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Alcohol-induced alterations in dopamine modulation of prefrontal activity

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Abstract

Long-term alcohol use leads to persistent cognitive deficits that may be associated with maladaptive changes in the neurocircuitry that mediates executive functions. Impairments caused by these changes can persist well into abstinence and have a negative impact on quality of life and job performance, and can increase the probability of relapse. Many of the changes that affect cognitive function appear to involve dysregulation of the mesocortical dopamine system. This includes changes in dopamine release and alterations in dopamine receptor expression and function in the medial prefrontal cortex (PFC). This review summarizes the cellular effects of acute and chronic ethanol exposure on dopamine release and dopamine receptor function in the PFC with the goal of providing greater understanding of the effects of alcohol-use disorders on the dopamine system and how this relates to deficits in the executive function of the PFC.

Keywords

dopamine; prefrontal cortex; alcohol; cognition

1. Introduction

Cognitive dysfunction commonly occurs as a result of prolonged alcohol exposure and can persist well into abstinence, causing significant impairments in executive processes such as top-down inhibitory control, decision-making, and behavioral flexibility. Each of these aspects of executive function relies on a balance of excitatory and inhibitory activity in the prefrontal cortex (PFC) that supports synchronous activity of cellular networks within the cortex and with subcortical structures that mediate these processes. This balance is critically dependent upon a precise level of dopamine and dopamine receptor activity in this brain region, which tunes the networks by facilitating synchronous activation and by limiting activity in space and time to provide specificity over the flow of information in these networks (Arnsten, Cai, Murphy, & Goldman-Rakic, 1994; Floresco, 2013; Goldman-Rakic, 1998). Chronic alcohol-induced alterations in dopamine signaling produce deficits in

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executive function that not only affect quality of life, but also increase the probability of relapse to alcohol drinking (Fein, Bachman, Fisher, & Davenport, 1990; Rando et al., 2011). Studies in human alcoholics have demonstrated that higher levels of dopamine (DA) receptor binding in PFC may be protective against developing alcohol-use disorder (AUD) (Volkow et al., 2006). Human imaging studies have also reported decreases in prefrontal volume of alcoholics; the severity of such changes was also correlated with higher probability of relapse (Rando et al., 2011). Furthermore, alcoholics and control subjects show similar fMRI activity and similar performance on simpler tasks that do not require high cognitive demand. However, increased fMRI activity in frontal regions of alcoholics is observed as cognitive load increases that does not support enhanced performance on the task, but instead results in larger disparities between control and alcohol-dependent subjects (Parsons & Nixon, 1998).

Similar observations have been made in rodent models of alcohol dependence where confounds such as genetic predisposition and environmental influences can be controlled (Trantham-Davidson et al., 2014). A detailed understanding of the cellular effects of alcohol that contribute to cognitive dysfunction is important for the development of novel therapeutic strategies aimed at the mesocortical dopamine system to improve cognitive function and treat AUDs.

2. Dopamine and DA receptors

Dopamine (DA) is a catecholamine neurotransmitter that is primarily (although not exclusively) synthesized in the substantia nigra and ventral tegmental area (VTA). The release of DA from the substantia nigra principally controls motor function by modulating the activity of brain structures that make up the direct and indirect pathways that subserve planned motor sequences. The primary reward system in the brain is the VTA dopamine system. The VTA sends DAergic afferents to brain regions such as the PFC and nucleus accumbens (NAcc) that process cues associated with obtaining natural rewards such as food and various other forms of goal-directed behaviors. Exposure to substances that have rewarding properties, including alcohol and other drugs of abuse, enhances DA release from the VTA to subcortical structures such as the nucleus accumbens and promotes reward-seeking behavior. However, with prolonged exposure to addictive substances, persistent elevations in DA result in compensatory changes that take place in both subcortical and cortical regions that appear to promote anhedonia during withdrawal and prolonged deficits in cognitive function.

