

Advances in Neurobiology 17

Han-Ting Zhang
Ying Xu
James M. O'Donnell *Editors*

Phosphodiesterases: CNS Functions and Diseases

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Editors

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Foreword

The cyclic nucleotides, cAMP and cGMP, have long been known as important second messengers that can modulate a multitude of central nervous system (CNS) functions. It also has long been known that one of the most effective ways to regulate cyclic nucleotide tone in various compartments in the cell is to inhibit or activate the activity of one or more cyclic nucleotide phosphodiesterases (PDEs). In fact, many natural products that have as part of their function the ability to inhibit cAMP or cGMP PDE activity have been used as mood and disease ameliorating agents for centuries. Probably the best known of these is theophylline, a major component of tea.

We now know that eleven different gene families of PDEs exist, many of which contain several genes. In addition, most of these genes code for more than one mRNA by virtue of multiple start sites and/or alternative splicing events. In more recent years, our knowledge of the cellular and subcellular expression, localization, and functions of the various PDE variants has begun to be sorted out. Some are modified by myristyl, palmitoyl, or isoprenyl groups thereby altering their subcellular localization. Others bind to specific AKAPS (A Kinase Anchoring Proteins) that in turn can alter their subcellular localization. Still others bind to different scaffolding proteins. Ultimately, each cell type has evolved mechanisms to express a distinct subset of PDEs in discrete functional compartments in the cell. The aggregate effect of these expression patterns is to allow the PDEs to control the amplitude and duration of the cAMP and cGMP signals in specific regions of the cell. Ultimately these expression patterns work together to allow the cyclic nucleotide to coordinate the regulation of many different processes in the cell.

PDE localization and cyclic nucleotide coordination is particularly important in the CNS where different combinations of PDEs are expressed for example in the presynaptic space, while others are present in the postsynaptic area. Similarly, the PDEs that control the cyclic nucleotides in the vicinity of the nucleus are likely to be different than those in the vicinity of the Golgi, or ER, or mitochondria. Up to now, as can be seen in the various chapters of this book, most of our knowledge of PDE function in the brain is based on localization studies and empirical observations using PDE family-selective inhibitors or mice having targeted disruptions of

specific PDE subtypes. A few studies have started to explore in a non-biased manner the roles for specific combinations of different PDEs on specific functions in the cell (Golkowski et al., *Cellular Signaling* 28:764–778, 2016); however, for the most part these types of approaches have not yet taken place for CNS functions.

In this book, cutting-edge chapters by experts in the field explore what currently is known about many of the CNS functions postulated to be controlled by cyclic nucleotide PDEs. As mentioned most of these descriptions come from studies using family-selective PDE inhibitors or whole animal PDE knockout models. After an initial introduction on the cyclic nucleotide signaling circuitry and its implications for CNS function and disease, in Chap. 1, Neves-Zaph provides a detailed current view for PDE diversity in the CNS and the associated cAMP signaling networks. This is followed by an excellent chapter by Schulke and Brandon on the role(s) for PDE10A in the basal ganglia. This PDE has long been known to be highly expressed in this region of the brain and is thought to act largely as a cAMP-inhibited cGMP in these cells. Clinical trials for PDE10 inhibitors in several diseases including Huntington's disease, Schizophrenia, and Parkinson's disease are either in process or recently completed.

In Chap. 3, Hu, Pan, and Zhang discuss the possible interactions of cell division kinase 5 (CDK5) and PDE modulated cyclic nucleotide levels in CNS cell function and neuropsychiatric and neurodegenerative diseases. Interestingly, it was found recently in a phosphoproteomic study in another tissue that many different predicted CDK substrates were altered in response to PDE inhibitors (Golkowski et al., *Cellular Signaling* 28:764–778, 2016).

Rolipram, the prototype for PDE4 inhibitors, was originally developed as a possible antidepressant agent. Since that time our understanding of the multiple isozymes in this gene family has increased enormously. The next several chapters discuss the status of PDE4 inhibition on cognitive function and diseases. In Chap. 4, Bolger describes our current understanding for the role(s) of PDE4s in the regulation of depression and more recently their use as possible targets for memory enhancement and affective disorders. In the next chapter Clapcote discusses the possibilities for targeting the specific isozyme of PDE4, PDE4B, for treatment of cognitive impairment and possibly also obesity-related diseases. In Chap. 6, Heckman, Blokland, and Prickaerts discuss not only the possible roles for PDE4 inhibitors but also of PDEs 1 and 2 as a treatment for age-related cognitive decline, and in Chap. 7 Hansen and Zhang give their views on the role(s) of PDE4 in the same processes.

Chapter 8 by Kelly switches to a discussion of the possible role(s) of PDE11A in regulation of social function. This PDE will catalyze the hydrolysis of both cAMP and cGMP and is expressed widely in the brain.

