result in dysregulated cAMP signalling in specific cellular compartments as has been found in the mitochondrion [128, 130].

In contrast to the absence of studies that focus on the pro-cognitive effects of PDE4-Is in schizophrenia, different studies have been initiated in the past few years that investigate the cognitive effects of PDE4-Is in AD and related disorders. However, the status and outcomes of these studies including MK-0952 and MEM1414 remain unclear. Another PDE4-I named HT-0712 was tested in a 28-day Phase 2a study including 56 subjects with age-associated memory impairment. No formal peer-reviewed publication is available, but the compound was reported to have no effects on measures of short-term memory and a statistically significant 15% increase on long-term memory as assessed with a word learning task (www.dartneuroscience.com). Recently, a follow-up Phase 2 study has started to test again the effects of HT-0712 on age-associated memory impairment (ClinicalTrials.gov identifier: NCT02013310). In depression, another compound, ND1251, was reported to improve memory in a group of 8 subjects (<http://www.outsourcing-pharma.com/Preclinical-Research/PDE4-re-emerges-as-depression-therapy>). Again, no details on methodology are available to the scientific community.

In the field of dementia, studies have been performed in larger groups. Denbutylline is a xanthine derivate with PDE4 inhibitory activity [131]. In total, 336 patients with different types of dementia received denbutylline for 16 weeks [132]. Patients were divided over three dosage groups; 25, 50 or 100 mg twice a day, in addition to a placebo group. Every four weeks patients performed a cognitive battery consisting of the MMSE, digit symbol substitution subtests of the Wechsler Adult Intelligence Scale, and the vocabulary subtest of this scale. Patients on denbutylline showed a 3% increase on the MMSE, which was statistically different from the 4% decrease in the placebo group. However, the clinical meaning of the increase needs to be determined.

Saletu *et al.* (1992; [133]) performed a study in which 96 mildly to moderately demented patients were assigned to either denbufylline (100 mg BID) or placebo treatment for a period of 12 weeks. In addition, electrophysiological correlates were included. Assessments included Clinical Global Impression, the Mini-Mental State [134], the SCAG [135], the Digit-Symbol Substitution Test [136], and secondary target variables: the Trail-Making Test [137] and the Digit Span Test [136]. In both groups, patients showed treatment induced improvements on all tasks, with significantly stronger increases in the denbufylline group as compared to the placebo group. Clinical Global Impression was reduced with one point in the denbufylline group, based on which the authors concluded that the denbufylline induced changes were clinically relevant.

In sum, PDE4 seems to be a promising target for cognitive improvement, in particular memory improvement. More detailed knowledge of the functional meaning of the different genetic variation as found in schizophrenia in relationship to PDE4 functioning is needed, but the findings reported so far may be reasonably solid. This potentially offers a starting point for investigations into the possible positive effects of PDE4-Is in schizophrenia.

PDE5

In contrast to the previous PDEs, PDE5 is cGMP specific [11]. PDE5 mRNA has been detected in Purkinje cells and – to a limited amount – in the hippocampus, cortex and dentate gyrus in rodents and healthy adults, but its expression is questionable in the brains of people suffering from AD and age-matched controls [108, 109] which limits the translational value of results from this cognitively impaired group, as well as the possibility to treat older patients with this group of drugs.

Different PDE5-Is are available for clinical use and include among others sildenafil, vardenafil, tadalafil, udenafil and avanafil. The PDE-5 inhibitor sildenafil, marketed under the name Viagra [138], is the most evaluated PDE-I in schizophrenia. Focus was on improving erectile dysfunction (ED), related to antipsychotic medication use. Since Prickaerts *et al.* [139] showed that PDE5 inhibition can also enhance memory function in rats, research shifted towards the potential of PDE5-Is as cognition enhancers (for a review see [92]). It has been demonstrated that PDE5 inhibition can improve memory, learning and executive functioning in unimpaired as well as impaired rodents. Two animal studies showed pro-cognitive effects of PDE5-Is in models affiliated to schizophrenia, i.e. PCP and MK-801, using the extradimensional-intradimensional (ED/ID) test of cognitive flexibility and an object recognition task respectively [112, 140]. Of note, the PDE5-I UK-343,664 which failed to penetrate the blood brain barrier, could not prevent MK-801 induced memory disruption [140]. These promising results in rodents were preceded by positive effects of the PDE5-I sildenafil on executive functioning in a prefrontal task in cynomolgus macaques [141].

