Chapter 1

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

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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 specifc PDE4 inhibitors provokes an ant-iinflammatory response. Specifcally, 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-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interferon-gamma (IFN-γ), and they are secreted primarily by microglia [19–21]; [3]. In the M1 activation, microglial cells may become

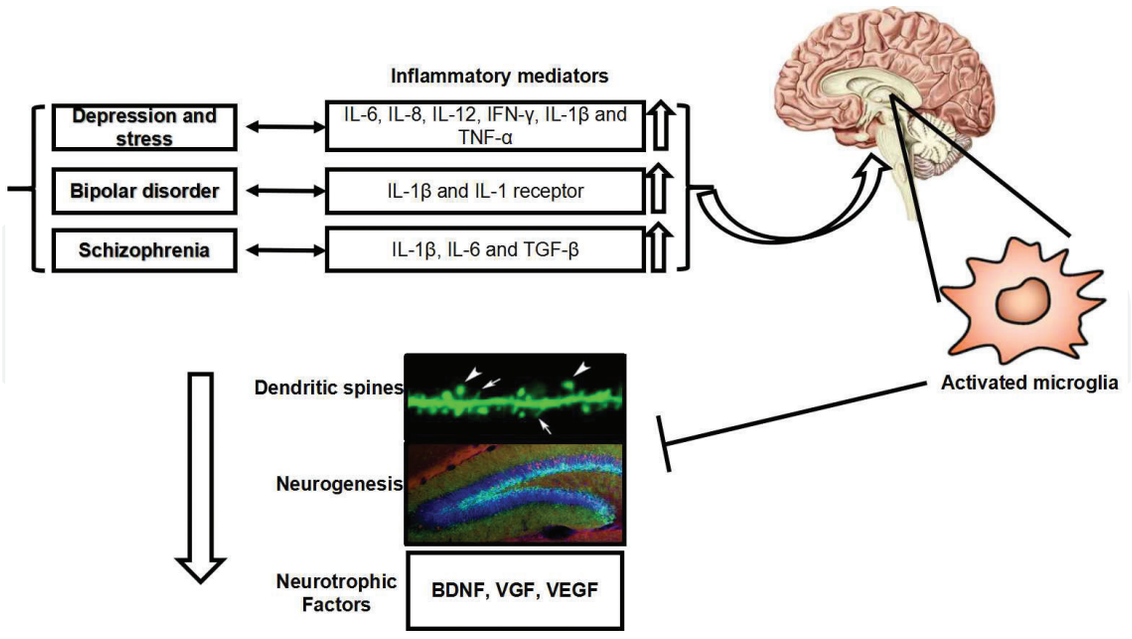


Figure 1. Summary of neuroinflammatory responses and microglial abnormalities observed in psychiatry disorders. A large body of evidence [8–13] supports the involvement of neuroinflammatory mechanisms, including microglial activation, downregulation of dendritic spines, neurogenesis, and neurotrophic 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-β (TGF-β), 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-1β 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)-α, interleukin (IL)-1β, 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)-γ, and TNF-α, 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.

