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EXPERT OPINION

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PDE Inhibition and cognition enhancement

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There has been an increasing interest in the development of phosphodiesterase (PDE) inhibitors for the treatment of cognitive dysfunctions. In this editorial, the mechanism of action of PDEs is briefly described, while the effects of different PDE inhibitors in preclinical models are reviewed. Based on the expression of PDE mRNA in the human brain, it is suggested that PDE1 and PDE10 inhibitors are strong candidates for the development of cognition enhancers. However, the complex nature of the expression of PDEs in the brain warrants further research into the role of PDEs in the signaling pathways in brain circuits. The development of PDE inhibitors, which are selective for PDE splicing isoforms, may be promising for future drug development.

Keywords: brain, cAMP, cGMP, cognition, memory, phosphodiesterase

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1. Phosphodiesterases, cAMP, and cGMP

The phosphodiesterases (PDEs) are a superfamily of enzymes that metabolize the ubiquitous intracellular second messengers cAMP and cGMP. The PDEs are encoded by 21 genes that are classified into 11 different families based on amino acid sequence similarity, catalytic characteristics, and regulatory properties [1]. Some PDEs specifically degrade cGMP (PDE5, 6, and 9), some specifically degrade cAMP (PDE4, 7, and 8) and some have a dual-specificity (PDE1, 2, 3, 10, and 11). PDE families are further divided into isoforms on the basis of encoding gene (e.g., PDE4A-D) and splicing isoforms (e.g., PDE4D1 – PDE4D9); in total, more than 100 PDE isoforms can be distinguished [2]. PDE isoforms have distinct localization at the tissue, cell, and subcellular levels, with extensive overlap being the rule rather than exception. Thus, the PDEs are essential to coordinate optimal cAMP or cGMP concentrations in both spatial and temporal dimensions [1] and PDE inhibition offers a means for specific manipulation of cyclic nucleotide signaling for therapeutic benefit [3,4].

2. PDE inhibition and cognition

The cyclic nucleotides play critical roles in regulating synaptic plasticity, and, consequently, PDE inhibitors are of considerable interest as treatments for cognitive dysfunction. Cognition is the process by which the brain absorbs information and then analyzes this information in the present context to respond and plan for the future. These incredibly complex computations are mediated by the continual adjustment of the strength of synapses. At the molecular level, cAMP and cGMP signaling supports many neuronal functions, from the regulation of neurotransmitter release to the firing properties of neurons (e.g., [5,6]). PDE inhibition is well studied for modulating cyclic nucleotide signaling related to long-term potentiation processes [7,8]. Thus, PDE inhibitors are predicted to improve the storage of new memories and, indeed, data from animals support this notion [9-13]. Moreover, it has been shown that cGMP and cAMP are involved in early- and late consolidation

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processes, respectively [14]. There is also experimental evidence that PDEs can increase cellular cGMP levels which may also contribute to the enhanced cognitive performance after PDE inhibition [15]. However, while cognitive dysfunction is a common feature of almost all neuropsychiatric illness, the nature of the behavioral dysfunction and the underlying molecular mechanisms are unique to each condition. Thus, the challenge is to map specific PDE inhibitors to specific neuropsychiatric conditions to maximize efficacy [16].

To date, the vast majority of PDE inhibitors are competitive at the catalytic site and so inhibit all splicing isozymes within a target gene family (i.e., PDE8 inhibitors inhibit both PDE8A and PDE8B isoforms). This is because catalytic domains within families are very highly conserved. Thus, current efforts focus on mapping PDE families to brain circuits implicated in specific disease processes and, in parallel, investigating the functional effects of PDE family inhibitors on molecular processes related to cognitive behaviors. An overview of approved patents of PDE inhibitors is shown in **Table 2**.