Two studies have been performed in patients with schizophrenia that describe the effect on cognitive parameters. Goff *et al.* [89] demonstrated that acute add-on treatment with sildenafil 50 and 100 mg, did not affect cognition and positive or negative symptoms in 17 patients suffering from schizophrenia. The effects of sildenafil on five cognitive domains were assessed immediately and during a 48 h delayed recall, using a verbal learning task, letter-number sequencing, digit symbol, category fluency, continuous performance, and spatial span.

In contrast to the absence of positive effects in response to acute treatment with sildenafil, a study in which this drug was administered chronically did find a positive effect. Akhondzadeh *et al.* (2011) demonstrated that chronic administration of sildenafil as augmentation therapy to risperidone treatment further reduced negative symptoms in people suffering from schizophrenia. Cognitive measures were not included in this study. However, considering the similarity in dysfunctional pathways as described for cogni-

tive and negative symptoms, pro-cognitive effects can be expected to coincide with improvement of negative symptoms.

In healthy adults, acute administration of sildenafil has also shown not to affect the behavioural performance on cognitive tasks. However, some effects on late phase Event-Related Potentials were found [142-144]. These effects could be explained as enhanced ability to focus attention, and select relevant target stimuli that would become apparent under demanding situations [143].

Low-dose treatment with the PDE5-I udenafil for two months led to an improved performance on the Korean MMSE and an assessment battery of frontal executive functioning in men suffering from ED [145, 146].

Overall, with regard to cognition, PDE5-Is have yielded mixed results. Animal data, including pharmacological models mimicking characteristic features of schizophrenia, seem promising and encouraged the initiation of clinical trials. Due to the age-related decline in PDE5 levels, treatment with PDE5-Is would not be indicated in elderly, but in subjects with ED with a mean age of 55 years, cognitive improvement was reported [145]. In patients with schizophrenia, two studies were performed [89, 91]. Positive effects were reported only after chronic treatment [91]. In this study, tests assessing cognitive performance were not included. However, the reported improvement of negative symptoms suggests that chronic PDE5 inhibition may induce cognitive improvement in schizophrenia.

PDE7

Relatively low expression of the cAMP-specific PDE type 7 family [109] might possibly explain the limited interest for the development of specific inhibitors for this family. However, the low availability of the target enzyme is not necessarily a disadvantage. The pharmacological target of PDE-Is is an intracellularly acting enzyme, which differ with regard to pharmacodynamic profile from receptors. In case of enzymes, limited inhibition might therefore prove to be optimal.

Two preclinical studies have been published that describe the effects of a PDE7-I on cognition. Lipina *et al.* (2013; [147]) performed a study in C57BL/6J mice treated with VP1.15 (3 mg/kg and 7.5 mg/kg), a dual inhibitor of PDE7 and glycogen synthase kinase-3 (GSK-3). GSK-3 is known to interact with DISC1.

