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PDE inhibitors in psychiatry – future options for dementia, depression and schizophrenia?

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Phosphodiesterases are key enzymes in cellular signalling pathways. They degrade cyclic nucleotides and their inhibition via specific inhibitors offers unique 'receptor-independent' opportunities to modify cellular function. An increasing number of *in vitro* and animal model studies point to innovative treatment options in neurology and psychiatry. This review critiques a selection of recent studies and developments with a focus on dementia/neuroprotection, depression and schizophrenia. Despite increased interest among the clinical neurosciences, there are still no approved PDE inhibitors for clinical use in neurology or psychiatry. Adverse effects are a major impediment for clinical approval. It is therefore necessary to search for more specific inhibitors at the level of different PDE sub-families and isoforms.

Introduction

Phosphodiesterases (PDEs) are a class of key enzymes within the intracellular signal transduction cascade that follow activation of many types of membrane-bound receptors. PDEs degrade cyclic Adenosine Mono Phosphate (cAMP) and/or cyclic Guanosine Mono Phosphate (cGMP) by hydrolysis of phosphodiester bonds. Thereby, they regulate intracellular levels of these ubiquitous second messengers. In addition to the direct regulatory effects, rising intracellular concentrations of cAMP/cGMP facilitate bonding to their target enzymes, Protein Kinase A (PKA) and Protein Kinase G (PKG) [1]. Activated protein kinases phosphorylate substrates, such as ion channels, contractile proteins and transcription factors that regulate pivotal cellular functions [2,3]. Localization, duration of action and concentration of cyclic nucleotides within specific subcellular domains convey signal strength and specificity. Any change within these parameters may contribute to alterations in neuronal function [4]. Due to their unique properties and participation in a variety of cellular mechanisms, alterations in PDE activity can affect multiple cellular processes, including apoptosis, differentiation, lipogenesis, glycogenolysis, gluconeogenesis and muscle contraction [5].

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Twenty-one genes are currently known to encode at least 11 different PDE families (PDE1 to PDE11) [6,7]. Three genes (and splice variants) constitute the PDE1 family. Its sensitivity to calmodulin is unique; depending on gene and splice variant, PDEs differentially hydrolyse cAMP and cGMP. The PDE2 family hydrolyses cAMP and cGMP with preference for cGMP [8] and an increase of cAMP hydrolysis if cGMP is present at the same time. Three variants of a single gene exist. PDE2 has a functional role in the heart [9]. In the brain it is localized in olfactory epithelia and sensory neurons, bulb and tubercle and hippocampus pyramidal and granular cells [10–12]. PDE3 has a high affinity for cGMP while hydrolyzing cAMP in a rate 10 times higher than that of cGMP. The presence of cGMP has therefore the quality of a competitive inhibitor of cAMP [13]. Two genes with splice variants constitute the PDE3 family which plays a critical role in cardiac contraction [14]. The most extensive PDE family at present is PDE4; including four genes with various splice variants [15]. PDE4 hydrolyses solely cAMP. Rolipram is the prototype PDE4 inhibitor and has received noticeable interest by the scientific and pharmaceutical communities. The multitude of subtypes suggests that PDEs exhibit differentially compartmentalized expression [16]. Transgenic mice models of reduced PDE4 function underscore the importance of this PDE family for psychiatric conditions [17]. PDE5 exclusively binds cGMP without being activated by calcium (or calmodulin).

