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Forum Minireview

Advanced Research on Dopamine Signaling to Develop Drugs for the Treatment of Mental Disorders: Biochemical and Behavioral Profiles of Phosphodiesterase Inhibition in Dopaminergic Neurotransmission

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Abstract. Dopamine plays a central role in the regulation of psychomotor functions. The effect of dopamine is largely mediated through the cAMP/PKA signaling cascade and therefore controlled by phosphodiesterases (PDEs). Multiple PDEs with different substrate specificities and subcellular localization are expressed in the striatum, and the functional roles of PDE10A, PDE4, and PDE1B are extensively studied. Biochemical and behavioral profiles of PDE inhibition by selective inhibitors and/or genetic deletion related to dopaminergic neurotransmission are compared among those PDEs. The inhibition of PDE up-regulates cAMP/PKA signaling in three neuronal subtypes, resulting in the stimulation of dopamine synthesis at dopaminergic terminals, the inhibition of dopamine D_2–receptor signaling in striatopallidal neurons, and the stimulation of dopamine D_1–receptor signaling in striatonigral neurons. Predominant roles of PDE families or isoforms are implicated in each neuronal subtype: PDE4 at dopaminergic terminals, PDE10A and PDE4 in striatopallidal neurons, and PDE1B in striatonigral neurons. PDE10A and PDE4 inhibition may exhibit D_2 antagonist–like, antipsychotic effects, whereas PDE1B inhibition may exhibit D_1 agonist–like effects in the striatum. Development of PDE isoform–specific inhibitors is essential for better understanding of the function of each PDE isoform and treatment of neuropsychiatric disorders.

Keywords: cAMP, DARPP-32, dopamine, phosphorylation, striatum

1. Introduction

Dopamine plays a central role in the regulation of psychomotor functions. The cAMP/PKA signaling cascade is essential for dopamine neurotransmission. Dopamine, acting on D_1 receptors, stimulates cAMP/PKA signaling via $G_{s/olf}$-mediated activation of adenylyl cyclase (1), whereas dopamine, acting on D_2 receptors, inhibits cAMP/PKA signaling via G_i-mediated inactivation of adenylyl cyclase (2). At presynaptic dopaminergic terminals, the synthesis of dopamine by tyrosine hydroxylase (TH) (3, 4) and the release of dopamine (5, 6) are also regulated by the cAMP/PKA signaling cascade. Activity of cAMP/PKA signaling is determined by the balance of synthesis and degradation of cAMP. Regulation of cAMP synthesis by dopamine and other neurotransmitter receptors has been extensively studied. In spite of the importance of cAMP degradation by phosphodiesterases (PDEs), the precise roles of each PDE isoform in dopaminergic signaling are not fully understood, due to the diversity of PDE families and isoforms expressed in the striatum and the complexity of their regulation.

PDEs are encoded by 21 genes and subdivided into 11 families (PDE1 – PDE11) according to structural and functional properties (7). Furthermore, many PDE isoform variants are produced by alternative splicing. The brain expression and subcellular localization of PDE

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isoforms are tightly regulated. Multiple PDEs are expressed in neurons, and each PDE plays specific roles in cAMP and cGMP signaling, which are determined by substrate specificities (cAMP and/or cGMP), regulatory factors (e.g., activation or inhibition by cAMP or cGMP, activation by calcium/calmodulin, and regulation by phosphorylation), and subcellular localization (cytosolic or membrane-bound). Several PDE families are expressed in the striatum. PDE10A, PDE1B, and PDE7B are enriched in the striatum, and PDE4 (A, B, and D isoforms), PDE2A, and PDE9A, which are widely distributed in the brain, are also expressed in the striatum (8, 9). These PDEs interact with dopamine systems and modulate dopamine-mediated behaviors.

2. DARPP-32: a mediator of cAMP/PKA-dependent signals

Dopamine, acting on D_1 and D_2 receptors, modulates cAMP/PKA signaling. In postsynaptic striatal neurons, DARPP-32, a dopamine- and cAMP-regulated phosphoprotein of M_r = 32 kDa, is a major target for the cAMP/PKA signaling cascade (10, 11). DARPP-32 is expressed in both D_1 receptor–enriched striatonigral and D_2 receptor–enriched striatopallidal neurons (12). Phosphorylation at Thr34 by PKA converts DARPP-32 into a potent inhibitor of the wide-spectrum protein phosphatase-1 (PP-1). The inhibition of PP-1 thereby controls the phosphorylation state and activity of many downstream physiological effectors, including various neurotransmitter receptors and voltage-gated ion channels. Mice lacking DARPP-32 are deficient in their molecular, electrophysiological, and behavioral responses to dopamine, drugs of abuse, and antipsychotic medication, indicating an essential role for DARPP-32 in dopaminergic signaling (13). In addition, by analyzing DARPP-32 phosphorylation at Thr34 (PKA-site) in slices and in vivo, we can evaluate the activity of PKA with high specificity and sensitivity. For determination of activity of cAMP/PKA signaling, analysis of DARPP-32 phosphorylation at Thr34 is more sensitive than measurement of cAMP because DARPP-32 is present in medium spiny neurons where activity of cAMP/PKA signaling is modulated by dopamine. The changes in PKA activity induced by PDE inhibitors are reflected on the phosphorylation state of DARPP-32 at Thr34.