An extensive cognitive battery was evaluated assessing the effects of PDE7-Is on the following domains: locomotor activity (open field), information processing (PrePulse Inhibition (PPI) of Acoustic Startle Response), attention (Latent Inhibition (LI), and memory (Puzzle-box, spatial object recognition, Y-maze, fear conditioning). VP1.15 facilitated PPI, enhanced LI, facilitated working/episodic memory and long-term cued fear memory. In addition, two pharmacological models affiliated to schizophrenia were evaluated to study the effect of VP1.15 on specific cognitive deficits. Mice received i.p. treatment with d-amphetamine to increase DA levels, and the NMDA antagonist MK-801. The authors report results obtained from the pharmacologically impaired animals on early information processing only. Amphetamine induced PPI and LI deficits could be reversed with VP1.15. MK-801 impaired PPI and LI as well, but VP1.15 treatment was unable to correct this in the MK-801 model.

In a mouse model of AD, double transgenic APP/Ps1 mice (5-month-old) received S14 injection (i.p., 5 mg/kg daily for 4 weeks) [148]. S14 attenuated nonspatial visual recognition memory to the extent that it equalled values of wildtype control mice.

The absence of clinical trials with PDE7-Is makes it hard to predict effects in schizophrenia. Both VP1.15 and S14 inhibit PDE7, but their potential effects on DISC1 via GSK-3 could contribute to the cognitive effects as well. The development of PDE7-Is without GSK-3 inhibition will shed light on the mechanism of the reported pro-cognitive effects. Regardless of the dual inhibitory

activity, these inhibitors might prove beneficial in the treatment of cognitive symptoms in schizophrenia.

PDE8

The cAMP-specific PDE type 8 is expressed throughout the brain, with particularly strong PDE8B expression in all cortex regions, hippocampus, thalamus and hypothalamus [109]. The distribution of PDE8 makes it an attractive target for cognitive improvement. However, to our knowledge, PDE8-Is have not been tested on cognition.

PDE9

The development of PDE9-Is is still in an early phase, but one PDE9AI has entered clinical trials that focus specifically on cognitive effects in mild to moderate AD. The first report on cognitive effects of PDE9-Is appeared in 2008. Van der Staay *et al.* (2008; [149]) showed enhanced acquisition, consolidation, and retention of long-term memory in a social recognition task and a tendency to enhance long-term memory in an object recognition task in rodents following BAY 73-6691 injection. Moreover, using the MK-801 model, BAY 73-6691 could partially restore disrupted functioning of the working memory as assessed with T-maze continuous alternation [149].

A second PDE9A-I named PF-04447943 is a potent inhibitor of human recombinant PDE9A, with IC₅₀ values reaching 12 nM and relatively good brain penetration with mouse B:P ratio 0.39 [150]. In rodents, this compound was able to significantly improve cognitive performance at 1-3 mg/kg p.o. in different assays. In mice, natural forgetting was improved in both Y maze spatial recognition and a social recognition model. In rats pre-treated with scopolamine, PF-04447943 attenuated novel object recognition [151] and attention [152]. In addition, PF-04447943 fully restored D-amphetamine-induced deficits in sensory gating [150], an early information filtering process, known to be disturbed in schizophrenia [153]. The PDE9A-I PF-4449613, was able to restore this deficit as well, but less efficiently. See table 2 for an overview.

In human subjects, PF-04447943 was tested in a Phase II study in patients with mild to moderate AD [154]. Ninety-one subjects received 25 mg (BID) for twelve weeks and were compared to a control group (n=100). Cognitive performance was assessed at a three week interval with Alzheimer's Disease Assessment Scale-cognitive subscale, The Neuropsychiatric Inventory and Clinical Global Impression-Improvement scale. However, no effects were found on cognition in humans.

In sum, positive effects in rodents have been shown after PDE9-I treatment on different cognitive parameters relevant for schizophrenia. One clinical trial was performed in AD patients [154], but only limited data is available from this trial and results were described of one dose only. With the narrow effective range of PDE-Is, it is advisable to study at least three different dosages in a broader range. Moreover, in this study, cognitive functioning was assessed with commonly used and validated scales, but the results have limited relevance for cognitive functioning in patients with schizophrenia. Considering the effects of PDE9 on cGMP and their comparable expression (Table 1), inhibitors of this type of PDE might induce effects similar as PDE5-Is. However, at this point, it is too early to draw any conclusions on the effects of PDE9-Is in schizophrenia. Additional pre-clinical and broad range clinical studies are necessary to assess the potential of this PDE-I.

