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Review Article

PDE4 inhibition and enhancement of human memory and cognition

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Abstract

Activation of the adenylyl cyclase – PKA – CREB signaling pathway has been shown to be critical for learning and the creation and consolidation of memory. The PDE4, or cAMP-specific, phosphodiesterases (PDEs) are important modulators of cAMP levels in the central nervous system. The establishment of the essential role of PDE4 isoforms in learning and memory has been based on a long-standing interplay between experiments in genetically-tractable organisms, such as flies and mice, and pharmacological studies in rodents, primates and humans. Collectively, these diverse approaches have demonstrated the pivotal role of PDE4s in learning and memory and that pharmacological targeting of PDE4s can enhance learning, memory and cognition in humans. However, several challenges remain before PDE4 inhibitors can be used clinically in disorders of cognition and memory. Current priorities in PDE4 drug discovery focused on the CNS include 1) further refinement of isoform selectivity; 2) more precise action at CNS targets implicated in cognition and memory, such as those in forebrain and hippocampus, while reducing undesired action at other CNS (area postrema) and non-CNS targets (CFTR, gastric acid secretion) that account for the limiting side effects of many, but not all, PDE4 inhibitors in clinical trials; and 3) improved pharmacokinetics and dosing.

Keywords: Roflumilast, Apremilast, Zatolmilast, Nerandomilast, Orismilast

Genetic and Pharmacologic Evidence for PDE4 Action in Learning and Memory

Two distinct, but intertwining, threads of inquiry have demonstrated that the PDE4, or cAMP-selective, phosphodiesterases, have an essential role in human cognition, learning and memory. Study of genetically-modified preclinical models, and of humans with mutations in the *PDE4D* gene, has provided some of the most rigorous proof of the importance of PDE4 signaling in the CNS. More recently, clinical trials of PDE4-selective inhibitors have shown promising clinical activity in disorders of cognition and memory.

Genetic Models of PDE4 Action in the CNS

Studies in *Drosophila melanogaster* and aplysia

Extensive genetic study of the fruit fly *Drosophila melanogaster* has demonstrated a vital role for many elements of cAMP signaling in learning and short-term memory [1]. Mutations in several *Drosophila* genes, including *rutabaga*, which encodes adenylyl cyclase [2], *DCO*, encoding the cAMP-dependent protein kinase (protein kinase A; PKA) catalytic subunit [3], and *dunce*, which encodes a PDE closely homologous to mammalian PDE4 enzymes [4-8], produce clear alterations in numerous experimental tests of learning [9]. Extensive study of plasticity in the gill and siphon reflex, which serves as a measure of learning, in the marine mollusk *Aplysia* has demonstrated the critical role of PKA and other cAMP signaling elements in this process [10,11]; see refs. [12,13] for a review.

cAMP signaling components in learning and memory in genetically-modified mice

Several different genetic approaches have been utilized to study the roles of cAMP signaling elements in learning and memory in mice. Heterozygous and homozygous gene knockout studies have shown that knockout of specific adenylyl cyclase isoforms produces profound alterations in long-term potentiation, a key attribute of learning [14,15]. Knockouts of PKA regulatory or catalytic subunits produce defects in hippocampal long-term depression and depotentiation [16-18]. Knockouts of the cyclic nucleotide response element binding protein (CREB) also produce deficiencies in long-term memory [19,20].

As an alternative approach, expression of an inhibitory form of the PKA regulatory subunit, expressed as a transgene off the Ca^{++}/calmodulin protein kinase IIα (CamKIIα) promoter [21], produces defects in long-term potentiation in the CA1 area of the hippocampus [22]. Similarly, expression of a dominant-negative mutant of CamKIIα, expressed off its own promoter, produces deficiencies in long-term potentiation and spatial learning [21,23-25]. Expression of a transgenic CREB with a mutation at its PKA-phosphorylation site (S133A), which serves as a dominant-negative, produces deficiencies in long-term conditioned fear memories [26,27]; see ref. [28] for a review. Collectively, these genetic studies provide compelling evidence for the role of cAMP signaling pathways in synaptic plasticity, learning and memory [29,30]. They also demonstrate that a variety of genetic approaches can be employed to study cAMP signaling in mice, with compatible results; specifically, both knockout (total animal or tissue-specific) approaches and, as an alternative, transgenic expression of a dominant-negative mutant, can successfully produce reproducible phenotypes in mice that provide insights into the mechanisms of learning, memory and cognition.