Chapter 9 by Dörner-Ciossek, Kroker, and Rosenbrock changes the focus to cGMP and the cGMP-selective PDE, PDE9. The original localization studies of this PDE suggested a possible role in cognitive function and this aspect is discussed. It is thought that this PDE may be particularly important in controlling the downstream output of the nitric oxide (NO) signaling pathways, particularly at the synapse.

Chapter [10](#) by Padovan-Neto and West and Chap. [11](#) by Fusco and Paldino discuss the roles for PDEs in Parkinson's and Huntington's diseases, respectively. Parkinson's disease has been a target of PDE10 inhibitors and the results of recent trials are discussed in that chapter. PDE10 is highly implicated in DOPA function as it is most highly expressed in the striatum. The possible role(s) of PDE inhibitors as treatments for Huntington's disease are discussed largely in the context of PDE4, PDE5, and PDE10 inhibition.

Chapters [12](#), [13](#), and [14](#) discuss the roles of PDE inhibitors as modulators of psychiatric disorders. In Chap. [12](#), Zhang, Leuptow, Zhang, O'Donnell, and Xu give us more details on the possible roles of PDE2 in psychiatric and neurodegenerative disorders. This PDE is also called the cGMP-stimulated PDE by virtue of a high-affinity binding site on its N-terminal GAF domain. Its high expression in the limbic system has directed interest to its possible roles in these disorders. In Chap. [13](#), Wennogle, Hoxie, Peng, and Hendrick discuss in more detail the possible unique role for PDE1s in degenerative and cognitive function. PDE1s are activated by calcium and calmodulin. The authors also briefly discuss early clinical results with selective PDE1 inhibitors with regard to safety and function. In Chap. [14](#), Snyder and Vanover discuss their views on the roles for PDE inhibitors in the treatment of schizophrenia.

In Chap. [15](#), Wen, Liang, and Zhang discuss the targeting of PDEs for treatment of substance abuse. The roles for dopamine and cyclic nucleotide in the reward circuitry of the brain have made PDE inhibition a logical target for investigation in this area.

Finally, in Chap. [17](#), Wang and Ke discuss the crystal structures of PDEs in relation to the architecture of the binding pockets for substrate and inhibitors. Crystal structures for many of the PDE catalytic subunits with their selective PDE inhibitors have been solved and have provided much needed information on the physical basis for selectivity among PDE inhibitors. With the more recent realization that in order to see appreciable changes in function more than one PDE must be inhibited; this information will become even more crucial to our understanding of how to design selective PDE inhibitors on the basis of both their binding and functional effects.

Overall, this book provides a current up-to-date view of the status of research on the roles for cyclic nucleotide PDEs in CNS function and also the use of PDE isozyme selective inhibitors as approaches to treatment of several different CNS-mediated diseases. As expected, some approaches have proven more successful than others, but the current studies clearly set the stage for further advances in our understanding of CNS signaling and likely also in the treatment of CNS disorders.

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Preface

Phosphodiesterases (PDEs), a superfamily of enzymes catalyzing the hydrolysis of the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), have been studied for half a century. This area has been developed quickly during the recent two decades, particularly since the discovery of sildenafil (Viagra®), a selective PDE5 inhibitor, for treatment of male sexual dysfunction in 1998; additional PDE5 inhibitors were approved later (tadalafil, Cialis®; vardenafil, Levitra®). Other family-selective PDE inhibitors have been developed for clinical use since then, i.e., roflumilast (Daxas®) approved by the US FDA in 2011 for treating chronic obstructive pulmonary disease (COPD) and apremilast (Otezla®; 2014) for psoriasis and psoriatic arthritis; both are selective PDE4 inhibitors. Nevertheless, while many of the 11 PDE families are involved in the mediation of intracellular signaling in the central nervous system (CNS) and could be targets for CNS diseases, PDE inhibitors are not available yet for treating neurological or psychiatric conditions. This has been due to the difficulty of overcoming significant side effects (e.g., emesis for PDE4 inhibitors), challenges encountered in synthesizing promising inhibitors (e.g., inhibitors that are selective for a subtype within a PDE family), and an incomplete understanding of the role of the various PDEs in cellular function in the brain. Therefore, it is necessary and important to understand the roles of PDEs in CNS functions, CNS diseases, and the utility of novel PDE inhibitors. To address this, we have published a special issue entitled “Targeting Phosphodiesterases (PDEs) for Treatment of CNS Diseases” in *Current Pharmaceutical Design* (Volume 21, Issue 3, 2015); the review articles have received relatively high citations since publication. We decided to publish a book focusing on the similar topic in order to have comprehensive discussions from experts with a broad expertise in PDE research. The purpose of this book is to characterize the contributions of PDEs to brain functions and identify PDEs and their isoforms as potential targets for treatment of CNS diseases, including psychiatric diseases such as depression, anxiety, and schizophrenia, and neurodegenerative diseases such as Alzheimer’s disease, Huntington’s disease, and Parkinson’s disease, as well as other CNS disorders such as stroke, alcoholism, and drug abuse.

