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Phosphodiesterase regulation of alcohol drinking in rodents

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Abstract

Alcohol use disorders are chronically relapsing conditions characterized by persistent drinking despite the negative impact on one's life. The difficulty of achieving and maintaining sobriety suggests that current treatment options fail to fully address the underlying causes of alcohol use disorders, and thus identifying additional pathways controlling alcohol consumption may uncover novel targets for medication development to improve treatment options. One family of proteins recently implicated in the regulation of alcohol consumption is the cyclic nucleotide phosphodiesterases (PDEs). As an integral component in the regulation of the second messengers cyclic AMP and cyclic GMP, and thus their cognate signaling pathways, PDEs present intriguing targets for pharmacotherapies to combat alcohol use disorders. As activation of cAMP/cGMP-dependent signaling cascades can dampen alcohol intake, PDE inhibitors may provide a novel target for reducing excessive alcohol consumption, as has been proposed for PDE4 and PDE10A. This review highlights preclinical literature demonstrating the involvement of cyclic nucleotide-dependent signaling in neuronal and behavioral responses to alcohol, as well as detailing the capacity of various PDE inhibitors to modulate alcohol intake. Together these data provide a framework for evaluating the potential utility of PDE inhibitors as novel treatments for alcohol use disorders.

Keywords

alcohol; ethanol; adenylyl cyclase; guanylyl cyclase; cAMP; cGMP; PKA; PKG; phosphodiesterase; PDE4; PDE10A

Introduction

Alcohol use disorders pose a significant societal burden, afflicting about 10% of the American population (Stinson et al., 2005) and contributing to 5.9% of deaths worldwide (World Health Organization, 2014). Alcohol use disorders are chronically relapsing conditions with recidivism rates of 40–60% (Moos & Moos, 2006). These high relapse rates

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highlight the need to identify new treatment targets so medications can be developed to better address the underlying causes of excessive alcohol use. One class of proteins that has recently gained attention as a putative regulator of alcohol drinking is the cyclic nucleotide phosphodiesterases (PDEs).

PDEs are essential regulators of a variety of functions in the central nervous system, with prominent roles in synaptic plasticity (Sanderson & Sher, 2013) and learning and memory (Liddie, Anderson, Paz, & Itzhak, 2012; Roesler et al., 2014; Rutten et al., 2007; Werenicz et al., 2012). PDE inhibitors have improved cognitive deficits in rodent models of neurological dysfunction (Wang, Zhang, Zhang, & Li, 2015), including the neurodegenerative disorders Alzheimer's, Huntington's and Parkinson's diseases (Fusco & Giampà, 2015) and neuropsychiatric disorders such as schizophrenia (Ramirez & Smith, 2014) and depression (Liebenberg, Harvey, Brand, & Brink, 2010; Zhang, 2009). Many of the disease-related dysfunctions ascribed to PDEs suggest possible relevance to the pathology of alcohol use disorders. Striatal PDEs negatively regulate dopaminergic signaling (Ramirez & Smith, 2014), which could alter the reinforcing efficacy of alcohol. Treatment with PDE inhibitors in rodent models of Huntington's disease has been shown to increase corticostriatal brain-derived neurotrophic factor (BDNF) expression (Fusco & Giampa, 2015), a therapeutic effect that might also reduce excessive alcohol drinking since escalating alcohol intake is accompanied by reduced corticostriatal BDNF expression (Logrip, Janak, & Ron, 2009), whereas BDNF infusion into the dorsal striatum reduces alcohol self-administration (Jeanblanc et al., 2009). The involvement of PDEs in learning and memory processes is directly applicable to addictive disorders, which have been characterized as diseases of maladaptive synaptic plasticity with molecular adaptations producing excessive strengthening of drug-related memories to drive drug-seeking behaviors (Lüscher & Malenka, 2011; Nestler, 2013; Tronson & Taylor, 2013). If the aberrant plasticity supporting alcohol seeking in addicted individuals is susceptible to PDE regulation, then elucidating the PDEs able to modulate alcohol consumption may identify new medication targets to reduce recidivism in alcohol-dependent patients. Central to the understanding of how PDEs might control alcohol use is their unique capacity for modulating the propagation of signals dependent on cyclic nucleotides.