3. PDE localization

Knowledge of the localization of PDE isoforms in different brain regions is essential in targeting inhibitors to different neuropsychiatric treatments, though only a first step. Several detailed and informative comparative analyses of PDE expression in the brain have been recently published [17]. **Table 1** provides an overview of the major areas of mRNA expression for different PDEs throughout the human brain (except for PDE3), illustrating a number of points relevant to PDE drug discovery. First, several of the PDE families have notably restricted distributions, including PDE10A, which is very highly expressed in striatal medium spiny neurons, PDE11, which shows particularly high expression levels in dorsal root ganglia, and PDE6, which is only expressed in retina. For PDE10A, localization has been an important clue and guide in directing the evaluation of PDE10A inhibitors for the treatment of schizophrenia [18] and Huntington's disease [19]. However, PDE10A is an exception, and the majority of PDEs are more broadly distributed. In fact, brain structures (cortex, hippocampus, striatum) implicated in higher cognitive functions, such as learning and memory, express a highly overlapping array of PDEs, including PDE1, 2, 4, 8, and 9. This raises two issues. The first is that the response to systemically administered inhibitors is likely to be the summation of effects across the distributed circuits in which an entire family is expressed. As noted above, a number of PDE inhibitors have been shown to enhance LTP at the Schaffer collateral/CA1 synapse, suggesting that these compounds may impact hippocampal memory processes (e.g., [10,12]). However, it has mostly not been determined whether these compounds also affect LTP in other circuits and how such effects may integrate to impact cognition. Second, PDEs overlap at the circuit and cellular levels but likely regulate different signaling processes in discrete subcellular compartments (e.g., [6]). Again using the example of Schaffer collateral/CA1 LTP, it is reasonable to speculate that the different PDE inhibitors that are impacting this process are doing so at different steps and stages. Thus, continued work is warranted to better understand the localization of PDE splicing isoforms at the cellular and, particularly, the subcellular level both to guide investigation for therapeutic utilities and to aid in interpreting complex effects of systemic inhibitors.

Of note, there is a discrepancy between the relatively low expression of PDE5 and PDE4D mRNA in the human brain and studies report cognition enhancing effects of these inhibitors in rats and mice [13,20]. It could be argued that mRNA levels may not be directly related with enzyme levels. Further, there may be species differences in the expression of PDEs. Finally, PDE5 may be less suitable as a target for drug treatment, because a decrease in expression with aging and absence in the Alzheimer brain has been reported [21,22].

Finally, it should be noted that most of the PDEs expressed in the brain are also expressed quite extensively in the periphery, including 2A, 4B and 8B. Knowledge of the peripheral distribution may aid in anticipating unwanted side effects.

4. Functional effects of PDE inhibitors

Analysis of the effects on brain function and behavior is the other essential aspect in developing therapeutic rationales for PDE inhibitors in the treatment of cognitive dysfunction. Effects of PDE inhibitors on hippocampal LTP are certainly consistent with the general notion that PDE inhibitors will impact synaptic plasticity. However, this data offers little further insight into differentiating the various PDE families as cognition targets. A comparative analysis of the effects of family-specific PDE inhibitors on different aspects of synaptic transmission that culminate in LTP would be extremely valuable. There is now emerging data on the effects of PDE inhibitors on the regulation of phosphorylation of downstream targets related to synaptic plasticity that may begin to provide insight into differentiation [23]. However, there is surprisingly little information in CNS tissues linking specific PDEs to *upstream* cyclase activator cascades. A better understanding of what is driving the formation of a cyclic nucleotide pool regulated by a PDE may provide a valuable context for targeting inhibitors to treat particular brain dysfunction.

The most extensive body of data is again around the effects of PDE4 inhibitors [24]. Recently, inhibitors of PDE2, 5, 9, and 10 have also been reported to improve the performance in various memory and cognitive tasks [13]. However, as with LTP, this emerging body of data has not yet offered much in the way of differentiating PDE cognition targets. An interesting example is the recent publication demonstrating that PDE2, 4, 5, and 10 inhibitors reverse a deficit in extra-dimensional set shifting induced in rats by subchronic NMDA receptor inhibition [25]. This assay may model executive function deficits in patients with schizophrenia measured in the Wisconsin Card

Table 1. mRNA expression of different PDE subtypes in selected regions of the human brain relevant for learning and memory (frontal cortex, parietal cortex, temporal cortex, hippocampus, and caudate nucleus).

PDE family	PDE subtype	Strong mRNA expression in selected brain regions relevant for learning and memory	Strong mRNA expression in peripheral tissues
1	A	*	Small intestine
	B	Frontal cortex, parietal cortex, temporal cortex, striatum, hippocampus	
	C	Frontal cortex, parietal cortex, hippocampus	pancreas, stomach, small intestine, heart, kidney, bladder, and lung
2	A	Frontal cortex, parietal cortex, striatum, hippocampus	Adrenal gland, liver, pancreas, stomach, small intestine, kidney, bladder, and spleen
3	A	*	
	B	*	
4	A	Frontal cortex, parietal cortex, temporal cortex	Pancreas, stomach, small intestine, and skeletal muscle
	B	Frontal cortex, parietal cortex, hippocampus	Liver, pancreas, small intestine, skeletal muscle, kidney, bladder, lung, and spleen
	C	*	
	D	*	
5	A	*	
7	A	*	
	B	*	
8	A	*	Adrenal gland, liver, pancreas, stomach, small intestine, and kidney
	B	Frontal cortex, parietal cortex, temporal cortex, hippocampus	Thyroid, pancreas, small intestine, and kidney
9	A	*	Pancreas, small intestine, kidney, bladder, lung, spleen, and stomach
10	A	Caudate nucleus	Kidney
11	A	*	

Only the PDE subtypes with mRNA expression levels of more than 20% compared to the PDE subtype with highest mRNA expression in that region are depicted (based on [17]).

