

## Mood Disorders and Allostatic Load

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*The brain controls both the physiologic and the behavioral coping responses to daily events as well as major stressors, and the nervous system is itself a target of the mediators of those responses through circulating hormones. The amygdala and hippocampus interpret what is stressful and regulate appropriate responses. The amygdala becomes hyperactive in posttraumatic stress disorder (PTSD) and depressive illness, and hypertrophy of amygdala nerve cells is reported after repeated stress in an animal model. The hippocampus expresses adrenal steroid receptors. It undergoes atrophy in several psychiatric disorders and responds to repeated stressors with decreased dendritic branching and reduction in number of neurons in the dentate gyrus. Stress promotes adaptation ("allostasis"), but a perturbed diurnal rhythm or failed shutoff of mediators after stress ("allostatic state") leads, over time, to wear and tear on the body ("allostatic load"). Neural changes mirror the pattern seen in the cardiovascular, metabolic, and immune systems, that is, short-term adaptation versus long-term damage. Allostatic load leads to impaired immunity, atherosclerosis, obesity, bone demineralization, and atrophy of nerve cells in brain. Allostatic load is seen in major depressive illness and may also be expressed in other chronic anxiety disorders such as PTSD and should be documented. Biol Psychiatry 2003;54:200–207 © 2003 Society of Biological Psychiatry*

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### Introduction

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 (Sachar et al 1970). We now know that adrenocortical hormones enter the brain and produce effects ranging from steroid psychosis that can be blocked by a glucocorticoid antagonist (mefipristone; Belanoff et al 2001; Chu et al 2001) to a wide range of effects on the normal brain that I review here. In Cushing's disease,

depressive symptoms exist that can be relieved with surgical correction of the hypercortisolemia.

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 (Sheline et al 1999; Starkman et al 1999). Moreover, there are a variety of other anxiety-related disorders, such as posttraumatic stress disorder (PTSD), 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 hypothalamic-pituitary-adrenal (HPA) axis, but also including endogenous neurotransmitters, such as glutamate.

There is another side to the story, however: the role of stress hormones and other mediators in allostasis (maintaining stability, or homeostasis, through change), that is, the process of adaptation to events in daily life. When mediators of allostasis, such as cortisol and adrenalin (but also neurotransmitters and other tissue and hormonal mediators), are released in response to stressors or lifestyle factors such as diet, sleep-wake cycles, and exercise, they promote adaptation and are generally beneficial. When they are not turned off when no longer needed, or are not turned on when they are needed, or are overused by excessive challenge, cumulative changes lead to a wear and tear, called "allostatic load," on the body and brain.

This article is about allostasis and allostatic load as organizing concepts for understanding, on one hand, the short-term adaptation of the brain and body to acute stressors or to the daily rhythm of sleep and activity, and, on the other hand, the pathophysiology that is evident in major depression and other chronic anxiety-related disorders when the mediators of allostasis are dysregulated or either over- or underactive over many months and years. After describing these concepts, I briefly review the role of the biological mediators of stress in the protective and damaging aspects of stress on the brain and body. I then consider the dynamics of the HPA axis in relation to both normal adaptive effects and the pathophysiology associated with depressive illness; I also suggest that other anxiety-related disorders also fit the model of allostasis and allostatic load and should be studied for their systemic manifestations.

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## Protective and Damaging Effects of the Mediators of Adaptation

Individual differences in the progression of a number of disorders that accumulate with time can be conceptualized as an accumulation of wear and tear of daily experiences, lifestyle, and major life stressors that interact with the genetic constitution and predisposing early life experiences (Geronimus 1992). The neuroendocrine system, autonomic nervous system, and immune system are mediators of adaptation to challenges of daily life, referred to as “allostasis” (Sterling and Eyer 1988). Physiologic mediators, such as adrenalin, glucocorticoids, and cytokines, act on receptors in various tissues and organs to produce effects that are adaptive in the short run but can be damaging if the mediators are not shut off when no longer needed. A state of heightened activity of mediators, such as a chronic elevation of glucocorticoids in a flattened diurnal rhythm or as a result of chronic stress, is referred to as an “allostatic state.” As a result, their effects on target cells are prolonged, leading to other consequences that may include receptor desensitization and tissue damage. This is “allostatic load” (McEwen 1998; McEwen 2000a,b; McEwen and Stellar 1993), which refers to the “cost” of adaptation.

