Selective phosphodiesterase inhibitors: a promising target for cognition enhancement

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Abstract
Rationale One of the major complaints most people face during aging is an impairment in cognitive functioning. This has a negative impact on the quality of daily life and is even more prominent in patients suffering from neurodegenerative and psychiatric disorders including Alzheimer’s disease, schizophrenia, and depression. So far, the majority of cognition enhancers are generally targeting one particular neurotransmitter system. However, recently phosphodiesterases (PDEs) have gained increased attention as a potential new target for cognition enhancement. Inhibition of PDEs increases the intracellular availability of the second messengers cGMP and/or cAMP.

Objective The aim of this review was to provide an overview of the effects of phosphodiesterase inhibitors (PDE-Is) on cognition, the possible underlying mechanisms, and the relationship to current theories about memory formation.

Materials and methods Studies of the effects of inhibitors of different PDE families (2, 4, 5, 9, and 10) on cognition were reviewed. In addition, studies related to PDE-Is and blood flow, emotional arousal, and long-term potentiation (LTP) were described.

Results PDE-Is have a positive effect on several aspects of cognition, including information processing, attention, memory, and executive functioning. At present, these data are likely to be explained in terms of an LTP-related mechanism of action.

Conclusion PDE-Is are a promising target for cognition enhancement; the most suitable candidates appear to be PDE2-Is or PDE9-Is. The future for PDE-Is as cognition enhancers lies in the development of isoform-specific PDE-Is that have limited aversive side effects.

Keywords PDE inhibitors · Cognition · cAMP · cGMP · Memory · LTP

One of the problems many people come to face as they age is a decline in cognitive functions, which has a negative impact on their daily activities and quality of life (Mattson et al. 2002). The loss of cognitive functioning is even more serious in patients suffering from pathological conditions such as Alzheimer’s disease or other types of dementia. Also in depressed and schizophrenic patients, prominent cognitive deficits are present (Blaney 1986; Frith 1996). Since these deficits have a major impact on the quality life of these patients, it is of utmost importance to develop strategies or drugs that counteract cognitive decline. So far, several preventive strategies have been described which could ameliorate or slow down the cognitive decline resulting from brain aging. Research has focused on avoiding genetic and environmental factors that cause neuronal dysfunction and death or by enhancement of the ability of neurons to adapt to...
the aging process (Mattson et al. 2002). Examples of avoiding genetic factors are genetic counseling or germ line gene therapy and examples of avoiding environmental factors are dietary restrictions or behavioral modification. These strategies can induce successful aging and can reduce the risk of cognitive decline and dementia (for review, see Mattson et al. 2002). Despite these strategies, there is a great need for drugs that counteract the processes involved in aging and more specifically the decline of cognitive functions and memory.

For cognition enhancement or reversal of cognitive deficits, different drug targets have been suggested based on neurotransmitter systems. Serotonergic, cholinergic, and monoaminergic neurotransmitter systems have been shown to be involved in cognition. Furthermore, cognitive performance, including memory, can be improved by numerous biological factors such as neuromodulators, hormones, intracellular molecules, plant extracts, and nutritional ingredients, which enhance neurotransmission, blood flow, glucose metabolism, or have free radical scavenging properties (Cahill et al. 1994; Davis and Squire 1984; De Zazzo and Tully 1995; Izquierdo et al. 1998; McGaugh 1989; Messier 2004; Parrott et al. 2004).

Second messengers cAMP and cGMP

A relatively novel and promising field in cognition research focuses on the involvement of second messenger systems. Neurotransmitter receptors can be divided into two main groups according to the way in which receptor and effector function are coupled. One group consists of ionotropic (ion channel) receptors and the other consists of the GTP-binding protein (G protein) coupled receptor. G protein activation engages second messenger cascades (Shah and Catt 2004). Traditionally, the cyclic adenosine monophosphate (cAMP) second messenger system (Gs and Gi linked) and the phosphoinositol second messenger system (Gq-linked) received the most attention. The second messenger cAMP is synthesized by adenylyl cyclase (AC), which is stimulated or inhibited by Gs or Gi, respectively. The second messenger complex inositol-1,4,5-triphosphate/diacylglycerol (IP3/DAG) is formed out of the hydrolysis of phosphatidylinositol 4,5-biphosphate (PIP2) by phospholipase C (PLC) after activation by Gq. 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. DAG activates calcium-dependent protein kinase (PKC) in the presence of calcium (Ca$^{2+}$), which is mobilized by IP3. PKC has an effect on CREB via the MAP kinase pathway. Of note, Ca$^{2+}$ can also bind to calmodulin. This so-called Ca$^{2+}$/CaM complex activates Ca$^{2+}$/CaM protein kinase (CaMK), which can activate calcium-dependent protein kinase (PKC) as well, but also PKA. On the other hand, PKA can also activate the MAP kinase pathway. Thus, interplay exists between the cAMP second messenger system and the phosphoinositol second messenger system. Recently, the cyclic guanosine monophosphate (cGMP) second messenger system receives more and more attention. cGMP is produced by guanylate cyclase (GC) which is stimulated by nitric oxide (NO) (Murad et al. 1978). cGMP activates cGMP-dependent protein kinase (PKG), which in turn phosphorylates certain proteins which influence the synthesis and/or release of other neurotransmitters, and thus signal transduction (Schmidt et al. 1993).

Cyclic nucleotide phosphodiesterases (PDEs) are enzymes which play an important role in the abovementioned intracellular signal transduction pathways. This is because these enzymes hydrolyze the second messengers cAMP and cGMP by breaking their phosphodiester bond with the corresponding monophosphate (Bender and Beavo 2006). There are 11 families of PDEs (PDE1–PDE11) and 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 variants (e.g., PDE4D1–PDE4D9). In total, there are more than 100 specific human PDEs (Bender and Beavo 2006).

Localization of PDEs

PDE1 is predominantly localized in the brain, heart, smooth muscles, and lungs (Dent et al. 1998; Sonnenburg et al. 1998; Yan et al. 1994). In addition, PDE2 can be found in the brain, heart, adrenal cortex, and platelets (Ito et al. 1996; Martins et al. 1982; Van Staveren et al. 2003). Furthermore, the localization of PDE3 includes the brain, heart, smooth muscles, kidneys, and platelets (Reinhardt et al. 1995; Shakur et al. 2001). PDE4 is expressed in a wide variety of tissues, e.g., brain, lungs, and testes (Perez-Torres et al. 2000; Reyes-Irisarri et al. 2008; Richter et al. 2005; Salanova et al. 1999). PDE5 has been detected in the brain, lungs, smooth and skeletal muscles, kidneys, and platelets (Giordano et al. 2001; Hotston et al. 2007; Kotera et al. 2000; Yanaka et al. 1998). In contrast, PDE6 has been found in the pineal gland and the rod and cone cells of the photoreceptor layer of the retina (Holthues and Vollrath 2004; Morin et al. 2001; Stearns et al. 2007). PDE7 was identified in the brain, heart, liver, skeletal muscles, kidneys, testes, and pancreas (Hetman et al. 2000; Hotston et al. 2007; Kotera et al. 2000; Yanaka et al. 1998). While the localization of PDE8 includes the brain, liver, kidneys, colon, testes, ovary, spleen, and thyroid (Fisher et al. 1998a; Gamanuma et al. 2003; Hayashi et al. 1998, 2002; Kobayashi et al. 2003; Soderling et al. 1998; Wang et al. 2001). Also, PDE9 is located in the brain, kidneys, spleen, prostate, and various gastrointestinal tissues (Andreeva et al. 2001; Fisher et al. 1998b; Rentero...
et al. 2003; Soderling et al. 1998; van Staveren and Markerink-van Ittersum 2005; Van Staveren et al. 2003; Wang et al. 2003). The localization of PDE10 comprises the brain, heart, muscles, testes, and thyroid (Fujishige et al. 1999; Loughney et al. 1999; Soderling et al. 1999). And finally, it has been shown that PDE11 is primarily located in the pituitary, liver, skeletal muscles, kidneys, testes, prostate, and thyroid (Fawcett et al. 2000).

The localizations of the different PDE isoforms differ between specific brain areas as is illustrated in detail in Table 1. Since PDEs are involved in the regulation of second messenger signaling in numerous important body and brain structures, specific inhibitors of the PDE families have been generated. PDE inhibitors (PDE-Is) increase the intracellular amount of cAMP and/or cGMP by inhibiting the enzymatic degradation of these second messengers, dependent on the substrate specificity of the corresponding PDE (see also Table 2). Several selective PDE-Is and the substrate, i.e., cAMP and/or cGMP, of their target PDEs are classified in Table 2.