PDEs regulate a variety of intracellular signaling cascades through deactivation of the second messengers cyclic adenosine 3',5'-monophosphate (cAMP) and cyclic guanosine 3', 5'-monophosphate (cGMP). More than 100 PDE isoforms encoded by 21 different genes have been sorted into 11 families, based on structure and enzymatic activity, and are classified as cAMP-specific (PDE4, PDE7, PDE8), cGMP-specific (PDE5, PDE6, PDE9), or dual specificity (PDE1, PDE2, PDE3, PDE10, PDE11), indicating activity at both cAMP and cGMP (Bender & Beavo, 2006; Conti & Beavo, 2007). Together with the adenylyl (AC) and guanylyl (GC) cyclases that synthesize cAMP and cGMP, respectively, PDEs play a critical role in maintaining cyclic nucleotide levels, thereby regulating myriad intracellular signaling cascades that employ cAMP or cGMP as second messengers. Primary signaling pathways sensitive to PDE modulation of cyclic nucleotide levels include G protein-coupled receptor signaling via the cAMP/cAMP-dependent protein kinase (PKA) pathway, nitric oxide and natriuretic peptide receptor signaling through cGMP/cGMP-dependent protein kinases (PKG) and cyclic nucleotide-gated ion channel activation by both cAMP and cGMP

(Podda & Grassi, 2014). A vast body of literature has examined the involvement of cAMP- and cGMP-dependent signaling in patterning alcohol-related behaviors, providing clues to the possible therapeutic utility of PDE inhibitors for alcohol use disorders.

Cyclic nucleotide signaling regulates molecular and behavioral responses to alcohol

Adenylyl cyclase, cAMP, and PKA

Cyclic nucleotides and their signaling partners play integral roles both in acute responses to alcohol and as sites of adaptation to chronic alcohol exposure. In particular, the cAMP/PKA signaling pathway has been implicated in the regulation of molecular and behavioral responses to alcohol. Recruitment of cAMP/PKA upon acute alcohol application has long been established *in vitro*, where alcohol has been shown to increase cAMP levels, leading to elevated PKA activity, nuclear translocation of the PKA catalytic subunit, Cα, and increased gene expression via activation (phosphorylation) of the cAMP response element binding protein (CREB) (Asher, Cunningham, Yao, Gordon, & Diamond, 2002; Constantinescu, Diamond, & Gordon, 1999; Dohrman, Diamond, & Gordon, 1996; Gordon, Collier, & Diamond, 1986). Activation of cAMP signaling upon acute alcohol treatment may result, at least in part, from potentiating the stimulus-responsiveness of cAMP's synthetic enzymes, the ACs (Nelson, Hellevuo, Yoshimura, & Tabakoff, 2003; Yoshimura & Tabakoff, 1995). Electrophysiological studies have highlighted the importance of the AC/cAMP/PKA pathway in the potentiation of inhibitory GABAergic transmission by acute alcohol. For example, alcohol acutely increases GABAergic potentials in the central nucleus of the amygdala (CeA), at least in part via a presynaptic mechanism (Roberto, Madamba, Moore, Tallent, & Siggins, 2003); however, this effect was lost in mice with a partial deletion of AC7 (Cruz et al., 2011), previously shown to decrease AC activity (Hines et al., 2006). Pharmacological inhibition of AC or PKA similarly blunted alcohol's ability to potentiate GABA release in the cerebellum (Kelm, Criswell, & Breese, 2008), while postsynaptic inhibition of PKA blocked alcohol potentiation of evoked GABAergic potentials in the basolateral amygdala (BLA) (Silberman, Ariwodola, & Weiner, 2012). A single alcohol injection *in vivo* also may increase GABA release in the ventral tegmental area (VTA) 24 h later via a PKA-dependent mechanism and occlude long-term potentiation of GABAergic transmission (Guan & Ye, 2010; Melis, Camarini, Ungless, & Bonci, 2002), despite continued responsiveness of VTA neurons to cAMP and cGMP mimetics. Taken together, these data demonstrate the recruitment of AC/cAMP/PKA signaling pathways in the acute neuronal response to alcohol.

Whereas acute alcohol potentiates neuronal cAMP-dependent signaling, chronic alcohol exposure may dysregulate this pathway. Chronic alcohol consumption reduced stimulus-dependent AC activity in the cortex (Saito, Lee, Hoffman, & Tabakoff, 1987) and hippocampus (Valverius, Hoffman, & Tabakoff, 1989), but inconsistently in cerebellar neurons (Valverius et al., 1989; Wand, Diehl, Levine, Wolfgang, & Samy, 1993) of mice. In rats, increased expression of mRNA for the PKA inhibitor PKI in the medial prefrontal cortex (mPFC), nucleus accumbens (NAc), and amygdala was demonstrated after chronic intermittent alcohol vapor exposure in rats (Repunte-Canonigo, Lutjens, van der Stap, &

Sanna, 2007), while reduced levels of phosphorylated CREB were observed in the cortex, CeA, and medial amygdala (MeA) during withdrawal from chronic consumption of an alcohol-containing liquid diet (Pandey, Roy, & Mittal, 2001; Pandey, Roy, & Zhang, 2003). It should be noted that increased PKA activity has been reported in the NAc after chronic alcohol intake via liquid diet (Ortiz et al., 1995), but no changes were seen in cortical PKA activity or in CeA or MeA PKA Cα levels during withdrawal (Pandey et al., 2001, 2003). Given the wealth of evidence for recruitment of AC/cAMP/PKA signaling by acute alcohol, these chronic alcohol-induced alterations in AC/cAMP/PKA activity suggest that this pathway may be poised to shape behavioral responses to alcohol.