3. Role of PDEs in direct and indirect pathway neurons

The inhibitory outputs from the basal ganglia (GPi/SNpr) are regulated by striatonigral/direct pathway and striatopallidal/indirect pathway neurons in the striatum (14, 15) (see Fig. 1). Direct pathway neurons inhibit GPi/SNpr neurons (dis-inhibition of output) and therefore activate thalamocortical motor circuits, whereas indirect pathway neurons activate GPi/SNpr neurons (pro-inhibition of output) and therefore inhibit thalamocortical motor circuits. Corticostriatal glutamatergic projections activate both direct and indirect pathway neurons. Nigrostriatal dopaminergic projections induce opposite effects on direct and indirect pathway neurons. D_1 receptors preferentially expressed in direct pathway neurons activate cAMP/PKA signaling and potentiate glutamate-induced excitation of direct pathway neurons. In contrast, D_2 receptors preferentially expressed in indirect pathway neurons inhibit cAMP/PKA signaling and counteract glutamate-induced excitation of indirect pathway neurons. Segregation of D_1 and D_2 receptors in direct and indirect pathway neurons, respectively, is strongly supported by recent studies using bacterial artificial chromosome (BAC) transgenic mice, in which the expression of EGFP, Flag- or Myc-tagged DARPP-32, or EGFP-tagged ribosome is driven by D_1- or D_2-receptor promoters (12, 16, 17). Thus, activation of D_1 and D_2 receptors by dopamine cooperatively leads to activation of thalamocortical motor circuits by potentiating dis-inhibition and attenuating pro-inhibition, respectively.

Several types of PDEs such as PDE10A, PDE4, and PDE1B are expressed in direct and indirect pathway neurons. The inhibition of PDEs can result in activation of cAMP/PKA signaling both in direct and indirect pathway neurons. If the function of the PDE (e.g., PDE10A and PDE4) is predominant in indirect pathway neurons, the inhibition of the PDE and activation of cAMP/PKA signaling results in activation of indirect pathway neurons, leading to the inhibition of thalamocortical motor circuits. Conversely, if the function of the PDE (e.g., PDE1B) is predominant in direct pathway neurons, the inhibition of the PDE and activation of cAMP/PKA signaling results in activation of direct pathway neurons, leading to the activation of thalamocortical motor circuits. Thus, PDE inhibitors that predominantly act in indirect pathway neurons work like dopamine D_2–receptor antagonists and inhibit motor function, whereas PDE inhibitors that predominantly act in direct pathway neurons work like dopamine D_1–receptor agonists and activate motor function. The balance of action of each PDE inhibitor in indirect and direct pathway neurons determines the behavioral effects.

4. Role of PDE10A in dopaminergic neurotransmission

PDE10A is a dual substrate PDE that hydrolyzes both cAMP and cGMP, and it has a higher affinity for cAMP