By far, not all classes of PDEs have selective inhibitors. In addition, these inhibitors might have poor penetration properties concerning the blood–brain barrier. In the literature, only five PDE-Is have been implicated in behavioral cognition studies, namely, PDE 2, 4, 5, 9, and 10 inhibitors, as will become evident in this review. These inhibitors are widely available, can be administered peripherally, and show central effects. The existing literature on PDE-Is and cognition is rapidly emerging and procognitive effects of PDE-Is have been described in fish, rodents, monkeys, and man (e.g., Best et al. 2008; Rutten et al. 2007b, 2008a; Schultheiss et al. 2001). Studies were conducted to assess the effects of PDE-Is on intact cognition as well as in cognitive deficit models. In addition, knockout models have been developed to study the role of PDEs in cognition processes. This review provides a comprehensive overview of the currently available literature on the effects of selective PDE-Is on cognition in preclinical models. Furthermore, possible implications for human studies are discussed. Finally, the underlying mechanisms of action for the procognitive effects of PDE-Is are

### Table 1 Localization of the different PDE isoforms in the adult brain of rodents and humans

| Isoform | Localization in the brain | Species | Reference |
|---------|--------------------------|---------|-----------|
| PDE1A   | Hippocampus, cortex, olfactory bulb, striatum, thalamus, cerebellum | Human, rat, mouse | Billingsley et al. (1990); Cho et al. (2000); Lal et al. (1999); Yan et al. (1994) |
| PDE1B   | Hippocampus, cortex, olfactory bulb, striatum | Mouse | Cho et al. (2000); Polli and Kincaid (1994); Reed et al. (1998) |
| PDE1C   | Hippocampus, cortex, amygdala, cerebellum | Mouse | Yan et al. (1996) |
| PDE2A   | Hippocampus, cortex, striatum, amygdala, hypothalamus, midbrain | Human, rat, mouse | Bolger et al. (1994); Repaske et al. (1993); Reyes-Irisarri et al. (2007); van Staveren et al. (2004, 2003) |
| PDE3    | Throughout the brain | Rat | Bolger et al. (1994) |
| PDE4A   | Hippocampus, cortex, olfactory bulb, striatum, thalamus, hypothalamus, amygdala, midbrain, cerebellum | Human, rat, mouse | Braun et al. (2007); Cherry and Davis (1999); Cho et al. (2000); D’Sa et al. (2005); Fujita et al. (2007) |
| PDE4B   | Hippocampus, cortex, striatum, hypothalamus, midbrain, cerebellum | Human, rat, mouse | Braun et al. (2007); Cherry and Davis (1999); Cho et al. (2000); Fujita et al. (2007) |
| PDE4D   | Hippocampus, cortex, striatum, hypothalamus, midbrain, cerebellum | Human, rat, mouse | Cherry and Davis (1999); Cho et al. (2000); Fujita et al. (2007); McLachlan et al. (2007); Richter et al. (2005) |
| PDE5A   | Hippocampus, cortex, cerebellum | Human, rat, mouse | Reyes-Irisarri et al. (2007); van Staveren et al. (2004, 2003) |
| PDE7A   | Hippocampus, cortex, olfactory bulb, striatum | Human, rat | Miro et al. (2001); Perez-Torres et al. (2003) |
| PDE7B   | Hippocampus, cortex, striatum, midbrain | Human, rat | Perez-Torres et al. (2003); Sasaki et al. (2002) |
| PDE8B   | Hippocampus, cortex, olfactory bulb, striatum, midbrain | Human, rat | Kobayashi et al. (2003); Perez-Torres et al. (2003) |
| PDE9A   | Hippocampus, cortex, olfactory bulb, striatum, thalamus, hypothalamus, amygdala, midbrain, cerebellum | Human, rat, mouse | Reyes-Irisarri et al. (2007); van Staveren et al. (2004, 2003) |
| PDE10   | Hippocampus, cortex, striatum, midbrain, cerebellum | Rat | Seeger et al. (2003) |

Note that this table does not provide information with respect to the level of expression of the different isoforms in the brain. In addition, expression can implicate mRNA levels or protein levels dependent on the study referred to.
discussed and a concomitantly novel theory describing the relationship between different stages of memory consolidation and different types of long-term potentiation (LTP) is proposed.

Effects of selective PDE-Is on cognition

PDE2

So far, only a couple of studies have been published that investigated the effects of PDE2 inhibition in behavioral models. To our knowledge, BAY 60-7550 is the only selective PDE2-I which has been tested in animal models of cognition (Boess et al. 2004; Domek-Lopacinska and Strosznajder 2008; Rutten et al. 2007b). It has been shown that BAY 60-7550 improved memory acquisition and consolidation in the object recognition task in both rats and mice and consolidation in the social recognition task in rats (Boess et al. 2004; Domek-Lopacinska and Strosznajder 2008; Rutten et al. 2007b). In addition, this PDE2-I improved acquisition and consolidation in the object recognition task in age-impaired rats (Domek-Lopacinska and Strosznajder 2008).

Furthermore, BAY 60-7550 reversed the MK-801-induced working memory deficit in the T-maze in mice (Boess et al. 2004). A more detailed overview of these studies is provided in Table 3.

PDE4

The next section provides a general summary of the available literature on PDE4-Is and cognition. A more detailed overview is provided in Table 4.
Imanishi et al. 1997; Zhang et al. 2000, 2005, 2004). Of note, the effects of rolipram on spatial working memory are twofold; on one hand, rolipram tended to improve working memory in young rhesus monkeys in a delayed responding task (Ramos et al. 2003). However, on the other hand, rolipram had a negative effect on working memory in aged monkeys in this task (Ramos et al. 2003, 2006).

The effects of rolipram on information processing have been studied in several behavioral setups in the prepulse inhibition and startle response task. Rolipram did not only facilitate information processing in unimpaired mice and zebrafish, but also reversed deficits caused by D-amphetamine in mice (Best et al. 2008; Kanes et al. 2007). In contrast, PDE4-I RO-20-1724 did not reverse the prepulse inhibition deficit caused by D-amphetamine (Halene and Siegel 2008). In another model of information processing, sensory gating, this PDE-I increased the amplitudes of P20 and N40 in the CA3 area during the first stimulus and reversed the N40 deficit in the first click caused by D-amphetamine (Halene and Siegel 2008). Additionally, executive functioning was improved in an object retrieval task in cynomolgus macaques after the administration of rolipram (Rutten et al. 2008a). In this task, monkeys try to retrieve a food reward from a transparent box with one open side that alternates between trials. This is a prefrontal cortical-mediated task likely to capture attention and response inhibition, and rolipram treatment significantly dose-dependently enhanced performance, as measured by an increased percentage of correct first reaches.

Besides deficit models based on pharmacological or surgical interventions, the use of transgenic animals, i.e., isoform-specific knockout models of PDE4B or PDE4D, have been recently introduced to study the role of PDE4 in the central nervous system (CNS). It was shown that PDE4B knockout (KO) in mice had no effect on spatial memory performance in the water escape task and the passive avoidance task (Siuciak et al. 2008a). Furthermore, these mice showed an impairment in information processing in the prepulse inhibition task (Siuciak et al. 2008a), although they performed similar to wild-type animals on conditioned avoidance responding (Siuciak et al. 2007). A recent study

| Table 3 Overview of effects of PDE2-Is on cognition |
|-----------------------------------------------|
| **Task (cognitive process, area involved)** | **Model (species)** | **Treatment** | **Results** | **Reference** |
| Object recognition task (object memory, hippocampus and rhinal cortex) | Unimpaired (rat) | BAY 60-7550 (3 mg/kg, p.o.) immediately after 1 h, 3 h or 6 h after first trial (24 h interval T1–T2) | BAY 60-7550 (3 mg/kg, immediately after T1 or 3 h after T1) improved memory consolidation | Rutten et al. (2007b) |
| | Unimpaired (rat) | BAY 60-7550 (0.3, 1 or 3 mg/kg, p.o.) immediately after first trial (24 h interval T1–T2) | BAY 60-7550 (1 or 3 mg/kg, immediately after T1) improved memory consolidation | Boess et al. (2004) |
| | Impaired by age, 3, 12 and 24 months old (rat) | BAY 60-7550 (0.3 mg/kg, s.c.) 1 h before first trial or immediately after first trial (2 h interval T1–T2) | BAY 60-7550 1 h before T1 improved acquisition in all age groups. In addition, it improved consolidation in animals of 3 and 12 months when given immediately after T1 | Domek-Lopacinska and Strosznajder (2008) |
| | Unimpaired (mouse) | BAY 60-7550 (0.3, 1 or 3 mg/kg, p.o.) immediately after first trial (24 h interval T1–T2) | BAY 60-7550 (0.3 or 1 mg/kg, immediately after T1) improved memory consolidation | Boess et al. (2004) |
| Social recognition (social memory, hippocampus and amygdala) | Unimpaired (rat) | BAY 60-7550 (0.3, 0.6, 1, 2, 3 or 6 mg/kg, p.o.) immediately after first trial (24 h interval T1–T2) | BAY 60-7550 (1, 2, 3, or 6 mg/kg, immediately after T1) improved memory consolidation | Boess et al. (2004) |
| | Unimpaired (rat) | BAY 60-7550 (0.3 mg/kg, p.o.) immediately after first trial (24 h interval T1–T2) | BAY 60-7550 (3 mg/kg) reversed MK-801 induced deficit | Boess et al. (2004) |
| T-maze (working memory, hippocampus) | Impaired by MK-801, 0.125 mg/kg, i.p., 30 min before test session (mouse) | BAY 60-7550 (0.3, 1, or 3 mg/kg, p.o.) 30 min before test session | BAY 60-7550 (3 mg/kg) reversed MK-801 induced deficit | Boess et al. (2004) |

