

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Reducing Neuroinflammation in Psychiatric Disorders: Novel Target of Phosphodiesterase 4 (PDE4) and Developing of the PDE4 Inhibitors

---

Chuang Wang, Zhen Wang, Mengmeng Li,  
Chenli Li, Hanjie Yu, Dongsheng Zhou and  
Zhongming Chen

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.69154>

---

## Abstract

Multiple lines of evidence support the pathogenic role of neuroinflammation in psychiatric illness. Cyclic adenosine monophosphate (cAMP) is a critical regulator of microglia homeostasis; as the predominant negative modulator of cyclic AMP signaling within microglia, and phosphodiesterase 4 (PDE4) represents a promising target for modulating immune function. The approach for pharmacological manipulation of cAMP levels using specific PDE4 inhibitors provokes an anti-inflammatory response. Specifically, PDE4 inhibitors have recently emerged as a potential therapeutic strategy for neuroinflammatory, neurodegenerative, and psychiatric diseases. Mechanistically, PDE4 inhibitors produce an anti-inflammatory and neuroprotection effect by increasing the accumulation of cAMP and activating protein kinase A (PKA), the signaling pathway of which is thought to play an important role in the development of psychiatric disorders. This chapter reviews present knowledge of the relationship between neuroinflammation and classical psychiatric disorders (major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia) and demonstrates the signaling pathways that underlie the use of PDE4 inhibitors in neuroinflammation. In addition, among the four subtypes (A-D) of PDE4, it remains unclear which one exerts suppressive effects on neuroinflammation. Understanding how PDE4 and neuroinflammation interact can reveal pathogenic clues and help target new preventive and symptomatic therapies for psychiatric illness.

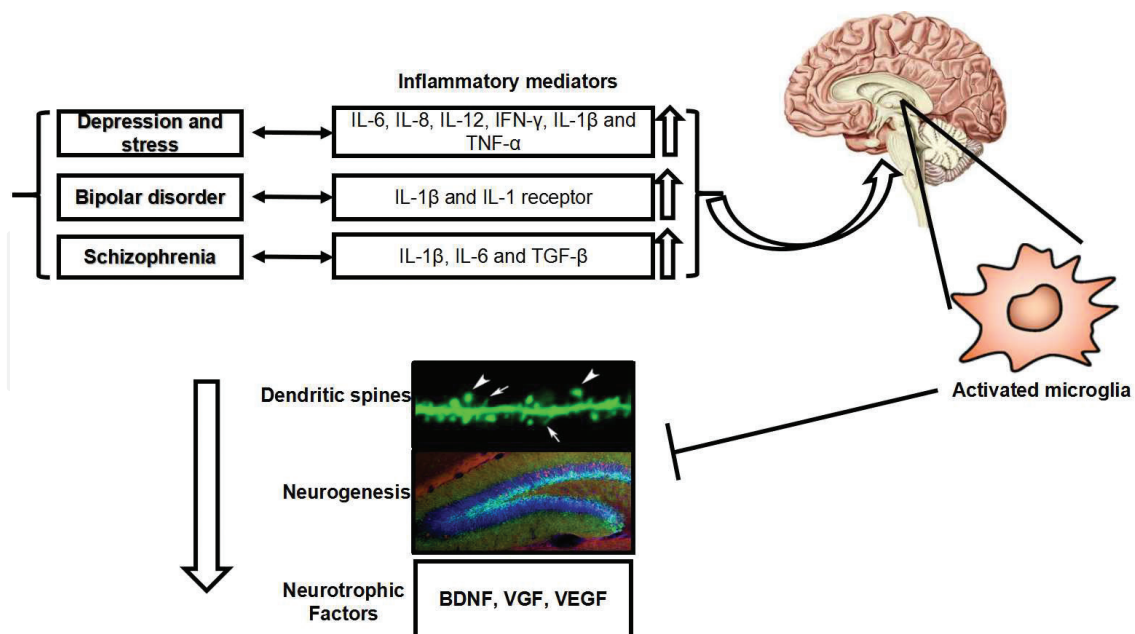
**Keywords:** cyclic adenosine monophosphate (cAMP), phosphodiesterase 4 (PDE4), psychiatric disorders, neuroinflammation

---

## 1. Introduction: the possibility that inflammation is the common mediator of psychiatric disorders

Classical psychiatric disorders, including major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia, affect a significant percentage of the world population. More recently, inflammatory and immunological abnormalities have been documented in patients with classical psychiatric disorders, even though the exact mechanisms underlying this association are not known. A growing body of evidence suggests that activation of the immune response following systemic infection often results in neuroinflammation and consequently induces psychiatric symptoms in animal models and humans (as shown in **Figure 1**) [1–6]. Specifically, inflammation in the context of the nervous system termed “neuroinflammation” has been reported in patients with psychiatric disorders [7] and is typically associated with microglial activation.

Microglia, the resident phagocytes of the CNS, are ubiquitously distributed in the brain and are usually the first to be activated in response to tissue damage or brain infections [14]. At the same time, microglia are important players in the maintenance and plasticity of neuronal circuits, contributing to the protection and remodeling of synapses [15–16]. They provide ongoing immune surveillance and regulate developmental synaptic pruning [17–18]. Microglial activation can be divided into two distinct types: a classical M1 and an alternative M2 activation. Proinflammatory cytokines include interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-2 (IL-2), interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon-gamma (IFN- $\gamma$ ), and they are secreted primarily by microglia [19–21]; [3]. In the M1 activation, microglial cells may become



**Figure 1.** Summary of neuroinflammatory responses and microglial abnormalities observed in psychiatry disorders. A large body of evidence [8–13] supports the involvement of neuroinflammatory mechanisms, including microglial activation, downregulation of dendritic spines, neurogenesis, and neurotrophic factors in the pathophysiology of psychiatric disorders.

hyperramified or ameboid/phagocytic [22], and may synthesize proinflammatory molecules, superoxide radicals, glutamate [23–24], and nitric oxide (NO) and ultimately clear infections and repair tissues. Alternatively, M2 activation, which can be triggered by cytokines such as IL-4, IL-13, or IL-25 [25]; [22], has been associated with a release of antiinflammatory cytokines (e.g. IL-10, insulin-growth factor-1(IGF-1), transforming growth factor- $\beta$  (TGF- $\beta$ ), and neurotrophic factors) [22], which facilitate healing and limit neuronal injury [7]. Cytokine response phenotypes are classified as either proinflammatory T-helper 1 (Th1) or antiinflammatory T-helper 2 (Th2) according to the immune functions they regulate. The key to neuroinflammation effects on psychiatric disorders appears to lie within the dysregulation of the control and release of pro- and antiinflammatory cytokines. In fact, Th1 and Th2, which are responsible for pathogen elimination and antibody regulation, respectively, were also found to be altered in untreated depressed patients [26]. Microglia activation is one of the mechanisms by which peripheral immune challenges can alter brain functioning [27, 28]; [1]. In fact, patients with psychiatric disorders have been shown to present an increase in serum levels of proinflammatory cytokines [29–32]; [8]. Interestingly, investigations involving animal models of depression and postmortem dorsal anterior cingulate matter from individuals suffering from MDD delineate altered expression of microglial activation markers, as well as chronicity-dependent fluctuations in microglial concentration in areas of the brain associated with mood regulation [33–36]; [10, 13]. Additionally, microglial activation was also greater in the ventral prefrontal white matter in individuals who committed suicide [37]. Altogether, these studies suggest that microglial activation may be considered as an important marker in MDD.

Bipolar disorder is a severe mood disorder characterized by recurrent episodes of mania followed by depression. The pathophysiology of BD is yet to be well understood, while recent studies have indicated that abnormal immunological functions may be a contributing factor [38–42]. Recently, positron emission tomography (PET) studies have shown microglial overactivation in the brain of patients with various psychiatric disorders [43–45]; [9] including bipolar disorder [42]. Consistent with the previous studies, it was revealed that in BD, the immune system is chronically activated by microglia, which in turn produces cytokines that render the brain to a vulnerable and unstable state, precipitating mood disturbances [45–47]. In fact, higher levels of IL-1 $\beta$  were associated with dysfunction and increased suicide risk in patients with BD [48].

