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Epigenetic mechanisms of alcoholism and stress-related disorders

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ABSTRACT

Stress-related disorders, such as anxiety, early life stress, and posttraumatic stress disorder appear to be important factors in promoting alcoholism, as alcohol consumption can temporarily attenuate the negative affective symptoms of these disorders. Several molecules involved in signaling pathways may contribute to the neuroadaptation induced during alcohol dependence and stress disorders, and among these, brain-derived neurotrophic factor (BDNF), corticotropin releasing factor (CRF), neuropeptide Y (NPY) and opioid peptides (i.e., nociceptin and dynorphin) are involved in the interaction of stress and alcohol. In fact, alterations in the expression and function of these molecules have been associated with the pathophysiology of stress-related disorders and alcoholism. In recent years, various studies have focused on the epigenetic mechanisms that regulate chromatin architecture, thereby modifying gene expression. Interestingly, epigenetic modifications in specific brain regions have been shown to be associated with the neurobiology of psychiatric disorders, including alcoholism and stress. In particular, the enzymes responsible for chromatin remodeling (i.e., histone deacetylases and methyltransferases, DNA methyltransferases) have been identified as common molecular mechanisms for the interaction of stress and alcohol and have become promising therapeutic targets to treat or prevent alcoholism and associated emotional disorders.

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1. Introduction

Alcoholism is a chronic, relapsing brain disorder that is characterized by compulsion to seek alcohol, loss of control in limiting alcohol intake, and experiencing a negative emotional state during withdrawal (Koob & Volkow, 2010; Koob, 2014). Genetic and environmental factors interact and appear to be equally important in the development of alcohol addiction (Schuebel, Gitik, Domschke, & Goldman, 2016; Starkman, Sakharkar, & Pandey, 2012). Stress and other psychiatric disorders, such as anxiety and mood disorders, can increase susceptibility to the development of alcohol-use disorder (AUD; Fig. 1). In fact, the presence of stress-related disorders leads subjects to consume alcohol in an attempt to attenuate the negative affective symptoms seen during addiction (Fig. 1; Becker, 2012; Bolton, Robinson, & Sareen, 2009; Kushner, Abrams, & Borchardt, 2000).

Several adverse life events have the ability to either initiate or exacerbate AUD. For example, it has been demonstrated that exposure to early life stress (ELS) and other common forms of stress, such as acute or chronic stress and posttraumatic stress disorder (PTSD), are predictive factors of AUD (Enoch, 2011; Müller et al., 2015; Sinha, 2007). ELS can promote alterations in the hypothalamic-pituitary-adrenal (HPA) axis, and lead to changes in brain morphology and gene expression of the mesolimbic reward pathway, all of which are implicated in the development of alcohol addiction (Enoch, 2011). Furthermore, negative affective states, such as anxiety and depression, are often comorbid with AUD (Koob, 2014; Shorter, Hsieh, & Kosten, 2015). In this regard, it has been reported that in the United States almost 1 in 2 patients suffering with PTSD also has a diagnosis of AUD (Pietrzak, Goldstein, Southwick, & Grant, 2011).

Alcohol exposure can affect both the brain reward and stress systems (Koob & Le Moal, 2001; Koob & Volkow, 2010). The mesocorticolimbic dopamine system has been implicated in the acute reinforcing effect of several drugs of abuse, including alcohol. Furthermore, neuroadaptations produced in the HPA axis and extrahypothalamic brain stress systems due to chronic ethanol exposure are involved in the withdrawal/negative affect state of alcoholism (Koob, 2013, 2014). In particular, several studies report

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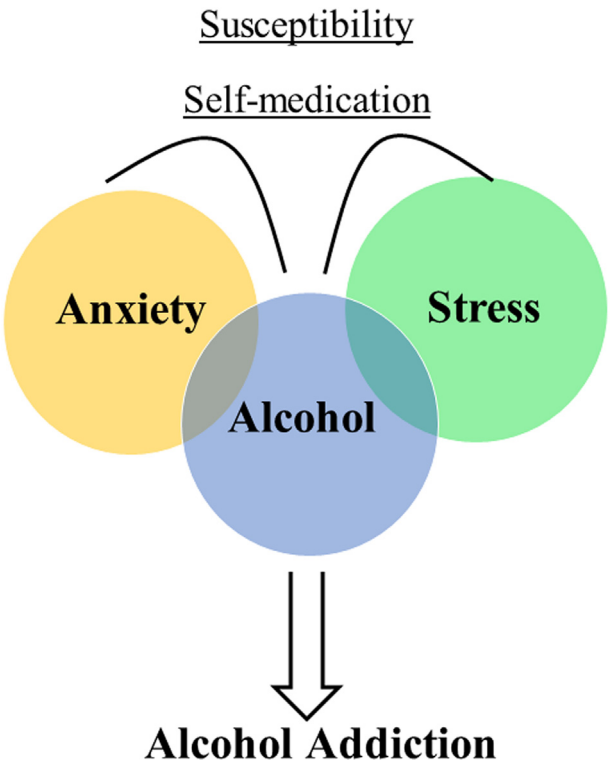

Fig. 1. Relationship among stress, anxiety, and alcohol consumption. Stress and other psychiatric disorders, such as anxiety, can increase the susceptibility to develop alcohol addiction, as subjects consume alcohol in an attempt to self-medicate and attenuate the negative symptoms of mood disorders.

that neurobiological changes in the extended amygdala are critical for the interaction between alcohol addiction and stress-related disorders such as anxiety (Koob, 2008; Koob & Volkow, 2010; Pandey, 2003, 2004). In fact, both stress and addiction can induce similar epigenetic modifications underlying changes in neurochemical pathways and synaptic plasticity in various structures of the extended amygdala, suggesting a common link between alcoholism and stress-related disorders (Cadet, 2016; Moonat & Pandey, 2012; Schuebel et al., 2016; Spanagel, Noori, & Heilig, 2014; Stamatakis et al., 2014).