Recruitment of AC/cAMP/PKA by a single alcohol application indicates possible involvement in establishing the initial sensitivity to alcohol's sedative effects. Multiple rodent lines display a direct relationship between cAMP and sedation duration. Rats bred for elevated alcohol intake are slower to fall asleep after high alcohol doses than their lower drinking counterparts, as has been displayed for alcohol-preferring (P) vs. nonpreferring (NP) and high alcohol drinking (HAD) vs. low alcohol drinking (LAD) rat lines (Froehlich & Wand, 1997; Kurtz, Stewart, Zweifel, Li, & Froehlich, 1996). Both preferring lines also show deficits at one node of cAMP-regulated signaling, with lower AC activation in HAD vs LAD rats (Froehlich & Wand, 1997) and decreased CREB phosphorylation in P vs. NP rats (Pandey, Zhang, Roy, & Xu, 2005). Reduced sedation to alcohol, relative to wild type littermates, has been observed in mice lacking AC5 (Kim, Kim, Baek, Lee, & Han, 2011) or the PKA regulatory subunit RIIβ (Fee et al., 2004; Thiele et al., 2000), mutations that decrease stimulus-induced cAMP production (Lee et al., 2002) or PKA activation (Thiele et al., 2000), respectively. Central PKA activation upon infusion of the cAMP mimetic Sp-cAMPS significantly increased alcohol-induced sedation (Kumar et al., 2012), providing additional support for cAMP involvement in alcohol's sedative effects. It should be noted that several mouse lines display the opposite pattern, with increased alcohol-induced sleep time in mice lacking other AC isoforms (AC1 and AC1/AC8 knockouts) (Maas, Vogt, et al., 2005), or with reduced AC (Gnas heterozygotes) or PKA (R[AB]+ expressing) activity (Wand, Levine, Zweifel, Schwindinger, & Abel, 2001; Yang, Oswald, & Wand, 2003). Nonetheless, the data primarily suggest that lower cAMP-directed signaling reduces initial sensitivity to alcohol sedation.

Activation of AC/cAMP/PKA may regulate alcohol consumption as well, since both AC5 and RIIβ knockouts drank more alcohol relative to wild-type counterparts when provided continuous access to 2-bottle choice alcohol vs. water in the home cage (Fee et al., 2004; Kim et al., 2011; Thiele et al., 2000). Interestingly, loss of RIIβ appears to regulate alcohol taking independent of alcohol seeking, as operant alcohol self-administration was at least twice as high in wild-type females as in knockout females and all males (Ferraro, Sparta, Knapp, Breese, & Thiele, 2006). Mouse lines displaying an inverse relationship between AC/cAMP/PKA activity and alcohol-induced sedation did not uniformly consume more alcohol, as might be predicted. Whereas reduced 2-bottle choice alcohol intake was observed in Gnas haploinsufficient and R(AB)+ expressing mice (Wand et al., 2001), sedation-sensitive AC1 knockouts did not differ from their wild-type counterparts in alcohol consumption, and AC8 knockouts consumed significantly less alcohol than wild types, despite minimal differences in alcohol-induced sedation (Maas, Vogt, et al., 2005). These

data suggest that while sedation to and consumption of alcohol generally demonstrate inverse relationships, the genetic determination of these two behaviors may be regulated by distinct ACs, perhaps via differential behavior-specific AC engagement. Downstream of AC activation, signals converge on the synthesis of cAMP and activation of PKA, a central regulator of alcohol drinking. High and low levels of alcohol consumption in P and NP rats, respectively, can be normalized by pharmacologically altering PKA activation (Pandey et al., 2005). CeA infusion of the PKA activator Sp-cAMPS significantly reduced P rats' alcohol drinking, whereas the PKA inhibitor Rp-cAMPS significantly increased NP rats' alcohol intake (Pandey et al., 2005). Rp-cAMPS infused into the NAc similarly enhanced alcohol drinking in outbred Sprague-Dawley rats, whereas Sp-cAMPS did not decrease intake below the modest baseline levels (Misra & Pandey, 2006). It should be noted that most genetic and pharmacological manipulations of AC/cAMP/PKA signaling did not alter alcohol metabolism, nor did they affect consumption of bitter or sweet solutions, with one exception (Kim et al., 2011). Together, these data support a vital function for neuronal AC/cAMP/PKA signaling in the regulation of alcohol intake.

