Chapter 15
Targeting Phosphodiesterases in Pharmacotherapy for Substance Dependence

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Abstract Substance dependence is a chronic relapsing brain disorder associated with adaptational changes in synaptic plasticity and neuronal functions. The high levels of substance consumption and relapse rate suggest more reliable medications are in need to better address the underlying causes of this disease. It has been well established that the intracellular second messengers cyclic AMP (cAMP) and cyclic GMP (cGMP) and their signaling systems play an important role in the molecular mechanisms of substance taking behaviors. On this basis, the phosphodiesterase (PDE) superfamily, which crucially controls cyclic nucleotide levels by catalyzing their hydrolysis, has been proposed as a novel class of therapeutic targets for substance use disorders. This chapter reviews the expression patterns of PDEs in the brain with regard to neural structures underlying the dependent process and highlights available evidence for a modulatory role of PDEs in substance dependence.

Keywords Substance dependence • Central nervous system • cAMP • cGMP • Signal transduction • Phosphodiesterase

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15.1 Introduction

Substance dependence, also known as drug addiction, is a chronic relapsing brain disorder. It can be characterized by compulsive and repetitive use of alcohol, nicotine or other drugs of abuse despite negative consequences, as well as multiple physical and psychological signs indicating tolerance and withdrawal (American Psychiatric Association 2000; World Health Organization 2004). Misuse of substances constitutes one of the most serious public health issues worldwide, which requires more reliable medical approaches to better control substance consumption and the high relapse rates. Exploration into specific mechanisms of the dependent process may contribute to uncover novel therapeutic targets for medication development.

From a neurobiological perspective, dependence can be defined as an adaptive state of the central nervous system (CNS) (Koob and Le Moal 1997; Koob 2003a). This process is associated with abnormal synaptic plasticity and a series of neuronal dysfunctions that possibly develop as early as the first exposure to addictive substances (Wang et al. 2014; Pandey et al. 2005a; Jing et al. 2011; Qin et al. 2013; Liu et al. 2012; Luo et al. 2011). The best established molecular mechanism of the adaptational changes in individual neuron involves dysregulated intracellular signal transduction, especially in the second messengers cyclic AMP (cAMP) and cyclic GMP (cGMP) as well as their signaling systems (Peregud et al. 2013; Pandey et al. 2005a; Nestler 2004; Javadi et al. 2013). Accumulating evidence indicates that altered activity of cAMP and/or cGMP signaling plays an important role in the motivational aspects, rewarding properties, and relapsing features of substance taking behaviors (Pandey et al. 2001, b; Wen et al. 2015; Kleppisch and Feil 2009).

Intracellular cAMP and cGMP signal transduction is triggered by elevated levels of cAMP and cGMP, which are generated by adenylyl cyclase (AC) and guanylyl cyclase (GC), respectively. However, the concentrations of these cyclic nucleotides are crucially determined by the activity of phosphodiesterases (PDEs), which represent the only known enzyme superfamily that catalyze the hydrolysis of cAMP and cGMP. PDEs have been studied for about six decades and consist of more than 100 different protein products transcribed from at least 21 genes in human genome (Lugnier 2006). All PDE isoforms can be identified in 11 families (PDE 1–11) according to their structural and functional characteristics (Lugnier 2006; Bender and Beavo 2006), and are classified into three groups based on their substrates: cAMP-specific PDEs (PDE4, PDE7, PDE8), cGMP-specific PDEs (PDE5, PDE6, PDE9), or dual substrate PDEs (PDE1, PDE2, PDE3, PDE10, PDE11). Most mammalian cell types express PDEs. In the CNS, which contains all the PDE isoforms (Menniti et al. 2006), the activity of PDEs have been reported as essential regulators for multiple CNS functions, including synaptic plasticity (Sanderson and Sher 2013), learning and memory (Blokland et al. 2006; Rose et al. 2005). Based on the significant involvement of cAMP and cGMP signaling in the key features of substance taking behaviors, PDEs have been proposed as potential therapeutic targets for substance use and abuse (Logrip 2015; Mu et al. 2014; Lai et al. 2014; Thompson

et al. 2004; Iyo et al. 1995; Wen et al. 2015). This chapter provides an overview of PDE expression profiles in the brain with regard to neural structures underlying the dependent process and highlights recent evidence that implicates a regulatory role of PDEs in substance dependence.

15.2 Neural Structures Underlying Substance Dependence

Neurobiological responses to addictive substances involve complex interactions between different parts of the CNS (Daglish et al. 2005). Although differing in primary actions on the brain, addictive substances are likely to share similar neural mechanisms underlying their rewarding properties and dependent process (Li et al. 2008; Nestler 2005). The limbic corticostriatal circuitry, consisting of neural circuit across multiple limbic cortical brain regions, has been considered as the key neural system mediating the motivation, rewarding, and behavior response to substances of abuse (Lingford-Hughes et al. 2010). The development of dependence can be seen as a dysfunction of these processes. Among the key brain structures in this circuitry, the nucleus accumbens (NAc), ventral tegmental area (VTA), amygdala, and hippocampus are of most importance to the dependent process. Their general function and neurochemical modulation will be briefly discussed here.

In the initial steps of dependent behaviors, psychoactive substances exert their euphoric and rewarding effects mainly through activation of the mesolimbic dopaminergic system, which begins in the VTA of the midbrain and projects to the NAc and prefrontal cortex (Moore and Bloom 1978). Preclinical studies have shown that increased dopamine (DA) release in the NAc represents the primary regulator of rewarding properties for nearly all substances of misuse (Hyman and Malenka 2001; Chao and Nestler 2004; Imperato and Di Chiara 1986). This up-regulation of DA levels can be attributed to stimulation of dopaminergic neurons in the VTA (e.g. opiates, alcohol), DA reuptake blockade in the NAc (e.g. cocaine), or blockade combined with DA release from neuronal terminals (e.g. amphetamine) (Lingford-Hughes et al. 2010). The NAc can be divided into core (NAcC) and shell (NAcSh) subregions based on different morphology and functions (Heimer et al. 1991). The NAcC, which is linked to the caudate putamen and substantia nigra, is involved in motor function that facilitates reward acquisition (Heimer et al. 1997). However, the NAcSh shares similar afferent projections and neurochemical modulation with the central nucleus of the amygdala (CeA), leading to its inclusion in the "extended amygdala" (EA) structure (Koob 2003a). Addictive substances usually cause higher DA release in the NAcSh than in the NAcC (Zocchi et al. 2003). Therefore, the NAc, especially the NAcSh, takes part in the initial positive reinforcement of addictive substance exposure, contributing to habit-forming patterns of substance use.

Studies to date indicate that, despite positive reinforcing properties of addictive substances, the anhedonic or dysphoric states (e.g. anxiety, depression) derived from pre-existing conditions or substance withdrawal are also implicated as a negative reinforcer in substance use and abuse (Koob 2003b; Thompson et al. 2012;

Koob and Kreek 2007). Continuous substance consumption or relapse is considered as a way to alleviate these aversive conditions (Koob et al. 1993; Pandey 2003). The amygdala appears to be closely involved in modulating the negative emotional states (Koob et al. 1998; Pandey 2004). The interconnected nuclei of the amygdala can be grouped into the central, medial, and basolateral divisions, each with different afferent and efferent projections (Pitkanen et al. 1997). The central and medial amygdala (CeA and MeA, respectively), which represent major components of the EA structure, are shown to be critical for the innate and withdrawal-induced dysphoric reactions, especially anxiety-like behaviors (Koob et al. 1998; Moonat et al. 2010). Dysregulated neural functions in the CeA and MeA can offer genetic predisposition to excessive substance use in animal models (Moonat et al. 2013; Pandey et al. 2005a, b; Prakash et al. 2008). On the other hand, the basolateral nuclei of amygdala (BLA) is necessary for motivational value or sensory specific properties of substance reinforcers (Fuchs and See 2002; Fuchs et al. 2006). Lesions of the BLA disrupt drug-seeking behavior in rodent models (Fuchs and See 2002; Meil and See 1997). Moreover, the nonadrenergic nucleus of locus coeruleus (LC) is specifically involved in the development of opiate dependence and withdrawal. Biochemical changes in LC regulate chronic actions of opiates and attenuate somatic signs of opiate withdrawal symptoms (Han et al. 2006; Lane-Ladd et al. 1997; Punch et al. 1997; Guitart et al. 1992).

The hippocampus is an important brain structure for declarative memory, i.e. memory of events and facts. To some extent, physical and psychological dependence to addictive substances can be conceptualized as maladaptive memories obtained from repeated substance exposure (Milton and Everitt 2012). It has been well-established that exposure to contexts previously associated with drug use can promote relapse in both human and animal models (O'Brien et al. 1992; Kearns and Weiss 2007). Inactivation of the dorsal hippocampus leads to reduction in the context-induced reinstatement of drug seeking in rodents (Fuchs et al. 2007; Fuchs et al. 2005). Meanwhile, neurogenesis in the hippocampus has been shown to alleviate anxiety and depression, two important factors that can promote substance taking behaviors (Li et al. 2009; Li et al. 2011).

15.3 Biodistribution of PDEs in the Brain

In situ hybridization is widely used in examining mRNA expression of a single PDE subtype in different brain regions, and shows more consistent results than immunohistochemistry detecting PDE protein expression (Bender and Beavo 2006). The later application of quantitative real-time polymerase chain reaction (RT-PCR) has enabled quantitative comparison of the expression levels for all PDEs in different tissues (Lakics et al. 2010). Available data shows that PDEs are widely distributed in the brain in a tissue- and cell-specific manner, and their expression patterns are distinct among different subtypes.

15.3.1 cAMP-Specific PDEs

Among the 11 PDE families, PDE4 is most important in the control of intracellular cAMP (Zhang 2009). There are four subtypes (PDE4A, 4B, 4C, and 4D) and at least 25 different splice variants of PDE4, among which PDE4B is most highly expressed across the human brain (Lakics et al. 2010). PDE4B is abundantly expressed in the cortex, amygdala, striatum, hippocampus, hypothalamus, and cerebellum, suggesting its possible role in DA-associated and emotion-related processes (Zhang 2009). PDE4A and PDE4D share a similar distribution pattern with PDE4B but at lower expression levels in DA-enriched brain regions. Relative abundant expression of PDE4D in area postrema and nucleus of solitary tract may account for the side effects of nausea and emesis associated with PDE4 inhibitor treatment (Perez-Torres et al. 2000). In contrast to these PDE4 subtypes, PDE4C is predominantly located in peripheral tissues, with little CNS functions.

The PDE7 family is encoded by two genes, PDE7A and 7B. Relatively low levels of PDE7 mRNA are detected in the hippocampus, cortex, striatum, and hypothalamus, with PDE7B as the major isoform (Reyes-Irisarri et al. 2005; Lakics et al. 2010). PDE7B has a very selective and high expression in the Purkinje cells.

PDE8 expression is detected throughout the human brain, albeit at relative low levels. PDE8 has two subtypes, PDE8A and 8B. PDE8A mRNA levels are similar to PDE8B in the cerebellum, thalamus, and substantia nigra, but lower in all other CNS tissues. To date, no data regarding the effects of PDE8 inhibitors have been reported.

15.3.2 cGMP-Specific PDEs

PDE5A, the only isoform of PDE5, is expressed in cerebellar Purkinje neurons. Its expression level appears to be very low in the human brain compared with other PDEs.

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

Moderate levels of PDE9A mRNA are present in cerebellar Purkinje cells, hippocampus, hypothalamus, and substantia nigra. A selective PDE9 inhibitor has been shown to improve learning and memory in rodents (van der Staay et al. 2008).

15.3.3 PDEs with Dual Enzyme Specificity

Three subtypes of PDE1 (PDE1A, 1B, and 1C) have been shown to exhibit comparable distribution patterns in the human brain, with PDE1A expressed at the lowest levels. PDE1B and PDE1C are highly distributed in the cortex, hippocampus, striatum, substantia nigra, and cerebellum. PDE1B is the most prevalent PDE isoform in

the NAc, while PDE1B together with PDE10A is the most abundant in the caudate nucleus. The high levels of PDE1B in the caudate putamen and NAc indicate its possible enrollment in rewarding and motivational behaviors. Compared to PDE1B, PDE1C has much higher expression levels in the substantia nigra and hypothalamus and similar expression levels in the cortex, hippocampus, and cerebellum.