PDE10

PDE10 is a member of the dual substrate PDE family and thus affecting the breakdown of both cAMP and cGMP [11]. PDE10 mRNA is most pronouncedly expressed in the caudate nucleus and nucleus accumbens, similar to PDE1, and to a lesser extent in the CA regions of the hippocampus and the cortex in both rodents and humans [109, 155-157].

One of the most widely used PDE10-Is is papaverine. Due to the increased attention for PDE10-Is as treatment for schizophrenia, more selective PDE10-Is have been developed, including TP-10, PQ-10, MP-10, OMS824, THPP-1 and hydrazine-based small molecules, that are specific for the PDE10A isoform. These PDE-Is were developed with a focus on schizophrenia because of the high expression of PDE10A in the striatum, the single discovered isoform of the PDE10 family. PDE10 is thought to be predominantly expressed in the striatal indirect pathway and therefore considered as therapeutic drug target to treat the positive symptoms [88].

PDE10 inhibition improves memory function in unimpaired as well as in impaired rodents, including the reversal of MK-801-induced memory deficits as assessed with the object recognition task and social odor recognition [111, 158]. Furthermore, papaverine was able to reverse PCP-induced deficits in the attention shifting task in rats [112, 159] and compound 56, a hydrazine-based small molecule, was able to reduce PCP-induced hyperactivity [160], which should be predictive of antipsychotic property [161]. Additionally, PDE10-Is showed positive effects on information processing in general [113], but also more specifically on auditory gating and pre-pulse inhibition in rats, by reversing D-amphetamine [162] and MK-801-induced deficits [158] respectively. Finally, PDE10 inhibition disrupted conditioned avoidance responding, which is a preclinical model predictive of antipsychotic activity, showed less susceptibility to extrapyramidal side effects and improved social approach/avoidance performance in rodents [158, 162, 163].

The above studies all describe the acute effects of PDE10-Is. One study describing long-term treatment in 8weeks old wildtype mice reported mild cognitive disturbances and increased anxiety after 42 days of papaverine treatment [164]. The behavioural effects were accompanied by a decrease in CREB levels within the hippocampus. Treatment with the PDE10-I THPP-1 improved novel object recognition in rats and object retrieval in ketamine treated rhesus macaques. Rats receiving THPP-1 showed increased phosphorylation in the striatum of all target proteins, the GluR1 subunit of the AMPA receptor, ERK and CREB. THPP-1 seems to induce changes in biological activity of components of dopaminergic and glutamatergic pathways within the striatum [165]. The GluR1 subunit is regulated by D1 activation, and both ERK and CREB are involved in transcription in dopaminergic and glutamatergic cells. Moreover, in MK-801 treated rats, THPP-1 attenuated psychomotor activation, which has claimed to be predictive of antipsychotic property [165].

In patients with schizophrenia, the PDE10A-I PF-2545920 (or MP-10) was tested in a second Phase-II clinical study after a first study had been terminated, the reasons of which were not disclosed. PF-2545920 5mg, 15 mg and placebo were administered (BID) to three groups of 74 patients, and 36 additional subjects received the atypical antipsychotic risperidone. Patients were diagnosed with schizophrenia and presented with an acute exacerbation of their symptoms [166]. After 4 weeks of treatment, the PF-2545920 treatment group showed no improvement as compared to the placebo group, whereas the risperidone group did show a decrease in total Positive and Negative Symptom Scale (PANNS) score. Whether there were any effects on cognition in these patients is not known to us. Moreover, cognitive effects should not be assessed in the acute state [167]. Thus, the usefulness of PDE10 inhibition to treat schizophrenia appears limited based on this first study. However, pre-clinical data including cognitive parameters are encouraging. Therefore, a study on cognitive outcomes in patients not in acute state is warranted.