The brain is the master controller of the three systems noted above and is also a target of these systems, subject to both protection and damage (McEwen 1998). Neurotransmitters, like hormones, are usually released during a discrete period of activation and are then shut off, and the mediators themselves are removed from the intracellular space by reuptake or metabolism so as not to prolong their effects. When this does not happen, however, there is allostatic load, and the brain is at increased risk for damage (Lowy et al 1995; Moghaddam et al 1994).

## Roles of Stress-Related Hormones in Adaptation and Structural Plasticity

I now look at some of the positive, adaptive effects that one mediator of allostasis, glucocorticoids, produces in the brain. The amygdala and hippocampus are both involved in contextual fear conditioning and in passive avoidance learning. In fear conditioning, glucocorticoids enhance learned fear (Corodimas et al 1994) and modulate information flow through the lateral amygdala, and they play an important role in forming the memory of context in contextual fear conditioning (Stutzmann et al 1998) but not of the actual effect of footshock in rats that are already familiar with the context in which the shock is administered (Pugh et al 1997a, 1997b). This suggests that the hippocampal role in contextual fear conditioning is enhanced by moderate levels of glucocorticoids, but that fear

conditioning is either not so dependent on glucocorticoids or is so strong that glucocorticoid influences are difficult to demonstrate. Moreover, in passive avoidance, both catecholamines and glucocorticoids play a role in facilitating the learning (Cahill et al 1994; Roozendaal 2000). Adrenal steroids also play a supporting role in the learning of a spatial navigation task in mice (Oitzl et al 2001).

Other evidence for glucocorticoid actions supports an inverted U-shaped dose-response curve in which low to moderate levels of adrenal steroids enhance acquisition of tasks that involve the hippocampus, whereas high levels of glucocorticoids disrupt task acquisition (Conrad et al 1999a; Diamond et al 1992, 1999; Pugh et al 1997b). Adrenal steroids have biphasic effects upon excitability of hippocampal neurons that may underlie their biphasic actions on memory and recall (Diamond et al 1992; Pavlides et al 1994, 1995; Pavlides and McEwen 1999).

One of the ways that stress hormones modulate function within the brain is by changing the structure of neurons. There is structural plasticity within the dentate gyrus cornu ammonis 3 (DG-CA3) system, in that new neurons continue to be produced in the dentate gyrus throughout adult life (Gould et al 2000) and CA3 pyramidal cells undergo remodeling of their dendrites (McEwen 1999; McEwen and Magarinos 2001). The subgranular layer of the dentate gyrus contains cells that have properties of astrocytes (e.g., expression of glial fibrillary acidic protein) that give rise to granule neurons (Seri et al 2001). There are many hormonal and neurochemical facilitators of neurogenesis and cell survival in the dentate gyrus, including insulin-like growth factor (IGF)-1, serotonin, and estradiol (Aberg et al 2000; Czeh et al 2001; Gould et al 2000; Malberg et al 2000; Trejo et al 2001).

Neurogenesis or survival of newly born cells is increased by putting mice in a complex (“enriched”) environment (Kempermann et al 1997). Moreover, a form of classical conditioning that activates the hippocampus (“trace conditioning”) leads to prolongation of the survival of newly born dentate gyrus neurons (Gould et al 1999; Shors et al 2001). 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 receptors and endogenous opioids (Cameron et al 1998; Eisch et al 2000; Gould and Tanapat 1999; McEwen 1999).

Another form of structural plasticity is the remodeling of dendrites in the CA3 region of the hippocampus (McEwen and Magarinos 2001). CA3 pyramidal neurons in hippocampus receive mossy fiber input from the granule neurons that are undergoing replacement, and the mossy fiber input is a powerful excitatory amino acid input that is responsible for remodeling of the length and branching of

dendrites. Such remodeling is seen in animals living in a dominance hierarchy (Blanchard et al 2001; McKittrick et al 2000). In hibernating hamsters, it occurs in a matter of hours and reverses itself just as quickly when the animals are aroused from torpor (Magarinos et al, unpublished). Along with suppressed neurogenesis, this remodeling is an important target of allostatic load in chronic stress.