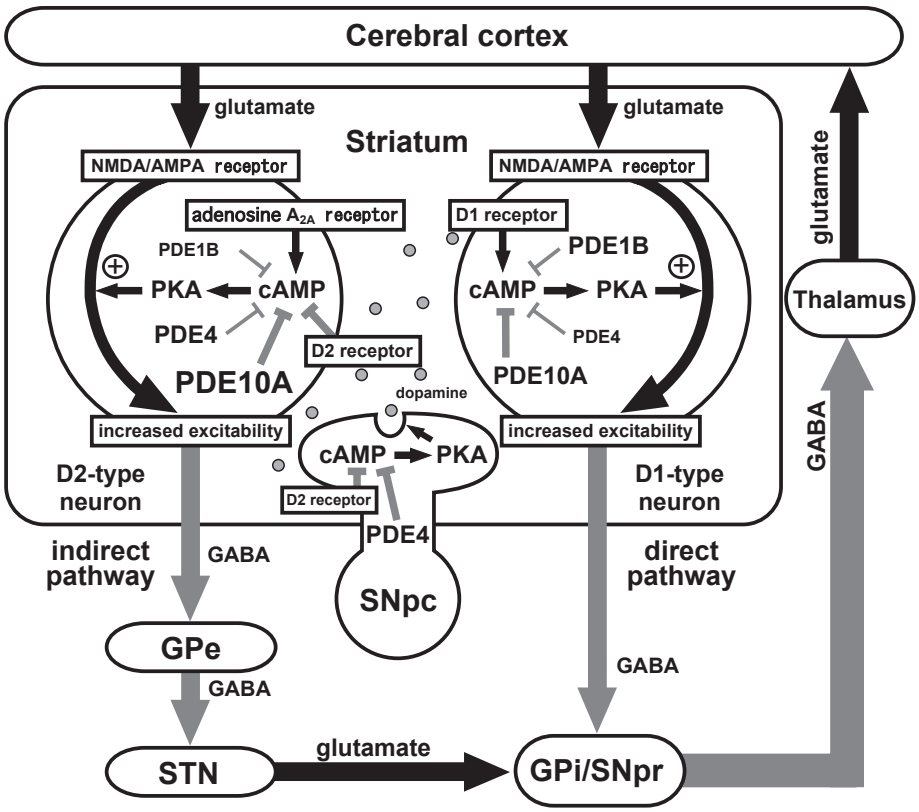

Fig. 1. Basal ganglia-thalamocortical circuitry. Output neurons in the striatum are medium spiny neurons (MSNs), which consist of striatonigral/direct pathway and striatopallidal/indirect pathway neurons. Direct pathway neurons project to the output nuclei of the basal ganglia: the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNpr). Indirect pathway neurons project to the output nuclei by way of the external segment of the globus pallidus (GPe) and the subthalamic nucleus (STN). Direct pathway neurons are GABAergic and inhibit tonically active neurons in GPi/SNpr. Indirect pathway neurons are also GABAergic and activate neurons in GPi/SNpr via inhibition of GPe GABAergic neurons and activation of STN glutamatergic neurons. Direct and indirect pathway neurons induce opposing effects on the output neurons in GPi/SNpr, resulting in dis-inhibition and pro-inhibition of output, respectively, to motor areas of the thalamus and cortex. SNpc, substantia nigra pars compacta.

than for cGMP by approximately 20-fold (7, 18). PDE10A mRNA and protein are expressed at high levels in the striatum, nucleus accumbens, and olfactory tubercle and expressed at lower levels in the hippocampal pyramidal cell layer, dentate gyrus granule cell layer, and cerebellar granule cell layer (19). In the striatum, PDE10A is expressed in two types of medium spiny neurons (direct and indirect pathway neurons), but not in interneurons (20 – 22). Among three splice variants, PDE10A2 associates with the membrane, and PDE10A1 and PDE10A3 are present in the cytosol (23). PDE10A2, the primary splice variant of PDE10A expressed in the striatum (23), is localized to membranes in dendrites and spines of medium spiny neurons (20). PDE10A2 is phosphorylated by PKA at a threonine residue (Thr16) within the N-terminal region (23). The phosphorylation seems to induce the translocation of PDE10A2 from membrane to cytosol, thereby controlling cAMP/PKA signaling within the spines.

4.1. Biochemical evaluation of PDE10A functions in the striatum

Papaverine, an opium alkaloid primarily used for the treatment of visceral spasm and vasospasm, was found to selectively inhibit PDE10A with an IC_{50} of 36 nM (24). Papaverine was used to explore the physiological role of PDE10A in the regulation of striatal function. Recently, potent PDE10A inhibitors, TP-10 (IC_{50} = 0.3 nM) and MP-10 (IC_{50} = 0.18 nM), with 3000-fold selectivity over other PDE families were developed (25). Using these PDE10A inhibitors, PDE10A was shown to hydrolyze both cAMP and cGMP in the striatum in vivo (24 – 26). Inhibition of PDE10A by papaverine increases the phosphorylation of cAMP-response element–binding protein (CREB) and extracellular receptor kinase (ERK) by activating cAMP/PKA signaling (24, 27, 28). We examined the effect of papaverine on the phosphorylation of PKA substrates using neostriatal slices. Papaverine robustly increased the phosphorylation of DARPP-32 at Thr34 and GluR1 at Ser845 in striatal medium spiny neurons (21) (Fig. 2A). The effect of papaverine was mediated through the potentiation of cAMP/PKA signaling, but not cGMP/PKG signaling. Under in vivo conditions, papaverine stimulated cAMP/PKA signaling, leading to the phosphorylation of GluR1 at Ser845 in striatal neurons, as observed in slice preparations. Similarly to papaverine, inhibition of PDE10A by TP-10 and/or MP-10 in the striatum in vivo was demonstrated to induce the phosphorylation of CREB, GluR1, and DARPP-32 at PKA-sites (25, 26). Inhibition of PDE10A by papaverine also increased tyrosine hydroxylase (TH) phosphorylation at Ser40 (PKA-site), but only at a high concentration