T1 trial 1, T2 trial 2, p.o. per os, i.p. intraperitoneal
| Task (cognitive process, area involved) | Model (species) | Treatment | Results | Reference |
|----------------------------------------|----------------|-----------|---------|-----------|
| Water escape task (spatial memory, hippocampus) | Impaired by microsphere embolism-induced cerebral ischemia (rat) | Rolipram (3 mg/kg, i.p.) 10 days, after embolism | Rolipram attenuates acquisition deficit measured at days 7–9 | Nagakura et al. (2002) |
| | Impaired by PDE4B KO (mouse) | – | No effect | Siuciak et al. (2008a) |
| Delayed matching to position water maze (spatial memory, hippocampus) | Unimpaired (rat) | L-454,560 (0, 0.1, 0.3, or 1 mg/kg, p.o.) 30 min before testing | L-454,560 (0.3 and 1 mg/kg) improved performance | Huang et al. (2007) |
| Radial arm water maze (spatial memory, hippocampus) | Impaired by APP-PS1 Alzheimer KO (mouse) | Rolipram (0.03 mg/kg, s.c.) for 3 weeks | Improvement when tested at 2 months after 3-week treatment | Gong et al. (2004) |
| | Impaired by PS1/PDAPP KO (mouse) | Rolipram (0.03 mg/kg, s.c.) once a day for 2 weeks before testing | Rolipram improved working memory | Costa et al. (2007) |
| Barnes circular maze (spatial memory, hippocampus) | Impaired by age, 18 months old (mouse) | Rolipram (0.016 mg/kg, i.p.) 40 min before training | More mice acquire the task and number of errors is reduced | Bach et al. (1999) |
| Radial arm maze (working and reference memory, hippocampus) | Impaired by scopolamine 0.5/1.0 mg/kg, i.p., 30 min before test (rat) | Rolipram (0.01–1 mg/kg, i.p.) 45 min before test | MED: 0.1 (working memory) and 0.01 mg/kg (reference memory) | Zhang and O’Donnell (2000) |
| | Impaired by scopolamine, 0.5 mg/kg, i.p., 30 min before test (rat) | Given 30 min before test | MED (working memory): (+)-rolipram 0.02–0.2 mg/kg, (−)-rolipram 0.01–0.02 and 0.2/0.5 mg/kg (bi phasic), (+)-rolipram 20/50 mg/kg | Egawa et al. (1997) |
| | Impaired by MK-801, 0.1 mg/kg, i.p., 60 min before test (rat) | Rolipram (0.01–0.1 mg/kg, i.p.) 30 min before test | MED: 0.05 (working memory) and 0.1 mg/kg (reference memory) | Zhang et al. (2000) |
| | Impaired by MK-801, 0.1 mg/kg, i.p., 60 min before testing (rat) | Rolipram (0.1 mg/kg, i.p.), MEM 1018 or MEM 1091 (0.1–2.5 mg/kg, i.p.) 45 min before test | MED: 0.1 mg/kg rolipram working memory, MED: 2.5 mg/kg MEM 1018 working and reference memory MED:2.5 mg/kg MEM 1091 on reference memory | Zhang et al. (2005) |
| | Impaired by MEK inhibitor UO126, 8 μg/rat into hippocampus, given twice: 60 and 30 min before test (rat) | Rolipram (0.05, 0.1 mg/kg, i.p.) 30 min before test | MED: 0.1 mg/kg (reference memory) | Zhang et al. (2004) |
| Passive avoidance (inhibitory avoidance learning, hippocampus and amygdala) | Impaired by (1) protein synthesis inhibitor anisomycin, 150 mg/kg, s.c., 30 min before training, (2) low baseline (mouse) | Rolipram (3 or 10 mg/kg, i.p., immediately after training or 3 h after training | MED 10 mg/kg, given immediately after training (1+2) | Randt et al. (1982) |
| | Impaired by scopolamine, 1 mg/kg, i.p., 30 min before acquisition (mouse) | Rolipram (1–30 mg/kg, i.p.) 30 min before acquisition | MED: 10 mg/kg | Imanishi et al. (1997) |
| | Impaired by scopolamine, 1.5 mg/kg, i.p., immediately after training (mouse) | Rolipram (10 or 30 mg/kg, p.o.) 30 min before training | MED: 30 mg/kg | Ghelardini et al. (2002) |
| Task (cognitive process, area involved) | Model (species) | Treatment | Results | Reference |
|----------------------------------------|-----------------|-----------|---------|-----------|
| Impaired by scopolamine, 3 mg/kg, i.p., 30 min before retention test (rat) | Given 60 min before retention test. (±)-rolipram 0.01–0.1 mg/kg, p.o.; (−)-rolipram 0.005–0.02 mg/kg, p.o.; (−)-rolipram 0.3–10 mg/kg, p.o. | MED: (±)-rolipram 0.02–0.1 mg/kg, (−)-rolipram 0.01–0.02 mg/kg, (±)-rolipram 2 mg/kg; no effect at 10 mg/kg | Egawa et al. (1997) |
| Impaired by MK-801 0.1 mg/kg, i.p., 60 min before test (rat) | Rolipram (0.1 mg/kg, i.p.) 30 min before test | MED: ±0.1 mg/kg | Zhang et al. (2000) |
| Impaired by MK-801, 0.1 mg/kg, i.p., 60 min before testing (rat) | Rolipram (0.1 mg/kg, i.p.), MEM 1018 or MEM 1091 (0.1–2.5 mg/kg, i.p.) 45 min before test | MED: rolipram 0.1 mg/kg, MEM1018 0.1–2.5 mg/kg, and MEM 1091 0.5–2.5 mg/kg on reversal latency | Zhang et al. (2005) |
| Impaired by MEK inhibitor U0126, 8 μg/rat into hippocampus, given twice: 60 and 30 min before test (rat) | Rolipram (0.1 mg/kg, i.p.) 30 min before test or 30 μg/rat into hippocampus, 20 min before test | Reversal retention deficit 48 h post training | Zhang et al. (2004) |
| Impaired by PDE4B KO (mouse) | – | No effect | Siuciak et al. (2008a) |
| Three-panel runway task (working memory, hippocampus and prefrontal cortex) | Impaired by scopolamine, 0.56 mg/kg, i.p., 15 min before first trial (rat) | Rolipram (0.032 or 0.1 mg/kg, i.p.) 30 min before first trial | MED: 0.1 mg/kg for decrease errors | Imanishi et al. (1997) |
| Impaired by cerebral ischemia by four-vessel occlusion (rat) | Rolipram (0.032 or 0.1 mg/kg, i.p.) 30 min before first trial (immediately after reperfusion) | MED: 0.1 mg/kg for decrease errors | Imanishi et al. (1997) |
| Inhibitory avoidance learning (hippocampus and amygdala) | Impaired by ECS immediately after training (rat) | Rolipram (0.1 or 0.32 mg/kg, i.p.) just before ECS | MED: 0.32 mg/kg for decrease errors | Imanishi et al. (1997) |
| | Impaired by (1) protein synthesis inhibitor anisomycin, 150 mg/kg, s.c., 30 min before training, (2) low baseline (mouse) | Rolipram (3 or 10 mg/kg, i.p., immediately after training or 3 h after training) | MED 10 mg/kg, given immediately after training (1+2) | Randt et al. (1982) |
| Contextual fear conditioning (learning, hippocampus and amygdala) | Unimpaired (mouse) | Rolipram (0.03 mg/kg, s.c.) 30 min before training | Improved retention 24 h after training | Barad et al. (1998) |
| | Unimpaired (rat) | Rolipram 0.5 mg/kg/day for 7 days chronic delivery by osmotic minipumps | Improved memory consolidation and slower extinction of conditioned fear | Monti et al. (2006) |
| | Impaired by TG2576 KO Alzheimer mice (mouse) | Rolipram (0.1 mg/kg, i.p.) 30 min prior to training | Improvement in mutants and wild-type | Comery et al. (2005) |
| | Impaired by APP-PS KO Alzheimer mice (mouse) | Rolipram 0.1 μM/kg for 3 weeks | Improvement when tested 2 months following 3-week treatment | Gong et al. (2004) |
| | Impaired by PDE4D KO (mouse) | – | Impairment LTM for context and cued fear | Rutten et al. (2008b) |
| Object recognition task (object memory, hippocampus and rhinal cortex) | Unimpaired young (rat) | Rolipram (0.01, 0.03 or 0.1 mg/kg, i.p.) given: (1) 30 min before training, (2) directly after training, (3) 3 h after training | | Rutten et al. (2006) |
| Task (cognitive process, area involved) | Model (species) | Treatment | Results | Reference |
|----------------------------------------|-----------------|-----------|---------|-----------|
| Unimpaired young (rat)                 | Rolipram (0.03 mg/kg, i.p.) given: (1) directly after training, (2) 1 h after training, (3) 3 h after training, (4) 6 h after training | Rolipram (0.03 mg/kg 3 h after T1) improved memory consolidation in ORT | Rutten et al. (2007b) |
| Impaired by scopolamine, 0.1 mg/kg, i.p., 30 min before training (rat) | Rolipram (0.03, 0.1 or 0.3 mg/kg, i.p.) 30 min before training | Rolipram (0.1 mg/kg) reversed scopolamine-induced STM deficit | Rutten et al. (2006) |
| Impaired by acute tryptophan depletion, 3 h before training (rat) | Rolipram (0.01, 0.03 or 0.1 mg/kg, i.p.) 30 min before training | Rolipram (0.1 mg/kg) reversed ATD induced STM deficit | Rutten et al. (2007a) |
| Unimpaired (rat)                       | Subchronic treatment of rolipram (0.5 mg/kg, p.o.) for 5 days. Testing before, during (day 2–3) and after treatment (T1–T2 24 h) | Subchronic rolipram treatment improved object recognition memory. Timing of final dose did not affect performance | Rutten et al. (2008c) |
| Impaired by heterozygous CBP mutation (mouse) | Rolipram (0.1 mg/kg, i.p.) or HT0712 (0.001–0.5 mg/kg, i.p.) 20 min before training | MED: 0.1 mg/kg for both drugs. Improved object recognition at 24 h | Bourtchouladze et al. (2003) |
| Delayed responding                      | Rolipram (0.01–100 μg/kg, i.m.) 1 h before testing | At 0.1 μg/kg, trend for improvement in young subjects. Aged subjects impaired by 10 μg/kg | Ramos et al. (2003) |
| Impaired by age (rhesus monkey)        | Rolipram (0, 0.001–0.05 μg/kg, i.m.) 2 h before testing and guanfacine (0, 0.0001–0.01 mg/kg, i.m. (one animal 0.5 mg/kg)) | Rolipram alone no effect. Rolipram reversed beneficial effect of guanfacine on working memory | Ramos et al. (2006) |
| Object retrieval (cynomolgus macaque)  | Rolipram (0.003, 0.01, or 0.03 mg/kg, i.m.) 30 min before testing | Rolipram (0.01, 0.33 mg/kg) improved object retrieval performance | Rutten et al. (2008a) |
| Unimpaired (mouse)                     | Rolipram (0.1, 0.66, 1 or 10 mg/kg, i.p.) 15 min before testing | Rolipram (0.66, 1, 10 mg/kg) increased PPI and decreased startle response | Kanes et al. (2007) |
| Impaired by d-amphetamine, 10 mg/kg, i.p., 15 min before testing (mouse) | d-amphetamine (10 mg/kg, i.p.) and rolipram (0.66 mg/kg, i.p.) 15 min before testing | Rolipram attenuated the PPI deficit caused by d-amphetamine, but had no effect on startle response | Kanes et al. (2007) |
| Impaired by PDE4B KO (mouse)           | – | Increased startle response and decreased PPI (independent of startle response) | Siuciak et al. (2008a) |
| Impaired by d-amphetamine, 5 mg/kg (mouse) | RO-20-1724 (0.25, 2.5, or 4 mg/kg, s.c.) or rolipram (mg/kg, s.c.), 5 min before testing | RO-20-1724 did not reverse PPI deficit caused by d-amphetamine | Halene and Siegel (2008) |
| Startle response (zebrafish)           | Rolipram (3, 10, or 30 μM) | Rolipram (3 μM) enhanced startle response | Best et al. (2008) |
| Acquisition of conditioned avoidance responding (mouse) | – | No effect | Siuciak et al. (2007) |
showed more controversial data demonstrating enhanced LTP but impaired fear conditioning in PDE4D knockout mice (Rutten et al. 2008b). In addition, a variety of transgenic mice models was used in combination with the administration of PDE4-Is. It has been shown that acute as well as chronic treatment of PDE4-Is improved long-term memory (LTM) functioning in a Rubenstein–Taybi syndrome and two Alzheimer’s disease KO mouse models for cognitive impairment in the fear conditioning and object recognition task (Bourtchouladze et al. 2003; Comery et al. 2005; Gong et al. 2004). Also, PDE4-I rolipram improved working memory and spatial memory in a transgenic model of Alzheimer’s disease, i.e., PS1/PDAPP KO mice in the radial arm water maze (Costa et al. 2007; Gong et al. 2004).