Phenotypes of mice with knockouts of PDE4D

The successful use of knockout (KO) approaches to study several different elements of cAMP signaling pathways in mice, as described above, provided an impetus to the study of the CNS phenotypes of mice with knockouts in various members of the PDE4 family. The PDE4s are members of a large superfamily of cyclic nucleotide phosphodiesterases, designed PDE1 through PDE11, which are encoded by 21 different genes. The PDE4s are encoded by 4 different genes in mammals, designated *PDE4A* through *PDE4D* in humans, with additional isoform diversity produced by alternative mRNA splicing and the use of multiple promoters in each gene; see ref. [31] for a review. Mice with knockouts of each *Pde4* gene are available, with *Pde4a, Pde4b* and *Pde4d* KO mice having been studied most extensively. *Pde4a*-/- (homozygous KO) mice display anxiogenic-like behavior [32], but the full range of CNS phenotypes of these mice has yet to be determined. We have discussed the CNS phenotypes of *Pde4b*-/- mice in detail elsewhere [33]. The available data on the CNS phenotypes of *Pde4d* -/- mice are conflicting [34-36]. *Pde4d*-/- mice may have decreased immobility in forced-swim and tail-suspension tests, mimicking an antidepressant effect [35]. The *Pde4d*-/- genotype may improve performance in tests of learning and memory [36], although this effect was not detected in studies performed by a second group [34]. Significant non-CNS phenotypes, such as slow growth, small adult size, and impaired fertility are also seen in some *Pde4d*-/- mice [37,38]. More generally, the behavioral phenotypes that are typically seen in knockout mice may be highly dependent on strain background, which does not appear to have been standardized among these studies. In addition, each study employed a different subset of behavioral assays to characterize the phenotypes seen in these mice, which greatly hampers critical, side-by-side, comparison of these studies. Experimental factors, such as differences in assay conditions, sample size, or age at the time of study, could also explain some of the differing results noted to date.

The human *PDE4D* and mouse *Pde4d* genes each encode at least 11 different protein isoforms [39-43]; see ref. [44] for a review. The different isoforms differ in length, enzymatic properties, sub-cellular localization, their ability to interact with other cellular proteins, and their distribution in cells and tissues. All enzymatically-active *Pde4d* isoforms share an identical catalytic domain, located in the carboxyl-terminal portion of the protein, and therefore can be inhibited by PDE4-selective inhibitors. Among the best-studied PDE4D isoforms is PDE4D5, which is highly conserved among mammals and contains a unique amino-terminal domain of 88 amino acids. PDE4D5 interacts selectively with the signaling proteins RACK1 [45-47] and β-arrestin2 [48-51], and this selective interaction is mediated, at least in part, by its unique amino-terminal domain. To date, *Pde4d*-/- mice have been generated by targeting exons that encode the PDE4D catalytic domain, thereby disrupting all of the enzymatically-active isoforms encoded by the *Pde4d* gene. Therefore, *Pde4d*-/- mice have a phenotype that reflects the combined loss of all 11 PDE4D isoforms, which prevents study of the effect(s) of any individual isoform, such as PDE4D5. Given the presence of these multiple PDE4D isoforms, each with unique properties, it would be desirable to utilize an experimental approach that would target a single PDE4D isoform; such an approach is described in the next section.

Phenotypes of mice that express dominant-negative forms of PDE4D

We and other groups have used a dominant-negative approach to the study of the role(s) of select PDE4 isoforms in the CNS. This approach is conceptually identical to the use of dominant-negative or inhibitory mutants of PKA, CamKIIα, or CREB as genetic probes of cAMP signaling in the CNS, as described in the studies cited above. The PDE4 studies have used engineered versions of select PDE4 isoforms with mutations of an aspartate deep in the catalytic domain that is responsible for metal-binding and therefore catalysis [48,49]. Mutation of this aspartate totally abolishes the catalytic activity of the isoform, with no detectable effect on the stability of the protein, its ability to be targeted to specific sub-cellular locations, or its interactions with other proteins. Instead, the mutant serves to displace the corresponding endogenous PDE4 isoform from its protein partner(s), thereby preventing the hydrolysis of cAMP in the specific sub-cellular compartment(s) where that isoform is normally expressed.