The VTA is a highly heterogeneous region that includes neurons that release dopamine, glutamate, or GABA, as well as neurons that co-release DA with glutamate or GABA. The GABAergic neurons make up a small percentage of cells in this region (approximately 20%) and include both local interneurons and projection neurons that modulate other brain structures. The interneurons play a very important role in tonic inhibition of activity of VTA DAergic and glutamatergic projection neurons that mediate reward signaling, and it appears that alcohol-induced changes in GABAergic activity in the VTA can indirectly affect DA and glutamate release to other brain regions. Therefore, contrary to the long-held view of the VTA as principally consisting of dopaminergic nuclei, it is becoming increasingly apparent

that it may be more appropriately viewed as a heterogeneous structure composed mainly of amino-acid releasing neurons but with an additional DA-releasing component (Gorelova, Mulholland, Chandler, & Seamans, 2012). Regardless of the complexity of the neurotransmitter systems of the VTA, it is clear that DA plays a critical role in the rewarding effect of drugs of abuse, and that changes in this system may underlie many aspects of addiction (for review see Lapish, Seamans, & Chandler, 2006).

3. Acute ethanol enhances dopamine release

Extracellular levels of DA in target regions of the VTA such as the PFC and NAcc are controlled by two distinct firing patterns (Bannon & Roth, 1983; Chiodo, 1988; Chiodo, Bannon, Grace, Roth, & Bunney, 1984; Hoffman & Beninger, 1988; White & Wang, 1984). The tonic or low-frequency firing mode results in low ambient DA levels in target regions (Phillips & Wightman, 2004). In contrast, the phasic mode is associated with a much higher firing frequency that results in a transient increase in DA. This is thought to signal salience that is time-locked to the appearance of rewarding stimuli and reward-related cues. These initial observations of phasic DA signaling associated with reward learning lead to the development of the incentive salience hypothesis for the function of VTA DA. In particular, the pioneering studies by Shultz and colleagues revealed that in the early stages of learning a new task, DA neurons fire in phasic burst patterns in response to the presentation of a reward (Schultz, 1994, 1999). Over time, as the stimulus-action-reward relationship is encoded, the bursting mode of firing in DA neurons shifts to become time-locked to presentation of the stimulus or visual cue. If a reward is not delivered when it is expected, DA neuron firing falls below tonic/basal levels, signaling a reward-prediction error. This suggests that these fluctuations in DA cell firing support learning by providing information about the cues associated with rewards as well as the time when the stimuli no longer predict reward delivery, and this promotes engagement of a different strategy to obtain rewards.

Acute exposure to alcohol results in both reduced anxiety and a pleasurable hedonic state due to its rewarding properties. Together, these are thought to provide the subjective experience of alcohol intoxication that initially signals alcohol as a rewarding substance. While the anxiolytic effect of alcohol is due in part to its effects on various neurotransmitter systems (e.g., GABA or glutamate), increased DA release also contributes to reduced anxiety and mediates the reinforcing properties of ethanol. There are likely multiple mechanisms by which acute ethanol can enhance DA release that involve direct effects of ethanol on intrinsic excitability of VTA DA neurons. Acute ethanol itself has direct effects on DA VTA neurons that result in higher firing frequency and increased excitability. Under baseline conditions in the absence of acute alcohol, DA neurons in the VTA fire in spontaneous, low-frequency pacemaker-like bursts that occur in the absence of outside synaptic inputs. The pacemaker frequency is set by an inward cation current, termed I_h, that is activated by hyperpolarization (Neuhoff, Neu, Liss, & Roeper, 2002). Acutely, ethanol enhances this current resulting in increased firing and likely enhancement of dopamine release in target regions such as the NAcc core (NAccC) and PFC (Brodie & Appel, 1998; Okamoto, Harnett, & Morikawa, 2006). Recent work has shown that when non-pacemaker DA neurons (i.e., they do not exhibit I_h) are examined, ethanol also enhances firing in this population (Mrejeru, Martí-Prats, Avegno, Harrison, & Sulzer, 2015). This suggests that

while the overall effect of acute ethanol is to increase DA release to target regions, the mechanism of how this occurs may be circuit-specific (Lammel et al., 2008; Mrejeru et al., 2015; Neuhoff et al., 2002).

