Neurobiology of Alcohol Dependence and Implications on Treatment

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SUMMARY

The process of alcohol dependence has been conceptualized as a progress from controlled alcohol intake to compulsive alcohol consumption or a shift from alcohol intake for pleasure to compulsory alcohol seeking behavior. Hereditary and physical factors and the interaction of individuals with their environment, as well as permanent changes in the neurotransmitter and neurohormonal systems in the brain due to alcohol use, have an important role in the etiology of alcohol dependence. The effects of ethanol on the neurotransmitter, neuropeptide, and neuroendocrine systems not only account for its acute physiological and euphoric/reinforcing effects but also seem to be responsible for the development of dependence. While the motivation for alcohol use is mainly positive reinforcement in the earlier phases of alcohol consumption, both positive and negative reinforcements are involved in the process once dependence has developed. This event, termed allostasis, is caused by a neuroadaptive process due to chronic alcohol consumption. It seems that the most important neuroadaptive changes in progression from occasional alcohol intake to dependence are the: (1) down-regulation of the dopamine and gamma aminobutyric acid systems; (2) permanent upregulation in the glutamate system; and (3) dysregulation in the stress systems (corticotropin-releasing hormone and serotonin) of the brain. In this paper, we will review the adaptive changes caused by chronic alcohol consumption, which are important in the development of dependence, and address the potential therapeutic contributions of interventions to these changes in alcohol dependence.

Keywords: Alcohol dependence, neurobiology, reward, stress, gamma aminobutyric acid, glutamate

INTRODUCTION

Alcohol was the first psychopharmacological agent to be discovered, and production as a euphoric substance dates back to 8000 B.C. Alcohol dependence is a disorder, which has a long known human history. It has become increasingly common within the last few centuries due to the advancement of alcohol distillation methods and the production of beverages with a high alcoholic content (Gately 2011).

Alcohol dependence has many neurobiological aspects in the brain and is characterized by loss of control in alcohol consumption, extensive desire for alcohol use, and persistent use despite awareness of adverse health-related and social consequences. Hereditary and physical factors, and the interaction of individuals with their environment, as well as permanent changes in the neurotransmitter and neurohormonal systems in the brain due to alcohol use, play the most important role in the etiology of alcohol dependence (Koob 2003). Alcohol acts on several neurotransmitter systems such as dopamine (DA), gamma aminobutyric acid (GABA), glutamate, serotonin, norepinephrine (NE), and endogenous opiates. It is thought that hereditary and environmental factors play a role at a half-and-half ratio on the development of alcohol dependence (Goldman et al. 2005). However, hereditary and environmental factors are beyond the scope of this review. In this article, we will review the adaptive neurochemical

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changes thought to be largely responsible for the development of dependence.

It is known that alcohol affects the brain diffusely. Alcohol acts acutely on the cellular membranes and intracellular signal transduction systems in the brain. Thus, it causes some alterations in the function of neurotransmitter- and neurohormone-related membrane receptors and ligand-gated and voltage-gated ion channels. It is thought that the majority of the acute effects of alcohol are related to its direct effects on ion channels such as GABA-A, glycine, acetylcholine, serotonin, and N-methyl-D-aspartate (NMDA) receptors (Trudell et al. 2014). Alcohol also affects the opioid and corticotrophin releasing hormone (CRH) systems and some other neuroendocrine and neuropeptide systems in the brain.

The above-mentioned effects of ethanol on the neurotransmitter, neuropeptide, and neuroendocrine systems not only account for its acute physiological and euphoric/ reinforcing effects but also seem to be responsible for the development of neuroadaptation (allostasis), which is considered as the main factor in dependence, tolerance, and withdrawal symptoms. Indeed, it is the neuroadaptive process which is mainly responsible for the tolerance phenomenon, an attempt to reduce the acute effects of the substance and to restore brain homeostasis (Eşel 2001, 2005, Koob 2013).

The development of dependence has been conceptualized as a progress from controlled alcohol intake to compulsive alcohol consumption or a shift from alcohol intake for pleasure to compulsory alcohol seeking behavior (Marcinkiewcz 2015). While the motivation for alcohol consumption is mainly positive reinforcement in the earlier phases of alcohol consumption, both positive and negative reinforcements are involved in the process once dependence has developed. These behavioral alterations are caused by neuroplasticity or the neuroadaptive process due to chronic alcohol consumption. Neuroadaptive changes in the reward, stress, glutamate, and GABA systems are particularly involved in the development of dependence (Banerjee 2014).

