Role of Corticotrophin-Releasing Factor in Alcohol Dependence
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Introduction

The search for molecular mechanisms that contribute to the initiation and maintenance of alcohol addictive processes has become a major focus of the neuroscience of alcoholism. Both genetic and environmental factors are known to contribute in the individual’s susceptibility to alcohol dependence or alcoholism. One of the most relevant environmental risk factors for alcoholism is stress and the Corticotrophin-Releasing Factor (CRF) plays a central role in the modulation of the stress response. Hence, the following review aims:

• To examine the role of CRF and its receptor CRF₁ in the etiology and maintenance of alcohol dependence.
• To search human polymorphisms in the CRF system involved in genetic susceptibility to become an alcoholic.
• To study the potential power of the CRF system as a target to treat alcoholic patients.

Conceptual framework: alcohol addiction

Alcohol addiction is a chronic relapsing disorder characterized by a compulsion to seek and take alcohol, loss of control in limited intake and withdrawal syndrome in the absence of the drug.

Three recurrent and cyclical phases are commonly seen: binges/intoxication, withdrawal/negative affect and preoccupation/anticipation phase.

Figure 1. Alcohol abuse primarily disrupts the brain reward and stress systems and causes a shift from homeostasis to an allostatic state, the post dependent state. Figure 2. There is a progression from positive reinforcement like behaviour and the escalated use of alcohol during the development of alcohol dependence (Koob GF, 2013).

CRF signaling

In terms of addiction, CRF is considered a pro-stress and anti-reward polypeptide.

Hypothalamic CRF-positive neurons mediate endocrine stress responses through activation of pituitary CRF receptors, whereas the behavioral stress responses are largely mediated by extrahypothalamic CRF receptors primarily located in the amygdala and BNST.

Figure 3. CRF drives the Hypothalamic-Pituitary Adrenal (HPA) axis by acting to release ACTH in the portal system of the pituitary. Moreover, CRF activates the sympathetic system through actions in the brainstem and mediates arousal and behavioral responses to stressors through actions in the amygdala, other forebrain regions, and central midbrain such as the ventral tegmental area (Koob GF, 2010).

Figure 4. The first contribution of CRF to alcohol dependence is the HPA axis activation, which is involved in the dysphoric effects of alcohol withdrawal. Figure 5. Systemic administration of CRF₁ antagonists (such as OX21015) attenuates both the heightened anxiety-like behaviour and the escalated alcohol self-administration of dependent rodents at doses that do not alter intake of non-dependent animals (Heilig et al., 2005).

CRF signaling in alcohol-dependence

Alcohol, as most of the stressors, can activate HPA axes. This activation is CRF-dependent. Specifically, alcohol acts directly on CRF-positive neurons of the PVN of the hypothalamus. As alcohol consumption continues, the HPA axis becomes blunted, but the repeated exposure of the brain to high levels of glucocorticoids can “sensitize” the extra-hypothalamic CRF systems, which are involved in the dysphoric effects of alcohol withdrawal.

CRF release, as well as CRF₁ receptor levels, are increased in the amygdala and drive excessive alcohol self-administration in dependent rodents, both during withdrawal and long after withdrawal has subsided.

As GABA and CRF are coloculated in about half of the mostly GABAergic neurons in the CeA, some data have implicated the GABA system in the upregulation of CRF system within the amygdala.

CRF involves in genetic susceptibility to become alcohol dependent

Alcohol dependence has an estimated heritability of 50-60%, with many susceptibility loci contributing individually to a small degree. Supporting the translational relevance of the genetic results in animal models, polymorphisms in CRF₁ receptor gene molecules have also been studied and associated with alcohol use-phenotypes.

Genetic association of CRF system polymorphisms to human alcohol phenotypes

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<th>Gene</th>
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Genetic association of CRF system polymorphisms to human alcohol phenotypes

Gene/locus: CRH polymorphism

Case-control association of CRH polymorphism to alcohol dependence

GFRα1 gene encodes CRF₁ receptor and Gnrh gene encodes CRH-binding protein, which mediate the ability of CRF to interact with its receptor.

CRF system as a major target to treat alcohol dependence

Blocking hyperactive signalling at CRF₁ in individuals with a story of dependence or innate susceptibility to alcohol dependence could inhibit heavy drinking and reduce the risk of relapse, the two main therapeutic objectives in alcoholism treatment.

CRF₁ antagonists decrease alcohol self-administration in dependent rodents at doses that do not alter intake of non-dependent animals (Heilig et al., 2005).

Potentiating nociocisin-CRF or neuropeptide Y-CRF interactions may also emerge as possible treatments of alcohol dependence due to the ability of these two anti-stress peptides to prevent and reverse pre-synaptic GABA release induced by CRF in CeA.

References

Koob GF. Addiction is a Reward/Deficit and Stress Surfeit Disorder. Front Psychiatry 2013;4:72.
Koob GF. The role of CRF and CRF-related peptides is the dark side of addiction. Brain Res 2012;1343:1-14.

Methodology

Bibliographic research:

• Search for scientific literature on Pubmed database.
• From November 2013 to March 2014.
• Keywords used: “CRF”, “addiction”, “alcohol dependence” or a combination of them.
• Papers and reviews selected according to the journal impact factor and the date of publication.

• Positive reinforcement: euphoric effects of alcohol that lead to the promotion of its consumption, primarily lead by the dopaminergic mesolimbic pathway.

• Negative reinforcement: development of anxiety, depression and other dopaminergic dysfunctions which can be caused by the abrupt cessation of alcohol consumption.

Conclusions

• The development of alcohol dependence is associated with neuroadaptive changes at functional, neurochemical and structural levels.

• CRF contributes to alcohol dependence via:
  - Genetic results in animal models suggest that CRF contributes to a stress component that leads from homeostasis to an allostatic state.
  - This component that drives from homeostasis to an allostatic state (negative reinforcement) is characterized by a compulsion to seek and take alcohol, loss of control in limited intake and withdrawal/negative affect and preoccupation/anticipation phase.

• CRF, the amygdala and BNST.
• CRF activates the sympathetic system through actions in the brainstem and mediates arousal and behavioral responses to stressors through actions in the amygdala, other forebrain regions, and central midbrain such as the ventral tegmental area (Koob GF, 2010).

• Alcohol abuse primarily disrupts the brain reward and stress systems and causes a shift from homeostasis to an allostatic state, the post dependent state, the term used to refer the sum of adaptive and between-system neuromodulations that are induced as an individual becomes dependent on alcohol and remain even in the absence of the drug.

• Hypothalamic CRF-positive neurons mediate endocrine stress responses through activation of pituitary CRF₁ receptors, whereas the behavioral stress responses are largely mediated by extrahypothalamic CRF₁ receptors primarily located in the amygdala and BNST.

• The search for molecular mechanisms that contribute to the initiation and maintenance of alcohol addictive processes has become a major focus of the neuroscience of alcoholism. Both genetic and environmental factors are known to contribute in the individual’s susceptibility to alcohol dependence or alcoholism. One of the most relevant environmental risk factors for alcoholism is stress and the Corticotrophin-Releasing Factor (CRF) plays a central role in the modulation of the stress response. Hence, the following review aims:
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