PDE2A is found highly expressed across the human brain. It represents the most prevalent PDE in hippocampal and cortical regions and second highest in the NAc, supporting its role in learning, memory, and rewarding properties (Boess et al. 2004).

PDE3 is comprised of PDE3A and PDE3B. It shows relatively high levels only in the cerebellum, with negligible expression in other parts of the brain.

PDE10A shows high levels of expression in the striatum, substantia nigra, cerebellum, and hypothalamus. In the caudate nucleus, it is one of the two most prevalent PDE, the other being PDE1B. Selective inhibition of PDE10 has been shown to exhibit antipsychotic activity in rodent models, indicating therapeutic potential of PDE10 inhibitors in schizophrenia (Siuciak et al. 2006; Schmidt et al. 2008).

PDE11 is the most recently described PDE family, with PED11A being the only isoform. PDE11A is present at particularly low levels in most brain regions in human except the dorsal root ganglia.

The distinct distribution patterns and substrate-specific modulation of PDE isoenzymes indicate their potential regulation of different neural functions. Therapeutic effects may be achieved via chemical or biological manipulation of specific PDE isoforms, although studies regarding their CNS functions are needed for further demonstrations.

15.4 Cyclic Nucleotide Signaling in Substance Dependence

The main cellular signal pathways sensitive to PDE regulation are the second messenger cAMP and cGMP signal transduction together with the cyclic nucleotide-gated ion channels (Podda and Grassi 2014). In the cAMP signal system, AC catalyzed cAMP generation is functionally coupled to multiple neuronal receptors via guanine nucleotide binding proteins (G proteins). Elevated cAMP levels ultimately lead to phosphorylation of the gene transcription factor cAMP response element-binding protein (CREB) via cAMP-dependent protein kinase (PKA). CREB occupies a central position for the interaction of multiple intracellular signal cascades, including the signal pathways from Ras to extracellular regulated kinases (ERK1/2) and p38 mitogen activated protein kinase (MAPK) (Impey et al. 1999; Mayr and Montminy 2001; Lonze and Ginty 2002). Phosphorylated CREB (pCREB) regulates gene expression by binding to the cAMP response element (CRE) region in the promoter regions of their target genes (Shaywitz and Greenberg 1999). The above impacts of the cAMP signaling render it a critical modulator in experience-based neuroadaptations. On the other hand, intracellular cGMP is synthesized by cytosolic soluble guanylyl cyclases (sGCs) and membrane-bound particulate guanylyl cyclases (pGCs) in response to nitric oxide (NO) and natriuretic peptides

(NP), respectively. Elevated cGMP levels activate cGMP-dependent protein kinase (PKG) and alter cellular functions via phosphorylation of substrate proteins. In comparison with PKA, PKG plays only a minor role in the regulation of CRE-dependent gene transcription (Collins and Uhler 1999). However, both cAMP- and cGMP-mediated signals have been shown to play an integral role in patterning behavior responses to substance exposure.

15.4.1 cAMP Signal Transduction

Signal transduction triggered by cAMP, Ca^{2+}, neurotrophic factors, or other cellular stimuli ultimately culminates in specific gene expression patterns via CREB phosphorylation or dephosphorylation (Xing et al. 1998; Impey et al. 1999; Lonze and Ginty 2002). For addictive substances with primary actions on G protein coupled receptors (GPCRs) (e.g. opiates and cannabis), stimulatory or inhibitory G-proteins (Gs or Gi, respectively) mediates their post-receptor actions via CREB phosphorylation or dephosphorylation. Likewise, substances with primary actions on other types of targets (e.g. alcohol and cocaine) also induce functional changes in cAMP signal system. Since CREB has been implicated in the expression of many immediate early genes (e.g. c-fos) and neuropeptide genes [e.g. neuropeptide Y (NPY)], CREB phosphorylation may be an important early nuclear event mediating long-term consequences of substance use and abuse. Moreover, DA represent the common modulator for euphoric effects of most addictive substances, with its D_1 (D1, D5)- and D_2 (D2, D3 and D4)-like receptors all coupled to G proteins (Hopf et al. 2003; Kebabian and Greengard 1971). On these grounds, it is hypothesized that the cAMP signaling represents a common route for intracellular actions induced by addictive substances in the CNS (Table 15.1).

The three types of opioid receptors (μ, δ, and κ) all belong to the GPCR superfamily. Opiates mainly act on the μ-opioid receptors (MORs) which are negatively coupled to AC-activated cAMP generation via inhibitory Gi proteins (Childers 1991). Acute morphine exposure *in vitro* down-regulates cAMP signal transduction in neurons and brain tissues of the striatum, frontal cortex, LC, and dorsal raphe (Kaplan et al. 1998; Duman et al. 1988). Compounds that increase intracellular cAMP levels attenuate morphine-induced discriminative-stimulus effects in the rat models, indicating they decrease the reinforcing properties of morphine (Yan et al. 2006). On the contrary, chronic opiate exposure leads to a compensatory up-regulation of the cAMP signaling in a brain region-specific manner (Nestler and Aghajanian 1997; Kaplan et al. 1998; Duman et al. 1988). The LC and dorsal root ganglion/spinal cord exhibit enhanced levels of AC and PKA after chronic morphine exposure, while the NAc and amygdala show increased AC and PKA activity, and the thalamus shows increased PKA activity only (Nestler 2015; Kaplan et al. 1998; Duman et al. 1988). Activated cAMP transduction is also detected following opiate removal or naloxone administration, which may contribute to features of withdrawal (Kaplan et al. 1998; Guitart et al. 1992). Decreased CREB levels in the

Table 15.1 Main types of addictive substances and their impact on cAMP signal transduction

Category	Substances	Primary action target	cAMP signal transduction		
			Acute exposure	Chronic exposure	Withdrawal
Opiates	Morphine	MOR (GPCR)	↓	↑	↑
	Heroin	MOR (GPCR)		↑	↑
Cannabis		CB1 receptor (GPCR)	↓	↑/↓	
Sedatives	Alcohol	GABA/glutamate receptor	↑	↓/–	↓/↑
Stimulants	Amphetamine		↑	↓	↓
	Methamphetamine		↑	↑	↑/↓
	Cocaine	DA transporter	↑	↑/↓	↑/↓
	Nicotine	N-AChR	–	↓	↑/↓

↑ increase in levels or function,↓ decrease in levels or function, – remain unchanged, *MOR* μ-opioid receptor, *GPCR* G-protein coupled receptor, *GABA* γ-aminobutyric acid, *N-AChR* nicotinic acetylcholine receptor

LC via genetic CREB knockout or knockdown attenuate the severity of opiate withdrawal symptoms (Lane-Ladd et al. 1997; Punch et al. 1997; Maldonado et al. 1996; Han et al. 2006). Thus, alterations in the cAMP pathway are involved in both the acute reinforcing effects of and long-term adaptive responses to opiate exposure (Lane-Ladd et al. 1997; Punch et al. 1997), supporting a crucial role of the cAMP signals in opiate dependent process. Similar cAMP modulation is observed with heroin. In rodents exhibiting heroin-seeking behaviors, activated cAMP signaling can reduce the rewarding properties of heroin (Sun et al. 2015). Chronic heroin treatment increases AC activity, cAMP generation and CREB phosphorylation in the rat NAc, while spontaneous withdrawal increases pCREB in the caudate putamen (Jiang et al. 2012; Edwards et al. 2009). Agents that inhibit cAMP signal transduction alleviate heroin withdrawal symptoms (Jiang et al. 2012). However, in humans, chronic heroin consumption leads to decreased amount and activity of AC in the temporal cortex (TC), but not the NAc, of heroin addicted brains, indicating a down-regulating mechanism of cAMP signaling (Shichinohe et al. 2001; Shichinohe et al. 1998).

The endogenous cannabinoid (CB) receptors, including CB1, CB2 receptors, and GPR55, are all functionally coupled to G proteins (Baker et al. 2006; Munro et al. 1993). Upon cannabis derivative binding, CB receptors negatively regulate AC activity and inhibit cAMP signal transduction via Gi proteins. CB1 (the brain type) receptors, with confined expression on presynaptic terminals, represent the predominant type of CB receptors expressed in the CNS, while CB2 (the peripheral type) receptors are mainly located in leukocytes of peripheral tissues (Pertwee et al. 2010). Activation of CB1 receptors usually causes inhibition of neurotransmitter release. The reduction of inhibitory neurotransmitters, such as γ-aminobutyric acid (GABA), is critically responsible for stress and reward mechanisms related to cannabis dependence.

Alcohol has many different effects on the CNS. The pleasurable effects are thought to be mediated via MORs in the VTA, while other effects, such as ataxia, sedation and anxiolysis, are mediated through the GABA-benzodiazepine receptor complex (Lingford-Hughes et al. 2010). Acute ethanol exposure causes activation in cAMP signal transduction both *in vitro* (Asher et al. 2002; Constantinescu et al. 2002; Gordon et al. 1986) and *in vivo* (Asyyed et al. 2006; Yang et al. 1996), which might be attributed to stimulation in AC activity (Nelson et al. 2003; Yoshimura and Tabakoff 1995). Among the nine membrane-bound AC isoforms (AC1–9), the activity of AC7 is most sensitive to ethanol exposure with 2–3 fold greater cAMP generation than other isoforms (Yoshimura and Tabakoff 1995; Yoshimura and Tabakoff 1999). On the other hand, chronic ethanol treatment attenuates acute ethanol induced rapid increase in cAMP signal transduction. Decreased cAMP signaling is detected in the mouse cortex (Saito et al. 1987) and hippocampus (Valverius et al. 1989) as well as in the rat cerebellum (Yang et al. 1996, Yang et al. 1998a, b) and striatum (Yang et al. 1998a, b) after long-term alcohol exposure. It should be noted that chronic voluntary ethanol intake decreases CREB phosphorylation in the NAcSh, but not the NAcC, in rats (Li et al. 2003; Misra et al. 2001). Down-regulated cAMP signaling is also found in the rat cortex and CeA in response to ethanol withdrawal, while CREB phosphorylation and CRE-DNA binding ability in the cortical structure remain unaffected during long-term ethanol exposure (Pandey et al. 2001a, b; Pandey et al. 2003; Pandey et al. 1999a, b). In contrast, hippocampal pCREB levels in the rat brain are increased during ethanol withdrawal after being decreased by chronic ethanol treatment (Bison and Crews 2003). Thus, different neurons or brain regions may differ in intracellular cAMP signal transduction in response to ethanol exposure, which ultimately results in distinct alcohol-induced effects.

In addition to mediating the intracellular actions of alcohol, key elements of the cAMP signaling have been proposed to act as genetic factors for the predisposition and modulation of alcohol tolerance and dependence. AC1 and AC8 are the only AC isoforms primarily activated by calcium through activation of calmodulin. Decreased AC1 levels have been found in cortical structures of postmortem brains from clinical alcoholic patients who have been abstinent from alcohol for at least 6 months (Sohma et al. 1999; Hashimoto et al. 1998). The subsequent RT-PCR analysis has shown that mRNA levels of AC1 and AC8 are lower in blood cells of alcoholics with a positive family history compared to non-drinker controls (Sohma et al. 1999). In preclinical studies, Muglia and colleagues have demonstrated that AC1 knockout mice display enhanced sensitivity to ethanol-induced sedative effect, while AC8 knockout lead to decreased voluntary ethanol intake (Maas et al. 2005). In contrast, mice lacking AC5 display increased ethanol intake and preference as well as reduced sensitivity to ethanol sedation (Kim et al. 2011). The opposite modulation pattern of AC5 compared with AC1 and AC8 may be attributed to its different brain distribution feature. AC5 shows a preferential concentration in the dorsal striatum and NAc (Kim et al. 2008), while calmodulin-sensitive AC1 and AC8 are predominantly expressed in olfactory system and neocortex (Muglia et al. 1999; Xia et al. 1991). On the other hand, Pandey and colleagues have found that CREB, pCREB, and downstream NPY expression are innately lower in the NAcSh, but not in the NAcC,

of alcohol-preferring C57BL/6 (C57) mice compared to non-preferring DBA/2 (DBA) mice (Misra and Pandey 2003; Belknap et al. 1993). Similarly, levels of CREB and pCREB have been shown to be lower in the CeA and MeA, but not in the BLA, in alcohol-preferring (P) rats compared with non-preferring (NP) rats.