Havekes, Vecsey and their colleagues have demonstrated that expression of the PDE4A5-D577A mutant (also called PDE4D5-catnull), expressed in the mouse hippocampus off the CamKIIα promoter, using a viral construct, reverses or attenuates several protein-phosphorylation events that are associated with sleep deprivation [52-54]. It also prevents or reduces learning/memory deficits that are normally associated with sleep deprivation [54]. No such effect was seen with expression of a double mutant, PDE4A5-catnullΔ4, containing both the D577A mutation and removal of the unique PDE4A5 amino-terminal domain, which is responsible for its intracellular targeting and/or interactions with other signaling

components. These data demonstrate the value of a dominant-negative experimental approach to the study of the functional roles of specific PDE4 isoforms in the CNS, with particular emphasis on learning and memory.

Previously, we have utilized a similar approach to characterize the functions of a PDE4B isoform, specifically PDE4B1, one of 5 isoforms, all highly conserved, encoded by the human *PDE4B* and mouse *Pde4b* genes [33]. The PDE4B1-D564A mutation, at a highly-conserved catalytic domain aspartate homologous to PDE4A5-D577 (see preceding paragraph), was expressed as a transgene under the control of the CamKIIα promoter. The expression of genes under the control of this promoter is preferentially limited to adult forebrain excitatory neurons, including those in the hippocampus, amygdala, cortex, and striatum [21]. Mice expressing the PDE4B1-D564A transgene showed increased phosphorylation of CREB and ERK1/2, increased hippocampal neurogenesis, and enhanced baseline synaptic transmission and long-term potentiation (LTP; ref. [33]). Our data supported the use of a dominant-negative, isoform-selective approach to the study of PDE4B1 function in the CNS and the role of PDE4B isoforms in CNS functions.

These studies with PDE4A5-D577A and PDE4B1-D564A provided an impetus to the use of a conceptually-similar approach to PDE4D isoforms, most notably PDE4D5; ref. [44]. We therefore generated transgenic mice with the critical metal-binding aspartate mutation, PDE4D5-D556A, expressed off the CamKIIα promoter [44]. We chose PDE4D5 because (1) human PDE4D5 (GenBank AF012073) and mouse PDE4D5 (GenBank XP_006517707.1) are extremely similar, being identical in length and having a 98% amino acid identity [39]; (2) PDE4D5 mRNA is expressed in several regions of the mouse CNS [55, 56] compatible with it being targeted by a transgene driven by the CamKIIα promoter; (3) PDE4D5 interacts with several important signaling proteins, most notably RACK1 and β-arrestin2, as outlined above. PDE4D5 appears to have a pivotal role in regulating signaling through the β2-adrenergic receptor [48,49,57-59] and therefore these experiments might provide insights into its role(s) in β2-adrenergic signaling in the CNS.

When overexpressed in cell-based systems, PDE4D5-D556A produces no change in total PDE4 enzymatic activity, but instead disrupts PDE4D5 cellular function in a dominant-negative fashion by producing an equilibrium displacement of endogenous PDE4D5 from its protein partner(s), most notably RACK1 and β-arrestin2 [48,49,51]. In our mouse model, the PDE4D5-D556A transgene appears to have acted in a dominant-negative fashion, blocking PDE4D5 function in regions of the CNS where PDE4D5 is active, and increasing cAMP levels. Elevation of cAMP activated PKA, leading to enhanced phosphorylation of CREB, and/or stimulated other cAMP effectors, such as EPAC [60-62] or cyclic nucleotide-gated ion channels [63]. These putative changes in cAMP signaling were associated with significant alterations in behavior, most notably affecting hippocampal-dependent positional learning (place preference), based on their performance in the Morris water maze [44]. In contrast, the PDE4D5-D556A transgene had no detectable effect on associative fear conditioning. A marked, sex-dependent effect of the transgene on behavior in an open field test was also observed [44].