In addition to its effects on intrinsic excitability, acute ethanol can also modulate GABAergic transmission and disinhibit DA neurons in the VTA. Since elevated levels of DA are observed in areas like the NAcc and PFC following ethanol exposure, one possibility is that DA neurons in the VTA are disinhibited from tonic control over their firing by GABAergic neurons in this region. Ethanol has different effects on GABAergic transmission in the VTA depending on which cell population is assessed, with some GABAergic neurons showing enhanced firing and others reduced firing (Xiao & Ye, 2008). When firing of GABAergic neurons of the VTA is attenuated, which presumably enhances DA release, it appears this is a delayed effect with respect to the time of ethanol administration such that the DA neurons respond to ethanol before the GABAergic cells respond. This suggests that while the increase in DA cell firing is not initially dependent on disinhibition, the prolonged reinforcing effects of alcohol may depend on this delayed and more persistent disinhibitory effect that maintains reinforcement and supports continued ethanol consumption (Adermark, Söderpalm, & Burkhardt, 2014; Burkhardt & Adermark, 2014; van Zessen, Phillips, Budygin, & Stuber, 2012). However, electrophysiological slice experiments revealed that acute bath application of alcohol increases firing only in a subset of VTA neurons that lack D2 autoreceptors. Again, this interesting observation suggests that acute ethanol may have distinct, circuit-specific effects, since PFC projections from the VTA lack D2 autoreceptors (Lammel et al., 2008; Mrejeru et al., 2015).

Interestingly, voltammetry experiments, where DA levels were measured in mPFC, have shown both increases (Robinson, Howard, McConnell, Gonzales, & Wightman, 2009) and decreases in mPFC DA release in response to acute ethanol administration (Shnitko, Kennerly, Spear, & Robinson, 2014). The opposing effects appear to be due to different firing modes such that under baseline firing conditions in the VTA, ethanol appears to enhance DA release in mPFC, but when firing is electrically stimulated, ethanol has an attenuating effect on mPFC DA. This appears to be due to differences in DA clearance or availability when the different firing modes are being examined (S. R. Wang et al., 2011). Another explanation is that while acute ethanol may increase firing rate in some VTA neurons, the amount of DA that is released with each stimulated pulse is actually reduced by acute ethanol. However, in an area like the nucleus accumbens where DA is cleared by the dopamine transporter (DAT), the clearance rate is attenuated by acute ethanol, ultimately producing increased DA levels. In contrast, in the PFC, where DA is cleared by the norepinephrine transporter and the enzyme COMT, acute ethanol may influence DA levels differently due to distinct ways in which DA is cleared from the synapse.

Additionally, a “first hit” hypothesis has been proposed in which metabolites of alcohol have reinforcing properties that may be distinct from the effects of alcohol itself (Israel, Quintanilla, Karahanian, Rivera-Meza, & Herrera-Marschitz, 2015). Acetaldehyde is a metabolite of alcohol that is formed by the oxidization of ethanol by alcohol dehydrogenase and has been shown to have its own reinforcing properties. For example, alcohol-preferring P rats will self-administer acetaldehyde into the posterior VTA (Rodd et al., 2005a, 2005b)

and stimulate the release of DA into the NAcc (Deehan, Engleman, Ding, McBride, & Rodd, 2013; Deehan, Hauser, Wilden, Truitt, & Rodd, 2013). In addition, reducing acetaldehyde levels by decreasing catalase activity was shown to prevent the DA signal in the NAcc (Karahanian et al., 2015), indicating that acetaldehyde alone is sufficient to produce this reward signal. Follow-up studies have further shown that ethanol-induced DA release in NAcc could be blocked by reducing acetaldehyde levels in the VTA (Karahanian et al., 2011, 2015). This suggests that acetaldehyde, at least in part, directly contributes to the reinforcing properties of ethanol. In addition, an indirect mechanism for acetaldehyde facilitation of release could be the ability of acetaldehyde and DA to directly react to form the product salsolinol (Myers, 1985). Of note, salsolinol has been shown to support self-administration when delivered directly into the posterior VTA (Rodd et al., 2008). Interestingly, follow-up studies using patch clamp electrophysiology revealed that salsolinol acts at μ-opioid receptors on GABAergic neurons in the VTA to hyperpolarize the membrane potential, resulting in disinhibition of DA-releasing neurons and presumably elevated DA release to NAcc (Palm & Nylander, 2014; Xie et al., 2012). The ability of salsolinol to promote DA release and drinking is controversial, however, possibly due to difficulties in measuring brain concentrations of the compound. Newer methods of measurement will likely yield future pharmacological studies that will clarify its role in promoting drinking and the mechanisms which mediate its effects (Hipólito, Sánchez-Catalán, Martí-Prats, Granero, & Polache, 2012).