It has been proposed that the notion of "allostasis", which is defined as achieving stability by modification or re-establishing homeostasis at a different set-point, can also be applied to describe permanent changes during development of dependence (Koob 2013). Such adaptations occur due to the alterations in gene expression caused by the epigenetic effects or direct influences on the transcription factors of alcohol at the cellular level. Thus, the efforts made by the brain to adapt to all new conditions such as a new environment, stressful life events or the development of addictions can be considered as allostasis (Most et al. 2014a).

The most important adaptation processes in the progress from occasional alcohol intake to dependence are the down-regulation in the DA and GABA systems, permanent hyperactivity in the glutamate system, and dysregulation in the brain stress systems (Roberto et al. 2012). Negative emotional conditions and alcohol seeking behavior occur due to all these processes, thus triggering relapses (Koob 2013). Now, we are addressing these adaptive changes that cause, or at least significantly contribute to, alcohol dependence.

Dopamine System

It is well-known that the DA system is of importance in the acute rewarding effects of alcohol, craving behavior, and development of alcohol dependence (Esel 2005, Sengül and Dilbaz 2013, Tabakoff and Hoffman 2013). It is accepted that the primary structures comprising the reward system in the brain include the extended amygdala, mesolimbic dopaminergic pathway, ventral tegmental area (VTA), nucleus accumbens (NAc), ventral striatum, and prefrontal cortex (Ma and Zhu 2014). DA is the most important neurotransmitter in the reward system. It mediates the reinforcing effects of all addictive drugs (Volkow et al. 1999).

The main acute effect of alcohol on the DA system is to increase DA release from and firing rate of dopaminergic neurons projecting from the substantia nigra and VTA to the limbic system (Comings and Blum 2000). The dose-response relationship between alcohol intake and DA release from the NAc has been reported in many animal studies (Yim and Gonzales 2000, Yoshimoto et al. 1992). Likewise, it has been shown in animal studies that the ethanol-induced increase in DA activity originates from DA release from the presynaptic terminal but not from the blockade of DA re-uptake (Yim and Gonzales 2000).

The interactions between dopaminergic system and other neurotransmitter systems are also important in the central effects of alcohol. Dopaminergic neurotransmission projecting from the VTA to the NAc is under control of GABAergic inhibition. On the other hand, it is also controlled by serotonergic neurons via 5-HT1B, 5-HT2C and 5-HT3 receptors on GABA neurons at the VTA (Tabakoff and Hoffman 2013). For example, selective 5-HT1B agonists increase extracellular dopamine level by inhibiting GABA release from the VTA (Yan et al. 2004). Besides, 5-HT3 receptors at the brain reward structures also modify dopaminergic neurotransmission. Indeed, 5-HT3 agonists increase extracellular dopamine release in the NAc and the VTA (Campbell and McBride 1995). Thus, dopaminergic effect of acute alcohol intake might be mediated, at least in part, by its serotonergic effects.

Effects of chronic alcohol use on the DA system have also been investigated and a hypo-dopaminergic state has been observed in the brain due to chronic alcohol use. It has been proposed that this hypo-dopaminergic state is somehow related to negative emotions such as the dysphoria and craving

observed during abstinence, and in turn relapses in alcohol-dependents (Koob 2013, Most et al. 2014a, Volkow 2010). Indeed, a decreased DA release in the striatum during alcohol withdrawal has been shown in animal studies (Rossetti et al. 1992). It has also been reported that chronic alcohol consumption results in a down-regulation in both D2 and D1 receptors (Vasconcelos et al. 2003).

As for human studies, decreased sensitivity of D2 receptors has been shown in neuroendocrine challenge studies in alcohol-dependent patients (Marchesi et al. 1997, Wiesbeck et al. 2000). A reduction in the presence of D2 receptors in some brain structures such as striatum has been reported in positron emission tomography (PET) studies in alcoholic patients (Volkow et al. 2002, Martinez et al. 2005). Furthermore, the finding of decreased DA release in response to methylphenidate in the striatum confirmed this suggestion (Volkow et al. 2007, 2013). In a study using single photon emission computerized tomography (SPECT), it was shown that increased striatal D2 receptor intensity in individuals with alcohol dependence could be linked to early relapse (Guardia et al. 2000). In addition, there are imaging studies which found decreased levels of dopamine transporter in some regions of the brain in individuals with alcohol dependence (Laine et al. 1999, Repo et al. 1999, Tupala et al. 2001). In addition to the down-regulation of the D2 receptors, some authors proposed that decreased dopaminergic activity due to chronic alcohol use may stem from either reduced DA release from dopaminergic neurons (Diana et al. 2003) or from a decreased number of neurons releasing DA in the NAc (Shen 2003).