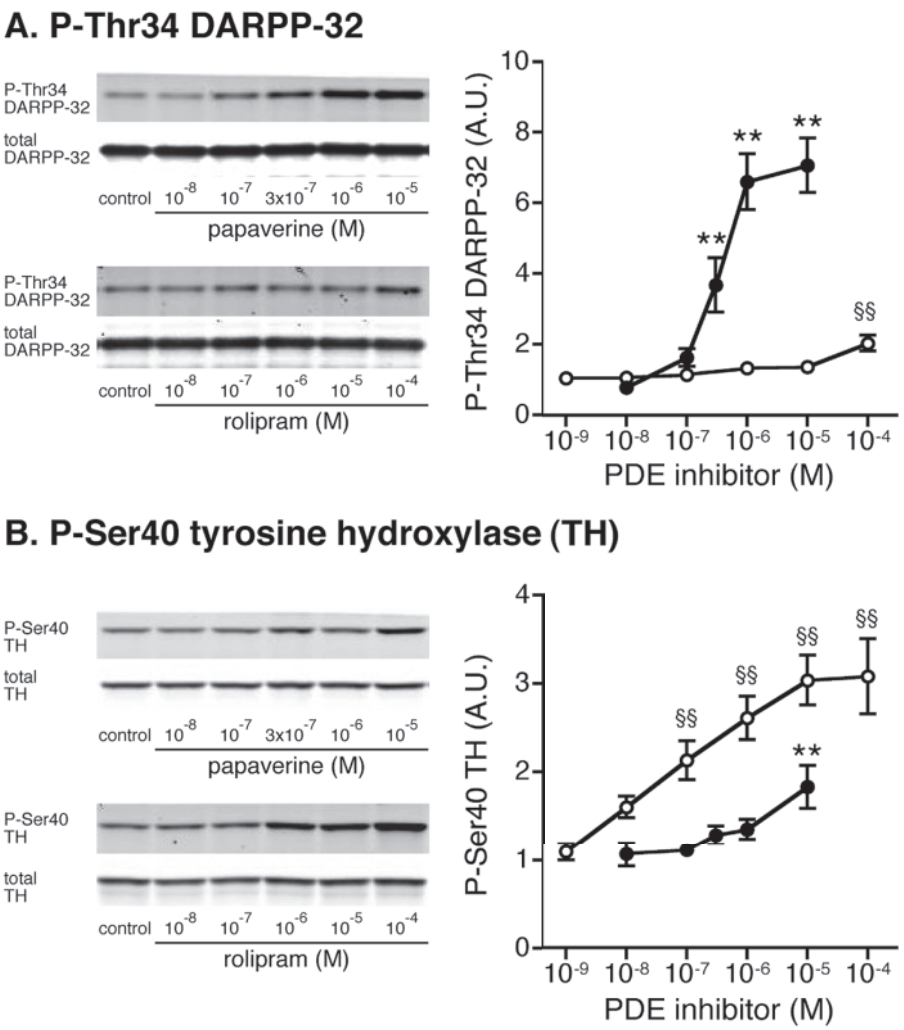

Fig. 2. Effect of a PDE10A inhibitor, papaverine, and a PDE4 inhibitor, rolipram, on DARPP-32 and tyrosine hydroxylase (TH) phosphorylation in neostriatal slices. Mouse neostriatal slices were treated with various concentrations of papaverine (closed circles) or rolipram (open circles) for 60 min. Papaverine robustly increased DARPP-32 Thr34 phosphorylation in striatal neurons (A), and rolipram increased TH Ser40 phosphorylation at dopaminergic terminals (B). $^{**}P < 0.01$ compared with control slices for papaverine; $^{\S\S}P < 0.01$ compared with control slices for rolipram; one-way ANOVA followed by Newman-Keuls test. Adapted with permission from Ref. 21.

(Fig. 2B). In addition, papaverine did not affect dopamine metabolism in the striatum in vivo (21), suggesting that PDE10A does not play a major role at dopaminergic terminals.

PDE10A is abundantly expressed in direct and indirect pathway neurons, and the expression levels are similar in the two types of neurons (20 – 22). In agreement, PDE10A regulates cAMP/PKA signaling (21) as well as gene expression (29) in both direct and indirect pathway neurons. In direct pathway neurons, PDE10A inhibition by papaverine activates cAMP/PKA signaling, leading to the potentiation of dopamine D_1–receptor signaling. In indirect pathway neurons, PDE10A inhibition by papaverine also activates cAMP/PKA signaling by simultaneously potentiating adenosine A_{2A}–receptor signaling and inhibiting dopamine D_2–receptor signaling. Since the balance of cAMP/PKA signaling between the direct and indirect pathways determines the output from the basal ganglia, neuronal type–specific regulation of DARPP-32 phosphorylation was studied using neostriatal slices from D1-DARPP-32-Flag/D2-DARPP-32-Myc mice (21), in which Flag-tagged DARPP-32 and Myc-tagged DARPP-32 are expressed selectively in direct and indirect pathway neurons under the control of D_1- and D_2-receptor promoters, respectively (12). PDE10A inhibition by papaverine increases Myc-tagged DARPP-32 phosphorylation 6-fold in indirect pathways, whereas Flag-tagged DARPP-32 phosphorylation is increased only 2-fold in direct pathway neurons (Fig. 3). Thus, PDE10A inhibitors activate cAMP/PKA signaling in indirect and direct pathway neurons, but the action of PDE10A inhibitors predominates in indirect pathway neurons. A recent electrophysiological study showing that PDE10A inhibition has greater facilitatory effect on corticostriatal synaptic activity in indirect pathway neurons supports the interpretation (30). The biochemical features of PDE10A inhibitors resemble those of antipsychotic drugs, which act primarily as D_2-receptor antagonists and increase DARPP-32 phosphorylation in indirect pathway neurons (12).