Schizophrenia is a chronic and debilitating disorder that affects 0.5–1% of the world population [49]. Evidence suggests that the dopamine dysfunction hypothesis [50–51] has defined schizophrenia for many years, a growing number of research investigations and scientific curiosity have developed around the immune system and the role of neuroinflammation in precipitating psychotic symptoms in a subset of patients with psychosis [52–55]; [5, 6], providing a detailed review of the theories and mechanisms that support a role for inflammation in schizophrenia.

## 2. Cyclic nucleotide signaling and neuroinflammation

Several mechanisms can account for the high comorbidity of neuroinflammation and psychiatric disorders. These mechanisms include direct effects of cytokines on the neuronal environment or indirect effects via downregulation of cyclic nucleotide signaling [56–58].

Understanding cyclic nucleotide signaling mechanisms that underlie neuroinflammation and psychiatric disorder comorbidity may yield effective pharmaceutical targets that can treat both conditions simultaneously beyond traditional antipsychotic drugs. There is growing evidence that adenosine cyclic 3,5-monophosphate (cAMP) exerts many of its physiological effects by activating cAMP-dependent protein kinase (PKA), which in turn phosphorylates and regulates the functions of downstream protein targets including ion channels, enzymes, and transcription factors [59]. Specifically, cAMP is a ubiquitous regulator of the inflammatory response and is also a key second messenger that influences glial activity [60, 61]. Additionally, recent findings have also suggested that cAMP/cAMP response element-binding (CREB) signaling is closely involved in antiinflammatory responses [62] by suppressing the activation of glial cells (both microglia and astrocytes), decreasing the production of proinflammatory mediators, including tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, IL-12, and nitric oxide, and increasing the expression of antiinflammatory factor IL-10 [63–65]. Therefore, previous work has shown that the application of cAMP analogs, adenylyl cyclase (AC) activators, or PDE inhibitors, to increase the levels of intracellular cAMP, antagonizes the changes in microglial cell morphology and their production of proinflammatory cytokines when they are exposed to inflammatory stimuli [66–67]. Intracellular cAMP signaling has been well established in the mediation of memory [68–71] and depression-like behaviors [72, 73]; [57]. cAMP activates protein kinase A (PKA), which phosphorylates and activates the subsequent downstream target CREB protein [74, 75] and is important for mediating synaptic plasticity [76, 77]; [74]. In addition, increases in cAMP levels during inflammation inhibit the production of proinflammatory cytokines and stimulate the formation of IL-10, an antiinflammatory factor [78, 79]. Conversely, inflammatory molecules, including lipopolysaccharide (LPS), interferon (IFN)- $\gamma$ , and TNF- $\alpha$ , can dramatically reduce cyclic AMP levels in microglia, leading to changes in their phenotype and function [80]; [56]. Therefore, cAMP/CREB signaling may play a beneficial role in inflammatory responses and apoptosis of psychiatric disorders. Given that cAMP levels are regulated by a balance between the activities of two enzymes: AC and cyclic nucleotide phosphodiesterase (PDE), the pharmacological manipulation using specific PDE inhibitors, in particular, PDE4 inhibitors provoke profound antiinflammatory responses [81] and beneficial effects on psychiatric disorders [82]; [57]. Selective inhibitors of PDE4 are currently used in clinical practice for the treatment of cardiovascular disorders and erectile dysfunction, and other PDE inhibitors are under development for the treatment of CNS and inflammatory disorders. This chapter focuses on the development of PDE4 and PDE4 subtype inhibitors which have been reported as treatment for neuroinflammation.

### **3. PDE4 and specific PDE4 subtype inhibitors in neuroinflammation**

#### **3.1. PDE4 and the distribution of its subtypes in CNS**

PDE4, one of the 11 PDE enzyme families, specifically catalyzes hydrolysis of cyclic AMP (cAMP); it has four subtypes (PDE4A–D) with at least 25 splice variants. Detailed analyses of the expression pattern of the human PDE4 isogenes have recently appeared [83, 84]. All four

subtypes, PDE4A, PDE4B, PDE4C, and PDE4D, are found in most tissues although, notably, PDE4C is absent in blood (as shown in **Table 1**). PDE4 plays a critical role in the control of intracellular cAMP concentrations. PDE4 gene members are distributed throughout the brain and are expressed in various neurons. PDE4 specifically hydrolyzes cAMP to inactive AMP. High levels of cytosolic cAMP lead to the activation of PKA and further induce the phosphorylation of transcription factors, such as CREB and cAMP-dependent transcription factor-1 (ATF-1) to drive cAMP-driven genes, which involve in the regulation of proinflammatory and antiinflammatory pathways (as shown in **Figure 2**). However, the differential distribution of the four PDE4 subtypes (PDE4A–D) in the brain [85] may be attributed to the different regulation of cAMP-mediated signaling in CNS. PDE4A and PDE4D are highly expressed in the cortex, olfactory bulb, hippocampal formation, and brainstem, whereas PDE4B is mainly expressed in the amygdala, striatum, and hypothalamus [86–88]. By contrast, PDE4C exhibits a distribution different from those of PDE4A and PDE4D and appears to be limited to the thalamus and cerebellum [89, 90]. Because of the unique distribution of PDE4 isoform and its significance in various physiological functions in CNS, PDE4 presents promising pharmaceutical drug target treatment for psychiatric disorders.

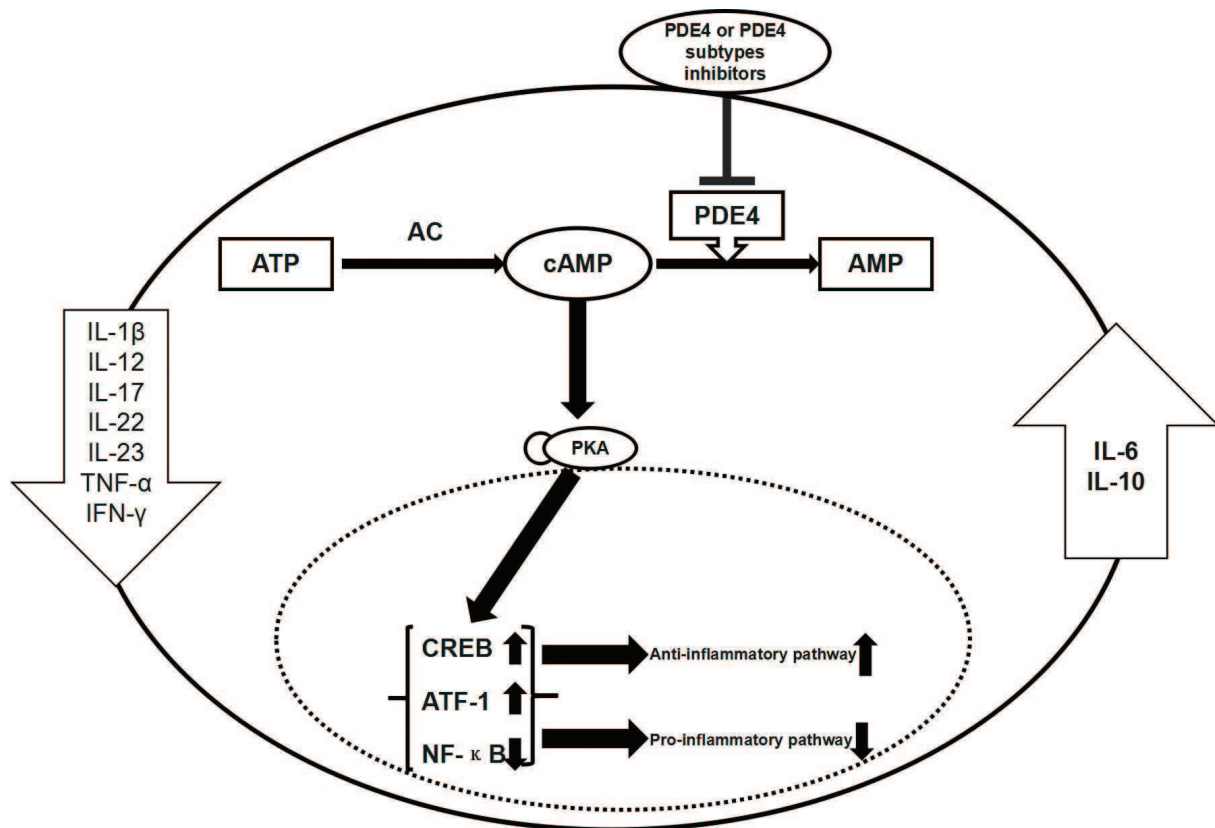
### 3.2. Traditional PDE4 inhibitors

The search for selective inhibitors of PDE4 as novel antiinflammatory drugs has continued for more than 40 years. Recent findings have also suggested that cAMP/CREB/brain-derived neurotrophic factor (BDNF) signaling is closely involved in antiinflammatory responses [66], depression, and antidepressant actions [91]; [68]. PDE4 inhibition has been a target

Location	Level of expression			
	PDE4A	PDE4B	PDE4C	PDE4D
Brain	++	++	++	++
Liver	++	++	++	++
Lung	++	++	++	++
Trachea	++	++	++	++
Kidney	++	++	++	++
Placenta	++	++	++	++
Heart	++	++	++	++
Blood	++	++	–	++
Neutrophils	±	++	–	±
Eosinophils	++	++	–	++

++ , expression.  
± , very weak expression.  
– , no expression.