In summary, impaired dopaminergic function in the brain due to chronic alcohol consumption leads to an ongoing negative emotional state, which in turn triggers relapses by contributing to the negative reinforcement effect of alcohol. Based on these findings, it has been long thought that agents affecting the dopaminergic system could be used in the prevention of relapses in individuals with alcohol dependence. Thus, it has been suggested that D2 antagonist agents such as tiapride, flupentixol, and quetiapine could attenuate drinking behavior by decreasing the rewarding effects of alcohol; however, studies did not support this idea (Wiesbeck et al. 2001, Bender et al. 2007, Litten et al. 2012). Aripiprazole, another antipsychotic agent, has been proposed to decrease craving and to enhance positive subjective emotions in the long run (Martinotti et al. 2007, Brunetti et al. 2012). In a meta-analysis on the benefits of antipsychotic agents in alcohol dependence, it was concluded that they have no benefits on abstinence days, craving, or amount of alcohol consumed in alcohol-dependent patients (Kishi et al. 2013). Similarly, it can be suggested that agents such as bromocriptine (D2 agonist) and lisuride (D1 antagonist, D2 agonist) may decrease alcohol consumption by a counter effect to D2 receptor down-regulation in alcohol dependence (Lawford et al. 1995, Schmidt et al. 2002). In sum, it seems that no DA-related agent is as yet available for preventing relapses in alcohol dependence (Ma and Zhu 2014, Zindel and Kranzler 2014).

GABA system

Alcohol impairs the balance between GABA, the primary inhibitory neurotransmitter, and glutamate, the primary excitatory neurotransmitter, in the brain (Liang and Olsen 2014). It seems that the effects of ethanol on the GABA system are associated with its reinforcing effect in one way or another. Ethanol is a positive allosteric modulator of the GABA-A receptors. During acute alcohol withdrawal, a decrease in central GABA activity is one of the most important causes of excitation and negative emotions due to elevated reward threshold (Koob 2003). GABA-A receptors are related to many of the acute effects of alcohol and also contribute to the development of tolerance and dependence as well as withdrawal symptoms (Enoch 2008).

The vast majority of the acute central effects of alcohol such as anxiolytic, sedative and anticonvulsant effects, as well as its disruptive effects on cognitive and motor functions occur via the agonistic effects of alcohol on GABA-A receptors. Actually, these acute effects of alcohol can be inhibited by GABA antagonists (Koob 2004).

GABA-A receptors are composed of 5 subunits, all of which can have several isoforms. The majority of receptors have two α-, two ß-, and one γ-subunits. GABA-A receptors may have different subunit isoforms in the different brain regions (Minier and Sigel 2004, Sigel et al. 2006). Therefore, depending on the subunit isoforms of GABA-A receptors, different acute effects of alcohol may develop. For instance, it seems that α2 GABA-A receptors are related to the sedative-hypnotic effects, while α1 GABA-A receptors are related to the locomotor suppressive effects of alcohol (Kumar et al. 2009).

The mechanism underlying the acute GABAergic effect of alcohol has not yet been fully elucidated. It has been proposed that alcohol enhances GABA transmission through complex mechanisms by influencing both presynaptic and postsynaptic GABA-A receptors in the brain areas such as the cerebellum and mesolimbic reward pathways (Enoch 2008, Roberto et al. 2003). Moreover, it has also been reported that alcohol not only affects GABA synthesis and release (Most et al. 2014b, Roberto 2004), but also has a regulatory effect on GABA transmission by increasing adenylate cyclase and protein kinase C activities in the central amygdala (CeA) synapses (Bajo et al. 2008, Cruz et al. 2012, Tabakoff and Hoffman 2013). In addition, it has some effects on GABA-B receptors (Most et al. 2014a) and indirect effects on GABA activity through endogenous neuroactive steroids (Koob 2004, Kumar et al. 2009).