A major negative reinforcer of alcohol use and abuse is anxiety. Correspondingly, brain-region specific deficits of CREB function mentioned in the preceding paragraph correlated with anxiety-like behavior and higher alcohol preference in P rats (Pandey et al. 2005a, b; Pandey et al. 1999a, b). Pandey and co-workers have shown increased anxiety-like behavior and higher ethanol preference in CREB-haplodeficient mice compared to wild-type littermates (Pandey et al. 2004); they also demonstrated that infusions of the PKA inhibitor Rp-cAMP into the CeA inhibited CREB phosphorylation provoked anxiety-like behavior and increased ethanol consumption in NP rats (Pandey et al. 2005a, b). In contrast, acute ethanol treatment via voluntary intake or systemic injections increases pCREB levels and produce anxiolytic-like effects in P rats, but not in NP rats. Pharmacological activation of CREB signaling in the CeA by the PKA activator Sp-cAMP or NPY decreases both anxiety levels and ethanol consumption in P rats. These results suggest an important role of CREB function in anxiety-like and alcohol drinking behaviors. In addition to being associated with an innately higher alcohol preference, anxiety is involved in withdrawal symptoms. Sprague-Dawley (SD) rats withdrawn from ethanol after chronic exposure display anxiety-like behavior, which is correlated with decreased levels of pCREB and NPY in the CeA or MeA, while expression of total CREB remains unchanged (Pandey et al. 2003). Infusions of Sp-cAMP directly into the CeA increase pCREB and NPY expression to normal levels, and prevent the development of anxiety-like behavior in response to abstinence in SD rats. In contrast, Rp-cAMP infusions into the CeA decrease CREB phosphorylation and provoke anxiety and increase alcohol preference in normal SD rats (Pandey et al. 2003). Taken together, these results suggest the activity of cAMP signaling is negatively related to alcohol drinking behavior. Deficits of CREB activation in the NAc and/or CeA, either innately or due to alcohol withdrawal, may promote alcohol intake; blocking these deficits may decrease alcohol consumption and prevent alcohol addiction.

Although psychostimulants, such as amphetamine, cocaine, and nicotine, don't directly act on GPCRs, altered cAMP signal transduction is also found as neuronal response to these drug exposure. Acute and chronic amphetamine treatment causes increased CREB phosphorylation and CRE-mediated transcription in rodent striatum and primary striatal cultures (Konradi et al. 1994; Turgeon et al. 1997; Shaw-Lutchman et al. 2003; Cole et al. 1995). CREB has also been shown to be necessary for amphetamine induced *c-fos* gene expression and possibly the long-term adaptive responses of amphetamine administration (Konradi et al. 1994). Similar modulatory patterns have also observed following methamphetamine exposure. Extended access to methamphetamine self-administration causes increased stiatal and hippocampal CREB phosphorylation and downstream gene expression in rat models (Krasnova et al. 2016; Liu et al. 2014). Likewise, both acute and chronic cocaine treatment results in increased cAMP generation and signal transduction in the NAc neurons of rats (Terwilliger et al. 1991; Zhdanova and Giorgetti 2002). However, continuous intracerebroventricular

(ICV) infusions of cocaine decreases CREB phosphorylation in the rat caudate putamen (Di Benedetto et al. 2007), indicating a brain region-specific pattern of cocaine action on cAMP signaling. Chronic intermittent administration of psychostimulants, such as cocaine and amphetamine, can produce a sensitized behavioral response characterized by locomotor hyperactivity and stereotyped behavior in rodent models (Post and Rose 1976). This behavioral sensitization involves the changes in mesolimbic DA systems (Heidbreder et al. 1996; Parsons and Justice 1993; Post and Rose 1976), and is thought to underlie drug craving and relapse (Steketee 2005). Pretreatment with selective AC activator in the VTA induces sensitization to the locomotor stimulant effects of amphetamine and cocaine, while intra-VTA microinjection of PKA inhibitor blocks amphetamine-induced behavioral sensitization (Tolliver et al. 1996). Similarly, concurrent intra-NAc injection of 8-bromo-cAMP, an analogue of cAMP which activates PKA, increases locomotor activity in responses to acute cocaine exposure and the subsequent challenge (Miserendino and Nestler 1995). Moreover, repeated ICV injection of forskolin, a direct AC activator, enhances behavioral sensitization to systemic cocaine administration in rats (Schroeder et al. 2004). These findings suggest that enhanced cAMP signal transduction can potentiate the sensitizing effects of psychostimulants and may underlie a molecular mechanism for the development of behavioral sensitization. Similar with the case in alcohol dependence, down-regulation of CREB-mediated signal transduction via overexpression of a dominant-negative mutant CREB in the NAcSh decrease the threshold of cocaine to induce conditioned place preference (CPP) in rat models; conversely, up-regulated CREB signaling by CREB overexpression in the NAcSh increases cocaine doses to induce CCP and makes low doses of this drug aversive (Carlezon et al. 1998). These results indicate that innate levels of CREB signal transduction in the NAcSh play a critical role in regulating rewarding properties of cocaine. Finally, acute nicotine administration activates neuronal nicotinic acetylcholine receptors (nAChRs), which belong to the ligand-gated ion channel receptor family, but exhibits no impact on PKA activity; whereas chronic nicotine exposure results in nAChR desensitization and decreased PKA activity in the rat brain, suggesting inhibited PKA signaling may be responsible for nicotine tolerance and dependence (Sun et al. 2004).

In summary, the cAMP/PKA/CREB signal pathway is prominently involved in rewarding properties and neuroadaptational responses to addictive substances. Activation of this signaling is considered as an important compensatory mechanism to decrease the motivational properties of drugs of abuse.

15.4.2 cGMP Signal Transduction

Although relatively fewer studies have investigated the involvement of cGMP-mediated signaling in substance use and abuse, components of this signal system may also play a role in the neuronal adaptations and behavioral responses to multiple substances. Most of the cGMP effects are mediated via activation of PKG and its effects on subsequent targets. In the CNS, the canonical NO/sGC/cGMP/PKG pathway modulates

long-term changes in synaptic activity and contributes to many forms of learning and memory processes (Kleppisch and Feil 2009). Studies have shown that cGMP reduces DA release in cells and in brain regions related to addictive behaviors in animal models (Samson et al. 1988; Guevara-Guzman et al. 1994; Thiriet et al. 2001).

Activated cGMP signal transduction via *in situ* injection of cGMP-elevating agents in the median prefrontal cortex, but not the NAc, reduces intravenous cocaine self-administration (Deschatrettes et al. 2013). Besides, stimulation of cGMP signaling in the VTA decreases cocaine-induced locomotor hyperactivity and relative gene expression in dopaminergic brain regions. This effect is reversed by pretreatment with a selective PKG inhibitor (Jouvert et al. 2004). However, systemic increases in NO or cGMP availability promote cocaine-induced behavior sensitization and hippocampal long-term potentiation (LTP) (Gabach et al. 2013). These results indicate that cGMP signaling pathway may have brain region- or system-specific effects on neuroadaptation and behavioral response to cocaine.

Chronic ethanol exposure increases cGMP levels in the rat cortex, striatum, and hippocampus, while cessation of this treatment decreases cortical and striatal cGMP to normal levels (Uzbay et al. 2004). Consistent with previous studies implicating cGMP signaling in the modulation of anxiety (Li et al. 2005; Volke et al. 2003), PKG type II knockout mice show increased anxiety-like behaviors, reduced ethanol's sedative effects, and potentiated voluntary alcohol consumption (Werner et al. 2004). Conversely, pharmacological activation of cGMP signaling in either the VTA or the prefrontal cortex reduces alcohol deprivation and causes higher ethanol intake, an effect that can be reversed by PKG inhibition (Romieu et al. 2008). Thus, the activity of cGMP signaling is negatively correlated to alcohol-drinking behaviors in a way similar to cAMP signaling.

The cGMP signaling pathway has also been implicated in morphine and nicotine use. In an electrophysiological study, GC activation has been shown to initiate a novel form of LTP in GABA-mediated synaptic transmission. Morphine exposure *in vitro* and *in vivo* prevented this type of LTP by inhibiting presynaptic glutamate release or interrupting the signaling from NO to GC, respectively, indicating the involvement of cGMP signaling in neuroadaptations to opioid drugs (Nugent et al. 2007). In addition, opiate withdrawal studies have shown selective sGC inhibition suppressed the behavioral signs of morphine withdrawal precipitated by naloxone (Sullivan et al. 2000). With regards to nicotine, a genome wide study has identified an association of the human PKG type I gene with nicotine dependence (Uhl et al. 2007).

15.5 Role of PDEs in the Process of Substance Dependence

The crucial involvement of cAMP and cGMP-mediated signals in substance dependence raises the possibility of their essential modulators, PDEs, as potential therapeutic targets for the treatment of this disease. As the brain expression profile and substrate specificity are distinct among PDE isoforms, it is hypothesized that more than one PDE may be involved in the dependent process. Available evidence has

revealed the enrollment of several subtypes of PDEs in substance dependent animal models (Table 15.2). However, further studies are still needed to verify their modulatory mechanism and the functional roles of other PDEs in substance related disorders.

15.5.1 PDE1

The PDE1 family consists of three subtypes of dual-substrate PDEs, which are activated by calcium and calmodulin (Bender and Beavo 2006). With high expression level in the striatum as well as the regulation of both cAMP and cGMP signaling, PDE1 has been proposed to play a role in substance dependent behaviors. However, the selective PDE1 inhibitor vinpocetine showed no significant effect on alcohol intake in the two-bottle choice test via systemic administration (Blednov et al. 2014). Microinjections of the PDE1 inhibitor into drug dependence-related brain nuclei may aid to better determine whether PDE1 modulates substance actions in the CNS. Nevertheless, it is noteworthy that vinpocetine shows cognitive-enhancing effects by facilitating LTP (Molnar and Gaal 1992) and improving memory consolidation (Deshmukh et al. 2009) in rodent models. Furthermore, it ameliorates learning and memory impairment in rodents exposed to alcohol during fetal development (Filgueiras et al. 2010). It remains to be studied whether this protective effect on cognition is present against other substances or in adulthood as well.

15.5.2 PDE3

PDE3 is expressed at relatively low levels throughout the brain, and mainly known for its cardiovascular modulations. Correspondingly, the PDE3 inhibitors milrinone and olprinone show negative effects on alcohol intake when tested in the two-bottle choice test (Blednov et al. 2014). Further studies are needed to detect the CNS actions of PDE3.

