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 CRF_1 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.

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.

Conceptual framework: alcohol addiction

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

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

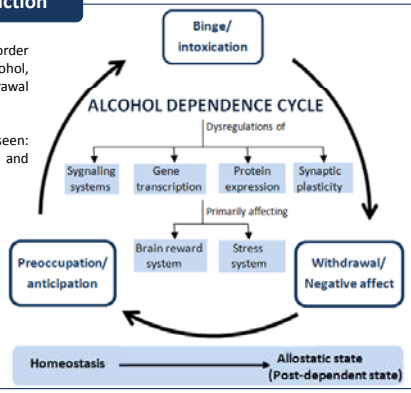


Figure 1. Alcohol abuse primarily disrupts the brain reward and stress systems and causes a shift from homeostasis to an allostatic state, the post dependent-state, term used to reflect the sum of within and between-system neuroadaptations that are induced as an individual becomes dependent on alcohol and remain even in the absence of the drug.

During the development of alcoholism two major psychiatric states can be distinguished: the positive and the negative reinforcement.

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

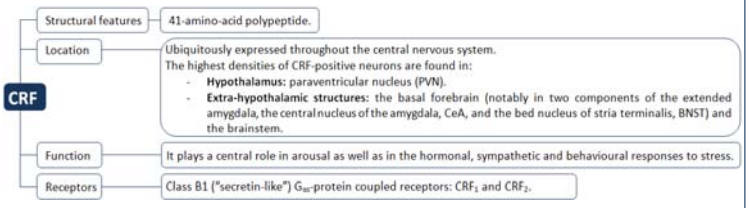
Negative reinforcement: development of anxiety, depression and other dysphoric psychiatric sequelae which can be caused by the abrupt cessation of alcohol consumption

The **"kindling"/stress hypothesis** of alcoholism proposes that the adaptive changes that accompany an escalating abuse of alcohol interact with stress to maintain the pathology of alcoholism.

Figure 2. There is a progression from positive reinforcement to negative reinforcement 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** trough activation of **pituitary CRF_1 receptors,** whereas the **behavioural stress responses** are largely mediated by **extra-hypothalamic CRF_1 receptors** primarily located in the amygdala and BNST.

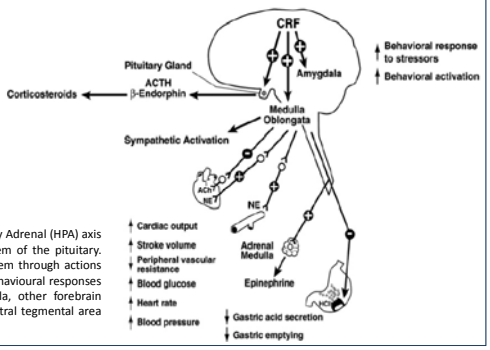


Figure 3. CRF drives the Hypothalamic-Pituitary Adrenal (HPA) axis by acting to release ACTH in the portal system of the pituitary. Moreover, CRF activates the sympathetic system through actions in the brainstem and mediates arousal and behavioural responses to stressors through actions in the amygdala,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

CRF signaling in alcohol-dependence

Alcohol, as most of the stressors, **can activate HPA axis. 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 CRF_1 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 colocalized 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.

Positive reinforcement

Negative reinforcement

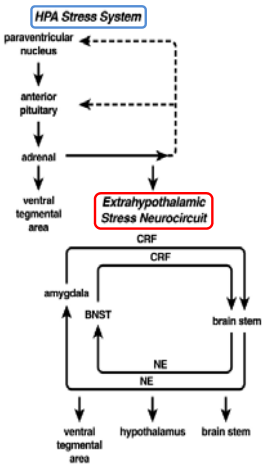


Figure 4. The first contribution of CRF to alcohol dependence is the HPA axis activation, being glucocorticoids linked both to facilitation of reward (positive reinforcement) and to sensitization of extra-hypothalamic CRF systems, which contributes to a stress component that drives from homeostasis to an allostatic state (negative reinforcement) *(Koob GF, 2010)*.

CRF involved 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 human CRF system molecules have also been studied and associated with alcohol use phenotypes.

Genetic association of CRF system polymorphisms to human alcohol phenotypes

Gene	SNP	Allele	Phenotype
Crhr1	rs1876831	C allele (homozygous)	Greater future drinking and earlier onset of drinking in an interactive relation to stress history
Crhr1	rs1876831	H2 haplotype (minor allele, homozygous)	Protected against early child abuse-associated increases in alcohol consumption and dependence
Crhr1	rs242938	A allele (homozygous)	Greater alcohol drinking when exposed to stress
Crhbp	rs100055255	-	Severity of stress imagery-induced alcoholic craving and dysphoria
Crhbp	rs3811939	-	Comorbid alcohol use disorder in patients with schizophrenia
Crhr1	rs110402		Elevated CRF_1/CRF-BP mRNA ratio in mononuclear blood cells

Crhr1 gene encodes CRF_1 receptor and Crhbp gene encodes CRF-binding protein, which moderates the ability of CRF to interact with its receptor.

CRF system as a major target to treat alcohol dependence

Blocking hyperactive signalling at CRF_1 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.

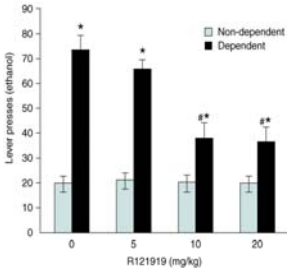


Figure 5. Systemic administration of **CRF_1 antagonists** (such as R121919) attenuates both the heightened anxiety-like behaviour and the escalated alcohol self-administration of dependent rodents at doses that do not alter intake of non-dependent animals *(Heilig M et al., 2007)*.

Potentiate **nociceptin-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.

Conclusions

- The development of alcohol dependence is associated with neuroadaptive changes at functional, neurochemical and structural levels.
- CRF contributes to alcohol dependence via:
  - HPA axis activation (positive reinforcement).
  - Extra-hypothalamic CRF system recruitment primarily within the amygdala (negative reinforcement), which contributes to a stress component that leads from homeostasis to an allostatic state.
- Targeting CRF signalling is emerging as a key approach to treat alcoholic patients for whom, due to experiential or genetic reasons, stress and negative reinforcement play a major role in their alcohol dependence cycle.

References

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