We are very grateful to the authors, who are internationally recognized experts in the PDE research area, for their contributions of excellent chapters, which cover almost all aspects of the CNS diseases described above. We sincerely appreciate the efforts of the reviewers who made many helpful suggestions to improve the book. We gratefully acknowledge Linda Nguyen and Yongxu Huang for their assistance in editing the manuscripts. We know that, despite the hard work of the dedicated team, it is inevitable to miss some points, papers, and any issues related to the subject of this book. Any feedback from readers would be appreciated and important for improving our next edition.

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About the Editors



Han-Ting Zhang received his M.D. from Southern Medical University (formerly the First Military Medical University) in Guangzhou and M.S. and Ph.D. of pharmacology from Beijing Institute of Pharmacology and Toxicology, the Military Academy of Medical Sciences, China, in 1995. He worked as a postdoctoral fellow at Louisiana State University Health Sciences Center in 1998 and then at the University of Tennessee Health Science Center in 2000. In 2005, Dr. Zhang joined the Departments of Behavioral Medicine and Psychiatry and Physiology and Pharmacology as a faculty at West Virginia University School of Medicine, Morgantown,

WV, USA. He has been a tenured associate professor there since 2012. Dr. Zhang is also a “Taishan scholar” overseas distinguished expert and professor of pharmacology at Taishan Medical University (adjunct), China.

Dr. Zhang’s major research interests focus on intracellular signaling in the mediation of neurodegenerative and psychiatric disorders. More specifically, he is interested in exploring the roles of phosphodiesterase (PDE)-mediated cyclic nucleotide (cAMP, cGMP) signaling in depression, anxiety, alcohol dependence, drug abuse, and cognition deficits associated with neurodegenerative disorders such as Alzheimer disease. Development of novel drugs for treating these disorders is also one of his research foci.

Dr. Zhang has published more than 80 research papers and review articles and 18 book chapters, most of which focuses on PDEs, in particular the PDE4 enzyme family. He has been awarded the NARSAD Young Investigator Award twice (2006 and 2008). Dr. Zhang has been served as the guest chief editor of *Current Pharmaceutical Design* and currently serves as the deputy chief editor/associate editor for *Metabolic Brain Disease*, *Frontiers in Pharmacology*, *Frontiers in Aging Neuroscience*, *Translational Neuroscience Review*, *eNeuroscience*, and *Austin Psychiatry* and editorial board member for *Scientific Reports* and several other international journals.



Ying Xu received her Ph.D. degree from Peking University in 2006. She has been a research assistant professor in the School of Pharmacy and Pharmaceutical Sciences at the State University of New York at Buffalo since 2013. Dr. Xu has long been working in drug discovery focusing on treatment of neuropsychiatric disorders. Her research includes the effects and molecular mechanism of natural polyphenols and target synthetic drugs on neurodegenerative and psychiatric disorders, such as age-related cognitive disorders, depression, anxiety, and neuropathic pain. Her recent work has focused on development of small molecule drugs, particularly phosphodiesterase-2 and phosphodiesterase-9 inhibitors, on central nervous system disorders.

Dr. Xu was the winner of the 2015 New Investigator Award (NIA) in the American Association of Colleges of Pharmacy. She is serving for seven peer-reviewed journals as an editorial board member and serving as the deputy chief editor or associate editor for *Metabolic Brain Disease* and *Frontiers in Aging Neuroscience*. Dr. Xu published more than 60 peer-reviewed research papers, reviews, and book chapters.



James M. O'Donnell received his B.S. in psychology from Carnegie Mellon University and Ph.D. in pharmacological and physiological sciences from the University of Chicago; he completed postdoctoral training in neuropsychopharmacology at the University of Pennsylvania. He was appointed the 11th dean of the University at Buffalo School of Pharmacy and Pharmaceutical Sciences in 2013, where he also holds academic appointments as professor of pharmaceutical sciences and professor of pharmacology and toxicology (adjunct). Previously, he held research or faculty positions at Los Alamos National Laboratory, Louisiana State University,

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Dr. O'Donnell's research has focused on the relationship between the neurochemical and behavioral effects of drugs, primarily those used to treat neuropsychiatric illnesses. This work has been supported by the NIH, primarily the National Institute of Mental Health, and has involved collaborations with scientists at other universities and biotech and pharmaceutical companies. He has been active in teaching professional and graduate students in the areas of pharmacology and neuroscience and served as director of an NIGMS-supported, T32 predoctoral training grant at the interface of behavioral and biomedical sciences.

He has served on NIH review panels in the neuroscience and drug discovery areas, including as founding chair of the Pathophysiological Basis of Mental

Disorders and Addictions study section, and is associate editor for the Journal of Pharmacology and Experimental Therapeutics. He is a member of a number of scientific and professional societies, was elected fellow of the American College of Neuropsychopharmacology and the American Association for the Advancement of Science, and cochaired the Gordon Research Conference on Cyclic Nucleotide Phosphodiesterases.

