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Interactive report

The neurobiology of stress: from serendipity to clinical relevance[1]

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Abstract

The hormones and other physiological agents that mediate the effects of stress on the body have protective and adaptive effects in the short run and yet can accelerate pathophysiology when they are over-produced or mismanaged. Here we consider the protective and damaging effects of these mediators as they relate to the immune system and brain. 'Stress' is a principle focus, but this term is rather imprecise. Therefore, the article begins by noting two new terms, allostasis and allostatic load that are intended to supplement and clarify the meanings of 'stress' and 'homeostasis'. For the immune system, acute stress enhances immune function whereas chronic stress suppresses it. These effects can be beneficial for some types of immune responses and deleterious for others. A key mechanism involves the stress–hormone dependent translocation of immune cells in the blood to tissues and organs where an immune defense is needed. For the brain, acute stress enhances the memory of events that are potentially threatening to the organism. Chronic stress, on the other hand, causes adaptive plasticity in the brain, in which local neurotransmitters as well as systemic hormones interact to produce structural as well as functional changes, involving the suppression of ongoing neurogenesis in the dentate gyrus and remodelling of dendrites in the Ammon's horn. Under extreme conditions only does permanent damage ensue. Adrenal steroids tell only part of the story as far as how the brain adapts, or shows damage, and local tissue modulators — cytokines for the immune response and excitatory amino acid neurotransmitters for the hippocampus. Moreover, comparison of the effects of experimenter-applied stressors and psychosocial stressors show that what animals do to each other is often more potent than what experimenters do to them. And yet, even then, the brain is resilient and capable of adaptive plasticity. Stress-induced structural changes in brain regions such as the hippocampus have clinical ramifications for disorders such as depression, post-traumatic stress disorder and individual differences in the aging process.

Keywords: Stress; Homeostasis; Allostasis; Immune function; Adaptive plasticity; Hippocampus; Dendrite; Neurotransmitter; Glucocorticoid; Adrenalectomy; Adrenal steroid; Learning; Memory; Cognitive function; Psychiatric disorder

1. Introduction

Stress is an aspect of our daily lives and conversations, and yet there is considerable ambiguity in the meaning of this word. The brain is the master controller of the interpretation of what is stressful and the behavioral and physiological responses that are produced. The brain is also a target of stress, along with the immune system, metabolic and cardiovascular systems and other systems of the body. Stress hormones play a major role in mediating both adaptive and maladaptive responses, and they do so by interacting with specific aspects of the physiology of each tissue. What is often overlooked is that the stress hormones are protective in the short run and yet can participate in damage when they are overproduced or not shut off when no longer needed.

Animals are continually learning and some experiences are classified as 'stressful' in part because stress hormones are produced. Contrary to the late Hans Selye, who emphasized physical stressors [133], psychological and experiential factors are among the most powerful of stressors: e.g., novelty, withholding of reward, and anticipation of punishment rather than the punishment itself are among the most potent activators of HPA and ANS activity [89,90].

Although stress is often thought about as bad and damaging, recent studies paint a different picture as far as the brain and also the immune system are concerned. The main point is that the brain appears to handle repeated stress over weeks by showing adaptive plasticity in which

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local neurotransmitters as well as systemic hormones interact to produce structural as well as functional changes. Likewise, the immune system responds to acute stress by showing enhanced responses, and this is mediated by adrenal steroids and catecholamines, as well as by locally-produced cytokines and cell adhesion molecules. Thus, systemic levels of adrenal steroids and catecholamines, the classical stress hormones, do not tell the whole story as far as how the brain adapts. Moreover, comparison of the effects of experimenter-applied stressors and psychosocial stressors show that what animals do to each other is often more potent than what we, as experimenters, do to them. Yet, even then, there is reason to believe that the brain is resilient and capable of adaptive plasticity. The changes in the brain and immune system produced by acute and repeated stress and the underlying mechanisms have turned out to have unexpected clinical ramifications. After discussing these, the article will consider future directions of this research and consider important unanswered questions.

