Stress, depression and hippocampal damage

Stress is part and parcel of the daily interaction between an organism and its environment. Most responses to stressful environments are adaptive and allow an animal to reestablish its homeostatic balance. It is the maladaptive responses to stress that are thought to be relevant in the precipitation and exacerbation of psychiatric disorders like depression and post-traumatic stress disorder (PTSD) (Sapolsky 1996).

Amongst the prime targets of stress in the brain is the hippocampus, which has high receptor levels for corticosteroids that are released during stress (McEwen 1999). Over the years evidence has built up that stress leads to damage of the hippocampus. Initial reports from Uno *et al* (1989) indicated that primates exposed to psychosocial stress in the wild had considerable hippocampal neuronal loss. Laboratory experiments then clarified that stress exerts diverse effects on different hippocampal subfields (McEwen 1999). Chronic stress causes atrophy and eventually may lead to the death of hippocampal CA3 neurons. In addition, stress also suppresses ongoing adult neurogenesis in the hippocampal dentate gyrus (DG) subfield. Unlike most regions of the brain where neuronal proliferation is restricted to discrete stages of development, the DG retains the ability to exhibit neurogenesis throughout adulthood in several species, including rodents, primates and humans (Kempermann and Gage 1998). The influence of stress on neurogenesis and neuronal atrophy/death are likely parts of a cascade of events that eventually results in stress-induced hippocampal damage. Hippocampal damage is thought to play an important role in the etiology of stress-related psychiatric disorders, and decreases in hippocampal volume have been observed in patients of recurrent, major depression and PTSD (Brown *et al* 1999).

Depressive disorders have often been associated with high levels of circulating corticosteroids. Several brain regions including the hippocampus mediate central control of the hypothalamo-pituitary-adrenocortical (HPA) axis which regulates secretion of the stress responsive corticosteroids. The hippocampus is known to provide an inhibitory feedback to the HPA axis. Hippocampal damage then would result in disinhibition of the HPA axis and excessive circulating corticosteroids, which in turn are known to cause further hippocampal damage, thus setting in motion a self-perpetuating vicious cycle (Fuchs and Flugge 1998). In addition to a reduction in hippocampal volume, a decreased feedback control of the HPA axis has also been observed in patients of major depression.

The mechanisms underlying the damaging influences of stress are as yet unclear, although a number of factors have

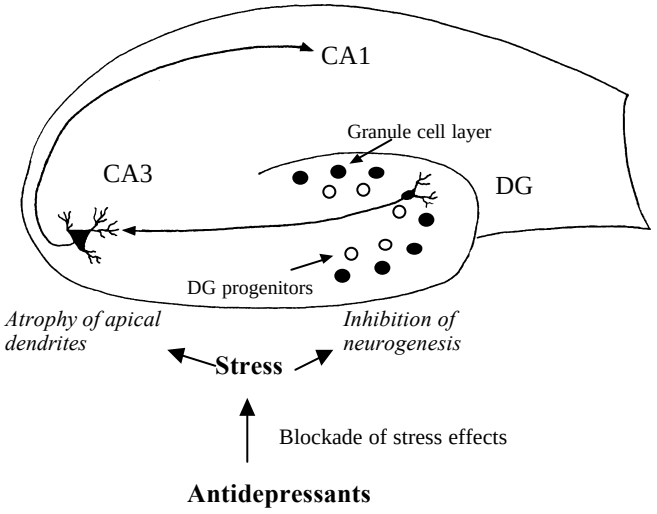

Figure 1. Schematic diagram of the hippocampus and the influence of stress and antidepressant treatments on the hippocampal subfields. The CA1, CA3 and DG comprise the main hippocampal anatomical subfields. The granule cells within the DG project via the mossy fibre pathway onto CA3 pyramidal neurons, which in turn send Schaffer collaterals that make synapses on CA1 pyramidal neurons. Exposure to stressful stimuli leads to CA3 dendritic atrophy and neuronal loss and a suppression of ongoing neurogenesis in the DG. Certain antidepressant treatments have been shown to block stress-induced CA3 dendritic atrophy and enhance DG neurogenesis.

been implicated. Activation of glutamatergic and serotonergic neurotransmitter pathways, disturbed calcium homeostasis, increased corticosteroid levels and altered growth factor expression are amongst the chain of events that are set into motion by stress. Glutamate, serotoninand corticosteroids all exert powerful influences on CA3 atrophy and DG neurogenesis. There is evidence to show that this atrophy is reversible and one can envisage that ongoing hippocampal neurogenesis is also likely to recover on adaptation to stress. There are likely several checks and balances on the path to stress-induced hippocampal damage. The question that arises then is what leads to the breakdown of these checks and balances and can one reinstate them?

The possibility that hippocampal damage may be reversible suggests that reversal of the stress-induced damage may be a potential therapeutic target for antidepressant treatments. The therapeutic action of these treatments is dependent on chronic administration for several weeks suggesting that it is a long term adaptation that underlies their therapeutic efficacy. It is possible that one potential target for antidepressant treatments is the blockade and reversal of stress effects in the different hippocampal subfields, as well as positive influences on hippocampal structural plasticity. Indeed, certain antidepressants prevent the stress-induced CA3 dendritic atrophy. We have recently shown that electroconvulsive seizure administration, which is clinically used as a potent antidepressant treatment, increases the sprouting of the mossy fiber pathway of hippocampal granule cell neurons (Duman and Vaidya 1988). In addition, recent data indicate that chronic antidepressant treatments enhance the proliferation of neuronal progenitor cells within the DG of the hippocampus (Duman *et al* 1999).

Overall accumulating evidence suggests that hippocampal structural plasticity may be a critical component of both adaptive and maladaptive stress responses, and in addition may also be a component of the therapeutic adaptations following chronic antidepressant treatment.

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