Guanylyl cyclase, cGMP, and PKG

While fewer studies have investigated the involvement of cGMP-mediated signaling in the molecular response to alcohol and intake control, data suggest that cGMP/PKG signaling regulates alcohol drinking similarly to cAMP/PKA. Consumption of an alcohol-containing liquid diet for at least 2 weeks increased cGMP levels in the cortex, striatum, and hippocampus, with cortical and striatal levels normalizing within 24 h of diet removal (Uzbay et al., 2004). Alcohol induction of cGMP likely contributes to regulation of alcohol-related behaviors, as deletion of the gene encoding PKG type II reduced alcohol's sedative effects and potentiated alcohol intake, without affecting alcohol clearance or consumption of sweet solutions (Werner et al., 2004). Conversely, increasing cGMP levels in either the VTA or the mPFC via infusion of the C-type natriuretic peptide reduced the ability of alcohol deprivation to enhance drinking, an effect that was reversed by inhibiting PKG (Romieu, Gobaille, Aunis, & Zwiller, 2008). Together, these data indicate similar roles for cGMP and cAMP in suppressing alcohol intake, and suggest that a delicate balance may exist between the activities of the cAMP and cGMP synthetic enzymes, AC and GC, and the degrading enzymes, the PDEs, to maintain moderate alcohol consumption.

Phosphodiesterase regulation of alcohol intake

The wealth of data implicating cyclic nucleotide-dependent signaling in the suppression of alcohol consumption suggests the possibility that PDEs may promote alcohol intake through reduction of cyclic nucleotide activity. Given the wide variety of PDEs, identifying those likely to support high levels of alcohol drinking has presented a particular challenge. Many PDEs are expressed in brain regions that subserve reward and motivated behaviors, including the frontal cortex and striatum (Lakics, Karran, & Boess, 2010), and overlapping expression patterns in these areas indicate that multiple PDEs may regulate alcohol-related behaviors. The fact that both cAMP- and cGMP-dependent signaling modulate alcohol intake also suggests that more than one PDE may regulate alcohol consumption. Microarray analyses have variably identified *Pde1a*, *Pde1b*, *Pde4b*, or *Pde10a* as genes differentially

expressed in whole brain samples from alcohol-naïve high (HAP) vs. low (LAP) alcohol-preferring mouse lines (*Pde4b, Pde10a*; Mulligan et al., 2006) or in frontal cortex samples from C57BL/6J mice following a single 4-h intake period (*Pde1a*; Mulligan et al., 2011) or chronic intermittent intake (*Pde1b, Pde10a*; Osterndorff-Kahanek, Ponomarev, Blednov, & Harris, 2013), but the functionality of these adaptations was not confirmed. Efforts to pharmacologically identify PDEs regulating alcohol intake have tested the ability of multiple nonspecific and specific PDE inhibitors to reduce alcohol consumption in rodent drinking models, with varying efficacy (Table 1). The nonspecific PDE inhibitor propentofylline failed to significantly alter alcohol intake under a continuousaccess 2-bottle choice paradigm (Blednov, Benavidez, Black, & Harris, 2014), whereas another nonspecific inhibitor, ibudilast (Gibson et al., 2006), reduced alcohol consumption in multiple rodent models utilizing limited, 2-h daily alcohol access (Bell et al., 2013). Ibudilast decreased alcohol drinking in two distinct alcohol-preferring rat lines (P and HAD1), significantly reducing both maintenance and relapse-like drinking. Ibudilast also dose-dependently decreased the heightened alcohol intake of mice made physically dependent on alcohol through multiple cycles of intermittent alcohol vapor inhalation, with minimal effects on drinking in non-dependent mice. Together, these data suggest that nonspecific PDE inhibitors may reduce the heightened alcohol drinking observed in genetically preferring and alcohol-dependent rodents, with little impact on more moderate levels of alcohol consumption. However, it remains to be determined whether the differential success of these nonspecific inhibitors resulted from differences in the drinking paradigms (moderate vs. higher levels of alcohol intake) or from the distinct PDE inhibitory profiles of the drugs. The dramatic effect of manipulating cyclic nucleotide signaling on alcohol drinking, even at moderate levels of consumption, suggests the likely participation of one or more PDEs in regulating alcohol intake. The following sections detail the use of specific PDE inhibitors to investigate the involvement of individual PDEs in the modulation of alcohol consumption and related behaviors.