The extensive experimentation that has been performed with the dominant-negative mouse models has a number of methodological limitations. First of all, for the transgene to produce the desired effect in the CNS, it needs to be expressed at a level sufficiently high to displace all, or at least a functionally significant proportion, of the wild-type PDE protein from its binding partners. In the reported studies, expression of the transgene in brain tissues was typically performed using immunoblotting; cell-based functional assays were not felt to be feasible in brain tissue. Therefore, some uncertainty remains whether these mutants were indeed acting in a true dominant-negative fashion in the brain. There may also be significant methodological differences in the assays employed by the two groups performing these studies. Other issues, such as sample size, treatment of the mice prior to the performance of the assays, or age at the time of study, may also complicate critical analysis of their results.

Promising Human Clinical Trials with Roflumilast

Following the pioneering work of Barad [64] and Bach [65] on the pro-cognitive effects of PDE4 inhibitors in pre-clinical models, a series of human clinical trials has demonstrated the value of roflumilast as an enhancer of cognitive function in both healthy adults and those with age-related memory dysfunction [66-71]. Roflumilast is a PDE4 inhibitor currently marketed in oral form for chronic obstructive pulmonary disease (COPD) and as a topical formulation for inflammatory skin disorders, but has yet to receive marketing approval for any CNS indication. Clinical use of roflumilast in CNS indications is likely to be limited by typical side effects of the drug, including nausea, emesis and diarrhea [72,73]. These side effects are typical of most 1st- and 2nd-generation PDE4 selective inhibitors (i.e., are class-specific). Nausea/emesis has probably been the most commonly-encountered limiting side effect in clinical trials of these agents, and reflects action at both CNS (i.e., area postrema) and non-CNS (gastric acid secretion, GI motility) targets. The non-infectious diarrhea that is seen in many patients with roflumilast probably reflects its activation of CFTR, a Cl^- ion channel, in GI mucosa [72]. The generation of PDE4 inhibitors lacking these side effects is a major emphasis in PDE4 drug discovery, as will be described in the next sections.

Implications for CNS Drug Discovery – Potential Obstacles

Precision targeting of the PDE4 catalytic region

Clinically-available PDE4 inhibitors, specifically roflumilast, apremilast and crisaborole, act at the catalytic domain of the PDE4 enzymes, where they serve, at least in part, as competitive inhibitors of cAMP hydrolysis [74-76]. Given the high degree of homology among the catalytic domains of the enzymes encoded by the 4 PDE4 genes, which have at least 90% amino acid sequence homology [7,31,77,78], it is not surprising that these 3 drugs, as well as the vast majority of PDE4-selective inhibitors that have been synthesized to date, have similar potencies against isoforms encoded by all 4 PDE4 genes (i.e., IC_{50} values differing by less than 10-fold). For example, GEBR-7b and GEBR-32a, which has been extensively tested against several different PDE4D isoforms, has a difference in IC_{50} for PDE4D isoforms, as compared to PDE4A or PDE4B isoforms, of less than 10-fold [79-82]. These data suggest that exclusive targeting of the PDE4 catalytic domains is unlikely to produce the specificity of action required for selectivity for different isoforms encoded by any one PDE4 gene.

Importance of isoform specificity

Among the important lessons gained from studies employing dominant-negative transgenes is the importance of isoform specificity. Although each of the *PDE4A*, *PDE4B,* and *PDE4D* genes encodes multiple isoforms, the 3 studies summarized above each focused on the effects of a single isoform encoded by each of these genes. This experimental design contrasts with gene knockout studies, which affect all the isoforms encoded by each gene. Similarly, the studies using gene "knockdowns" with lentiviral siRNAs as probes of PDE4 function in the CNS have used constructs that appear to target multiple isoforms [36,83-89]. The significant phenotypes produced by targeting individual isoforms in the dominant-negative studies provides strong functional evidence that each isoform has an important and unique biological function. It is unlikely that the full therapeutic potential of PDE4 inhibition will be reached until agents are developed that can target individual isoforms with a high degree of selectivity.