2. Protective and damaging effects of stress mediators: homeostasis and allostasis

Before discussing the brain and its adaptive responses to stress, it is important to consider the definition of some key terms. Stress is often defined as a threat, real or implied, to homeostasis, and homeostasis refers to the maintenance of a narrow range of vital physiological parameters necessary for survival. In common usage, stress usually refers to an event or succession of events that cause a response, often in the form of 'distress' but also, in some cases, referring to a challenge that leads to a feeling of exhilaration, as in 'good' stress. But, the term 'stress' is full of ambiguities. It is often used to mean the event (stressor) or the response (stress response). It is frequently used in the negative sense of 'distress', and sometimes it is used to describe a chronic state of imbalance in the response to stress. In this article, 'stress' will be used to describe an event or events that are interpreted as threatening to an individual and which elicit physiological and behavioral responses. The brain is the key organ involved in interpretation and responding to potential stressors. But before considering its role, the following are some additional key terms and the way they are used in this article.

2.1. Stress response

The most commonly studied physiological systems that respond to stress are the HPA axis and the autonomic nervous system, particularly the sympathetic response of the adrenal medulla and sympathetic nerves. These systems respond in daily life according to stressful events as well as to the diurnal cycle of rest and activity. Thus, these systems do more than respond to 'stressors' even though they are frequently identified as 'stress response systems'. Behaviorally, the response to stress may consist of fight-or-flight reactions or potentially health-related behaviors such as eating, alcohol consumption, smoking and other forms of substance abuse. Another type of reaction to a potentially stressful situation is an increased state of vigilance, accompanied, at least in our own species, by enhanced anxiety and worrying, particularly when the threat is ill-defined or imaginary and when there is no clear alternative behavioral response that would end the threat. The behavioral responses to stress and these states of anxiety are both capable of exacerbating and potentiating the production of the physiological mediators of health outcomes.

2.2. Homeostasis

Homeostasis, in a strict sense, applies to a limited number of systems like pH, body temperature and oxygen tension, components of the internal milieu, that are truly essential for life and are, therefore, maintained over a narrow range, as a result of their critical role in survival. These systems are not activated or varied in order to help the individual adapt to its environment. In contrast, systems that show 'variation to meet perceived/anticipated demands' [145] characterizes the state of the organism in a changing world and reflects the operation of most body systems in meeting environmental challenges, e.g., through fluctuating hormones, heart rate and blood pressure, cytokines of the immune system, and other tissue mediators like neurotransmitters and hormones. Those mediators are most certainly not held constant, although their levels may usually operate within a range, and they participate in processes leading to adaptation as well as contributing to pathophysiology when they are produced insufficiently or in excess, i.e., outside of the normal range.

2.3. Allostasis

Allostasis is a term introduced by Sterling and Eyer [145] to characterize how blood pressure and heart rate responses vary with experiences and time of day and also to describe changes in the set point of these parameters in hypertension. The change in set point was used by them as the primary example that distinguishes allostasis from homeostasis. Yet there is a much broader implication of what they wrote. In their paper, they state: ''Allostasis emphasizes that the internal milieu varies to meet perceived and anticipated demand''. This led us [100] to define allostasis more broadly than the idea of a changing set point, namely, as the process for actively maintaining homeostasis. This is important because, in our view, the systems that vary according to demand, like the HPA axis and ANS, actually help maintain those systems that are truly homeostatic. Moreover, large variations in the HPA axis and ANS do not lead directly to death as would large deviations in oxygen tension and pH.

Therefore, we propose that allostasis is a much better term for physiological coping mechanisms than is homeostasis, which should be reserved for the parameters that are essentially maintained for survival. Therefore, allostasis is the process that keeps the organism alive and functioning, i.e., maintaining homeostasis or 'maintaining stability through change' and promoting adaptation and coping, at least in the short run [94,99].

We note, however, that another view of homeostasis is that it can also mean the operation of coordinated physiological processes which maintain most of the steady states of the organism [16]. In this interpretation, homeostasis and allostasis might seem to mean almost the same thing. The problem with this use of 'homeostasis' is that it does not distinguish between those systems essential for life and those that maintain them.

What are some examples of allostasis? Sterling and Eyer [145] used variations in blood pressure as an example: e.g., in the morning, blood pressure rises when we get out of bed and blood flow is maintained to the brain when we stand up in order to keep us conscious. This type of allostasis helps to maintain oxygen tension in the brain. There are other examples: e.g., catecholamine and glucocorticoid elevations during physical activity mobilize and replenish, respectively, energy stores needed for brain and body function under challenge. These adaptations maintain essential metabolism and body temperature.