**Table 1.** Expression patterns of mRNAs for the human phosphodiesterase 4 (PDE4) subtype genes.



**Figure 2.** The antiinflammatory mechanisms of PDE4 and PDE4 subtype inhibitors. cAMP as a regulator of immunity. Adenylate cyclases (AC) produce cAMP from adenosin-tri-phosphate (ATP). High levels of cytosolic cAMP lead to the activation of protein kinase A (PKA) and further induce the phosphorylation of transcription factors, such as CREB and cAMP-dependent transcription factor-1 (ATF-1) to drive cAMP-driven genes. Phosphodiesterase 4 (PDE4) decreases intracellular cAMP levels and counterbalances the intracellular cAMP effect. However, PDE4 or subtype inhibitors block PDE4 or its subtypes. As PDE4 or subtypes degrade cAMP to AMP, cAMP levels rise during apremilast treatment. The elevation of intracellular cAMP leads to the activation of PKA. This results in the phosphorylation and activation of transcription factors like CREB and ATF-1. On the other hand, NF- $\kappa$ B is inactivated. This transcriptional regulation is responsible for the reduced production of proinflammatory mediators like IL-1 $\beta$ , IL-12, IL-17, IL-22, IL-23, TNF- $\alpha$ , and IFN- $\gamma$  and the increased production of IL-6 and the antiinflammatory mediator IL-10.

of therapeutic drug research since the 1970s, with the prototypic PDE4 inhibitor, rolipram being tested in clinical trials in the 1980s [92]. Notably, PDE4 inhibitor rolipram that readily produces antidepressant-like actions [93, 94], which are associated with increased level of cAMP and its downstream targets of cAMP-dependent protein kinase A (PKA), CREB, and BDNF [95]; [68]. Therefore, the potential PDE4 inhibitors may be an efficient alternative strategy to play antidepressant action especially in depressive disorder induced by inflammation. Consistent with this hypothesis, the previous studies have demonstrated that rolipram reduces neuroinflammation and promotes axonal regeneration and functional recuperation following spinal cord injury [96–98]; [62]. More evidence have shown that PDE4 inhibitor rolipram reduces the production of proinflammatory cytokines and modulates the activity of cAMP-mediated signaling and thus regulates CREB phosphorylation and the downstream effectors [99]; [62, 68], showing that potential PDE4 inhibitors may be suitable to antagonize psychiatric disorders. Unfortunately, the development of PDE4 inhibitor rolipram for therapeutic purposes has been hindered by side effects, such as emesis [100, 101]. Based on the

demonstration of significant efficacy in preclinical models, multiple PDE4 inhibitors have entered clinical development, and none have reached the market. Roflumilast and apremilast have been approved for peripheral inflammatory disorders, such as severe chronic obstructive pulmonary disease (COPD) and psoriatic arthritis (PA), respectively; however, their full immunomodulatory activity is limited to doses which are estimated to inhibit PDE4 by 50% due to the incidence of nausea and emesis at higher exposures. Unfortunately, the two PDE4 inhibitors (roflumilast and apremilast) approved for peripheral inflammatory disorders lack brain penetration and are dose limited by side effects making them unsuitable for modulating microglial function. Despite the challenges and complications that have been encountered during the development of PDE4 inhibitors, these drugs may provide a genuinely novel class of antineuroinflammatory agents, and there are several compounds in development that could fulfill that promise.

### 3.3. The novel potential PDE4 inhibitors

Notably, it has been recently reported that a pyrazolopyridine compound, etazolate, is a new-generation selective PDE4 inhibitor and is proven to be of particular significance in neuropsychiatric conditions [102, 103]; [94]. Previous studies reported that etazolate belongs to PDE4 inhibitor family and that treatment with etazolate restored cAMP levels [66, 94, 103]. In most of the clinical phase II or Phase IIb studies, etazolate has shown that it could be a potential candidate for the treatment of Alzheimer's disease [102]. Additionally, in several preclinical studies, etazolate has shown significant antidepressant- and anxiolytic-like effects in acute and chronic rodent models [104, 105]; [66, 103]. Specifically, it is reported that the expression of PDE4A, PDE4B, and PDE4D in the hippocampus was significantly increased by lipopolysaccharide (LPS) in mice. In addition, an etazolate significantly reversed the elevated IL-1 $\beta$  expression in hippocampus and prefrontal cortex induced by LPS [103], indicating significant antineuroinflammatory response. Although limited preclinical studies have been conducted on etazolate, the recent clinical trial results on its safety and tolerance are encouraging [106]. However, in March 2014, the development of the etazolate was stopped as the company transformed into a specialty in vitro diagnostics company.

Recently, more and more novel selective PDE4 inhibitors (as shown in **Table 2**) have been designed and explored in different rodent models, displaying a safer profile compared to traditional agents [107–111]; [66, 75], supporting further evaluation of these novel PDE4 inhibitors in a clinical setting.

### 3.4. PDE4 subtype inhibitors

Particular attention has been given to the PDE4 isoforms owing to the antiinflammatory effects observed after their inhibition in vitro and in vivo [81]. Of the four major phosphodiesterase 4 (PDE4) subtypes, PDE4A, PDE4B, or PDE4D, all of which are found to some extent in every inflammatory cell type studied, could be important regulators of inflammatory processes. Only PDE4C, which is present in the lung [112] but has only rarely and inconsistently been reported in any isolated inflammatory cell type, can be eliminated on the basis of its



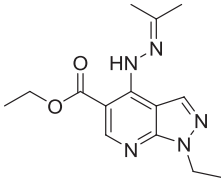
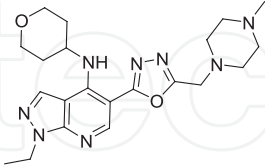
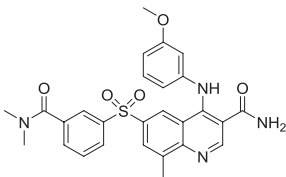
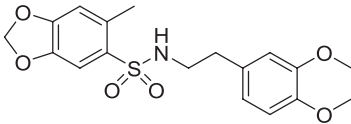
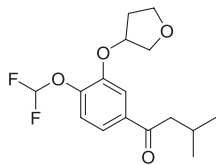
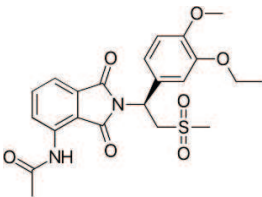
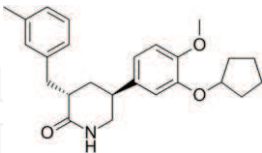
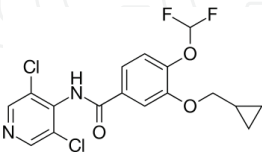
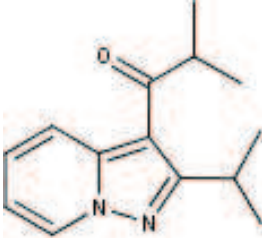
Novel PDE4 inhibitors	Chemical structures	Active indications	Highest status
Etazolate		Depression, anxiety, traumatic brain injury	Phase 2 clinical to discontinued
EPPA-1		In vitro and in vivo anti-inflammatory potencies	Discovery
GSK256066		Antiinflammatory activities	Phase 2 clinical to discontinued
LASSBio-448		Antiinflammatory activities	Discovery
FFPM		Reverses learning and memory deficits and appears to have potential antiinflammatory effects with little emetic potential	Discovery
Apremilast		Ankylosing spondylitis; Atopic dermatitis; Behcet's disease; Hidradenitis suppurativa; Psoriasis; Psoriatic arthritis; Ulcerative colitis	Launched
HT-0712		Cognitive disorder	Phase 2 clinical
Roflumilast		Alzheimer's disease; Asthma; Chronic obstructive pulmonary disease; Schizophrenia	Launched
Ibudilast		Alcoholism; Amphetamine dependence; Drug dependence; Neuropathic pain; Opiate dependence; Traumatic brain injury	Phase 2 clinical

