

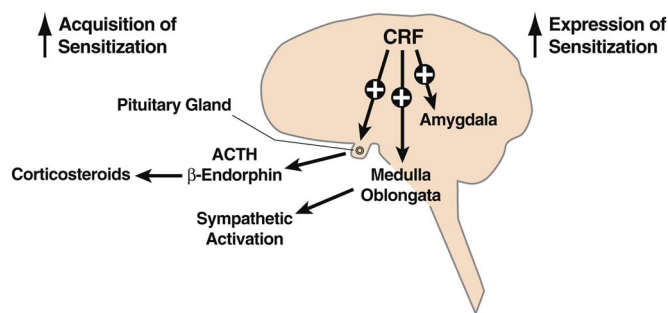
# Corticotropin-releasing factor, neuroplasticity (sensitization), and alcoholism

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**S**ensitization is a ubiquitous biological phenomenon that has a role in the neuroadaptation of many different functions, from learning and memory to stress responsiveness. Historically, a specific form of sensitization termed psychomotor sensitization (mistermed in my view as “behavioral sensitization”) is induced by repeated administration of drugs of abuse and has been linked to the neuroadaptive changes associated with increased drug-seeking behavior associated with addiction. Largely observed with psychostimulant drugs, psychomotor sensitization has been considered a model for the increased incentive salience contributing to the increased motivation to seek drugs in individuals with a previous history of drug use. Psychomotor sensitization also has been observed with repeated administration of ethanol in mice, but not in rats, and psychomotor sensitization to ethanol also has been linked to activation of both the hypothalamic-pituitary-adrenal (HPA) system and extrahypothalamic brain stress systems (Fig. 1). However, the exact mechanism for stress-induced sensitization has remained elusive.

Corticotropin-releasing factor (CRF) is a 41-amino-acid polypeptide that controls hormonal, sympathetic, and behavioral responses to stressors (1). CRF in the paraventricular nucleus of the hypothalamus controls the pituitary adrenal response to stress (2). Other peptides with structural homology to CRF, the urocortin family of peptides (urocortins 1, 2, and 3), also modulate behavioral and autonomic responses to stress and may have roles in other homeostatic functions, such as appetite. Substantial CRF- and urocortin 1-like immunoreactivity is present in the basal forebrain and autonomic midbrain and hindbrain nuclei. The endogenous selective CRF<sub>2</sub> agonists—the type 2 urocortins—include urocortin 2 and urocortin 3 and have neuroanatomical distributions that are distinct from those of CRF and urocortin 1, notably in hypothalamic nuclei. Two CRF receptors have been identified, CRF<sub>1</sub> and CRF<sub>2</sub>. The CRF<sub>1</sub> receptor has abundant, widespread expression in the brain that overlaps significantly with the distribution of CRF and urocortin 1. The CRF<sub>2(a)</sub> receptor is local-



**Fig. 1.** CNS actions relevant to alcohol-induced psychomotor sensitization. CRF is a neuropeptide in the brain that controls autonomic, hormonal, and behavioral responses to stressors. New data show that CRF also has a role in the neuroplasticity associated with addiction. The present study extends the role of CRF to the psychomotor sensitization associated with repeated administration of alcohol. The hypothalamic-pituitary-adrenal responses produced by CRF appear to be more involved in the *acquisition* of sensitization, whereas extrahypothalamic CRF systems, likely to be in structures such as the amygdala, appear to be important for the *expression* of sensitization. These results, combined with previous studies on the role of CRF in the development of alcohol dependence, suggest a key role for CRF in the neuroplasticity associated with addiction.

ized neuronally in brain areas that are distinct from those of the CRF/urocortin 1/CRF<sub>1</sub> receptor system and overlaps significantly with the distribution of the type 2 urocortins. CRF and urocortin 1 bind to both the CRF<sub>1</sub> and the CRF<sub>2</sub> receptors. Type 2 urocortins also differ from urocortin 1 and CRF with respect to their high functional selectivity for the CRF<sub>2</sub> receptor.

In this issue of PNAS, Pastor *et al.* (3) show that mice lacking CRF<sub>1</sub> and CRF<sub>2</sub> receptors (double-constitutive knockouts) do not show psychomotor sensitization to ethanol. Further analysis revealed that knockout of the CRF<sub>1</sub> receptor also blocked the psychomotor sensitization to ethanol. Administration of a CRF<sub>1</sub> receptor antagonist attenuated the acquisition and blocked the expression of ethanol-induced psychomotor sensitization. Knockout of the CRF<sub>2</sub> receptor, knockout of urocortin-1, and blockade of glucocorticoid receptors failed to block expression of ethanol-induced psychomotor sensitization. The authors hypothesize that CRF may have a key role in ethanol-induced psychomotor sensitization in acquisition (via activation of the HPA axis) and in expression (via the extrahypothalamic CRF stress system).

These results provide new insights into the role of the brain and pituitary stress systems in the neuroadaptations associated with chronic administration of drugs of abuse and alcohol. In partic-

ular, the study provides an elegant demonstration of the power of the molecular genetic approach in solving a problem and provides novel directions for therapeutic intervention in a chronic relapsing disorder. Previous studies using pharmacological approaches showed that CRF could facilitate psychomotor sensitization either via the HPA axis (4) or via extrahypothalamic sites (5–7). However, the specific CRF-like peptide, the specific CRF receptor, and the specific functional role had not been identified. Here, Pastor *et al.* (3) demonstrates unequivocally that the neuropeptide must be CRF and the receptor must be CRF<sub>1</sub>. Positive results with knockout mice provide a powerful means of testing a hypothesis, and one must employ a tortured compensatory logic to argue the contrary.

A parallel “sensitization” phenomenon that is important for alcohol dependence is hypothesized to involve neuroplasticity in the activation of both HPA and extrahypothalamic CRF systems. Progressive changes in the HPA axis are observed during the transition from acute administration to chronic administration of drugs of abuse.

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The author declares no conflict of interest.

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