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REVIEW PAPER

Effects of Selective Phosphodiesterases-4 Inhibitors on Learning and Memory: A Review of Recent Research

Sheng Peng · Haiyan Sun · Xiaoqing Zhang · Gongjian Liu · Guanglei Wang

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Abstract Phosphodiesterase-4 (PDE-4) regulates the intracellular level of cyclic adenosine monophosphate. Recent studies demonstrated that PDE-4 inhibitors can counteract deficits in long-term memory caused by aging or increased expression of mutant forms of human amyloid precursor proteins, and can influence the process of memory function and cognitive enhancement. Therapeutics, such as ketamine, a drug used in clinical anesthesia, can also cause memory deficits as adverse effects. Targeting PDE-4 with selective inhibitors may offer a novel therapeutic strategy to prevent, slow the progress, and, eventually, treat memory deficits.

Keywords Phosphodiesterase-4 · Phosphodiesterase-4 inhibitors · Memory · Cognition · Memory deficits · Ketamine

Abbreviations

PDE-4	Phosphodiesterase-4
cAMP	Cyclic adenosine monophosphate
UCR	Upstream conserved regions
LTP	Long-term potentiation
PKA	Protein kinase A
CREB	cAMP response element binding protein
CBP	CREB-binding protein
ERK	Extracellular regulated protein

S. Peng · X. Zhang
Department of Anesthesiology, Tongji Hospital, Tongji University School of Medicine, Shanghai 200065, China

H. Sun
Department of Anesthesiology, Zhangjiagang Hospital of Traditional Chinese Medicine, Zhangjiagang 215600, China

G. Liu · G. Wang (✉)
Department of Anesthesiology, Affiliated Hospital of Xuzhou Medical College, No. 99 West Huaihai Road, Xuzhou 221002, China
e-mail: penghill@gmail.com

Introduction

Phosphodiesterase-4 (PDE-4) is an enzyme that catalyzes hydrolysis of cyclic adenosine monophosphate (cAMP) to inactive 5-nucleotide monophosphates, AMP, thus regulating a variety of biological metabolism and cellular functions. Recent studies demonstrated that PDE-4 inhibitors can counteract deficits in long-term memory caused by pharmacological agents, aging, or increased expression of mutant forms of human amyloid precursor proteins, and can influence the process of memory function and cognitive enhancement.

Ketamine is one of the drugs used in clinical anesthesia. There are concerns about adverse effects of ketamine on cognitive impairments. Regulation of cAMP/PDE-4 pathway is an important therapeutic target for prevention of cognitive impairments caused by ketamine. In this review, we will discuss the effects of PDE-4 inhibitors on memory and learning ability. The review will also summarize the rationale for developing new PDE-4 based drugs for prevention and therapy of pediatric cognitive impairments caused by ketamine.

PDE-4

PDE-4 includes four subtypes called PDE-4A, PDE-4B, PDE-4C, and PDE-4D [1]. All subtypes have 3 highly homologous regions in amino acid sequence, including one catalytic domain in a central portion of amino acid

sequence and two upstream conserved regions (UCR1 and 2) in the *N* terminus [2]. The PDE-4 variants are generally divided into two subgroups: long form that has both UCR1 and UCR2, and short form that lacks either UCR1 or UCR2, or both sequences [3]. The existence of PDE-4 variants may be responsible for differences in the regulation of enzyme activity.

The subtypes of PDE-4 are specifically expressed in the regions of the brain or nervous system [4]. Thus, PDE-4C is mainly expressed in peripheral nervous system, while other three subtypes are widely distributed in central nervous system. PDE-4A and PDE-4D are abundantly expressed, while PDE-4B is expressed at low levels in a rat hippocampal CA1 area that is closely related to the function of learning and memory [4].

PDE-4 Inhibitors

In addition to their anti-inflammatory activity, PDE-4 inhibitors exhibit the antidepressant-like and memory-enhancing effects, and are able to improve cognitive function. PDE-4 inhibitors can be divided into six classes: xanthine (theophylline), catechol diethers (rolipram), benzamides (roflumilast), quinazoline diketone (nitraquazone), benzofurans, and others (variegated aromatic compounds). PDE4 inhibitors are currently divided into three generations. The clinical use of first generation (rolipram) is limited because of extensive adverse effects (emesis etc.). The second generation inhibitors (cilomilast, roflumilast) exhibit fewer and less extensive adverse effects due to a higher selectivity toward PDE-4. Importantly, these inhibitors maintain efficient anti-inflammatory properties. Recently, a novel third-generation inhibitor, EPPA-1, was developed and showed a further improved therapeutic index [5].

