At Issue: Stress, Hippocampal Neuronal Turnover, and Neuropsychiatric Disorders

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Abstract

Stress-induced changes in the glucocorticoid system may be toxic for hippocampal cells in animals. Recently, neurogenesis has been shown in the rat, the primate, and the human hippocampus. Because chronic stress is associated with some neuropsychiatric disorders, including schizophrenia, it is possible that an imbalance in the normal turnover of hippocampal cells plays a role in the pathophysiology not only of schizophrenia but also of other neuropsychiatric disorders that involve high levels of stress. New therapeutic possibilities arise if such a process is proven to occur.

Keywords: Schizophrenia, neurodegeneration, neurogenesis, cortisol, stress, hippocampus.


Structural imaging and postmortem studies have demonstrated decreased volume in certain brain structures in patients with schizophrenia, posttraumatic stress disorder, and depression. These disorders are very different in their clinical presentation and underlying pathophysiology, but reduced hippocampal volume has been reported in all three. It has been proposed that the hippocampal volume reduction in schizophrenia may be mediated via stress-induced glucocorticoid neurotoxicity (Benes 1997; Walker and Diforio 1997). Such a mechanism might apply to all three conditions. Baseline and postdexamethasone plasma cortisol levels have been shown to be increased not only in schizophrenia but also in affective disorders (Breier and Buchanan 1992; Risch et al. 1992). Lupien et al. (1998) reported that current and long-term cortisol levels correlate with hippocampal volume reduction and cognitive impairments in aged humans. Reduced limbic tissue volume has been associated with an increased severity of psychopathology in schizophrenia (Bogerts et al. 1993), the total duration of major depression (Sheline et al. 1996), and the severity of combat exposure in war veterans with posttraumatic stress disorder (Gurvits et al. 1996). In patients with Cushing’s syndrome, hippocampal volumes and memory dysfunction have been inversely correlated to cortisol levels in plasma (Starkman et al. 1992).

Recent findings challenge the accepted beliefs that neurons do not divide after central nervous system maturation and that any changes in the adult brain are due to dendritic proliferation, pruning, apoptosis, or gliosis. Gould et al. (1998) first found evidence for hippocampal neuronal division in the dentate gyrus of adult monkeys, and Eriksson et al. (1998) recently reported the same in humans. In monkeys, substantial reductions in cell proliferation were found after exposure to a stressful experience (Gould et al. 1998). If neurons in the human hippocampus are constantly dividing and dying, the smaller volume in the hippocampus of patients with neuropsychiatric disorders could be due to an imbalance in the dynamic process of division and cell death. This imbalance could explain the absence of gliosis in the postmortem studies of the hippocampus in schizophrenia patients.

As for when an alteration in cell turnover might play a role in schizophrenia, the evidence is somewhat contradictory. The impairment in function and the severity of psychotic symptoms are typically greatest in the first years following the onset of psychosis (McGlashan 1988), so the greatest stress-mediated brain changes might be expected to occur during this period. Consistent with this view is the finding that children with early-onset schizo-
Although the relevance of a stress-related imbalance in hippocampal cell turnover is somewhat speculative, it is an important possibility to consider because the presence of such a process would raise new avenues for therapeutic intervention. Several studies have shown that higher cortisol levels are associated with markers of poorer prognosis in schizophrenia (for a review, see Walker and Diforio 1997). If stress plays an important role in brain abnormalities and these abnormalities, in turn, exacerbate the patient's condition, psychosocial techniques for reducing stress or pharmacological techniques for blocking the glucocorticoid-related damage might decrease disease severity and improve long-term course.

References


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