Table 2. Development of novel PDE4 inhibitors.

distribution. This distribution characteristic provides many opportunities for selective therapeutic targeting [113, 114] and the potential to reduce the incidence of side effects attributed to PDE4 inhibition. The previous studies revealed that PDE4B might be the critical subtype that controls the inflammatory responses [115–117]. The work by Conti's group [115] identified PDE4B to be the primary PDE4 enzyme involved in proinflammatory responses to LPS in macrophages and leukocytes. Reports have suggested that mice deficient in PDE4A display anxiogenic-like behavior [118], while PDE4B is closely related with neuroinflammation [119]. Therefore, subtype selective inhibitors targeting PDE4B are of high interest given the critical role PDE4B plays in immune function versus the association of PDE4D with nausea and emesis. However, it is difficult to directly link PDE4 inhibitor-mediated efficacy to changes specifically in microglial cell function, and even more so whether these effects selectively involve PDE4B. The difficulty in establishing these links is because these investigations have almost exclusively used pharmacological inhibitors that are administered systemically and which show similar affinity toward all PDE4 family members, being designed largely to inhibit enzyme activity by binding to the catalytic site. Recently, the crystal structures of PDE4B have been exploited to develop subtype-selective PDE4 inhibitors [120]. The novel PDE4B inhibitor A33, which has an IC<sub>50</sub> of 32 nM against PDE4B1, is 49-fold more selective for PDE4B versus PDE4D and does not appreciably inhibit any other PDEs [121]. Specifically, A33 inhibits all PDE4B isoforms and is 49-fold more selective toward PDE4B compared with PDE4D and does not appreciably inhibit other PDEs [120, 121]. Interestingly, TNF- $\alpha$  levels at 6-hour postsurgery of traumatic brain injury (TBI) were significantly reduced by A33, suggesting that an inflammatory pathway mediated by PDE4B is inhibited with A33 [122]; [115] (Jin and Conti; Jin et al.). However, further studies to determine the antineuroinflammatory mechanisms of A33 may yield insights into the processes involved in the improvements of psychiatric disorders with A33 treatment.

## 4. Conclusions

A large body of evidence supports the involvement of neuroinflammatory mechanisms in the pathophysiology of psychiatric disorders. Drugs that interfere with these mechanisms, such as PDE4 inhibitors, could be a novel and important new pathway for the treatment of these disorders. Furthermore, continued drug discovery efforts to identify safe and well-tolerated, brain-penetrant PDE4 inhibitors are a reflection of the confidence in the rationale for modulation of this target to produce meaningful therapeutic benefit in a wide range of neurological conditions and injury.

## Acknowledgements

This research was supported by National Natural Science Foundation of China (No. 81671337; No.81201050; No.81541087); Natural Science Foundation of Zhejiang province (No. LQ12H09001); Natural Science Foundation of Ningbo (No. 2012A610251); Ningbo municipal innovation team of life science and health (2015C110026); new-shoot Talents

Program of Zhejiang province; and Student Research and Innovation Program of Ningbo University. This project is also sponsored by K.C. Wong Magna funded in Ningbo University and Li Dak Sum Yip Yio Chin Kenneth Li Marine Biopharmaceutical Development Fund, National 111 Project of China.

## Author details

Chuang Wang<sup>1,2,3,4\*</sup>, Zhen Wang<sup>6\*</sup>, Mengmeng Li<sup>1,2,3</sup>, Chenli Li<sup>1,2,3</sup>, Hanjie Yu<sup>1,2,3</sup>, Dongsheng Zhou<sup>1,5</sup> and Zhongming Chen<sup>1,5</sup>

\*Address all correspondence to: wangchuang@nbu.edu.cn

1 Ningbo Key Laboratory of Behavioral Neuroscience, Ningbo University School of Medicine, Ningbo, Zhejiang, P.R. China

2 Zhejiang Provincial Key Laboratory of Pathophysiology, Ningbo University School of Medicine, Ningbo, Zhejiang, P.R. China

3 Department of Physiology and Pharmacology, Ningbo University School of Medicine, Ningbo, Zhejiang, P.R. China

4 Li Dak Sum Yip Yio Chin Kenneth Li Marine Biopharmaceutical Research Center, Ningbo University, Ningbo, Zhejiang, P.R. China

5 Ningbo Kangning Hospital, Ningbo, Zhejiang, P.R. China

6 CAS Key Laboratory for Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China

## References

- [1] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*. 2008;**9**(1):46-56. DOI: 10.1038/nrn2297
- [2] Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: Endotoxin reduces ventral striatum responses to reward. *Biological Psychiatry*. 2010;**68**(8):748-754. DOI: 10.1016/j.biopsych.2010.06.010
- [3] Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology*. 2012;**37**(1):137-162. DOI: 10.1038/npp.2011.205
- [4] Cho HJ, Eisenberger NI, Olmstead R, Breen EC, Irwin MR. Preexisting mild sleep disturbance as a vulnerability factor for inflammation-induced depressed mood: A human experimental study. *Translational Psychiatry*. 2016;**6**:e750. DOI: 10.1038/tp.2016.23

- [5] Notter T, Coughlin JM, Gschwind T, Weber-Stadlbauer U, Wang Y, Kassiou M, Vernon AC, Benke D, Pomper MG, Sawa A, Meyer U. Translational evaluation of translocator protein as a marker of neuroinflammation in schizophrenia. *Molecular Psychiatry*. 2017. DOI: 10.1038/mp.2016.248
- [6] Miller BJ, Goldsmith DR. Towards an immunophenotype of schizophrenia: Progress, potential mechanisms, and future directions. *Neuropsychopharmacology*. 2017;**42**(1):299-317. DOI: 10.1038/npp.2016.211
- [7] Najjar S, Pearlman DM, Devinsky O, Najjar A, Zagzag D. Neurovascular unit dysfunction with blood-brain barrier hyperpermeability contributes to major depressive disorder: A review of clinical and experimental evidence. *Journal of Neuroinflammation*. 2013;**10**:142. DOI: 10.1186/1742-2094-10-142
- [8] Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2005;**29**(2):201-217. DOI: 10.1016/j.pnpbp.2004.11.003
- [9] Suzuki K, Sugihara G, Ouchi Y, Nakamura K, Futatsubashi M, Takebayashi K, Yoshihara Y, Omata K, Matsumoto K, Tsuchiya KJ, Iwata Y, Tsujii M, Sugiyama T, Mori N. Microglial activation in young adults with autism spectrum disorder. *JAMA Psychiatry*. 2013;**70**(1):49-58. DOI: 10.1001/jamapsychiatry.2013.272
- [10] Torres-Platas SG, Cruceanu C, Chen GG, Turecki G, Mechawar N. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. *Brain, Behavior, and Immunity*. 2014;**42**:50-59. DOI: 10.1016/j.bbi.2014.05.007
- [11] Cattaneo A, Cattane N, Begni V, Pariante CM, Riva MA. The human BDNF gene: peripheral gene expression and protein levels as biomarkers for psychiatric disorders. *Translational Psychiatry*. 2016;**6**(11):e958. DOI: 10.1038/tp.2016.214
- [12] Apple DM, Fonseca RS, Kokovay E. The role of adult neurogenesis in psychiatric and cognitive disorders. *Brain Research*. 2017;**1655**:270-276. DOI: 10.1016/j.brainres.2016.01.023
- [13] Churchward MA, Tchir DR, Todd KG. Microglial function during glucose deprivation: Inflammatory and neuropsychiatric implications. *Molecular Neurobiology*. 2017. DOI: 10.1007/s12035-017-0422-9
- [14] Stertz L, Magalhaes PV, Kapczinski F. Is bipolar disorder an inflammatory condition? The relevance of microglial activation. *Current Opinion in Psychiatry*. 2013;**26**(1):19-26. DOI: 10.1097/YCO.0b013e32835aa4b4
- [15] Ji K, Akgul G, Wollmuth LP, Tsirka SE. Microglia actively regulate the number of functional synapses. *PLoS One*. 2013;**8**(2):e56293. DOI: 10.1371/journal.pone.0056293
- [16] Mosser CA, Baptista S, Arnoux I, Audinat E. Microglia in CNS development: Shaping the brain for the future. *Progress in Neurobiology*. 2017;**149-150**:1-20. DOI: 10.1016/j.pneurobio.2017.01.002

