Neuropharmacology 87 (2014) 51–58

Contents lists available at ScienceDirect

Neuropharmacology

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

Invited review

# Alcohol: A stimulant activating brain stress responsive systems with persistent neuroadaptation

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ARTICLE INFO

*Article history:*
Available online 12 June 2014

*Keywords:*
HPA axis
POMC
Dynorphin
Mu opioid receptor
Kappa opioid receptor
Vasopressin
V1b receptor

ABSTRACT

Addictive diseases, including addiction to alcohol, opiates or cocaine, pose massive public health costs. Addictions are chronic relapsing brain diseases, caused by drug-induced direct effects and persistent neuroadaptations at the molecular, cellular and behavioral levels. These drug-type specific neuroadapations are mainly contributed by three factors: environment, including stress, the direct reinforcing effects of the drug on the CNS, and genetics. Results from animal models and basic clinical research (including human genetic study) have shown important interactions between the stress responsive systems and alcohol abuse. In this review we will discuss the involvement of the dysregulation of the stress responsive hypothalamic–pituitary–adrenal (HPA) axis in alcohol addiction (Section I). Addictions to specific drugs such as alcohol, psychostimulants and opiates (e.g., heroin) have some common direct or downstream effects on several brain stress-responsive systems, including vasopressin and its receptor system (Section II), POMC and mu opioid receptor system (Section III) and dynorphin and kappa opioid receptor systems (Section IV). Further understanding of these systems, through laboratory-based and translational studies, have the potential to optimize early interventions and to discover new treatment targets for the therapy of alcoholism.

This article is part of the Special Issue entitled 'CNS Stimulants'.



## 1. Introduction

Alcoholism constitutes a major global public health problem and there remains a critical need for the development of medications for the treatment of excessive alcohol use and alcohol addiction. There are three broad types of factors which contribute to the development of alcoholism: environment (including stress), the direct reinforcing effects of alcohol and persistent molecular and neurobiological changes caused by alcohol in the CNS, and individual genetics. Our laboratory, as well as others, has implicated the dysregulation of the brain stress responsive systems, including the hypothalamic–pituitary–adrenal (HPA) axis, at least in part, in the acquisition and persistence of, and relapse to alcohol addiction. There is an increasing literature demonstrating that alcohol is a stimulant which activates the brain stress responsive systems, and in turn the abnormal brain stress responsive systems contribute to alcohol consumption, the development of alcoholism and relapse of alcohol use. The purpose of this review will be to provide an overview of some of our recent laboratory research, which combines animal modeling for laboratory based research and basic clinical research to elucidate the biology of addiction, along with studies on the genetic correlates. We propose that a bi-directional, translational approach will help refine future targets for pharmacotherapy for alcoholism and other specific addictive diseases.

## 2. Section I. Stress responsive hypothalamic–pituitary–adrenal (HPA) axis

Stress increases both corticotrophin releasing factor (CRF) and arginine vasopressin (AVP) secretion into the pituitary portal circulation from terminals of the hypothalamic paraventricular nucleus (PVN). The interaction between CRF and $CRF_1$ receptors on corticotropes initiates the release and biosynthesis of pro-opiomelanocortin (POMC)-derived peptides in the anterior pituitary (Vale et al., 1981). Hypothalamic AVP which activates V1b receptors stimulates ACTH secretion from the corticotropes in the anterior pituitary (Lolait et al., 1995; Aguilera and Rabadan-Diehl., 2000). Both CRF/$CRF_1$ receptor and AVP/V1b receptor systems are also widely distributed in rodent brains, suggesting that both may be mediators of the actions of central stress responsive systems (Roper et al., 2011).