To our knowledge, no studies have been published in which the effects of PDE4-Is on cognition in humans are described. However, PDE4-I MK 0952 is now entering phase 2 clinical trials for cognition enhancement (Merck and Co. 2006).

PDE5

Prickaerts et al. (1997) were the first to describe memory-enhancing effects of PDE5 inhibition using the PDE5-I zaprinast. However, zaprinast is not selective for PDE5, as it also inhibits PDE1, 9, 10, and 11 (Bender and Beavo 2006). Recently, more highly selective PDE5 inhibitors have been developed mainly for the treatment of erection disorder, e.g., sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) (Setter et al. 2005). The next section will give a general summary of the available literature on PDE5-Is and cognition; a more detailed overview is provided in Table 5.

So far, several studies have shown positive effects of selective PDE5-Is on memory performance in the object recognition task in adult rats; zaprinast (Domel-Lopacinska and Strosznajder 2008; Prickaerts et al. 1997), sildenafil (Prickaerts et al. 2005, 2002b), and vardenafil (Prickaerts et al. 2002b; Rutten et al. 2007b) improve memory consolidation. In addition, Rutten et al. (2005) showed that sildenafil also improved memory consolidation in mice in this task. Previous work from our group showed that zaprinast reversed the object memory deficits induced by the NOS inhibitor 7-nitroindazole in rats in the object recognition task (Prickaerts et al. 1997). However, zaprinast was unable to reverse memory deficits in aged rats in this task (Domel-Lopacinska and Strosznajder 2008).

Several studies have shown spatial memory improvement in an adapted version of the elevated plus-maze in rats (Singh and Parle 2003) and mice (Patil et al. 2004a) after treatment with a PDE5-I. Furthermore, sildenafil treatment ameliorated the deficits induced by diabetes or ECS in this task (Patil et al. 2004a, 2006). Previous studies showed no effects of PDE5-Is on spatial tasks in healthy rats, i.e., the water escape task or the Y-maze (Prickaerts et al. 2004). However, since only one dose was tested in this study, further investigation will be needed. Finally, in hyperammonemia and portacaval shunt deficit models for liver failure, both sildenafil and zaprinast reversed spatial recognition deficits of rats in the Y-maze (Erceg et al. 2006, 2005a, b). Recent work adds to this since sildenafil reversed the effects the nitric oxide synthase (NOS) inhibitor L-NAME in a complex maze learning paradigm (Devan et al. 2006, 2007).

Furthermore, various studies investigated the effects of PDE5-Is on active and passive avoidance learning in rats, mice, and neonatal chicks. Although one study failed to show

### Table 4 (continued)

| Task (cognitive process, area involved) | Model (species)                          | Treatment                                                      | Results                                                                                           | Reference                         |
|----------------------------------------|------------------------------------------|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------|
| Auditory event-related                  | Unimpaired (mouse)                       | RO-20-1724 (0.1, 0.25, 0.5, 1, 2.5 mg/kg, s.c.), 5 min before testing | First click: RO-20-1724 increased amplitude of P20 (at a dose of 0.25, 0.5, 1 mg/kg) and of N40 at a dose of (0.25, 0.5, 2.5 mg/kg) in CA3 area. No effects on second click | Halene and Siegel (2008)          |
| potentials (information processing, frontal cortex) | Impaired by d-amphetamine, 0.5 mg/kg (mouse) | RO-20-1724 (0.25 mg/kg, s.c.), 5 min before testing           | First click: P20 no effect. N40 RO-20-1734 reversed deficit caused by d-amphetamine in CA3 area. No effects on second click | Halene and Siegel (2008)          |

This table is an adapted and updated version of the overview (Table 3) in Blokland et al. (2006) KO knockout, i.m. intramuscular, i.p. intraperitoneal, p.o. per os, s.c. subcutaneous, MEK MAPK/ERK kinase, T1 trial 1, T2 trial 2, ECS electroconvulsive shocks, ATD acute tryptophan depletion, ORT object recognition task, MED minimum effective dose.
Table 5 Overview of effects of PDE5-Is on cognition

