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REVIEW

Cyclic nucleotide phosphodiesterases: potential therapeutic targets for alcohol use disorder

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Abstract

Alcohol use disorder (AUD), which combines the criteria of both alcohol abuse and dependence, contributes as an important causal factor to multiple health and social problems. Given the limitation of current treatments, novel medications for AUD are needed to better control alcohol consumption and maintain abstinence. It has been well established that the intracellular signal transduction mediated by the second messengers cyclic AMP (cAMP) and cyclic GMP (cGMP) crucially underlies the genetic predisposition, rewarding properties, relapsing features, and systemic toxicity of compulsive alcohol consumption. On this basis, the upstream modulators phosphodiesterases (PDEs), which critically control intracellular levels of cyclic nucleotides by catalyzing their degradation, are proposed to play a role in modulating alcohol abuse and dependent process. Here, we highlight existing evidence that correlates cAMP and cGMP signal cascades with the regulation of alcohol-drinking behavior and discuss the possibility that PDEs may become a novel class of therapeutic targets for AUD.

Keywords Alcohol use disorder (AUD) · Central nervous system · Alcohol dependence · cAMP · cGMP · Phosphodiesterase (PDE)

Introduction

Alcohol use disorder (AUD), according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), combines the criteria of both alcohol abuse and dependence, which used to be separate disease classifications (American Psychiatric Association 2013). AUD can be defined as a compulsive pattern of alcohol drinking and seeking despite harmful consequences and has been linked to a wide array of health and social problems. Although current treatments show effectiveness in alleviating some symptoms of AUD, the worldwide high levels of alcohol consumption and relapse rates still address the need to explore novel medical therapies with greater efficacy in reducing alcohol intake and/or maintaining abstinence. Indicated by a series of recent studies, cyclic nucleotide phosphodiesterases (PDEs) may represent a promising class of therapeutic targets for alcohol-related disorders.

In mammalians, PDEs are the only known enzymes that catalyze the hydrolysis of the cyclic AMP (cAMP) and cyclic GMP (cGMP). Compared to the enzymes catalyzing the synthesis of cAMP and cGMP, namely adenylyl cyclase (AC) and guanylyl cyclase (GC), PDEs play a more important role in regulating the intracellular levels of the cyclic nucleotides and their downstream signal transductions (Bender and Beavo 2006). To date, more than 100 different protein products transcribed from at least 21 genes have been identified in the PDE superfamily, which consists of 11 families (PDE 1–11) (Lugnier 2006; Bender and Beavo 2006; Conti and Beavo 2007; Menniti et al. 2006). All the PDEs can be divided into three categories based on their substrate specificity: cAMP-specific PDEs (i.e., PDE4, PDE7, and PDE8), cGMP-specific PDEs (i.e., PDE5, PDE6, and PDE9), and dual-substrate PDEs (i.e., PDE1, PDE2, PDE3, PDE10, and PDE11).

As the cAMP and cGMP signaling pathways are extensively involved in neural functions and synaptic transmission in the central nervous system (CNS), PDEs, the upstream regulators

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of the cyclic nucleotide signaling, have also been tested for physiological and pathological relevance of various neuropsychiatric disorders, including depression (Zhang 2009; Zhang et al. 2002), anxiety (Zhang et al. 2008), and schizophrenia (Snyder and Vanover 2017); neurodegenerative diseases, including Alzheimer's disease (Garcia-Osta et al. 2012; Heckman et al. 2015; Wang et al. 2012) and Parkinson's disease (Banerjee et al. 2012; Garcia et al. 2014); and ischemic stroke (Blokland et al. 2006; Braun et al. 2007; McLachlan et al. 2007; Millar et al. 2005; Nakayama et al. 2007; Zee et al. 2006). PDE inhibitors exhibited antidepressant- and anxiolytic-like, as well as cognition/memory-enhancing effects in various animal models (Li et al. 2009; Xu et al. 2011; Zhang et al. 2000; Zhang et al. 2005; Zhang et al. 2006). These results suggest a critical involvement of PDEs in emotion, learning, and memory processes, which are also recognized as fundamental components in the development of substance-dependent behaviors (Milton and Everitt 2012; Torregrossa et al. 2011). Accumulating evidence has proven that neuroadaptive changes mediated by cAMP and cGMP signal transductions critically underlie the genetic predisposition, rewarding properties, relapsing features, and systematic toxicity of alcohol-drinking behaviors (Pandey 2004; Pandey et al. 2001b). Based on these findings, PDEs have been proposed to play a modulatory role in alcohol dependence and abuse (Gong et al. 2017; Hu et al. 2011; Liu et al. 2017a; Logrip 2015; Wen et al. 2015; Wen et al. 2017). In this review, we focus on the available evidence that indicates a regulatory role of cAMP- and cGMP-mediated signal transduction in alcohol use and abuse and discuss the possibility that PDEs may become a novel class of therapeutic targets for AUD.

Role of cyclic nucleotide signaling in alcohol use and abuse

The development of alcohol abuse or dependence is a chronic, habit-forming process involving multiple neuronal dysfunctions in different structures of the CNS. Like other drugs of abuse, alcohol produces rewarding properties by stimulating the mesolimbic dopaminergic system, which begins in the ventral tegmental area (VTA) of the midbrain and projects to the nucleus accumbens (NAc) and other limbic brain regions (Gonzales et al. 2004; Koob 2003). Increased dopamine (DA) release in the shell rather than the core of the NAc regulates positive reinforcing properties of addictive substances (Zocchi et al. 2003) and contributes to the promotion of alcohol-drinking behavior (Chao and Nestler 2004; Hyman and Malenka 2001; Imperato and Di Chiara 1986). On the other hand, anhedonic or dysphoric states, such as anxiety and depression, which may be due to pre-existing conditions or abrupt cessation of repeated alcohol consumption, may account for the motivational aspects of alcohol abuse and relapse (Conway et al. 2006; Koob and Le Moal 1997; Pandey 2003). This is supported by the fact that some antidepressants are effective in treating alcoholism (Johnson 2003; Stoltenberg 2003; Zalewska-Kaszubska et al. 2008). Amygdaloid brain structures, specifically the central (CeA) and medial (MeA) nuclei, have been shown to be critical for the innate and withdrawal-induced negative affective states, especially anxiety-like behavior (Pandey et al. 2003; Pandey et al. 2004; Pandey et al. 2005). Thus, cellular substrates with a common role in both euphoric and dysphoric pathways may be of greater efficacy in modulating the development of alcohol abuse and dependence. Cyclic nucleotide signaling, particularly the cAMP signal transduction, has been recognized as one of the best elucidated cell signal systems in regulating both positive and negative aspects of alcohol-dependent process.

cAMP signal transduction

Intracellular cAMP signaling is functionally coupled to various receptors on the plasma membrane via guanine nucleotide binding proteins (G-protein). AC-catalyzed cAMP generation activates protein kinase A (PKA), and ultimately leads to changes in cAMP-inducible gene transcription patterns via phosphorylation of cAMP-responsive element-binding protein (CREB) (Pandey et al. 2001a, b). Important CREB target genes include neuropeptide Y (NPY), corticotrophin-releasing factor (CRF), brain-derived neurotrophic factor (BDNF), and activity-regulated cytoskeleton-associated protein (Arc), all of which play an important role in modulating CNS functions. This renders cAMP signaling a critical modulator in experience-based neuroadaptation and the complex responses to multiple addictive substances (Carlezon et al. 2005). Although the cAMP signaling cascade has been shown to participate in addictive behavior to opiates, cannabis, methamphetamine, cocaine, and nicotine, its role in modulating the alcohol-dependent process has been most profoundly studied (Pandey 2004, Wen et al. 2017).

Alcohol has a diverse pharmacological profile in the CNS. Its euphoric properties can be mediated by μ-opioid receptors (MORs), which are negatively coupled to AC activity; other effects, i.e., sedation, anxiolysis, and ataxia, are mediated via the GABA-benzodiazepine receptor complex (Lingford-Hughes et al. 2010). The intracellular action of alcohol exposure can be transduced by multiple membrane functional sites, including G-protein coupled receptors (GPCRs), voltage gated calcium channels (VGCCs), receptors for tyrosine kinases (RTK), or *N*-methyl-D-aspartate (NMDA). Their downstream signals ultimately culminate in specific patterns of nuclear gene expression via the gene transcription factor CREB. Plenty of evidence demonstrates that acute ethanol exposure leads to activation in cAMP signal transduction both in vitro (Asher et al. 2002;

Table 1 Role of PDEs in alcohol dependence

PDE Isoform	Inhibitor	Animal	Two-bottle choice drinking		Alcohol self-administration	Alcohol withdrawal symptoms	Reference
			Alcohol consumption	Alcohol preference			
PDE1	Vinpocetine	C57BL/6J mice	-	-			Blednov *et al.* (2014)
PDE3	Milrinone		-	-			
	Olprinone		-	-			
PDE4	Rolipram		↓[a]	↓[a]			Hu *et al.* (2011)
	Ro-20 1724		↓	↓			
	Rolipram		↓	↓			Blednov *et al.* (2014)
	Piclamilast		↓	↓			
	Mesopram		↓	↓			
	CDP840		↓	↓			
	Rolipram	FH/Wjd rats	↓[a]	↓[a]	↓[a]		Wen *et al.* (2012)
	Rolipram	C57BL/6J mice				↓	Gong *et al.* (2017)
		FH/Wjd rats				↓	
	Rolipram	P rats	↓[b]				Franklin *et al.* (2015)
		HAD1 rats	↓[b]				
	Ro-20 1724	P rats	↓[b]				
		HAD1 rats	↓[b]				
	Roflumilast	C57BL/6J mice	↓[a]	↓[a]			Liu *et al.* (2017a)
PDE5A	Zaprinast[c]	C57BL/6J mice	-	-			Blednov *et al.* (2014)
PDE10A	TP-10	Scr:sP rats[d]			↓		Logrip *et al.* (2014)
PDE10A	TP-10	Wistar rats			↓[b]		Logrip *et al.* (2014)
Nonspecific	Propentofylline	C57BL/6J mice	-	-			Blednov *et al.* (2014)
	Ibudilast[e]	P rats	↓				Bell *et al.* (2015)
		HAD1 rats	↓				
		C57BL/6J mice	↓				