PDE1 and alcohol-related cognitive deficits

The PDE1 family of dual-specificity phosphodiesterases, comprised of 3 subtypes each encoded by a distinct gene, is unique among PDEs in its activation by calcium/calmodulin (Goraya & Cooper, 2005). PDE1 is widely expressed in the brain, particularly in the cortex and hippocampus (Lakics et al., 2010), and the compensatory up-regulation of cortical PDE1 activity in mice expressing a constitutively active form of Gαs (Kelly et al., 2009) suggests a central role for PDE1 in the maintenance of cortical cAMP levels. Elevated cortical *Pde1a/b* expression after acute or chronic intermittent alcohol consumption (Mulligan et al., 2011; Osterndorff-Kahanek et al., 2013) indicates that cortical PDE1 might regulate behaviors altered by excessive alcohol consumption; however, the PDE1 inhibitor vinpocetine did not significantly change the moderate levels of alcohol consumed by nondependent mice provided continuous 2-bottle choice access to alcohol (Blednov et al., 2014). It remains to be determined whether PDE1 inhibitors might yet prove efficacious to reduce binge-like alcohol drinking or the high alcohol intake of alcohol-dependent rodents. Intriguingly, vinpocetine has shown remarkable promise for ameliorating cognitive deficiencies in rodents exposed to alcohol during early postnatal development, the equivalent of the third trimester in human embryonic development. Alcohol exposure during this period causes

cortical neurodegeneration that is exacerbated by genetic deletion of AC1 and/or AC8 (Maas, Indacochea, et al., 2005). Inhibition of PDE1 by vinpocetine reversed alcohol exposure-related cortical deficits, rescuing ocular dominance plasticity in ferrets and mice (Lantz, Wang, & Medina, 2012; Medina, Krahe, & Ramoa, 2006) and preventing Morris water maze acquisition impairments in rats (Filgueiras, Krahe, & Medina, 2010). Similar improvement of fetal alcohol-related deficits in ocular dominance plasticity can be generated by co-administration of inhibitors to PDE4 and PDE5, but not by treatment with either inhibitor alone (Krahe, Paul, & Medina, 2010; Lantz et al., 2012), implying that PDE1 inhibitors improve fetal alcohol-related pathology through coordinated elevations in cAMP and cGMP. It is of interest for future investigations to determine whether PDE1 inhibitors similarly reduce cognitive deficits due to excessive alcohol consumption in adulthood, as well as whether PDE1 plays a role in patterning alcohol intake, a function now well established for PDE4.

PDE4 regulation of alcohol intake

The cAMP-selective PDE4 family is comprised of 4 subtypes (PDE4A–D), each encoded by a unique gene, with at least 25 isoforms identified to date (Richter, Menniti, Zhang, & Conti, 2013). PDE4 is widely expressed in the brain, with enrichment in reward-responsive brain regions, particularly for PDE4B (Cherry & Davis, 1999). PDE4 has been shown to participate in synaptic plasticity (Rutten et al., 2008, 2011; Wiescholleck & Manahan-Vaughan, 2012; Zhong et al., 2012) and memory, with PDE4 inhibitors utilized to enhance memories or rescue pharmacologically generated memory deficits (Werenicz et al., 2012; Zhang, Crissman, Dorairaj, Chandler, & O'Donnell, 2000; Zhang & O'Donnell, 2000; Zhang et al., 2004). PDE4 may also regulate emotional behavior, as the PDE4 inhibitor rolipram decreased depressive-like and anxiety-like behaviors in mice (Li et al., 2009). Deletion of PDE isoform 4D recapitulated rolipram's suppression of depressive-like behavior (Zhang et al., 2002); however, *Pde4b* knockout mice displayed heightened anxiety-like behavior (Zhang et al., 2008). Overall, the data support the ability of PDE4 inhibitors to rescue aberrant memories and ameliorate negative emotional states, properties that could suggest efficacy of PDE4 inhibitors to decrease alcohol consumption.

Reduction in alcohol drinking upon treatment with PDE4 inhibitors was first demonstrated in mice provided unlimited 2-bottle choice access to alcohol (Hu et al., 2011). Twice daily administration of the PDE4 inhibitors rolipram or Ro 20–1724 dose-dependently reduced alcohol intake without significantly affecting 2-bottle choice sucrose or quinine consumption. Rolipram did not alter alcohol metabolism or alcohol-induced sedation, and while it did produce a short-lived reduction in locomotor activity, this should have similarly affected intake of all reinforcers, not just alcohol. Together these data support a specific involvement of PDE4 in the regulation of alcohol intake. Single daily doses of PDE4 inhibitors also reduced 2-bottle choice alcohol drinking and preference in mice, resulting in shorter duration reductions in alcohol drinking by rolipram, CDP 840, and piclamilast, but producing an extended suppression of alcohol intake across the entire 24-h access period by mesopram (Blednov et al., 2014). In addition, all 4 PDE4 inhibitors reduced 3-h limited-access 2-bottle choice drinking. Inhibitors targeting several other PDEs did not alter alcohol consumption under the continuous-access paradigm (Table 1), but they have yet to be tested