Modifications in the epigenome regulate gene expression affecting neuronal differentiation, maturation, and plasticity (Karpova, Sales, & Joca, 2016; Murrell, Rakyan, & Beck, 2005). The term "epigenetic" refers to chemical modifications of the DNA and histone proteins around which the DNA is wrapped (Holliday, 2006). Together, the DNA-protein complex is known as chromatin. Therefore, chemical alterations contribute to regulating the chromatin state, making it more or less accessible to transcription factors (Kouzarides, 2007). Histone chemical modifications occur mainly at lysine (K) amino acid residues located in the tails of histones 3 and 4 (H3 and H4). However, other histones, such as H2A and H2B, can be modified as well. Covalent alterations include acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, citrullination, and ADP-ribosylation, and modulate the chromatin structure differently (Kouzarides, 2007; Krishnan, Sakharkar, Teppen, Berkel, & Pandey, 2014). Among these, histone acetylation and methylation are the most studied chemical modifications. For example, histone lysine acetylation is associated with the transcriptionally active state of the chromatin and is regulated by two classes of enzymes; histone acetyltransferases (HATs) and histone deacetylases (HDACs), which add and remove acetyl groups, respectively (Kouzarides, 2007; Strahl & Allis, 2000). Based on the lysine residue targeted, the addition of methyl groups seems to have different meanings with respect to transcription. For instance, the mono- and tri-methylation of lysine 4 on histone 3 (H3K4) is related to gene activation, whereas di- and tri-methylation of H3K9 and H3K27 are considered repressive markers. Interestingly, the mono-methylation of H3K9 and H3K27 modulates gene transcription in an opposite way compared to di- and tri-methylation of these same residues, suggesting that the valence of modifications is also important in regulating the chromatin structure (Kouzarides, 2007; Strahl & Allis, 2000). Epigenetic alterations have been observed during alcohol dependence (Krishnan et al., 2014; Starkman et al., 2012), in several psychiatric disorders (Guidotti, Dong, Tueting, & Grayson, 2014; Jawahar, Murgatroyd, Harrison, & Baune, 2015; Renthal et al., 2007), and in animal models of alcoholism exhibiting emotional disorders, such as anxiety and stress (Cadet, 2016; Moonat & Pandey, 2012).

Besides histone modifications, DNA methylation is a common epigenetic alteration able to affect the chromatin structure (Holliday, 2006). DNA methylation is represented by the addition of a methyl group to the DNA sequence, in particular to the cytosine nucleotides, and is regulated by DNA methyltransferases (DNMTs). When DNA is methylated, chromatin condenses and the transcription complex will not be able to bind DNA, thus silencing the gene expression (Klose & Bird, 2006). Moreover, methyl-CpG binding domain proteins (MBDs) can recognize portions of the DNA sequence enriched with methylated cytosine and guanidine nucleotides (CpG). In turn, these proteins recruit enzymes responsible for further epigenetic alterations that contribute to the condensed state of the chromatin (Boyes & Bird, 1991; Nan et al., 1998). Alcohol, as well as stress, can lead to epigenetic modifications that may be associated with synaptic remodeling and behavioral phenotypes such as anxiety and depression (Moonat & Pandey, 2012). This review aims to summarize recent findings on the epigenetic mechanisms regulating gene expression alterations during alcoholism and stress. First, we will provide an overview of the molecules regulating synaptic plasticity that are known to be related to both alcohol dependence and stress disorders, and then discuss their regulation by epigenetic mechanisms, particularly histone acetylation and methylation and DNA methylation, underlying these disorders (Figs. 2 and 3).

2. Common molecules of alcohol addiction and stress

Several genes are involved in the neuroadaptation mechanisms induced by both alcohol dependence and stress disorders (Spanagel et al., 2014). As mentioned above, addictive processes involve both the brain reward and stress systems (Koob, 2013, 2014). Despite the fact that it is known that alcohol dependence and stress-related disorders share similar neuronal pathways, a full characterization of the mechanisms regulating the activity of genes (i.e., epigenetic mechanisms) is still emerging, adding layers of molecular complexity to the regulation of their function.

Approximately 20 years ago, Koob and colleagues proposed an elegant "allostatic theory" for alcohol addiction, in which prolonged and excessive alcohol exposure is able to produce adaptive changes in brain function, resulting in a deviation of the regulatory system from its homeostatic level (Koob & Le Moal, 1997, 2001; Koob, 2003; Roberts, Heyser, Cole, Griffin, & Koob, 2000). Positive and negative reinforcement seem to play an important role in this allostatic process, as well as the recruitment of the brain stress system (Koob, 2003). Several neurotransmitters are involved in mediating stress processes, including corticotropin-releasing factor (CRF), dynorphin (DYN) and its receptor (the κ opioid [KOP]