BEHAVIORAL PHARMACOLOGY OF STRESS:

FOCUS ON CNS CORTICOTROPIN-RELEASING FACTOR

George F. Koob, Karen Thatcher-Briton, Abdelouahhab Tazi, and Michel Le Moal

1. Dept of Basic and Clinical Research, Scripps Clinic and Research Foundation, 10666 North Torrey Pines Road, La Jolla, CA 92037
2. Psychobiologie des Comportements Adaptatifs, INSERM Unite-254, Rue Camille St. Saens, 33078 Bordeaux, France
3. Dept of Psychiatry, San Diego Veterans Administration Medical Center & UCSD, Sch. of Med., La Jolla, CA 92161

INTRODUCTION

Stress is a hypothetical construct which has been extensively studied for the past three decades at different levels of analysis. It is a ubiquitous concept in physiology, psychology and medicine that often eludes precise definition. Hans Selye conceptualized stress as "a nonspecific response to any demand upon the body (usually, but not always, noxious), or anything which causes an alteration of homeostatic processes (1)". A more modern version of this definition, taken from Burchfield (2) has emphasized the concept of psychological homeostasis or the maintenance of a normal mood state at rest. All emotions then are changes from this state. Indeed, as Dr. John Mason showed so elegantly, without emotional changes accompanying a stressor, the stress response is minimal (3). Thus commonly accepted physiological "stressors" (heat, exercise, hunger) do not elicit a "stress response" when they are presented in a way that eliminates their psychological (emotional) effects (fear, conflict, uncertainty, frustration).

The importance of psychological variables in the stress response emphasizes the need for a neurobiological substrate to process the interaction of sensory stimuli with the ultimate psychoendocrine stress response. It is presumably through central nervous system pathways of the limbic system to the hypothalamus that the stress response is triggered by psychological factors. There is, however, an alternate means by which behavioral or physiological responses to stress or anxiety might be mediated by neurohormones classically involved in stress. That is via a direct neurotropic action in the central nervous system.

The sequencing and subsequent synthesis of corticotropin releasing factor (CRF) (4) has provided a direct opportunity to study the central control of the HPA axis, and numerous studies support the hypothesis that
CRF is the critical mediator of stress-induced changes in the pituitary adrenocortical response to stress. Although CRF was originally isolated and characterized on the basis of its ability to induce ACTH release, it is now known to exert a surprisingly broad spectrum of action in the central nervous system. CRF appears to act within the brain as a mediator of certain autonomic nervous system, visceral and behavioral actions independent of its action on the pituitary. These effects are not abolished by hypophysectomy or adrenalectomy. These actions, in concert with the wide anatomical distribution of CRF in brain regions outside the areas hypothalamic-pituitary-adrenal axis (5), provide a tenable basis for hypothesizing that CRF may simultaneously activate and coordinate neuroendocrine, autonomic circulatory, metabolic and behavioral responses to stressful stimuli.

**CRF and Central Nervous System Arousal**

Corticotropin releasing factor CRF has central nervous system activating properties when administered directly into the central nervous system. Intraventricular (ICV) injection of CRF produces elevation of plasma epinephrine, norepinephrine and glucose (6,7). These effects are reproducible in hypophysectomized animals but are abolished by ganglionic blocking agents (8) suggesting an involvement of the sympathetic autonomic system. CRF injected ICV also produces a profound dose-dependent activation of the electroencephalogram (EEG) (9). Doses of 0.015 to 0.15 nmol produced a long lasting activation of EEG, and after a 2-hour delay some interictal spikes occurred in the amygdala and hippocampus. Higher doses (1.5-3.75 nmol) were characterized by consistent amygdala interictal spikes and after discharges and, after a delay of 4 to 7 hours, some motor seizures. These seizures developed over time in a manner not unlike those produced by amygdala "kindling" paradigms. At the cellular level, CRF produces increases in the firing frequencies of cells within the locus coeruleus (10) a system thought to be of importance in the mechanisms by which the brain is able to attend selectively to certain novel external events.

The autonomic and electrophysiological activation produced by central administration of CRF is paralleled by a dose-dependent locomotor activation (11,12). These effects appear to be independent of direct mediation by the pituitary-adrenal system since they were observed in hypophysectomized and dexamethasone-treated rats (see figure 1) (13,14,15). Taken together with the fact that this activation is seen only with central administration, these observations suggested that CRF exerted its effects within the central nervous system. Although other peptides such as the endorphins and ACTH have been shown to produce increases in spontaneous behavioral activity. the locomotor activation caused by CRF is not antagonized by the opiate antagonist naloxone, or by low doses of the dopamine receptor antagonist alpha flupenthixol (12). Nor is this activation reversed by 6-hydroxydopamine lesions of the region of the nucleus accumbens, lesions that reverse the locomotor-stimulated effects of indirect sympathomimetics (16). ACTH, itself, injected centrally failed to increase locomotor activity but instead produced an increase in grooming behavior as has been observed by others (17).