PDE11

PDE11 is the most recently discovered family of PDEs and is a dual substrate PDE [11]. This family contains one gene, PDE11A,

with four isoforms (PDE11A1-PDE11A4). The physiological role of PDE11A is not clear yet.

DISCUSSION AND CONCLUSION

PDE-Is prolong the availability of the second messengers cAMP and/or cGMP. These second messengers play an important role within the neurotransmitter systems that are affected in schizophrenia. Since neurotransmitter systems are subject to strong interactions, malfunctioning of one system can induce or aggravate problems of a second system. In theory, optimizing the signalling of the hypofunctional postsynaptic NMDA receptors on GABAergic interneurons in the frontal cortex should improve both positive symptoms and negative/cognitive symptoms. The hypofunctional post-synaptic NMDA receptors in these neurons prevent sufficient inhibition of the glutamatergic cortical brainstem projection, a descending pathway projecting from the prefrontal cortex to brainstem centers, including the ventral tegmental area [57]. The second messengers cAMP and cGMP are involved in the synthesis and release of glutamate. Limiting the degradation of cAMP and cGMP by introducing PDE-Is restores the signal of the inhibitory GABAergic interneuron.

With regard to the cognitive symptoms and the underlying neurochemical disturbances that are thought to operate in schizophrenia, the reduced dopaminergic tone in the PFC should be targeted (see Fig. 2). In this area, the D1 receptor is the main post-synaptic DA receptor. As described above, D1 receptors are Gs-coupled receptors which act via cAMP signalling. Thus, in addition to opti-

malisation of NMDA function in GABAergic interneurons in the cortex, PDE-Is could have a binary effect by simultaneously improving the signal of post-synaptic D1 receptors. Preferably, these effects should be limited to the frontal cortex. PDEs for which selective inhibitors are available are present in the frontal cortex in humans (see Table 1) and offer potential for treatment options. This has already been demonstrated in mouse brain with the PDE4-I rolipram [168]. Moreover, in addition to enhanced D1 signalling, the authors showed an increased pre-pulse inhibition of the acoustic startle response in mice, suggestive of its ability to improve early information processing.

Of the three PDE-Is actually tested in patients with schizophrenia, i.e. PDE3, 5, and 10, only the PDE3-I cilostazol showed indications for improvement of cognitive symptoms. This is in contrast to the encouraging results with PDE5-Is and PDE10-Is obtained in animal studies in which NMDA antagonists were applied, mimicking the dysfunctional NMDA receptors as described in schizophrenia. Thus, the question arises why this does not translate to humans, especially since the inhibition of PDE3 apparently does show indications of positive effects in humans. Characteristic for PDE3-Is is their dual inhibitory activity in combination with their ability to increase cerebral blood flow. At this point, it is unclear whether the cognitive improvement is related to PDE inhibitory activity affecting both cAMP and cGMP levels, to increased cerebral blood flow, or to a combined effect. Moreover, PDE3 mRNA as well as PDE5 and PDE10 mRNA show low relative expression rates within the human brain, including the PFC, with the exception of the high

Table 2. Cognitive outcomes of PDE-I treatment in preclinical models related to schizophrenia.

PDE family	Model	Animal	Test	Outcome
2	MK-801	rat	T-maze continuous alternation [110]	+
		rat	Object recognition task [111]	+
4	PCP	rat	Extradimensional-intradimensional test [112]	+
		rat	Extradimensional-intradimensional test [112]	+
5	MK-801	rat	Object recognition task [140]	+ (*)
		rat	Extradimensional-intradimensional test [112]	+
7 (**)	MK-801	mouse	Prepulse inhibition [147]	=
	D-amphetamine	mouse	Prepulse inhibition [147]	+
			Latent inhibition [147]	+
9	MK-801	mouse	T-maze continuous alternation [149]	+
		mouse	Prepulse inhibition of acoustic startle response [150]	=
	D-amphetamine	rat	Auditory gating [150]	+
	Ketamine	rat	Radial arm maze [150]	+
10	MK-801	rat	Object recognition task [111]	+
		rat	Prepulse inhibition of acoustic startle response [158]	+
		mouse	Social odor recognition [158]	+
	PCP	rat	Extradimensional-intradimensional test [112; 159]	+
	D-amphetamine	rat	Auditory gating [162]	+
		rat	Object retrieval [165]	+
	Ketamine	rhesus		+

