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-
Schizophrenia have structural abnormalities that resemble those of adults, with the exception that no significant differences in temporal lobe areas have been found present on initial admission (Jacobsen et al. 1998). At a 2-year followup, these same children show significantly greater reduction of temporal lobe structures, including the hippocampus, than the normal control group. The same group of researchers has recently replicated the finding with a larger sample and a longer followup extending through adolescence (Giedd et al. 1999). In a longitudinal study of adults, Gur et al. (1998) found that first episode patients showed greater temporal lobe reduction than previously treated patients after a mean of 30 months followup, which led those authors to suggest that “neuropsychoanatomical changes are more evident early in psychosis” (p. 150). An independent group found an association between a smaller right hippocampus and illness duration in people with chronic schizophrenia (Velakoulis et al. 1999). In contrast, another longitudinal study of patients after first hospitalization did not find any reduction of the amygdala-hippocampus complex after a minimum 4-year followup (DeLisi et al. 1997). Although some of the longitudinal studies in first episode patients point toward an increased reduction in hippocampal volume in stages of the disease when the symptomatology, and possibly the stress experienced, is heightened, additional hippocampal longitudinal studies are required before more firm conclusions can be drawn.

There is also evidence for volume reduction in the hippocampus prior to the onset of psychosis. For instance, in a cross-sectional study, bilateral hippocampal volume reduction was found in both first episode and chronic patients (Hirayasu et al. 1998; Whitworth et al. 1998). Another factor that further complicates the interpretation of hippocampal changes in schizophrenia is that the stress related to poor function may long precede the onset of flagrant psychosis. In one study, a substantial number of patients with schizophrenia had a prodromal phase with a mean length of 5 years prior to first admission, and had had psychotic symptoms for 1 year (Hafner and an der Heiden 1997). In most studies, there is an average gap of many months (or some years) between the first florid symptoms and the time when the magnetic resonance imaging (MRI) is obtained. Therefore, an alteration in hippocampal size, even if present in first episode patients, would be compatible with stress-induced changes.

Hippocampal changes at the onset of illness and changes during the subsequent course are not mutually exclusive, and either could be consistent with a stress-mediated imbalance in hippocampal cell death and division. Some of the changes observed in first episode patients could occur as a consequence of the stress caused by the disease prior to the time the MRI was taken, or even prior to the onset of psychosis, when patients with schizophrenia have serious problems functioning. Nor is an imbalance of neurogenesis in the hippocampus mediated by stress-induced glucocorticoid neurotoxicity mutually exclusive with changes during early hippocampal development. It has been shown that psychosocial stressors experienced by the mother during pregnancy (Huttunen and Niskanen 1978) and prenatal and perinatal complications such as viral infection, nutritional deficiency, and obstetric complications (Mednick and Hollister 1995; Susser et al. 1996; Dalman et al. 1999) are related to an increased risk for schizophrenia. The hippocampus is highly susceptible to stress during fetal development, and prenatal exposure to glucocorticoids is related to elevated baseline and poststress cortisol levels, as well as hippocampal volume, in nonhuman primates (Uno et al. 1994). There is evidence that pre- and perinatal complications have effects on the hypothalamic-pituitary-adrenal axis, making it more sensitive to stress later in life (Benes 1997; Walker and Diforio 1997). An already abnormal brain may be more susceptible to the proposed neuronal turnover imbalance, and further changes could take place after the onset of the illness. Because the hippocampus is involved in glucocorticoid regulation (Walker and Diforio 1997), an insult to this structure could subsequently result in increased cortisol levels, creating a vicious circle.

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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