Project 5: Stress, HPA Axis Dysfunction and Relapse in Alcoholism

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The hypothalamic-pituitary-adrenal (HPA) system is posited as a key biologic link in stress-induced relapse. The HPA axis provides a regulatory feedback network between the brain and the body's behavioral and physiologic responses to stress, recovery, and adaptation. Both trauma and chronic alcohol use produce persistent disturbances in the HPA response to stress. The chronic use of alcohol may also impair the stress-induced release of neurosteroids, compounds that directly modulate GABAergic activity. Thus, altered glucocorticoid and neurosteroid responsiveness during abstinence may impair the central nervous system's ability to mount an appropriate response to environmental stressors, heightening the probability of relapse. However, the relationship between stress, relapse, and HPA axis disturbances remains tentative. In the proposed study, the investigators will expand their extensive work on stress, HPA axis disturbances, and substance use disorders to directly assess the contribution of trauma, stress, and alcohol use upon pituitary-adrenocortical functioning in alcohol dependence. The relative contribution of adrenocortical disruption and episodic stress to prospective drinking behaviors will then be determined.

Hypothesis: We hypothesize (1) that lifetime trauma, recent stress, and chronic alcohol use will additively contribute to HPA axis disruption, (2) alterations in glucocorticoid and neurosteroid release, moderated by episodic stress, will predict a return to drinking. Genotyping and linkage analysis will also be obtained. Methods: One hundred treatment-seeking, one-month abstinent, alcohol-dependent subjects will be studied. Standardized assessments will be used to assess childhood and adult trauma as well as recent (six months) stress. Pituitary-adrenal (including ACTH, cortisol, and neurosteroids) responses to both neuroendocrine [ovine corticotropin releasing hormone (oCRH), cosyntropin, and dexamethasone] and experiential (public speaking) challenges will be measured. Drinking behavior and episodic stress will be prospectively assessed for six months following neuroendocrine assessment.

Significance: If our hypotheses are supported, a definitive connection between previous trauma, biological stress response mechanisms, and ongoing stress upon prospective drinking behavior will be demonstrated. The identification of a specific biologic mechanism that underlies this association will provide a fertile framework for the development of targeted pharmacological interventions to decrease relapse in this vulnerable population. In addition, elucidating the concurrent contributions of stress-response biologic systems and externals stressors will provide the therapist and patient with a constellation of specific risk factors for focused treatment.