[a] The effects were selective to alcohol without altering sucrose intake or self-administration

[b] The effect was nonselective between alcohol and sucrose

[c] highest selectivity for PDE5, less potent at PDE1, PDE10, and PDE11

[d] Scr:sP rat: Sardinian alcohol-preferring rats of The Scripps Research Institute subline

[e] Non-specific but with preference on PDE3, 4, 10, 11

Constantinescu et al. 2002; Gordon et al. 1986) and in vivo (Asyyed et al. 2006; Yang et al. 1996), which might be induced by elevated AC activity (Nelson et al. 2003; Yoshimura and Tabakoff 1995). However, chronic ethanol treatment attenuates this effect in a brain region-specific manner. Downregulated cAMP signaling is detected in the mouse cerebral cortex (Saito et al. 1987) and hippocampus (Valverius et al. 1989); in rats, similar responses are detected in the cerebellum (Yang et al. 1996; Yang et al. 1998a, b) and striatum (Yang et al. 1998a, b), but not in the cortical structure. Moreover, alcohol withdrawal also causes decreased cAMP signal transduction in the rat cerebral cortex and CeA (Pandey et al. 2001a, b; Pandey et al. 2003; Pandey et al. 1999a, b), but increased pCREB levels in the hippocampus, which is reduced during chronic alcohol treatment (Bison and Crews 2003).

In addition to the rapid and prolonged regulation of the intracellular actions of alcohol, key elements in cAMP signaling may serve as genetic predisposition and modulation targets for alcohol-drinking behavior. In clinical alcoholic patients with at least 6-month abstinence from alcohol, lower AC1 isoform levels are detected in the cortical structure compared to that in non-drinkers (Hashimoto et al. 1998; Sohma et al. 1999). The following RT-PCR analysis also reveal decreased mRNA levels of AC1 and AC8 in blood cells of alcoholic patients with a positive family history (Sohma et al. 1999). These results are supported by preclinical studies that AC1 knockout mice exhibit enhanced sensitivity to the sedative effect of alcohol, while AC8 knockout leads to decreased voluntary alcohol intake (Maas et al. 2005). On the contrary, mice lacking AC5 exhibit increased alcohol intake and preference but reduced sensitivity to alcohol-induced

sedation (Kim et al. 2011). The opposite modulation pattern of these AC isoforms may be due to their different brain distributions: AC5 is predominantly expressed in the NAc and dorsal striatum (Kim et al. 2008), while calmodulin-sensitive AC1 and AC8 exhibit high levels in the neocortex and olfactory system (Muglia et al. 1999; Xia et al. 1991). Moreover, basal expression of CREB, pCREB, and downstream neuropeptide Y (NPY) has been found to be innately lower in the NAc shell, rather than the NAc core, in alcohol-preferring C57BL/6 (C57) mice compared to non-preferring DBA/2 (DBA) mice (Belknap et al. 1993; Misra and Pandey 2003). Partial deletion of CREB gene promote anxiety-like and alcohol-drinking behavior (Pandey et al. 2004). Similarly, lower expression of CREB and pCREB in the CeA and MeA, but not the basolateral nucleus of amygdala (BLA), is correlated with higher alcohol intake and anxiety levels in alcohol-preferring (P) rats compared to non-preferring (NP) rats (Pandey et al. 1999a, b; Pandey et al. 2005). Acute alcohol exposure activates CREB phosphorylation and reduces anxiety levels in P rats. By CeA microinfusions, Sp-cAMP, a PKA activator, or NPY decreases anxiety levels and alcohol intake in P rats, while the PKA inhibitor Rp-cAMP provokes anxiety-like behavior and increases alcohol consumption in NP rats (Pandey et al. 2005). In addition, the CREB function is also related to anxiety-like behavior in response to abrupt alcohol abstinence. In Sprague-Dawley (SD) rats with chronic alcohol exposure, alcohol withdrawal-induced anxiety-like behavior is accompanied by decreased pCREB and NPY expression in the CeA or MeA; these are reversed by microinfusions of Sp-cAMP into the CeA. Consistently, Rp-cAMP infusions decrease pCREB and increase both anxiety levels and alcohol preference (Pandey et al. 2003). Together, the findings described above demonstrate a negative correlation between cAMP signaling and alcohol-drinking behavior. Key elements in cAMP signal system may play a role in regulating alcohol use and abuse.

It should be noted that alcohol-induced neurotoxicity may also be related to the modulation of cAMP signaling. Ataxia, the earliest recognized physical effect of alcohol exposure, has been shown to be associated with the development of alcoholism (Acquaah-Mensah et al. 2006; Durcan et al. 1991). Intra-cerebellar microinfusions of cAMP or its analogue, forskolin (an AC activator), or Sp-cAMP attenuates alcohol-induced ataxia, whereas Rp-cAMP exhibits an opposite effect (Dar 1990, 2001). In addition, sensitivity and tolerance to the sedative effect of alcohol may also be mediated at least in part through cAMP signal transduction. Rats selectively bred for low-alcohol drinking (LAD) exhibit higher sensitivity to alcohol-induced sedation which is correlated to greater expression of stimulatory G-protein alpha in the frontal cortex and hippocampus compared to high-alcohol drinking (HAD) rats, while HAD rats develop tolerance to the sedative effect more rapidly (Froehlich and Wand 1997). Moreover, activation of cAMP signaling is strongly linked to the promotion of neuron survival and the protective effect against alcohol-induced neuronal apoptosis. Thus, activated cAMP signal transduction may serve as a protective factor against the neurotoxicity of alcohol (Jiao et al. 2007; Karacay et al. 2007; Monti et al. 2002; Walton et al. 1999).

cGMP signal transduction

The cGMP-mediated signal transduction can be activated by increased cGMP generation, which is catalyzed by membrane-bound particulate guanylyl cyclases (pGCs) and cytosolic soluble guanylyl cyclases (sGCs) in response to natriuretic peptides (NPs) and nitric oxide (NO), respectively. Stimulation of cGMP signaling eventually leads to altered cell function via phosphorylation of substrate proteins by cGMP-dependent protein kinase (PKG) (Collins and Uhler 1999). It has been shown that the NO/sGC/cGMP/PKG signal cascade modulates neuroadaptive changes in synaptic activity and plays a role in the development of multiple learning and memory processes (Kleppisch and Feil 2009, Xu et al. 2015). Moreover, cGMP can produce an inhibitory effect on DA release in brain regions involved in addiction (Guevara-Guzman et al. 1994; Samson et al. 1988; Thiriet et al. 2001). These features indicate a potential contribution of cGMP signaling to addictive behavior, which has been demonstrated in several addictive substances, including cocaine (Deschatrettes et al. 2013) and morphine (Nugent et al. 2007).

Although it has been less investigated in the modulation of alcohol-drinking behavior, cGMP signaling may also be involved in mediating intracellular actions of alcohol exposure. Increased cGMP levels in the cortex, striatum, and hippocampus are detected in rats with chronic access to alcohol; discontinuation of alcohol consumption reduces cerebrocortical and striatal cGMP to normal levels (Uzbay et al. 2004). Consistent with the evidence demonstrating the cGMP signaling in modulating anxiety (Ding et al. 2014; Li et al. 2005; Volke et al. 2003), mice deficient in PKG type II exhibit anxiety-like behavior, reduced sensitivity to alcohol sedation, and increased voluntary alcohol intake (Werner et al. 2004). On the other hand, activation of cGMP signaling by neuropeptide CNP in either the VTA or prefrontal cortex inhibits alcohol deprivation-stimulated alcohol intake, an effect partially reversed by the selective inhibitor of PKG (Romieu et al. 2008). Thus, the findings from limited studies support that the activity of cGMP signaling is negatively correlated to alcohol-drinking behavior in a way similar to cAMP signaling, although further investigations are needed to elucidate the regulatory mechanisms of the cGMP signal pathway.

Biodistribution of PDEs in the brain

Studies to date indicate that PDE isoforms are widely distributed in the CNS where all the 11 families can be found (Menniti et al. 2006). Their expression patterns appear to be tissue- and/or cell-specific and different among isoforms.

Among the 11 PDE families, PDE1 is the only PDE family activated by calcium/calmodulin. It consists of three different subtypes (PDE1A, 1B, and 1C), with dual-specificity to both cAMP and cGMP (Wennogle et al. 2017). These three subtypes exhibit comparable expression across the human brain, with PDE1A at the lowest level. PDE1B and 1C are found to be expressed at similar levels in the cortex, hippocampus, and cerebellum. PDE1B ranks as the most prevalent PDE isoform in the caudate putamen (together with PDE10A) and the NAc, indicating its role in rewarding and motivational behaviors. Compared to PDE1B, PDE1C is expressed at much higher levels in the substantia nigra and hypothalamus (Lakics et al. 2010).