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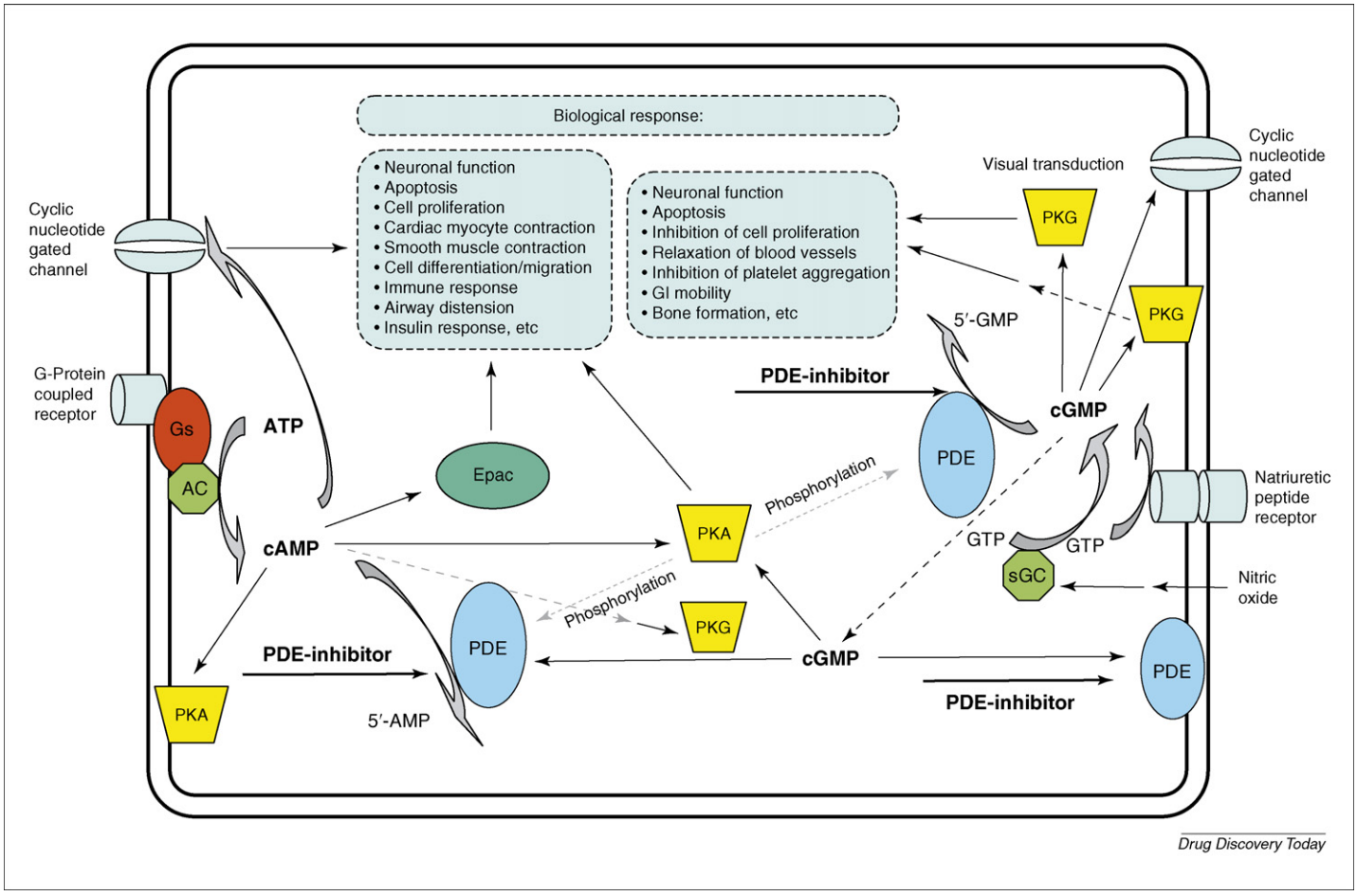

FIGURE 1

Schematic representation of intracellular phosphodiesterase activity: cAMP and cGMP are synthesized by Adenylyl Cyclase (AC) and (soluble) Guanylyl Cyclase (sGC). Cyclic nucleotides act on Protein Kinase A (PKA for cAMP) and Protein Kinase G (PKG for cGMP), cAMP activated exchange protein (Epac) and cyclic nucleotide-gated channels. PKA and PKG themselves can modify proteins (and thereby enzyme activity levels) via phosphorylation. The endpoints of cAMP and cGMP pathways with respect to cellular and physiological effects are shown under "Biological response". While this figure is not exhaustive, it highlights the complexity of cyclic nucleotide signaling, including the mechanisms of precise control of cAMP/cGMP levels by phosphodiesterase (PDE) activity. It is important to note that cAMP/cGMP are ubiquitous second messenger substrates with the ability to move unimpeded within the cell. Therefore, the diversity of effects cannot be attributed only to the magnitude of interactions between constituents of nucleotide pathways. Rather, the localized activity of phosphodiesterases and other effector proteins is crucial for the development of pinpointed pharmacological manipulation with fewer collateral effects on other systems. Table 1 notes the relationship between each PDE family and either cAMP or cGMP.