Part I
PDEs and Signaling, Circuitry, and
Implications of CNS Functions and
Disorders

Chapter 1

Phosphodiesterase Diversity and Signal Processing Within cAMP Signaling Networks

Susana R. Neves-Zaph

Abstract A large number of neuromodulators activate G-protein coupled receptors (GPCRs) and mediate their cellular actions via the regulation of intracellular cAMP, the small highly diffusible second messenger. In fact, in the same neuron several different GPCRs can regulate cAMP with seemingly identical timecourses that give rise to distinct signaling outcomes, suggesting that cAMP does not have equivalent access to all its downstream effectors and may exist within defined intracellular pools or domains. cAMP compartmentalization is the process that allows the neuron to differentially interpret these various intracellular cAMP signals into cellular response. The molecular mechanisms that give rise to cAMP compartmentalization are not fully understood, but it is thought that phosphodiesterases (PDEs), the enzymes that degrade cAMP, significantly contribute to this process. PDEs, as the sole mechanism of signal termination for cAMP, hold great promise as therapeutic targets for pathologies that are due to the dysregulation of intracellular cAMP signaling. Due to their diverse catalytic activity, regulation and localization each PDE subtype expressed in a given neuron may have a distinct role on downstream signaling.

Keywords cAMP • Protein kinase A • Phosphodiesterase • PDE • GluA1 • AMPAR trafficking

1.1 Introduction

Cyclic adenosine monophosphate (cAMP), the classical second messenger, is a critical intracellular mediator of the actions of most neuromodulators in the brain. The original studies that elucidated classical cAMP signaling described it as a straightforward linear pathway, where neuromodulator-activated G-protein coupled receptors (GPCRs) activate membrane adenylyl cyclases (ACs) inducing the synthesis of cAMP. This increase

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in cAMP activates cAMP-dependent protein kinase (PKA) leading to a series of phosphorylation events that result in the regulation of ion channels, enzymes, and changes in transcriptional and translational activities. The termination of the signal is due to the activity of 3'-5' cyclic nucleotide phosphodiesterases (PDEs), enzymes that degrade cAMP into 5'AMP.

Studies in the last 20 years have highlighted the underappreciated complexity of this once considered simple signaling pathway. First, PKA is not the sole direct effector of cAMP. Additional cAMP targets, such as Exchange Protein Activated by Cyclic AMP (EPACs, guanine nucleotide exchange proteins that activate small GTPases Rap1 and Rap2), and cyclic nucleotide gated channels have been identified and are also involved in relaying cAMP downstream action into cellular outcomes. Additionally, the abundance of highly regulated isoforms responsible for the production and degradation of cAMP further complicates the picture. There are nine genes coding for G-protein activated ACs, with variants expressed from each gene. The large number of possible cyclase isoforms pales in comparison with the vast multiplicity of PDE isoforms identified so far. The PDE superfamily consists of 11 gene families, with most families containing several genes giving rise to a total of 21 coding PDE genes and potentially generating close to 100 isoforms variants. These variants display diverse enzymatic characteristics, regulation and localization, and any given cell may express tens of these different isozymes, creating a cell type-specific cAMP processing profile.

PDEs have garnered a tremendous amount of attention due to their role as the exclusive degradation activity for cyclic nucleotides. Several studies using specific pharmacological inhibitors and genetic ablation approaches have identified PDEs as key contributors to normal neuronal function. Despite all this, the identity of downstream signaling controlled by each PDE isoform is still poorly understood. The fundamental questions that remain are: if all PDEs have the same termination role in cAMP signaling, why is there such a large number of distinct PDEs expressed in a given neuron? And what is the identity of the intracellular signaling derived from the cAMP pool controlled by each of these PDEs? In this chapter we will review how the diversity of PDEs found in neurons contributes to the fine tuning the amplitude and duration of cAMP signaling, and how regulation of these activities can further modulate cAMP processing in neurons.

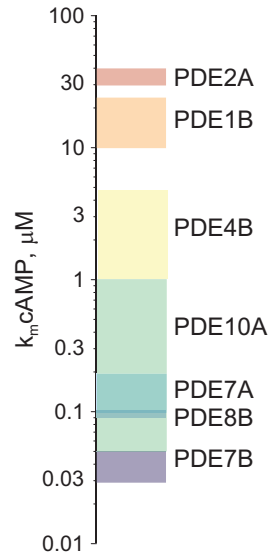
1.2 The Range of Kinetic Characteristics of PDE Isoforms Fine-Tunes cAMP Levels

A great deal of attention is paid to the expression level of each PDE in specific neuron types or brain regions. Yet, in order to gauge the actual contribution of these enzymes in cAMP signaling other factors must also be taken into account, such as their affinity and catalytic activity for cAMP, as these kinetic features can range widely for each PDE family. For instance, a PDE with modest cellular expression but possessing high affinity and catalytic activity may have a substantial role in cAMP dynamics. These enzymes act on a substrate whose levels are dynamically

regulated as cellular cAMP levels can vary up to 100-fold upon receptor-mediated cyclase stimulation. At rest, most neurons exhibit cAMP levels in the low to mid nanomolar range and receptor activation of cyclases increases cAMP levels up to micromolar range, with the specific cAMP cellular concentrations dependent on the identity of ACs/PDEs expressed, and GPCRs activated (Bacskai et al. 1993; Mironov et al. 2009). Additionally, cAMP is not homogenously distributed throughout the neuron, leading to the possibility that not all PDEs have equal access to their substrate (Bacskai et al. 1993; Li et al. 2015; Neves et al. 2008). The nonlinear nature of all these factors makes it challenging to intuit the contribution of each PDE to cyclic nucleotide homeostasis and signaling.

