Fundamental aspects of hypothalamic-pituitary-adrenal regulation

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The hypothalamic-pituitary-adrenal (HPA) axis orchestrates behavioural and physiological adaptations to disturbance of homeostasis. The following features are discussed:
1. The HPA axis has an ultradian rhythm (about one pulse per hour) resulting in phasic activation of corticotrophin-releasing hormone (CRH) and vasopressin (AVP) release from hypothalamic parvocellular neurons (PVN), pituitary ACTH release and adrenocortical secretion. The pulse generator is located in hypothalamus, but adrenal modulation may occur, as is the case during the circadian corticosterone rhythm. Previous experience and the nature of the stressor are determinants of pulsatility. The pattern rather then the absolute level of stress hormone seems to mediate adaptive HPA functions.
2. Depending on the nature of the stressor different cocktails of ACTH secretagogs are pulsatile released from the PVN. The afferents to PVN are stressor-specific. Sensory stimuli (pain, blood loss, infection, inflammation, hypoglycemia) reach the PVN directly via ascending projections from the brain stem. Psycho-social stimuli involving emotional and cognitive processes require information processing in limbic (amygdala, hippocampus, frontal cortex) structures that modulate trans-synaptically via a GABA-ergic network indirectly the PVN and the HPA axis.
3. Adrenal cortisol and corticosterone (CORT) act in brain stress centers with an enormous diversity depending on stressor context. The rapid CORT modulation of the HPA pulse and associated behaviours occurs through poorly understood non-genomic actions. Genomic CORT actions are mediated by high affinity mineralocorticoid receptors (MR) and lower affinity glucocorticoid receptors (GR) co-localized in limbic neurons. MR controls gene networks underlying behaviours preventing disturbance of homeostasis, while its recovery is facilitated by GR-mediated actions. MR/GR imbalance is thought to cause mal-adaptive responses to HPA activity. This dysregulation may underlie stress-related brain disorders (such as depression) characterized by impaired emotional and cognitive processes, and co-morbid immune, metabolic and cardiovascular diseases in genetically predisposed individuals.

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