Zaprinast is a prototypical PDE5 inhibitor, resulting in an increase of cGMP with associated vasodilatation [18]. Similar activity at the catalytic subunits of PDE5 and PDE6 are the likely cause of sildenafil-induced side effects on visual function. This is because the PDE6 family plays a major role in phototransduction [19]. PDE7 and 8 gene families both encompass two genes with high affinity for cAMP suggesting a possible role for modulation of memory by PDE7 [20]. PDE9 is highly specific for cGMP and activity at this enzyme may also contribute to behavioural state regulation and learning [21]. The PDE10 family hydrolyses cAMP and cGMP, and various splice variants have been implicated in long-term potentiation with recent studies showing an association with neurodegenerative disease [22,23]. PDE11 has two substrates and a recent pharmacogenetic study shows evidence for a possible role of this enzyme family in depression [24].

Adding to this functional heterogeneity, each PDE family contains a number of sub-families and isoforms (>50) that are unique with respect to three-dimensional structure, kinetic properties, mode of regulation, intracellular localization, cellular expression and inhibitor sensitivity. Modifying the rate of cyclic nucleotide formation or degradation via PDEs will change the activation state of related pathways (Figure 1). Therefore, PDE inhibitors can prolong or enhance the effects of physiological processes mediated by cAMP or cGMP. It is noteworthy that PDEs are the most important means of inactivating intracellular cAMP in the brain, suggesting that PDE inhibitors present a potentially powerful means to manipulate second messengers involved in learning, memory and mood [4,15,25,26].

Several medications have already exploited the therapeutic potential of selective PDE inhibitors. PDE5 inhibitors such as sildenafil, tadalafil and vardenafil have had distinctive clinical benefit and notable commercial success for the treatment of erectile dysfunction. The quest to develop novel treatments for unmet medical needs, across multiple diseases, has expanded the therapeutic use of selective PDE inhibitors. In June 2005, the U.S. Food and Drug Administration (FDA) approved registration of

TABLE 1

Selected overview of PDE inhibitors

Substance	PDE family	Nucleotide substrate	Potential benefit	Model	Subject
Bay 60-7550	PDE2	cAMP/cGMP	Memory improvement	Social/object recognition, T-maze	Rat [36,40]
Cilostazol	PDE3	cAMP/cGMP	Neuroprotection	Cerebral hypoperfusion (water maze, immunohistochemistry)	Rat [47]
MK 0952	PDE4	cAMP	Memory improvement	Phase-II clinical trial	Human [63]
RO 20-1724	PDE4	cAMP	Depression	Differential reinforcement of low response rate (DRL)	Rat [71]
Rolipram	PDE4	cAMP	Memory improvement	Object recognition	Rat [37]
				Radial-arm maze	Rat [75,106]
			Neuroprotection	Carotid artery occlusion, immunostaining	Mouse [52]
			Depression	Cell-injury models	Rat [53]
				Phase-II clinical trial	Human [76]
				DRL	Rat [71]
				Learned helplessness	Rat [32]
				Tail suspension, forced swim test	Mouse [17]
			Schizophrenia	Evoked potentials	Mouse [29,89]
				Acoustic startle and prepulse inhibition	Mouse [29,89]
Sildenafil	PDE5	cGMP	Memory improvement	Attention, verbal recognition, evoked potentials	Human [42]
				Avoidance learning	Rat [107]
					Mouse [35]
				Passive avoidance	Chick [30]
				Object recognition	Mouse [108]
					Rat [34]
				Elevated-plus/T-maze (cognitive impairment model)	Rat [107,109]
			Neuroprotection	Phase-I clinical trial	Human [64]
				Middle cerebral artery occlusion	Rat [110]
Tadalafil	PDE5	cGMP	Neuroprotection	Middle cerebral artery occlusion	Rat [111]
Trequinsin	PDE3	cAMP/cGMP	Neuroprotecion	Cell-injury models	*In vitro* [53]
			Depression	DRL	Rat [81]
Vardenafil	PDE5	cGMP	Memory improvement	Object recognition, immunohistochemistry	Rat [34,36]
Zaprinast	PDE5	cGMP	Memory improvement	Object recognition	Rat [33]
				Y-maze	Rat [112]
			Depression	DRL	Rat [81]

Several PDE inhibitors have been examined for memory improvement, neuroprotection, depression and schizophrenia using preclinical animal models and early clinical trials in humans. Studies in humans are thus far limited to rolipram and several PDE inhibitors that already have approval for use in humans including sildenafil, vardenafil, tadalafil and cilostazol.

sildenafil for pulmonary arterial hypertension. Other applications for PDE inhibitors currently under investigation include asthma, atopic dermatitis, psoriasis and heart failure [27,28]. Based on preclinical models, there is growing interest in their use for CNS disorders (Table 1). Specifically, PDE inhibitors are currently being investigated as possible memory enhancers, antidementia drugs, antidepressants and antipsychotic agents [17,29–32].