4. Chronic alcohol decreases DA release

While the effect of acute ethanol is to initially increase spontaneous DA transmission and promote reward (Robinson et al., 2009; Schier, Dilly, & Gonzales, 2013), allostatic changes in the DA circuitry occur with prolonged exposure. Interestingly, while somewhat normal levels of functioning in daily life can be observed under the influence of alcohol in chronic users (Koob, 2003a, b), anhedonia, aversion, and blunted reward processing accompany alcohol withdrawal that may relate to a hypodopaminergic state in target areas like cortex and nucleus accumbens (Koob & Volkow, 2010; Trevisan et al., 1998). While little is known about the mechanisms that mediate the decrease in DA transmission, one possible explanation is that chronic ethanol exposure decreases I_h current density, resulting in reduced firing of VTA DA neurons that has been observed during withdrawal (Diana et al., 1993; Okamoto et al., 2006). Sensitization of DA D2 autoreceptors has been shown to reduce DA release in monkeys (Budygin et al., 2003) and mice (Karkhanis et al., 2015), and to reduce DA release and increase uptake in the NAcc core in mice following exposure to chronic ethanol (Karkhanis et al., 2015). Taken together, these findings are consistent with the idea that chronic ethanol-induced attenuation of DA transmission may mediate the aversive state of withdrawal and, as discussed below, may contribute to cognitive deficits that are associated with increased vulnerability to relapse during abstinence.

5. Cognition relies on appropriate stimulation of DA receptors in PFC

The medial prefrontal cortex (mPFC) is generally divided into ventral and dorsal aspects that serve specific roles in mediating distinct components of executive function. In the rodent mPFC, the dorsal portion is composed of the anterior cingulate (ACC) and prelimbic

regions, and the ventral aspect contains the infralimbic and orbitofrontal regions. The anterior cingulate cortex is primarily responsible for behavioral inhibition and decision-making when emotion-related cues can be used to guide responding. The prelimbic cortex is just ventral to the ACC and it has been implicated in execution of goal-directed behaviors and likely subserves some aspects of working memory. Ventral to the PrL cortex, the infralimbic cortex is generally thought to serve an opposing role on the action sequences generated by the PrL region. In particular, its outputs to the NAcc shell and BLA are thought to inhibit drug seeking and fear responding, respectively (Peters, Dieppa-Perea, Melendez, & Quirk, 2010; Peters, LaLumiere, & Kalivas, 2008). Interestingly, more recent studies into the circuitry of habitual responding reveal that the IfL outputs to NAcc shell also mediate habitual responding, and dopaminergic modulation of this pathway can significantly impact habitual vs. goal-directed responding (Barker, Taylor, & Chandler, 2014). The orbital frontal cortex mediates behavioral flexibility and valuation of reinforcers to promote formation of strategies aimed at maximizing reward magnitude. Dopamine afferents project to each of these cortical regions with a larger percentage of projection neurons targeting the deeper layers in addition to relatively less dense innervation to superficial layers. In addition, DA receptors are expressed on both excitatory and inhibitory neurons and can significantly modulate synchronization of network activity as well as overall activation and synaptic responses in both cell types.

In the mPFC, stimulation of DA receptors influences neuronal firing in different ways that relate in part to the G-protein coupled signaling pathways associated with the different types of DA receptors. DA D1-like receptors, which include the D1 and D5 subtypes, are coupled to Gs and Gq proteins and enhance activation of PKA signaling. In both pyramidal neurons and GABAergic interneurons in the PFC, PKA activation results in increased firing and enhancement of glutamate and GABA-evoked currents (Chen, Bohanick, Nishihara, Seamans, & Yang, 2007; Gonzalez-Islas & Hablitz, 2001, 2003). Activation of DA D2-like receptors, which include the D2, D3, and D4 subtypes, is coupled to Gi/o proteins and inhibits PKA activity. In pyramidal neurons, inhibition of PKA results in decreased firing and attenuation of glutamatergic and GABAergic responses (Gonzalez-Islas & Hablitz, 2001; Wang, Zhong, & Yan, 2002). A potential cellular mechanism for the loss of behavioral flexibility observed in rats following chronic ethanol administration is the loss of D2/D4 receptor modulation of cellular targets such as glutamate receptors, GABA receptors, and ion channels that modulate excitability of pyramidal neurons (Fig. 1). While no changes in D2/D4 receptor expression were observed, it is possible that the G-protein coupled signaling pathways downstream of the D2/D4 receptors are affected by ethanol, and this disrupts the synchronization of pyramidal networks that mediates some aspects of executive function, such as behavioral flexibility (Trantham-Davidson et al., 2014).

