Sex, Stress and the Brain: From Serendipity to Clinical Relevance

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Bruce S. McEwen, Ph.D.

Laboratory of Neuroendocrinology The Rockefeller University 1230 York Avenue, New York, NY 10065

Neuroendocrinology has evolved to encompass the feedback actions of hormones on neural targets above the hypothalamus which influence many aspects of brain function and behavior that also can more indirectly influence hormone secretion. Along with other advances in neuroscience, neuroendocrine studies have revealed that the adult brain is much more resilient and adaptable than previously believed, and that adaptive structural plasticity involves growth and shrinkage of dendritic trees, turnover of synapses and limited amounts of neurogenesis in the forebrain, especially the dentate gyrus of the hippocampal formation. Stress and sex hormones help to mediate adaptive structural plasticity, which has been extensively investigated in hippocampus and to a lesser extent in prefrontal cortex, amygdala and nigrostriatal and mesolimbic systems, all brain regions that are involved in cognitive and emotional functions. We now know that stress and sex hormones exert their effects on brain structural remodeling through both classical genomic, as well as nongenomic mechanisms and they do so in collaboration with neurotransmitters and other intra- and extracellular mediators. This will be illustrated for estrogen actions on synapse formation in the hippocampus and for stressinduced remodeling of dendrites and synapses in the hippocampus, amygdala and prefrontal cortex. Translational studies will be described showing how information from animal models has informed studies on the human brain using modern imaging methods and neuropsychological methods. The influence of early developmental events such as early life stress and brain sexual differentiation will be noted along with the interactions between sex hormones and the effects of stress on the brain. Because hormones influence so many aspects of brain structure and function and because hormone secretion is governed by the cognitive and emotional brain, the role of brain plasticity must be considered in understanding how the social environment "gets under the skin" to affect brain and body resilience and vulnerability to disorders of the brain and body as well as the aging process. Supported by NIH Grants NS07080, MH41256, 5P01 AG16765, 5P50MH58911.