Phosphodiesterase and dementia/cognition

Cyclic AMP/cGMP regulation plays a crucial role in a variety of memory-related processes. Prickaerts *et al.* demonstrated an improvement of memory when the cGMP- and PDE5-specific inhibitor zaprinast was administered to rats immediately after training in an object recognition task [33]. Zaprinast increased the time rats spent exploring a novel object relative to a previously experienced one, whereas vehicle-treated animals did not. This finding is interpreted to mean that the rats remember the previously experienced object and therefore choose to explore the novel one. This increased memory for previously experienced objects lasted for four hours and suggests that zaprinast treatment improved memory of the previously experienced object. The results with zaprinast were replicated with chicks in a passive avoidance task [30]. Other selective PDE5 inhibitors have been evaluated by the same author more recently [34]. Sildenafil and vardenafil improved performance in the object recognition task for 24 hours after being administered immediately after training. Similarly, sildenafil has also been tested in one-trial learning tests in mice using a passive avoidance task, following exposure to an electric shock [35]. Sildenafil, administered immediately after the learning trial, improved the retention performance 48 hours later. Assessments of different PDE inhibitors administered at different time points after a learning experience, indicated that these drugs consolidate memory, most likely via elevating central cAMP and cGMP levels in rats and mice [36–38]. So far, this was demonstrated

for selective inhibitors of PDE families 2 (vardenafil), 4 (rolipram) and 5 (Bay 60-7550). It is likely that memory consolidation has a structural correlation and that neuronal plasticity including long-term potentiation is critical for its formation [39]. Studies indicate that central cAMP/cGMP levels likely affect synaptic plasticity in rats [40,41]. The PDE2 inhibitor Bay 60-7550 enhanced long-term potentiation in cultured neurons and hippocampal slices while no alteration of basal synaptic transmission was observed. Furthermore, it improved performance in social and object recognition memory tasks [40]. However, memory is a complex process, consisting of multiple components, reducing the ability to generalize a proposed beneficial role to other forms of learning or other classes of PDEs.

A review of Medline (June 28, 2007) yielded only two studies in humans investigating the effects of a PDE5 inhibitor on cognitive processes in healthy humans. Sildenafil had no effect on attention or verbal recognition, but did cause an alteration of auditory event-related potentials (ERPs). These ERP changes were interpreted as indicative of an enhanced ability to focus attention and select relevant target stimuli [42]. For sildenafil, the second study indicates a slight improvement in reaction time. A lack of stronger results may be due to the fact that only a single dose was administered [43]. CNS effects of sildenafil are suggested by case reports and case studies describing increased emotional reactivity and psychological disturbances in men taking sildenafil [44]. However, the incidence of adverse effects such as these may be related to coexisting disorders and/or excessive dosing [45]. Nevertheless, studies indicate that a number of PDE inhibitors are capable of penetrating the blood brain barrier [29,42,46,47]. Dosage and frequency of drug intake are important parameters that might need further adjustment to show memory-enhancing effects. Although, little is known about the cognitive effects of other PDE families, long-term potentiation in rats is associated with an upregulation of PDE10A splice variants [22].

Neuroprotection and dementia

The role of cAMP in functional and metabolic regulation of the nervous system has been emphasized in a number of studies. Early studies by Nishino *et al.* highlight a significant decrease in cAMP in patients with Parkinson's disease [48]. Furthermore, PDE1A2 is inhibited by some antiparkinson drugs, suggesting a potential role of PDE1A2 in Parkinson's disease [49,50]. Although additional recent studies in humans could not be identified in our review of the literature, two studies used a cerebral hypoperfusion model in rats to demonstrate neuroprotective efficacy of the PDE3 inhibitor cilostazol [47,51]. A hypoperfusion model in mice also showed enhanced proliferation of newborn hippocampal neurons under physiological conditions, but not after ischemia [52]. The neuroprotective efficacy of other PDE inhibitor subtypes was recently demonstrated using lesion models with rat cortical neurons [53].