| Task (cognitive process, area involved) | Model (species) | Treatment | Results | Reference |
|----------------------------------------|----------------|-----------|---------|-----------|
| Object recognition task (object memory, hippocampus and rhinal cortex) | Unimpaired (rat) | Sildenafil citrate (1, 3, or 10 mg/kg, p.o.) 30 min before or immediately after first trial (24 h interval T1–T2) | Sildenafil (3 mg/kg T0 or 10 mg/kg T1-30 min) improves memory consolidation | Prickaerts et al. (2005) |
| Unimpaired (rat) | Zaprinast (3 or 10 mg/kg, i.p.) immediately after first trial (4 h interval T1–T2) | Zaprinast (10 mg/kg) improved memory consolidation | Prickaerts et al. (1997) |
| Unimpaired (rat) | Sildenafil (1, 3, or 10 mg/kg, p.o.) immediately after first trial (24 h interval T1–T2) | Sildenafil (3 mg/kg) improved memory consolidation in ORT | Prickaerts et al. (2002b) |
| Unimpaired (rat) | Vardenafil (0.1, 0.3, 1, or 3 mg/kg, p.o.) immediately after first trial (24 h interval T1–T2) | Vardenafil (0.3 mg/kg) improved memory consolidation in ORT | Prickaerts et al. (2002b) |
| Unimpaired (rat) | Vardenafil (1 mg/kg, p.o.) immediately after, 1 h, 3 h, or 6 h after first trial (24 h interval T1–T2) | Vardenafil (1 mg/kg immediately after T1) improved memory consolidation in ORT | Rutten et al. (2007b) |
| Unimpaired (mouse) | Sildenafil (0.3, 1 or 3 mg/kg, p.o.) immediately after first trial (24 h interval T1–T2) | Sildenafil (1 mg/kg) improved memory consolidation in ORT | Rutten et al. (2005) |
| Impaired by NOS inhibitor (rat) | 7-nitroindazole (10 or 30 mg/kg, i.p.); zaprinast (3 or 10 mg/kg, i.p.) immediately after first trial (24 h interval T1–T2) | Zaprinast (10 mg/kg) reversed the NOS-I (10 mg/kg) deficit in ORT | Prickaerts et al. (1997) |
| Impaired by age, 3, 12, and 24 months old (rat) | Zaprinast (0.3 mg/kg, s.c.) 1 h before first trial or immediately after first trial (2 h interval T1–T2) | Zaprinast 1 h before T1 improved acquisition in 3-month-old animals. In addition, it improved consolidation in animals of 3 months when given immediately after T1 | Domek-Lopacinska and Strosznajder (2008) |
| Adapted version of elevated plus-maze (spatial memory, hippocampus) | Unimpaired (rat) | Sildenafil (2, 4, or 8 mg/kg, i.p.) 30 min before or immediately after first trial | Sildenafil (8 mg/kg) before T1 marginally increased spatial memory acquisition. Sildenafil (2, 4, 8 mg/kg) immediately after T1 increased spatial memory retention | Singh and Parle (2003) |
| Unimpaired (mouse), age-impaired (mouse) | Sildenafil (0.25, 0.5, or 1 mg/kg, i.p.) immediately after first trial | Sildenafil improved spatial memory performance in young (0.5 and 1.0 mg/kg) and aged (0.25–1 mg/kg) animals | Patil et al. (2004a) |
| Unimpaired (mouse), age-impaired (mouse) | Zaprinast (0.5, 1 or 2 mg/kg, i.p.) immediately after first trial | Zaprinast improved spatial memory performance in young (1.0 and 2.0 mg/kg) and aged (0.5–2 mg/kg) animals | Patil et al. (2004a) |
| Impaired by diabetes-STZ (rat) | Streptozotocin (STZ) (60 mg/kg, i.p.), sildenafil (0.25, 0.5, or 1 mg/kg, i.p.) immediately after training | Sildenafil (all doses) reversed STZ spatial memory deficits | Patil et al. (2006) |
| Task (cognitive process, area involved) | Model (species) | Treatment | Results | Reference |
|----------------------------------------|----------------|-----------|---------|-----------|
| Impaired by diabetes-LPS (mouse)       | Lipopolysaccharide (LPS: 50 μg, i.p.) and sildenafil (0.25, 0.5, or 1 mg/kg, i.p.) or zaprinast (0.5, 1, or 2 mg/kg, i.p.) immediately after training | Sildenafil (0.5 and 1 mg/kg) and zaprinast (1 and 2 mg/kg) reversed LPS spatial memory deficits | Patil et al. (2004a) |
| Impaired by electroconvulsive shock (rat) | Shocks (0.2 mA, 0.2 s/day for 15 days) sildenafil (0.5, 1, or 2 mg/kg, i.p.) immediately after training | Sildenafil (0.5 and 1 mg/kg) and zaprinast (1 and 2 mg/kg) reversed spatial memory deficits | Patil et al. (2006) |
| Y-maze (spatial memory, hippocampus and cerebellum) | Unimpaired (rat) | Vardenafil (3 mg/kg, p.o.) daily after last trial | No effects on spatial recognition | Prickaerts et al. (2004) |
| Impaired by hyperammonemia (rat)       | Sildenafil (50 mg/L) in drinking water 2 days before training | Sildenafil (in drink water) reversed spatial recognition deficits | Erceg et al. (2005a) |
| Impaired by hyperammonemia (rat)       | Ammonium acetate containing diet (28 days before testing), zaprinast (50 μM, 0.25 μL/h, 2 days before testing) in cerebral ventricle | Zaprinast (through minipump) reversed spatial recognition deficits | Erceg et al. (2005b) |
| Impaired by portacaval shunts (rat)    | Portacaval shunt operation 28 days before test. Sildenafil (50 mg/L) in drinking water 2 days before training | Sildenafil (in drink water) reversed spatial recognition deficits | Erceg et al. (2005b) |
| Water escape task (spatial memory, hippocampus) | Unimpaired (rat) | Zaprinast (10 mg/kg, i.p.) daily after last trial | No effects on acquisition or retention of spatial memory | Prickaerts et al. (2004) |
| Complex maze learning (learning, hippocampus) | Impaired by NOS inhibitor (rat) | L-NAME (60 mg/kg, i.p.) 30 min before training, sildenafil (1, 1.5, 3, or 4.5 mg/kg, i.p.) 15 min before training | Sildenafil (1.5 mg/kg) attenuated the L-NAME deficit in maze learning | Devan et al. (2006) |
| Impaired by NOS inhibitor (rat)        | L-NAME (0, 45 μg/kg, i.c.v.) 30 min before training, sildenafil (0, 1.5, or 3 mg/kg, i.p.) 15 min before training | Sildenafil (3 mg/kg) attenuated the L-NAME deficit in maze learning | Devan et al. (2007) |
| Active avoidance learning (hippocampus) | Impaired by scopolamine, 0.75 mg/kg, i.p., 30 min before training (rat) | Sildenafil (1.5, 3, or 4.5 mg/kg, i.p.) 15 min before training | Sildenafil (3 mg/kg) reversed the scopolamine deficit in active avoidance task | Devan et al. (2004) |
| Unimpaired (mouse)                     | Sildenafil (1, 3, 10, or 30 mg/kg, i.p.) 30 min before training or immediately after training | Sildenafil (3 mg/kg) improved performance (both 30 min before and immediately after training) in active avoidance | Baratti and Boccia (1999) |
| Passive avoidance learning (hippocampus) | Unimpaired (rat) | Sildenafil (1, 3, 10, or 20 mg/kg, i.p.) immediately after training in young and old rats | Sildenafil has no effect on retention performance in passive avoidance | Shafiei et al. (2006) |
| Unimpaired (neonate chick)             | Zaprinast (0.1–750 μM/side, i.c.) immediately after training | Zaprinast (>100 μM) enhanced early consolidation | Campbell and Edwards (2006) |
### Table 5 (continued)

| Task (cognitive process, area involved) | Model (species) | Treatment | Results | Reference |
|----------------------------------------|-----------------|-----------|---------|-----------|
| Unimpaired (young chick)                | Sildenafil (100 μM/side, i.c.) immediately after training. Retention times between 10 and 180 min | Zaprinast impaired performance (at a retention of 40, 60, 90, and 120 min) | Edwards and Lindley (2007) |
| Unimpaired (mouse), age-impaired (mouse) | Sildenafil (0.25, 0.5, or 1 mg/kg, i.p.) immediately after first trial | Sildenafil improved consolidation in young (0.5 and 1.0 mg/kg) and aged (0.25–1 mg/kg) animals | Patil et al. (2004a) |
| Unimpaired (mouse), age-impaired (mouse) | Zaprinast (0.5, 1, or 2 mg/kg, i.p.) immediately after first trial | Zaprinast improved spatial memory performance in young (1.0 and 2.0 mg/kg) and aged (0.5–2 mg/kg) animals | Patil et al. (2004a) |
| Impaired by diabetes (rat)              | STZ (60 mg/kg, i.p.), sildenafil (0.25, 0.5, or 1 mg/kg, i.p.) immediately after training | Sildenafil (all doses) reversed STZ memory deficit caused by diabetes | Patil et al. (2006) |
| Impaired by electroconvulsive shock (rat) | Shocks (0.2 mA, 0.2 s/day for 15 days), sildenafil (0.5, 1, 2 mg/kg, i.p.) immediately after training | Sildenafil (all doses) reversed memory deficit caused by ECS | Patil et al. (2006) |
| Impaired by diabetes-LPS (mouse)        | Lipopolysaccharide (LPS, 50 μg, i.p.) and sildenafil (0.25, 0.5, or 1 mg/kg, i.p.) or zaprinast (0.5, 1, 2 mg/kg, i.p.) immediately after training | Sildenafil (0.5 and 1 mg/kg) and zaprinast (1 and 2 mg/kg) reversed LPS induced memory deficits | Patil et al. (2004b) |
| Object retrieval (executive functioning and response inhibition, prefrontal cortex) | Sildenafil (0.3, 1, or 3 mg/kg, i.m.) 30 min before testing | Sildenafil (1, 3 mg/kg) improved object retrieval performance | Rutten et al. (2008a) |
| Seven different psychophysical tests (psychophysical performance, various brain areas) | Sildenafil (100 mg, p.o.) 1 h before testing | Sildenafil enhanced performance on the simple reaction time test; other tests no effect | Grass et al. (2001) |
| Auditory selective attention and ERPs (attention, prefrontal cortex) | Sildenafil (100 mg, p.o.) 1 h before testing | Sildenafil had no effect on the behavioral measurements of attention. However, an increase in the ERP components N1d and P3 indicates an improvement of attention | Schultheiss et al. (2001) |
| Verbal recognition memory and ERPs (memory and information processing, hippocampus and frontal cortex) | Sildenafil (100 mg, p.o.) 1 h before testing | Sildenafil had no effect on the behavioral measurements of memory. However, a reduction in negativity between 150 and 250 ms might indicate an effect on information processing | Schultheiss et al. (2001) |

_i.c.v._ intracerebroventricular, _i.c._ intracerebral, _i.p._ intraperitoneal, _LPS_ lipopolysaccharide, _NOS_ nitric oxide synthase, _ORT_ object recognition task, _p.o._ per os, _T1_ trial 1, _T2_ trial 2, _STZ_ streptozotocin
improvement in learning performance after sildenafil treatment in unimpaired and aged rats (Shafiei et al. 2006), others have shown improvements in unimpaired and aged mice and in neonatal chicks (Baratti and Boccia 1999; Campbell and Edwards 2006; Patil et al. 2004a). In contrast, Edwards and Lindley (2007) found that zaprinast could also have a negative effect on learning and memory when given at a high dose. Memory impairments in avoidance learning caused by scopolamine, diabetes, or ECS in rats were reversed by sildenafil treatment (Devan et al. 2004; Patil et al. 2006). In addition, zaprinast as well as sildenafil reversed memory deficits caused by a model for diabetes in mice (Patil et al. 2004a).