+: normalizes disrupted function at optimal dose; *Memory disruption was not restored with the PDE5-I UK-343,664, a PDE5-I that does not penetrate the BBB; **VP1.15 was used in this study which is not selective for PDE7, but also inhibits glycogen synthase kinase-3.

expression of PDE10 in the caudate nucleus [109]. Similar to PDE3, PDE10 is a dual inhibitor, but its action is assumed to be predominantly directed at cAMP. PDE5 has only cGMP as substrate. As mentioned above, it is likely that an increase in cognitive functioning is related to upregulation of NMDA receptor – D1 receptor signalling pathways. The former can be stimulated by increasing cAMP and/or cGMP, while the latter can be stimulated by increasing cAMP only. In the end, the exact location of specific PDEs in these signalling pathways determines their role. Whether this contributes to the discrepancy between human and animal studies remains to be investigated. Another point of discussion is the kind of animal models that have been used to test the potential of PDE-Is. Until now, cognitive function has been assessed only in animal models dependent on pharmacologically induced symptoms that are mechanistically and behaviourally related to schizophrenia (Table 2). Genetic models, lesion models and models of developmental disorders of primary brain structures have the advantage of sustained distortion of normal function, including developmental aspects and the absence of drug interactions [169]. Preferably, cognitive testing should not be limited to pharmacological models.

Direct comparison of the methodological aspects of the human studies reveals some major differences which might explain the different outcomes. The PDE3-I cilostazol was administered for eight weeks [91], whereas the PDE5-I sildenafil was administered acutely in a trial in which cognition was assessed [89]. Long-term treatment with sildenafil did improve negative symptoms [91]. Since negative and cognitive symptoms in schizophrenia largely rely on the same signalling pathways [57], it is conceivable that patients with a diagnosis of schizophrenia will benefit from chronic sildenafil treatment with regard to their cognitive impairments. However, these patients were tested in the active phase of the illness, with the threshold for the negative subscale of the PANNS set at a minimum score of 20. Cognitive effects should preferably be assessed in a stable phase [167]. It is difficult to predict whether sildenafil will have an equally strong effect on negative and possibly cognitive symptoms in the absence of acute pathology.

More generally, it has been acknowledged that many factors among which clinical status, disease severity and duration, and pharmacological profile, contribute to the heterogeneity of patient populations, which hampers comparability. Guidelines developed specifically to assess more uniformly the effects of cognition en-

hancers in patients with schizophrenia [167] were followed only partly by the studies described above, or were not described explicitly. For instance, indications on disease severity, and illicit drug and medication use were not always provided, or patients were unstable, or stable for a relatively brief period of time.

At this point, it is too early to draw conclusions from the studies performed in human subjects (Table 3). The finding of improved negative symptoms with sildenafil and improved cognitive functions after cilostazol are encouraging. However, since the cilostazol study was performed according to an open-label design and included only six subjects [90], replication in a larger, well-controlled sample is warranted.