In contrast to pyramidal neurons, the effects of D2-like receptors on interneurons in the PFC is not as clear cut, in large part due to the wide diversity of interneuron types. The interneuron subtype in the PFC that appears to be most responsive to D2/D4 receptor stimulation is the parvalbumin-positive, fast-spiking subtype (Gorelova, Seamans, & Yang, 2002). These cells undergo a developmental transition in responding to D2 receptor stimulation during adolescence that occurs in parallel with the maturation of cognitive function during the transition to adulthood. In rodents, D2 receptor modulation of the

activity of fast-spiking interneurons (FSINs) is not observed until postnatal day 45 and this modulation increases until it plateaus in early adulthood (~postnatal day 60) (Tseng & O'Donnell, 2007a). Another interesting property of FSINs is that their activation is critical for the generation of gamma oscillations and the synchronous, recurrent excitatory activity between pyramidal neurons that is hypothesized to mediate working memory (Curley & Lewis, 2012; Lewis, Curley, Glausier, & Volk, 2012). FSINs have a distinct firing profile that includes short-duration action potentials and high firing frequency that is thought to be necessary for recruiting large populations of neurons simultaneously and with high temporal specificity. These neurons contain potassium channels of the Kv 3.1/3.2 family that confer these firing characteristics by limiting action potential duration and shortening the after-hyperpolarization to produce high firing rates (Harvey, Lau, Civillico, Rudy, & Contreras, 2012). Our laboratory recently showed that D4 receptor stimulation enhances firing in FSINs at least in part by enhancing the Kv3.2-mediated current. In addition, our data revealed that in slices from rats exposed to chronic ethanol, this D4-mediated enhancement of firing and Kv3.2 currents is absent but remains normal in control animals. This uncoupling of D4 receptors from their targets that modulate intrinsic excitability may explain the cognitive deficits that persist following chronic ethanol exposure, due to reductions in gamma oscillations that are critical for behavioral flexibility (Trantham-Davidson et al., 2014). These findings present another possibility for the cellular mechanisms that might mediate the loss of behavioral flexibility observed in rats that have received chronic alcohol exposure (Fig. 1), and restoring activity selectively in these neurons may restore at least some aspects of cognitive function.

Many aspects of cognitive function such as behavioral flexibility, planning of goal-directed strategies, and inhibitory control are dependent upon a balance of activation of D1 and D2 receptors in the PFC (Arnsten et al., 1994; Floresco & Magyar, 2006; Gao, Wang, & Goldman-Rakic, 2003). While earlier work established an inverted U-shaped relationship for DA levels such that optimal levels of DA transmission are needed to facilitate working memory, more recent work suggests that other cognitive processes such as behavioral flexibility and decision-making require different levels of tone on D1 and D2 receptors for optimal performance, and the amount needed depends on the specific aspect of cognition that is needed to perform the task (Floresco, 2013).

The prefrontal cortex receives dense DAergic projections to the deep layers of the medial regions, especially in the prelimbic and infralimbic regions that are involved in planning, execution of goal-directed behaviors, and habit formation (Arnsten & Li, 2005; Floresco & Phillips, 2001; Goldman-Rakic, 1996; Hitchcott, Quinn, & Taylor, 2007; Robbins, 2000; Roesch-Ely et al., 2005). Transient increases in DA stimulate D1 receptors to enhance both glutamatergic and GABAergic inhibition to increase synchronization and promote network excitability (Kroener, Chandler, Phillips, & Seamans, 2009; Lapish, Durstewitz, Chandler, & Seamans, 2008). This results in more efficient processing of highly salient/reward-related items in the environment, and this has been termed the D1-dominated state. In contrast, lower, ambient levels of DA target D2 receptors that decrease excitatory and inhibitory influences so that multiple items in the environment can be attended to at once. Because of this, networks under the influence of this D2-dominated state can flexibly respond to

changes in environmental cues to execute updated strategies aimed at obtaining reinforcers (Durstewitz, Seamans, & Sejnowski, 2000).