Finally, a recent study showed that the PDE5-I sildenafil dose-dependently improved performance in a prefrontal task, i.e., the object retrieval task (see above), in cynomolgus macaques (Rutten et al. 2008a).

Most research regarding the cognition-enhancing effects of PDE5-Is so far has focused on preclinical animal models; there are only two papers in which the effects of the PDE5-I sildenafil on human cognition were investigated. Grass et al. (2001) have shown that 100 mg sildenafil enhanced performance in a simple reaction time test when given 1 h before testing. However, no effects were found on short-term memory (STM), divided attention, and other psycho-motor tasks (Grass et al. 2001). In addition, Schultheiss et al. (2001) studied the effects of sildenafil (100 mg, 1 h before testing) on auditory attention and word recognition. Again, no cognition-enhancing effects were found with regard to the behavioral measures.

In both studies, STM tasks were performed that are thought to measure memory performance processes comparable to the object recognition task in rats. However, the object recognition task in animals usually measures more aspects of memory, such as that for object and for location, even though only the object memory itself might have been measured. The human tasks, on the other hand, only assess memory for words, pictures, or location, but never the combination of these aspects. Possibly, the fact that spatial information was lacking in the human studies has caused this discrepancy in findings.

Sildenafil changed certain components of event-related potentials (ERPs) in the study of Schultheiss et al. (2001). The Nd component, although it only showed a marginally significant effect, was increased after treatment with sildenafil. This indicates improved focused attention. The P3 component, which measures controlled processes of target selection, was significantly enhanced after the administration of sildenafil (Schultheiss et al. 2001). Again, this is evidence for improvements after treatment with sildenafil. Finally, a reduced negativity between 150 and 250 ms was found in the word recognition experiment after sildenafil treatment; this may also indicate an effect on information processing, although the exact role of this component remains uncertain (Schultheiss et al. 2001).

Several possible explanations for not finding any cognition-enhancing effects after PDE5-I treatment in humans in contrast to the results in animal studies exist. First, only one dose of sildenafil on one specific time point was tested in both studies. Investigating different doses, both higher and lower, at different administration time points might reveal possible cognition-enhancing effects in humans. In addition, a “ceiling effect” might have occurred in the cognitive tasks; this means that healthy subjects in these studies already perform at their maximal level, so their performance cannot be further improved. A final explanation might be that the number of participants was not sufficient, since only six participants were tested by Grass et al. (2001), whereas Schultheiss et al. (2001) examined ten healthy participants.

PDE9

To our knowledge, only one paper has been published in which the effects of PDE9 inhibition on cognition are described (Van der Staay et al. 2008). In this paper, the potent and selective PDE9-I BAY 73-6691 was used (Wunder et al. 2005). It was shown that this PDE9-I improved memory consolidation in unimpaired mice in the object recognition and social recognition task (Van der Staay et al. 2008). Furthermore, this PDE9-I reversed the MK-801- or scopolamine-induced memory deficit in the T-maze and the passive avoidance task, respectively (Van der Staay et al. 2008). More detailed information can be found in Table 6.

PDE10

Only very recently, PDE10-Is have become a target for CNS research, especially concerning the cognitive deficits related to schizophrenia (Schmidt et al. 2008). In the next section, a summary of the available literature on PDE10-Is and cognition will be given; a more detailed overview can be found in Table 7.

Chronic treatment with the PDE10-I papaverine impaired spatial memory and reversal learning in unimpaired mice in the Morris water maze (Hebb et al. 2008). Administration of TP-10 did not have an effect on information processing in a prepulse inhibition task in unimpaired and MK-801-impaired mice (Schmidt et al. 2008). However, TP-10 reversed the auditory gating deficit caused by D-amphetamine in rats (Schmidt et al. 2008). Papaverine improved attention in the attention shifting task in rats that were impaired by subchronic phencyclidine/piperidine (PCP) treatment, a model of schizophrenia, whereas no effect was found in unimpaired rats (Rodefer et al. 2005).
Several studies also used KO models to study the role of PDE10 in cognition. It was shown that PDE10A knockout in a DBA1LacJ background had no effect on learning and memory in the passive avoidance and water escape task in mice (Siuciak et al. 2006, 2008b). In addition, these mice showed the same conditioned avoidance response as wild-type mice; however, these KO mice required more training to reach the performance of wild-type animals (Siuciak et al. 2006, 2008b).

The data discussed in the previous paragraphs showed that PDE-Is can improve cognition in impaired animals, but can also induce a cognitive impairment in healthy animals. There are several explanations that might account for these contradictory findings. First, the cognitive impairment in healthy animals caused by papaverine was the result of a subchronic treatment, which was not found after acute treatment in impaired animals. Secondly, different aspects of cognition were addressed in these studies. In the healthy animals, learning and memory were studied, whereas in the impaired animals, information processing and attention were investigated. Thirdly, improving cognition of a healthy individual is not the same as restoring impaired cognition; the underlying processes, and thus the effect of a compound, may differ.

### Mechanisms of action

There are several mechanisms of action which could account for the cognition-enhancing effects of PDE-Is. First, it has been proposed that these effects could be the result of vasodilatory properties of PDE-Is. Secondly, cognition enhancement could be a consequence of emotional arousal. Finally, positive effects may be due to enhanced second messenger signaling (cAMP and/or cGMP) resulting in facilitated LTP processes. All three mechanisms will be discussed in the next sections.

### Table 6 Overview of effects of PDE9-I on cognition

| Task (cognitive process, area involved) | Model (species) | Treatment | Results | Reference |
|----------------------------------------|-----------------|-----------|---------|-----------|
| Object recognition task (object memory, hippocampus and rhinal cortex) | Unimpaired (rat) | BAY 73-6691 (0.1, 0.3, 1, or 3 mg/kg, p.o.) 30 min before T1 | BAY 73-6691 (0.1, 0.3 mg/kg) had an intermediate effect on memory consolidation | Van der Staay et al. (2008) |
| Passive avoidance (learning, hippocampus) | Impaired by scopolamine, 0.03 mg/kg, s.c., 30 min before testing (rat) | BAY 73-6691 (0.3, 1, or 3 mg/kg, p.o.) 60 min before testing | BAY 73-6691 (1, 3 mg/kg) attenuated the scopolamine-induced retention deficit | Van der Staay et al. (2008) |
| Social recognition (social memory, hippocampus and amygdala) | Unimpaired (rat) | BAY 73-6691 (0, 0.03, 0.3, or 3 mg/kg, p.o.) 60 min before the first trial (T1), immediately after T1 or 60 min before trial 2 (T2) | BAY 73-6691 (0.3, 3 mg/kg) 60 min before T1, or BAY 73-6691 (0.03, 0.3, 3 mg/kg) immediately after T1 and 60 min before T2 improved memory consolidation | Van der Staay et al. (2008) |
| | Unimpaired (rat) | BAY 73-6691 (0 or 1 mg/kg, p.o.) 60 min before the first trial (T1) with a familiar juvenile or BAY 73-6691 (1 mg/kg, p.o.) 60 min before the first trial (T1) with a novel juvenile (24 h interval T1–T2) | BAY 73-6691 (1 mg/kg) improved memory consolidation with a familiar as well as a novel juvenile | Van der Staay et al. (2008) |
| | Unimpaired (mouse) | BAY 73-6691 (0, 0.03, 0.3, or 3 mg/kg, p.o.) 30 min before the first trial (24 h interval T1–T2) | BAY 73-6691 (0.3, 3 mg/kg) 30 min before T1 improved memory consolidation | Van der Staay et al. (2008) |
| T-maze (working memory, hippocampus) | Impaired by MK-801, 0.06 mg/kg, s.c., 30 min before testing (mouse) | BAY 73-6691 (0, 1, 3, or 10 mg/kg, p.o.) 60 min before testing | BAY 73-6691 (10 mg/kg) attenuated the MK-801 induced deficit in alternation rate | Van der Staay et al. (2008) |

*p.o.* per os, *T1* trial 1, *T2* trial 2, *s.c.* subcutaneous
Blood flow

An increase in blood flow and concomitantly an increase in glucose metabolism might be related to the observed cognitive enhancements after PDE-I treatments as predominantly investigated and observed in rodents. This is because PDE-Is increase the levels of cAMP and cGMP, and vasodilatation properties can be attributed to both cyclic nucleotides (Dundore et al. 1993; Paterno et al. 1996).