In addition, the effects of alcohol on the GABA system can indirectly mediate its effects on other neurotransmitters. For instance, some of the dopaminergic effects of alcohol may occur via the GABAergic system. The finding that GABA inhibits dopaminergic neurons is supported by baclofen-mediated (a GABA-B agonist) DA suppression in alcohol dependence (Pitman et al. 2014). Conversely, DA can directly inhibit GABA receptors in some brain structures (Hoerbelt et al. 2015). Moreover, the primary localization of D2 receptors in the striatum is the GABAergic neurons (Volkow et al. 1996). Thus, it is proposed that disruption in GABA modulation by DA may contribute to alcohol dependence (Hoerbelt et al. 2015). In light of these findings, it is apparent that interactions between the GABA and DA systems are of importance in the regulation of the brain reward and stress systems, which play a significant role in the development of dependence.

As a result of chronic alcohol consumption, a reduction in gene expression of GABA-A receptor subunits develops over time (Biggio et al. 2003, Cagetti et al. 2003, Malcolm 2003). One of the findings supporting this is the decreased number of GABA-A receptor-benzodiazepine complexes in the frontal lobes of individuals with alcohol dependence in imaging studies (Abi-Dargham et al. 1998). Reduced GABA function in chronic alcohol consumption can be due to either a regional decrease in the number of GABA-A receptors or to an alteration in the arrangement of GABA-A receptor subunits, leading to decreased receptor sensitivity (Mihic 1999, Kumar et al. 2009, Roberto et al. 2012).

Down-regulation in GABA-A receptors due to chronic alcohol consumption largely accounts for the failure of central inhibition and thus, the excitation symptoms observed in acute alcohol withdrawal. Moreover, reduced GABA-A-Bz receptor activity contributes to the initiation of drinking. In addition, the fact that withdrawal symptoms become more severe during repeated abstinence periods due to decreased GABA receptor functions indicates the role of neuroadaptation in the GABA system on the kindling of withdrawal (De Witte et al. 2003).

In light of these findings, it is suggested that agents enhancing GABA activity can be used in the treatment of alcohol dependence. For instance, there are animal and human studies suggesting that baclofen, a selective GABA-B receptor agonist, can decrease relapses by attenuating craving (Addolorato et al. 2000, Peters et al. 2013, Imbert et al. 2015); however, there is no consensus on this topic (Gorsane et al. 2013). It was shown that gamma hydroxybutyric acid (GHB), another GABA-B agonist, reduced alcohol intake in animals (Colombo et al. 2012) and craving in humans (Maremmani et al. 2011). It has been shown that gabapentine, a GABA analog, improves craving and many of negative emotions experienced during abstinence in alcohol-dependent individuals (Furieri and Nakamura-Palacios 2007, Mason et al. 2014). It has also been reported that topiramate, a GABAergic drug, prolongs abstinence duration and decreases craving, alcohol consumption, and relapses (Martinotti et al. 2014).

Glutamate system

Glutamate is the main excitatory neurotransmitter in the brain. Glutamate receptors are considered in 2 classes, namely metabotropic and ionotropic receptors. NMDA, α-amino-3-hydroxi-5-methyl-isoxazolepropionic acid (AMPA) and kainate receptors are ionotropic receptors (Nakanishi 1992).It is known that the glutamate system has an important role in the acute behavioral effects of alcohol, development of alcohol dependence, alcohol withdrawal syndrome, and familial predisposition to alcohol dependence (Esel 2006). It is proposed that glutamatergic signaling, particularly projecting from the prefrontal cortex, amygdala, and hippocampus to the NAc and VTA, plays a significant role in triggering relapses in alcohol dependence (Kalivas et al. 2005).

Acute alcohol exposure inhibits all glutamate receptors in a dose-dependent manner. However, NMDA is the most susceptible glutamate receptor to the effects of alcohol (Most et al. 2014b, Tabakoff and Hoffman 2013). Acute alcohol intake inhibits NMDA receptors in a dose-dependent manner (Lovinger et al. 1989, Faingold et al. 1998, Lovinger and Roberto 2013). Through the effects on NMDA receptors, acute alcohol intake also suppresses intracellular calcium elevation and long-term potentiation (LTP) in hippocampal neurons (Schummers et al. 1997). Acute NMDA blockade by alcohol seems to contribute to cognitive dysfunction during acute alcohol intoxication (Lovinger et al. 1989).