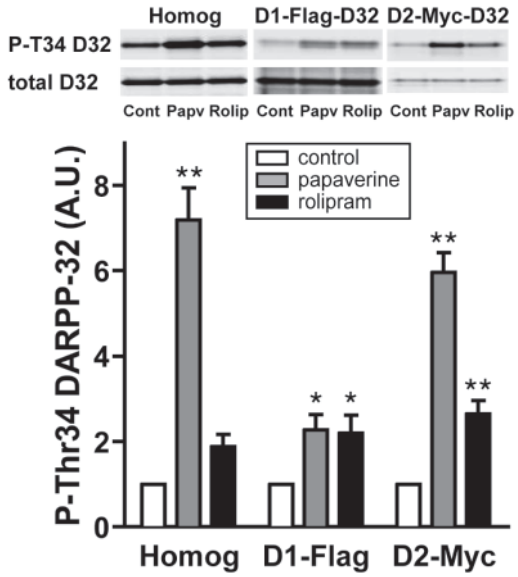

Fig. 3. Neuronal type-specific regulation of DARPP-32 Thr34 phosphorylation by papaverine and rolipram in neostriatal slices from D1-DARPP-32-Flag/D2-DARPP-32-Myc mice. Neostriatal slices from D1-DARPP-32-Flag/D2-DARPP-32-Myc mice were incubated with papaverine (10 μM) or rolipram (100 μM) for 60 min. Flag-tagged DARPP-32, expressed in D_1 receptor-enriched striatonigral/direct pathway neurons, and Myc-tagged DARPP-32, expressed in D_2 receptor-enriched striatopallidal/indirect pathway neurons, were immunoprecipitated, and the phosphorylation of endogenous DARPP-32 (Homog), Flag-tagged DARPP-32 (D1-Flag) and Myc-tagged DARPP-32 (D2-Myc) was analyzed. *$P < 0.05$, **$P < 0.01$ compared with control; one-way ANOVA followed by Newman-Keuls test. Reproduced with permission from Ref. 21.

4.2. Effects of PDE10A inhibitors on dopamine-related behavior

PDE10A inhibition by papaverine, TP-10, and MP-10 displayed behavioral phenotypes of antipsychotics such as inhibition of spontaneous locomotor activity, amphetamine- and phencyclidine (PCP)-stimulated locomotor activity, and conditioned avoidance responding (24 – 26) (Table 1). PDE10A inhibitors also induced catalepsy, which is a model predictive of antipsychotic activity and extrapyramical side effects (24 – 26). However, the intensity of catalepsy induced by TP-10 is less than that induced by typical and atypical antipsychotics such as haloperidol and ziprasidone, respectively (25). Furthermore, PDE10A inhibitors increase social interaction of mice in the social approach / social avoidance test (SASA) and enhance performance in the social odor recognition task (SOR), suggesting the potential usefulness of PDE10A inhibitors for the treatment of negative symptoms and cognitive deficits as well as positive symptoms in schizophrenics (26).

4.3. Behavioral phenotypes of PDE10A knockout mice

Behavioral phenotypes of PDE10A knockout mice are similar to the behavioral effects of PDE10A inhibitors (22, 31, 32) (Table 1). PDE10A knockout mice with genetic background of DBA1LacJ ($PDE10A^{DBA}$) and C57BL/6N ($PDE10A^{C57}$) show a decrease in spontaneous locomotor activity and PCP/MK-801–stimulated locomotor activity and a delayed acquisition or decrease in conditioned avoidance responding. These behavioral phenotypes can be explained by the increase in cAMP/PKA signaling in indirect pathway neurons rather than in direct pathway neurons. However, the genetic background of mice can affect psychostimulant-stimulated locomotor activity. In $PDE10A^{DBA}$-knockout mice, for example, amphetamine-stimulated locomotor activity is similar to that seen in wild-type mice (31), although PDE10A inhibitors inhibit locomotor activity in CD rats. By comparison, $PDE10A^{C57}$-knockout mice show an increase in amphetamine-stimulated locomotor activity (32). In $PDE10A^{C57}$-knockout mice with genetic background of C57BL/6N, the tone of dopaminergic neurotransmission is high, and therefore actions of psychostimulants to increase the release of dopamine and activate dopamine D_1 receptor/cAMP/PKA signaling in direct pathway neurons are likely enhanced. Interestingly, $PDE10A2^{C57}$-knockout mice show an increase in social interaction (22), supporting the utility of PDE10A inhibitors for the treatment of negative symptoms of schizophrenics.

5. Role of PDE4 in dopaminergic neurotransmission

PDE4 is a cAMP-specific PDE with high affinity for cAMP ($K_m = 1 – 10$ μM) (7). The PDE4 family is encoded by four genes (PDE4A – PDE4D), and each isoform has multiple variants. More than 20 variants are derived from the four PDE4 genes by alternative mRNA splicing (7, 8, 33). In the CNS, PDE4A, PDE4B, and PDE4D are widely distributed, but the expression of PDE4C is restricted to the olfactory bulb in rodent brain (34, 35). Notably, the strongest PDE4B immunoreactivity is detected in the nucleus accumbens, whereas it is moderate in the caudate putamen (34).

Each PDE4 variant has a modular structure consisting of a variant-specific N-terminal domain, regulatory domains termed upstream conserved region 1 (UCR1) and UCR2, a conserved catalytic domain, and an isoform-specific C-terminal domain (7, 33). PDE4 long forms contain both a UCR1 and a UCR2, whereas short forms contain only UCR2 or a portion of UCR2. UCR1/2 interacts with the catalytic domain and constitutively inhibits the catalytic activity. The phosphorylation of UCR1 by