15.5.3 PDE4

Widely distributed in the brain, the cAMP-specific PDE4 exhibits a multitude of effects on the CNS. Pharmacological blockade or genetic knockout of PDE4 produces anti-depressive (Li et al. 2009; Zhang 2009; Zhang et al. 2002), anxiolytic (Siuciak et al. 2007; Rutter et al. 2014; Ankur et al. 2013) and antipsychotic (Kelly et al. 2007) effects; enhances LTP (Chen et al. 2010; Navakkode et al. 2004); and improves performance in learning and memory (Barad et al. 1998; Rutten et al. 2008; Li et al. 2011; Zhang et al. 2000; Zhang et al. 2004). The ability of PDE4

Table 15.2 Overview of PDEs role in substance dependence

PDE isoform	Substance	Inhibitor	Animal	Behavioral paradigm	Results	Reference
PDE1	Alcohol	Vinpocetine	C57BL/6J mice	Two-bottle choice drinking	Vinpocetine did not affect alcohol intake	Blednov et al. (2014)
PDE3	Alcohol	Milrinone	C57BL/6J mice	Two-bottle choice drinking	Milrinone or olprinone showed no significant effecteffect on alcohol intake or preference	Blednov et al. (2014)
		Olprinone				
PDE4	Methamphetamine	Rolipram	Wistar rats	Behavioral sensitization	Rolipram inhibited methamphetamine-induced behavioral sensitization	Iyo et al. (1995, 1996)
	Cocaine	Rolipram	Wistar rats	Operant self-administration	Rolipram and Ro-20 1724 suppressed the initiation of cocaine self-administration	Knapp et al. (1999)
		Ro-20 1724				
		Rolipram	Wistar rats	Discrete trial	Rolipram augmented cocaine's reinforcing effect	Knapp et al. (2001)
		Rolipram	Swiss Webster mice	Behavioral sensitization	Rolipram prevented cocaine-induced locomotor sensitization	Janes et al. (2009)
		Rolipram	Sprague-Dawley rats	CPP[a]	Rolipram impaired the acquisition, but not the expression or extinction, of cocaine-induced CPP	Zhong et al. (2012), Liddie et al. (2012)
			B6129S mice			

	Morphine	Rolipram	C57BL/6J mice	Naloxone precipitated withdrawal	Rolipram blocked withdrawal behavioral manifestations in morphine dependent mice	Hamdy et al. (2001)
		Rolipram Diazepam	Sprague-Dawley rats	Naloxone precipitated withdrawal	Either rolipram or diazepam co-administration attenuated morphine withdrawal symptoms	Gonzalez-Cuello et al. (2007), Nunez et al. (2009)
		Rolipram	Swiss Webster mice	CPP	Rolipram inhibited the acquisition but not expression of morphine-induced CPP	Thompson et al. (2004)
	Heroin	Rolipram	Sprague-Dawley rats	Operant self-administration	Rolipram decreased heroin-seeking behaviors	Lai et al. (2014)
	Alcohol	Rolipram	C57BL/6J mice	Two-bottle choice drinking	Rolipram, Ro-20 1724, selectively decreased alcohol intake	Hu et al. (2011)
		Ro-20 1724				
		Rolipram	C57BL/6J mice	Two-bottle choice drinking	Rolipram, piclamilast, CDP840 and mesopram all decreased alcohol intake in both continuous and limited access two bottle choice drinking	Blednov et al. (2014)
		Piclamilast				
		Mesopram				
		CDP840				
		Rolipram	FH/Wjd rats	Operant self-administration	Rolipram selectively inhibited alcohol seeking and drinking behaviors	Wen et al. (2012)
				Two-bottle choice drinking		

(continued)

Table 15.2 (continued)

PDE isoform	Substance	Inhibitor	Animal	Behavioral paradigm	Results	Reference
PDE5A	Cocaine	Sildenafil	Wistar rats	Behavioral sensitization	Sildenafil potentiated behavioral sensitization to cocaine	Gabach et al. (2013)
		Zaprinast[b]	Wistar rats	Operant self-administration	Zaprinast reduced cocaine self-administration	Deschatrettes et al. (2013)
	Alcohol	Zaprinast	C57BL/6J mice	Two-bottle choice drinking	Zaprinast had no effect on alcohol consumption	(Blednov et al. (2014)
PDE 9A	Cocaine	BAY-73-6691	B6129S mice	CPP	BAY-73-6691 facilitated extinction and diminished the reinstatement of cocaine CPP	Liddie et al. 2012)
PDE10A	Cocaine	Papaverine	B6129S mice	CPP	Papaverine had no effect on the extinction of cocaine CPP	Liddie et al. (2012)
	Alcohol	TP-10	Scr:sP[c]	Operant self-administration	TP-10 decreases alcohol self-administration in both alcohol-preferring Scf:sP rats and alcohol-dependent or nondependent Wistar rats	Logrip et al. (2014)
			Wistar rats			

Nonspecific	Cocaine	IBMX[d]	Sprague-Dawley rats	Behavioral sensitization	IBMX attenuated development of cocaine-induced behavioral sensitization	Schroeder et al. (2012)
	Alcohol	Propentofylline	C57BL/6J mice	Two-bottle choice drinking	Propentofylline has no effect on alcohol intake	Blednov et al. (2014)
		Ibudilast[e]	P rats	Two-bottle choice drinking	Ibudilast decreased alcohol intake in P rats, HAD1 rats, and C57BL/6J mice	Bell et al. (2015)
			HAD1 rats			
			C57BL/6J mice			

[a]*CPP* conditioned place preference
[b]Highest selectivity for PDE5, less potent at PDE1, PDE10 and PDE11
[c]Scr:sP: sardinian alcohol-preferring rats of The Scripps Research Institute subline
[d]IBMX, isobutylmethylxanthine, both nonspecific PDE inhibitor and A1 receptor antagonist
[e]Nonspecific but with preference to PDE3, PDE4, PDE10 and PDE11

inhibition to ameliorate negative emotional state and improve memory performance suggests that PDE4 may play a role in substance use disorders.

The functional role of PDE4 has first proved in animal models of methamphetamine-induced behavioral sensitization (Nishikawa et al. 1983). This sensitization appears to be mediated by enhanced DA efflux in mesolimbic and/or nigrostriatal DA systems (Kalivas and Stewart 1991; Akimoto et al. 1990). Co-administration of the selective PDE4 inhibitor rolipram inhibits methamphetamine-induced locomotor sensitization by increasing cAMP levels while not affecting DA release (Iyo et al. 1996). However, stereotyped behavior is not altered by rolipram, indicating PDE4 partly regulates behaviors related to hyperdopaminergic activity.

Consistently, rolipram co-administration prevents the development of locomotor sensitization to cocaine, but has no effect on cocaine-induced activation of the ERK transcriptional pathway in the NAc (Janes et al. 2009), which represents critical neuroadaptation for cocaine-related behavioral plasticity (Girault et al. 2007; Valjent et al. 2006). However, these results conflicts with the above mentioned findings revealing that enhanced cAMP levels increase behavioral sensitization to cocaine and amphetamine (Miserendino and Nestler 1995; Tolliver et al. 1996). These discrepancies may be attributable to different experimental procedures of drug treatment and behavior measurement procedures. In studies involving cocaine self-administration, both rolipram and Ro 20-1724 prolong the latency for cocaine self-administration and reduce the number of cocaine infusions (Knapp et al. 1999). This suppression of cocaine-seeking behavior is consistent with the results obtained from D1-like receptor agonists, indicating a negative modulatory influence of PDE4 inhibitors on motivational systems and mesolimbic dopaminergic neurotransmission. Moreover, intra-VTA or systemic injections of rolipram can attenuate the acquisition, but not the expression, of cocaine-induced CPP (Thompson et al. 2004; Zhong et al. 2012). Systemic rolipram administration shows no effect on the extinction of cocaine CPP (Liddie et al. 2012), but can increase *c-fos* expression in the NAcSh, but not NAcC or caudate putamen (Thompson et al. 2004). Finally, intra-NAc infusions of rolipram produce enhancement of the sensitivity of brain stimulation reward (BSR) pathways, an effect that is potentiated when combined with systemic cocaine administration (Knapp et al. 2001). On the contrary, systemic administration of rolipram blocks the effects of BSR or raises BSR thresholds, indicating a NAc-specific role of rolipram. The above results suggest that PDE4 inhibition can produce suppression in multiple behaviors related to cocaine exposure possibly through activation of cAMP signaling in mesolimbic DA systems, including the VTA and NAc.

Research regarding PDE4 functions in the development of morphine dependence has been mainly focused on morphine withdrawal. Naloxone-participated withdrawal symptoms following cessation of chronic morphine exposure are usually associated with up-regulation of the cAMP and cGMP signal pathways as well as immediate early gene expression in rodent models. Studies from Abe and coworkers demonstrated that the elevated cAMP signaling following morphine withdrawal may be attributed to lack of PDE4 activation (Kimura et al. 2006). A combination of rolipram and morphine chronic treatment significantly reduces

naloxone-precipitated withdrawal manifestations and prevents the increase in brain *c-fos* gene expression in morphine dependent mice (Hamdy et al. 2001). Similar results have also been observed in rat models. Co-administration of the PDE4 inhibitor rolipram or diazepam with morphine during the pre-treatment period significantly reduces withdrawal symptoms as well as the enhanced noradrenaline turnover and cAMP levels in the heart and hypothalamic paraventricular nucleus (PVN) of rats (Gonzalez-Cuello et al. 2007; Nunez et al. 2009). However, cGMP levels are not affected by these inhibitors, and *c-fos* expression is not modified in PVN either. Besides its involvement in the long-term dependent process, PDE4-mediated cAMP signaling has also been implicated in the establishment of reward valence to opiates. Rolipram by systemic administration reduces the acquisition, but not the expression, of morphine-induced CPP by increasing *c-fos* expression in the NAcSh but not NAcC (Thompson et al. 2004). Rolipram also decreases heroin-seeking behaviors, which is correlated with the increases in CREB phosphorylation in the NAc of rats (Lai et al. 2014).

Finally, PDE4 inhibitors have been shown to decrease alcohol seeking and consumption behaviors. Our studies showed that, in C57BL/6J mice and FH/Wjd rats, systemic administration of PDE4 inhibitors rolipram or Ro-20 1724 selectively reduced ethanol intake without altering total fluid or water intake in the two-bottle free-choice drinking paradigm (Hu et al. 2011; Wen et al. 2012). This inhibitory effect on ethanol drinking seemed to mainly result from PDE4 regulation and less likely to be related to taste preference, rolipram-induced sedation or nausea, or interference in alcohol metabolism. These findings were later confirmed by a similar study examining the effects of several selective PDE4 inhibitors, including rolipram, CDP840, piclamilast, and mesopram, in the two-bottle choice test (Blednov et al. 2014). These agents all produce a suppression in ethanol intake of C57BL/6J mice in both long-term and limited-access two-bottle choice drinking. Similar with our results, the effect of single-dose rolipram, CDP840, or piclamilast only lasts for the first 6 h, while mesopram exhibits a long-lasting reduction of ethanol intake. Moreover, rolipram also selectively reduced operant ethanol self-administration without altering sucrose or water seeking in FH/Wjd rats (Wen et al. 2012). All these data strongly support a positive correlation of PDE4 activity with alcohol dependent behaviors.

15.5.4 PDE5

The cGMP-specific PDE5 is a single gene PDE family. Studies of PDE5A have mainly focused on its regulation of smooth muscle vasodilation by using selective PDE5A inhibitors, such as sildenafil, vardenafil, and tadalafil. With the significant expression in cerebellar Purkinje cells, PDE5A has been shown to modulate memory performance (Xu et al. 2011) and produce antidepressant-like effects (Liebenberg et al. 2010).

As cGMP signaling may underlie many substance dependent processes, studies have begun to test the efficacy of PDE5A inhibitors in regulating addictive behaviors. PDE5A blockade by sildenafil increases cGMP availability, potentiates behavioral cocaine sensitization, and reduces threshold to generate hippocampal LTP (Gabach et al. 2013), a regulation pattern opposite to PDE4. Zaprinast, another PDE5A inhibitor, reduces intravenous cocaine self-administration by rats when injected into the prefrontal cortex, but not the NAc (Deschatrettes et al. 2013), which might involve epigenetic modulation in dopaminergic brain regions. Noteworthy, however, though zaprinast has the highest selectivity for PDE5A, it may also elicit effects through inhibition of PDE1, 9, 10 and 11 (Bender and Beavo 2006). Thus, while mainly targeting cGMP hydrolysis, it may also increase cAMP levels to some extent.

15.5.5 PDE9A

Along with high expression in the hippocampus, the expression of cGMP-specific PDE9A is also strong in cerebellar Purkinje cells. The selective PDE9 inhibitor BAY-73-6691 has been shown to enhance long-term memory and attenuate memory deficits associated with aging in rodent models (Domek-Lopacinska and Strosznajder 2010; van der Staay et al. 2008). Thus, PDE9A inhibition is considered as a potential therapeutic manipulation for memory deficits related to neurodegenerative disorders including Alzheimer's disease (Wunder et al. 2005). Likewise, in a mouse CPP model, acute administration of BAY-73-6691 facilitates extinction and diminishes the reinstatement of cocaine-induced place preference (Liddie et al. 2012), possibly by elevating cGMP levels in the amygdala and hippocampus, two areas involved in regulating emotional and spatial learning.