The PDE2 family is encoded by a single gene, i.e., *pde2a*, which is highly expressed across the human brain. It represents the most prevalent PDE in the cortex and hippocampus and second highest in the NAc (Lakics et al. 2010). Enriched PDE2A expression has also been found in the amygdala, hypothalamus, pituitary, and adrenal gland, suggesting its involvement in negative feedback inhibition of the limbic-hypothalamus-pituitary-adrenal (limbic-HPA) axis and likely some aspects of the development of addictive behavior (Boess et al. 2004; Nikolaev et al. 2005).

PDE3 is comprised of PDE3A and PDE3B, which display relatively low levels throughout the brain (Bolger et al. 1994). There is no evidence to date for the link between PDE3 and addictive behavior.

The PDE4 family is encoded by four genes (*pde4a-d*) with at least 25 splice variants. It is recognized as the most important PDE in controlling intracellular cAMP levels (Zhang 2009). A high distribution of PDE4 across the brain has been detected. PDE4B is abundantly expressed in the striatum, amygdala, cortex, hippocampus, hypothalamus, and cerebellum, suggesting its possible role in DA-associated and emotion-related processes (Perez-Torres et al. 2000). The distribution patterns of PDE4A and PDE4D are similar with that of PDE4B but at lower levels in DA-enriched brain regions. The high expression of PDE4D in the area postrema and nucleus of solitary tract may account for the side effects associated with PDE4 inhibitor treatment, such as nausea and emesis (Mori et al. 2010). Conversely, PDE4C is predominantly located in peripheral tissues, with little CNS functions.

PDE5A, the only isoform of PDE5, is mainly distributed in cerebellar Purkinje neurons. Its expression level appears to be very low in the human brain compared with other PDEs (Lakics et al. 2010). However, PDE5A has been shown to modulate memory performance (Xu et al. 2011) and produce antidepressant-like effects (Liebenberg et al. 2010).

PDE6 expression is confined to the pineal gland in the brain. It appears to play no direct role in neural functions (Bender and Beavo 2006).

PDE7 is encoded by two genes, *pde7a* and *pde7b*. Relatively low levels of PDE7 mRNA are detected in the striatum, cortex, hippocampus, and hypothalamus, with PDE7B as the major isoform (Lakics et al. 2010; Reyes-Irisarri et al. 2005). High PDE7B expression is specifically found in Purkinje cells.

PDE8 has two subtypes, PDE8A and 8B. Their expression is detected throughout the human brain, albeit at relatively low levels. To date, no data have been reported regarding the effects of PDE8 inhibitors.

Moderate levels of PDE9A mRNA are detected in cerebellar Purkinje cells, the hippocampus, hypothalamus, and substantia nigra. Selective PDE9 inhibitors have been shown to improve learning and memory in rodents (van der Staay et al. 2008).

The PDE10 family is encoded also by a single gene, i.e., *pde10a*, which is highly expressed in the striatum, substantia nigra, hypothalamus, and cerebellum. It ranks as the most prevalent PDE (together with PDE1B) in the caudate nucleus. In accordance with its brain distribution, selective inhibition of PDE10 exhibits antipsychotic activity in rodent models, indicating a role of PDE10 in mood disorders (Schmidt et al. 2008; Siuciak et al. 2006).

The most recently described PDE11 family also contains only one isoform, i.e., PDE11A (Loughney et al. 2005). PDE11A is present at particularly low levels in most human brain regions except the dorsal root ganglia.

The different distributions of PDEs in the brain and their roles in regulating neuronal function indicate that targeted inhibition of specific PDE isoforms may produce unique therapeutic benefits for CNS disorders. However, some side effects of PDE inhibitors also likely result from the complex expression patterns of PDEs in brain regions.

PDE regulation of alcohol-dependent behavior

The critical involvement of cAMP and cGMP signal pathways in mediating the development and maintenance of alcohol-drinking behavior renders their upstream modulators PDEs as the potential interfering targets for alcohol use and abuse (Fig. 1). The distribution patterns of PDEs in the CNS also support their role in addictive behavior. On this basis, a majority of PDEs have been investigated for the possible roles in the dependent process of alcohol or other addictive substances in animal models (Wen et al. 2017), although only a few of them were shown to be

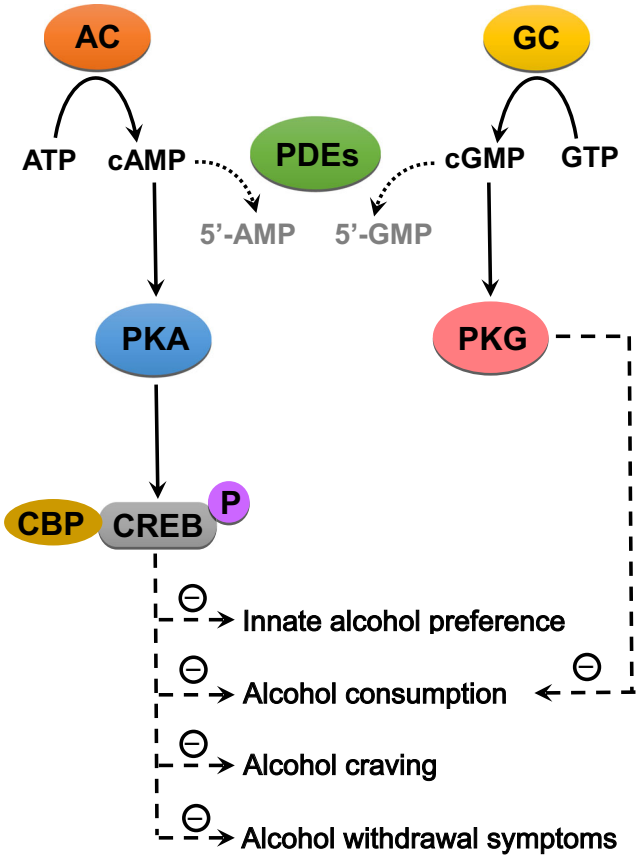

Fig. 1 Possible mechanisms of PDEs in modulating alcohol drinking behaviors. AC adenylate cyclase, ATP adenosine triphosphate, cAMP 3′ 5′ cyclic adenosine monophosphate, CBP CREB-binding protein, CREB cAMP-responsive element-binding protein, GTP guanosine triphosphate, PDEs phosphodiesterases, PKA protein kinase A, PKG protein kinase G, ⊖, negatively correlated

involved in addictive behaviors of substances, especially alcohol and cocaine (Fig. 2). Further studies are of necessity to verify their modulatory mechanisms and the functions of other PDEs in alcohol-related disorders (Table 1).

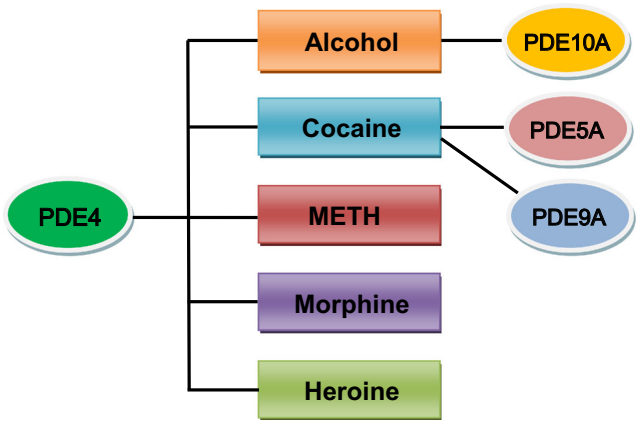

Fig. 2 PDEs involved in the dependent process to multiple substances. METH, methamphetamine

PDEs regulate positive and negative reinforcement of alcohol consumption

With high expression in addiction-related brain regions, PDE4 has been shown to play an important role in regulating behavioral responses to addictive substances. Inhibition of PDE4 prevents behavioral sensitization induced by methamphetamine (Iyo et al. 1996) or cocaine (Janes et al. 2009), suppresses operant self-administration of cocaine (Knapp et al. 1999) or heroin (Lai et al. 2014), blocks cocaine- or morphine-induced conditioned place preference (Zhong et al. 2012; Thompson et al. 2004), and attenuates naloxone-participated morphine withdrawal symptoms (Nunez et al. 2009; Gonzalez-Cuello et al. 2007; Hamdy et al. 2001). These results reveal an extensive correlation between PDE4 activity and the dependent process of substances of abuse, indicating PDE4 may also play a role in regulating alcohol use and abuse.

This assumption was first demonstrated by reduced alcohol drinking after systemic administration of the selective PDE4 inhibitor rolipram or Ro-20 1724 in C57BL/6J mice (Hu et al. 2011) and FH/Wjd rats (Wen et al. 2012), via the two-bottle free-choice drinking paradigm. As total fluid or sucrose intake was not affected, the decrease in alcohol consumption was more likely to be attributed to changes in behavioral response to alcohol, rather than to taste preference, interference in alcohol metabolism, or side effects related to PDE4 inhibition, such as nausea and sedation. Consistently, later researches also proved the role of PDE4 in alcohol consumption by using various PDE4 inhibitors, including rolipram, CDP840, piclamilast, mesopram (Blednov et al. 2014; Franklin et al. 2015), and most recently, roflumilast (Liu et al. 2017). These agents all led to decreased alcohol intake in C57BL/6J mice with long-term or limited-access two-bottle choice drinking. Among different rodent species, PDE4 inhibitors exhibited similar effects on alcohol consumption. Rolipram and Ro-20 1724 both reduced ethanol intake in alcohol-preferring (P) and high-alcohol-drinking (HAD1) rats, but with declination in sucrose intake (Franklin et al. 2015).