### Repeated Stress and Structural Changes in the Hippocampus and Amygdala

Dendritic remodeling and suppression of neurogenesis occurs in models of repeated stress in rodents. Repeated restraint stress for 6 hours per day for 21 days suppresses neurogenesis; continuing daily restraint out to 6 weeks results in decreased dentate gyrus neuron number and volume and reduction by half in the survival of cells born during the period of daily stress (Pham et al, unpublished). Besides suppressing neurogenesis, 21 days of daily restraint stress reduces branching and total length of apical dendrites of CA3 neurons (Magarinos and McEwen 1995a, 1995b). Repeated stress has also been reported to decrease the length and branching of dentate gyrus granule neurons and CA1 pyramidal neurons (Sousa et al 2000). Dendritic remodeling is also produced by daily exposure to elevated corticosterone (Magarinos et al 1999; McEwen 1999; Sousa et al 2000), and both stress- and glucocorticoid-induced remodeling are reversible (Conrad et al 1999b; Magarinos et al 1999).

Glucocorticoids are not acting alone, and their effects can be blocked by agents that interfere with glutamate and serotonin actions (McEwen 1999). Excitatory amino acids appear to be largely responsible for suppressing neurogenesis in the dentate gyrus, as well as participating in the remodeling of dendrites (Gould and Tanapat 1999; McEwen 1999). During restraint stress, extracellular levels of glutamate are elevated in the hippocampus, as shown by microdialysis (Lowy et al 1993; Moghaddam et al 1994). Adrenalectomy prevents the increased levels of extracellular glutamate during restraint stress (Lowy et al 1993), implying that adrenal secretions modulate the extracellular levels of glutamate.

Repeated restraint stress has a number of effects on behavior after 21 days or longer. These include cognitive impairment on spatial recognition memory and increased anxiety in an open field, as well as increased fear conditioning (Conrad et al 1999a, 1999b; Luine et al 1994) and increased aggression toward animals in the same cage that is manifested progressively during the dark period following the daily restraint stress (Wood et al, unpublished). The cognitive impairment is likely to be related to the structural changes in the hippocampus described earlier, whereas the anxiety, fear, and aggression may be due to

changes in the amygdala. A neural correlate of the increased anxiety, fear, and aggression is the recently reported hypertrophy of neurons in the amygdala (Chattarji et al 2000).

An animal model of chronic psychosocial stress has been influential and informative in showing that the hippocampal structural plasticity after chronic restraint stress can be generalized to another species and to a stressful situation that has consequences that are reminiscent of depressive illness (Czeh et al 2001). Repeated psychosocial stress for 28 days causes remodeling of dendrites of CA3 neurons, and the remodeling of CA3 dendrites can be prevented by daily treatment of intruder tree shrews with phenytoin, a drug that blocks the actions of excitatory amino acids (Magarinos et al 1996). Chronic psychosocial stress also causes reduced neurogenesis in the dentate gyrus (Czeh et al 2001; Gould et al 1997). The effects of psychosocial stress to suppress neurogenesis can be prevented by daily treatment with the antidepressant tianeptine (Czeh et al 2001). Other antidepressants have been reported to increase neurogenesis in the dentate gyrus (Malberg et al 2000), but so far the recent study on the tree shrew is the only animal study thus far to use an antidepressant to counteract the effects of an ongoing stress (Czeh et al 2001). Tree shrews show behavioral alterations—anhedonia and reduced exploratory activity—that are prevented by treatment with antidepressants (Van Kampen et al 2002). Therefore, these results have some relevance to what antidepressants may be doing in depressive illness.

### Allostatic States in Depressive Illness

Stress hormones are elevated in major depressive illness. In particular, the diurnal rhythm is distorted (Sachar et al 1970). Normally low evening levels of cortisol are increased in depression (Deuschle et al 1998; Young et al 1994) and the stress hormone axis in major depression is resistant to suppression by the synthetic glucocorticoid dexamethasone (Carroll et al 1968). It is also noteworthy that androgen levels are elevated in women with major depression, which undoubtedly reflects adrenal hyperactivity (Weber et al 2000). IGF-1 levels are also reported to be elevated in major depression, and this may reflect elevated growth hormone release as a result of the hypercortisolemia (Deuschle 1997). Each of these patterns of elevation constitute an “allostatic state,” as defined earlier, and they represent a pathway for the development of allostatic load in the brain and other organs throughout the body. I now examine some of these changes, focusing on the hypercortisolemia.