*Expression below 20% of maximally expressed PDE in a brain region.

Sorting Task. However, PDE2, 4, 5, and 10 differ radically in terms of cyclic nucleotide substrates, regulation, and brain localization, implying that the impact of inhibitors on set shifting has to be mediated by quite different mechanisms. Thus, the next challenge in evaluating the clinical potential of these compounds is to identify these underlying mechanisms and how they relate to brain dysfunction in schizophrenia. Such information will be essential in translating the preclinical data to human testing.

5. Patent status and future developments

Most patent applications have been on PDE4 and PDE10 and to a lesser extend on PDE2 and PDE9 (European Patent Office: www.epo.org). Evaluation of the claims in the patents shows that PDE4 inhibition is relatively specific for memory enhancement, whereas PDE10 inhibition is somewhat more related to the treatment of cognitive deficits in schizophrenia. Although PDE1, 2 and 9 seem also to be appealing targets for cognition enhancement, only relatively few patents have been approved yet. Recent patent applications have been filed for PDE1 and PDE10. Again this may be related with the brain/periphery expression profile of these PDEs. Further, there are various new applications for PDE4 inhibitors all claiming memory improvement. Ideally, PDE inhibitors would target specific PDE isoforms particularly implicated in neuropsychiatric disease states. As stated above, there are over 100 PDE splicing isoforms identified. However, to date, the level of specificity of PDE inhibitors is restricted to family specificity. The majority of PDE inhibitors are competitive blockers of cyclic nucleotide binding in the catalytic site. There is sufficient sequence variation between the catalytic domains of families to enable the discovery of compounds highly selective for single PDE families. The majority of patent activity to date is for different classes of family-specific inhibitors. It has proven to be extremely difficult to identify compounds specific for isozymes encoded by different genes within a single family. An encouraging breakthrough is the identification of compounds specific for the PDE4D isozyme [20] with reduced PDE4-associated side

Table 2. Overview of approved patents of PDE inhibitors claiming a positive effect on learning and memory.