Based on the current findings, the effect of PDE4 inhibition on alcohol consumption may result from two aspects of mechanisms. First, PDE4 may regulate the positive reinforcing properties of alcohol exposure, as rolipram selectively decreases operant alcohol self-administration without altering nature rewarding (sucrose seeking) or locomotor behavior (Wen et al. 2012). The activity of cAMP signaling in the NAc, especially the NAc shell, has been shown to negatively correlate with the rewarding properties of alcohol and other drugs of abuse (Chao and Nestler 2004; McClung and Nestler 2003; Knapp et al. 2001; Walters and Blendy 2001; Carlezon et al. 1998). Thus, PDE4 inhibitors may regulate alcohol consumption and preference by activating cAMP signal transduction in the NAc, where PDE4 has been found with high

expression. Moreover, PDE4 can directly regulate DA neurotransmission in the striatum (Liu et al. 2017a, b; Ramirez and Smith 2014), which represents the most important molecular mechanism in mediating the euphoric effects of most addictive substances including alcohol. In addition to positive reinforcing properties of alcohol, the innate or withdrawal-induced negative affective states also contribute as an important motivational impetus for alcohol abuse or relapse. Pharmacological inhibition or genetic knockout of PDE4 produces anxiolytic (Siuciak et al. 2007, Rutter et al. 2014, Ankur et al. 2013, Li et al. 2009), antidepressant (Li et al. 2009, Zhang 2009, Zhang et al. 2002), and antipsychotic (Kelly et al. 2007) effects. Furthermore, PDE4 inhibition has been proved to attenuate alcohol withdrawal-induced anxiety- and depressive-like behavior in mice and rats (Gong et al. 2017). Therefore, PDE4 regulation may be also involved in negative reinforcing aspects during the initiation and maintenance of alcohol consuming behavior.

Another PDE isoform found to be effective in regulating excessive alcohol drinking is PDE10A, which is a dual-substrate PDE family and has long been focused on their therapeutic potential in psychotic disorders. In multiple preclinical models, PDE10A inhibitors produce antipsychotic effects by reducing positive, cognitive, and negative symptoms related to schizophrenia (Grauer et al. 2009; Megens et al. 2014; Schmidt et al. 2008; Smith et al. 2013; Suzuki et al. 2015); they also critically modulate the striatal DA levels (Sotty et al. 2009; Schmidt et al. 2008), indicating a possible enrollment of PDE10A in neuronal responses to addictive substances. The relationship between PDE10A levels and alcohol self-administration was first proposed by Logrip and colleagues. By using repeated foot shock accompanied with operant alcohol self-administration training, they found that rats with a stress (foot shock) history and low baseline alcohol intake exhibited twofold elevation in alcohol self-administration after an extinction period, compared with baseline and low drinking stress-naïve controls (Logrip and Zorrilla 2012). This effect was correlated with increased *pde10a* mRNA levels in the prelimbic subdivision of the medial prefrontal cortex (mPFC). Moreover, stress history also elevated *pde10a* mRNA expression during both acute and prolonged abstinence from chronic intermittent alcohol vapor treatment (Logrip and Zorrilla 2014). Increased *pde10a* mRNA levels were observed in multiple subdivisions of the amygdala and mPFC in response to acute (8–10 h) alcohol withdrawal; however, only the BLA showed long-lasting elevation in *pde10a* after protracted (6 weeks) abstinence. Thus, upregulated PDE10A expression might be involved as a neuroadaptation in both positive and negative reinforcing properties associated with alcohol-dependent process. These findings are supported by subsequent researches through pharmacological blockade of PDE10A (Logrip et al. 2014). Systemic treatment of the selective PDE10A inhibitor TP-10 dose-dependently reduced relapse-like alcohol self-administration in rats with or without a stress experience, and also in genetically alcohol-preferring rats (Scr/sP) as well as alcohol-dependent and non-dependent Wistar rats. Results via region-specific microinjections of TP-10 implicated that the dorsolateral striatum, but not the NAc, plays an important role in PDE10A modulation on alcohol self-administration. However, TP-10 also reduced saccharin self-administration with a similar potency compared to alcohol, suggesting a non-specific modulating pattern of PDE10A on reinforcing properties of rewards.

On the other hand, the involvement of PDE4 and PDE10A in regulating alcohol consumption may be indirectly proved by the effect of the non-specific PDE inhibitor ibudilast with preferential inhibition of PDE3A, PDE4, PDE10A, and PDE11A (Gibson et al. 2006). Systemic administration of ibudilast leads to reduction in alcohol intake in alcohol-preferring P rats, high-alcohol-drinking (HAD) rats, and alcohol-dependent C57BL/6J mice (Bell et al. 2015). As PDE3 inhibition shows negative effects on alcohol intake (Blednov et al. 2014) and the expression of PDE11A is very low in the brain, the inhibitory effect of ibudilast on alcohol intake is likely to result from inhibition of PDE4 and PDE10A .

PDEs regulate alcohol-induced neurotoxicity

As a main adverse effect on the brain, alcohol-induced neurotoxicity consists of alcohol-related neuroinflammation and brain damage, which may cause cognition decline and neurodegeneration (Vetreno and Crews, 2014). In both human and animal studies, theses injuries can be mediated by alcohol-induced glial cell activation (Montesinos et al. 2016).

The dual-specificity PDE1 is widely expressed in the brain. Although it fails to affect alcohol intake in the two-bottle choice drinking test (Blednov et al. 2014), the selective PDE1 inhibitor vinpocetine has been shown to reverse cortical deficits, facilitate long-term potentiation, enhance dendritic spine complexity, restore neuronal plasticity (Medina et al. 2006; Lantz et al. 2012), and ameliorate hyperactivity and impairment of learning and memory (Filgueiras et al. 2010; Nunes et al. 2011) in animals exposed to alcohol during fetal development, implying a protective role of PDE1 inhibition in fetal alcohol-related pathology, including fetal alcohol spectrum disorder (FASD). These effects may be attributable to changes in ERK and MAPK signaling in the prefrontal cortex and hippocampus (Swart et al. 2017). Based on these findings, it is also of interest to study whether PDE1 inhibitors similarly prevent cognitive deficits caused by excessive alcohol consumption in adulthood. Moreover, the function of PDE1 in patterning alcohol intake remains to be investigated, as PDE1 exhibits relatively high expression levels in striatal structures. Microinjections of the PDE1 inhibitor into addiction-related brain nuclei may be helpful for this purpose.

In addition to regulating alcohol-drinking behavior, PDE4 is also well demonstrated for its role in regulating inflammation reactions and immune responses (Gobejishvili et al. 2006; Gobejishvili et al. 2008). In C57BL/6 mice with chronic access to alcohol exposure, elevated *pde4b* mRNA expression is associated with a robust activation of astrocytes and microglia, as well as significant increases in the inflammatory cytokines and the generalized inflammatory marker Cox-2 (Avila et al. 2017). In primary microglial cells, alcohol exposure leads to activation in microglial cells and selective elevation in *pde4b* expression with a minimum to no change in *pde4a* and *pde4d* isoforms. Moreover, pharmacological inhibition or genetic deletion of PDE4B markedly attenuated the above inflammation markers and glial cell activation. Together, these results strongly indicate the involvement of *pde4b* in coordinating alcohol-induced neuroinflammation, rendering an additional protective effect of PDE4 inhibitors in alcohol-related disorders.

PDEs as drug targets

Being critically involved in various physiological functions, PDEs have long been recognized as a promising class of therapeutic targets for pharmaceutical development. Since the first PDE inhibitor theophylline was identified, a series of PDE inhibitors have been approved as clinical medications, e.g., the PDE3 inhibitors amrinone and milrinone for treating chronic heart failure, the PDE4 inhibitors rofumilast for chronic obstructive pulmonary disease (COPD), cilomilast for asthma, and apremilast for psoriatic arthritis, and the PDE5 inhibitors sildenafil, vardenafil, and tadalafil for erectile dysfunction and pulmonary artery hypertension. Notably, in a recent human laboratory trial, the non-specific PDE inhibitor ibudilast shows effectiveness in treating clinical patients with mild-to-severe AUD (Ray et al. 2017). Although these drugs exhibit potent and positive clinical efficacy, the off-target side effects, such as gastrointestinal upsets, headache, and weight loss, may limit their therapeutic potentials (Rabe et al. 2005). With molecular biological approaches expanding access to multiple purified PDE isoenzymes, more systematic studies of PDE inhibitors are now available for new generation of highly selective isoenzyme-specific drugs. On this basis, discovery of novel PDE inhibitors with greater potency and/or fewer side effects for treating AUD are of broad translational potential.

Conclusion and future perspectives

As discussed above, PDEs, with potent actions on controlling intracellular cAMP and cGMP levels, may represent a novel class of therapeutic targets for alcohol use disorder. It has been hypothesized that more than one PDE family may be involved in alcohol-dependent process. Although current evidence only reveals PDE4 and PDE10A with definite effects on regulating alcohol consumption, other PDEs, such as PDE1, are still of interest to be investigated for their potential involvement in alcohol dependence and abuse. It is encouraging that PDE4 inhibitors also produce neuroprotective effects on alcohol exposure-related injuries in the brain. Further studies are of necessity to elucidate the modulatory mechanisms of PDE inhibitors and detect additional functions related to alcohol dependence and abuse.