Most research on cognitive impairment in schizophrenia has focused on prefrontal functions. However, dysfunction of the medial temporal lobe, affecting in particular episodic memory, is also observed in patients with a diagnosis of schizophrenia. An early meta-analysis showed considerable memory deficits in patients with schizophrenia, in particular impaired recall. The authors suggested that a combination of impaired consolidation and possibly impaired retrieval was the underlying problem [170]. Others have disputed this and claim that it can be attributed primarily to comorbid depressive states [171]. Irrespective of the underlying mechanism, stimulating synaptic plasticity within the medial temporal lobe should alleviate memory problems related to consolidation and retrieval. Therefore, results from studies in which PDE-Is were applied to ameliorate mental states characterized by impaired memory functioning, could predict the potential of PDE-Is with regard to retrieval in schizophrenia.

Memory function of both patients with AD and milder forms of memory impairment, as well as of healthy subjects has been assessed following PDE-I treatment. In AD, treatment with the PDE1-I vinpocetine and PDE9-I PF-04447943 did not improve memory. Remarkably, long-term treatment with the PDE3-I cilostazol 100 mg/day prevented further deterioration [117] and even improved memory [121] in mild to moderate AD patients. In a third study (Lee (personal communication); ClinicalTrials.gov identifier: NCT01409564), a dose of cilostazol twice as high was administered to AD patients, but was found to be ineffective in improving cognitive function. The effective dose range of PDE-Is is known to be fairly small, according to an inverted U-shape profile found in numerous preclinical studies (e.g. [92]). This could possibly explain

Table 3. General overview of outcomes of studies relating PDE-Is and cognitive functioning related to schizophrenia.

	Schizophrenia	Alzheimer's Disease	Aged/Mild impairment	Unimpaired subjects	Animal models of schizophrenia
PDE1	NT	=	+	+	NT
PDE2	NT	NT	NT	NT	+
PDE3	+	+/=	NT	NT	NT
PDE4	NT	NT	+	NT	+
PDE5	=	NT	NT	+/=	+
PDE6					
PDE7	NT	NT	NT	NT	+/=
PDE8	NT	NT	NT	NT	NT
PDE9	NT	=	NT	NT	+/=
PDE10	=	NT	NT	NT	+
PDE11	NT	NT	NT	NT	NT

=: no effect; +: improvement; NT: not tested

the discrepancy between results. Moreover, in the study of Shirayama *et al.* (2011) in patients with schizophrenia, cognitive improvement was achieved at doses as low as 50 mg daily.

The PDE1-I vinpocetine showed positive effects in Mild Cognitive Impairment [101], organic psychosyndromes [102], elderly with chronic cerebral dysfunction [103] as well as in healthy female volunteers [104]. In AD, mixed results have been described [100, 106]. Crucial for the function of PDE-Is are intact neuronal pathways. PDE-Is can exert their stimulatory effects only on intracellular cascades after binding of a first messenger to its receptor. Therefore, the effect of PDE-Is in AD might be dependent on the degree of neurodegeneration. In early or prodromal states, the effect of PDE-Is might be stronger due to higher availability of its target enzyme.

Positive findings in age-associated memory impairment have also been described for the PDE4-I HT-0712. Unfortunately, study details were not disclosed. However, in unimpaired subjects, single dose administration of the PDE5-I sildenafil did not show effects on a behavioural level, although electrophysiological changes were observed [142, 143]. This could be in line with the absence of memory improvement in patients with schizophrenia.

Inhibition of both cAMP and cGMP specific PDEs show positive results in animal models of schizophrenia as well as in human memory impairment. Combining these effects with a dual inhibitor might therefore be favourable. So far, positive effects on cognitive symptoms in schizophrenia have only been obtained in a study with the clear dual-substrate inhibitor cilostazol. Therefore, there is a need of a larger trial with a specific PDE3I. Other dual-substrate inhibitors including PDE1 and 2 that not have been tested in patients with schizophrenia yet, but might prove to be effective as well, especially considering their positive effect in animal studies on memory (PDE1-I; [172]; PDE2; [110]). PDE1 might be of special interest due to its specific calcium/calmodulin-dependent activity with no effect on basal cyclic nucleotide signalling. Increased levels of intracellular calcium trigger its enzymatic action. Since cognitive processes rely on neurotransmitter signalling, effects of PDE1 inhibition are therefore only effective during such processes, not affecting basal states.