- [17] Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. *Physiological Reviews*. 2011;**91**(2):461-553. DOI: 10.1152/physrev.00011.2010
- [18] Tremblay MÈ1, Stevens B, Sierra A, Wake H, Bessis A, Nimmerjahn A. The role of microglia in the healthy brain. *Journal of Neuroscience*. 2011;**31**(45):16064-16069. DOI: 10.1523/JNEUROSCI.4158-11.2011
- [19] Ehrhart J, Obregon D, Mori T, Hou H, Sun N, Bai Y, Klein T, Fernandez F, Tan J, Shytle RD. Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation. *Journal of Neuroinflammation*. 2005;**2**:29. DOI: 10.1186/1742-2094-2-29
- [20] Mattei D, Djodari-Irani A, Hadar R, Pelz A, de Cossio LF, Goetz T, Matyash M, Kettenmann H, Winter C, Wolf SA. Minocycline rescues decrease in neurogenesis, increase in microglia cytokines and deficits in sensorimotor gating in an animal model of schizophrenia. *Brain, Behavior, and Immunity*. 2014;**38**:175-84. DOI: 10.1016/j.bbi.2014.01.019
- [21] Yu Z, Fukushima H, Ono C, Sakai M, Kasahara Y, Kikuchi Y, Gunawansa N, Takahashi Y, Matsuoka H, Kida S, Tomita H. Microglial production of TNF-alpha is a key element of sustained fear memory. *Brain, Behavior, and Immunity*. 2017;**59**:313-321. DOI: 10.1016/j.bbi.2016.08.011
- [22] Boche D, Perry VH, Nicoll JA. Review: activation patterns of microglia and their identification in the human brain. *Neuropathology and Applied Neurobiology*. 2013;**39**(1):3-18. DOI: 10.1111/nan.12011
- [23] Barger SW, Goodwin ME, Porter MM, Beggs ML. Glutamate release from activated microglia requires the oxidative burst and lipid peroxidation. *Journal of Neurochemistry*. 2007;**101**(5):1205-1213. DOI: 10.1111/j.1471-4159.2007.04487.x
- [24] Takaki J, Fujimori K, Miura M, Suzuki T, Sekino Y, Sato K. L-glutamate released from activated microglia downregulates astrocytic L-glutamate transporter expression in neuroinflammation: The 'collusion' hypothesis for increased extracellular L-glutamate concentration in neuroinflammation. *Journal of Neuroinflammation*. 2012;**9**:275. DOI: 10.1186/1742-2094-9-275
- [25] Maiorino C, Khorrooshi R, Ruffini F, Lobner M, Bergami A, Garzetti L, Martino G, Owens T, Furlan R. Lentiviral-mediated administration of IL-25 in the CNS induces alternative activation of microglia. *Gene Therapy*. 2013;**20**(5):487-496. DOI: 10.1038/gt.2012.58
- [26] Song C, Halbreich U, Han C, Leonard BE, Luo H. Imbalance between pro- and anti-inflammatory cytokines, and between Th1 and Th2 cytokines in depressed patients: the effect of electroacupuncture or fluoxetine treatment. *Pharmacopsychiatry*. 2009;**42**(5):182-188. DOI: 10.1055/s-0029-1202263
- [27] Godbout JP, Moreau M, Lestage J, Chen J, Sparkman NL, O'Connor J, Castanon N, Kelley KW, Dantzer R, Johnson RW. Aging exacerbates depressive-like behavior in mice in response to activation of the peripheral innate immune system. *Neuropsychopharmacology*. 2008;**33**(10):2341-2351. DOI: 10.1038/sj.npp.1301649

- [28] Patterson SL. Immune dysregulation and cognitive vulnerability in the aging brain: Interactions of microglia, IL-1 $\beta$ , BDNF and synaptic plasticity. *Neuropharmacology*. 2015;**96**(Pt A):11-18. DOI: 10.1016/j.neuropharm.2014.12.020
- [29] Talaei A, Tavakkol Afshari J, Fayyazi Bordbar MR, Pouryousof H, Faridhosseini F, Saghebi A, Rezaei Ardani A, Talaei A, Tehrani M. A study on the association of interleukin-1 cluster with genetic risk in bipolar i disorder in Iranian patients: A case-control study. *Iranian Journal of Allergy, Asthma and Immunology*. 2016;**15**(6):466-475.
- [30] Dunne PW, Roberts DL, Quinones MP, Velligan DI, Paredes M, Wals-Bass C. Immune markers of social cognitive bias in schizophrenia. *Psychiatry Research*. 2017;**251**:319-324. DOI: 10.1016/j.psychres.2017.02.030
- [31] Wang AK, Miller BJ. Meta-analysis of cerebrospinal fluid cytokine and tryptophan catabolite alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder, and depression. *Schizophrenia Bulletin*. 2017. DOI: 10.1093/schbul/sbx035
- [32] Yoshimura R, Katsuki A, Atake K, Hori H, Igata R, Konishi Y. Influence of fluvoxamine on plasma interleukin-6 or clinical improvement in patients with major depressive disorder. *Neuropsychiatric Disease and Treatment*. 2017;**13**:437-441. DOI: 10.2147/NDT.S123121
- [33] Hinwood M, Morandini J, Day TA, Walker FR. Evidence that microglia mediate the neurobiological effects of chronic psychological stress on the medial prefrontal cortex. *Cerebral Cortex*. 2012;**22**(6):1442-1454. DOI: 10.1093/cercor/bhr229
- [34] Wohleb ES, Fenn AM, Pacenta AM, Powell ND, Sheridan JF, Godbout JP. Peripheral innate immune challenge exaggerated microglia activation, increased the number of inflammatory CNS macrophages, and prolonged social withdrawal in socially defeated mice. *Psychoneuroendocrinology*. 2012;**37**(9):1491-1505. DOI: 10.1016/j.psyneuen.2012.02.003
- [35] Kreisel T, Frank MG, Licht T, Reshef R, Ben-Menachem-Zidon O, Baratta MV, Maier SF, Yirmiya R. Dynamic microglial alterations underlie stress-induced depressive-like behavior and suppressed neurogenesis. *Molecular Psychiatry*. 2014;**19**(6):699-709. DOI: 10.1038/mp.2013.155
- [36] Lehmann ML, Cooper HA, Maric D, Herkenham M. Social defeat induces depressive-like states and microglial activation without involvement of peripheral macrophages. *Journal of Neuroinflammation*. 2016;**13**(1):224. DOI: 10.1186/s12974-016-0672-x
- [37] Schnieder TP, Trencavska I, Rosoklija G, Stankov A, Mann JJ, Smiley J, Dwork AJ. Microglia of prefrontal white matter in suicide. *Journal of Neuropathology & Experimental Neurology*. 2014;**73**(9):880-890. DOI: 10.1097/NEN.0000000000000107
- [38] Altamura AC, Buoli M, Pozzoli S. Role of immunological factors in the pathophysiology and diagnosis of bipolar disorder: Comparison with schizophrenia. *Psychiatry and Clinical Neurosciences*. 2014;**68**(1):21-36. DOI: 10.1111/pcn.12089
- [39] Barbosa IG, Machado-Vieira R, Soares JC, Teixeira AL. The immunology of bipolar disorder. *Neuroimmunomodulation*. 2014;**21**(2-3):117-122.