During the past few decades, novel PDE inhibitors have been widely studied for potential effects on systemic diseases, including many CNS disorders, in both preclinical experiments and clinical trials. As some PDE inhibitors have been reported with serious adverse reactions that hamper their clinical applications, further exploration by utilizing molecular or genetic manipulations may be needed to better elucidate the potential regulatory role of specific PDE subtypes or isoforms, which may contribute to the development of highly selective PDE inhibitors with less off-target side effects.

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References

Acquaah-Mensah GK, Misra V, Biswal S (2006) Ethanol sensitivity: a central role for CREB transcription regulation in the cerebellum. BMC Genomics 7:308

Ankur J, Mahesh R, Bhatt S (2013) Anxiolytic-like effect of etazolate, a type 4 phosphodiesterase inhibitor in experimental models of anxiety. Indian J Exp Biol 51:444–449

Asher O, Cunningham TD, Yao L, Gordon AS, Diamond I (2002) Ethanol stimulates cAMP-responsive element (CRE)-mediated transcription via CRE-binding protein and cAMP-dependent protein kinase. J Pharmacol Exp Ther 301:66–70

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5., 5th ed. edn. American Psychiatric Association, American Psychiatric Association

Asyyed A, Storm D, Diamond I (2006) Ethanol activates cAMP response element-mediated gene expression in select regions of the mouse brain. Brain Res 1106:63–71

Avila DV, Myers SA, Zhang J, Kharebava G, McClain CJ, Kim HY, Whittemore SR, Gobejishvili L, Barve S (2017) Phosphodiesterase 4b expression plays a major role in alcohol-induced neuro-inflammation. Neuropharmacology 125:376–385

Banerjee A, Patil S, Pawar MY, Gullapalli S, Gupta PK, Gandhi MN, Bhateja DK, Bajpai M, Sangana RR, Gudi GS, Khairatkar-Joshi N, Gharat LA (2012) Imidazopyridazinones as novel PDE7 inhibitors: SAR and in vivo studies in Parkinson's disease model. Bioorg Med Chem Lett 22:6286–6291

Belknap JK, Crabbe JC, Young ER (1993) Voluntary consumption of ethanol in 15 inbred mouse strains. Psychopharmacology 112: 503–510

Bell RL, Lopez MF, Cui C, Egli M, Johnson KW, Franklin KM, Becker HC (2015) Ibudilast reduces alcohol drinking in multiple animal models of alcohol dependence. Addict Biol 20:38–42

Bender AT, Beavo JA (2006) Cyclic nucleotide phosphodiesterases: molecular regulation to clinical use. Pharmacol Rev 58:488–520

Bison S, Crews F (2003) Alcohol withdrawal increases neuropeptide Y immunoreactivity in rat brain. Alcohol Clin Exp Res 27:1173–1183

Blednov YA, Benavidez JM, Black M, Harris RA (2014) Inhibition of phosphodiesterase 4 reduces ethanol intake and preference in C57BL/6J mice. Front Neurosci 8:129

Blokland A, Schreiber R, Prickaerts J (2006) Improving memory: a role for phosphodiesterases. Curr Pharm Des 12:2511–2523

Boess FG, Hendrix M, van der Staay FJ, Erb C, Schreiber R, van Staveren W, de Vente J, Prickaerts J, Blokland A, Koenig G (2004) Inhibition of phosphodiesterase 2 increases neuronal cGMP, synaptic plasticity and memory performance. Neuropharmacology 47:1081–1092

Bolger GB, Rodgers L, Riggs M (1994) Differential CNS expression of alternative mRNA isoforms of the mammalian genes encoding cAMP-specific phosphodiesterases. Gene 149:237–244

Braun NN, Reutiman TJ, Lee S, Folsom TD, Fatemi SH (2007) Expression of phosphodiesterase 4 is altered in the brains of subjects with autism. Neuroreport 18:1841–1844

Carlezon WJ, Duman RS, Nestler EJ (2005) The many faces of CREB. Trends Neurosci 28:436–445

Carlezon WJ, Thome J, Olson VG, Lane-Ladd SB, Brodkin ES, Hiroi N, Duman RS, Neve RL, Nestler EJ (1998) Regulation of cocaine reward by CREB. Science 282:2272–2275

Chao J, Nestler EJ (2004) Molecular neurobiology of drug addiction. Annu Rev Med 55:113–132

Collins SP, Uhler MD (1999) Cyclic AMP- and cyclic GMP-dependent protein kinases differ in their regulation of cyclic AMP response element-dependent gene transcription. J Biol Chem 274:8391–8404

Constantinescu A, Gordon AS, Diamond I (2002) cAMP-dependent protein kinase types I and II differentially regulate cAMP response element-mediated gene expression: implications for neuronal responses to ethanol. J Biol Chem 277:18810–18816

Conti M, Beavo J (2007) Biochemistry and physiology of cyclic nucleotide phosphodiesterases: essential components in cyclic nucleotide signaling. Annu Rev Biochem 76:481–511

Conway KP, Compton W, Stinson FS, Grant BF (2006) Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 67:247–257

Dar MS (1990) Central adenosinergic system involvement in ethanol-induced motor incoordination in mice. J Pharmacol Exp Ther 255: 1202–1209

Dar MS (2001) Modulation of ethanol-induced motor incoordination by mouse striatal A (1) adenosinergic receptor. Brain Res Bull 55:513–520

Deschatrettes E, Romieu P, Zwiller J (2013) Cocaine self-administration by rats is inhibited by cyclic GMP-elevating agents: involvement of epigenetic markers. Int J Neuropsychopharmacol 16:1587–1597

Ding L, Zhang C, Masood A, Li J, Sun J, Nadeem A, Zhang HT, O' DJ, Xu Y (2014) Protective effects of phosphodiesterase 2 inhibitor on depression- and anxiety-like behaviors: involvement of antioxidant and anti-apoptotic mechanisms. Behav Brain Res 268:150–158

Durcan MJ, Lister RG, Morgan PF, Linnoila M (1991) Interactions of intracerebroventricular pertussis toxin treatment with the ataxic and hypothermic effects of ethanol. Naunyn Schmiedeberg's Arch Pharmacol 344:252–258

Filgueiras CC, Krahe TE, Medina AE (2010) Phosphodiesterase type 1 inhibition improves learning in rats exposed to alcohol during the third trimester equivalent of human gestation. Neurosci Lett 473(3): 202–207

Franklin KM, Hauser SR, Lasek AW, McClintick J, Ding ZM, McBride WJ, Bell RL (2015) Reduction of alcohol drinking of alcohol-preferring (P) and high-alcohol drinking (HAD1) rats by targeting phosphodiesterase-4 (PDE4). Psychopharmacology 232:2251–2262

Froehlich JC, Wand GS (1997) Adenylyl cyclase signal transduction and alcohol-induced sedation. Pharmacol Biochem Behav 58:1021–1030

Garcia AM, Redondo M, Martinez A, Gil C (2014) Phosphodiesterase 10 inhibitors: new disease modifying drugs for Parkinson's disease? Curr Med Chem 21:1171–1187

Garcia-Osta A, Cuadrado-Tejedor M, Garcia-Barroso C, Oyarzabal J, Franco R (2012) Phosphodiesterases as therapeutic targets for Alzheimer's disease. ACS Chem Neurosci 3:832–844

Gibson LC, Hastings SF, McPhee I, Clayton RA, Darroch CE, Mackenzie A, Mackenzie FL, Nagasawa M, Stevens PA, Mackenzie SJ (2006) The inhibitory profile of Ibudilast against the human phosphodiesterase enzyme family. Eur J Pharmacol 538:39–42

Gobejishvili L, Barve S, Joshi-Barve S, McClain C (2008) Enhanced PDE4B expression augments LPS-inducible TNF expression in ethanol-primed monocytes: relevance to alcoholic liver disease. Am J Physiol Gastrointest Liver Physiol 295:G718–G724

Gobejishvili L, Barve S, Joshi-Barve S, Uriarte S, Song Z, McClain C (2006) Chronic ethanol-mediated decrease in cAMP primes macrophages to enhanced LPS-inducible NF-kappaB activity and TNF expression: relevance to alcoholic liver disease. Am J Physiol Gastrointest Liver Physiol 291:G681–G688

Gong MF, Wen RT, Xu Y, Pan JC, Fei N, Zhou YM, Xu JP, Liang JH, Zhang HT (2017) Attenuation of ethanol abstinence-induced anxiety- and depressive-like behavior by the phosphodiesterase-4 inhibitor rolipram in rodents. Psychopharmacology 234:3143–3151

Gonzales RA, Job MO, Doyon WM (2004) The role of mesolimbic dopamine in the development and maintenance of ethanol reinforcement. Pharmacol Ther 103:121–146

Gonzalez-Cuello A, Sanchez L, Hernandez J, Teresa CM, Victoria MM, Laorden ML (2007) Phosphodiesterase 4 inhibitors, rolipram and diazepam block the adaptive changes observed during morphine withdrawal in the heart. Eur J Pharmacol 570:1–9

Gordon AS, Collier K, Diamond I (1986) Ethanol regulation of adenosine receptor-stimulated cAMP levels in a clonal neural cell line: an in vitro model of cellular tolerance to ethanol. Proc Natl Acad Sci U S A 83:2105–2108