Importance of interactions with PDE4 partner proteins

Among the best-studied properties of PDE4 proteins is their interactions with a wide range of other cellular proteins. For example, PDE4A5 interacts selectively with the immunophilin homolog AIP1 (also known as XAP2, ref. [90]). PDE4B1, and probably other PDE4B isoforms, may functionally interact with the DISC1 protein [91-101]. As mentioned above, PDE4D5 interacts with RACK1 and β-arrestin2, as well as potentially other proteins. These protein-protein interactions have the potential to influence the folding of select PDE4 isoforms, their enzymatic properties, sensitivity to PDE4 inhibitors, their sub-cellular localization, and their ability to interact with other proteins. It is highly likely that many of the effects of the dominant-negative mutants, when expressed in the CNS, reflect alterations in their interactions with their associated partner proteins. For example, by dramatically increasing scaffold sites for β-arrestin2 and RACK1, PDE4D5-D556A may sequester these proteins and thereby block their normal functions in cells. This effect would produce a CNS phenotype that would differ from that seen with small-molecule inhibitors of the catalytic activity of PDE4D5. Finally, "long" PDE4 isoforms can form stable dimers that are regulated, at least in part, by PKA phosphorylation [102]; these important protein-protein interactions clearly can be affected by expression of our dominant-negative mutants, but has yet to be targeted convincingly by small-molecule agents.

Implications for PDE4 Drug Discovery – Potential Solutions

The potential value of allosteric modulators

Among the most important recent developments in PDE4 pharmacology is the development of compounds that allosterically target PDE4 isoforms **(Figure 1)**. These compounds target PDE4 isoforms by interacting, at least in part, with their amino-terminal

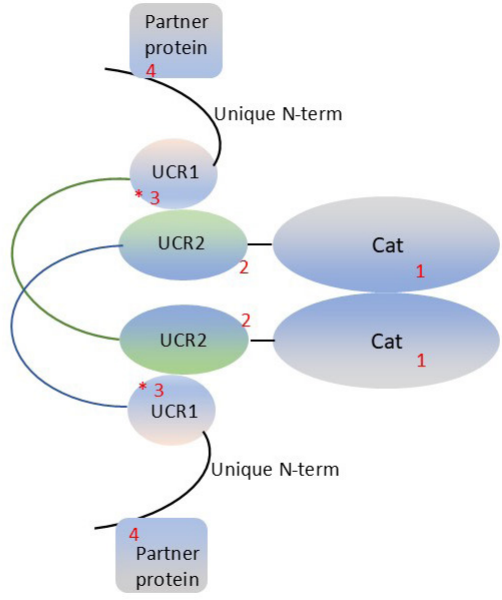

Figure 1. Schematic of PDE4 structure and potential sites for drug action. Long PDE4 isoforms, as shown here, contain UCR1, UCR2 and the catalytic domains of the enzyme. These 3 domains are linked by short, unstructured regions (shown as thin lines). Dimerization of long PDE4 isoforms is driven by *trans*-interaction between UCR1 and UCR2 and also by direct interaction between the catalytic domains. Classic competitive PDE4 inhibitors act on the catalytic domain (1) by displacing its physiologic substrate, cAMP. PDE4 allosteric modulators commonly act on a region of UCR2 that is located close to the catalytic domain (2) and, in many cases, act directly on the catalytic domain (1). Additional potential sites for drug action include regions of UCR1 and/or UCR2 that are required for dimerization (3), which may also affect the ability of the enzyme to be regulated by phosphorylation by PKA (asterisk, *) and potentially by other kinases. Finally, specific PDE4 isoforms bind, and can be regulated by, interactions with other proteins (e.g., RACK1 or β-arrestin2, both of which interact, at least in part, with the unique amino-terminal region of PDE4D5); these interactions may provide additional potential sites for drug action (4).

regulatory domains, UCR1 and UCR2; ref. [7]. Long PDE4 isoforms contain UCR1, UCR2 and the catalytic domain, while short isoforms lack UCR1, and super-short isoforms lack UCR1 and the amino-terminal half of UCR2. The dimerization of long PDE4 isoforms requires a *trans*-activation between UCR1 and UCR2 [102-106]. This process is regulated, at least in part, by PKA, which phosphorylates these isoforms at a conserved serine located at the amino-terminal end of UCR1 [107,108] and increases their catalytic activity (relative V_{max}). Intriguingly, mutations in amino acids in PDE4D UCR1 or UCR2 that are critical for PKA action and dimerization have been shown to cause acrodysostosis, an inherited human disorder of bone that is also associated with significant intellectual and cognitive dysfunction [102,109,110].