Neurons express a multitude of PDEs, and each PDEs may have a precise role depending on the signaling status of the cell and the resulting cellular levels of cAMP. For instance, medium spiny neurons (MSNs), the principal neurons of the striatum that receive dopaminergic stimulation express several PDE activities with a wide range of kinetic properties. MSNs are particularly enriched in PDE1B, PDE2A, PDE4B, PDE7A/B, PDE8B and PDE10A (Heiman et al. 2008; Kelly et al. 2014; Stephenson et al. 2012; Erneux et al. 1981; Martins et al. 1982; Repaske et al. 1993; Van Staveren et al. 2003). To illustrate the diverse kinetic profile of the PDEs expressed, the Michaelis Menten constant (K_m) value for cAMP for each MSN-expressed PDE is plotted in Fig. 1.1. It is striking that all these MSNs-expressed PDE subtypes cover three orders of magnitude of cAMP levels, with PDEs displaying high affinity (PDE7A/B, PDE8A and PDE10A), mid-affinity (PDE4B) or lower affinity (PDE1B and PDE2A) for cAMP degradation. Based solely on these K_m values, it is easier to appreciate how each PDE activity may have a distinct function during the induction and maintenance of basal and receptor-mediated cAMP levels. The high affinity PDEs may be maximally active even during basal conditions to

Fig. 1.1 PDEs enriched in MSNs display a wide range of affinities for cAMP. Michaelis Menten constant (K_m) for each PDE gene variant. Each box depicts the range of experimental K_m values reported in the literature for the various isoforms of each gene



regulate the basal tone of cAMP. Whereas the lower affinity PDEs may be responsible for the amplitude and duration of the receptor activated cAMP levels. To further illustrate this complexity, we explore the relationship between varying cAMP levels due to different cellular states (basal and DA stimulation), and the kinetic properties of PDEs on downstream cAMP signaling by employing an ordinary differential equations (ODEs)-based model of a simplified cAMP signaling scheme (Fig. 1.2a). The percent contribution of each PDE subtype for the degradation of cAMP dramatically changes with increasing cAMP levels due to dopamine stimulation (Fig. 1.2b). At low DA concentrations, the main PDE acting on cAMP is PDE10A, accounting for 80% of all degradation activity. These simulations results are in agreement with reported contributions of PDEs in MSNs. In MSNs, PDE10A accounted for the majority of the degradation activity acting on basal cAMP (Russwurm et al. 2015). Additionally, inhibition of PDE10A activity has a more robust effect on MSNs expressing D2 (Gi-coupled—dopamine receptor) than in D1-MSNs, suggesting that this high affinity PDE may have more significant role in neurons that display a decreased basal cAMP tone (Polito et al. 2015). As dopamine concentration is increased, cAMP levels rise to the high nanomolar/low micromolar range and the contribution of PDE4B becomes more prominent (Fig. 1.2b). At supersaturating concentrations of dopamine, cAMP levels accumulate to the micromolar range and the activity of PDE2 predominates. The kinetic characteristics of PDEs must be taken under consideration when testing the contribution of

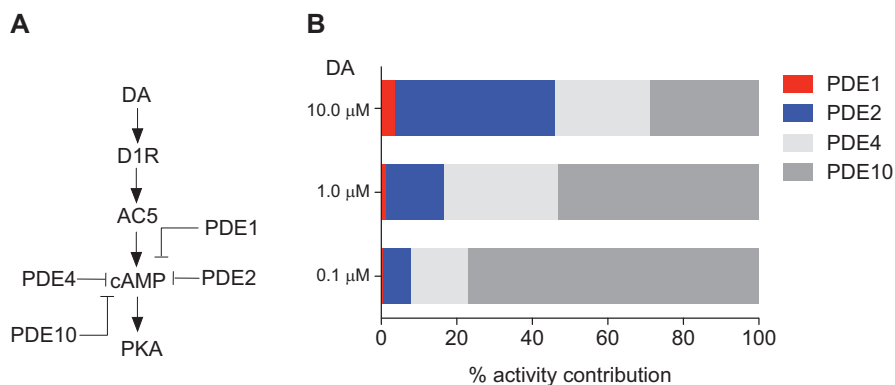


Fig. 1.2 The contribution of each PDE to cAMP levels is dependent on cellular state. **(a)** The model is based on our work (Song et al. 2013) and contains a depiction of dopamine-induced cAMP signaling in MSNs including: dopamine D1-receptor mediated activation of AC5, PKA activation, and detailed representations of cAMP degradation activities by PDE1B, PDE2A, PDE4B, and PDE10A with their appropriate reported kinetic parameters. For illustration purposes, the assumption is that these four PDE activities have access to the same local cAMP pool. PDE7 and PDE8 were not included for clarity sake as they cover the same cAMP range as PDE10A. To simplify the interpretation of the simulations, the initial concentrations of each PDE was kept equimolar, and total PDE concentration was constrain to achieve the reported basal and receptor activated cAMP levels in neurons. **(b)** integral of the velocity of each PDE reaction plotted as percent of each PDE subtype over total PDE activity of the simulation