Grauer SM, Pulito VL, Navarra RL, Kelly MP, Kelley C, Graf R, Langen B, Logue S, Brennan J, Jiang L, Charych E, Egerland U, Liu F, Marquis KL, Malamas M, Hage T, Comery TA, Brandon NJ (2009) Phosphodiesterase 10A inhibitor activity in preclinical models of the positive, cognitive, and negative symptoms of schizophrenia. J Pharmacol Exp Ther 331:574–590

Guevara-Guzman R, Emson PC, Kendrick KM (1994) Modulation of in vivo striatal transmitter release by nitric oxide and cyclic GMP. J Neurochem 62:807–810

Hamdy MM, Mamiya T, Noda Y, Sayed M, Assi AA, Gomaa A, Yamada K, Nabeshima T (2001) A selective phosphodiesterase IV inhibitor, rolipram blocks both withdrawal behavioral manifestations, and c-Fos protein expression in morphine dependent mice. Behav Brain Res 118:85–93

Hashimoto E, Frolich L, Ozawa H, Saito T, Maurer K, Boning J, Takahata N, Riederer P (1998) Reduced immunoreactivity of type I adenylyl cyclase in the postmortem brains of alcoholics. Alcohol Clin Exp Res 22:88S–92S

Heckman PR, Wouters C, Prickaerts J (2015) Phosphodiesterase inhibitors as a target for cognition enhancement in aging and Alzheimer's disease: a translational overview. Curr Pharm Des 21:317–331

Hu W, Lu T, Chen A, Huang Y, Hansen R, Chandler LJ, Zhang HT (2011) Inhibition of phosphodiesterase-4 decreases ethanol intake in mice. Psychopharmacology 218:331–339

Hyman SE, Malenka RC (2001) Addiction and the brain: the neurobiology of compulsion and its persistence. Nat Rev Neurosci 2:695–703

Imperato A, Di Chiara G (1986) Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. J Pharmacol Exp Ther 239:219–228

Iyo M, Bi Y, Hashimoto K, Inada T, Fukui S (1996) Prevention of methamphetamine-induced behavioral sensitization in rats by a cyclic AMP phosphodiesterase inhibitor, rolipram. Eur J Pharmacol 312:163–170

Janes AC, Kantak KM, Cherry JA (2009) The involvement of type IV phosphodiesterases in cocaine-induced sensitization and subsequent pERK expression in the mouse nucleus accumbens. Psychopharmacology 206:177–185

Jiao S, Liu Z, Ren WH, Ding Y, Zhang YQ, Zhang ZH, Mei YA (2007) cAMP/protein kinase A signalling pathway protects against neuronal apoptosis and is associated with modulation of Kv2.1 in cerebellar granule cells. J Neurochem 100:979–991

Johnson BA (2003) The role of serotonergic agents as treatments for alcoholism. Drugs Today (Barc) 39:665–672

Karacay B, Li G, Pantazis NJ, Bonthius DJ (2007) Stimulation of the cAMP pathway protects cultured cerebellar granule neurons against alcohol-induced cell death by activating the neuronal nitric oxide synthase (nNOS) gene. Brain Res 1143:34–45

Kelly MP, Isiegas C, Cheung YF, Tokarczyk J, Yang X, Esposito MF, Rapoport DA, Fabian SA, Siegel SJ, Wand G, Houslay MD, Kanes SJ, Abel T (2007) Constitutive activation of Galphas within forebrain neurons causes deficits in sensorimotor gating because of PKA-dependent decreases in cAMP. Neuropsychopharmacology 32:577–588

Kim KS, Kim H, Baek IS, Lee KW, Han PL (2011) Mice lacking adenylyl cyclase type 5 (AC5) show increased ethanol consumption and reduced ethanol sensitivity. Psychopharmacology 215:391–398

Kim KS, Lee KW, Baek IS, Lim CM, Krishnan V, Lee JK, Nestler EJ, Han PL (2008) Adenylyl cyclase-5 activity in the nucleus accumbens regulates anxiety-related behavior. J Neurochem 107:105–115

Kleppisch T, Feil R (2009) cGMP signalling in the mammalian brain: role in synaptic plasticity and behaviour. Handb Exp Pharmacol 191: 549–579

Knapp CM, Foye MM, Ciraulo DA, Kornetsky C (1999) The type IV phosphodiesterase inhibitors, Ro 20-1724 and rolipram, block the initiation of cocaine self-administration. Pharmacol Biochem Behav 62:151–158

Knapp CM, Lee K, Foye M, Ciraulo DA, Kornetsky C (2001) Additive effects of intra-accumbens infusion of the cAMP-specific phosphodiesterase inhibitor, rolipram and cocaine on brain stimulation reward. Life Sci 69:1673–1682

Koob GF (2003) Alcoholism: allostasis and beyond. Alcohol Clin Exp Res 27:232–243

Koob GF, Le Moal M (1997) Drug abuse: hedonic homeostatic dysregulation. Science 278:52–58

Lai M, Zhu H, Sun A, Zhuang D, Fu D, Chen W, Zhang HT, Zhou W (2014) The phosphodiesterase-4 inhibitor rolipram attenuates heroin-seeking behavior induced by cues or heroin priming in rats. Int J Neuropsychopharmacol 17:1397–1407

Lakics V, Karran EH, Boess FG (2010) Quantitative comparison of phosphodiesterase mRNA distribution in human brain and peripheral tissues. Neuropharmacology 59:367–374

Lantz CL, Wang W, Medina AE (2012) Early alcohol exposure disrupts visual cortex plasticity in mice. Int J Dev Neurosci 30:351–357

Li S, Doss JC, Hardee EJ, Quock RM (2005) Involvement of cyclic GMP-dependent protein kinase in nitrous oxide-induced anxiolytic-like behavior in the mouse light/dark exploration test. Brain Res 1038:113–117

Li YF, Huang Y, Amsdell SL, Xiao L, O'Donnell JM, Zhang HT (2009) Antidepressant- and anxiolytic-like effects of the phosphodiesterase-4 inhibitor rolipram on behavior depend on cyclic AMP response element binding protein-mediated neurogenesis in the hippocampus. Neuropsychopharmacology 34:2404–2419

Liebenberg N, Harvey BH, Brand L, Brink CB (2010) Antidepressant-like properties of phosphodiesterase type 5 inhibitors and cholinergic dependency in a genetic rat model of depression. Behav Pharmacol 21:540–547

Lingford-Hughes A, Watson B, Kalk N, Reid A (2010) Neuropharmacology of addiction and how it informs treatment. Br Med Bull 96:93–110

Liu X, Hao PD, Yang MF, Sun JY, Mao LL, Fan CD, Zhang ZY, Li DW, Yang XY, Sun BL, Zhang HT (2017a) The phosphodiesterase-4 inhibitor roflumilast decreases ethanol consumption in C57BL/6J mice. Psychopharmacology 234:2409–2419

Liu X, Zhong P, Vickstrom C, Li Y, Liu QS (2017b) PDE4 inhibition restores the balance between excitation and inhibition in VTA dopamine neurons disrupted by repeated in vivo cocaine exposure. Neuropsychopharmacology 42:1991–1999

Logrip ML (2015) Phosphodiesterase regulation of alcohol drinking in rodents. Alcohol 49:795–802

Logrip ML, Vendruscolo LF, Schlosburg JE, Koob GF, Zorrilla EP (2014) Phosphodiesterase 10A regulates alcohol and saccharin self-administration in rats. Neuropsychopharmacology 39:1722–1731

Logrip ML, Zorrilla EP (2012) Stress history increases alcohol intake in relapse: relation to phosphodiesterase 10A. Addict Biol 17:920–933

Logrip ML, Zorrilla EP (2014) Differential changes in amygdala and frontal cortex Pde10a expression during acute and protracted withdrawal. Front Integr Neurosci 8:30

Loughney K, Taylor J, Florio VA (2005) 3′,5′-cyclic nucleotide phosphodiesterase 11A: localization in human tissues. Int J Impot Res 17: 320–325

Lugnier C (2006) Cyclic nucleotide phosphodiesterase (PDE) superfamily: a new target for the development of specific therapeutic agents. Pharmacol Ther 109:366–398

Maas JJ, Vogt SK, Chan GC, Pineda VV, Storm DR, Muglia LJ (2005) Calcium-stimulated adenylyl cyclases are critical modulators of neuronal ethanol sensitivity. J Neurosci 25:4118–4126

McClung CA, Nestler EJ (2003) Regulation of gene expression and cocaine reward by CREB and DeltaFosB. Nat Neurosci 6:1208–1215

McLachlan CS, Chen ML, Lynex CN, Goh DL, Brenner S, Tay SK (2007) Changes in PDE4D isoforms in the hippocampus of a patient with advanced Alzheimer disease. Arch Neurol 64:456–457

Medina AE, Krahe TE, Ramoa AS (2006) Restoration of neuronal plasticity by a phosphodiesterase type 1 inhibitor in a model of fetal alcohol exposure. J Neurosci 26:1057–1060

Megens AA, Hendrickx HM, Hens KA, Fonteyn I, Langlois X, Lenaerts I, Somers MV, de Boer P, Vanhoof G (2014) Pharmacology of JNJ-42314415, a centrally active phosphodiesterase 10A (PDE10A) inhibitor: a comparison of PDE10A inhibitors with D2 receptor blockers as potential antipsychotic drugs. J Pharmacol Exp Ther 349:138–154