6. Effects of chronic alcohol on PFC and striatum

Relatively little is known about the effects of chronic alcohol exposure on DA transmission in the PFC. There is an increasing appreciation of the critical role of cognitive function in addiction and relapse that has emphasized the need to gain a greater understanding of how alcohol affects DA signaling in PFC. Cognitive deficits in human alcoholics and enhanced risk for developing alcohol-use disorders may result, at least in part, from alterations in D2 receptor expression in dlPFC and striatum (Kraschewski et al., 2009; Volkow et al., 1996, 2002). Furthermore, low D2 receptor function has been shown to increase alcohol consumption in rodent models of alcohol dependence (Bice et al., 2006; Morganstern & Tejani-Butt, 2010). High levels of D2 receptor expression may protect against alcoholism and have been shown to reduce drinking in human subjects (Kraschewski et al., 2009; Volkow et al., 2006). To date, most of the studies of chronic ethanol-induced changes in DA receptor function have focused on striatal changes and very few have focused on changes in PFC. However, the more recent appreciation of the important role that cognitive dysfunction plays in addiction has suggested that changes in DA receptors in PFC may accompany these changes that occur in striatum. Consistent with this idea, rats that received chronic exposure to alcohol showed a reduction of D2 receptor function in PFC in both pyramidal neurons and fast-spiking interneurons that was accompanied by deficits in performance of PFC-dependent measures of cognitive flexibility (Trantham-Davidson et al., 2014). These observations are in general agreement with recent studies examining prefrontal function in chronic alcohol-exposed mice (Holmes et al., 2012; Kroener et al., 2012). Cognitive flexibility relies on proper tuning of excitatory networks of pyramidal neurons that is critically modulated by GABAergic inputs from fast-spiking interneurons (FSINs), and as discussed above, DA modulates the activity of both cell types through activation of D1 and D2-like receptors (Adell & Artigas, 2004; Trantham-Davidson, Kröner, & Seamans, 2008; Trantham-Davidson & Lavin, 2004). Interestingly, the reduction of D2 and D4 receptor function that we recently reported appeared immediately after cessation of chronic alcohol exposure and remained attenuated for up to 4 weeks after the last exposure to alcohol (Trantham-Davidson et al., 2014). Although speculative, it is reasonable to suggest that this loss of D2 receptor function could result in dysregulation of both persistent network activity and tuning of those networks. Interestingly, since there were no differences in D2 or D4 receptor expression as measured by receptor autoradiography, a likely explanation for the observed loss of D2/D4 function in the PFC is an uncoupling of these receptors from their signaling pathways. This uncoupling could result in alterations in phosphorylation of downstream targets that modulate activity. In the adult PFC, D2/D4 receptor stimulation increases firing in FSINs (Tseng & O'Donnell, 2007b), resulting in more precise regulation over pyramidal cell networks. Therefore, attenuated D2 receptor stimulation of FSINs would negatively affect prefrontal function and could contribute to cognitive deficits observed in abstinent alcoholics that appear to play a role in relapse.

7. Developmental changes in the DA system

The prefrontal DA system undergoes significant changes that primarily begin during adolescence that continue into early adulthood (Yetnikoff, Reichard, Schwartz, Parsely, & Zahm, 2014). This critical period of developmental change may render this system relatively vulnerable to environmental insults during childhood and adolescence. This may be especially important for the effects of alcohol exposure given the high prevalence of drinking during adolescence, especially binge-like consumption. In rats, the DA innervation of striatum occurs during embryogenesis but continues to develop in cortex throughout adolescence and into early adulthood (Kalsbeek, Voorn, Buijs, Pool, & Uylings, 1988). The expression of DA receptors in the striatum also peaks at P50 and then decreases until P90. In striatum and PFC, DA receptor expression appears to follow a similar developmental trajectory such that the system is relatively vulnerable well into adulthood (Tarazi & Baldessarini, 2000). Exposure to alcohol during these critical periods of development could significantly affect formation of dopaminergic synapses and development of cortical and striatal circuitry that critically regulate cognitive function and reward-related behavior in a way that permanently damages the system. Consistent with this, we recently showed that adolescent exposure to alcohol results in deficits in behavioral flexibility on several PFC-dependent tasks that might relate, at least in part, to changes in dopaminergic modulation of cortical activity.