Chronic ethanol consumption causes elevation in NMDA receptor functions as well as non-NMDA glutamatergic receptor activity, presynaptic glutamate release, and extracellular glutamate levels (Holmes et al. 2013). The finding that chronic alcohol exposure results in an elevation in the levels of brain glutamate transporter in animal studies also supports the idea that chronic alcohol exposure increases extracellular glutamate levels (Sari 2014). In human studies, increased glutamate levels have been found in the cerebrospinal fluid (CSF) of alcohol-dependents (Tsai et al. 1998) and are correlated to severity of dependence (Umhau et al. 2010). In magnetic resonance spectroscopy (MRS) studies, increased glutamate levels was reported to exist in the hippocampus and anterior cingulate during early alcohol withdrawal (Lee et al. 2007, Hermann et al. 2012, Mon et al. 2012). In conclusion, there is a hyperglutamatergic state in alcohol-dependent individuals.

In agreement with the above-mentioned findings, in a study from our clinic, it was found that white blood cell glutamate transporter mRNA levels were increased in individuals with alcohol dependence at the early (day 1) and late (day 28) phases

of alcohol withdrawal when compared to controls, suggesting that this might have developed secondary to chronically high levels of extracellular glutamate (Ozsoy et al. 2016).

It is thought that increased glutamate activity in the central nervous system due to chronic alcohol use accounts for symptoms such as the excitation, craving, anxiety, and epileptic seizures seen in alcohol withdrawal. In addition, it is related to neurodegeneration and cognitive impairment in alcoholic patients (Holmes et al. 2013). It has been proposed that neurodegeneration resulting from chronic alcohol consumption is due to withdrawals rather than to chronic alcohol consumption itself. It is suggested that glutamate is the primary factor in neurodegeneration and that increased NMDA receptor function is a prerequisite for withdrawal-related neurotoxicity (Nagy et al. 2003, Thomas and Morrisett 2000). According to these findings, it can be suggested that NMDA antagonists may be able to prevent neurodegeneration due to alcohol withdrawal.

Based on these data, it can be suggested that agents with regulatory effects on glutamate activity may have some benefits, such as reducing alcohol consumption, suppressing the symptoms of withdrawal, hampering neurodegeneration due to alcohol, and preventing the development of alcohol dependence by decreasing neuroplasticity related to alcohol intoxication and withdrawal. Indeed, some of these agents are already in clinical use in the treatment of alcoholism (Krystal et al. 2003, Banerjee 2014). It seems that, theoretically, agents acting on glutamate activity could be used both in certain periods of the disease and for the prevention of progression to dependence. It has been found that acamprosate, a drug that attenuates glutamatergic activity, decreases alcohol consumption and prolongs the duration of abstinence in animal and human studies (Mann et al. 2008, Plosker 2015). In addition, agents which upregulate the glutamate transporter 1 (GLT1) gene expression, such as ceftriaxone, have been shown to reduce alcohol consumption in genetic animal models of alcohol dependence (Rao et al. 2015).

Serotonin system

It is thought that the serotonin system contributes to development of alcohol dependence throughout its effects on the reward and stress systems. There is a well-known association among serotonin deficiency, impulsivity, and alcohol consumption behavior (Virkkunen and Linnoila 1997). It has been proposed that both increased (by increasing anxiety) and decreased serotonergic activity (by increasing impulsivity and negative mood while decreasing stress tolerance) can trigger alcohol intake (Marcinkiewcz 2015). It has also been suggested that acute alcohol use increases serotonin activity in the reward and information processing areas in the brain, while chronic alcohol use decreases this activity (Sari et al. 2011). Thus, it seems that decreased serotonergic activity resulting from either genetic predisposition or chronic alcohol consumption may be responsible for increased alcohol consumption and relapses.

Platelet monoamine oxidase activity was found to be low during active alcohol consumption (Rommelspacher et al. 1994) and withdrawal period (Berggren et al. 2000, Esel et al. 2002, Demir et al. 2002). Therefore, it was proposed as an indirect evidence for decreased serotonin levels in the brain of alcoholics. In imaging studies, it was reported that 5-HT1A, 5-HT1C and 5-HT2C receptor sensitivities and the number of 5-HT transporters were decreased in several brain structures (Heinz et al. 1998, 2002, Mantere et al. 2002, Storvik et al. 2006, Sari et al. 2011) and it was proposed that such down-regulation could be associated to increased anxiety and depression in individuals with alcohol dependence.