15.5.6 PDE10A

PDE10A is a dual-specificity PDE that regulates both cAMP and cGMP activation. Its relatively high expression levels in striatal brain regions render it as a possible modulator of dopamine-associated and stress-related processes. Both of the PDE10A inhibitors, TP-10 and papaverine, exhibits antipsychotic properties by decreasing psychotic-like behaviors, including phencyclidine- or amphetamine-induced behavioral abnormalities (Grauer et al. 2009; Schmidt et al. 2008; Siuciak et al. 2006). These effects are likely attributed to suppression in mesolimbic dopaminergic neurotransmission (Sotty et al. 2009).

A positive relationship between PDE10A expression levels and stress or alcohol drinking patterns has been well established by Logrip and colleagues. In an operant alcohol self-administration model, the baseline of alcohol lever preference in high and low alcohol-drinking rats is positively correlated with BLA and CeA *Pde10a*

mRNA levels, respectively. Rats with a stress history of repeated footshock during alcohol self-administration training show increased *Pde10a* mRNA expression in the BLA. This stress history ultimately increases 'relapse' of alcohol self-administration in low alcohol-drinking rats following an extinction period; it does not alter alcohol seeking or intake in high alcohol-drinking rats or change sucrose self-administration in either group rats. This protracted effect of stress history shows a positive relationship to *Pde10a* mRNA levels in the prelimbic subdivision of the prefrontal cortex (Logrip and Zorrilla 2012). In addition to further supporting the negative reinforcing effects of aversive affective states on substance use and relapse these results demonstrate the involvement of stress-induced *Pde10a* expression in the motivational aspect of substance taking behaviors. Measurements of *Pde10a* mRNA expression have also been taken in alcohol withdrawal period (Logrip and Zorrilla 2014). In response to acute (8–10 h) alcohol withdrawal, *Pde10a* mRNA levels were increased in the MeA, BLA, as well as the infralimbic and anterior cingulate subdivisions of the prefrontal cortex. Following protracted (6w) withdrawal, *Pde10a* expression was increased only in the BLA, but down-regulated in the MeA, prelimbic prefrontal cortex, and dorsal striatum. These suggest that consistent up regulation of *Pde10a* mRNA expression in the BLA is a lasting neuroadaptation associated with alcohol dependence.

To confirm the above findings, the efficacy of the selective PDE10A inhibitor TP-10 was tested in alcohol self-administration models (Logrip et al. 2014). Relapse-like alcohol seeking and intake were decreased by systemic pretreated TP-10 in rats with or without a stress experience. TP-10 also reduced alcohol self-administration in genetically alcohol-preferring rats (Scr:sP) as well as in alcohol-dependent and non-dependent Wistar rats. Region-specific microinjections of TP-10 implicated the dorsolateral striatum as an additional structure to the NAc involved in modulating the inhibitory effects on alcohol seeking and drinking behavior. However, saccharin self-administration was also inhibited by TP-10, suggesting a nonspecific modulating pattern of PDE10A on reinforcing properties of rewards. On the other hand, the PDE10A inhibitor papaverine, despite increasing both cAMP and cGMP levels in the hippocampus and amygdala, didn't show any significant effect as the PDE9A inhibitor on cocaine-induced place preference after extinction training in a mice CPP model (Liddie et al. 2012). This may be attributable to lower density of PDE10A in the hippocampus, which play a key role in extinction learning, and less efficiency in hydrolyzing cGMP compared to PDE9A.

15.5.7 Nonspecific

Nonspecific PDE inhibitors have also been tested for efficacy in substance related behaviors. For instance, isobutylmethylxanthine (IBMX), a nonspecific PDE inhibitor and an adenosine receptor antagonist, attenuates the development of cocaine-induced behavior sensitization following ICV administration. However, whether this effect is resulted from direct enhancement of cAMP signal transduction or

inhibition of adenosine production along with A1 receptor-mediated noradrenergic activation needs to be further elucidated (Schroeder et al. 2012). In the two-bottle free choice drinking test, propentofylline does not alter alcohol consumption (Blednov et al. 2014), while ibudilast reduces alcohol intake in three different rodent models of alcohol dependence, i.e. alcohol-preferring P rats, high-alcohol drinking HAD1 rats, and alcohol dependent C57BL/6J mice (Bell et al. 2015). The effects observed with ibudilast may derive from its preferential inhibition of PDE3A, PDE4, PDE 10, and PDE11 (Gibson et al. 2006), demonstrating the down-regulating properties of PDE4 and PDE10A in alcohol drinking behavior.

15.6 Conclusions and Future Perspectives

As described above, PDEs represent promising therapeutic targets for treatment of substance dependence through regulation of cAMP and cGMP signal transduction. Based on the studies to date, PDE4, PDE5A, PDE9A, and PDE10A appear to play a functional role in modulating behavioral responses and neural adaptation to multiple substances. For the most part, inhibition of these PDEs produces suppression in substance-related behaviors. Additional studies are still needed to get more in-depth knowledge in the mechanisms of PDE mediations. For instance, more sophisticated technology including genetic manipulations should be employed to characterize the involvement and modulation patterns of individual PDE subtypes or isoforms in the dependent behavior. This may aid in the development of novel and specific PDE inhibitors that may reduce the off-target side effects of current PDE inhibitors (e.g. the emetic properties of PDE4 inhibitors), which represent a major hurdle for their clinical use (Rutter et al. 2014). On the other hand, the discovery of broader acting PDE inhibitors with fewer side effects may also be beneficial because substance dependence involves both cAMP and cGMP signaling as well as the interaction among multiple brain regions with different PDE distribution. Together, the available studies raise the possibility of PDEs as potential therapeutic targets for substance-related disorders. Further research into the CNS function of PDEs and the discovery and development of novel PDE inhibitors will provide a better basis for developing therapeutic manipulations with higher translational potential.

Conflict of Interest The authors declare that they have no conflicts of interest**.**

References

Akimoto K, Hamamura T, Kazahaya Y, Akiyama K, Otsuki S. Enhanced extracellular dopamine level may be the fundamental neuropharmacological basis of cross-behavioral sensitization between methamphetamine and cocaine–an in vivo dialysis study in freely moving rats. Brain Res. 1990;507(2):344–6.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed. Washington, DC: American Psychiatric Association; 2000. Text revision

Ankur J, Mahesh R, Bhatt S. Anxiolytic-like effect of etazolate, a type 4 phosphodiesterase inhibitor in experimental models of anxiety. Indian J Exp Biol. 2013;51(6):444–9.

Asher O, Cunningham TD, Yao L, Gordon AS, Diamond I. Ethanol stimulates cAMP-responsive element (CRE)-mediated transcription via CRE-binding protein and cAMP-dependent protein kinase. J Pharmacol Exp Ther. 2002;301(1):66–70.

Asyyed A, Storm D, Diamond I. Ethanol activates cAMP response element-mediated gene expression in select regions of the mouse brain. Brain Res. 2006;1106(1):63–71.

Baker D, Pryce G, Davies WL, Hiley CR. In silico patent searching reveals a new cannabinoid receptor. Trends Pharmacol Sci. 2006;27(1):1–4.

Barad M, Bourtchouladze R, Winder DG, Golan H, Kandel E. Rolipram, a type IV-specific phosphodiesterase inhibitor, facilitates the establishment of long-lasting long-term potentiation and improves memory. Proc Natl Acad Sci U S A. 1998;95(25):15020–5.

Belknap JK, Crabbe JC, Young ER. Voluntary consumption of ethanol in 15 inbred mouse strains. Psychopharmacology. 1993;112(4):503–10.

Bell RL, Lopez MF, Cui C, Egli M, Johnson KW, Franklin KM, Becker HC. Ibudilast reduces alcohol drinking in multiple animal models of alcohol dependence. Addict Biol. 2015;20(1):38–42.

Bender AT, Beavo JA. Cyclic nucleotide phosphodiesterases: molecular regulation to clinical use. Pharmacol Rev. 2006;58(3):488–520.

Bison S, Crews F. Alcohol withdrawal increases neuropeptide Y immunoreactivity in rat brain. Alcohol Clin Exp Res. 2003;27(7):1173–83.

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

Blokland A, Schreiber R, Prickaerts J. Improving memory: a role for phosphodiesterases. Curr Pharm Des. 2006;12(20):2511–23.

Boess FG, Hendrix M, van der Staay FJ, Erb C, Schreiber R, van Staveren W, de Vente J, Prickaerts J, Blokland A, Koenig G. Inhibition of phosphodiesterase 2 increases neuronal cGMP, synaptic plasticity and memory performance. Neuropharmacology. 2004;47(7):1081–92.

Carlezon WJ, Thome J, Olson VG, Lane-Ladd SB, Brodkin ES, Hiroi N, Duman RS, Neve RL, Nestler EJ. Regulation of cocaine reward by CREB. Science. 1998;282(5397):2272–5.

Chao J, Nestler EJ. Molecular neurobiology of drug addiction. Annu Rev Med. 2004;55:113–32.

Chen CC, Yang CH, Huang CC, Hsu KS. Acute stress impairs hippocampal mossy fiber-CA3 long-term potentiation by enhancing cAMP-specific phosphodiesterase 4 activity. Neuropsychopharmacology. 2010;35(7):1605–17.

Childers SR. Opioid receptor-coupled second messenger systems. Life Sci. 1991;48(21):1991–2003.

Cole RL, Konradi C, Douglass J, Hyman SE. Neuronal adaptation to amphetamine and dopamine: molecular mechanisms of prodynorphin gene regulation in rat striatum. Neuron. 1995;14(4):813–23.

Collins SP, Uhler MD. Cyclic AMP- and cyclic GMP-dependent protein kinases differ in their regulation of cyclic AMP response element-dependent gene transcription. J Biol Chem. 1999;274(13):8391–404.

Constantinescu A, Gordon AS, Diamond I. 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. 2002;277(21):18810–6.

Daglish M, Lingford-Hughes A, Nutt D. Human functional neuroimaging connectivity research in dependence. Rev Neurosci. 2005;16(2):151–7.

Deschatrettes E, Romieu P, Zwiller J. Cocaine self-administration by rats is inhibited by cyclic GMP-elevating agents: involvement of epigenetic markers. Int J Neuropsychopharmacol. 2013;16(7):1587–97.

Deshmukh R, Sharma V, Mehan S, Sharma N, Bedi KL. Amelioration of intracerebroventricular streptozotocin induced cognitive dysfunction and oxidative stress by vinpocetine – a PDE1 inhibitor. Eur J Pharmacol. 2009;620(1–3):49–56.

Di Benedetto M, D'Addario C, Candeletti S, Romualdi P. Alterations of CREB and DARPP-32 phosphorylation following cocaine and monoaminergic uptake inhibitors. Brain Res. 2007;1128(1):33–9.

Domek-Lopacinska KU, Strosznajder JB. Cyclic GMP and nitric oxide synthase in aging and Alzheimer's disease. Mol Neurobiol. 2010;41(2–3):129–37.

Duman RS, Tallman JF, Nestler EJ. Acute and chronic opiate-regulation of adenylate cyclase in brain: specific effects in locus coeruleus. J Pharmacol Exp Ther. 1988;246(3):1033–9.

Edwards S, Graham DL, Whisler KN, Self DW. Phosphorylation of GluR1, ERK, and CREB during spontaneous withdrawal from chronic heroin self-administration. Synapse. 2009;63(3):224–35.

Filgueiras CC, Krahe TE, Medina AE. Phosphodiesterase type 1 inhibition improves learning in rats exposed to alcohol during the third trimester equivalent of human gestation. Neurosci Lett. 2010;473(3):202–7.

Fuchs RA, See RE. Basolateral amygdala inactivation abolishes conditioned stimulus- and heroin-induced reinstatement of extinguished heroin-seeking behavior in rats. Psychopharmacology. 2002;160(4):425–33.

Fuchs RA, Evans KA, Ledford CC, Parker MP, Case JM, Mehta RH, See RE. The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. Neuropsychopharmacology. 2005;30(2):296–309.