- [40] Miklowitz DJ, Portnoff LC, Armstrong CC, Keenan-Miller D, Breen EC, Muscatell KA, Eisenberger NI, Irwin MR. Inflammatory cytokines and nuclear factor-kappa B activation in adolescents with bipolar and major depressive disorders. *Psychiatry Research*. 2016;**241**:315-322. DOI: 10.1016/j.psychres.2016.04.120
- [41] Nowakowski J, Chrobak AA, Dudek D. Psychiatric illnesses in inflammatory bowel diseases—psychiatric comorbidity and biological underpinnings. *Psychiatria Polska*. 2016;**50**(6):1157-1166. DOI: 10.12740/PP/62382
- [42] Ohgidani M, Kato TA, Haraguchi Y, Matsushima T, Mizoguchi Y, Murakawa-Hirachi T, Sagata N, Monji A, Kanba S. Microglial CD206 gene has potential as a state marker of bipolar disorder. *Frontiers in Immunology*. 2017;**7**:676. DOI: 10.3389/fimmu.2016.00676
- [43] van Berckel BN, Bossong MG, Boellaard R, Kloet R, Schuitemaker A, Caspers E, Luurtsema G, Windhorst AD, Cahn W, Lammertsma AA, Kahn RS. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. *Biological Psychiatry*. 2008;**64**(9):820-822. DOI: 10.1016/j.biopsych.2008.04.025
- [44] Takano A, Arakawa R, Ito H, Tateno A, Takahashi H, Matsumoto R, Okubo Y, Suhara T. Peripheral benzodiazepine receptors in patients with chronic schizophrenia: A PET study with [11C]DAA1106. *International Journal of Neuropsychopharmacology*. 2010;**13**(7):943-950. DOI: 10.1017/S1461145710000313
- [45] Dong XH, Zhen XC. Glial pathology in bipolar disorder: potential therapeutic implications. *CNS Neuroscience & Therapeutics*. 2015;**21**(5):393-397. DOI: 10.1111/cns.12390
- [46] Réus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, Kapczinski F, Quevedo J. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience*. 2015;**300**:141-154. DOI: 10.1016/j.neuroscience.2015.05.018
- [47] Klapal L, Igelhorst BA, Dietzel-Meyer ID. Changes in neuronal excitability by activated microglia: Differential Na(+) current upregulation in pyramid-shaped and bipolar neurons by TNF- $\alpha$  and IL-18. *Frontiers in Neurology*. 2016;**7**:44. DOI: 10.3389/fneur.2016.00044
- [48] Monfrim X, Gazal M, De Leon PB, Quevedo L, Souza LD, Jansen K, Oses JP, Pinheiro RT, Silva RA, Lara DR, Ghisleni G, Spessato B, Kaster MP. Immune dysfunction in bipolar disorder and suicide risk: is there an association between peripheral corticotropin-releasing hormone and interleukin-1 $\beta$ ? *Bipolar Disorder*. 2014;**16**(7):741-747. DOI: 10.1111/bdi.12214
- [49] Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, “just the facts” what we know in 2008. 2. Epidemiology and etiology. *Schizophrenia Research*. 2008;**102**(1-3):1-18. DOI: 10.1016/j.schres.2008.04.011
- [50] Brunelin J, Fecteau S, Suaud-Chagny MF. Abnormal striatal dopamine transmission in schizophrenia. *Current Medicinal Chemistry*. 2013;**20**(3):397-404.
- [51] Laruelle M. Schizophrenia: From dopaminergic to glutamatergic interventions. *Current Opinion in Pharmacology*. 2014;**14**:97-102. DOI: 10.1016/j.coph.2014.01.001

- [52] Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biological Psychiatry*. 2008;**63**(8):801-808. DOI: 10.1016/j.biopsych.2007.09.024
- [53] Drexhage RC, Knijff EM, Padmos RC, Heul-Nieuwenhuijzen LV, Beumer W, Versnel MA, Drexhage HA. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. *Expert Review of Neurotherapeutics*. 2010;**10**(1):59-76. DOI: 10.1586/ern.09.144
- [54] Uptegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naive first episode psychosis: A systematic review and meta-analysis. *Schizophrenia Research*. 2014;**155**(1-3):101-108. DOI: 10.1016/j.schres.2014.03.005
- [55] Inta D, Lang UE, Borgwardt S, Meyer-Lindenberg A, Gass P. Microglia activation and schizophrenia: Lessons from the effects of minocycline on postnatal neurogenesis, neuronal survival and synaptic pruning. *Schizophrenia Bulletin*. *Schizophr Bull*. 2017; **43**(3):493-496. DOI:10.1093/schbul/sbw088
- [56] Patrizio M. Tumor necrosis factor reduces cAMP production in rat microglia. *Glia*. 2004;**48**(3):241-249. DOI: 10.1002/glia.20074
- [57] Garcia AM, Martinez A, Gil C. Enhancing cAMP levels as strategy for the treatment of neuropsychiatric disorders. *Current Topics in Medicinal Chemistry*. 2016;**16**(29):3527-3535.
- [58] Ghosh M, Xu Y, Pearse DD. Cyclic AMP is a key regulator of M1 to M2a phenotypic conversion of microglia in the presence of Th2 cytokines. *Journal of Neuroinflammation*. 2016;**13**:9. DOI: 10.1186/s12974-015-0463-9
- [59] Yang H, Yang L. Targeting cAMP/PKA pathway for glycemic control and type 2 diabetes therapy. *Journal of Molecular Endocrinology*. 2016;**57**(2):R93-R108. DOI: 10.1530/JME-15-0316
- [60] Taskén K, Aandahl EM. Localized effects of cAMP mediated by distinct routes of protein kinase A. *Physiological Reviews*. 2004;**84**(1):137-167. DOI: 10.1152/physrev.00021.2003
- [61] Liou JT, Liu FC, Hsin ST, Yang CY, Lui PW. Inhibition of the cyclic adenosine monophosphate pathway attenuates neuropathic pain and reduces phosphorylation of cyclic adenosine monophosphate response element-binding in the spinal cord after partial sciatic nerve ligation in rats. *Anesthesia & Analgesia*. 2007;**105**(6):1830-1837. DOI: 10.1213/01.ane.0000287652.42309.5c
- [62] Wang C, Yang XM, Zhuo YY, Zhou H, Lin HB, Cheng YF, Xu JP, Zhang HT. The phosphodiesterase-4 inhibitor rolipram reverses A $\beta$ -induced cognitive impairment and neuroinflammatory and apoptotic responses in rats. *International Journal of Neuropsychopharmacology*. 2012;**15**(6):749-766. DOI: 10.1017/S146114711000836
- [63] Ottonello L, Morone MP, Dapino P, Dallegri F. Cyclic AMP-elevating agents down-regulate the oxidative burst induced by granulocyte-macrophage colony-stimulating factor (GM-CSF) in adherent neutrophils. *Clinical & Experimental Immunology*. 1995;**101**(3):502-506.



- [64] Pearse DD, Pereira FC, Marcillo AE, Bates ML, Berrocal YA, Filbin MT, Bunge MB. cAMP and Schwann cells promote axonal growth and functional recovery after spinal cord injury. *Nature Medicine*. 2004;**10**(6):610-616. Epub 2004 May 23. DOI: 10.1038/nm1056
- [65] Min KJ, Yang MS, Jou I, Joe EH. Protein kinase A mediates microglial activation induced by plasminogen and gangliosides. *Experimental & Molecular Medicine*. 2004;**36**(5):461-467. DOI: 10.1038/emm.2004.58
- [66] Guo J, Lin P, Zhao X, Zhang J, Wei X, Wang Q, Wang C. Etazolate abrogates the lipopolysaccharide (LPS)-induced downregulation of the cAMP/pCREB/BDNF signaling, neuroinflammatory response and depressive-like behavior in mice. *Neuroscience*. 2014;**263**:1-14. DOI: 10.1016/j.neuroscience.2014.01.008
- [67] Serezani CH, Ballinger MN, Aronoff DM, Peters-Golden M. Cyclic AMP: Master regulator of innate immune cell function. *The American Journal of Respiratory Cell and Molecular Biology*. 2008;**39**(2):127-132. DOI: 10.1165/rcmb.2008-0091TR
- [68] Li YF, Cheng YF, Huang Y, Conti M, Wilson SP, O'Donnell JM, Zhang HT. Phosphodiesterase-4D knock-out and RNA interference-mediated knock-down enhance memory and increase hippocampal neurogenesis via increased cAMP signaling. *Journal of Neuroscience*. 2011;**31**(1):172-183. DOI: 10.1523/JNEUROSCI.5236-10.2011
- [69] Poppinga WJ, Muñoz-Llanca P, González-Billault C, Schmidt M. A-kinase anchoring proteins: cAMP compartmentalization in neurodegenerative and obstructive pulmonary diseases. *British Journal of Pharmacology*. 2014;**171**(24):5603-5623. DOI: 10.1111/bph.12882
- [70] Lee D. Global and local missions of cAMP signaling in neural plasticity, learning, and memory. *Frontiers in Pharmacology*. 2015;**6**:161. DOI: 10.3389/fphar.2015.00161
- [71] Peng S, Yang X, Liu GJ, Zhang XQ, Wang GL, Sun HY. From the camp pathway to search the ketamine-related learning and memory. *European Review for Medical and Pharmacological Sciences*. 2015;**19**(1):161-164.
- [72] Zhou L, Ma SL, Yeung PK, Wong YH, Tsim KW, So KF, Lam LC, Chung SK. Anxiety and depression with neurogenesis defects in exchange protein directly activated by cAMP 2-deficient mice are ameliorated by a selective serotonin reuptake inhibitor, Prozac. *Translational Psychiatry*. 2016;**6**(9):e881. DOI: 10.1038/tp.2016.129
- [73] Zhang C, Xu Y, Zhang HT, Gurney ME, O'Donnell JM. Comparison of the pharmacological profiles of selective PDE4B and PDE4D inhibitors in the central nervous system. *Scientific Reports*. 2017;**7**:40115. DOI: 10.1038/srep40115
- [74] Li QQ, Shi GX, Yang JW, Li ZX, Zhang ZH, He T, Wang J, Liu LY, Liu CZ. Hippocampal cAMP/PKA/CREB is required for neuroprotective effect of acupuncture. *Physiology & Behavior*. 2015;**139**:482-490. DOI: 10.1016/j.physbeh.2014.12.001
- [75] Guo H, Cheng Y, Wang C, Wu J, Zou Z, Niu B, Yu H, Wang H, Xu J. FPPM, a PDE4 inhibitor, reverses learning and memory deficits in APP/PS1 transgenic mice via cAMP/PKA/

