
S-16 Post-traumatic Stress Disorder: Evidence for Trauma-induced Brain Dysfunction

S-16-1

Stress systems in the brain: molecules, nuclei and circuits

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While the peripheral endocrine components of the stress-responsive systems are well known, the same cannot be said of the stress axis within the CNS itself. One relay point in brain is now clear – the parvocellular subdivision of the paraventricular nucleus of the hypothalamus (mpPVN). Corticotropin releasing hormone (CRH) containing cells within this nucleus appears to be modulated by circuits responsive to stress. Earlier points in the stress circuit(s) in brain are currently only vaguely evident. We have divided the types of regulatory circuits involved in CNS control of stress into those which *activate* CRH cells and those which *inhibit* them.

Here, data from a series of studies on the *inhibitory arm* of the hypothalamo-pituitary-adrenal axis will be presented. A logical extension of this dichotomy is the presumption that among inhibitory circuits are those which respond to elevated circulating glucocorticoid levels and thereby provide 'negative feedback'. Among the studies discussed will be those involving hippocampus, glucocorticoid receptors, and subiculum connections to the bed nucleus of the stria terminalis and on to the mpPVN. A second set of studies is focused on the circuits which *activate* the PVN. These studies are rather new and take the view that many regions of CNS may be involved, with different areas mediating the responses to different classes of stressors. The ultimate goals of these studies are the identification of the *activation* and *inhibition circuits* and related neurochemistry involved in the control of the brain's response to stress.

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Fear conditioning and extinction: Basic neuronal mechanisms related to PTSD

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Our laboratory investigates neural systems involved in the induction and inhibition of fear and anxiety. Fear is a natural, adaptive response to threatening stimuli which prepares the organism to cope with the provocation. However, high levels of fear or long periods of stress can lead to abnormal, maladaptive behaviors which compromise the ability of the organism to cope with its environment. Our measure of conditioned fear uses the fear-potentiated startle paradigm where acoustic startle amplitude in rats is increased when elicited in the presence of a light previously paired with a shock. Drugs which reduce or increase anxiety in humans selectively reduce or increase fear-potentiated startle in rats.

A large amount of data now indicate that the amygdala is critically involved in fear and stress (cf. Davis, 1992). The natural pattern of behaviors produced by fear or stress can be blocked by lesions of the amygdala and produced by electrical stimulation of the amygdala. Anatomical data indicate that the central nucleus of the amygdala projects directly to hypothalamic and brainstem target areas critically involved in specific signs and symptoms of fear and stress. Lesions of the amygdala completely block fear-potentiated startle and low-level electrical stimulation of the amygdala increases startle. By