Fuchs RA, Feltenstein MW, See RE. The role of the basolateral amygdala in stimulus-reward memory and extinction memory consolidation and in subsequent conditioned cued reinstatement of cocaine seeking. Eur J Neurosci. 2006;23(10):2809–13.

Fuchs RA, Eaddy JL, Su ZI, Bell GH. Interactions of the basolateral amygdala with the dorsal hippocampus and dorsomedial prefrontal cortex regulate drug context-induced reinstatement of cocaine-seeking in rats. Eur J Neurosci. 2007;26(2):487–98.

Gabach LA, Carlini VP, Monti MC, Maglio LE, De Barioglio SR, Perez MF. Involvement of nNOS/NO/sGC/cGMP signaling pathway in cocaine sensitization and in the associated hippocampal alterations: does phosphodiesterase 5 inhibition help to drug vulnerability? Psychopharmacology. 2013;229(1):41–50.

Gibson LC, Hastings SF, Mcphee I, Clayton RA, Darroch CE, Mackenzie A, Mackenzie FL, Nagasawa M, Stevens PA, Mackenzie SJ. The inhibitory profile of Ibudilast against the human phosphodiesterase enzyme family. Eur J Pharmacol. 2006;538(1–3):39–42.

Girault JA, Valjent E, Caboche J, Herve D. ERK2: a logical AND gate critical for drug-induced plasticity? Curr Opin Pharmacol. 2007;7(1):77–85.

Gonzalez-Cuello A, Sanchez L, Hernandez J, Teresa CM, Victoria MM, Laorden ML. Phosphodiesterase 4 inhibitors, rolipram and diazepam block the adaptive changes observed during morphine withdrawal in the heart. Eur J Pharmacol. 2007;570(1–3):1–9.

Gordon AS, Collier K, Diamond I. 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. 1986;83(7):2105–8.

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. Phosphodiesterase 10A inhibitor activity in preclinical models of the positive, cognitive, and negative symptoms of schizophrenia. J Pharmacol Exp Ther. 2009;331(2):574–90.

Guevara-Guzman R, Emson PC, Kendrick KM. Modulation of in vivo striatal transmitter release by nitric oxide and cyclic GMP. J Neurochem. 1994;62(2):807–10.

Guitart X, Thompson MA, Mirante CK, Greenberg ME, Nestler EJ. Regulation of cyclic AMP response element-binding protein (CREB) phosphorylation by acute and chronic morphine in the rat locus coeruleus. J Neurochem. 1992;58(3):1168–71.

Hamdy MM, Mamiya T, Noda Y, Sayed M, Assi AA, Gomaa A, Yamada K, Nabeshima T. A selective phosphodiesterase IV inhibitor, rolipram blocks both withdrawal behavioral manifestations, and c-Fos protein expression in morphine dependent mice. Behav Brain Res. 2001;118(1):85–93.

Han MH, Bolanos CA, Green TA, Olson VG, Neve RL, Liu RJ, Aghajanian GK, Nestler EJ. Role of cAMP response element-binding protein in the rat locus ceruleus: regulation of neuronal activity and opiate withdrawal behaviors. J Neurosci. 2006;26(17):4624–9.

Hashimoto E, Frolich L, Ozawa H, Saito T, Maurer K, Boning J, Takahata N, Riederer P. Reduced immunoreactivity of type I adenylyl cyclase in the postmortem brains of alcoholics. Alcohol Clin Exp Res. 1998;22(3 Suppl):88S–92S.

Heidbreder CA, Thompson AC, Shippenberg TS. Role of extracellular dopamine in the initiation and long-term expression of behavioral sensitization to cocaine. J Pharmacol Exp Ther. 1996;278(2):490–502.

Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C. Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience. 1991;41(1):89–125.

Heimer L, Alheid GF, de Olmos JS, Groenewegen HJ, Haber SN, Harlan RE, Zahm DS. The accumbens: beyond the core-shell dichotomy. J Neuropsychiatry Clin Neurosci. 1997;9(3):354–81.

Hopf FW, Cascini MG, Gordon AS, Diamond I, Bonci A. Cooperative activation of dopamine D1 and D2 receptors increases spike firing of nucleus accumbens neurons via G-protein beta-gamma subunits. J Neurosci. 2003;23(12):5079–87.

Hu W, Lu T, Chen A, Huang Y, Rolf H, Judson Chandler L, et al. Inhibition of phosphodiesterase-4 decreases ethanol intake in mice. Psychopharmacology (Berl). 2011;218(2):331–9.

Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. Nat Rev Neurosci. 2001;2(10):695–703.

Imperato A, Di Chiara G. Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. J Pharmacol Exp Ther. 1986;239(1):219–28.

Impey S, Obrietan K, Storm DR. Making new connections: role of ERK/MAP kinase signaling in neuronal plasticity. Neuron. 1999;23(1):11–4.

Iyo M, Maeda Y, Inada T, Kitao Y, Sasaki H, Fukui S. The effects of a selective cAMP phosphodiesterase inhibitor, rolipram, on methamphetamine-induced behavior. Neuropsychopharmacology. 1995;13(1):33–9.

Iyo M, Bi Y, Hashimoto K, Inada T, Fukui S. Prevention of methamphetamine-induced behavioral sensitization in rats by a cyclic AMP phosphodiesterase inhibitor, rolipram. Eur J Pharmacol. 1996;312(2):163–70.

Janes AC, Kantak KM, Cherry JA. The involvement of type IV phosphodiesterases in cocaine-induced sensitization and subsequent pERK expression in the mouse nucleus accumbens. Psychopharmacology. 2009;206(2):177–85.

Javadi S, Ejtemaeimehr S, Keyvanfar HR, Moghaddas P, Aminian A, Rajabzadeh A, Mani AR, Dehpour AR. Pioglitazone potentiates development of morphine-dependence in mice: possible role of NO/cGMP pathway. Brain Res. 2013;1510:22–37.

Jiang LH, Wang J, Wei XL, Liang QY, Cheng TT. Exogenous sodium hydrosulfide can attenuate naloxone-precipitated withdrawal syndromes and affect cAMP signaling pathway in heroin-dependent rat's nucleus accumbens. Eur Rev Med Pharmacol Sci. 2012;16(14):1974–82.

Jing L, Luo J, Zhang M, Qin WJ, Li YL, Liu Q, Wang YT, Lawrence AJ, Liang JH. Effect of the histone deacetylase inhibitors on behavioural sensitization to a single morphine exposure in mice. Neurosci Lett. 2011;494(2):169–73.

Jouvert P, Revel MO, Lazaris A, Aunis D, Langley K, Zwiller J. Activation of the cGMP pathway in dopaminergic structures reduces cocaine-induced EGR-1 expression and locomotor activity. J Neurosci. 2004;24(47):10716–25.

Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Brain Res Rev. 1991;16(3):223–44.

Kaplan GB, Sethi RK, Mcclelland EG, Leite-Morris KA. Regulation of G protein-mediated adenylyl cyclase in striatum and cortex of opiate-dependent and opiate withdrawing mice. Brain Res. 1998;788(1–2):104–10.

Kearns DN, Weiss SJ. Contextual renewal of cocaine seeking in rats and its attenuation by the conditioned effects of an alternative reinforcer. Drug Alcohol Depend. 2007;90(2–3):193–202.

Kebabian JW, Greengard P. Dopamine-sensitive adenyl cyclase: possible role in synaptic transmission. Science. 1971;174(4016):1346–9.
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. Constitutive activation of Galphas within forebrain neurons causes deficits in sensorimotor gating because of PKA-dependent decreases in cAMP. Neuropsychopharmacology. 2007;32(3):577–88.
Kim KS, Lee KW, Baek IS, Lim CM, Krishnan V, Lee JK, Nestler EJ, Han PL. Adenylyl cyclase-5 activity in the nucleus accumbens regulates anxiety-related behavior. J Neurochem. 2008;107(1):105–15.
Kim KS, Kim H, Baek IS, Lee KW, Han PL. Mice lacking adenylyl cyclase type 5 (AC5) show increased ethanol consumption and reduced ethanol sensitivity. Psychopharmacology. 2011; 215(2):391–8.
Kimura M, Tokumura M, Itoh T, Inoue O, Abe K. Lack of cyclic AMP-specific phosphodiesterase 4 activation during naloxone-precipitated morphine withdrawal in rats. Neurosci Lett. 2006; 404(1–2):107–11.
Kleppisch T, Feil R. cGMP signalling in the mammalian brain: role in synaptic plasticity and behaviour. Handb Exp Pharmacol. 2009;191:549–79.
Knapp CM, Foye MM, Ciraulo DA, Kornetsky C. The type IV phosphodiesterase inhibitors, Ro 20-1724 and rolipram, block the initiation of cocaine self-administration. Pharmacol Biochem Behav. 1999;62(1):151–8.
Knapp CM, Lee K, Foye M, Ciraulo DA, Kornetsky C. Additive effects of intra-accumbens infusion of the cAMP-specific phosphodiesterase inhibitor, rolipram and cocaine on brain stimulation reward. Life Sci. 2001;69(14):1673–82.
Konradi C, Cole RL, Heckers S, Hyman SE. Amphetamine regulates gene expression in rat striatum via transcription factor CREB. J Neurosci. 1994;14(9):5623–34.
Koob GF. Neuroadaptive mechanisms of addiction: studies on the extended amygdala. Eur Neuropsychopharmacol. 2003a;13(6):442–52.
Koob GF. Alcoholism: allostasis and beyond. Alcohol Clin Exp Res. 2003b;27(2):232–43.
Koob G, Kreek MJ. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. Am J Psychiatry. 2007;164(8):1149–59.
Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997;278(5335):52–8.
Koob GF, Markou A, Weiss F, Schulteis G. Opponent process and drug dependence: neurobiological mechanisms. Semin Neurosci. 1993;5:351–8.
Koob GF, Sanna PP, Bloom FE. Neuroscience of addiction. Neuron. 1998;21(3):467–76.
Krasnova IN, Justinova Z, Cadet JL. Methamphetamine addiction: involvement of CREB and neuroinflammatory signaling pathways. Psychopharmacology. 2016;233(10):1945–62.
Lai M, Zhu H, Sun A, Zhuang D, Fu D, Chen W, Zhang HT, Zhou W. The phosphodiesterase-4 inhibitor rolipram attenuates heroin-seeking behavior induced by cues or heroin priming in rats. Int J Neuropsychopharmacol. 2014;17(9):1397–407.
Lakics V, Karran EH, Boess FG. Quantitative comparison of phosphodiesterase mRNA distribution in human brain and peripheral tissues. Neuropharmacology. 2010;59(6):367–74.
Lane-Ladd SB, Pineda J, Boundy VA, Pfeuffer T, Krupinski J, Aghajanian GK, Nestler EJ. CREB (cAMP response element-binding protein) in the locus coeruleus: biochemical, physiological, and behavioral evidence for a role in opiate dependence. J Neurosci. 1997;17(20):7890–901.
Li J, Li YH, Yuan XR. Changes of phosphorylation of cAMP response element binding protein in rat nucleus accumbens after chronic ethanol intake: naloxone reversal. Acta Pharmacol Sin. 2003;24(9):930–6.
Li S, Doss JC, Hardee EJ, Quock RM. Involvement of cyclic GMP-dependent protein kinase in nitrous oxide-induced anxiolytic-like behavior in the mouse light/dark exploration test. Brain Res. 2005;1038(1):113–7.
Li CY, Mao X, Wei L. Genes and (common) pathways underlying drug addiction. PLoS Comput Biol. 2008;4(1):e2.

Li YF, Huang Y, Amsdell SL, Xiao L, O'Donnell JM, Zhang HT. 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. 2009;34(11):2404–19.

Li YF, Cheng YF, Huang Y, Conti M, Wilson SP, O'Donnell JM, Zhang HT. Phosphodiesterase-4D knock-out and RNA interference-mediated knock-down enhance memory and increase hippocampal neurogenesis via increased cAMP signaling. J Neurosci. 2011;31(1):172–83.