- CREB signaling and anti-inflammatory effects. *Neuropharmacology*. 2017;**116**:260-269. DOI: 10.1016/j.neuropharm.2017.01.004
- [76] Vitolo OV, Sant' Angelo A, Costanzo V, Battaglia F, Arancio O, Shelanski M. Amyloid beta-peptide inhibition of the PKA/CREB pathway and long-term potentiation: Reversibility by drugs that enhance cAMP signaling. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;**99**(20):13217-13221. DOI: 10.1073/pnas.172504199
- [77] Forero DA, Herteleer L, De Zutter S, Norrback KF, Nilsson LG, Adolfsson R, Callaerts P, Del-Favero J. A network of synaptic genes associated with schizophrenia and bipolar disorder. *Schizophrenia Research*. 2016;**172**(1-3):68-74. DOI: 10.1016/j.schres.2016.02.012
- [78] Kast RE. Tumor necrosis factor has positive and negative self regulatory feed back cycles centered around cAMP. *International Journal of Immunopharmacology*. 2000;**22**(11):1001-1006.
- [79] Miao Y, He T, Zhu Y, Li W, Wang B, Zhong Y. Activation of Hippocampal CREB by Rolipram partially recovers balance between TNF- $\alpha$  and IL-10 levels and improves cognitive deficits in diabetic rats. *Cell Molecular Neurobiology*. 2015;**35**(8):1157-1164. DOI: 10.1007/s10571-015-0209-3
- [80] Patrizio M, Costa T, Levi G. Interferon-gamma and lipopolysaccharide reduce cAMP responses in cultured glial cells: Reversal by a type IV phosphodiesterase inhibitor. *Glia*. 1995;**14**(2):94-100. DOI: 10.1002/glia.440140204
- [81] Banner KH, Trevethick MA. PDE4 inhibition: A novel approach for the treatment of inflammatory bowel disease. *Trends in Pharmacological Sciences*. 2004;**25**(8):430-436. DOI: 10.1016/j.tips.2004.06.008
- [82] Duinen MV, Reneerkens OA, Lambrecht L, Sambeth A, Rutten BP, Os JV, Blokland A, Prickaerts J. Treatment of cognitive impairment in schizophrenia: Potential value of phosphodiesterase inhibitors in prefrontal dysfunction. *Current Pharmaceutical Design*. 2015;**21**(26):3813-3828.
- [83] Engels P, Fichtel K, Lübbert H. Expression and regulation of human and rat phosphodiesterase type IV isogenes. *FEBS Letters*. 1994;**350**(2-3):291-295.
- [84] Bolger GB, Rodgers L, Riggs M. Differential CNS expression of alternative mRNA isoforms of the mammalian genes encoding cAMP-specific phosphodiesterases. *Gene*. 1994;**149**(2):237-244.
- [85] Pérez-Torres S, Miró X, Palacios JM, Cortés R, Puigdomènech P, Mengod G. Phosphodiesterase type 4 isozymes expression in human brain examined by in situ hybridization histochemistry and [<sup>3</sup>H]rolipram binding autoradiography. Comparison with monkey and rat brain. *Journal of Chemical Neuroanatomy*. 2000;**20**(3-4):349-374.
- [86] Miró X, Pérez-Torres S, Artigas F, Puigdomènech P, Palacios JM, Mengod G. Regulation of cAMP phosphodiesterase mRNAs expression in rat brain by acute and chronic fluoxetine treatment. An in situ hybridization study. *Neuropharmacology*. 2002;**43**(7):1148-1157.

- [87] Fatemi SH, King DP, Reutiman TJ, Folsom TD, Laurence JA, Lee S, Fan YT, Paciga SA, Conti M, Menniti FS. PDE4B polymorphisms and decreased PDE4B expression are associated with schizophrenia. *Schizophrenia Research*. 2008;**101**(1-3):36-49. DOI: 10.1016/j.schres.2008.01.029
- [88] Reyes-Irisarri E, Pérez-Torres S, Miró X, Martínez E, Puigdomènech P, Palacios JM, Mengod G. Differential distribution of PDE4B splice variant mRNAs in rat brain and the effects of systemic administration of LPS in their expression. *Synapse*. 2008;**62**(1):74-79. DOI: 10.1002/syn.20459
- [89] Zhang KY, Ibrahim PN, Gillette S, Bollag G. Phosphodiesterase-4 as a potential drug target. *Expert Opinion on Therapeutic Targets*. 2005;**9**(6):1283-1305. DOI: 10.1517/14728222.9.6.1283
- [90] Zhang HT. Cyclic AMP-specific phosphodiesterase-4 as a target for the development of antidepressant drugs. *Current Pharmaceutical Design*. 2009;**15**(14):1688-1698.
- [91] D'Sa C, Duman RS. Antidepressants and neuroplasticity. *Bipolar Disorder*. 2002;**4**(3):183-194.
- [92] Bertolino A, Crippa D, di Dio S, Fichte K, Musmeci G, Porro V, Rapisarda V, Sastre-y-Hernández M, Schratzer M. Risperidone versus imipramine in inpatients with major, "minor" or atypical depressive disorder: a double-blind double-dummy study aimed at testing a novel therapeutic approach. *International Clinical Psychopharmacology*. 1988;**3**(3):245-253.
- [93] Fujita M, Hines CS, Zoghbi SS, Mallinger AG, Dickstein LP, Liow JS, Zhang Y, Pike VW, Drevets WC, Innis RB, Zarate CA Jr. Downregulation of brain phosphodiesterase type IV measured with <sup>11</sup>C-(R)-risperidone positron emission tomography in major depressive disorder. *Biological Psychiatry*. 2012;**72**(7):548-554. DOI: 10.1016/j.biopsych.2012.04.030
- [94] Jindal A, Mahesh R, Bhatt S. Type 4 phosphodiesterase enzyme inhibitor, risperidone rescues behavioral deficits in olfactory bulbectomy models of depression: Involvement of hypothalamic-pituitary-adrenal axis, cAMP signaling aspects and antioxidant defense system. *Pharmacology Biochemistry & Behavior*. 2015;**132**:20-32. DOI: 10.1016/j.pbb.2015.02.017
- [95] Manji HK, Duman RS. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. *Psychopharmacology Bulletin*. 2001;**35**(2):5-49.
- [96] Atkins CM, Oliva AA Jr, Alonso OF, Pearse DD, Bramlett HM, Dietrich WD. Modulation of the cAMP signaling pathway after traumatic brain injury. *Experimental Neurology*. 2007;**208**(1):145-158. DOI: 10.1016/j.expneurol.2007.08.011
- [97] Hannila SS, Filbin MT. The role of cyclic AMP signaling in promoting axonal regeneration after spinal cord injury. *Experimental Neurology*. 2008;**209**(2):321-332. DOI: 10.1016/j.expneurol.2007.06.020