Several studies suggest that the cAMP-response-element-binding-protein (CREB) is a key control point for long-term memory (LTM) formation [54–56]. Interestingly, deactivating CREB does not affect the ability to acquire or retain short-term memory (STM) but does impair LTM. Alternatively, increasing CREB function augments LTM while leaving acquisition and STM unchanged. Thus, CREB regulation produces parallel effects on LTM, indicating that the expression of CREB may be an obligatory target of cAMP-mediated modulation of memory consolidation. The accumulation of amyloid-beta peptide in animal models Alzheimer's disease (AD) leads to inhibition of CREB-mediated intracellular signalling pathways and impairs long-term potentiation [57]. These data suggest that PDE inhibitors, which enhance cGMP signalling, may be able to overcome the detrimental effects of amyloid-beta peptide on the CREB pathway and provide a novel approach to the treatment of AD [58]. These results require further clarification, including the role of local compartmentalization of cAMP/cGMP and target protein function.

The PDE4 inhibitor, rolipram, produces behavioural effects that are similar to the aforementioned CREB-dependent memory enhancement. For example, rolipram enables memory formation in less than half of the normal amount of training, suggesting that PDE4 inhibitors are a possible target for memory enhancement [55]. Although PDE4 and its inhibitors have been specifically implicated in modulating long-term memory, effects have also been observed for working memory. One study that examined aging rats and monkeys found that the beneficial effects of the G_i-coupled alpha 2A receptor agonist guanfacine on working memory were reversed by rolipram [59]. Once again, the effect of PDE inhibition cannot be separated from the intracellular site of action in order to explain the impact on different stages of memory. A proposed role for PDE7 and PDE8 inhibitors in the treatment of dementia comes from post-mortem studies of AD. Specifically, one study suggests that the expression of messenger RNA (mRNA) for the PDE7 and PDE8 isoenzymes is altered in brains of people affected with AD. Furthermore, the regulation of these PDE families in AD depends on the stage of illness [60]. Therefore, further research is needed to clarify the specific stages of illness during which PDE7 or PDE8 modulators may have therapeutic effects.

Promising yet inconsistent results have emerged from trials with the PDE4/PDE5 inhibitor denbufylline. In one clinical trial, 96 patients suffering from Alzheimer's disease or multiinfarct dementia (MID) received denbufylline or placebo for 2 weeks. Denbufylline, but not placebo, induced a statistically and clinically significant improvement in both AD and MID patients [61]. A later trial could not find a major affect under denbufylline [62].

A phase-II randomized, double-blind clinical trial is currently underway to determine if the PDE4 inhibitor MK-0952 can improve cognitive impairments in patients with AD during mild to moderate stages of disease [63]. Additionally, a phase-I clinical trial is presently assessing the efficacy and optimal dosage for sildenafil in the treatment of subacute ischemic stroke to assess possible neuroprotective properties of PDE5 inhibitors [64]. This is based on earlier preclinical *in vitro* studies in which zaprinast protected cultured spinal motor and non-motor neurons against chronic glutamate-induced and reactive oxygen species-induced toxicity [65]. Similarly, Otsuka Pharmaceuticals is exploring indications for a selective PDE3 inhibitor, cilostazol, in a phase-IV study. Cilostazol, an approved antiplatelet agent for the treatment of intermittent claudication, will be compared to aspirin with respect to prevention of stroke recurrence and safety for bleeding complications in acute stroke [66,67]. Little is known about the potential role of other PDE gene families in neuroprotection. However, there is some emerging data for PDE10 in this domain.

Using a mouse model of Huntingon's disease (HD), transgenic mice expressed a transgene that contains exon 1 of the human mutant HD mice. It was shown that the expression of the mutant gene was related to a decreased PDE10A2 mRNA transcription [68]. Thus, loss of PDE activity may contribute to dysregulation of intracellular cAMP/cGMP in brain areas responsible for the control of movements and cognition [4,23].

Phosphodiesterase and depression

Impairments in signal transduction have also been implicated as possible mechanisms of reduced plasticity and neuronal survival in major depressive disorders [69]. This hypothesis provides a framework in which the pathophysiology and pharmacotherapy for depressive illness converge on cAMP-mediated signalling rather than being organized by receptor or neurotransmitter systems [70]. In animal models, elevated intracellular cAMP levels have been shown to possess antidepressant-like effects. This can be achieved by PDE inhibition or by the stimulation of adrenergic receptors and numerous studies have focused on the PDE4 subtype for therapeutic interventions [15,26,71]. However, contradictory results have also been reported. The role of cGMP levels in this matter appears to be different.