Summarizing the rodent behavioral data with PDE5 inhibition (see Table 5), it appears that zaprinast and sildenafil are optimally effective at an oral dose of approximately 10 and 3 mg/kg, respectively. The effects of both zaprinast and sildenafil on blood pressure, which is negatively related to

### Table 7 Overview of effects of PDE10-Is on cognition

| Task (cognitive process, area involved) | Model (species) | Treatment | Results | Reference |
|----------------------------------------|-----------------|-----------|---------|-----------|
| Passive avoidance learning (hippocampus) | Impaired PDE10A KO (mouse) | – | Apparent effect, but this could be explained by a locomotor effect | Siuciak et al. (2006) |
| Acquisition of conditioned avoidance responding (CAR) (learning, hippocampus) | Impaired PDE10A KO (mouse) | – | No effect | Siuciak et al. (2008b) |
| | Impaired by PDE10A KO; DBA1LacJ background (mouse) | – | KO mice learned the task as well as WT, but needed more training | Siuciak et al. (2008b) |
| | Impaired by PDE10A KO; C57BL/6N background (mouse) | – | KO mice learned more training and did not reach performance of WT | Siuciak et al. (2008b) |
| Morris water maze (spatial memory, hippocampus) | Unimpaired (mouse) | Chronic treatment of papaverine (0, 5, 10, or 20 mg/kg, s.c.) daily for 14 days. Then, same treatment either prior of 30 min after testing | Papaverine (5 mg/kg, after testing) impaired latency and distance. In addition, papaverine (20 mg/kg, 30 min before testing and 5 mg/kg, 30 min after testing) increased the time spend in the old platform quadrant in reversal learning | Hebb et al. (2008) |
| Auditory gating (anesthetized) (information processing, frontal cortex) | Impaired by d-amphetamine, 1 mg/kg, i.v., 5 min before testing (rat) | TP-10 (0, 3 mg/kg); 5 min before testing | TP-10 reversed auditory gating deficit | Schmidt et al. (2008) |
| Prepulse inhibition (information processing, frontal cortex) | Unimpaired (mouse) | TP-10 (0, 0.32, 1, 3.2, or 10 mg/kg, s.c.) 30 min before testing | TP-10 had no effect on PPI or startle response | Schmidt et al. (2008) |
| | Impaired by MK-801, 0.178 mg/kg, s.c., 30 min before testing (mouse) | TP-10 (0, 1, 3.2, or 10 mg/kg, s.c.) 30 min before testing | TP-10 did not reverse PPI deficit | Schmidt et al. (2008) |
| Attention set-shifting task (attention, prefrontal cortex) | Impaired by subchronic PCP treatment, 5 mg/kg, i.p., twice a day for 7 days (rat) | Papaverine (0, 3, 10, or 30 mg/kg, i.p.) | Papaverine attenuated PCP induced deficits at all doses. No effect of papaverine on saline treated rats | Rodefer et al. (2005) |

**CAR** conditioned avoidance responding, **i.p.** intraperitoneal, **i.v.** intravenous, **KO** knockout, **PCP** phenylcyclohexylpiperidine, **PPI** prepulse inhibition, **s.c.** subcutaneous
blood flow, have been sparsely investigated in conscious rodents. Administration of zaprinast does not decrease the mean arterial blood pressure at a dose of 2 mg/kg (i.p.) in mice (Patil et al. 2004a) and 10 mg/kg (p.o.) in rats (Prickaerts et al. 1997). Yet, a decrease in blood pressure can be observed with zaprinast after systemic administration (i.v.) of doses higher than 10 mg/kg (Dundore et al. 1993).

One milligram per kilogram sildenafil (i.p.) did not affect the mean arterial blood pressure in mice up to 6 h after administration (Patil et al. 2004a). Yet sildenafil can decrease the mean arterial blood pressure up to 6 h, but an oral dose of at least 10 mg/kg was needed in rats (Rehse et al. 1999). Sildenafil has also been tested directly on cerebral blood flow as measured with laser Doppler flowmetry, although rats need to be anesthetized for this technique (Zhang et al. 2002). Surprisingly, localized cerebral blood flow was increased after oral administration of 2 mg/kg sildenafil.

Cerebral blood flow and glucose utilization have been investigated in mice with the $[^{13}N]$ammonia uptake and $[^{3}H]$2-deoxyglucose uptake technique (Ishikawa et al. 2002). It was found that, within 5 min after 3 mg/kg rolipram (i.p.) administration, blood flow and glucose metabolism in the brain were both decreased by approximately 20% and 40%, respectively. At 30 min after administration, glucose use was still decreased by 60%. One milligram per kilogram rolipram was also tested on central glucose use, which was found to be decreased by 40% at 15 min after administration. Of note, these doses of rolipram are rather high and behaviorally effective doses are in general below 1 mg/kg (i.p.) (see Table 4). Increasing the dose of rolipram above 1 mg/kg will only result in sedation and locomotor depression.

Taken together, the PDE4-Is and PDE5-Is tested in rodents can have peripheral and central vascular and metabolic effects, but these effects occur after treatment with doses that are higher than required for cognition enhancement. Moreover, detailed inspection of the behavioral data already suggests that a uniform cerebrovascular effect is not sufficient to explain the differential effects on cognitive processes. For instance, administration of a cGMP analog into the hippocampus improved early consolidation, whereas a comparable cAMP analog had no effect (Bernabeu et al. 1996; Prickaerts et al. 2002a). Along similar lines, sildenafil improved early consolidation, whereas rolipram did not (Rutten et al. 2007b). On the other hand, late consolidation processes are improved by rolipram while sildenafil is ineffective. Once more, these findings indicate that it is not likely that cerebrovascular and metabolic effects explain the cognitive improvements as observed in rodents.

Sildenafil 100 mg has effects on the CNS of humans as evident from influenced evoked potential and reaction times (Grass et al. 2001; Schultheiss et al. 2001). The same dose of sildenafil has been shown to increase heart rate and decreased diastolic blood pressure in healthy subjects (Kruuse et al. 2002). However, sildenafil had no effect on blood flow in the middle cerebral artery, just as there were no changes in radial and temporal artery diameters (Arnavaz et al. 2003; Kruuse et al. 2002). This indicates that the effects on cognition after sildenafil administration are not likely to be related to cerebrovascular mechanisms in humans as well.

**Emotional arousal**

Anecdotic report and case studies describe emotional arousal (anxiety, aggression) in men taking sildenafil (Milman and Arnold 2002). In rats, it has been demonstrated that sildenafil (1–3 mg/kg) has an anxiogenic effect (Kurt et al. 2004). Effects on emotion and arousal are likely since animal studies have shown that central cGMP is involved in sympathetic activation (Krukoff 1998). Concomitantly, anxiolytics including benzodiazepines reduced the stress-induced increase in central cGMP levels (Tang et al. 1997). cAMP levels were reduced as well after benzodiazepines administration, as found in vitro (Niles and Wang 1999); although increases in cAMP have also been observed (Cherry et al. 2001). In line with the latter observation, PDE4-I rolipram (0.1 mg/kg, s.c.) had an anxiolytic effect in rats (Silvestre et al. 1999). Yet it has to be noted again that the dose of rolipram is still relatively high and decreased locomotor activity might have interfered with the behavioral response. Nevertheless, it is evident that the cyclic nucleotides cAMP and cGMP play a role in arousal and emotional processes. Emotional arousal, to a certain maximum, is necessary for an optimal cognitive performance (Prickaerts and Steckler 2005). Thus, the effects of PDE-Is on cognition can be influenced by or attributed to effects on processes of emotions and arousal.

**Long-term potentiation**

Hippocampal LTP is the most established cellular model for the neuroplastic mechanisms that underlie learning and memory (Bliss and Collingridge 1993). LTP is described by the increase in the chemical strength of a synapse after tetanus stimulation that lasts for over an hour. Experimentally, series of short, high-frequency electric stimulations to a nerve cell synapse can strengthen or potentiate that synapse for several minutes to hours. Glutamate induces LTP via the activation of the ionotropic NMDA receptor, after which calcium enters the cell triggering various presynaptic and postsynaptic changes. The mechanism of LTP and its relationship to learning and memory is quite complicated. It depends on the fine-tuning of various components of the glutamatergic system including ionotropic and metabotropic glutamate receptors, other neurochemical systems, second messengers, and signal transduction pathways. Hippocampal LTP can, depending on the induction paradigm, last for less than 3 h or longer. The former is called early-phase LTP (E-
LTP) and the latter late-phase LTP (L-LTP). It has been suggested that E-LTP (or LTD1) can be transformed into L-LTP (LTP3), probably via an intermediate LTP2 form (Reymann and Frey 2007). Furthermore, it has been assumed that E-LTP is related to STM and L-LTP to LTM (Izquierdo et al. 2002).

In general, both presynaptic and postsynaptic mechanisms are related to LTP and can involve the second messengers cAMP and cGMP. Figure 1 provides a schematic overview of the cellular processes related to LTP and second messenger signaling. More in detail, a postsynaptic cAMP/PKA/CREB pathway (Impey et al. 1996) and cGMP/PKG/CREB pathway (Lu et al. 1999) are involved in L-LTP. A postsynaptic calmodulin-dependent protein kinase II (CaMKII) pathway (Sweatt 1999) and presynaptic cGMP/PKG pathway (Arancio et al. 1995) have been implicated in E-LTP.

Since PDE-Is influence the levels of the second messengers cAMP and/or cGMP, it can be argued that the procognitive effects of PDE-Is are related to the facilitation of LTP. Yet, only a limited number of studies has investigated the effects of PDE-Is on LTP. Most research has been aimed at the effects of PDE4 inhibition on LTP. The PDE4-I rolipram, when applied to hippocampal slices, has been shown to facilitate hippocampal LTD (Navakkode et al. 2004; Calabresi et al. 1999; Navakkode et al. 2005). Recent studies that investigated the effects of PDE-Is on LTD indicate that inhibition of PDEs may have a beneficial effect on synaptic plasticity. Since LTD is considered the underlying mechanism for learning and memory, it is relevant to evaluate the effects of PDE-Is on LTD in addition to and in parallel with behavioral studies.