- [98] Whitaker CM, Beaumont E, Wells MJ, Magnuson DS, Hetman M, Onifer SM. Rolipram attenuates acute oligodendrocyte death in the adult rat ventrolateral funiculus following contusive cervical spinal cord injury. *Neuroscience Letters*. 2008;**438**(2):200-204. DOI: 10.1016/j.neulet.2008.03.087
- [99] Reneerkens OA, Rutten K, Steinbusch HW, Blokland A, Prickaerts J. Selective phosphodiesterase inhibitors: A promising target for cognition enhancement. *Psychopharmacology (Berl)*. 2009;**202**(1-3):419-43. DOI: 10.1007/s00213-008-1273-x
- [100] Robichaud A, Savoie C, Stamatou PB, Tattersall FD, Chan CC. PDE4 inhibitors induce emesis in ferrets via a noradrenergic pathway. *Neuropharmacology*. 2001;**40**(2):262-269.
- [101] Dyke HJ, Montana JG. Update on the therapeutic potential of PDE4 inhibitors. *Expert Opinion on Investigational Drugs*. 2002;**11**(1):1-13. DOI: 10.1517/13543784.11.1.1
- [102] Drott J, Desire L, Drouin D, Pando M, Haun F. Etazolate improves performance in a foraging and homing task in aged rats. *The European Journal of Pharmacology*. 2010;**634**(1-3):95-100. DOI: 10.1016/j.ejphar.2010.02.036
- [103] Jindal A, Mahesh R, Bhatt S, Pandey D. Molecular modifications by regulating cAMP signaling and oxidant-antioxidant defence mechanisms, produce antidepressant-like effect: A possible mechanism of etazolate aftermaths of impact accelerated traumatic brain injury in rat model. *Neurochemistry International*. 2016. pii: S0197-0186(16)30114-0. DOI: 10.1016/j.neuint.2016.12.004
- [104] Jindal A, Mahesh R, Gautam B, Bhatt S, Pandey D. Antidepressant-like effect of etazolate, a cyclic nucleotide phosphodiesterase 4 inhibitor—an approach using rodent behavioral antidepressant tests battery. *The European Journal of Pharmacology*. 2012;**689**(1-3):125-131. DOI: 10.1016/j.ejphar.2012.05.051
- [105] Jindal A, Mahesh R, Bhatt S. Etazolate rescues behavioral deficits in chronic unpredictable mild stress model: modulation of hypothalamic-pituitary-adrenal axis activity and brain-derived neurotrophic factor level. *Neurochemistry International*. 2013;**63**(5):465-475. DOI: 10.1016/j.neuint.2013.08.005
- [106] Vellas B, Sol O, Snyder PJ, Ousset PJ, Haddad R, Maurin M, Lemarié JC, Désiré L, Pando MP; EHT0202/002 study group. EHT0202 in Alzheimer's disease: A 3-month, randomized, placebo-controlled, double-blind study. *Current Alzheimer Research*. 2011;**8**(2):203-212.
- [107] Davis TG, Peterson JJ, Kou JP, Capper-Spudich EA, Ball D, Nials AT, Wiseman J, Solanke YE, Lucas FS, Williamson RA, Ferrari L, Wren P, Knowles RG, Barnette MS, Podolin PL. 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]pyridin-4-amine (EPPA-1), with improved therapeutic index using pica feeding in rats as a measure of emetogenicity. *Journal of Pharmacology and Experimental Therapeutics*. 2009;**330**(3):922-931. DOI: 10.1124/jpet.109.152454

- [108] Tralau-Stewart CJ, Williamson RA, Nials AT, Gascoigne M, Dawson J, Hart GJ, Angell AD, Solanke YE, Lucas FS, Wiseman J, Ward P, Ranshaw LE, Knowles RG. GSK256066, an exceptionally high-affinity and selective inhibitor of phosphodiesterase 4 suitable for administration by inhalation: In vitro, kinetic, and in vivo characterization. *Journal of Pharmacology and Experimental Therapeutics*. 2011;**337**(1):145-154. DOI: 10.1124/jpet.110.173690
- [109] Zhang MZ, Zhou ZZ, Yuan X, Cheng YF, Bi BT, Gong MF, Chen YP, Xu JP. Chlorbipram: a novel PDE4 inhibitor with improved safety as a potential antidepressant and cognitive enhancer. *The European Journal of Pharmacology*. 2013;**721**(1-3):56-63. DOI: 10.1016/j.ejphar.2013.09.055
- [110] Rutter AR, Poffe A, Cavallini P, Davis TG, Schneck J, Negri M, Vicentini E, Montanari D, Arban R, Gray FA, Davies CH, Wren PB. GSK356278, a potent, selective, brain-penetrant phosphodiesterase 4 inhibitor that demonstrates anxiolytic and cognition-enhancing effects without inducing side effects in preclinical species. *Journal of Pharmacology and Experimental Therapeutics*. 2014;**350**(1):153-163. DOI: 10.1124/jpet.114.214155
- [111] Nunes IK, de Souza ET, Cardozo SV, Carvalho VF, Romeiro NC, Silva PM, Martins MA, Barreiro EJ, Lima LM. Synthesis, pharmacological profile and docking studies of new sulfonamides designed as phosphodiesterase-4 inhibitors. *PLoS One*. 2016;**11**(10):e0162895. DOI: 10.1371/journal.pone.0162895
- [112] Obernolte R, Ratzliff J, Baecker PA, Daniels DV, Zuppan P, Jarnagin K, Shelton ER. Multiple splice variants of phosphodiesterase PDE4C cloned from human lung and testis. *Biochimica et Biophysica Acta*. 1997;**1353**(3):287-297.
- [113] Siuciak JA, Chapin DS, McCarthy SA, Martin AN. Antipsychotic profile of rolipram: Efficacy in rats and reduced sensitivity in mice deficient in the phosphodiesterase-4B (PDE4B) enzyme. *Psychopharmacology (Berl)*. 2007;**192**(3):415-424. DOI: 10.1007/s00213-007-0727-x
- [114] Contreras S, Milara J, Morcillo E, Cortijo J. Selective inhibition of phosphodiesterases 4A, B, C and D isoforms in chronic respiratory diseases: Current and future evidences. *Current Pharmaceutical Design*. 2017. DOI: 10.2174/1381612823666170214105651.
- [115] Jin SL, Conti M. Induction of the cyclic nucleotide phosphodiesterase PDE4B is essential for LPS-activated TNF-alpha responses. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;**99**(11):7628-7633. DOI: 10.1073/pnas.122041599
- [116] Ma H, Shi J, Wang C, Guo L, Gong Y, Li J, Gong Y, Yun F, Zhao H, Li E. Blockade of PDE4B limits lung vascular permeability and lung inflammation in LPS-induced acute lung injury. *Biochemical and Biophysical Research Communications*. 2014;**450**(4):1560-1567. DOI: 10.1016/j.bbrc.2014.07.024
- [117] Huang H, Hong Q, Tan HL, Xiao CR, Gao Y. Ferulic acid prevents LPS-induced up-regulation of PDE4B and stimulates the cAMP/CREB signaling pathway in PC12 cells. *Acta Pharmacologica Sinica*. 2016;**37**(12):1543-1554. DOI: 10.1038/aps.2016.88

- [118] Hansen RT 3rd, Conti M, Zhang HT. Mice deficient in phosphodiesterase-4A display anxiogenic-like behavior. *Psychopharmacology (Berl)*. 2014;**231**(15):2941-2954. DOI: 10.1007/s00213-014-3480-y
- [119] Pearse DD, Hughes ZA. PDE4B as a microglia target to reduce neuroinflammation. *Glia*. 2016;**64**(10):1698-1709. DOI: 10.1002/glia.22986
- [120] Naganuma K, Omura A, Maekawara N, Saitoh M, Ohkawa N, Kubota T, Nagumo H, Kodama T, Takemura M, Ohtsuka Y, Nakamura J, Tsujita R, Kawasaki K, Yokoi H, Kawanishi M. Discovery of selective PDE4B inhibitors. *Bioorganic & Medicinal Chemistry Letters*. 2009;**19**(12):3174-3176. DOI: 10.1016/j.bmcl.2009.04.121
- [121] Fox D 3rd, Burgin AB, Gurney ME. Structural basis for the design of selective phosphodiesterase 4B inhibitors. *Cell Signal*. 2014;**26**(3):657-663. DOI: 10.1016/j.cellsig.2013.12.003
- [122] Jin SL, Lan L, Zoudilova M, Conti M. Specific role of phosphodiesterase 4B in lipopolysaccharide-induced signaling in mouse macrophages. *The Journal of Immunology*. 2005;**175**(3):1523-1531

