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Glucocorticoids, depression, and mood disorders: structural remodeling in the brain

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Abstract

The hippocampal formation expresses high levels of adrenal steroid receptors and is a malleable brain structure that is important for certain types of learning and memory. It is also vulnerable to the effects of stress and trauma. The amygdala is an important target of stress and mediates physiological and behavioral responses associated with fear and strong emotions. The prefrontal cortex plays an important role in working memory and executive function and is also involved in extinction of learning. All 3 regions are targets of stress hormones, and stress is known to precipitate and exacerbate mood disorders. In long-term depressive illness, the hippocampus and prefrontal cortex undergo atrophy, whereas the amygdala is hyperactive in anxiety and mood disorders and may undergo a biphasic change in structure—increasing in size in acute depression and shrinking on long-term depression. In animal models of acute and chronic stress, neurons in the hippocampus and prefrontal cortex respond to repeated stress by showing atrophy that leads to memory impairment, whereas neurons in amygdala show a growth response that leads to increased anxiety and aggression. Yet, these are not necessarily "damaged" and may be treatable with the right medications. The mechanisms that distinguish between protection and damage of brain cells from stress are discussed in this context.

1. Introduction

Stressful life events are known to precipitate depressive illness in individuals with certain genetic predispositions [1,2], and therefore, the study of depression and mood disorders needs to address the question: What do stressors do to the brain? We have known for some time that stress hormones such as cortisol are involved in psychopathology, reflecting emotional arousal and psychic disorganization rather than the specific disorder per se [3]. We now know that adrenocortical hormones enter the brain and produce a wide range of effects upon it (see Refs. [4-6]).

In Cushing's disease, there are depressive symptoms that can be relieved by surgical correction of the hypercortisolemia [6]. Both major depression and Cushing's disease are associated with chronic elevation of cortisol that results in gradual loss of minerals from bone and abdominal obesity. In major depressive illness, as well as in Cushing's disease, the duration of the illness and not the age of the subjects predicts a progressive reduction in volume of the hippocampus, determined by structural magnetic resonance imaging [7,8]. Moreover, there are a variety of other anxiety-related disorders, such as posttraumatic stress disorder, in which atrophy of the hippocampus has been reported, suggesting that this is a common process reflecting chronic imbalance in the activity of adaptive systems, such as the hypothalamus-pituitary-adrenal (HPA) axis, but also including endogenous neurotransmitters, such as glutamate.

Animal models of repeated stress have provided clues as to what may be going on in the human brain in Cushing's disease and major depressive illness, and the hippocampus is the best-studied brain region. The hippocampus contains receptors for adrenal steroids, which regulate excitability and morphological changes [9]. We shall first discuss the hippocampus and then turn to other stress-sensitive brain structures.

2. Adaptive structural plasticity

One of the ways that stress hormones modulate function within the brain is by changing the structure of neurons. Within the hippocampus, the input from the entorhinal cortex to the dentate gyrus is ramified by the connections between the dentate gyrus and the CA3 pyramidal neurons. One granule neuron innervates, on the average, 12 CA3

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neurons, and each CA3 neuron innervates, on the average, 50 other CA3 neurons via axon collaterals, as well as 25 inhibitory cells via other axon collaterals [9]. The net result is a 600-fold amplification of excitation, as well as a 300-fold amplification of inhibition, that provides some degree of control of the system. As to why this system exists, the dentate gyrus-CA3 system is believed to play a role in the memory of sequences of events, although long-term storage of memory occurs in other brain regions [10,11]. However, because the DG-CA3 system is so delicately balanced in its function and vulnerability to damage, there is also adapative structural plasticity, in that new neurons continue to be produced in the dentate gyrus throughout adult life [12] and CA3 pyramidal cells undergo remodeling of their dendrites in conditions such as hibernation and chronic stress [9,13].

2.1. Neurogenesis in the dentate gyrus

The subgranular layer of the dentate gyrus contains cells that have properties of astrocytes (eg, expression of glial fibrillary acidic protein) and which give rise to granule neurons [5]. After BrdU administration to label DNA of dividing cells, these newly born cells appear as clusters in the inner part of the granule cell layer, where a substantial number of them will go on to differentiate into granule neurons within as little as 7 days. In the adult rat, 9000 new neurons are born per day and survive with a half-life of 28 days [5].

There are many hormonal, neurochemical, and behavioral modulators of neurogenesis and cell survival in the dentate gyrus [12,14-17]. With respect to stress, certain types of acute stress and many chronic stressors suppress neurogenesis or cell survival in the dentate gyrus, and the mediators of these inhibitory effects include excitatory amino acids acting via N-methyl-D-aspartate (NMDA) receptors and endogenous opioids [5,9,12]. Chronic stress has even more potent effects on neurogenesis and neuronal survival [5].