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http://dx.doi.org/10.1016/j.neuropharm.2014.05.044
0028-3908/

Acute exposure to alcohol produces a potent activation of the HPA axis in humans (Jenkins and Connolly, 1968). After chronic alcohol exposure, alcoholic individuals develop a tolerance to this stimulant HPA effect of alcohol (Adinoff et al., 1990; Inder et al., 1995). For instance, when the tolerance developed, the HPA axis showed insensitive to stimulating effect of alcohol (O'Malley et al., 2002). Also, it has been found less HPA activation in response to a number of HPA functional tests in alcoholics and sons of alcoholics, including CRF and ACTH stimulation tests (Wand and Dobs, 1991), and stress tests (Vescovi et al., 1997; Sorocco et al., 2006). In contrast, acute alcohol withdrawal transiently activates HPA axis (Hundt et al., 2001; Zimmermann et al., 2003). Schuckit and his group have reported that lower responses of cortisol to modest doses of alcohol in sons of alcohol-dependent men are associated with a significant increase in the risk of future alcoholism (Schuckit et al., 1987, 1988, 1994). Also, studies from other groups confirm these reports and extended them to investigate opioid activity at the hypothalamic level (Wand et al., 1999) and CRF receptor at the pituitary level (Waltman et al., 1994) in sons of alcoholics. In another report, however, human subjects at high risk for excessive alcohol consumption have increased HPA responses to alcohol (Gianoulakis, 1993). Therefore, it has been hypothesized that the individuals may deliberately seek out alcohol drinking to achieve a state of the HPA activation, as alcohol use increases the HPA activity, and thereby physiological comfort. In support of this concept, the "pleasurable experiences", such as drinking alcohol, also increase stress hormonal levels in laboratory animals (see detailed discussion below). For instance, corticosterone itself has been found to be reinforcing and is self-administered by rodents orally (e.g., Deroche et al., 1993). In addition, preclinical investigations have found decreased alcohol drinking following exposure to CRF (Bell et al., 1998) and ACTH (Krishnan et al., 1991), both of which are involved in the activation of the HPA axis. Considering that increases in HPA hormones contributing to the rewarding aspects of alcohol, alcohol addicts might need to consume more alcohol to achieve the same effect after the HPA axis develops a tolerance after chronic exposure (Kreek and Koob, 1998; Koob and Kreek, 2007).

In rodents, the activation of endogenous CRF (but not AVP) contributes to the effects of acute alcohol on the HPA axis (e.g., Rivier and Vale, 1987, 1988). Chronic exposure to alcohol, however, reduces HPA hormonal response to the drug itself, which shows the development of HPA tolerance (Spencer and McEwen, 1990; Lee and Rivier, 1997; Zhou et al., 2000). In a recent study, we found that Sardinian alcohol-preferring vs. Sardinian alcohol-nonpreferring rats displayed lower levels of plasma ACTH and pituitary POMC mRNA after chronic voluntary alcohol drinking, supporting the concept that excessive alcohol consumption disrupted the HPA function (Zhou et al., 2013a). Of interest, abnormal HPA activity in response to the dexamethasone test during alcohol withdrawal has also been found in humans (Hundt et al., 2001). This is further supported by the findings that an increase in AVP mRNA, but not CRF mRNA, was found in mice and rats during more than 2-week alcohol or cocaine withdrawal with HPA abnormal activation (Zhou et al., 2011b; Pang et al., 2013) (see more details in Section II). However, few studies have specifically addressed the involvement of AVP and V1b receptor systems in relapse-like drinking and the HPA modulation after chronic withdrawal from long-term alcohol exposure in rodent models, though AVP is a potent modulator of brain stress responsive systems and HPA axis.