PDE	Application number	Compound class	Company
2	US20010911277 20010723	Alkyl and cycloakyl derivatives	–
2	WO2001EP08609 20010719	–	Bayer
2A	WO2004US10060 20040401	–	Memory Pharmaceuticals Corp.
2A	US20050545501 20050812	–	Memory Pharmaceuticals Corp.
4	US20050536250 20050520		–
4	BG20010105321D 20010309	Substituted 1,8-naphthridin-4(1H)-ones	
4	US20040517416 20041208	8-(biaryl) quinolines	Merck
4	US20040484172 20040120	Triazine derivatives	Merck
4	WO2003CA01799 20031119	[various]	Merck
4	US20030622117 20030718	Aminoindazole and aminobenzofuran analogs	Memory Pharmaceuticals Corp.
4	NZ20030547469 20030718	6-amino-1H-indazole and 4-aminobenzofuran compounds	Memory Pharmaceuticals Corp.
4	NZ20030537725 20030718	Aminobenzofuran compounds	Memory Pharmaceuticals Corp.
4	WO2003CA00957 20030623	8-(biaryl) quinolines	Merck
4	WO2002EP07113 20020627	Tyrosine hydrazides	Merck
4	WO2002JP06158 20020620	Pyrrolidine derivatives	Takeda
4	NZ20020527081 20020122	Aniline derivatives	Memory Pharmaceuticals Corp.
4	RU20030124303 20020122	Aniline derivatives	Memori Farmas Jutiklz Corp.
4	US20020054273 20020122	Pyrrole compounds	Icos Corp.
4	YUP57603 20020122	N-substituted aniline and diphenylamine analogs	Memory Pharmaceuticals Corp.
4	US20020051309 20020122	N-substituted aniline and diphenylamine analogs	Memory Pharmaceuticals Corp.
4	US20020030477 20020109	Benzoyl derivatives	Merck
4	NZ19980337698 19980310	Nicotinamide derivatives	Pfizer
4	MX2002PA00293 20020109	–	Memory Pharmaceuticals Corp.
4	EA20020000702 20001220	Substituted 8-arylquinoline compounds	Merck
4	JP19930172024 19930621	1,8-naphthyridine derivative	Green Cross Corp.
4	US20000719467 20001213	Arylalkanoylpyridazine derivatives	MERCK
4	NZ19990504933 19991102	Substituted quinoline-carboxylic acid (pyridinyl) amide compounds	Darwin Discovery Ltd
4	CZ19960000251 19960126	Arylalkylthiadiazinone derivative compounds	Merck
4	WO2006CA01729 20061023	4-oxo-1-3-substituted phenyl-1,4-dihydro-1, 8-naphthyridine-3-carboxamide compounds	Merck
4	MX2005PA05413 20050520	4-oxo-1-3-substituted phenyl-1,4-dihydro-1, 8-naphthyridine-3-carboxamide compounds	Merck
4	US20050534582 20050511	4-oxo-1-3-substituted phenyl-1,4-dihydro-1, 8-naphthyridine-3-carboxamide compounds	Merck
4D(6)	US20030682722 20031010	–	–
4D7	US20040492835 20041202	–	Memory Pharmaceuticals Corp.
7	US20020129270 20020503	Isoxazole derivative compounds	Merck
7	CZ20020001251 20001010	Benzo(thio)pyranoimidazolone derivatives	Merck
9a	EP20100184576 20030811	6-(cyclohexylmethyl)-1-(1-ethylpropyl)-1, 5-dihydro-4H-pyrazolo-(3,4-d) -pyrimidin-4-one	Boehringer Ingelheim Int [DE]
9a(?)	US20050524956 20051215	Novel alkyl-substituted pyrazolopyrimidine compounds	Bayer
10	KR20077015027 20070629	Pyrrolidyl derivatives of benzo-fused aza heteroaromatic compounds	Pfizer
10	WO2007IB02382 20070816	Heteroaromatic compounds	Pfizer
10	WO2007IB01696 20070615	Tricyclic heteroaryl compounds	Pfizer
10	US20070298782 20070426	Tricyclic heteraaryi compounds	Pfizer
10	US20070279869 20070209	Quinazoline compounds	Pfizer
10	US20070161718 20070122	Aminophthalazine compounds	Pfizer
10	US20070619218 20070103	Bicyclic heteroaryl compounds	Pfizer
10	WO2006IB03875 20061227	Bicyclic heteroaryl compounds	Pfizer
10	US20050257179 20051024	Pyrrolidyl derivatives of benzo-fused aza heteroaromatic compounds	Pfizer
10	NZ20020518478 20020419	1-[(3,4-dimethoxyphenyl)methyl]-6, 7-dimethoxyisoquinoline	Pfizer

Source: http://www.epo.org/.

Table 2. Overview of approved patents of PDE inhibitors claiming a positive effect on learning and memory (continued).

PDE	Application number	Compound class	Company
10A7	US20050546332 20050817	–	Memory Pharmaceuticals Corp.
10A7	WO2004US09878 20040330	–	Memory Pharmaceuticals Corp.
Not specified	KR20090087426 20090916	?	Korea Inst Sci & Tech.
Not specified	US20030694183 20031028	[various]	
Not specified	US20020216886 20020813	Nitrosated and/or nitrosylated derivatives	Nitromed, Inc.
Not specified	WO2001JP01720 20010306	Polypeptide	

Source: http://www.epo.org/.

effects, including emesis. This selectivity results from compound interaction with a region of PDE4D that lies outside the catalytic domain. Recently, small-molecule allosteric modulators of PDE4D were found that do not completely inhibit enzymatic activity (Imax 80 – 90%) [26,27]. It is claimed that these allosteric modulators may have a greatly reduced potential to cause side effects, including emesis, while maintaining activity in biological assays.

6. Expert opinion

There has been a strong interest in developing PDE inhibitors for the treatment of cognitive impairments. Preclinical studies have shown clear beneficial effects of various PDE inhibitors in models of learning, memory and schizophrenia. At present, clinical trials are already ongoing with an inhibitor of PDE4, 9 and 10, that is, MK0952, PF-4447943, and PF-2545920, respectively [27]. Other promising PDE types are 1B, 2A, 4B, and 8B but these are still in an early preclinical phase of development. Combining all available data, we expect that PDE1B and PDE10 inhibitors could be considered as the best candidates at present. This may lead to the development of drugs for treating cognitive dysfunctions, especially in schizophrenia.

Declaration of interest

FS Menniti is an employee of Mnemosyne Pharmaceuticals.

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