Liddie S, Anderson KL, Paz A, Itzhak Y. The effect of phosphodiesterase inhibitors on the extinction of cocaine-induced conditioned place preference in mice. J Psychopharmacol. 2012;26(10):1375–82.

Liebenberg N, Harvey BH, Brand L, Brink CB. Antidepressant-like properties of phosphodiesterase type 5 inhibitors and cholinergic dependency in a genetic rat model of depression. Behav Pharmacol. 2010;21(5–6):540–7.

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

Liu Q, Zhang M, Qin WJ, Wang YT, Li YL, Jing L, Li JX, Lawrence AJ, Liang JH. Septal nuclei critically mediate the development of behavioral sensitization to a single morphine injection in rats. Brain Res. 2012;1454:90–9.

Liu W, Peng QX, Lin XL, Luo CH, Jiang MJ, Mo ZX, Yung KK. Effect of rhynchophylline on the expression of p-CREB and sc-Fos in triatum and hippocampal CA1 area of methamphetamine-induced conditioned place preference rats. Fitoterapia. 2014;92:16–22.

Logrip ML. Phosphodiesterase regulation of alcohol drinking in rodents. Alcohol. 2015;49(8):795–802.

Logrip ML, Zorrilla EP. Stress history increases alcohol intake in relapse: relation to phosphodiesterase 10A. Addict Biol. 2012;17(5):920–33.

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

Logrip ML, Vendruscolo LF, Schlosburg JE, Koob GF, Zorrilla EP. Phosphodiesterase 10A regulates alcohol and saccharin self-administration in rats. Neuropsychopharmacology. 2014;39(7):1722–31.

Lonze BE, Ginty DD. Function and regulation of CREB family transcription factors in the nervous system. Neuron. 2002;35(4):605–23.

Lugnier C. Cyclic nucleotide phosphodiesterase (PDE) superfamily: a new target for the development of specific therapeutic agents. Pharmacol Ther. 2006;109(3):366–98.

Luo J, Jing L, Qin WJ, Zhang M, Lawrence AJ, Chen F, Liang JH. Transcription and protein synthesis inhibitors reduce the induction of behavioural sensitization to a single morphine exposure and regulate Hsp70 expression in the mouse nucleus accumbens. Int J Neuropsychopharmacol. 2011;14(1):107–21.

Maas JJ, Vogt SK, Chan GC, Pineda VV, Storm DR, Muglia LJ. Calcium-stimulated adenylyl cyclases are critical modulators of neuronal ethanol sensitivity. J Neurosci. 2005;25(16):4118–26.

Maldonado R, Blendy JA, Tzavara E, Gass P, Roques BP, Hanoune J, Schutz G. Reduction of morphine abstinence in mice with a mutation in the gene encoding CREB. Science. 1996;273(5275):657–9.

Mayr B, Montminy M. Transcriptional regulation by the phosphorylation-dependent factor CREB. Nat Rev Mol Cell Biol. 2001;2(8):599–609.

Meil WM, See RE. Lesions of the basolateral amygdala abolish the ability of drug associated cues to reinstate responding during withdrawal from self-administered cocaine. Behav Brain Res. 1997;87(2):139–48.

Menniti FS, Faraci WS, Schmidt CJ. Phosphodiesterases in the CNS: targets for drug development. Nat Rev Drug Discov. 2006;5(8):660–70.

Milton AL, Everitt BJ. The persistence of maladaptive memory: addiction, drug memories and anti-relapse treatments. Neurosci Biobehav Rev. 2012;36(4):1119–39.

Miserendino MJ, Nestler EJ. Behavioral sensitization to cocaine: modulation by the cyclic AMP system in the nucleus accumbens. Brain Res. 1995;2(674):299–306.
Misra K, Pandey SC. 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. 2003;74(6):967–75.
Misra K, Roy A, Pandey SC. Effects of voluntary ethanol intake on the expression of Ca(2+) / calmodulin-dependent protein kinase IV and on CREB expression and phosphorylation in the rat nucleus accumbens. Neuroreport. 2001;12(18):4133–7.
Molnar P, Gaal L. Effect of different subtypes of cognition enhancers on long-term potentiation in the rat dentate gyrus in vivo. Eur J Pharmacol. 1992;215(1):17–22.
Moonat S, Starkman BG, Sakharkar A, Pandey SC. Neuroscience of alcoholism: molecular and cellular mechanisms. Cell Mol Life Sci. 2010;67(1):73–88.
Moonat S, Sakharkar AJ, Zhang H, Tang L, Pandey SC. Aberrant histone deacetylase2-mediated histone modifications and synaptic plasticity in the amygdala predisposes to anxiety and alcoholism. Biol Psychiatry. 2013;73(8):763–73.
Moore RY, Bloom FE. Central catecholamine neuron systems: anatomy and physiology of the dopamine systems. Annu Rev Neurosci. 1978;1:129–69.
Mu Y, Ren Z, Jia J, Gao B, Zheng L, Wang G, Friedman E, Zhen X. Inhibition of phosphodiesterase10A attenuates morphine-induced conditioned place preference. Mol Brain. 2014;7:70.
Muglia LM, Schaefer ML, Vogt SK, Gurtner G, Imamura A, Muglia LJ. The 5′-flanking region of the mouse adenylyl cyclase type VIII gene imparts tissue-specific expression in transgenic mice. J Neurosci. 1999;19(6):2051–8.
Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365(6441):61–5.
Navakkode S, Sajikumar S, Frey JU. The type IV-specific phosphodiesterase inhibitor rolipram and its effect on hippocampal long-term potentiation and synaptic tagging. J Neurosci. 2004;24(35):7740–4.
Nelson EJ, Hellevuo K, Yoshimura M, Tabakoff B. Ethanol-induced phosphorylation and potentiation of the activity of type 7 adenylyl cyclase. Involvement of protein kinase C delta. J Biol Chem. 2003;278(7):4552–60.
Nestler EJ. Molecular mechanisms of drug addiction. Neuropharmacology 2004;47:Suppl 1, 24–32.
Nestler EJ. Is there a common molecular pathway for addiction? Nat Neurosci. 2005;8(11):1445–9.
Nestler EJ. Reflections on: “A general role for adaptations in G-Proteins and the cyclic AMP system in mediating the chronic actions of morphine and cocaine on neuronal function”. Brain Res. 2015;1645:71–4.
Nestler EJ, Aghajanian GK. Molecular and cellular basis of addiction. Science. 1997;278(5335):58–63.
Nishikawa T, Mataga N, Takashima M, Toru M. Behavioral sensitization and relative hyperresponsiveness of striatal and limbic dopaminergic neurons after repeated methamphetamine treatment. Eur J Pharmacol. 1983;88(2–3):195–203.
Nugent FS, Penick EC, Kauer JA. Opioids block long-term potentiation of inhibitory synapses. Nature. 2007;446(7139):1086–90.
Nunez C, Gonzalez-Cuello A, Sanchez L, Vargas ML, Milanes MV, Laorden ML. Effects of rolipram and diazepam on the adaptive changes induced by morphine withdrawal in the hypothalamic paraventricular nucleus. Eur J Pharmacol. 2009;620(1–3):1–8.
O’Brien CP, Childress AR, Mclellan AT, Ehrman R. Classical conditioning in drug-dependent humans. Ann N Y Acad Sci. 1992;654:400–15.
Pandey SC. Anxiety and alcohol abuse disorders: a common role for CREB and its target, the neuropeptide Y gene. Trends Pharmacol Sci. 2003;24(9):456–60.
Pandey SC. The gene transcription factor cyclic AMP-responsive element binding protein: role in positive and negative affective states of alcohol addiction. Pharmacol Ther. 2004;104(1):47–58.
Pandey SC, Mittal N, Lumeng L, Li TK. Involvement of the cyclic AMP-responsive element binding protein gene transcription factor in genetic preference for alcohol drinking behavior. Alcohol Clin Exp Res. 1999a;23(9):1425–34.

Pandey SC, Zhang D, Mittal N, Nayyar D. Potential role of the gene transcription factor cyclic AMP-responsive element binding protein in ethanol withdrawal-related anxiety. J Pharmacol Exp Ther. 1999b;288(2):866–78.

Pandey SC, Roy A, Mittal N. 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. 2001a;296(3):857–68.

Pandey SC, Saito T, Yoshimura M, Sohma H, Gotz ME. cAmp signaling cascade: a promising role in ethanol tolerance and dependence. Alcohol Clin Exp Res. 2001b;25(5):Suppl ISBRA, 46S–48S.

Pandey SC, Roy A, Zhang H. 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. 2003;27(3):396–409.

Pandey SC, Roy A, Zhang H, Xu T. Partial deletion of the cAMP response element-binding protein gene promotes alcohol-drinking behaviors. J Neurosci. 2004;24(21):5022–30.

Pandey SC, Chartoff EH, Carlezon WJ, Zou J, Zhang H, Kreibich AS, Blendy JA, Crews FT. CREB gene transcription factors: role in molecular mechanisms of alcohol and drug addiction. Alcohol Clin Exp Res. 2005a;29(2):176–84.

Pandey SC, Zhang H, Roy A, Xu T. Deficits in amygdaloid cAMP-responsive element-binding protein signaling play a role in genetic predisposition to anxiety and alcoholism. J Clin Invest. 2005b;115(10):2762–73.

Parsons LH, Justice JJ. Serotonin and dopamine sensitization in the nucleus accumbens, ventral tegmental area, and dorsal raphe nucleus following repeated cocaine administration. J Neurochem. 1993;61(5):1611–9.

Peregud DI, Iakovleva AA, Stepanichev M, Panchenko LF, Guliaeva NV. Role of NO/cGMP signaling cascade in the development of opium dependency. Eksp Klin Farmakol. 2013;76(3):3–6.

Perez-Torres S, Miro X, Palacios JM, Cortes R, Puigdomenech P, Mengod G. 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. 2000;20(3–4):349–74.

Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). Pharmacol Rev. 2010;62(4):588–631.

Pitkanen A, Savander V, Ledoux JE. Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala. Trends Neurosci. 1997;20(11):517–23.

Podda MV, Grassi C. New perspectives in cyclic nucleotide-mediated functions in the CNS: the emerging role of cyclic nucleotide-gated (CNG) channels. Pflugers Arch. 2014;466(7):1241–57.

Post RM, Rose H. Increasing effects of repetitive cocaine administration in the rat. Nature. 1976;260(5553):731–2.

Prakash A, Zhang H, Pandey SC. Innate differences in the expression of brain-derived neurotrophic factor in the regions within the extended amygdala between alcohol preferring and nonpreferring rats. Alcohol Clin Exp Res. 2008;32(6):909–20.

Punch LJ, Self DW, Nestler EJ, Taylor JR. Opposite modulation of opiate withdrawal behaviors on microinfusion of a protein kinase A inhibitor versus activator into the locus coeruleus or periaqueductal gray. J Neurosci. 1997;17(21):8520–7.

Qin WJ, Wang YT, Zhang M, Wen RT, Liu Q, Li YL, Chen F, Lawrence AJ, Liang JH. Molecular chaperone heat shock protein 70 participates in the labile phase of the development of behavioural sensitization induced by a single morphine exposure in mice. Int J Neuropsychopharmacol. 2013;16(3):647–59.

Reyes-Irisarri E, Perez-Torres S, Mengod G. Neuronal expression of cAMP-specific phosphodiesterase 7B mRNA in the rat brain. Neuroscience. 2005;132(4):1173–85.

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

Rose GM, Hopper A, De Vivo M, Tehim A. Phosphodiesterase inhibitors for cognitive enhancement. Curr Pharm Des. 2005;11(26):3329–34.

Rutten K, Misner DL, Works M, Blokland A, Novak TJ, Santarelli L, Wallace TL. Enhanced long-term potentiation and impaired learning in phosphodiesterase 4D-knockout (PDE4D) mice. Eur J Neurosci. 2008;28(3):625–32.

Rutter AR, Poffe A, Cavallini P, Davis TG, Schneck J, Negri M, Vicentini E, Montanari D, Arban R, Gray FA, Davies CH, Wren PB. 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. 2014;350(1):153–63.