each PDE. For instance, inhibiting a low affinity PDE under basal conditions may not produce a change in cAMP signaling reflective of the true intracellular role of such PDE. Thus, the strength of the extracellular stimuli and the catalytic activity of the defined PDEs are variables that must be taken into consideration when interpreting the function of each PDEs in downstream signaling.

1.3 Regulation of PDEs Activities Expands Their Catalytic Capabilities to Allow Rapid Signal Modulation and Integration

PDE activities are modulated by a number of regulatory mechanisms that allow the rapid and transient control of the intensity of cAMP signaling. These regulatory mechanisms may also be points of intracellular signaling integration, where modulation of the activity of PDEs may result in redirection of signals between different downstream targets. The PDE superfamily displays a variety of mechanisms that result in dynamic activity control such as allosteric binding by cyclic nucleotides, competitive inhibition and post-translational modifications (Leroy et al. 1996; Noyama and Maekawa 2003; Omori and Kotera 2007). An example of allosteric regulation of a PDE is the activation of PDE2A by cGMP. This allosteric regulation occurs due to cGMP binding to GAF-domain present in the N-terminus of PDE2A isoforms, resulting in a conformational change that enhances substrate access to the catalytic site (Martinez et al. 2002; Martins et al. 1982; Noyama and Maekawa 2003; Pandit et al. 2009; Rosman et al. 1997). This regulation results in significant degradation of cellular cAMP levels upon increases in cGMP in MSNs and has functional consequences to downstream targets (Lin et al. 2010; Polito et al. 2013; Wykes et al. 2002). Additionally, this type of cGMP regulation of cAMP levels may result in significant crosstalk interactions between PDEs, where inhibiting the activity of a PDE with cGMP activity may result in the unintended regulation of PDE2 activity (Zhao et al. 2015; Zhao et al. 2016).

The best-characterized example of PDE activity regulation by phosphorylation is observed in the PDE4 family as certain isoforms are regulated by a number of kinases (Mika and Conti 2016). Isoforms that contain the two conserved N-terminal regions, called “upstream conserved-regions” (UCR1 and UCR2), are classified as long isoforms and can form autoinhibitory domains that control PDE4 oligomerization and enzymatic activity (Cedervall et al. 2015; Xie et al. 2014). It is thought that phosphorylation events within the interface of these domains modulate their stability and can result in activation (enhanced degradation of cAMP) or inactivation (diminished degradation of cAMP) (Bender and Beavo 2006; Conti et al. 2003; Richter and Conti 2002). For instance, PDE4 activity can be regulated acutely by PKA phosphorylation within the UCR1 region, inducing conformational changes that increase PDE4 activity above basal levels (Lim et al. 1999). This PKA-phosphorylation is conserved in all PDE4 long isoforms and results in a twofold enhancement of degradation activity (Hoffmann et al. 1999; Sette and Conti 1996). It is believed that this regulation creates

a negative feedback loop mechanism that results in signal attenuation or termination of cAMP signaling (Fig. 1.3). A number of other protein kinases can also stimulate the phosphorylation of PDE4 resulting in the bidirectional control of the degradation of cAMP, making PDE4 a key node of signaling crosstalk. For instance, regulation of PDE4 activity by ERK phosphorylation results in a reduction of degradation activity (Hoffmann et al. 1999). Simultaneous phosphorylation by PKA, cancels the inhibitory effect of ERK regulation, returning activity to basal levels. More recently the identification of Cdk5 and CaMKII as additional regulators of PDE4 activity have highlighted the central role PDE4 in the integration of cAMP/Ca²⁺ signaling (Mika et al. 2015; Plattner et al. 2015). In particular, in D1-expressing MSNs Cdk5 can synergize with PKA activity to fully potentiate PDE4 hydrolytic activity (Plattner et al. 2015). Cdk5 phosphorylation of PDE4 induces a modest increase in basal activity, but in combination with PKA phosphorylation there is a 2.5-fold increase in cAMP degradation capability. Thus, these phosphorylation events can regulate the directionality and magnitude of PDE4 activity and dramatically modulate downstream signaling (Fig. 1.3).