Effects of PDE-4 Inhibitors on Learning and Memory

The memory is divided into short-term and long-term memory [6]. The formation of the short-term memory is a transcription- and translation-independent process, while long-term memory requires both [7]. A long-term potentiation (LTP), a form of transcription-dependent synaptic plasticity, received extensive attention as a model for the formation of long-term memory. LTP is classified into early (E-LTP) and late LTP (L-LTP) [8]. L-LTP requires increase in cAMP levels, activation of protein kinase A (PKA), and protein synthesis. PKA translocates into nucleus and activates cAMP response element binding protein (CREB). Both the deficiency and overexpression of components of the cAMP/CREB signaling pathway were demonstrated to play an important role in the activation of this pathway for L-LTP and long-term memory [9]. For example, in a mice behavioral study, both the deficiency in CREB subtype and overexpression of CREB-binding protein (CBP) indicated the important role of this type of transcription factor in the long-term memory storage [10]. Similarly, mice with down-regulated PKA activity exhibited impaired LTP and long-term memory [11]. Studies also demonstrated that overexpression of type 1 adenylyl cyclase leads to increased levels of cAMP and thereby to enhanced memory and LTP [12]. The above-mentioned studies clearly indicate that the cAMP signaling pathway plays a pivotal role in the long-term neurological and behavioral changes.

PDE-4 inhibitors can reduce the rate of cAMP hydrolysis, thereby increasing the levels of intracellular cAMP, and trigger the cAMP and ERK signaling pathways to regulate synaptic plasticity and enhance memory [13]. Through the increase in synaptic plasticity and hippocampus-dependent memory, PDE inhibitors rescue the deficits in cAMP signaling induced by sleep deprivation [14]. Further, it was demonstrated that rolipram in a dose-dependent fashion reverses the frequency of both working and reference memory errors caused by NMDA receptor inhibitor MK-801 [15]. The minimum effective doses of rolipram were 0.05 mg/kg for working memory and 0.1 mg/kg for reference memory. Rolipram also reversed the MK-801-induced deficits in latent inhibition of cued fear conditioning [16]. Rolipram can affect LTP formation [17]. Normally, E-LTP decays within 2–3 h with a maximum duration of up to 4 h, and is extended significantly (up to 6 h) by rolipram [17]. Rolipram can induce L-LTP through elevation of cAMP levels and potentiation of PKA activity [17]. It was suggested that PDE-4B, a PDE-4 subtype, plays an important role in LTP formation [17, 18]. In addition, rolipram can reverse both the scopolamine-induced deficits in working and reference memory [19]. These effects may be attributed to the elevation of cAMP, increase in LTP, and enhancement of synaptic plasticity [20].

Our previous study [21] demonstrated important role of cAMP in the ketamine-induced deficits in learning and memory of rats. We found that CREB, the cAMP regulated downstream protein, was involved in the ketamine-induced learning and memory impairments [21]. Further, mice with low levels of CREB suffer from significant impairment of LTP and long-term memory [22]. The increased expression of CREB significantly enhances both LTP and social cognition [23]. In addition, ERK was shown to be involved in the ketamine-induced learning and memory impairment [24], and that ERK exhibits its effect via the cAMP–ERK pathway by regulating cAMP levels via cross-talking with PDE-4 [25].

Prospects and Challenges

PDE-4 inhibitors are crucial for the regulation of memory and can be used as therapeutic targets in treatment of memory and recognition impairment. Several pharmaceutical companies are developing novel PDE-4 inhibitors for treatment of cognitive disorders. Currently, only one compound developed by Helicon Therapeutics is available clinically [6]. The phase 1 clinical trial was started in December 2004. HT-0712, a novel PDE-4 inhibitor, was used in the treatment of Rubinstein-Taybi syndrome, a human genetic disorder caused by mutation in a gene encoding CBP. If HT-0712 will be shown successful in clinical trials, then it can become a novel PDE-4 inhibitor for the treatment of cognitive disorders.

However, researchers are facing several challenges. First, the function of PDE-4 subtypes is not well understood, and highly selective inhibitors are lacking. Second, the mechanism by which phosphorylation of CREB affects learning memory is not clear. Another question to be answered is what area of the brain plays more important role in long-term memory performance.

