The biological response to stress is concerned with the maintenance of homeostasis in the presence of real or perceived challenges. This process requires numerous adaptive responses, involving changes in the central nervous and neuroendocrine systems. When a situation is perceived as stressful, the brain activates many neuronal circuits, linking centers involved in sensory, motor, autonomic, neuroendocrine, cognitive, and emotional functions in order to adapt to the demand. However, the details of the pathways by which the brain translates stressful stimuli into the final, integrated biological response are not completely understood. Nevertheless, it is clear that dysregulation of these physiological responses to stress can have severe psychological and physiological consequences, and there is substantial evidence to suggest that inappropriate regulation, disproportional intensity, or chronic and/or irreversible activation of the stress response is linked to the etiology and pathophysiology of anxiety, depression and metabolic-related disorders. Understanding the neurobiology of stress by focusing on the specific genes and brain circuits, which are associated with, or altered by, the stress response, will provide important insights into the brain mechanisms by which stress affects psychological and physiological disorders. The long-term goal of our research is to elucidate the pathways by which stress is perceived, processed, and transduced into neuroendocrine and behavioral responses. We are using integrated molecular (genetics and epigenetics), biochemical, physiological and behavioral methods, with focus on the generation of mutant mice models as an in vivo tool, to study the roles of specific stress-linked genes and brain circuits in coordinating the neuroendocrine, autonomic and behavioral responses to stressful challenges.