DREADD-ing Stress: Using Chemogenetics to Bypass Variability and Go Right to the Source with CRF Activation

Kristen R. Montgomery, Morgan S. Bridi, Lillian M. Folts, Ruth Marx-Rattner, Hannah C. Zierden, and Tracy L. Bale

High lifetime stress is one of the strongest predictors of neuropsychiatric disease development. Additional environmental and biological factors, including sex, interact with chronic stress to increase risk. Many neuropsychiatric disorders also have sex-biased presentations, with males having increased incidence of autism and schizophrenia and females having elevated risk for PTSD, depression, and anxiety. Understanding how risk factors interact is essential for developing novel treatments. Non-homeostatic stressors are processed by limbic structures that ultimately converge onto the paraventricular nucleus of the hypothalamus (PVN) where activation of corticotropin-releasing factor (CRF) neurons initiates the hypothalamic-pituitary-adrenal (HPA) axis. Current rodent stress models rely on sensory exposures to activate the HPA response; however, the robustness of the stress response varies with the individual animal's perception of the stressor. Here, we tested the hypothesis that chemogenetic activation of CRF neurons mimics the effects of sensory stressors while bypassing the variability of perception. We used the Gq-coupled DREADD receptor hM3Dq to activate CRF neurons by administering the DREADD ligand clozapine-N-oxide (CNO) to CRF-Cre+/hM3Dq+ (DREADD+) mice. To determine if chronic CNO administration induces a chronic stress-like state in DREADD+ animals, we administered CNO daily to male and female DREADD+ and DREADD- mice and monitored physiological changes and behavioral assessments indicative of a chronic stress state. We found that chronic CNO induced weight loss and thymus atrophy and elevated the HPA response to acute restraint stress in DREADD+ males but not females. In contrast, female, but not male, DREADD+ mice had significantly elevated freezing behavior following chronic CNO. These results demonstrate that chronic CRF activation has both sex and region-specific effects that may underlie different vulnerabilities to neuropsychiatric conditions.