Neuropharmacology xxx (2012) 1–10

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Review

New insights on neurobiological mechanisms underlying alcohol addiction☆

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ARTICLE INFO

Article history:
Received 24 May 2012
Received in revised form
22 September 2012
Accepted 24 September 2012

Keywords:
Alcohol
Dependence
Addiction
Metaplasticity
CRF
VTA
BNST
mGluR
Binge drinking
Dendritic spines

ABSTRACT

Alcohol dependence/addiction is mediated by complex neural mechanisms that involve multiple brain circuits and neuroadaptive changes in a variety of neurotransmitter and neuropeptide systems. Although recent studies have provided substantial information on the neurobiological mechanisms that drive alcohol drinking behavior, significant challenges remain in understanding how alcohol-induced neuroadaptations occur and how different neurocircuits and pathways cross-talk. This review article highlights recent progress in understanding neural mechanisms of alcohol addiction from the perspectives of the development and maintenance of alcohol dependence. It provides insights on cross talks of different mechanisms and reviews the latest studies on metaplasticity, structural plasticity, interface of reward and stress pathways, and cross-talk of different neural signaling systems involved in binge-like drinking and alcohol dependence.

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1. Introduction

The development of alcohol dependence progresses from impulsive to compulsive alcohol intake via repeated binging, withdrawal, and craving. It is characterized by alcohol consumption despite negative consequences and recurring episodes of abstinence and relapse (Koob, 2013). Recent studies have provided substantial information on the brain circuits that mediate various aspects of alcohol dependence. In particular, studies have shown that alcohol has profound impacts on multiple brain pathways and circuits related to reward, stress, habit formation, and decision-making, which work in concert leading to alcohol dependence/addiction. However, significant challenges remain in understanding, at the molecular and cellular level, how alcohol-induced neuroplasticity and neuroadaptation occur and how different neuropathways cross talk. In this article, we will discuss several neurobiological mechanisms and provide insights on interactions of different mechanisms in the vulnerability, development and maintenance of alcohol dependence. This article is not intended to be comprehensive but rather to focus on several areas that were discussed at a minisymposium at the 2011 Society for Neuroscience annual meeting. We will discuss metaplasticity of dopaminergic neurons, reward and stress pathways in mediating binge-like drinking, interaction of corticotropin-releasing factor (CRF) and

☆ The focus of this article is around the theme presented at a minisymposium at the 2011 Society of Neuroscience annual meeting.

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0028-3908/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.neuropharm.2012.09.022

GABAergic systems, and structural and functional changes of dendritic spines.

2. Mechanisms mediating the development of alcohol dependence

Excessive alcohol exposure or binge-like drinking impacts neuroplasticity and signaling associated with reward and stress pathways, as well as their interface. Here, we highlight the role of metaplasticity of the dopaminergic neurons in the ventral tegmental area (VTA), glutamate signaling in the Nucleus Accumbens (NAC), the CRF system in the central amygdala (CeA) in excessive or binge like alcohol exposure, and discuss the potential role of the BNST, the interface of between stress circuits and classical reward centers, in the development of alcohol dependence.

2.1. Metaplasticity in mesolimbic dopamine neurons and addiction vulnerability

Development of addiction involves a maladaptive form of learning and memory in which drug-related experiences are remembered powerfully, resulting in persistent and uncontrollable drug seeking behavior (Hyman et al., 2006). Synaptic plasticity is widely believed to be the key neural substrate underlying the formation and storage of memory in the brain (Kim and Linden, 2007; Malenka and Bear, 2004). Here, activity-dependent alterations in the efficacy of synaptic transmission are typically induced in a manner in which only those subset of synapses that are active in certain temporal proximity to the time of activity of postsynaptic neurons eventually become potentiated (long-term potentiation: LTP) or depressed (long-term depression: LTD). There is another form of plasticity, termed metaplasticity, which affects synapses of postsynaptic neurons in a global manner (Abraham, 2008; Abraham and Bear, 1996; Mockett and Hulme, 2008). This represents higher-order plasticity (i.e., plasticity of synaptic plasticity) in which previous life experiences, such as exposure to certain environmental stimuli (stress, addictive drugs, etc.), or even prior learning experience alter the "susceptibility" of synapses to undergo activity-dependent LTP/LTD, and thus the ability of animals/humans to learn new information in the future.