The interactions between UCR1, UCR2 and the catalytic region of long PDE4 isoforms provides the mechanistic basis for the development of allosteric modulators of PDE4 enzymes. These compounds typically interact with both the catalytic domain and the UCR1/2 domains, but, in the case of PDE4 allosteric activators, may interact solely with UCR1/2 [111-117]; see ref. [118] for a review. Given the large size of these molecules, and the resulting complex interactions with larger region(s) of the PDE4 dimer, it is perhaps not surprising that they show significant selectivity as inhibitors. For example, DI159687 (and several closely related compounds) has approximately a 20- to 54-fold selectivity (IC_{50}) for human long PDE4D isoforms, as opposed to human long PDE4B isoforms [111]. Similarly, zatolmilast (previously known as BPN14770) has approximately 200-fold selectivity for dimeric PDE4D, compared to dimeric PDE4B [115]. Zatolmilast is currently being tested in multiple human clinical trials for Fragile X Syndrome. NCS 613 appears to have selectivity for PDE4C [119-121]. Conversely, A-33 is approximately 100-fold selective for PDE4B isoforms, compared to PDE4D isoforms [122], although the relative IC_{50} data on this compound has been reported only by a single group (It has yet to be shown that A-33 interacts with UCR1/UCR2, in addition to the catalytic domain, consistent with a true allosteric modulator, although its structure is compatible with such an interaction [115].). The compound FCPR16, and the related compound 4e, also have significant selectivity for PDE4B [123-125]. Orismilast also has modest, although possibly significant, selectivity for PDE4B [126]. KVA-D-88 is also about 6-fold selective for PDE4B [127]. Nerandomilast (previously known as BI101550) shows selectivity for PDE4B that is 9-fold, 24.8-fold, and 870-fold greater than for PDE4D, PDE4A, and PDE4C, respectively [128]. The IC_{50} data for nerandomilast were reported only for short PDE4 isoforms; i.e., lacking UCR1, so it is uncertain whether this compound is a competitive inhibitor or an allosteric modulator. Nerandomilast was recently reported to meet key endpoints in a Phase III human clinical trial for idiopathic pulmonary fibrosis (IPF). The allosteric activator described by Mironid selectively activates long PDE4 isoforms via its interaction with UCR1/2 [117]. Collectively, these drug discovery efforts provide evidence that targeting of UCR1/2, in addition, or instead of, the catalytic domain, has the potential to target PDE4 isoforms selectively, using any of the following criteria: long forms v short forms, dimeric v monomeric forms; PKA-activated v basal forms; or long isoforms encoded by a specific PDE4 gene v all long PDE4 isoforms. In addition, targeting UCR1/2 can mimic critical PDE4 regulatory events, such as PKA phosphorylation [117].

The impressive number of new compounds with activity against various PDE4 isoforms is testimony to the current high level of activity in this field, but it creates significant short-term difficulties in attempting any comparative analysis of these very different chemical entities. In the majority of cases, the pre-clinical aspects of each of these compounds has been studied only by a single, industry-led, group. The types of enzymatic and functional assays, and even the exact end-points of these assays, varies substantially among these groups. Much of this reflects differences in the intended clinical uses of these modulators, which varies substantially, as outlined above. Many of these compounds have yet to enter clinical trials for any indication, and the majority of the clinical trials that have been performed to date have been focused on non-CNS indications. This situation is likely to improve with time: further studies of these compounds in pre-clinical CNS models, and then in appropriately-designed clinical trials in disorders of memory and cognition, will clarify the value of each of these compounds in the future.

Conclusions

Current momentum in PDE4 research has been propelled by a dynamic interplay between the study of genetically-modified pre-clinical models and the development of pharmacologic agents that target specific PDE4 isoforms with novel mechanisms of action. There are obvious parallels between modifying the action of PDE4s by genetic means and by many of these novel agents. Future developments are highly likely to enhance the value of both genetic tools and drug discovery. They will also continue to validate PDE4 as an experimental and therapeutic focus. Given their diverse pharmacologic effects, and the results already obtained from the genetic models, it is entirely possible that some of the newer PDE4 compounds will have activity in a variety of human CNS disorders, including those of cognition, learning and memory.

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