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References

1. O'Donnell, J. M., & Zhang, H. T. (2004). Antidepressant effects of inhibitors of cAMP phosphodiesterase (PDE4). *Trends in Pharmacological Sciences, 25*, 158–163.
2. Burgin, A. B., Magnusson, O. T., Singh, J., Witte, P., Staker, B. L., Bjornsson, J. M., et al. (2010). Design of phosphodiesterase 4D (PDE4D) allosteric modulators for enhancing cognition with improved safety. *Nature Biotechnology, 28*, 63–70.
3. Houslay, M. D. (2001). PDE4 cAMP-specific phosphodiesterases. *Progress in Nucleic Acid Research and Molecular Biology, 69*, 249–315.
4. Omori, K., & Kotera, J. (2007). Overview of PDEs and their regulation. *Circulation Research, 100*, 309–327.
5. Davis, T. G., Peterson, J. J., Kou, J. P., Capper-Spudich, E. A., Ball, D., Nials, A. T., Podolin, P. L., et al. (2009). The identification of a novel phosphodiesterase 4 inhibitor, 1-ethyl-5-{5-[(4-methyl-1-piperazinyl)methyl]-1,3,4-oxadiazol-2-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridine-4-amine (EPPA-1), with improved therapeutic index using pica feeding in rats as a measure of emetogenicity. *Journal of Pharmacology and Experimental Therapeutics, 330*, 922–931.
6. Ghavami, A., Hirst, W. D., & Novak, T. J. (2006). Selective phosphodiesterase (PDE)-4 inhibitors: a novel approach to treating memory deficit? *Drugs in R&D, 7*, 63–71.
7. Alberini, C. M. (2009). Transcription factors in long-term memory and synaptic plasticity. *Physiological Reviews, 89*, 121–145.
8. Sweatt, J. D. (1999). Toward a molecular explanation for long-term potentiation. *Learning and Memory, 6*, 399–416.
9. Xia, M., Huang, R., Guo, V., Southall, N., Cho, M. H., Inglese, J., et al. (2009). Identification of compounds that potentiate CREB signaling as possible enhancers of long-term memory. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 2412–2417.
10. Wood, M. A., Kaplan, M. P., Park, A., Blanchard, E. J., Oliveira, A. M., Lombardi, T. L., et al. (2005). Transgenic mice expressing a truncated form of CREB-binding protein (CBP) exhibit deficits in hippocampal synaptic plasticity and memory storage. *Learn and Memory, 12*, 111–119.
11. Lee, Y. S., Bailey, C. H., Kandel, E. R., & Kaang, B. K. (2008). Transcriptional regulation of long-term memory in the marine snail *Aplysia*. *Molecular Brain, 1*, 3.
12. Wang, H., Ferguson, G. D., Pineda, V. V., Cundiff, P. E., & Storm, D. R. (2004). Overexpression of type-1 adenylyl cyclase in mouse forebrain enhances recognition memory and LTP. *Nature Neuroscience, 7*, 635–642.
13. Li, Y. F., Cheng, Y. F., Huang, Y., Conti, M., Wilson, S. P., O'Donnell, J. M., et al. (2011). Phosphodiesterase-4D knock-out and RNA interference-mediated knock-down enhance memory and increase hippocampal neurogenesis via increased cAMP signaling. *Journal of Neuroscience, 31*, 172–183.
14. Vecsey, C. G., Baillie, G. S., Jaganath, D., Havekes, R., Daniels, A., Wimmer, M., et al. (2009). Sleep deprivation impairs cAMP signalling in the hippocampus. *Nature, 461*, 1122–1125.
15. Zhang, H. T., Crissman, A. M., Dorairaj, N. R., Chandler, L. J., & O'Donnell, J. M. (2000). Inhibition of cyclic AMP phosphodiesterase (PDE4) reverses memory deficits associated with NMDA receptor antagonism. *Neuropsychopharmacology, 23*, 198–204.
16. Davis, J. A., & Gould, T. J. (2005). Rolipram attenuates MK-801-induced deficits in latent inhibition. *Behavioral Neuroscience, 119*, 595–602.
17. Rutten, K., Wallace, T. L., Works, M., Prickaerts, J., Blokland, A., Novak, T. J., et al. (2011). Enhanced long-term depression and impaired reversal learning in phosphodiesterase 4B-knockout (PDE4B$^{-/-}$) mice. *Neuropharmacology, 61*, 138–147.
18. Navakkode, S., Sajikumar, S., & Frey, J. U. (2004). The type IV-specific phosphodiesterase inhibitor rolipram and its effect on hippocampal long-term potentiation and synaptic tagging. *Journal of Neuroscience, 24*, 7740–7744.
19. Rutten, K., Prickaerts, J., & Blokland, A. (2006). Rolipram reverses scopolamine-induced and time-dependent memory deficits in object recognition by different mechanisms of action. *Neurobiology of Learning and Memory, 85*, 132–138.
20. Alarcon, J. M., Malleret, G., Touzani, K., Vronskaya, S., Ishii, S., Kandel, E. R., et al. (2004). Chromatin acetylation, memory, and LTP are impaired in CBP ± mice: A model for the cognitive deficit in Rubinstein-Taybi syndrome and its amelioration. *Neuron, 42*, 947–959.
21. Peng, S., Zhang, Y., Ren, B., Zhang, J., & Wang, H. (2011). Effect of ketamine administration on memory consolidation, p-CREB and c-fos expression in the hippocampal slices of minor rats. *Molecular Biology Reports, 38*, 2401–2407.
22. Sweatt, J. D. (2004). Mitogen-activated protein kinases in synaptic plasticity and memory. *Current Opinion in Neurobiology, 14*, 311–317.
23. Kida, S., Josselyn, S. A., Pena de, O. S., Kogan, J. H., Chevere, I., Masushige, S., et al. (2002). CREB required for the stability of new and reactivated fear memories. *Nature Neuroscience, 5*, 348–355.
24. Peng, S., Zhang, Y., Zhang, J., Wang, H., & Ren, B. (2010). Effect of ketamine on ERK expression in hippocampal neural cell and the ability of learning behavior in minor rats. *Molecular Biology Reports, 37*, 3137–3142.
25. Houslay, M. D., & Baillie, G. S. (2003). The role of ERK2 docking and phosphorylation of PDE4 cAMP phosphodiesterase isoforms in mediating cross-talk between the cAMP and ERK signalling pathways. *Biochemical Society Transactions, 31*, 1186–1190.