8. Conclusion

Chronic alcohol-induced disruption of dopamine modulation of prefrontal activity plays a major role in the cognitive dysfunction that persists well into abstinence and may contribute to the high probability of relapse in dependent individuals. Despite this knowledge, relatively little is known about the mechanisms by which this occurs. While recent evidence suggests these deficits in cognitive control of behavior may be related to altered dopamine release and disruption of DA receptor functioning in the PFC, a better understanding is needed that can guide the development of highly selective pharmacological approaches to restore prefrontal function. Therapeutic restoration of cognitive control of behavior has the promise of reducing the rate of relapse and improving quality of life in individuals who suffer from alcohol-use disorders.

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Abbreviations

PFC	prefrontal cortex
mPFC	medial prefrontal cortex
PrL	prelimbic prefrontal cortex
IfL	infralimbic prefrontal cortex

NAcc	nucleus accumbens
NAccSh	nucleus accumbens shell
NAccC	nucleus accumbens core
DA	dopamine
VTA	ventral tegmental area
D2	D2 dopamine receptor
D1	D1 dopamine receptor
Str	striatum
FSIN	fast-spiking interneuron

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Highlights

- Acute exposure to alcohol results in increases in DA transmission in the striatum and PFC that contribute to the reinforcing properties of alcohol and controlled drinking patterns.
- Chronic exposure to alcohol results in decreased DA transmission that leads to cognitive dysfunction and the anhedonic state of withdrawal that may contribute to relapse.
- Pharmacological approaches aimed at resolving dysregulation of DA in the PFC could enhance treatment outcomes by improving cognition, thereby promoting control over goal-directed versus habitual alcohol-seeking behavior.

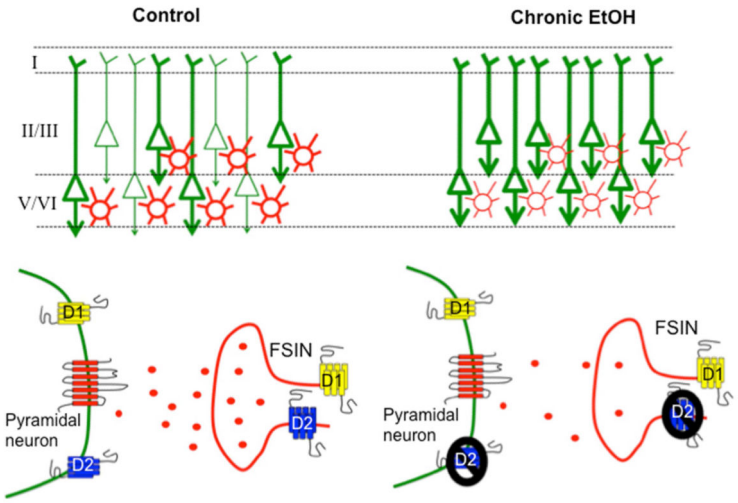

Fig. 1.

Cellular mechanisms that mediate alterations in mPFC synchrony and cognitive disruption following chronic ethanol exposure. Under control conditions (left panel), synchronous activation of appropriate cortical networks mediates cognitive control over behavior. At the cellular level this is achieved via dopamine modulation of intrinsic and synaptic currents within pyramidal neurons (green) and FSINs (red) to promote temporal and spatial precision over networks to increase specificity of information flow by synchronizing specific groups of neurons (symbolized by bold lines). Following chronic alcohol exposure (right panel), network synchrony is disrupted due to the reduction in D2/D4 receptor modulation of excitability of pyramidal neurons and FSINs. The loss of D2/D4 receptor-mediated recruitment of FSINs (lighter red color) results in desynchronization of pyramidal networks and loss of specificity over information flow (all pyramidal cells in bold green).