Endogenous opioids are critical in the modulation of the HPA axis. Animal and human studies have demonstrated that β-endorphin and dynorphin exert tonic inhibition and stimulation of HPA activity by acting on the mu opioid receptor and the kappa opioid receptor, respectively (e.g., Kreek and Koob, 1998; Zhou et al., 2010a). For instance, β-endorphin acting on the mu opioid receptor exerts tonic inhibition of CRF, and then of the HPA axis in both humans and rodents. Kappa opioid receptor agonists stimulate plasma corticosterone levels in rats (e.g., Laorden and Milanes, 2000). The stimulatory effects of the kappa opioid receptor agonists on the HPA axis were blocked by selective kappa opioid receptor antagonist nor-binaltorphimine (Pascoe et al., 2008). It is also found that kappa opioid receptor agonists (Ur et al., 1997) or partial agonists (Schluger et al., 1998) elevate plasma ACTH and cortisol levels in humans. Consistent with the evidence that dynorphin/kappa opioid receptor modulates stress via the HPA axis, our recent study demonstrates that pharmacological blockade of kappa opioid receptors with nor-binaltorphimine blunted ACTH and corticosterone responses induced by a yohimbine stressor and attenuated heroin seeking induced by yohimbine in rats trained to self-administer heroin (Zhou et al., 2013b).

Naltrexone is a selective mu opioid receptor antagonist. Numerous pharmacological studies provide consistent evidence that the opioid antagonists decrease alcohol reward, consumption, alcohol self-administration, alcohol craving and relapse episodes in human alcoholics. Since the endogenous β-endorphin acts on the mu opioid receptor to exert tonic inhibition of CRF in the paraventricular nucleus, part of the HPA axis, naltrexone acutely and persistently activates the HPA axis by disinhibiting the inhibition of the CRF by β-endorphin acting on the mu opioid receptors. Naltrexone has been used in the treatment of alcoholism (e.g., O'Malley et al., 1992; Volpicelli et al., 1992). In a human study, naltrexone treatment for 3 days results in persistent daily transient elevations of HPA activity (6-h time point) in alcohol-dependent subjects (Farren et al., 1999), just as found before in normal volunteers (Schluger et al., 1998). In a further study conducted in inpatient research unit (O'Malley et al., 2002), naltrexone treatment at 50 mg per day or placebo were provided in alcohol-dependent subjects for 6 days. Six hours after the last naltrexone dose or placebo, when plasma ACTH levels had returned to normal levels, a 2-h alcohol self-administration portion of the experiment (4 drinks per hour or $3 instead of each drink) was carried out. The naltrexone-treated subjects had less alcohol consumption ($1.9 \pm 0.7$ drinks) over the course of the 2-h period, compared with placebo-treated subject ($4.6 \pm 0.7$ drinks). Of great interest, the naltrexone-treated subjects showed the HPA axis activation, with higher plasma ACTH and cortisol levels than the placebo-treated group, during the 2-h drinking period. Also, plasma cortisol levels were negatively correlated with alcohol craving levels in both groups at the end of 2-h drinking period. This is the first laboratory study demonstrating that the activation of the HPA axis by naltrexone contributes to reduction in alcohol drinking and suppression of alcohol craving. These results confirm the hypothesis that naltrexone reduces desire to drink (alcohol craving) and the amount of alcohol consumed in alcohol-dependent subjects (O'Malley et al., 2002). It is hypothesized that naltrexone may reduce drinking via suppressing craving for alcohol and that this effect may be related in part to naltrexone's ability to activate the HPA axis, by disinhibiting the inhibition of the CRF by β-endorphin acting on the mu opioid receptors. Support for this hypothesis can be found in other studies (e.g., Schuckit, 1994).

Like the stimulatory effect of alcohol, cocaine stimulates HPA activity in humans. After a challenge dose of cocaine, ACTH response is significantly lower in cocaine dependent men than in occasional cocaine users, indicating that attenuation of cocaine's effects occurs after chronic cocaine use (Mendelson et al., 1998). Some human studies reported that cocaine addicted patients show higher basal plasma ACTH and cortisol levels even up to 3 months of withdrawal (Wilkins et al., 2005); however, other studies have found no difference or even lower in basal ACTH and cortisol levels during withdrawal (e.g., Mendelson et al., 1998; Ducat et al., 2014).