PDE10-Is have received most attention as potential drug to treat positive symptoms in schizophrenia due to the high expression of the target enzyme in the striatum [109]. Animal studies have indeed shown positive results, but the only study in human subjects with schizophrenia did not show improvement as assessed with the PANNS [166]. However, in this study subjects with acute exacerbation of their complaints were included. Therefore, the results of this study are most indicative of a possible effect of a PDE10-I on positive symptoms. As stated before, cognitive traits in schizophrenia are stable and persist in between episodes characterized by psychotic symptoms. Since impaired cognitive functioning is a strong contributor to the decreased quality of life, efforts should be made to improve overall cognitive functioning, in particular during periods in which patients are relatively stable. A clinical trial with a PDE10-I in which a cognitive test battery is included, will be needed before definite conclusions can be drawn on the potential of PDE10 inhibition to treat schizophrenia.

In conclusion, considering the critical role of the second messengers cAMP and cGMP in the effectuation of neurotransmitter signalling, preventing their breakdown directly potentiates the effects of different neurotransmitter systems throughout the brain. In schizophrenia, strengthening the signal of both the dysfunctional NMDA receptors and the post-synaptic D1 receptors in the PFC should improve cognitive functioning in these patients. Results from animal studies are hopeful, but still need to show their translational value. Taking into account the limited data available from clinical trials, PDE3-Is seem most promising, with positive effects reported on cognitive symptoms in schizophrenia and memory im-

provement in AD. Other dual inhibitors have shown positive effects on cognition in unimpaired subjects (PDE1-I) and animal models of schizophrenia (PDE2-I, PDE10-I) and long-term clinical trials in patients with schizophrenia in a stable phase are warranted. Especially PDE1-Is are of interest due to the calcium/calmodulin-dependent activity of PDE1s. cGMP specific PDE-Is seem promising as well considering their effects in animals models and the positive effects of the PDE5-I sildenafil on negative symptoms.

The field is still in its infancy, but the first results are encouraging. Cognitive improvement in patients with schizophrenia currently is an unmet need and the potential gain is significant. Current developments in the field of PDE-Is may be hopeful in this respect, and therefore further research on the cognition enhancing effects of PDE-Is in this disorder should be stimulated.

ABBREVIATIONS

PDE(-I)	=	phosphodiesterase (inhibitor)
DLPFC	=	dorsolateral prefrontal cortex
ACC	=	anterior cingulate cortex
IP ₃ /DAG	=	inositol-1, 4, 5, triphosphate/diacylglycerol
PIP ₂	=	phosphatidylinositol 4, 5-bisphosphate
PLC	=	phospholipase C
AC	=	adenylate cyclase
NMDA	=	N-Methyl-D-aspartate
CaMK	=	Ca ²⁺ /CaM protein kinase
AMPA	=	α -Amino-3-hydroxy-5-methylisoxazole-4-propionic acid
PKC	=	phosphokinase C
cAMP	=	cyclic adenosine monophosphate
CREB	=	cAMP response element binding protein
NOS	=	nitric oxide synthase
GC	=	guanylate cyclase
PKG	=	cGMP-dependent protein kinase
GABA	=	γ -Aminobutyric acid
DA	=	dopamine
D1/2 receptor	=	DA receptor type 1/2
5-HT	=	serotonin
ACh	=	acetylcholine
PCP	=	phenylcyclohexylpiperidine
AD	=	Alzheimer's Disease
MMSE	=	Mini-Mental State Exam
DISC1	=	Disrupted-in Schizophrenia-1
PPI	=	PrePulse Inhibition
LI	=	latent inhibition
GSK-3	=	glycogen synthase kinase-3
PANNS	=	Positive and Negative Symptom Scale

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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