Table 1. Role of PDE in the regulation of dopamine-related behaviors

	PDE10A inhibitor (papaverine)	PDE10A inhibitor (TP-10, MP-10)	PDE10A KO mouse	PDE4 inhibitor (rolipram)	PDE4B KO mouse	PDE4D KO mouse	PDE1B KO mouse
Catalepsy	**increased** (CD rat) (CF-1 mouse)	**increased** (Fisher 344 rat) (CF-1 mouse)	**ND**	**increased only at high dose** (CD rat)	**ND**	**ND**	**ND**
Spontaneous locomotor activity	**decreased** (CD rat)	**decreased** (CD rat)	**decreased** (DBA1LacJ mouse) (C57BL/6N mouse)	**decreased only at high dose** (CD rat)	**decreased** (C57BL/6N mouse)	**ND**	**increased** (C57BL/6 x 129svj) (C57BL/6N)
Psychostimulant-stimulated locomotor activity (AMPH, METH)	**decreased** (CD rat)	**decreased** (CD rat)	**similar to wild-type** (DBA1LacJ mouse) **increased** (C57BL/6N mouse)	**decreased** (CD rat)	**increased** (C57BL/6N mouse)	**ND**	**increased** (C57BL/6 x 129svj) (C57BL/6N mouse)
PCP/MK801-stimulated locomotor activity	**decreased** (CD rat)	**decreased** (CD rat)	**decreased** (DBA1LacJ mouse) (C57BL/6N mouse)	**decreased** (CD rat)	**ND**	**ND**	**increased** (C57BL/6N mouse)
Conditioned avoidance responding	**decreased** (CD rat) (DBA1LacJ mouse)	**decreased** (Fisher 344 rat) (CD rat) (CD-1, CF-1 mice)	**delayed acquisition** (DBA1LacJ mouse) **decreased** (C57BL/6N mouse)	**decreased** (CF rat) (C57BL/6N mouse)	**similar to wild-type** **decreased rolipram effect** (C57BL/6N mouse)	**ND**	**similar to wild-type** (C57BL/6N mouse)
Prepulse inhibition	**no change (or increased at high dose)** (C57BL/6J mouse)	**no change** (C57BL/6J mouse) (CD-1, CF-1 mice) **rescued MK-801 PPI deficit** (Long Evans rat)	**ND**	**increased** (C57BL/6N mouse) **rescued AMPH PPI deficit** (C57BL/6J mouse)	**decreased** (C57BL/6N mouse)	**ND**	**ND**
Others	**increased SOR** (CF-1 mouse) **increased social interaction (SASA)** (BALB/cJ mouse)	**increased SOR** (CF-1 mouse)	**increased social interaction** (C57BL/6 mouse)	**antidepressant-like effect** **rescued MK-801 cognitive deficit (radial arm maze) (passive avoidance)** (SD rat)	**anxiogenic-like behavior** (C57BL/6 x 129/Ola) **similar cognition to wild-type (Morris water maze) (passive avoidance)** (C57BL/6N mouse) (C57BL/6 x 129/Ola)	**antidepressant-like effect** (C57BL/6 x 129/Ola) **decreased emesis-related response** (C57BL/6 x 129/Ola)	**cognitive deficit (Morris water maze)** (C57BL/6 x 129svj)
References	(24, 26)	(25, 26)	(22, 31, 32)	(53, 56, 59, 62, 63)	(53, 65, 66)	(67, 68)	(71, 73)

( ): species, strain and genetic background. SOR, social odor recognition test; SASA, social approach/social avoidance test; ND, not determined. Light gray indicates the increase, whereas dark gray indicates the decrease in behavioral scores commonly examined. The table is in part derived with permission from Ref. 64.

PKA disrupts the inhibitory interaction of UCR2 with the catalytic domain (36, 37). The activation of PDE4 by PKA functions as a short-term feedback mechanism for the increase in cAMP. The PDE4B, 4C, and 4D catalytic domains contain a consensus motif for ERK phosphorylation (38, 39). PDE4 long forms are inhibited by ERK phosphorylation, whereas short forms are activated. Activation of the MAP kinase (ERK) pathway and the phosphorylation of PDE4 long forms by ERK lead to the inhibition of PDE4 activity and the stimulation of cAMP/PKA signaling. The phosphorylation of UCR1 by PKA overcomes the inhibition of PDE4, and activation of PDE4 results in the inhibition of cAMP/PKA signaling. Thus, activation of the MAP kinase pathway induces transient activation of cAMP/PKA signaling via inhibition of PDE4. Recently, Cdk5 was also shown to phosphorylate UCR1 and increase PDE4 activity via indirect mechanisms (40). Furthermore, transcription of a number of PDE4 genes is activated by the cAMP/PKA/CREB/CRE cascade (41, 42), and the induction of PDE4 genes by PKA works as a long-term feedback mechanism.

The N-terminal domain and UCR1/2 interact with variant-specific binding proteins, to direct the subcellular targeting of PDE4 variants (7, 33). Various targeting proteins have been identified, including arrestin, A-kinase anchoring protein (AKAPS), receptor for activated C-kinase 1 (RACK1), disrupted in schizophrenia 1 (DISC1), Src, and ERK. Among these targeting proteins, the interaction of PDE4B with DISC1 has received attention because DISC1 is a promising genetic susceptibility factor for schizophrenia (43, 44). In addition, disruption of the PDE4B gene by a balanced translocation segregates with schizophrenia (43), and PDE4B polymorphisms are associated with schizophrenia (45). Dysregulation of cAMP/PKA signaling by a DISC1/PDE4B complex may contribute to the molecular basis underlying schizophrenia.