The process opposed to LTP is long-term depression (LTD), which decreases or depresses the strength of a synapse for a certain amount of time as a result of either strong or persistent weak stimulation. Several studies have shown that PDE4-Is and PDE5-Is can induce or reinforce LTD in the hippocampus and the striatum among others (Bailey et al. 2003; Calabresi et al. 1999; Navakkode et al. 2005). Recently, it has been found that a deficit in LTD can result in memory impairment (Griffiths et al. 2008), which is in line with the theoretical neural network models that depend on bidirectional synaptic plasticity (LTP and LTD) to mediate learning and memory (Malenka 1994). Accordingly, it is now evident that, besides excitatory strengthening mechanisms in LTP, stabilization or suppression mechanisms, e.g., LTD, are also crucial for the regulation of synaptic plasticity (Abel et al. 1998). However, the exact underlying mechanisms remain elusive and the role of PDE-Is in these processes require further investigation.

**Time windows in memory processes**

PDE2, PDE4, and PDE9 inhibition improved both STM and LTM (see Tables 3, 4, and 6). PDE5 inhibition has only been investigated for LTM. Yet, based on the PDE9-I experiments (Van der Staay et al. 2008), it might be expected that PDE5 inhibition will result in STM improvements, though this needs to be confirmed in future studies. Taken together, treatment of rodents with different types of selective PDE-Is, which inhibit the degradation of the second messengers cAMP and/or cGMP, improved their STM as well as LTM. Furthermore, with respect to LTM, it appears that, for consolidation processes, a distinction can be made between early consolidation (<3 h) and late consolidation (>3 h) with cGMP being involved in the former and cAMP in the latter (Bermabeu et al. 1996; Izquierdo et al. 2006; Prickaerts et al. 2002a; Rutten et al. 2007b). These findings suggest that different underlying mechanisms should explain consoli-
tion processes. Or, in more detail, are different forms of LTP involved in different phases of LTM consolidation?

Defining STM as not requiring protein synthesis may implicate that the time window of E-LTP corresponds with the duration of STM (1–3 h) (Izquierdo et al. 2002). Presynaptic cGMP is involved in E-LTP (LTP1) (Arancio et al. 1995), but cAMP is probably not (Nguyen and Woo 2003). Thus, it can be argued that rolipram should not improve STM. However, we found that rolipram can improve STM (Rutten et al. 2006). This effect might be explained by a general enhancement of synaptic transmission by increasing neurotransmitter availability, as rolipram has been found to activate the cognition-related cholinergic system (Imanishi et al. 1997), and also the noradrenergic and dopaminergic neurotransmitter systems (Schoffelmeer et al. 1985).

L-LTP (LTP2 and LTP3) is dependent on protein synthesis and last longer than 3 h (Reymann and Frey 2007). It can be assumed that L-LTP is related to LTM. Figure 2 illustrates the interrelationship between STM and LTM with intermediate memory (IM) in between STM and LTM. It might be speculated that LTP2 is representing early consolidation/IM and LTP3 represents late consolidation/LTM. These questions clearly warrant further investigations.

E-LTP can be converted into L-LTP (Pang et al. 2004). This is in line with the idea that information in the STM can be transferred into LTM (Baddeley 2003). As presynaptic cGMP plays a role in E-LTP, theoretically, inhibition of cGMP degradation with, for instance, a PDE9-I should, therefore, be able to influence L-LTP/LTM via E-LTP/STM as well. But cGMP as well as cAMP are involved in postsynaptic L-LTP processes resulting in phosphorylation of the transcription factor CREB eventually. However, as described above, both cyclic nucleotides have different effects on consolidation processes. This implies that the signal transduction pathways are far more complex than known thus far. It seems likely that additional modulators are involved in regulating and mediating the timed effect of the second messengers cGMP and cAMP on memory processes.

Targeting cognitive functioning

The application of PDE-Is in studies of animal cognition enhancement has been fruitful. These studies have extended our fundamental knowledge about the possible underlying cellular and molecular mechanisms of learning, memory, and other cognitive functions. However, to predict which classes of PDE-Is are possibly the most effective cognition enhancers, in either preclinical or clinical studies, depends on various factors.

First, it is important to know the exact localization of specific PDE enzymes in the normal brain (see also Table 1).
The localization of the enzymes might predict that certain cognitive functions that are primarily located in specific brain structures may be enhanced by some PDE-Is, but not by others. For example, PDE10 is predominantly expressed in striatal areas (Schmidt et al. 2008) and is, therefore, a target for schizophrenia. In contrast, PDE4 is highly expressed in the hippocampus and cortex (Perez-Torres et al. 2000) and is, therefore, considered a better target for cognition enhancement. Of note, the development of a specific antibody against a selective PDE, preferentially of the level of isoform type, will more specifically target a PDE for a certain cognitive function (Fujita et al. 2007).

Secondly, it must be taken into account that the constitution of the brain changes with age and the distribution of PDEs can be modified by the aging process. As a consequence, a PDE-I can improve cognition in young subjects, but impair cognition in old subjects. Likewise, Ramos et al. (2003) demonstrated that rolipram had a positive effect on prefrontal cortex-dependent working memory in young rhesus monkeys, but had a negative effect on working memory in aged rhesus monkeys. However, rolipram improved performance in the passive avoidance task, a test of hippocampus-dependent memory, in both young and aged mice (Barad et al. 1998). With advancing age, opposite profiles between the function of PKA in the hippocampus and prefrontal cortex were suggested to explain the results of Ramos et al. (2003), i.e., the prefrontal cortex showed indices of increased PKA activity, while the hippocampus exhibited evidence of decreased PKA activity (Ramos et al. 2003). In addition, it has been shown that expression of PDE5 is strongly reduced in brains of Alzheimer’s disease patients (Reyes-Irisarri et al. 2007). However, PDE2 and PDE9 do not show this Alzheimer-related reduction in expression patterns, but show the same distribution as in healthy age-matched controls (Reyes-Irisarri et al. 2007). Along similar lines, PDE5 inhibition did not improve object memory in aged rats (Domek-Lopacinska and Strosznajder 2008). Consequently, when developing a PDE-I for the treatment of cognitive decline resulting from Alzheimer’s disease, PDE2-Is and PDE9-Is may be better targets in this population than PDE5-Is.

Thirdly, since most PDEs are transcribed by several genes, which give rise to multiple PDE splice variants and isoforms, further investigation into possible isoform-specific effects of PDE-Is is a field of great interest. For example, four isoforms of PDE4 mRNA have been found; PDE4A, PDE4B, PDE4C, and PDE4D. Indirect evidence suggests that PDE4A and PDE4B are involved in signaling pathways related to affective (Ye et al. 2000) and memory (Ahmed and Frey 2003) processes, respectively. Recently, the antidepressant potential of PDE4A in the hippocampus has been found to be related to specific splice variants of this PDE4 isoform (D’Sa et al. 2005). The same probably holds for PDE4B and memory (Ahmed and Frey 2005) or schizophrenia (Siuciak et al. 2008a). PDE4D KO mice have already been generated and these animals display both an antidepressant and procognitive profile (Zhang et al. 2002). Furthermore, it has been observed that the expression of the majority of PDE4D isoforms (1–9) was reduced in the hippocampus of patients with Alzheimer’s disease compared to healthy adults. Interestingly, PDE4D1 and PDE4D2 were increased in the brains Alzheimer’s patients (McLachlan et al. 2007). These findings underscore the relevance of further investigations into the role of isoform-specific PDEs in cognition enhancement.

Furthermore, the most widely used PDE4-I in behavioral studies, rolipram, produces severe dose-limiting emetic side effects including headache, gastric hypersecretion, and severe emesis (e.g., nausea) in humans (Zhu et al. 2001). Novel PDE4-Is are thought to produce less emetic side effects, but thus far no human cognition studies have been reported using these second-generation PDE4-Is. Thus far, only PDE5-Is can be prescribed to humans. However, particularly cardiovascular effects limit their usefulness as a general treatment for cognitive disorders, since patients with cardiovascular indications cannot be included. In addition, central effects including visual disturbances and headache limit the use of PDE5-I such as sildenafil (Kruuse et al. 2002). Especially chronic treatment with these drugs could be disadvantageous. Again, an isoform-specific PDE-I could circumvent the abovementioned side effects.

Future directions

In this review, we summarized all recent available literature of the cognition-enhancing effects of PDE-Is in preclinical studies. It has been shown that inhibitors of PDE2, PDE4, PDE5, PDE9, and PDE10 improve a wide range of cognitive processes, including information processing, attention, learning, memory, executive functioning, and response inhibition, in various behavioral models within different species. We argue that it is unlikely that blood flow is the mechanism underlying these procognitive effects. We feel that LTP appears to be a better substrate for the cognition-enhancing properties of PDE-Is.

Despite accumulating evidence for the procognitive effects of PDE-Is, further investigation is still required. First, more localization studies are required to obtain more knowledge about the localization of the specific PDE isoforms in different brain areas. In addition, the exact underlying working mechanisms of selective PDE-Is have to be investigated by using central administration paradigms, blood flow measurements, and parallel LTP experiments. Clearly, it is crucial to translate the procognitive findings in animals to human subjects. Since PDE5-Is are already clinically accepted for the treatment of erectile dysfunction, these drugs can be readily tested in human subjects. Besides neuropsychological...
tasks to address cognitive functioning, imaging studies (EEG and fMRI) are necessary to elucidate the central mechanisms underlying the cognition-enhancing effects of PDE inhibition.

Taken together, PDE-I s offer a promising target for cognitive enhancement. Yet, the future for cognition-enhancing PDE-I s lies in the development of isomorph-specific PDE-I s that are present in the aged or Alzheimer-diseased brain and that have limited aversive side effect profiles within the effective dose range for cognition enhancement. Suitable candidates appear to be PDE2-I s or PDE9-I s, although little is known about their side effect profiles and isoform specificity.

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