under limited-access conditions. Rolipram also demonstrated efficacy to reduce alcohol intake in Fawn Hooded rats, a strain displaying comorbid elevations in depressive-like behavior and alcohol intake (Rezvani, Parsian, & Overstreet, 2002). Rolipram dose-dependently reduced operant self-administration of alcohol, but not sucrose, as well as 2-bottle choice alcohol intake during the first 30 min of the drinking session (Wen et al., 2012). Chronic rolipram treatment also decreased 2-bottle choice alcohol consumption in Fawn Hooded rats, an effect that persisted for several days after cessation of treatment. Together, these data support a central role for PDE4 in the regulation of alcohol drinking. It should be noted that food intake also was reduced in Fawn Hooded rats on rolipram treatment days under the chronic dosing regimen, possibly due to its nauseating effects (Rock, Benzaquen, Limebeer, & Parker, 2009); however, the fact that sucrose intake was unaffected by chronic rolipram administration in mice (Hu et al., 2011) suggests that malaise is unlikely to be the sole factor underlying the efficacy of PDE4 inhibitors to reduce alcohol intake. Indeed, rolipram previously was shown to reduce intracranial self-stimulation thresholds – a sign of enhanced reward – when infused into the NAc (Knapp, Lee, Foye, Ciraulo, & Kornetsky, 2001), suggesting that PDE4 inhibitors may reduce alcohol intake by changing its reinforcing efficacy. Together, these data support further development of PDE4 inhibitors, particularly those with reduced emetic properties (Rutter et al., 2014), as treatments for alcohol use disorders.

Stress, alcohol intake, and phosphodiesterase 10A

Despite the efficacy of PDE4 inhibitors to decrease alcohol intake, the modulation of alcohol consumption observed upon altering cGMP-dependent signaling suggests that phosphodiesterases with cGMP hydrolytic activity may also participate in the regulation of alcohol drinking. PDE10A, a dual-specificity phosphodiesterase able to deactivate both cAMP and cGMP, may fulfill a role distinct from PDE4 in the regulation of alcohol consumption, as might be implied by their different striatal expression patterns and signaling profiles (Nishi et al., 2008). PDE10A expression is highly enriched in the striatum, although it also has been detected in cortical, hippocampal, and cerebellar tissues, albeit at lower levels (Coskran et al., 2006; Seeger et al., 2003). PDE10A has been implicated in the negative regulation of neuronal activity, as PDE inhibitors potentiated both cortically evoked neuronal activity in the striatum (Threlfell, Sammut, Menniti, Schmidt, & West, 2009) and amphetamine-induced reductions in VTA neuron firing rates (Sotty, Montezinho, Steiniger-Brach, & Nielsen, 2009). Changes in PDE10A expression could be a molecular adaptation contributing to synaptic plasticity, as hippocampal long-term potentiation induced elevated expression of *Pde10a* mRNA transcripts that appeared to preferentially target cGMP over cAMP (O'Connor et al., 2004). Whereas these studies suggest the possibility that PDE10A could participate in experience-dependent synaptic adaptations, medications development of PDE10A inhibitors has focused on their therapeutic potential to reduce antipsychotic-like behaviors, including conditioned avoidance of a shock-paired chamber and NMDA antagonist- or amphetamine-induced behavioral abnormalities (hyperlocomotion, potentiated acoustic startle, or deficits in acoustic gating) (Grauer et al., 2009; Megens et al., 2014; Schmidt et al., 2008; Smith et al., 2012; Sotty et al., 2009; Suzuki, Harada, Shiraishi, & Kimura, 2015). A common feature of these paradigms is the

utilization of stressors or addictive substances to generate maladaptive behaviors, suggesting that PDE10A might play a more general role in regulating the behavioral response to aversive and appetitive stimuli, including alcohol. PDE10A inhibition reduced amphetamine-induced dopamine release in the NAc (Sotty et al., 2009) and increased striatal dopamine turnover (Schmidt et al., 2008), indicating that PDE10A might regulate neuronal responses to reinforcers and thus alter motivated behaviors like alcohol self-administration.