5.1. Biochemical evaluation of PDE4 functions in the striatum and cortex

5.1.1. Role of PDE4 at dopaminergic terminals

PDE4 plays an important role in the regulation of

cAMP/PKA signaling at dopaminergic terminals in the striatum. Function of PDE4 has been analyzed using a selective PDE4 inhibitor, rolipram (IC_{50} 1 μM), with 100-fold selectivity over other PDE families (7). Dopaminergic neurons in the substantia nigra are known to express PDE4B and PDE4D (34). Inhibition of PDE4 by rolipram increases TH phosphorylation at Ser40 (PKA-site) in neostriatal slices (Fig. 2B) and in vivo (21). The PKA-dependent phosphorylation of TH at Ser40 increases the catalytic activity of TH (3, 4), the rate-limiting step in dopamine biosynthesis (46). It has been reported that rolipram increases dopamine synthesis without altering dopamine release (47, 48). In our study, the inhibition of PDE4 by rolipram in the presence of haloperidol resulted in the increase in DOPAC/dopamine ratio, but not HVA/dopamine ratio, in the striatum in vivo, suggesting the increase in metabolism of dopamine by monoamine oxidase (MAO) at dopaminergic terminals (21). Released dopamine can also be converted to HVA at extraneuronal sites, through the sequential metabolism by catechol-*O*-methyltransferase (COMT) and MAO, but the metabolism of released dopamine was not affected by rolipram. Our results demonstrate that rolipram primarily enhances dopamine synthesis and metabolism at dopaminergic terminals, rather than dopamine release.

Rolipram has been investigated in clinical trials for the treatment of Parkinson's disease. The therapeutic benefit of rolipram over L-DOPA or other dopaminergic drugs in Parkinsonism was not observed (49, 50).

5.1.2. Role of PDE4 in striatal neurons

In addition to the enhancement of dopamine synthesis by rolipram, the inhibition of PDE4 by rolipram weakly enhances cAMP/PKA signaling in striatal neurons in neostriatal slices and in vivo (21). Rolipram slightly increased the phosphorylation of DARPP-32 at Thr34 only at a high concentration, and the effect was much smaller than that of the PDE10A inhibitor papaverine (Fig. 2A). Rolipram treatment augmented adenosine A_{2A} receptor–mediated phosphorylation of DARPP-32 at Thr34, but had no effect on dopamine D_1 receptor–mediated phosphorylation. However, in neostriatal slices from D1-DARPP-32-Flag/D2-DARPP-32-Myc mice, rolipram induced the phosphorylation of both Flag- and Myc-tagged DARPP-32 in direct and indirect pathway neurons, respectively (Fig. 3). The expression of PDE4B at mRNA and protein levels has previously been reported in the caudate-putamen (34, 35). Immunohistochemical analysis in D1-DARPP-32-Flag/D2-DARPP-32-Myc mice revealed that PDE4B expression was higher in indirect pathway neurons than direct pathway neurons. These data suggest that PDE4 preferentially regulates cAMP/PKA signaling coupled to adenosine A_{2A} receptors in indirect pathway neurons compared to that coupled to dopamine D_1 receptors in direct pathway neurons. Activation of cAMP/PKA signaling in indirect pathway neurons elicited by the PDE4 inhibitor rolipram is expected to oppose dopamine D_2–receptor signaling in these cells, similar to the effects of the PDE10A inhibitor.

5.1.3. Role of PDE4 in cortical neurons

The prefrontal cortex (PFC) receives dopaminergic inputs from the ventral tegmental area (VTA), and activation of dopamine D_1 receptors in the PFC is involved in cognitive function (51, 52). PDE4 isoforms, including PDE4A, PDE4B, and PDE4D, are expressed in cortical neurons (34, 35). In the mouse frontal cortex, PDE4B is localized to cortical neurons that express DARPP-32, and the inhibition of PDE4 by rolipram enhances dopamine D_1 receptor–mediated phosphorylation of DARPP-32 at Thr34, indicating that PDE4 exerts strong biochemical control over dopamine D_1 receptor/cAMP/PKA signaling in the frontal cortex (A. Nishi, M. Kuroiwa, and G. Snyder, unpublished observations).

5.2. Effects of PDE4 inhibitors on dopamine-related behavior

The PDE4 inhibitor rolipram, like the PDE10A inhibitor, inhibits dopamine D_2–receptor signaling. At the same time, rolipram stimulates dopamine synthesis, indicating that PDE4 inhibition raises dopaminergic tone in the striatum. Therefore, rolipram mimics the biochemical effects of dopamine D_2 antagonists and to some extent D_1 agonists. With regard to dopamine-mediated behaviors, rolipram inhibited spontaneous locomotor activity (only at high doses), amphetamine- and PCP-stimulated locomotor activity, and conditioned avoidance responding (53) (Table 1). In animal models of schizophrenia, rolipram rescued amphetamine-induced reductions in auditory-evoked potentials (54), MK801-induced deficits in latent inhibition (55), and amphetamine-induced deficits in prepulse inhibition (56). These behavioral effects of rolipram likely occur due to antagonism of dopamine D_2–receptor signaling.