Despite the extensive insight into the regulation of PDE4 activity, the identity of the intracellular signaling derived from the cAMP domain controlled by each PDE4 isoform is still limited. GluA1, a subunit of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), is a target of PDE4-regulated PKA activity (Nishi et al. 2008; Song et al. 2013). This phosphorylation event is of particular importance for AMPAR trafficking, as PKA phosphorylation of S845 promotes AMPAR membrane insertion at extra-synaptic and peri-synaptic sites, and primes GluA1-containing AMPAR for synaptic insertion (Esteban et al. 2003; Serulle et al. 2007; Snyder et al. 2000). DARPP32, a highly enriched striatal protein that is also a major target of PDE4-regulated PKA (Nishi et al. 2008), is a potent inhibitor of protein phosphatase-1 (PP1) when phosphorylated at T32 DARPP32 (Hemmings et al. 1984; Ouimet et al. 1984; Svenningsson et al. 2004). PP1 dephosphorylation of Ser845 induces the endocytosis of GluA1 (Shen et al. 1999; Snyder et al. 2000). Therefore, the balance between PKA and PP1 activities determines the phosphorylation state of AMPAR, and is tightly coupled to the dendritic levels of cAMP and the activity of PDEs.

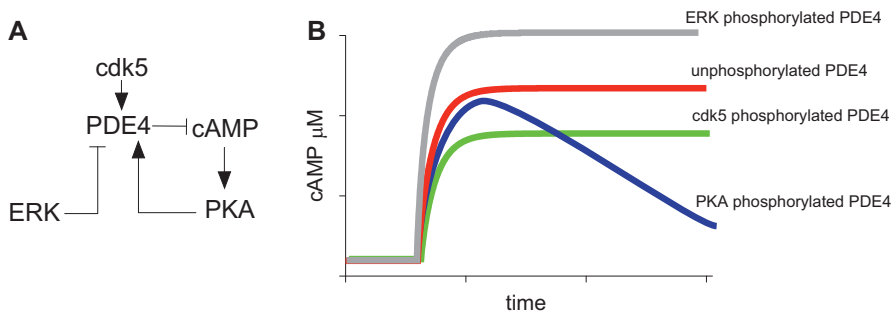


Fig. 1.3 Acute regulation of PDE4 activity by phosphorylation produces diverse cAMP dynamics. (a) PDE4 activity is regulated by a number of kinases. (b) The phosphorylation of PDE4 results in distinct cAMP dynamics

We have studied the role of PDE4 and its regulation by ERK on dopamine-induced AMPAR trafficking in MSNs. Dopamine stimulation increases active ERK levels resulting in the phosphorylation and inhibition of PDE4 (Song et al. 2013). We found that ERK, by inhibiting PDE4 activity, amplifies dopamine-induced GluA1 phosphorylation, and GluA1 membrane insertion by altering the balance between PKA and PP1, as the ERK mediated increase in PKA-phosphorylation of DARPP32 prevents PP1 from dephosphorylating GluA1. Blocking this ERK-mediated regulation of PDE4 activity results in a decrease in cAMP levels, GluA1-S845 and DARPP32-T34 phosphorylation. This leads to a robust decrease in GluA1-containing AMPAR surface expression. Conversely, co-treatment of dopamine and brain-derived neurotrophic factor, a neurotrophin that activates ERK independently of cAMP, enhances ERK-phosphorylation of PDE4, resulting in an increase of GluA1 phosphorylation, and GluA1 insertion by tipping the PKA/PP1 balance in favor of PKA. It is possible that other stimuli that activate ERK, such as Ca^{++} -activated Ras, may modulate PDE4 activity and result in GluA1 trafficking changes, making PDE4 a point of integration for AMPAR trafficking regulation. Similarly, cdk5 regulation of PDE4 also resulted in significant decrease in cAMP signaling. Inhibition of cdk5 induces an increase in the PKA-mediated phosphorylation of DARPP32 at T32, and GluA1 at S845. Interestingly, one must note that cdk5 also directly phosphorylates DARPP32 at T75, resulting in a form of DARPP32 that is inhibitory to PKA. Thus cdk5 mediates the phosphorylation and activation of PDE4, along with the simultaneous phosphorylation of DARPP32 to inhibit PKA, resulting in the synergistic dampening of cAMP signaling. Whether this regulation of PDE4 by cdk5 also affects surface expression of GluA1 remains to be confirmed.