A relationship between PDE10A levels and alcohol self-administration was first suggested by the observation that *Pde10a* mRNA expression in the prelimbic subdivision of the mPFC correlated with operant alcohol self-administration during a relapse-like period (Logrip & Zorrilla, 2012). In a subset of rats – those with a history of lower alcohol consumption prior to extinction training – a history of stress resulted in a doubling in self-administration levels upon renewed alcohol access, relative to baseline and low-drinking stress-naïve controls. Those same previously low-drinking stress history rats showed elevated prelimbic *Pde10a* expression relative to low-drinking controls, as well as a correlation between prelimbic *Pde10a* expression and relapse-like alcohol self-administration. Stress history also increased *Pde10a* mRNA levels in the BLA, independent of high vs. low self-administration classification, an effect similarly observed during both acute and prolonged abstinence from chronic intermittent alcohol vapor exposure (Logrip & Zorrilla, 2014). Whereas *Pde10a* expression was elevated in multiple subdivisions of the mPFC and amygdala 8–10 h into withdrawal, only the BLA showed a persistent increase in PDE10A after 6 weeks of abstinence. The similar patterns of elevated *Pde10a* mRNA expression in stress history and acutely withdrawn rats, both of which display elevated alcohol self-administration, suggested that increased PDE10A might be a neuroadaptation involved in potentiating alcohol intake and therefore that PDE10A inhibitors might reduce excessive alcohol consumption.

Treatment with the selective PDE10A inhibitor TP-10 dose-dependently reduced alcohol self-administration in all groups tested, not only in rats with a history of stress, alcohol dependence, or a genetic predisposition toward high alcohol intake (Scr:sP), but also in stress-naïve controls and non-dependent rats (Logrip, Vendruscolo, Schlosburg, Koob, & Zorrilla, 2014). This broad efficacy of TP-10 to reduce alcohol self-administration was due, at least in part, to inhibition of PDE10A in the dorsolateral striatum (DLS), as site-specific DLS infusion of TP-10 dose-dependently reduced alcohol self-administration, whereas the same infusion into the NAc did not significantly alter alcohol intake. Surprisingly, TP-10 reduced both alcohol and saccharin self-administration with equivalent potency, indicating that, unlike the alcohol-specific effects of PDE4 inhibitors, PDE10A may function more generally to regulate motivated behavior. In support of this theory, mice deficient in PDE10A showed deficits in acquiring reward cue-related actions (Piccart, Langlois, Vanhoof, & D'Hooge, 2013) and selectively consumed less highly palatable, but not standard, food (Nawrocki et al., 2013). Nonetheless, inhibiting PDE10A significantly reduced alcohol self-administration in multiple rat models of treatment-resistant high-drinking populations, i.e., stress history, alcohol-dependent, and genetically alcohol-preferring rats. Taken together, the data support further development of PDE10A inhibitors as novel treatments for disordered use of any reinforcing substance, including alcohol.

Translational potential of PDE inhibitors

Preclinical data suggest PDE inhibitors as novel therapeutics for alcohol use disorders, yet to date clinical trials for this indication have been limited. The exception is ibudilast, which is currently in a Phase 1 clinical trial for alcohol use disorders (ClinicalTrials.gov identifier: NCT02025998 [Ray, Roche, Heinzerling, & Shoptaw, 2014]), as well as in Phase 2 clinical trials for methamphetamine dependence (NCT01860807) and oxycodone abuse (NCT01740414). Multiple clinical trials have been initiated for the use of PDE inhibitors to treat cognitive deficits in neurodegenerative diseases, depression, and schizophrenia (Wang et al., 2015), including the PDE1 inhibitor vinpocetine, which recently completed Phase 1 of a clinical trial for improvement of cognition in epilepsy (NCT02011971). Because of the varied functions subserved both centrally and peripherally by PDEs, a major hurdle for the clinical use of PDE inhibitors has been the incidence of off-target side effects, such as emetic (Rock et al., 2009) and cataleptic (Grauer et al., 2009) properties of PDE4 and PDE10A inhibitors, respectively. While some side effects can be minimized through reduced dosing, efforts are underway to develop inhibitors with reduced side effect profiles, particularly with regard to reducing the emetic properties of PDE4 inhibitors (Burgin et al., 2010; Rutter et al., 2014). Whether through the discovery of specific PDE inhibitors with fewer off-target effects, or by identifying broader acting drugs such as ibudilast with reduced negative effects, the preclinical data strongly support the continued development of PDE inhibitors as pharmacotherapies for alcohol use disorders.