Examples of allostasis go beyond the immediate control of body temperature and pH to broader aspects of individual survival, e.g., from pathogens or physical danger. In the immune system, we will see below that acute stress-induced release of catecholamines and glucocorticoids facilitates the movement of immune cells to parts of the body where they are needed to fight an infection or to produce other immune responses [25]. Finally, in the brain, glucocorticoids and catecholamines act in concert to promote the formation of memories of events of potentially dangerous situations so that the individual can avoid them in the future [125]. Yet, each of these adaptive processes has a potential cost to the body when allostasis is either called upon too often or is inefficiently managed, and that cost is referred to as 'allostatic load'.

2.4. Allostatic load

Whereas allostasis refers to the process of adaptation to challenges, 'allostatic load' refers to the price the body pays for being forced to adapt to adverse psychosocial or physical situations, and it represents either the presence of too much allostasis or the inefficient operation of the allostasis response systems, which must be turned on and then turned off again after the stressful situation is over. What are the damaging, as well as the adaptive effects, in different systems? For example, glucocorticoids, so-named because of their ability to promote conversion of protein and lipids to usable carbohydrates, serve the body well in the short run by replenishing energy reserves after a period of activity, like running away from a predator. Glucocorticoids also act on the brain to increase appetite for food and to increase locomotor activity and food seeking behavior [69], thus regulating behaviors which control energy input and expenditure. This is very useful when we do manual labor or play active sports, but it is not beneficial when we grab a pizza and a beer while watching television or writing a paper. Inactivity and lack of energy expenditure creates a situation where chronically-elevated glucocorticoids that may result from either poor sleep, ongoing stress, or as side effects of rich diet can impede the action of insulin to promote glucose uptake. One of the results of this interaction is that insulin levels increase, and, together, insulin and glucocorticoid elevations promote the deposition of body fat and this combination of hormones also promotes the formation of atherosclerotic plaques in the coronary arteries [6].

For the heart, we see a similar paradox. Getting out of bed in the morning requires an increase in blood pressure and a reapportioning of blood flow to the head so we can stand up and not faint [145]. Our blood pressure rises and falls during the day as physical and emotional demands change, providing adequate blood flow as needed. Yet repeatedly elevated blood pressure promotes generation of atherosclerotic plaques, particularly when combined with a supply of cholesterol and lipids and oxygen free radicals that damage the coronary artery walls [87]. Beta adrenergic receptor blockers are known to inhibit this cascade of events and to slow down the atherosclerosis that is accelerated in dominant male cynomologus monkeys exposed to an unstable dominance hierarchy [88]. Thus, catecholamines and the combination of glucocorticoids and insulin can have dangerous effects on the body, besides their important short-term adaptive roles [6].

We now shall consider protective and damaging effects of mediators of allostasis in the immune system and brain, two systems that are less well-understood.

3. Stress and immune function

The immune system is regulated by neural input from sensory, sympathetic and parasympathetic nerves [7], as well as by circulating hormones, of which the glucocorticoids are among the most prominent [97,142]. Long regarded as inhibitors of immune function, adrenal steroids have now been recognized as having biphasic effects upon immune function, as shown recently in studies of delayed-type hypersensitivity (DTH) [25,28]. This makes more sense, because the organism's response to acute challenge is in other respects protective. Under acute stress, energy reserves are mobilized, vegetative processes and reproduction are suppressed, and the body is made ready for fight or flight, which may involve wounding. Thus the immune

defense system should acutely gear up to protect the organism from infections and accelerate wound healing.

A primary underlying mechanism for these effects is the translocation or 'trafficking' of immune cells between the blood and different primary, secondary and tertiary immune tissues (see [7,142]). Elevations of stress hormones, both glucocorticoids and catecholamines, direct the movement of various cell types of the immune system. Lymphocytes, monocytes and NK cells are all reduced in number in blood and increased in number in tissues, such as the skin, as a result of acute stress or acute glucocorticoid administration [27,29] (see Fig. 1).