PDE4 was first identified as a homologue of the *dunce* gene in the fruit fly, *Drosophila melanogaster*, mutations of which resulted in learning and memory deficits (57, 58). Subsequent work supported a role for PDE4 in learning and memory processes (59), including activation of cAMP/PKA/CREB signaling and facilitation of long-term potentiation (LTP) in the hippocampus (60, 61). Furthermore, rolipram reverses MK801-induced cognitive deficits in radial arm maze (62) and passive avoidance tests (63). The PDE4 inhibitor also exerts antidepressant-like effects presumably via induction of BDNF

and neurogenesis in the hippocampus (59). The pharmacological profile of the PDE4 inhibitor, including positive effects on mood and cognition, further supports its possible efficacy for the treatment of negative symptoms and cognitive deficits in addition to positive symptoms in schizophrenics (64).

5.3. Behavioral phenotypes of PDE4B- and PDE4D-knockout mice

To determine the functional roles of each PDE4 isoform, behavioral phenotypes for PDE4B- and PDE4D-knockout mice have been investigated (53, 65, 66) (Table 1). PDE4B-knockout mice exhibit reduced spontaneous locomotor activity, consistent with the antipsychotic profile seen with the PDE4 inhibitor rolipram. Unexpectedly, these mice also exhibit enhanced amphetamine-stimulated locomotor activity and impaired prepulse inhibition, behaviors consistent with a pro-psychotic behavioral profile (65). The studies in PDE4B-knockout mice generally fail to recapitulate the antipsychotic effects of rolipram, and the discrepancy might be explained by the lack of PDE4B selectivity of rolipram and chronic compensatory mechanisms for PDE4B-gene deletion (64). In addition, PDE4B knockout mice display anxiogenic-like behavior (66), but no alteration in cognitive function (65, 66).

PDE4D-knockout mice display phenotypes in tail-suspension and forced-swim tests that mimic the effects of antidepressant medications and were insensitive to the antidepressant-like effects of rolipram, suggesting that PDE4D is a target for pharmacotherapy of depression (67). However, the fact that the inhibition of PDE4D is responsible for emesis induced by PDE4 inhibitors (68) presents significant challenges for the use of PDE4D inhibitors in the treatment of depression. Unexpectedly, PDE4D-knockout mice exhibit behavioral deficits in long-term memory formation, despite the observed enhancement of LTP in hippocampus (69) by rolipram. Although these data suggest an involvement of PDE4D in memory and learning, it is unclear how to reconcile the opposing effects on memory of PDE4 inhibitors like rolipram and the behavior of PDE4D-knockout mice.

6. Role of PDE1B in dopaminergic neurotransmission

PDE1B is a dual substrate PDE with a higher affinity for cGMP (K_m = 2.4 μM) than for cAMP (K_m = 24 μM) (7). PDE1B is activated by Ca^{2+} and calmodulin, providing a mechanism for crosstalk between Ca^{2+} and cyclic nucleotide signaling. PDE1B is abundantly expressed in the striatum (70), and striatal PDE1B is localized to all DARPP-32–positive medium spiny neurons, indicating the PDE1B expression in both direct and indirect pathway neurons (A. Nishi and M. Kuroiwa, unpublished observations). Biochemical studies in PDE1B-knockout mice revealed that the function of dopamine D1 receptors to stimulate the phosphorylation of DARPP-32 and GluR1 at PKA-sites is potentiated in striatal slices from PDE1B-knockout mice (71). In behavioral analysis, PDE1B-knockout mice exhibited an increase in psychostimulant- and NMDA receptor antagonist–stimulated locomotor activity (71 – 73) (Table 1). The gene knockout has provided conflicting data regarding the influence of PDE1B on memory performance. Two reports have tested the performance of PDE1B-null mice compared with wild-type littermates in the Morris water maze, with different results. In one study, PDE1B-deficient mice displayed impaired spatial memory performance and use a less efficient search strategy in the spatial memory task (71). These deficits in spatial memory performance could not replicated in a subsequent study (72). The basis for the differences in spatial memory performance in the two studies is unclear, although the differing genetic background of mice used in these studies could contribute. The PDE1B-knockout mice did not display deficits in mouse models of cognition that do not rely upon spatial information, including the conditioned avoidance response paradigm and the passive avoidance task (73). The role of PDE1B in other behavioral tests for antipsychotic and antidepressant activity has not yet been investigated. We hypothesize that PDE1B predominantly regulates cyclic nucleotide signaling in direct pathway neurons, whereas PDE10A exerts predominant effects in indirect pathway neurons.

7. Conclusion

Multiple PDE isoforms are differentially expressed in three neuronal subtypes in the striatum: dopaminergic terminals, indirect pathway neurons, and direct pathway neurons. The inhibition of PDE induces the up-regulation of cAMP signaling in the three neuronal types, resulting in i) stimulation of dopamine synthesis, ii) inhibition of dopamine D_2–receptor signaling (D_2 antagonist–like, antipsychotic effect), and iii) stimulation of dopamine D_1–receptor signaling (D_1 agonist–like effect). Biochemical and behavioral studies demonstrate that PDE10A inhibition preferentially down-regulates dopamine D_2–receptor signaling, PDE4 inhibition preferentially stimulates dopamine synthesis and less efficiently down-regulates dopamine D_2–receptor signaling, and PDE1B inhibition preferentially up-regulates dopamine D_1–receptor signaling. Development of isoform-selective PDE inhibitors is extremely important for the treatment of neuropsychiatric disorders.

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