

Preface

The term “stress” is universally recognized as difficult to define, and yet, people typically report experiencing stress as an almost everyday experience. A commonly used definition of stress is the perception of an event that threatens homeostasis, the normal equilibrium of bodily function, and an insufficient ability to cope with environmental challenges. The types of stressors humans have experienced have changed over the history of our species, such as the primarily physical challenges faced by our distant ancestors, as compared to purely psychological stressors, which are far more common in our modern societies. The body elaborates a complex response to stressors, the so-called stress response, which is orchestrated by the brain and involves multiple physiological systems, including interactions of the autonomic nervous system with central neuroendocrine systems. It is well-known to psychiatrists and neurologists (indeed, also to the layman) that stress is a major risk factor for neuropsychiatric, neurodegenerative and metabolic diseases, but exactly how stress may facilitate or trigger these diseases is still very much debated, and insufficiently understood. A further complication is represented by the observation that stress is bi-faced, and may have positive or negative influences on the bodily functions, depending on the type and duration of the stressor, as well as on the individual’s response to the stressor.

The science of the study of stress can trace its origins to the pioneering work of Claude Bernard, who in the 19th century developed the idea of the constancy of the internal environment (*le milieu intérieur*) as the necessary condition for a free and stable life (*la vie constante ou libre*). According to Bernard “all the vital mechanisms ... have only one object, that of preserving constant the conditions of life in the internal environment”. Bernard’s theorizing regarding the *milieu intérieur* was extended in the 1920’s by Walter Cannon, who coined the term “homeostasis”, which described processes by which physiological systems preserve the stability of the internal environment. Cannon’s work addressed how perturbations from a setpoint, or the optimal physiological state, were corrected by negative feedback mechanisms. Cannon also coined the phrase “acute stress response” (ASR), which described his view that animals react to life threatening experiences with the now classic “fight or flight” response, produced by activation of the sympathetic nervous system. Cannon’s description of the ASR and fight or flight responses were to

become the activational stage of an individual's response to a threat, as described by Hans Selye, the first true stress researcher. Selye conceptualized stress in terms of a set of non-specific responses he referred to as the "general adaptation syndrome", which described the three stage process of activation, adaptation, and ultimately, exhaustion of resources, all of which contributed to stress-induced pathology.

Bernard and Cannon's seminal ideas on homeostasis and Selye's general adaptation syndrome provide a structure for categorizing the impressive body of research in the chapters of this book which were written by prominent neuroscientists. Selye's "activational" phase of stress is manifested as increased activity in the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, and ultimately, as activation of brain emotion, memory and attention centers. The first section of this book addresses research on neural mechanisms underlying the activational phase of the stress response with techniques that were unimaginable in the times of Bernard, Cannon and Selye. The six chapters in section one are a compendium of state-of-the-art approaches which have characterized cellular, molecular and physiological responses to stress. Joels, Popoli, Yan, Campolongo, Hill, Bains and their co-authors have described how stress neuromodulators, with an emphasis on corticosterone and endocannabinoids, as well as stress effects on glutamate and GABA neurotransmitter systems, exert dramatic effects on synaptic physiology in diverse brain areas, including the hippocampus, amygdala, prefrontal cortex and hypothalamus.

The second of Selye's phases in the general adaptation syndrome can be considered the brain's attempt to adapt to the challenge of the stress experience. One feature of the neural adaptation to stress is the rapid development of synaptic and behavioral plasticity to adopt efficient behavioral responses to current, and future, stress challenges. The second section of this book focuses on this issue, with scholarly reviews that emphasize the capacity of the brain to generate synaptic plasticity underlying emotional memory processing. The five chapters by Segal, Kim, Diamond, Howland, Sandi and their co-authors describe the modulation of synaptic plasticity by behavioral stress and neuromodulators, with an emphasis on influence of corticosterone on the dorsal and ventral hippocampus, subiculum, prefrontal cortex and amygdala.

The condition in which homeostasis seems to fail is analogous to the "exhaustion" phase of Selye's general adaptation syndrome. This area of research, which has generated a vast amount of work on stress-induced psychopathology, is addressed in the third section of the book. Here, prominent clinicians and preclinical researchers have integrated basic stress research with findings from clinical studies to enhance our understanding of how acute and chronic stress are linked to pathological states, including common diseases of Western society, such as immune, cardiovascular and psychiatric disorders. The erudite chapters written by Sibille, Rajkowska, McCullumsmith, Reagan, Sanacora and their co-authors addressed diverse approaches to the study of how stress modulators, with an emphasis on glutamate and GABA, are linked to neural and glial involvement in major depressive disorder, schizophrenia and psychosis, as well as metabolic disorders, such as obesity, diabetes and metabolic syndrome. The chapter by Sanacora and co-authors analyzes how stress-related effects on the glutamate system can drive the development of novel therapeutic strategies.

Finally, a recent watershed event in the development of our appreciation of the complexity of the science of stress is the extension of the homeostasis concept to “allostasis”, which means “stability through change”. Whereas homeostasis was conceptualized as a relatively static process involving stability around a fixed setpoint, allostasis is a more dynamic, adaptive process in which a setpoint can change, for example, as a result of repeated acute stress experiences. Thus, in allostasis, the concept of negative feedback mechanisms and stability around a setpoint is maintained, but it is the setpoint, itself, that can change as a function of life’s experiences.

The editors are pleased to point out that Bruce McEwen, one of the most prolific and influential of all stress researchers, has provided his perspective on allostasis in the introduction to the book. For over four decades, Bruce has advanced the boundaries of our understanding of the neurobiology and neuroendocrinology of stress with his elegant and comprehensive research on behavioral and brain processes involved in the “good and bad” sides of the neuroendocrinology of stressful experiences. In the introduction, Bruce has discussed his conception of allostasis, and in particular his contribution to our understanding of allostatic load, which is the toll that chronic stress takes on the body. Finally, he has provided a balanced overview of the involvement of glucocorticoids in the behavioral and physiological responses of neuroendocrine and autonomic systems as a major component of lifestyle effects on behavior and brain health.

The editors are well-aware that the works reported in this volume are only a small part of the great scientific effort undertaken at present to understand the brain under stress, and wish to apologize for all findings and lines of evidence that could not be included or mentioned here. Although the title of this volume was restricted to the relationship between stress and neuropsychiatric disorders, undoubtedly the reviews and primary results provided here will be of interest to bench scientists, as well as clinicians, to learn of the latest research on fundamental neuroendocrine stress mechanisms and stress-related diseases.

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