Treatment with memantine, a noncompetitive NMDA receptor antagonist, has been shown to reduce immobility in the forced swim test (FST) in mice, a result that is interpreted as an antidepressant-like effect [72,73]. Pretreatment with sildenafil reversed this increased mobility effect following memantine. This indicates that increasing cGMP level via PDE5 inhibitors like sildenafil may block antidepressant effects in this validated animal model of depression [73]. To add to the contrary, a 2006 genetic study of 284 Mexican Americans found that the diagnosis of major depressive disorder is associated with single nucleotide polymorphisms in PDE9A and PDE11A. Furthermore, antidepressant responsiveness was significantly associated with polymorphisms in PDE1A and PDE11A. Because cGMP is the exclusive substrate of PDE9, while PDE1 and PDE11 hydrolyse both cAMP and CGMP, these data suggest a role for cGMP levels in the development of depressive disorders as well as a possible role in treatment response [24].

The inhibition of PDE4D by rolipram produces antidepressant-like and memory enhancing effects in animal models [17,52,74,75]. Rolipram has also been tested as a potential monotherapy for depression [76]. Activity of rolipram at the PDE4D subtype may represent a significant aspect of its action because several norepinephrine and serotonin reuptake inhibitors with proven antidepressant efficacy share this characteristic [77]. Thus, inhibition of PDE4 may represent a shared mechanism for efficacy among different classes of antidepressants [26,29]. Notably, PDE4 is the predominant enzyme that hydrolyses cAMP formed by the stimulation of beta-adrenergic receptors, which are thought to mediate the effects of several known antidepressant agents [78–80].

The PDE4 family is composed of multiple sub-families (PDE4A, PDE4B and PDE4D) that vary in their cerebral distribution, suggesting differential roles for each sub-families [15,25]. Some investigators have suggested that the PDE4D gene product may be particularly involved in the mediation of depressive symptoms and antidepressant responsiveness [26,77]. Other studies have evaluated this hypothesis by assessing the behavioural phenotypes and pharmacological sensitivity in PDE4D knockout mice [17]. These studies indicate that PDE4D knockout mice display decreased immobility in tail-suspension and forced-swim tests, which have positive predictive value for an antidepressant-like effect in humans. Although desipramine and fluoxetine produced similar effects in complete PDE4D knockouts, heterozygous PDE4D knockout and wild-type mice, only rolipram produced antidepressant-like effects in wild-types. Potentiation of cAMP formation through isoproterenol could only be induced in wild types. Together with studies by O'Donnell and colleagues, these results strongly suggest that PDE4D is an essential mediator of the antidepressant-like effects of rolipram and provides further evidence that PDE4D-regulated cAMP signalling plays a role in the pathophysiology and pharmacotherapy of depression [26,71,81]. A clinical trial sponsored by the National Institute of Mental Health is currently trying to elucidate the hypothesis of phosphodiesterase manipulation as a common feature shared by many antidepressants. In this study, (R)-[^{11}C] rolipram positron emission tomography (PET) is being used to compare PDE4 levels between unmedicated depressed patients and healthy subjects [82].

Brain-derived neurotrophic factor (BDNF) is also thought to play an important role in development, plasticity and survival of neurons in the central nervous system and has been implicated as a possible mediator of depressive disorders [83]. Itoh *et al.* administered rolipram, imipramine and their combination to rats performing a learned helplessness task, which is proposed to have predictive value as an animal model for depression. In this model, CREB activity and BDNF levels in frontal cortex and hippocampus were significantly increased by treatment with a combination of rolipram and imipramine compared to those in imipramine-only treated rats. The repeated coadministration of rolipram and imipramine significantly reduced the escape failures in rats. Imipramine alone could not ameliorate the escape behaviour to a similar level, even at the highest dose tested. Thus, coadministration of PDE4 inhibitors with classical antidepressants might enhance the effect of receptor-bound drugs [32].

Phosphodiesterase and schizophrenia

All currently approved antipsychotic medications produce their beneficial effects through antagonism of the dopamine (DA) D2 receptor. Specifically, the treatment of positive symptoms of schizophrenia, and other forms of psychosis, appears to be related to antagonism of the D2 receptor. The DA D2 receptor is a G-protein-coupled, membrane-bound receptor, linked to the inhibition of adenylyl cyclase [84]. The binding of dopamine to this receptor subtype leads to a cascade of events that decrease adenylyl cyclase activity, which, in turn, reduces cAMP formation and activation of PKA. PKA activity is thought to effect the long-term adaptive changes that produce therapeutic benefits of antipsychotic medications over the course of weeks or months of treatment. The phosphorylation of many intracellular substrates including ion channels and DNA binding proteins depends heavily on the activation of this pathway. Antipsychotic medications are thought to oppose the activity of DA at the D2 receptor and, therefore, increase intracellular cAMP levels and its downstream effects. Thus, an intact cAMP signal transduction pathway seems to be essential for antipsychotic drug action (Figure 1) [85].

