Dynamics of neuroendocrine stress response: bistability, timing, and control of hypocortisolism in PTSD

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The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine system that regulates numerous physiological processes. Disruptions in its activity are correlated with stress-related diseases such as post-traumatic stress disorder (PTSD) and major depressive disorder. We characterize "normal" and "diseased" states of the HPA axis as basins of attraction of a dynamical system describing the inhibition of peptide hormones, corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), by circulating glucocorticoids such as cortisol (CORT). Our model includes ultradian oscillations, CRH self-upregulation of CRH release, and distinguishes two components of negative feedback by cortisol on circulating CRH levels: a slow direct suppression of CRH synthesis and a fast indirect effect on CRH release. The slow regulation mechanism mediates external stress-driven transitions between the stable states in novel, intensity, duration, and timing-dependent ways. We find that the timing of traumatic events may be an important factor in determining if and how the hallmarks of depressive disorders will manifest. Our model also suggests a mechanism whereby exposure therapy of stress disorders may act to normalize downstream dysregulation of the HPA axis.