Menniti FS, Faraci WS, Schmidt CJ (2006) Phosphodiesterases in the CNS: targets for drug development. Nat Rev Drug Discov 5:660–670

Millar JK, Pickard BS, Mackie S, James R, Christie S, Buchanan SR, Malloy MP, Chubb JE, Huston E, Baillie GS, Thomson PA, Hill EV, Brandon NJ, Rain JC, Camargo LM, Whiting PJ, Houslay MD, Blackwood DH, Muir WJ, Porteous DJ (2005) DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling. Science 310:1187–1191

Milton AL, Everitt BJ (2012) The persistence of maladaptive memory: addiction, drug memories and anti-relapse treatments. Neurosci Biobehav Rev 36:1119–1139

Misra K, Pandey SC (2003) Differences in basal levels of CREB and NPY in nucleus accumbens regions between C57BL/6 and DBA/2 mice differing in inborn alcohol drinking behavior. J Neurosci Res 74:967–975

Montesinos J, Alfonso-Loeches S, Guerri C (2016) Impact of the innate immune response in the actions of ethanol on the central nervous system. Alcohol Clin Exp Res 40:2260–2270

Monti B, Marri L, Contestabile A (2002) NMDA receptor-dependent CREB activation in survival of cerebellar granule cells during in vivo and in vitro development. Eur J Neurosci 16:1490–1498

Mori F, Perez-Torres S, De Caro R, Porzionato A, Macchi V, Beleta J, Gavalda A, Palacios JM, Mengod G (2010) The human area postrema and other nuclei related to the emetic reflex express cAMP phosphodiesterases 4B and 4D. J Chem Neuroanat 40:36–42

Muglia LM, Schaefer ML, Vogt SK, Gurtner G, Imamura A, Muglia LJ (1999) The 5′-flanking region of the mouse adenylyl cyclase type VIII gene imparts tissue-specific expression in transgenic mice. J Neurosci 19:2051–2058

Nakayama T, Asai S, Sato N, Soma M (2007) PDE4D gene in the STRK1 region on 5q12: susceptibility gene for ischemic stroke. Curr Med Chem 14:3171–3178

Nelson EJ, Hellevuo K, Yoshimura M, Tabakoff B (2003) Ethanol-induced phosphorylation and potentiation of the activity of type 7 adenylyl cyclase. Involvement of protein kinase C delta. J Biol Chem 278:4552–4560

Nikolaev VO, Gambaryan S, Engelhardt S, Walter U, Lohse MJ (2005) Real-time monitoring of the PDE2 activity of live cells: hormone-stimulated cAMP hydrolysis is faster than hormone-stimulated cAMP synthesis. J Biol Chem 280:1716–1719

Nugent FS, Penick EC, Kauer JA (2007) Opioids block long-term potentiation of inhibitory synapses. Nature 446:1086–1090

Nunes F, Ferreira-Rosa K, Pereira MS, Kubrusly RC, Manhaes AC, Abreu-Villaca Y, Filgueiras CC (2011) Acute administration of vinpocetine, a phosphodiesterase type 1 inhibitor, ameliorates hyperactivity in a mice model of fetal alcohol spectrum disorder. Drug Alcohol Depend 119:81–87

Nunez C, Gonzalez-Cuello A, Sanchez L, Vargas ML, Milanes MV, Laorden ML (2009) Effects of rolipram and diazepam on the adaptive changes induced by morphine withdrawal in the hypothalamic paraventricular nucleus. Eur J Pharmacol 620:1–8

Pandey SC (2003) Anxiety and alcohol abuse disorders: a common role for CREB and its target, the neuropeptide Y gene. Trends Pharmacol Sci 24:456–460

Pandey SC (2004) The gene transcription factor cyclic AMP-responsive element binding protein: role in positive and negative affective states of alcohol addiction. Pharmacol Ther 104:47–58

Pandey SC, Mittal N, Lumeng L, Li TK (1999a) Involvement of the cyclic AMP-responsive element binding protein gene transcription factor in genetic preference for alcohol drinking behavior. Alcohol Clin Exp Res 23:1425–1434

Pandey SC, Roy A, Mittal N (2001a) Effects of chronic ethanol intake and its withdrawal on the expression and phosphorylation of the creb gene transcription factor in rat cortex. J Pharmacol Exp Ther 296:857–868

Pandey SC, Roy A, Zhang H (2003) The decreased phosphorylation of cyclic adenosine monophosphate (cAMP) response element binding (CREB) protein in the central amygdala acts as a molecular substrate for anxiety related to ethanol withdrawal in rats. Alcohol Clin Exp Res 27:396–409

Pandey SC, Roy A, Zhang H, Xu T (2004) Partial deletion of the cAMP response element-binding protein gene promotes alcohol-drinking behaviors. J Neurosci 24:5022–5030

Pandey SC, Saito T, Yoshimura M, Sohma H, Gotz ME (2001b) cAmp signaling cascade: a promising role in ethanol tolerance and dependence. Alcohol Clin Exp Res 25:46S–48S

Pandey SC, Zhang D, Mittal N, Nayyar D (1999b) Potential role of the gene transcription factor cyclic AMP-responsive element binding protein in ethanol withdrawal-related anxiety. J Pharmacol Exp Ther 288:866–878

Pandey SC, Zhang H, Roy A, Xu T (2005) Deficits in amygdaloid cAMP-responsive element-binding protein signaling play a role in genetic predisposition to anxiety and alcoholism. J Clin Invest 115:2762–2773

Perez-Torres S, Miro X, Palacios JM, Cortes R, Puigdomenech P, Mengod G (2000) Phosphodiesterase type 4 isozymes expression in human brain examined by in situ hybridization histochemistry and[3H]rolipram binding autoradiography. Comparison with monkey and rat brain. J Chem Neuroanat 20:349–374

Rabe KF, Bateman ED, O'Donnell D, Witte S, Bredenbroker D, Bethke TD (2005) Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 366:563–571

Ramirez AD, Smith SM (2014) Regulation of dopamine signaling in the striatum by phosphodiesterase inhibitors: novel therapeutics to treat neurological and psychiatric disorders. Cent Nerv Syst Agents Med Chem 14:72–82

Ray LA, Bujarski S, Shoptaw S, Roche DJ, Heinzerling K, Miotto K (2017) Development of the neuroimmune modulator ibudilast for the treatment of alcoholism: a randomized, placebo-controlled, human laboratory trial. Neuropsychopharmacology 42:1776–1788

Reyes-Irisarri E, Perez-Torres S, Mengod G (2005) Neuronal expression of cAMP-specific phosphodiesterase 7B mRNA in the rat brain. Neuroscience 132:1173–1185

Romieu P, Gobaille S, Aunis D, Zwiller J (2008) Injection of the neuropeptide CNP into dopaminergic rat brain areas decreases alcohol intake. Ann N Y Acad Sci 1139:27–33

Rutter AR, Poffe A, Cavallini P, Davis TG, Schneck J, Negri M, Vicentini E, Montanari D, Arban R, Gray FA, Davies CH, Wren PB (2014) GSK356278, a potent, selective, brain-penetrant phosphodiesterase 4 inhibitor that demonstrates anxiolytic and cognition-enhancing effects without inducing side effects in preclinical species. J Pharmacol Exp Ther 350:153–163

Saito T, Lee JM, Hoffman PL, Tabakoff B (1987) Effects of chronic ethanol treatment on the beta-adrenergic receptor-coupled adenylate cyclase system of mouse cerebral cortex. J Neurochem 48:1817–1822

Samson WK, Bianchi R, Mogg R (1988) Evidence for a dopaminergic mechanism for the prolactin inhibitory effect of atrial natriuretic factor. Neuroendocrinology 47:268–271

Schmidt CJ, Chapin DS, Cianfrogna J, Corman ML, Hajos M, Harms JF, Hoffman WE, Lebel LA, McCarthy SA, Nelson FR, Proulx-LaFrance C, Majchrzak MJ, Ramirez AD, Schmidt K, Seymour PA, Siuciak JA, Tingley FR, Williams RD, Verhoest PR, Menniti FS (2008) Preclinical characterization of selective phosphodiesterase 10A inhibitors: a new therapeutic approach to the treatment of schizophrenia. J Pharmacol Exp Ther 325:681–690

Siuciak JA, Chapin DS, Harms JF, Lebel LA, McCarthy SA, Chambers L, Shrikhande A, Wong S, Menniti FS, Schmidt CJ (2006) Inhibition of the striatum-enriched phosphodiesterase PDE10A: a novel approach to the treatment of psychosis. Neuropharmacology 51:386–396

Siuciak JA, Chapin DS, McCarthy SA, Martin AN (2007) Antipsychotic profile of rolipram: efficacy in rats and reduced sensitivity in mice deficient in the phosphodiesterase-4B (PDE4B) enzyme. Psychopharmacology 192:415–424

Smith SM, Uslaner JM, Cox CD, Huszar SL, Cannon CE, Vardigan JD, Eddins D, Toolan DM, Kandebo M, Yao L, Raheem IT, Schreier JD, Breslin MJ, Coleman PJ, Renger JJ (2013) The novel phosphodiesterase 10A inhibitor THPP-1 has antipsychotic-like effects in rat and improves cognition in rat and rhesus monkey. Neuropharmacology 64:215–223

Snyder GL, Vanover KE (2017) PDE inhibitors for the treatment of schizophrenia. Adv Neurobiol 17:385–409