There have been efforts to reproduce antipsychotic effects using novel receptor-independent mechanisms, including inhibition of the enzymes that degrade cAMP. The rationale for this approach is that a disruption of cAMP formation in animals replicates many phenotypic markers of schizophrenia, including deficits in prepulse inhibition (PPI) of startle, event-related potentials (ERP), as well as learning and memory [86–88]. PDE inhibitors, in particular, have been shown to meet several key criteria as antipsychotic agents in preclinical animal models and may present a new class of receptor-independent treatment approach [29,89]. For example, Maxwell *et al.* used amphetamine-induced abnormalities in auditory event-related potentials to study the antipsychotic potential of non-receptor based compounds such as rolipram. Amphetamine is an indirect dopamine agonist and an established model to produce auditory sensory processing deficits similar to those seen in schizophrenia. Currently approved antipsychotic treatments reverse the effects of amphetamine in this paradigm. Similarly, rolipram reverses the ERP abnormalities caused by amphetamine [29]. Concordantly, Kanes *et al.* explored antipsychotic-like activity for rolipram using behavioural measures [89]. To test this hypothesis, the effect of an acute treatment with rolipram on acoustic startle and PPI was studied in C57BL/6J mice. PPI is disrupted in unmedicated schizophrenia patients and the ability to increase PPI in mice is predictive of the antipsychotic efficacy of a drug. Treatment with rolipram significantly increased PPI at doses that do not alter the acoustic startle response. Rolipram also blocked the disruptive effects of amphetamine on PPI and induced catalepsy at high doses, thus exhibiting many of the same behavioural effects as traditional antipsychotic medications. Several lines of research suggest that the antipsychotic effects of rolipram are likely mediated by PDE4B. Siuciak *et al.* observed a threefold shift in the ED50 of rolipram in PDE4B knockout mice undergoing conditioned avoidance responding [90]. Similar to the study by Kanes, rolipram produced catalepsy only at the highest dose, suggesting a lower dose for behavioural efficacy than for adverse events. It appears, therefore, to have a pharmacological profile similar to that of some newer antipsychotics that claim to reduce motor side effect liability at therapeutic doses. However rolipram produces nausea and emesis at doses that overlap the therapeutic range, suggesting that more selective agents may be needed.

There are also important associations between members of the PDE4 family and genetic susceptibility factors for schizophrenia. DISC1 (Disrupted in Schizophrenia 1) is among the genes associated with schizophrenia [91–93]. The familial DISC1 association is the product of a balanced chromosomal translocation (*t*(1;1 1)(q42;q14) [94,95]. This observation followed a study in which Millar *et al.* identified an individual with schizophrenia who carried a DISC1 translocation and had a history of repeated psychotic episodes characterized by auditory hallucinations and delusions [96]. The authors demonstrated that the breakpoint of the translocation on chromosome 1 disrupts the gene encoding for phosphodiesterase 4B (PDE4B) enzyme, using fluorescence *in situ* hybridization. According to the finding in this study, elevated cellular cAMP levels lead to increased PDE4B activity, affecting cAMP catabolism with an associated psychiatric outcome. This result was confirmed by another recent case control association study [97]. Complementary evidence from mice is consistent with this data. Genetic and behavioural assessment of mice demonstrated reduced binding of two mutant DISC1 proteins to the DISC1 binding partner PDE4B. Mice with these mutations exhibit phenotypes related to depression and schizophrenia [98].

Several studies have suggested that nicotinic agents may hold therapeutic potential in schizophrenia. Interestingly, PDE4B has been associated with the effects of nicotine in the brain. Chronic exposure to nicotine decreases the expression of PDE4B mRNA in prefrontal cortex of adolescent rats treated with 12 mg/day. Researchers determined that increasing the dose to 24 mg/day resulted in extension of this finding to other brain regions including the nucleus accumbens and hippocampus. These findings suggest that chronic nicotine exposure is responsible for a dose-dependent down-regulation of PDE4B [99]. This study underlines the complex relationship between smoking and schizophrenia.