The mesolimbic dopaminergic system that originates in the VTA is critically involved in the learning of information related to rewards, including addictive drugs (Morikawa and Paladini, 2011; Schultz, 1998). A growing body of evidence indicates that plasticity and metaplasticity of synapses on dopamine neurons play important roles in reward-based learning and the development of addiction (Hyman et al., 2006; Kauer and Malenka, 2007). It is well established that *in vivo* exposure to different classes of addictive drugs or to stress produces rather global potentiation of AMPA receptor (AMPAR)-mediated glutamatergic transmission onto VTA dopamine neurons (Argilli et al., 2008; Bellone and Luscher, 2006; Conrad et al., 2008; Faleiro et al., 2004; Saal et al., 2003; Ungless et al., 2001). This is thought to saturate AMPAR potentiation and occlude subsequent LTP induction. However, it has recently been proposed that this metaplasticity is a consequence of down-regulation of synaptic NMDA receptors (NMDARs), resulting in suppression of LTP induction (Mameli et al., 2011). This study further demonstrated the emergence of an anti-Hebbian form of AMPAR LTP, confirming that AMPAR potentiation is not saturated. It has also been reported that Hebbian AMPAR LTP may actually be enhanced because of a global reduction in GABAergic inhibition after *in vivo* cocaine exposure (Liu et al., 2005; Pan et al., 2011). Therefore, glutamatergic synapses at dopamine neurons appear to exhibit multiple forms of metaplasticity of AMPAR-mediated transmission. Furthermore, *in vivo* exposure to addictive drugs suppresses LTP of $GABA_A$-mediated transmission via disruption of the LTP induction mechanism (Guan and Ye, 2010; Niehaus et al., 2010; Nugent et al., 2007), indicating that metaplasticity can be induced at GABAergic synapses as well. In principle, various forms of metaplasticity in dopamine neurons, and also in dopamine projection areas [reviewed by Lee and Dong (2011)], should regulate how rapidly and efficiently drug-related events and actions are remembered and, possibly, how long those memories persist, thus affecting the vulnerability to develop addiction. Therefore, establishing the roles of metaplasticity would be an important area of addiction research, which requires manipulating neuroadaptive mechanisms underlying metaplasticity in behaving animals without interfering with synaptic transmission or synaptic plasticity per se.

NMDAR activation in the VTA is necessary for dopamine neuron burst firing and phasic dopamine release in projection areas that occur in response to rewards or reward-predicting stimuli (Sombers et al., 2009; Zweifel et al., 2009). A previous study has reported LTP of NMDAR-mediated transmission that is induced by pairing sustained glutamatergic input stimulation with post-synaptic bursts of action potentials (APs) (Harnett et al., 2009). LTP induction requires amplification of AP-evoked Ca^{2+} signals by preceding synaptic activation of metabotropic glutamate receptors (mGluRs) coupled to the generation of inositol 1,4,5-trisphosphate (IP_3) (Cui et al., 2007). The synaptic stimulation-burst pairing protocol used for LTP induction may resemble the neural activity experienced during cue-reward conditioning in behaving animals, in that cue presentation would give rise to working memory-type sustained glutamatergic input activity, while the reward would elicit dopamine neuron burst firing (Brown et al., 1999; Funahashi et al., 1989). Therefore, this form of Hebbian NMDAR plasticity might contribute to the acquisition of burst responses to environmental stimuli paired with rewards during conditioning (Schultz, 1998).

Recent studies show that repeated *in vivo* exposure to amphetamine or ethanol causes enhancement of NMDAR LTP induction in VTA dopamine neurons (Ahn et al., 2010; Bernier et al., 2011). This form of NMDAR metaplasticity results from an increase in the potency of IP_3 in producing amplification of AP-evoked Ca^{2+} signals, most likely via increased protein kinase A (PKA)-mediated phosphorylation of IP_3 receptors (IP_3Rs) causing enhanced IP_3 sensitivity (Wagner et al., 2008). Importantly, intra-VTA infusion of a PKA inhibitor attenuates amphetamine-induced contextual learning assessed using a conditioned place preference (CPP) paradigm and previous ethanol experience facilitates subsequent acquisition of cocaine-induced CPP (Bernier et al., 2011). Interestingly, CRF, which is increased in the VTA by stressful stimuli or acute withdrawal from addictive drugs (Koob and Zorrilla, 2010; Wise and Morales, 2009), is capable of further amplifying the PKA-mediated increase in IP_3 in ethanol-treated animals. These data suggest that PKA-dependent regulation of IP_3R sensitivity, which gates the "inducibility" of NMDAR plasticity in VTA dopamine neurons, may represent a common neural substrate by which ethanol, other addictive drugs, and stress influence the capacity of animals to learn reward- and drug-associated environmental stimuli. Given that CRF neurons from the BNST and the CeA project to the VTA (Rodaros et al., 2007; Swanson et al., 1983), the action of CRF on NMDAR metaplasticity in the VTA represents a possible feed forward mechanism mediating the cross-talk between stress and reward pathways. Moreover, as discussed in a later section, PKA plays an essential role in regulating CRF-induced GABA release in the CeA (Ameri, 1999; Cruz et al., 2011a). Thus, PKA regulates two important mechanisms, metaplasticity and CRF-induced GABA release, which contribute to the vulnerability and the maintenance of alcohol dependence.

Please cite this article in press as: Cui, C., et al., New insights on neurobiological mechanisms underlying alcohol addiction, Neuropharmacology (2012), http://dx.doi.org/10.1016/j.neuropharm.2012.09.022