Sohma H, Hashimoto E, Shirasaka T, Tsunematsu R, Ozawa H, Boissl KW, Boning J, Riederer P, Saito T (1999) Quantitative reduction of type I adenylyl cyclase in human alcoholics. Biochim Biophys Acta 1454:11–18

Sotty F, Montezinho LP, Steiniger-Brach B, Nielsen J (2009) Phosphodiesterase 10A inhibition modulates the sensitivity of the mesolimbic dopaminergic system to D-amphetamine: involvement of the D1-regulated feedback control of midbrain dopamine neurons. J Neurochem 109:766–775

Stoltenberg SF (2003) Serotonergic agents and alcoholism treatment: a simulation. Alcohol Clin Exp Res 27:1853–1859

Suzuki K, Harada A, Shiraishi E, Kimura H (2015) In vivo pharmacological characterization of TAK-063, a potent and selective phosphodiesterase 10A inhibitor with antipsychotic-like activity in rodents. J Pharmacol Exp Ther 352:471–479

Swart PC, Currin CB, Russell VA, Dimatelis JJ (2017) Early ethanol exposure and vinpocetine treatment alter learning- and memory-related proteins in the rat hippocampus and prefrontal cortex. J Neurosci Res 95:1204–1215

Thiriet N, Jouvert P, Gobaille S, Solov'Eva O, Gough B, Aunis D, Ali S, Zwiller J (2001) C-type natriuretic peptide (CNP) regulates cocaine-induced dopamine increase and immediate early gene expression in rat brain. Eur J Neurosci 14:1702–1708

Thompson BE, Sachs BD, Kantak KM, Cherry JA (2004) The type IV phosphodiesterase inhibitor rolipram interferes with drug-induced conditioned place preference but not immediate early gene induction in mice. Eur J Neurosci 19:2561–2568

Torregrossa MM, Corlett PR, Taylor JR (2011) Aberrant learning and memory in addiction. Neurobiol Learn Mem 96:609–623

Uzbay IT, Celik T, Aydin A, Kayir H, Tokgoz S, Bilgi C (2004) Effects of chronic ethanol administration and ethanol withdrawal on cyclic guanosine 3′,5′-monophosphate (cGMP) levels in the rat brain. Drug Alcohol Depend 74:55–59

Valverius P, Hoffman PL, Tabakoff B (1989) Hippocampal and cerebellar beta-adrenergic receptors and adenylate cyclase are differentially altered by chronic ethanol ingestion. J Neurochem 52:492–497

van der Staay FJ, Rutten K, Barfacker L, Devry J, Erb C, Heckroth H, Karthaus D, Tersteegen A, van Kampen M, Blokland A, Prickaerts J, Reymann KG, Schroder UH, Hendrix M (2008) The novel selective PDE9 inhibitor BAY 73-6691 improves learning and memory in rodents. Neuropharmacology 55:908–918

Volke V, Wegener G, Vasar E (2003) Augmentation of the NO-cGMP cascade induces anxiogenic-like effect in mice. J Physiol Pharmacol 54:653–660

Walters CL, Blendy JA (2001) Different requirements for cAMP response element binding protein in positive and negative reinforcing properties of drugs of abuse. J Neurosci 21:9438–9444

Walton M, Woodgate AM, Muravlev A, Xu R, During MJ, Dragunow M (1999) CREB phosphorylation promotes nerve cell survival. J Neurochem 73:1836–1842

Wang C, Yang XM, Zhuo YY, Zhou H, Lin HB, Cheng YF, Xu JP, Zhang HT (2012) The phosphodiesterase-4 inhibitor rolipram reverses Abeta-induced cognitive impairment and neuroinflammatory and apoptotic responses in rats. Int J Neuropsychopharmacol 15:749–766

Wen RT, Feng WY, Liang JH, Zhang HT (2015) Role of phosphodiesterase 4-mediated cyclic AMP signaling in pharmacotherapy for substance dependence. Curr Pharm Des 21:355–364

Wen RT, Liang JH, Zhang HT (2017) Targeting phosphodiesterases in pharmacotherapy for substance dependence. Adv Neurobiol 17: 413–444

Wen RT, Zhang M, Qin WJ, Liu Q, Wang WP, Lawrence AJ, Zhang HT, Liang JH (2012) The phosphodiesterase-4 (PDE4) inhibitor rolipram decreases ethanol seeking and consumption in alcohol-preferring fawn-hooded rats. Alcohol Clin Exp Res 36:2157–2167

Wennogle LP, Hoxie H, Peng Y, Hendrick JP (2017) Phosphodiesterase 1: a unique drug target for degenerative diseases and cognitive dysfunction. Adv Neurobiol 17:349–384

Werner C, Raivich G, Cowen M, Strekalova T, Sillaber I, Buters JT, Spanagel R, Hofmann F (2004) Importance of NO/cGMP signalling via cGMP-dependent protein kinase II for controlling emotionality and neurobehavioural effects of alcohol. Eur J Neurosci 20:3498–3506

Xia ZG, Refsdal CD, Merchant KM, Dorsa DM, Storm DR (1991) Distribution of mRNA for the calmodulin-sensitive adenylate cyclase in rat brain: expression in areas associated with learning and memory. Neuron 6:431–443

Xu Y, Pan J, Sun J, Ding L, Ruan L, Reed M, Yu X, Klabnik J, Lin D, Li J, Chen L, Zhang C, Zhang H, O'Donnell JM (2015) Inhibition of phosphodiesterase 2 reverses impaired cognition and neuronal remodeling caused by chronic stress. Neurobiol Aging 36:955–970

Xu Y, Zhang HT, O'Donnell JM (2011) Phosphodiesterases in the central nervous system: implications in mood and cognitive disorders. Handb Exp Pharmacol 204:447–485

Yang X, Diehl AM, Wand GS (1996) Ethanol exposure alters the phosphorylation of cyclic AMP responsive element binding protein and cyclic AMP responsive element binding activity in rat cerebellum. J Pharmacol Exp Ther 278:338–346

Yang X, Horn K, Baraban JM, Wand GS (1998a) Chronic ethanol administration decreases phosphorylation of cyclic AMP response element-binding protein in granule cells of rat cerebellum. J Neurochem 70:224–232

Yang X, Horn K, Wand GS (1998b) Chronic ethanol exposure impairs phosphorylation of CREB and CRE-binding activity in rat striatum. Alcohol Clin Exp Res 22:382–390

Yoshimura M, Tabakoff B (1995) Selective effects of ethanol on the generation of cAMP by particular members of the adenylyl cyclase family. Alcohol Clin Exp Res 19:1435–1440

Zalewska-Kaszubska J, Gorska D, Dyr W, Czarnecka E (2008) Lack of changes in beta-endorphin plasma levels after repeated treatment with fluoxetine: possible implications for the treatment of alcoholism–a pilot study. Pharmazie 63:308–311

Zee RY, Brophy VH, Cheng S, Hegener HH, Erlich HA, Ridker PM (2006) Polymorphisms of the phosphodiesterase 4D, cAMP-specific (PDE4D) gene and risk of ischemic stroke: a prospective, nested case-control evaluation. Stroke 37:2012–2017

Zhang HT (2009) Cyclic AMP-specific phosphodiesterase-4 as a target for the development of antidepressant drugs. Curr Pharm Des 15: 1688–1698

Zhang HT, Crissman AM, Dorairaj NR, Chandler LJ, O'Donnell JM (2000) Inhibition of cyclic AMP phosphodiesterase (PDE4) reverses memory deficits associated with NMDA receptor antagonism. Neuropsychopharmacology 23:198–204

Zhang HT, Huang Y, Jin SL, Frith SA, Suvarna N, Conti M, O'Donnell JM (2002) Antidepressant-like profile and reduced sensitivity to rolipram in mice deficient in the PDE4D phosphodiesterase enzyme. Neuropsychopharmacology 27:587–595

Zhang HT, Huang Y, Masood A, Stolinski LR, Li Y, Zhang L, Dlaboga D, Jin SL, Conti M, O'Donnell JM (2008) Anxiogenic-like behavioral phenotype of mice deficient in phosphodiesterase 4B (PDE4B). Neuropsychopharmacology 33:1611–1623

Zhang HT, Huang Y, Suvarna NU, Deng C, Crissman AM, Hopper AT, De Vivo M, Rose GM, O'Donnell JM (2005) Effects of the novel PDE4 inhibitors MEM1018 and MEM1091 on memory in the radial-arm maze and inhibitory avoidance tests in rats. Psychopharmacology 179:613–619

Zhang HT, Zhao Y, Huang Y, Deng C, Hopper AT, De Vivo M, Rose GM, O'Donnell JM (2006) Antidepressant-like effects of PDE4 inhibitors mediated by the high-affinity rolipram binding state (HARBS) of the phosphodiesterase-4 enzyme (PDE4) in rats. Psychopharmacology 186:209–217

Zhong P, Wang W, Yu F, Nazari M, Liu X, Liu QS (2012) Phosphodiesterase 4 inhibition impairs cocaine-induced inhibitory synaptic plasticity and conditioned place preference. Neuropsychopharmacology 37:2377–2387

Zocchi A, Girlanda E, Varnier G, Sartori I, Zanetti L, Wildish GA, Lennon M, Mugnaini M, Heidbreder CA (2003) Dopamine responsiveness to drugs of abuse: a shell-core investigation in the nucleus accumbens of the mouse. Synapse 50:293–302