It has been proposed that selective PDE10A inhibitors represent novel therapeutic agents for individuals with schizophrenia. In mice, papaverine, a PDA10A inhibitor, is associated with increased cGMP levels in the striatum and increased phosphorylation of CREB, which are both crucial for striatal function [100]. Interestingly, papaverine was also found to reduce deficits caused by chronic phencyclidine treatment, a recognized animal model for schizophrenia [101].

Limitations

Despite the abundance of studies indicating a potential role for PDEs and their inhibitors in CNS-borne diseases like AD, depression or schizophrenia, certain *caveats* must be considered. The first consideration relates to the potential reasons why there are no PDE inhibitors currently available for CNS illness. One reason may be the incidence and types of adverse effects that occur with existing PDE inhibitors. Although preliminary adverse effect profiles of the newer PDE4 inhibitors appear to be improved, older prototype PDE4 inhibitors had substantial adverse effects, most notably headache, nausea and emesis. It is noteworthy that rolipram was not commercialised, despite promising preclinical and phase-II study data [76]. Unfortunately, the mechanisms responsible for the side effects of PDE4 inhibitors are still not well understood. A second consideration results from the necessary lag between drug target discovery and practical application of the resulting ideas. The majority of studies for PDE inhibitors in CNS illness have been basic investigations using animal models of memory, neurodegeneration, depression and psychosis. The transfer of these results must incorporate differences between humans and rodents, as well as toxicological and regulatory issues. To the best of our knowledge, only very few studies to date have investigated the CNS effects of a PDE inhibitor in humans [42]. Additionally, it is possible that the positive findings in the beforementioned study by Schultheiss *et al.* were a product of increased cerebral blood flow rather than neuronal in nature. Zaprinast was also previously shown to cause relaxation of cerebral arteries in a concentration-dependent manner in guinea-pigs [102].

The effects of PDEs and their inhibitors have been known for many years and there is a concrete demand for novel treatments that may capitalize on several of these known properties. However, efforts by both the academic and pharmaceutical scientific communities have not yet yielded practical PDE-related therapeutic

interventions for CNS illness. Although there are links between susceptibility genes for CNS illnesses, including DISC1 for schizophrenia and CREB for memory enhancement, these relationships lack sufficient specificity to identify concrete targets for each illness. Nevertheless, the lack of specificity among currently available PDE inhibitors is not necessarily unfavourable. For example, the most selective DA D2-specific antagonist antipsychotic medications do not necessarily produce a more favourable clinical outcome. Specifically, clozapine has been shown to be superior to all other agents, despite a broad pharmacological profile at therapeutic doses [103,104]. There are, in fact, many G-protein-coupled receptors that are relevant for schizophrenia. Unfortunately, both older and newer atypical antipsychotic medications only improve the positive symptoms of schizophrenia, such as delusions and hallucinations [105]. Because the adverse effects of PDE inhibitors have limited their utilization in schizophrenia, we have no empirical knowledge regarding how this class of agents might affect negative symptoms in schizophrenia. This remains one of the most important and elusive therapeutic targets for a major CNS disorder such as schizophrenia and therefore presents the horizon for a major breakthrough.

Conclusions/future directions

The growing knowledge related to the molecular pharmacology of PDEs has already fostered development of selective inhibitors. From the pharmacological point of view, the development of more specific inhibitors for all isoenzymes appears to be a sensible approach to pursue the outstanding clinical needs in CNS disorders. The challenge remains to identify selective inhibitors given the high degree of identity among the active sites of many of the isoenzymes. From a clinical perspective, that follows decades of pharmacologically similar antipsychotic medications, the challenge will be to determine whether a shift from targeting receptors with a shared second messenger pathway, might allow for a more direct, receptor-independent approach to manipulating different cellular functions. To test this hypothesis, the adverse event profiles that have limited clinical acceptance of PDE inhibitors will have to be reduced. Identification of new PDE isoforms, as well as variants of those previously described, has implicated involvement of PDEs in various pathological conditions. By employing advanced techniques, like tissue-specific conditional gene disruption and conditional RNA interference expression in mice, it may be feasible to probe PDE function and validate drug targets. Further understanding of the real-time enzyme kinetics and subcellular localization are additional areas of potential benefit. Since cAMP rapidly diffuses within cells, the concept of sequestered or compartmentalized PDE populations is appealing to explain the plethora of cellular manipulations attributed to PDE function achieved with only two cyclic nucleotides [15]. It is, therefore, important to understand the local, intracellular mechanisms of PDE function and its inhibition for a concerted intervention that minimises undesired side effects due to a lack of specificity.

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