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:

1. To examine the role of CRF and its receptor CRF1 in the etiology and maintenance of alcohol dependence.
2. 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: binge/intoxication, withdrawal/negative affect and preoccupation/anticipation phase.

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 extra-hypothalamic CRF receptors primarily located in the amygdala and BNST.

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

Genetic association of CRF system polymorphisms to human alcohol phenotypes

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Allele</th>
<th>Polymorphism</th>
<th>Functional significance</th>
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</thead>
<tbody>
<tr>
<td>OXTR</td>
<td>rs19277</td>
<td>C/T</td>
<td>Exon 3 deletion</td>
<td>Decreased AVP binding and dysregulated stress response</td>
</tr>
<tr>
<td>CRF1</td>
<td>rs102473</td>
<td>C/T</td>
<td>Decreased alpha activity</td>
<td></td>
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</tbody>
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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.

Methodology

References