2.2. Remodeling of dendrites

Another form of structural plasticity is the remodeling of dendrites in the hippocampus [13]. Chronic restraint stress (CRS) causes retraction and simplification of dendrites in the CA3 region of the hippocampus [9]. Such dendritic reorganization is seen in rats undergoing adaptation of psychosocial stress in the visible burrow system. The visible burrow system is an apparatus with an open chamber where there is a food and water supply and several tunnels and chambers. Contrary to expectation, it was the dominant that had a more extensive pattern of debranching of the apical dendrites of the CA3 pyramidal neurons in the hippocampus, compared to the subordinate rats, which showed reduced branching compared to the cage controls [18]. What this result emphasizes is that it is not adrenal size or presumed amount of physiological stress per se that determines dendritic remodeling but a complex set of other factors that modulates neuronal structure. We refer to the phenomenon as “dendritic remodeling” and we generally find that it is a reversible process.

The role of adrenal steroids in the structural remodeling described above reflects many interactions with neurochemical systems in the hippocampus, including serotonin, γ-aminobutyric acid, and excitatory amino acids [5,9,13]. Probably the most important interactions are those with excitatory amino acids such as glutamate. Excitatory amino acids released by the mossy fiber pathway play a key role in the remodeling of the CA3 region of the hippocampus, and regulation of glutamate release by adrenal steroids may play an important role [5,9,19-21].

3. What about permanent damage as a result of stress?

There is always concern that severe and prolonged stress may damage the brain [22], and in the case of depressive illness, there is a high degree of lifetime recurrence of major depression, which suggests that an underlying pathophysiologic process is involved. What we are learning from animal models of stress and trauma effects in the hippocampus is that the remodeling of the hippocampus in response to stress is largely reversible if CRS is terminated at the end of 3 weeks [5]. Yet, it is well established that glucocorticoids exacerbate damage to the hippocampus caused by ischemia and seizures [22-24]. Yet, the brain protects itself, as for example, in the phenomenon of ischemia preconditioning [25,26]; namely, that prior stimulation of the hippocampus by a small ischemic event can induce a protective mechanism that may reduce the damage produced by a full-scale ischemic event. It is not clear if the same mechanisms might be operative when stress is applied, but these are under investigation.

We do know that in the hippocampus, there is a delicate balance between the generation of damage and destruction and the mechanisms that lead to dendrite retraction during more gradual repetitive simulation, which we propose is a protective response, analogous to a fuse box, that does not totally disconnect the circuit and allows it to function. As discussed above, this also means that the hippocampus may become somewhat more vulnerable to damage as a result of repeated stress but that, owing to protective mechanisms put in place during stress, it is not as vulnerable as it might be if these mechanisms were not present.

4. Stress-induced changes in the prefrontal cortex and amygdala

Repeated stress also causes changes in other brain regions such as the prefrontal cortex and amygdala. Repeated stress causes dendritic shortening in medial prefrontal cortex but produces dendritic growth in neurons in amygdalae [5,9,21,27-30]. Along with many other brain regions, the amygdala and prefrontal cortex also contain adrenal steroid receptors; however, the role of adrenal steroids, excitatory

amino acids, and other mediators has not yet been studied in these brain regions [5].

Acute stress induces spine synapses in CA1 region of hippocampus (see Ref. [31]), and chronic stress also increases spine synapse formation in hippocampus and amygdalae [5]. Moreover, chronic CRS for 21 days or longer impairs hippocampal-dependent cognitive function [5,32] and enhances amygdala-dependent unlearned fear and fear conditioning, which are consistent with the opposite effects of stress on hippocampal and amygdala structure. Chronic stress also increases aggression between animals living in the same cage, and this is likely to reflect another aspect of hyperactivity of the amygdala [5].

5. Conclusion

Animal stress models not only tell us how the human brain may change under repeated stress, but they also provide clues about stress-induced behavioral depression, which is relevant to human depressive illness. Psychosocial stress in an animal model of depressive illness, the tree shrew, suppresses neurogenesis and causes dendritic shrinkage in hippocampus [15,33,34].

Translational studies of brain changes in major mood and anxiety disorders such as unipolar and bipolar depression and posttraumatic stress disorder are showing that changes in volume of structures such as hippocampus, prefrontal cortex, and amygdala must be considered as part of the neurobiological consequences of these illnesses [6,22,35-37]. Structural remodeling in these brain regions is important for human psychiatric disorders because the altered circuitry is likely to contribute to impaired cognitive function and affect regulation. Moreover, stress is widely acknowledged as a predisposing and precipitating factor in psychiatric illness [1,38]. Thus, animal models are relevant to human psychiatric disorders by showing the delicate balance between protection and damage and by providing mechanisms that raise the hopeful possibility that brain changes, in at least some major psychiatric disorders, may be treatable if we can find the right agents or therapies and intervene in time.

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