1.4 The Diversity of PDE Subcellular Localizations Promotes Signal Specificity

Different GPCRs expressed in the same neuron can increase cAMP with similar temporal dynamics, but resulting in distinct cellular outcomes, raising the question of how the cell differentially decodes signals from these receptors. This concept, called cAMP compartmentalization where gradients of the second messenger are localized within defined domains that are functionally distinct, remains poorly understood. The advent of novel imaging technologies has allowed the examination of the non-homogenous nature of cAMP signaling in neurons (Bacskai et al. 1993; Li et al. 2015; Neves et al. 2008). Since the intracellular diffusion of cAMP is fast, studies have focused on determining the mechanisms that permit cAMP to accumulate within these domains to target downstream signaling with high specificity (Saucerman et al. 2014). There is some evidence that physical constraints, such as cell shape, can affect cAMP diffusion and may play a role in cAMP compartmentalization. In fact, neurons display significantly higher concentration of cAMP in dendrites versus cell body, pointing to surface-to-volume ratio-driven accumulation of cAMP (Bacskai et al. 1993; Li et al. 2015; Neves et al. 2008). It is thought that since

dendrites are high surface to volume ratio regions, cAMP accumulates due to the mostly plasma membrane location of cyclases (surface), and the predominant cytoplasmic localization of PDEs (volume) (Neves et al. 2008). Also, in these regions diffusion of cAMP may be hindered, further promoting accumulation of cAMP (Meyers et al. 2006).

PDEs also significantly play a role in the formation and maintenance of cAMP compartmentalization to ensure precise spatial and temporal signal propagation to downstream effectors (Perino et al. 2012, Sample et al. 2012; Taylor et al. 2013; Tsvetanova and von Zastrow 2014). Although the precise manner by which PDEs contribute to compartmentalization is still a matter of debate, there is strong evidence that points to PDEs acting as enzymatic barriers. This is supported by the observation that irrespective of cell type, inhibition of PDEs results in an increase in the spatial range of cAMP signaling (Zaccolo and Pozzan 2002; Neves et al. 2008). Two possible barrier-mechanisms have been proposed to explain such data (reviewed in Conti et al. 2014): (1) PDEs function to keep cAMP from leaving signaling compartments; or (2) PDEs maintain cAMP to minimal levels within subdomains to prevent activation of downstream signaling (Terrin et al. 2006).

PDEs exhibit a wide range of subcellular locations that may contribute to their role in cAMP compartmentalization, with many displaying signal-driven translocations and interactions with macromolecular complexes. Thus, even low expressing PDEs targeted to the appropriate location may play a significant role in downstream signaling. In this context, subcellular localization of PDEs adds an additional layer of complexity to cAMP cellular action by directing a degradation activity to specific location of downstream effectors. Thus, not only will each PDE isoform act on specific ranges of cellular cAMP concentration but also at a defined location, and only affecting a subset of PKA or EPAC activities.

PDEs employ various localization mechanisms, and this very much depends on isoform identity as even splice variants derived from the same PDE gene may utilize diverse subcellular targeting strategies. For instance PDE2A1 is cytosolic, while splice variant PDE2A3 contains myristoylation sites in its N-terminal region that allow association with synaptic membrane regions, whereas PDE2A2 associates directly with the plasma membrane via a hydrophobic motif (Russwurm et al. 2009; Yang et al. 1994). A great number of PDEs exhibit specific subcellular targeting by interacting with scaffolds. In particular, members of the PDE4, PDE7 and PDE10 families interact with scaffolds to bring them in close proximity to other signaling intermediates, such as protein kinases, protein phosphatases, and GTPases allowing further means of efficient crosstalk and downstream regulation. Several members of the A Kinase Anchoring Proteins (AKAP) scaffold family bind to both PKA and PDEs (Carlisle Michel et al. 2004; Dodge et al. 2001; Terrenoire et al. 2009). Moreover, some interactions with scaffolds can be dynamic and signal-driven, as seen with the interaction of PDE10A with AKAP150. PDE10A is enriched in membranes of spines and dendrites and found mostly palmitoylated and in association with AKAP150 (Charych et al. 2010; Kotera et al. 2004; Xie et al. 2006). Upon PKA phosphorylation of PDE10A, the affinity of PDE10A for AKAP150 is reduced, promoting its dissociation from the AKAP150 complex (Russwurm et al. 2015).

Unlike PKA phosphorylation of PDE4, PDE10 phosphorylation by PKA has no effect on its catalytic activity. Hence, this additional spatial dimension to PDEs places their specific range of catalytic activity within a local cAMP pool and neighboring downstream effectors.

1.5 Conclusions

The contribution of each PDE isoform to cAMP signaling is context specific: the role of a PDE under basal conditions may be significantly different than in receptor activated conditions due to their kinetic properties. Regulation of PDE activity and localization demonstrate the complex series of controls that serve not only to tune the intensity of local cAMP signaling but also how this signaling can be effectively funneled to different downstream intracellular targets.

Significant advances in cyclic nucleotide imaging have started to elucidate the spatial aspect of cAMP signaling controlled by PDEs. However, much work remains to be done. Although the identity of local cAMP functional domains controlled by PDEs can be discerned by monitoring downstream signaling, current experimental methods lack the resolution to image these domains raising into question their nature. Computational studies have also provided mechanistic detail into the role of PDEs in cAMP signaling and highlighted their significant potential for signaling integration across time and space.

Understanding the diversity of cellular PDEs may provide novel mechanistic insight into designing therapeutic strategies for psychiatric disorders involving dopaminergic dysregulation, such as drug addiction, Parkinson's disease and schizophrenia.

Conflict of Interest The author declares no conflicts of interest.

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