Published in final edited form as:
Biol Psychiatry. 2008 January 15; 63(2): 137–138.

Alcoholism, CRF and Molecular Genetic Allostasis

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Alcoholism, or Substance Dependence on alcohol, is a chronic relapsing disorder characterized by loss of control over intake (compulsive use) and the emergence of a negative emotional state during abstinence. Stress long has been considered a key element in the etiology of alcohol dependence, yet the exact mechanisms by which stress exacerbates and interacts with alcohol dependence have remained elusive. Recent work on the brain neurotransmitter corticotropin-releasing factor (CRF) [see footnote on nomenclature] has provided new insights into the stress-alcohol dependence interaction. Two papers in this issue of *Biological Psychiatry* (1,2) provide an exciting molecular mechanism for this interaction that may have heuristic value for future translational advances.

CRF is a 41 amino acid polypeptide with a wide distribution throughout the brain but high concentrations of cell bodies in the paraventricular nucleus of the hypothalamus, the basal forebrain (notably the amygdala and bed nucleus of the stria terminalis) and the brainstem. Central administration of CRF mimics the behavioral response to activation and stress in rodents, and administration of competitive CRF receptor antagonists generally have anti-stress effects (3). Two major CRF receptors have been identified, with CRF_1 receptor activation associated with increased stress responsiveness and CRF_2 receptor activation associated with decreases in feeding and decreased stress responsiveness, although there is some controversy in this area depending on the location of the CRF_2 receptors in question.

In the current issue of *Biological Psychiatry*, Sommer et al. (1) studied rats using an animal model of alcohol dependence and showed that CRF and expression of the *crh1* transcript within the amygdala are upregulated in postdependent animals. Animals trained to self-administer alcohol in a two-bottle, free-choice procedure and exposed to intermittent ethanol vapors to induce dependence showed a doubling of ethanol intake and increased sensitivity to stress which was reversed by a CRF receptor antagonist. CRF mRNA was increased in the central nucleus of the amygdala, and *crh1* transcript expression was increased in the basolateral amygdala, with a concomitant decrease in *crh2* transcript expression in the basolateral amygdala.

These new results fit well with a burgeoning dataset implicating an increase in extrahypothalamic CRF function with the excessive drinking associated with alcohol

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[1]The correct International Union of Pharmacology nomenclature for the peptide corticotropin-releasing factor is CRF, though some clinicians persist in terming it corticotropin-releasing “hormone.” The correct Human Genome Organisation gene classification is *crh1* and *crh2*. This commentary adheres to these standard, accepted terminologies.

Financial Disclosures
The author declares he has no real or perceived financial conflicts of interest in the preparation of this manuscript.

dependence in animal models. Rats with either a genetic predisposition for anxiety-like behavior and excessive drinking, or with a history of dependence, show decreases in drinking with administration of CRF_1 antagonists administered systemically (4,5). CRF antagonists also block stress-induced reinstatement to alcohol and other drugs of abuse (6). These effects have been localized to the region of the central nucleus of the amygdala; local injection of a CRF_1/CRF_2 antagonist produced similar effects (7). A CRF_2 agonist microinjected into the central nucleus of the amygdala also had a similar effect, consistent with the opposing actions on *crh1* and *crh2* gene transcripts in the present Sommer results. Thus, it appears that not only is there increased expression of CRF neuropeptide activity in the amygdala in dependent rats, but also an increase in CRF_1 receptor activity and a concomitant decrease in CRF_2 receptor activity. Another innovative aspect of the Sommer results is that these molecular and behavioral effects persist into protracted abstinence, supporting the data from earlier pharmacological studies (8). Altogether, these results demonstrate numerous targets for treatment of alcohol dependence and open a new vista for addiction treatment in general.

In Blomeyer et al. (2) in the current issue, an ongoing cohort from the Mannheim Study of Children at Risk were genotyped for two alleles of the CRF_1 receptor. Results showed that individuals homozygous for the C allele of one single nucleotide polymorphism of the CRF_1 receptor (rs1876831) drank higher maximum amounts of alcohol per occasion and had greater lifetime rates of heavy drinking but only in relation to negative life events. No similar gene × environment interactions were observed for the other *crh1* allele (rs242938). These results are consistent with the observation that the genetically selected Marchigian-Sardinian alcohol preferring (msP) rat line has high alcohol preference with increased behavioral responsivity to stress and an innate upregulation of the *crh1* transcript in several brain regions. Both the single nucleotide polymorphism observed in Marchigian rats and the one in the human study were in non-coding regions of the gene that can potentially influence transcription, with the former in a promoter region and the latter in an intron. Together these results suggest the exciting possibility that certain single nucleotide polymorphisms in the human population may predict vulnerability to certain subtypes of excessive drinking syndromes and, perhaps somewhat more mundane but equally provocative, may predict responsiveness to the use of CRF receptor antagonists for the treatment of alcoholism. Of course, as the authors noted, some caution must be considered given the relatively small sample size for a genetic association study. Replication of this association with attention to defined phenotypes will be an important future pursuit.

Finally, the two present studies have provided molecular insight into a hypothesized conceptual framework for addiction that, in a sense, is reorienting neurobiology of addiction field. Addiction, and alcoholism in particular, has been hypothesized to reflect a break with homeostasis that represents a chronic change in reward set point that results in the emergence of a negative emotional state during abstinence. Continued drug taking to “self-medicate” the elevation in reward set point produces short-term relief but drives the set point further from homeostasis. Such a physiological change represents a classic allostatic mechanism (9) and has been hypothesized to be driven by not only decreases in reward neurotransmission (e.g., the action of opioid peptides or dopamine), but also by recruitment of brain stress systems such as CRF, neuropeptide Y, and norepinephrine (10). Most remarkable about the two studies in this issue of *Biological Psychiatry* is that a molecular target has been identified supporting the dark (stress) side of this conceptual framework that can be influenced by both the genetic makeup of the organism (“being born that way”) and by excessive drug taking (environmental insult) resulting in a possible gene × environment interaction. The implications of the CRF story for the treatment, diagnosis, and prevention of alcoholism are profound.

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