It is known that there are many interactions between stress response and serotonin systems. It is thought that early life stressors can predispose individuals to aggressiveness, impulsivity, and alcohol dependence by decreasing 5-HT function in the brain (Higley et al. 1996). Prolonged stress and subsequent increases in glucocorticoid levels may lead to a reduction in the serotonin functions in the brain and may trigger relapses (van Praag 2005). In particular, it is proposed that stress-related craving is closely related to the serotonergic system (Anton 2001, Sengül and Dilbaz 2013). Therefore, it can be thought that serotonin may be a major mediator in the well-known relationship between stress and relapses.

Based on these findings, the effectiveness of serotonergic drugs in the treatment of alcohol dependence has been under debate. There are controversial findings on the effectiveness of serotonergic drugs such as selective serotonin re-uptake inhibitors (SSRIs), 5-HT1A agonists (e.g., buspirone), and 5-HT3 antagonists (e.g., ondansetron) in alcoholic patients. Although some positive outcomes were observed (Arborelius et al. 1993, Higley et al. 1998, Le and Shaham 2002), serotonergic drugs can be generally considered ineffective in the treatment of alcohol dependence. However, they may be effective in some subgroups such as early-onset alcoholism (Zindel and Kranzler 2014, Marcinkiewcz 2015).

CRH system

Stress-inducing factors have a significant role in the development, maintenance and relapses of alcohol dependence (Spanagel et al. 2014). For instance, stressful events increase alcohol consumption and relapses (Sinha 2008). In addition, early life stressors are widely accepted to be an important predispositional factorin alcohol dependence (Stewart 1996).

For years, the relationship between stress and alcohol consumption has been explained by the tension-reduction hypothesis, which posits that drinking alcohol reduces stress and that individuals under stress drink alcohol to benefit from this

effect (Fouquerau et al. 2003). However, emerging evidence has shown that this relationship is more complex than previously supposed. While alcohol is known to be a substance that can reduce anxiety, it has an acute activating effect on the brain stress systems (Becker 2012, Rivier 2014). It is known that acute alcohol intake elevates circulating adrenocorticotropic hormone (ACTH) and cortisol levels (Zhou et al. 2000, Richardson et al. 2008, Willey et al. 2012). It is thought that the acute stimulatory effect of alcohol on the hypothalamo-pituitary adrenal (HPA) axis depends on an increase in CRH release from paraventricular nucleus (Ogilvie et al. 1998, Sarnyai et al. 2001). In conclusion, acute alcohol intake causes physiological alterations similar to stress rather than attenuating the effects of stress.

There is a very complex interaction between alcohol and the stress response system. Stress aggravates alcohol consumption and appears to be one of the important factors in the maintenance of alcohol dependence. On the other hand, chronic alcohol consumption disrupts an individual's ability to cope with stress by inducing permanent adaptive changes in the stress response system over time. The relationship between alcoholism and stress becomes further complicated due to the presence of two distinct CRH-related stress systems (hypothalamic and extra-hypothalamic) in the brain.

The two components of the stress response system in the brain are the hypothalamo-hypophyseal and extra-hypothalamic systems. It is thought that both systems are involved in the acute effects of alcohol as well as the negative mood symptoms observed during abstinence. As in the hypothalamo-hypophyseal system, CRH1 receptors are widely expressed in many other brain regions responding to stress such as the neocortex, extended amygdala, medial septum, hippocampus, thalamus, and cerebellum (Zorilla et al. 2014). The CRH activity in these structures constitutes the extra-hypothalamic CRH system and plays a significant role in stress response. It is proposed that the extra-hypothalamic CRH system is mainly involved in negative emotional states. In particular, it is reported that the extended amygdala, which is composed of CeA, bed nucleus of the stria terminalis (BNST) and the NAc cortex, is associated with behavioral components of fear and anxiety in animals (Ciocchi et al. 2010, Davis et al. 2010). In alcohol dependence, it is proposed that CeA has a significant role in the formation of negative mood during withdrawal and subsequent phases, thus triggering relapses (Roberto et al. 2012).