Regarding the brain, I noted earlier the studies showing that hippocampal volume loss in major depressive illness is related to duration of the depression rather than to age

per se of the patients (Bremner et al 2000; Sheline et al 1996, 1999). Not all studies report such changes (e.g., Rusch et al 2001; Vakili et al 2000), and the reasons for these different results are beyond the scope of this discussion, but they may be explained by differences in the duration of depression, as well as gender and age. (See the article by Sheline in this issue.)

It should be noted that hippocampal size in elderly twins shows only 40% genetic contribution, with the predominant influence being environmental (Sullivan et al 2001). This emphasizes the importance of experiential factors and allostatic load in determining hippocampal volume.

In relation to geriatric depression, hippocampal atrophy has been reported in relation to depression in the elderly (Steffens et al 2000), with an association detected with presence of the apolipoprotein E4 genotype that is linked to Alzheimer's disease risk (Kim et al 2002).

Sheline and colleagues described in their magnetic resonance imaging study evidence for discontinuities that might represent sites of damage (Sheline et al 1996). Although some recent postmortem studies on brains from depressed individuals did not show neuron loss in hippocampus (Lucassen et al 2001; Muller et al 2001), the duration of the depression and the subtype of depression were not carefully controlled. Thus the possibility that neural damage may ultimately occur in major depression cannot be disregarded, particularly when depression lasts a long time. Moreover, in a recent study in young depressed subjects, hippocampal volume was not smaller in first episode depression but declined rapidly over several years even while treatment was underway (MacQueen et al 2003).

If permanent damage occurs, how might it come about? There are specific situations in which damage to the hippocampus is known to occur that is exacerbated by glucocorticoids. The hippocampus is vulnerable to ischemic damage (Sapolsky and Pulsinelli 1985) and to damage from kainic acid induced seizures (Roozendaal et al 2001). The former involves the CA1 and subiculum to a greater extent and the latter, the CA3 region, as discussed earlier. Based on the discussion earlier in this article about excitatory amino acids and structural remodeling, there may be a fine line between the conditions that lead to reversible remodeling of neurons and the circumstances that can cause permanent damage (for further discussion, see McEwen 2000a,b).

It is important to note that other brain regions besides hippocampus are affected in depressive illness and undergo structural changes. One region is the prefrontal cortex, and structural imaging (Drevets et al 1997) showed loss of volume in familial pure depressive disorder, whereas autopsy studies (Rajkowska 2000; Rajkowska et al 1999, 2001) have shown loss of volume and glial cells as well as neuronal density in both unipolar and bipolar

disorder. There is one animal study showing that chronic glucocorticoid treatment induces loss of dendrites in the rat prefrontal cortex (Wellman 2001); however, much more work needs to be done on this brain region.

Depressive illness is associated with a hyperactivation of the amygdala (Drevets et al 1992; Sheline et al 2001) and more recently with an actual enlargement of the amygdala in first episode major depression (Frodl et al 2002), although shrinkage of the amygdala has also been reported with increased duration of depression (Sheline et al 1999). The amygdala hypertrophy is reminiscent of the increased dendritic branching reported in rats after repeated immobilization stress (described earlier; see also Chattarji et al 2000). Because the amygdala integrates information related to fear and strong emotions and also sends outputs via the central nucleus for autonomic arousal and via the basal nucleus for more active aspects of coping (LeDoux 1996), the elevation of amygdala activity may be a first step that leads to overactivation of systems involved in physiologic and behavioral coping.

The long-term consequences of this may well be a wear and tear on the body that results in a number of pathophysiologic consequences, because the amygdala regulates both autonomic nervous system activity and corticotropin and cortisol production through outputs of its central nucleus (Schulkin et al 1994). There are reports that in recurrent major depression of long duration, the amygdala may undergo shrinkage (Sheline et al 1998, 1999). It is thus possible that initial hypertrophy gives way to atrophy in this important brain structure.

