

STRESS AND THE HIPPOCAMPUS: DEPRESSION-INDUCED HIPPOCAMPAL ATROPHY

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Stress physiology involves the study of stressors, either physical or emotional, which disrupt homeostasis and of the bodily responses which operate to return the system to normal homeostasis. Walter Cannon described the “flight or fight” response as an appropriate desirable adaptation to an acute stress. These acute adaptations involve secretion of sympathetic catecholamines, mobilization of energy, increase in cardiovascular and pulmonary tone, and suppression of the inflammatory response. Hans Selye was the first to recognize that the stress response could also be deleterious; he pioneered the concept that chronic stress could cause disease (Selye, 1976). This is particularly appropriate in understanding the deleterious processes which can affect the hippocampus.

Under normal conditions the hypothalamic pituitary adrenal (HPA) axis effects an appropriate acute response to stress; there is an endocrine cascade starting with the brain, continuing to the pituitary and ending with secretion of glucocorticoids by the adrenal gland. Negative feedback loops operate at each of these levels to restore the system to normal homeostasis. However, during conditions of chronic stress alterations occur in the system so that the feedback mechanisms do not operate normally and damage is produced to hippocampal neuronal cells.

There is considerable evidence in animals to indicate that repeated episodes of stress are associated with damage to hippocampal neurons. Work in animal systems has demonstrated that repeated episodes of stress or elevated glucocorticoid levels, also characteristic of depression, can produce neurotoxic damage to hippocampal pyramidal cells. As little as 21 days of restraint stress in rats resulted in atrophy of apical dendrites of CA3 pyramidal neurons (Watanabe et al., 1992). Similarly, restraint stress or chronic multiple stressors, for example shaking in addition to restraint, produced dendritic atrophy of CA3 neurons. These two different paradigms produced different degrees of adrenal activation. Multiple stressors produced a more robust increase in corticoster-