ABSTRACT: KEYNOTE ADDRESS

STRESS, SEX AND THE HIPPOCAMPUS: FROM SERENDIPITY TO CLINICAL RELEVANCE

Bruce S. McEwen, PhD
Lab Neuroendocrinology, Rockefeller University, New York, NY

The hippocampal formation, which expresses high levels of adrenal steroid receptors, is a plastic brain structure that is important for certain types of learning and memory. It is also vulnerable to insults such as stroke, seizures and head trauma. The hippocampus is also sensitive and vulnerable to the effects of stress and stress hormones and it is responsive to the actions of sex hormones as well, both during development and adult life. Stress and sex hormones regulate 3 types of structural plasticity in the adult hippocampus: synaptogenesis, reorganization of dendrites, and neurogenesis in the dendrite gyrus. Developmentally-programmed sex differences are also seen in the hippocampus. Suppression of dentate gyrus neurogenesis and atrophy of dendrites of hippocampal pyramidal neurons are produced by chronic psychosocial stress, involving the actions of adrenal steroids acting in concert with excitatory amino acid neurotransmitters. As far as we can tell, these changes are reversible as long as stress is terminated after a number of weeks. However, there are also reports that much longer durations of psychosocial stress leads to permanent loss of hippocampal pyramidal neurons. In the human hippocampus, MRI studies along with neuropsychological testing have revealed memory impairment and atrophy of the whole human hippocampus in some individuals as they age. This is reminiscent of individual differences in aging in rodents, which appear to reflect life-long patterns of stress hormone reactivity that are developmentally programmed, although a developmental influence upon human individual differences is only a matter of speculation. Hippocampal atrophy is also found in Cushing's syndrome, post-traumatic stress disorder and recurrent depressive illness, indicating that this brain structure is vulnerable and involved in stress, and stress hormone related disorders. Knowledge of underlying anatomical changes and the mechanism of hippocampal atrophy may help in developing treatment strategies to either reverse or prevent them.

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BIOGRAPHICAL SKETCH:

Bruce S. McEwen, PhD
Lab Neuroendocrinology, Rockefeller University, New York, NY

Bruce McEwen received an A.B. in Chemistry from Oberlin College, summa cum laude in 1959 and a Ph.D. in Cell Biology from The Rockefeller University in 1964. Wishing to go abroad and study the fledging field of neurobiology, he went to Sweden to study in

the laboratory of Holger Hyden and was a USPHS Postdoctoral Fellow in Goteborg, Sweden in 1964-65.

After a brief sojourn at the University of Minnesota, he returned to The Rockefeller University in 1966 to join the laboratory of Prof. Neal E. Miller, as a cell biologist in a physiological psychology group. He has remained at Rockefeller throughout his career. At present, Dr. McEwen is The Alfred E. Mirksy Professor and Head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at The Rockefeller University in New York City. A member of the National Academy of Sciences and the Institute of Medicine, he was President of the Society for Neuroscience in 1997-1998 and is past-President of the International Society of Neuroendocrinology.

As a neuroscientist and neuroendocrinologist, he studies environmentally-regulated, variable gene expression in brain mediated by circulating steroid hormones and endogenous neurotransmitters in relation to brain sexual differentiation and the actions of sex, stress and thyroid hormones on the adult brain. Dr. McEwen combines molecular, anatomical, pharmacological, physiological and behavioural methodologies and makes an effort to relate his findings to human clinical information.

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