Summary

PDEs are essential players in neuronal signal propagation through regulation of cAMP and cGMP second messenger availability, and thus may negatively affect cyclic nucleotide-dependent moderation of alcohol intake. Early studies into PDE regulation of alcohol consumption have suggested that PDE inhibitors, particularly those targeting PDE4 and PDE10A, may be effective treatments to reduce alcohol drinking. Intriguingly, PDEs have also been proposed as a site of neuroadaptation underlying the persistence of alcohol use disorders, as suggested by elevated BLA *Pde10a* mRNA expression even 6 weeks after cessation of alcohol exposure. However, much remains unknown about the involvement of PDEs in alcohol use disorders and the therapeutic efficacy of PDE inhibitors. For instance, alcohol-induced neuroadaptations in PDE expression likely generate more complex behavioral alterations than the simple modulation of drinking, such as the amelioration of fetal alcohol-related cognitive deficits by PDE1 inhibition. Additionally, PDE4 inhibitors have been shown to reduce depressive-like behaviors (Zhang, 2009) and have been proposed as general cognitive enhancers (Richter et al., 2013). While it remains to be determined whether most PDE inhibitors improve or exacerbate cognitive and emotional deficits generated by excessive alcohol use, the intriguing possibility exists that PDE inhibitors could ameliorate multiple negative outcomes in alcohol-dependent individuals. The studies covered in this review highlight the deleterious impact of reduced neuronal cAMP and cGMP signaling, which may both be caused by and contribute to excessive alcohol consumption. Reduction of PDE activity can reverse deficits in cAMP/cGMP levels and thus warrant further exploration into the efficacy of multiple PDE inhibitors as novel treatment targets for alcohol use disorders.

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HIGHLIGHTS

- Reduced cAMP and cGMP levels can increase alcohol intake
- PDEs may contribute to excessive alcohol use by reducing cAMP/cGMP levels
- PDE inhibitors are proposed as treatments for excessive alcohol intake
- PDE4 and PDE10A inhibitors are highlighted for reducing drinking in rodents

Table 1

Phosphodiesterase inhibitor regulation of alcohol consumption in rodents

Reference	Strain	Behavioral Paradigm	Inhibitor	PDE Target	Alcohol Intake	Sweet Solution
Hu et al. (2011)	C57BL/6J mice	2-bottle choice continuous access to 7–12% (*v/v*) alcohol vs. water	Rolipram	PDE4[b]	↓	
			Ro-20–1724	PDE4[b]	↓	N/A
Wen et al. (2012)	Alcohol-preferring Fawn-hooded rats	Operant self-administration of 5% (*v/v*) alcohol vs. water	Rolipram	PDE4[b]	↓	
		2-bottle choice continuous access to 5% (*v/v*) alcohol vs. water			↓	
		2-bottle choice intermittent access to 10% (*v/v*) alcohol vs. water			↓	N/A
Bell et al. (2013)	Alcohol-preferring P rats	2-bottle choice 2-h limited access to 15% (*v/v*) alcohol vs. water (maintenance & relapse)	Ibudilast	Nonspecific; PDE3,4,10,11 preferring[c]	↓	N/A
	Alcohol-preferring HAD1 rats	2-bottle choice 2-h limited access to 15% (*v/v*) alcohol vs. water (maintenance & relapse)			↓	N/A
	C57BL/6J mice	Alternating cycles of 2-bottle choice [2-h limited access to 15% (*v/v*) alcohol vs. water for 5 days, then 2 days off] and chronic ethanol vapor exposure [16-h vapor/day for 4 days, then 3 days abstinence]			↓	N/A
Blednov et al. (2014)	C57BL/6J mice	2-bottle choice continuous access to 15% alcohol vs. water	Propentofylline	Nonspecific[d]		N/A
			Vinpocetine	PDE1[b]		N/A
			Milrinone	PDE3[b]		N/A
			Olprinone	PDE3[e]		N/A
			CDP840	PDE4[f]	↓	N/A
			Mesopram	PDE4[g]	↓	N/A
			Piclamilast	PDE4[h]	↓	N/A
			Rolipram	PDE4[b]	↓	N/A

Reference	Strain	Behavioral Paradigm	Inhibitor	PDE Target	Alcohol Intake	Sweet Solution
			Zaprinast	PDE5; less potent at PDE1, PDE10, PDE11[b]		N/A
		limited 3-h 2-bottle choice access to 15% alcohol vs. water	CDP840	PDE4[f]	↓	N/A
			Mesopram	PDE4[g]	↓	N/A
			Piclamilast	PDE4[h]	↓	N/A
			Rolipram	PDE4[b]	↓	N/A
Logrip et al. (2014)	Wistar rats	operant self-administration of 10% (*v/v*) naïve and stress history rats	TP-10	PDE10A[i]	↓	↓
		operant self-administration of 10% (*w/v*) alcohol in vapor-dependent and nondependent rats			↓	N/A
	Scr:sP alcohol-preferring rats	operant self-administration of 20% (*v/v*) alcohol			↓	N/A

[a] Sucrose or saccharin intake under the same behavioral procedure (self-administration or 2-bottle choice access);

[b] Bender and Beavo (2006);

[c] Gibson et al. (2006);

[d] Meskini, Némoz, Okyayuz-Baklouti, Lagarde, & Prigent (1994);

[e] Mizushige, Ueda, Yukiiri, & Suzuki (2002);

[f] Hughes et al. (1996);

[g] Dinter et al. (2000);

[h] Ashton et al. (1994);

[i] Schmidt et al. (2008)