Whether or not there is brain damage in depressive illness of long duration, there certainly appears to be altered brain structural changes that may or may not be reversible if suitable pharmacologic agents and behavioral and psychotherapies can be found.

Besides the brain changes in major depression, there are other changes in the body that reflect dysregulated HPA and autonomic activity and are slow in developing. These constitute allostatic load that produces cumulative pathophysiology that may also be reversible if caught in time. Such cumulative, long-term effects include bone mineral loss (Cizza et al 2001; Michelson et al 1996; Schweiger et al 2000) and abdominal fat deposition (Thakore et al 1997; Mann and Thakore 1999; Weber-Hamann et al 2002).

Sleep disruption may be a key feature that leads to these consequences, because even short periods of sleep deprivation in otherwise normal individuals elevate evening cortisol and glucose levels and increase insulin levels and insulin resistance (Plat et al 1999; Spiegel et al 1999). This combination of long-term allostatic load, together with dysregulation of the autonomic nervous system in major depression (Thayer et al 1998), is associated with in-

creased blood platelet reactivity (Lederbogen et al 2001a; Musselman et al 1996; Walsh et al 2002) and increased risk for cardiovascular disease (Ballenger et al 2001; Heuser 2002; Musselman et al 1998; Perlmutter et al 2000).

There are parallels between the story for major depression and what is known about psychiatric and somatic features of Cushing's disease involving melancholia, depression, abdominal obesity, bone mineral loss, and increased risk for cardiovascular disease (Condren and Thakore 2001; Gold et al 1986; Starkman and Schteingart 1981; Starkman et al 1981). In addition, there is evidence for hippocampal atrophy in Cushing's disease along with memory impairments (Forget et al 2000; Mauri et al 1993; Starkman et al 1992). Interestingly, hippocampal volume loss in Cushing's disease is at least partially reversible over several years after correction of the hypercortisolemia (Bourdeau et al 2002; Heinz et al 1977; Starkman et al 1999).

Finally, a largely unexplored area concerns the effects of antidepressant medication on the brain and body changes associated with depressive illness. On one hand, certain antidepressants may contribute to some of the associated pathophysiology, such as cardiovascular instability (Lederbogen et al 2001b). On the other hand, withdrawal from antidepressant treatment may cause imbalances in neurotransmitter systems, with elevations of excitatory amino acid tone (Harvey et al 2002), and contribute to the allostatic load that occurs as the depressive state continues.

## Conclusions

In the case of depressive illness, and likely in other anxiety-related disorders, there appears to be a pattern of systemic pathophysiology that reflects allostatic states leading to allostatic load and producing cumulative changes in both brain and body. The hippocampus appears to play an important role, because it is involved in cognitive functions related to contextual, episodic, and spatial memory, and it is also a key structure in shutting off the HPA axis after psychological stressors (Jacobson and Sapolsky 1991). Dysfunction of the hippocampus can then lead to elevated cortisol levels in the aftermath of stress and also to an inability to associate context with fear—that is, discriminate situations that are fear-producing from those that are not. A key issue, then, is whether stress and allostatic load damage the brain, and particularly, the hippocampus.

Yes, perhaps they do, but the brain has a huge capacity for adaptive plasticity, and the animal studies raise the question whether the atrophy is reversible. We have also seen that there is damage to the brain in stroke and seizures that is caused by excessive excitatory amino acids, aided by glucocorticoids. Insofar as the same combination operates in long-term depressive illness and other psychiatric disorders of long duration, the question is when and how to intervene to prevent such damage.

Finally, it is possible to suggest a sequence of changes in depressive illness:

- Amygdala hyperactivity;
- HPA dysregulation resulting, at least in part, from disruption of normal sleep patterns;
- Delayed atrophy of hippocampus, prefrontal cortex, along with bone mineral loss and abdominal obesity;
- Increased risk of cardiovascular disease.

It is important to document whether other anxiety disorders also cause the dysregulation of the HPA axis and other mediators of allostasis. If so, a similar comorbidity of systemic and neural pathophysiology may also occur to that seen in long-term depressive illness. Such a pattern of allostatic load needs to be evaluated in other anxiety disorders such as PTSD, bipolar illness, and borderline personality disorder to see if there is a common pattern that arises from the physiologic dysregulation that Edward Sachar originally recognized in his pioneering studies.

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