Saito T, Lee JM, Hoffman PL, Tabakoff B. Effects of chronic ethanol treatment on the beta-adrenergic receptor-coupled adenylate cyclase system of mouse cerebral cortex. J Neurochem. 1987;48(6):1817–22.

Samson WK, Bianchi R, Mogg R. Evidence for a dopaminergic mechanism for the prolactin inhibitory effect of atrial natriuretic factor. Neuroendocrinology. 1988;47(3):268–71.

Sanderson TM, Sher E. The role of phosphodiesterases in hippocampal synaptic plasticity. Neuropharmacology. 2013;74:86–95.

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. Preclinical characterization of selective phosphodiesterase 10A inhibitors: a new therapeutic approach to the treatment of schizophrenia. J Pharmacol Exp Ther. 2008;325(2):681–90.

Schroeder JA, Hummel M, Unterwald EM. Repeated intracerebroventricular forskolin administration enhances behavioral sensitization to cocaine. Behav Brain Res. 2004;153(1):255–60.

Schroeder JA, Ruta JD, Gordon JS, Rodrigues AS, Foote CC. The phosphodiesterase inhibitor isobutylmethylxanthine attenuates behavioral sensitization to cocaine. Behav Pharmacol. 2012;23(3):310–4.

Shaw-Lutchman TZ, Impey S, Storm D, Nestler EJ. Regulation of CRE-mediated transcription in mouse brain by amphetamine. Synapse. 2003;48(1):10–7.

Shaywitz AJ, Greenberg ME. CREB: a stimulus-induced transcription factor activated by a diverse array of extracellular signals. Annu Rev Biochem. 1999;68:821–61.

Shichinohe S, Ozawa H, Saito T, Hashimoto E, Lang C, Riederer P, Takahata N. Differential alteration of adenylyl cyclase subtypes I, II, and V/VI in postmortem human brains of heroin addicts. Alcohol Clin Exp Res. 1998;22(3 Suppl):84S–7S.

Shichinohe S, Ozawa H, Hashimoto E, Tatschner T, Riederer P, Saito T. Changes in the cAMP-related signal transduction mechanism in postmortem human brains of heroin addicts. J Neural Transm (Vienna). 2001;108(3):335–47.

Siuciak JA, Chapin DS, Harms JF, Lebel LA, Mccarthy SA, Chambers L, Shrikhande A, Wong S, Menniti FS, Schmidt CJ. Inhibition of the striatum-enriched phosphodiesterase PDE10A: a novel approach to the treatment of psychosis. Neuropharmacology. 2006;51(2):386–96.

Siuciak JA, Chapin DS, Mccarthy SA, Martin AN. Antipsychotic profile of rolipram: efficacy in rats and reduced sensitivity in mice deficient in the phosphodiesterase-4B (PDE4B) enzyme. Psychopharmacology. 2007;192(3):415–24.

Sohma H, Hashimoto E, Shirasaka T, Tsunematsu R, Ozawa H, Boissl KW, Boning J, Riederer P, Saito T. Quantitative reduction of type I adenylyl cyclase in human alcoholics. Biochim Biophys Acta. 1999;1454(1):11–8.

Sotty F, Montezinho LP, Steiniger-Brach B, Nielsen J. 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. 2009;109(3):766–75.

Steketee JD. Cortical mechanisms of cocaine sensitization. Crit Rev Neurobiol. 2005;17(2):69–86.

Sullivan ME, Hall SR, Milne B, Jhamandas K. Suppression of acute and chronic opioid withdrawal by a selective soluble guanylyl cyclase inhibitor. Brain Res. 2000;859(1):45–56.

Sun X, Liu Y, Hu G, Wang H. Activities of cAMP-dependent protein kinase and protein kinase C are modulated by desensitized nicotinic receptors in the rat brain. Neurosci Lett. 2004;367(1):19–22.

Sun A, Zhuang D, Zhu H, Lai M, Chen W, Liu H, Zhang F, Zhou W. Decrease of phosphorylated CREB and ERK in nucleus accumbens is associated with the incubation of heroin seeking induced by cues after withdrawal. Neurosci Lett. 2015;591:166–70.

Terwilliger RZ, Beitner-Johnson D, Sevarino KA, Crain SM, Nestler EJ. A general role for adaptations in G-proteins and the cyclic AMP system in mediating the chronic actions of morphine and cocaine on neuronal function. Brain Res. 1991;548(1–2):100–10.

Thiriet N, Jouvert P, Gobaille S, Solov'eva O, Gough B, Aunis D, Ali S, Zwiller J. C-type natriuretic peptide (CNP) regulates cocaine-induced dopamine increase and immediate early gene expression in rat brain. Eur J Neurosci. 2001;14(10):1702–8.

Thompson BE, Sachs BD, Kantak KM, Cherry JA. The Type IV phosphodiesterase inhibitor rolipram interferes with drug-induced conditioned place preference but not immediate early gene induction in mice. Eur J Neurosci. 2004;19(9):2561–8.

Thompson LL, Claus ED, Mikulich-Gilbertson SK, Banich MT, Crowley T, Krmpotich T, Miller D, Tanabe J. Negative reinforcement learning is affected in substance dependence. Drug Alcohol Depend. 2012;123(1–3):84–90.

Tolliver BK, Ho LB, Reid MS, Berger SP. Evidence for involvement of ventral tegmental area cyclic AMP systems in behavioral sensitization to psychostimulants. J Pharmacol Exp Ther. 1996;1(278):411–20.

Turgeon SM, Pollack AE, Fink JS. Enhanced CREB phosphorylation and changes in c-Fos and FRA expression in striatum accompany amphetamine sensitization. Brain Res. 1997;749(1):120–6.

Uhl GR, Liu QR, Drgon T, Johnson C, Walther D, Rose JE. Molecular genetics of nicotine dependence and abstinence: whole genome association using 520,000 SNPs. BMC Genet. 2007;8:10.

Uzbay IT, Celik T, Aydin A, Kayir H, Tokgoz S, Bilgi C. Effects of chronic ethanol administration and ethanol withdrawal on cyclic guanosine 3′,5′-monophosphate (cGMP) levels in the rat brain. Drug Alcohol Depend. 2004;74(1):55–9.

Valjent E, Corvol JC, Trzaskos JM, Girault JA, Herve D. Role of the ERK pathway in psychostimulant-induced locomotor sensitization. BMC Neurosci. 2006;7:20.

Valverius P, Hoffman PL, Tabakoff B. Hippocampal and cerebellar beta-adrenergic receptors and adenylate cyclase are differentially altered by chronic ethanol ingestion. J Neurochem. 1989;52(2):492–7.

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. The novel selective PDE9 inhibitor BAY 73-6691 improves learning and memory in rodents. Neuropharmacology. 2008;55(5):908–18.

Volke V, Wegener G, Vasar E. Augmentation of the NO-cGMP cascade induces anxiogenic-like effect in mice. J Physiol Pharmacol. 2003;54(4):653–60.

Wang YT, Qin WJ, Liu Q, Li YL, Liang H, Chen F, Lawrence AJ, Zhang XL, Liang JH. Chaperone heat shock protein 70 in nucleus accumbens core: a novel biological target of behavioural sensitization to morphine in rats. Int J Neuropsychopharmacol. 2014;17(3):469–84.

Wen RT, Feng WY, Liang JH, Zhang HT. Role of phosphodiesterase 4-mediated cyclic AMP signaling in pharmacotherapy for substance dependence. Curr Pharm Des. 2015;21(3):355–64.

Wen R-T, Zhang M, Qin W-J, Liu Q, Wang W-P, Lawrence AJ, et al. The phosphodiesterase-4 (PDE4) inhibitor rolipram decreases ethanol seeking and consumption in alcohol-preferring fawn-hooded rats. Alcohol Clin Exp Res. 2012;36(12):2157–67.

Werner C, Raivich G, Cowen M, Strekalova T, Sillaber I, Buters JT, Spanagel R, Hofmann F. Importance of NO/cGMP signalling via cGMP-dependent protein kinase II for controlling emotionality and neurobehavioural effects of alcohol. Eur J Neurosci. 2004;20(12):3498–506.

World Health Organization. International statistical classification of diseases and related health problems. 10th revision. 2nd ed. Geneva: World Health Organization; 2004.

Wunder F, Tersteegen A, Rebmann A, Erb C, Fahrig T, Hendrix M. Characterization of the first potent and selective PDE9 inhibitor using a cGMP reporter cell line. Mol Pharmacol. 2005;68(6):1775–81.

Xia ZG, Refsdal CD, Merchant KM, Dorsa DM, Storm DR. Distribution of mRNA for the calmodulin-sensitive adenylate cyclase in rat brain: expression in areas associated with learning and memory. Neuron. 1991;6(3):431–43.

Xing J, Kornhauser JM, Xia Z, Thiele EA, Greenberg ME. Nerve growth factor activates extracellular signal-regulated kinase and p38 mitogen-activated protein kinase pathways to stimulate CREB serine 133 phosphorylation. Mol Cell Biol. 1998;18(4):1946–55.

Xu Y, Zhang HT, O'Donnell JM. Phosphodiesterases in the central nervous system: implications in mood and cognitive disorders. Handb Exp Pharmacol. 2011;204:447–85.

Yan Y, Nitta A, Mizuno T, Nakajima A, Yamada K, Nabeshima T. Discriminative-stimulus effects of methamphetamine and morphine in rats are attenuated by cAMP-related compounds. Behav Brain Res. 2006;173(1):39–46.

Yang X, Diehl AM, Wand GS. 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. 1996;278(1):338–46.

Yang X, Horn K, Wand GS. Chronic ethanol exposure impairs phosphorylation of CREB and CRE-binding activity in rat striatum. Alcohol Clin Exp Res. 1998a;22(2):382–90.

Yang X, Horn K, Baraban JM, Wand GS. Chronic ethanol administration decreases phosphorylation of cyclic AMP response element-binding protein in granule cells of rat cerebellum. J Neurochem. 1998b;70(1):224–32.

Yoshimura M, Tabakoff B. Selective effects of ethanol on the generation of cAMP by particular members of the adenylyl cyclase family. Alcohol Clin Exp Res. 1995;19(6):1435–40.

Yoshimura M, Tabakoff B. Ethanol's actions on cAMP-mediated signaling in cells transfected with type VII adenylyl cyclase. Alcohol Clin Exp Res. 1999;23(9):1457–61.

Zhang HT. Cyclic AMP-specific phosphodiesterase-4 as a target for the development of antidepressant drugs. Curr Pharm Des. 2009;15(14):1688–98.

Zhang HT, Crissman AM, Dorairaj NR, Chandler LJ, O'Donnell JM. Inhibition of cyclic AMP phosphodiesterase (PDE4) reverses memory deficits associated with NMDA receptor antagonism. Neuropsychopharmacology. 2000;23(2):198–204.

Zhang HT, Huang Y, Jin SL, Frith SA, Suvarna N, Conti M, O'donnell JM. Antidepressant-like profile and reduced sensitivity to rolipram in mice deficient in the PDE4D phosphodiesterase enzyme. Neuropsychopharmacology. 2002;27(4):587–95.

Zhang HT, Zhao Y, Huang Y, Dorairaj NR, Chandler LJ, O'Donnell JM. Inhibition of the phosphodiesterase 4 (PDE4) enzyme reverses memory deficits produced by infusion of the MEK inhibitor U0126 into the CA1 subregion of the rat hippocampus. Neuropsychopharmacology. 2004;29(8):1432–9.

Zhdanova IV, Giorgetti M. Melatonin alters behavior and cAMP levels in nucleus accumbens induced by cocaine treatment. Brain Res. 2002;956(2):323–31.

Zhong P, Wang W, Yu F, Nazari M, Liu X, Liu QS. Phosphodiesterase 4 inhibition impairs cocaine-induced inhibitory synaptic plasticity and conditioned place preference. Neuropsychopharmacology. 2012;37(11):2377–87.

Zocchi A, Girlanda E, Varnier G, Sartori I, Zanetti L, Wildish GA, Lennon M, Mugnaini M, Heidbreder CA. Dopamine responsiveness to drugs of abuse: A shell-core investigation in the nucleus accumbens of the mouse. Synapse. 2003;50(4):293–302.