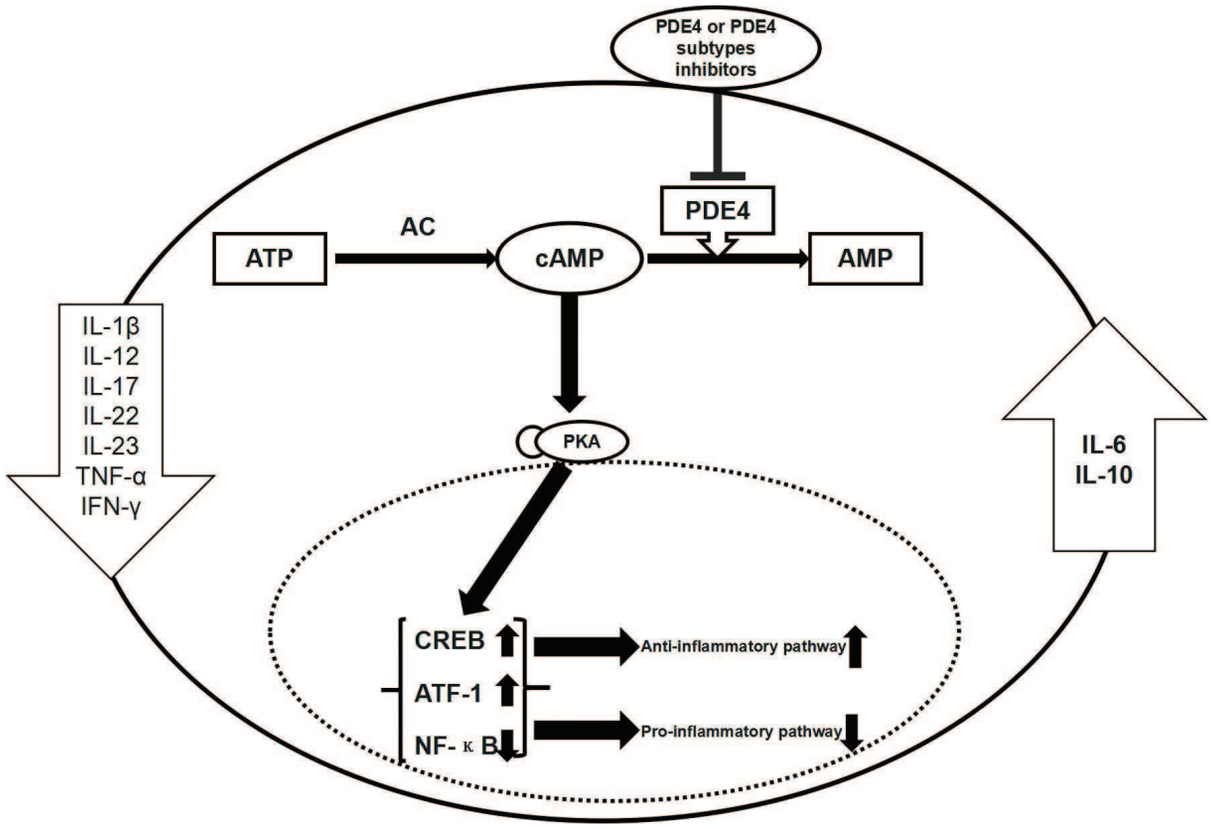


Figure 2. The antiinflammatory mechanisms of PDE4 and PDE4 subtype inhibitors. cAMP as a regulator of immunity. Adenylate cyclases (AC) produce cAMP from adenosin-tri-phosphate (ATP). High levels of cytosolic cAMP lead to the activation of protein kinase A (PKA) and further induce the phosphorylation 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-κB is inactivated. This transcriptional regulation is responsible for the reduced production of proinflammatory mediators like IL-1β, IL-12, IL-17, IL-22, IL-23, TNF-α, and IFN-γ 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-1β 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

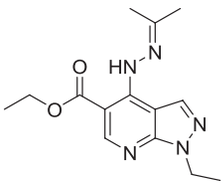
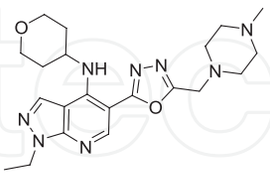
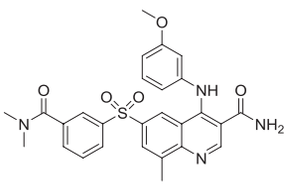
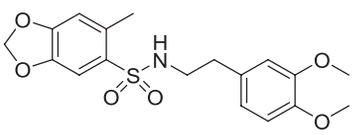
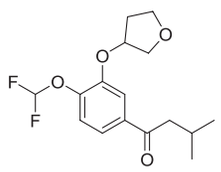
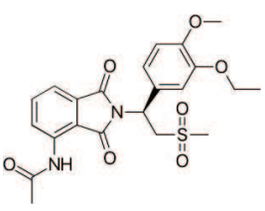
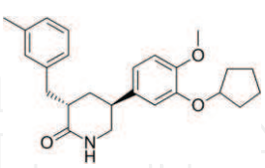
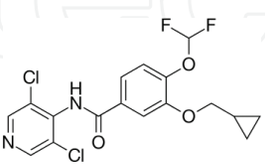
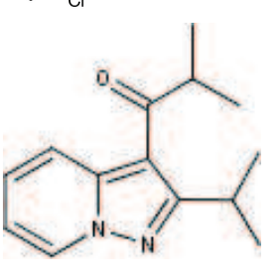
Novel PDE4 inhibitors	Chemical structures	Active indications	Highest status
Etazolate		Depression, anxiety, traumatic brain injury	Phase 2 clinical to discontinued
EPPA-1		In vitro and in vivo anti inflammatory potencies	Discovery
GSK256066		Antiinflammatory activities	Phase 2 clinical to discontinued
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 IC50 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-α 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.

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