Although there has been some controversy related to the changes in the hypothalamic CRH system during chronic alcohol consumption, the widely accepted changes are as follows (Esel 2001,2005, Lu and Richardson 2014): enhanced hypothalamic CRH release, an increase in basal functions of the HPA axis, and a decrease in the HPA axis responses to alcohol and stress. In animal studies, it was reported that chronic alcohol use causes a decrease in hypophyseal sensitivity to CRH, attenuating ACTH, ß-endorphin, and cortisol responses to stress (Zorilla et al. 2001). In a study from our clinic, it was found that cortisol and dehydroepiandrosterone sulphate (DHEAS) responses to a physical stressor were deficient, while ACTH responses were normal, during acute alcohol withdrawal in alcohol-dependent patients, suggesting that insufficient response to physical stress of the HPA axis could originate from an abnormality at the adrenal level, which might be due to chronic hypercortisolemia reported in individuals with alcohol dependence (Esel et al. 2014).

As a result of chronic alcohol consumption, significant adaptive changes occur in the extra-hypothalamic CRH system. In animals, it has been reported an increase in the synthesis and release of CRH in the CeA and BNST during abstinence (Funk et al. 2006, Roberto et al. 2010). Therefore, due to their effects on this system, CRH1 antagonists may be beneficial in acute alcohol withdrawal by reducing anxiety and preventing reinstatements (Logrip et al. 2011, Parylak et al. 2011). It is proposed that up-regulation in CRH activity in the extended amygdala due to chronic alcohol consumption may be responsible for anxiety and dysphoria during withdrawal, and thus for relapses via negative reinforcement mechanisms (Becker 2012, Heilig et al. 2010, Zorrilla et al. 2014). In summary, it may be suggested that a permanent up-regulation develops in the hypothalamic and extra-hypothalamic CRH systems as well as CRH1 receptors (Koob 2013).

In addition, it is known that the CRH system is involved in stress-induced relapses. It is possible that permanent abnormalities in the HPA axis induced by alcohol may increase the likelihood of relapses by increasing vulnerability to stress during a prolonged withdrawal period (Rasmussen et al. 2000, Valdez et al. 2002). It is proposed that interplay between the stress response and reward systems in the brain is also important in the relapses (Spanagel et al., 2014). There are abundant amounts of mineralocorticoid (MC) and glucocorticoid (GC) receptors on the mesolimbic reward pathways (Reul and de Kloet 1985). In animals, it has been reported that reinforcing effects and facilitating role for alcohol consumption of corticosteroids are mediated by GC receptors on the reward system. Elevated GC levels due to stress increase mesolimbic dopaminergic activity, which partly explains the facilitative effect of stress on alcohol use (Spanagel et al. 2014). It has been proposed that the activation of extra-hypothalamic CRH system rather than the HPA axis is important in the relapses induced by stressors (Le et al. 2000, Zorilla et al. 2014).

It is thought that CRH and GC antagonists can be used to prevent stress-induced relapses in individuals with alcohol dependence. It was reported that CRH receptor antagonists such as antalarmin decreased stress-induced reinstatements in animal studies (McBride et al. 2002, Cippitelli et al. 2012). However, human studies failed to confirm such beneficial

effects of these agents (Kwako et al. 2015). It was also reported that GC receptor antagonists such as mifepristone decreased alcohol consumption in both animals and humans (Koenig and Olive 2004, Simms et al. 2012, Vendruscolo et al. 2015).

In light of these findings, it can be suggested that the effects of alcohol on the extra-hypothalamic CRH system are important in relieving anxiety, and thus in a negative reinforcement effect during the early phases of alcohol use, in reinstatements due to negative mood during acute and prolonged abstinence, and in stress-induced reinstatements during prolonged abstinence. Altogether, these effects are involved in the development of dependence (Silberman et al. 2009).

CONCLUSION

Neuroadaptive changes in several neurotransmitter, neuropeptide and neuroendocrine systems resulting from long-term alcohol consumption are involved in the development and maintenance of alcohol dependence. These changes account for many symptoms observed in the long run in alcohol-dependent individuals. In particular, it has been increasingly recognized that permanent adaptive changes in the reward and stress systems of the brain are strongly associated with the development and maintenance of alcohol dependence and with relapses. The development of novel and effective agents acting on the neuroadaptive changes caused by alcohol in these systems may allow us to make significant advances in the treatment of alcohol dependence.

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