Once immune cells have marginated and begun to enter the tissue, other factors become involved as local mediators of further activation of immune function. Interferon gamma is an important factor in the stress-enhancement of the DTH response, and this has been shown by a lack of a stress effect in mice lacking the receptor for IFN gamma [30]. Furthermore, immunoneutralization of IFN gamma in normal mice also blocks the stress effect. Thus, although IFN gamma is not required for the baseline DTH response, it is evidently important for the manifestations of the effects of acute stress. IFN gamma is known to induce expression of antigen-presenting and cell-adhesion molecules on endothelial cells and macrophages and cell adhesion molecules on leukocytes. It is also significant that glucocorticoids induce IFN gamma receptors on monocytes. (For discussion and refererences, see [30]).

What about the effects of chronic stress? Acute stress shows a dose dependency to activate the DTH response, and this is related to the magnitude of glucocorticoid secretion [28]. Exogenous glucocorticoids mimic this dose dependency, but at higher glucocorticoid doses, there is an inverted U dose response curve and suppression of the DTH response is seen [25] (see Fig. 2). Dexamethasone, which does not bind to serum corticosteroid binding globulin (CBG), mimics the suppressive effects of high dose glucocorticoids [25]. Chronic stress over 3–5 weeks produces a suppression of the DTH response and also suppressed the initial sensitization of the response [28] (see Fig. 3). An important factor in this suppression is the lack of immune cell trafficking, and this may be due, at least in part, to habituation of the corticosterone response to stress [28].

These findings are relevant to the extensive literature on the effects of stress on immune function in animals and humans [142]. Enhancement of immune function, in the case of an autoimmune disease, may be deleterious, whereas it may be beneficial where there is a pathogen involved; conversely, suppression of immune function may be beneficial where an autoimmune disorder is concerned, whereas it may be dangerous where a pathogen is involved [25]. Thus, the immune system exemplifies the contrasting aspects of 'protection' and 'damage' and the effects of stress and stress hormones are highly relevant to human disease. Now we turn to the brain and consider how it handles both acute and repeated stress.

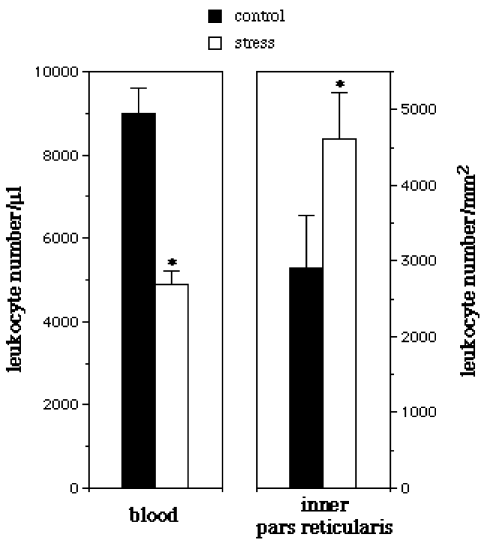

Fig. 1. Immune cells are depleted reversibly from the blood during stress-induced elevation of glucocorticoids and marginate on blood vessel walls and enter tissues such as the skin. From [26].

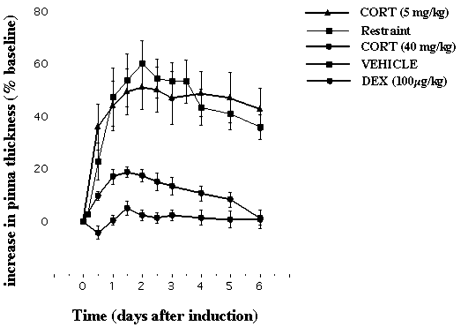

Fig. 2. Physiological doses of corticosterone mimic effects of stress in enhancing the DTH response in the ear, whereas high doses of corticosterone and dexamethasone, which does not bind to CBG, suppresses the DTH response. From [25].

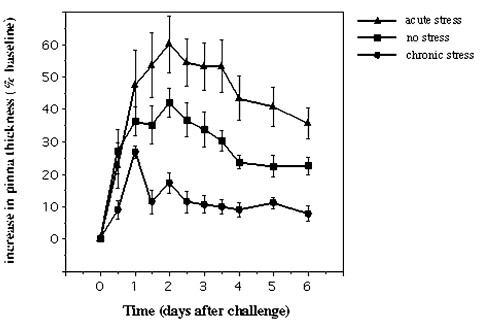

Fig. 3. Acute stress enhances, whereas chronic stress suppresses, the DTH response. From [25,28].

4. Stress, adaptive plasticity and the hippocampus

The brain is the key to interpreting and responding to potentially stressful events; it is also a target for the actions of stress hormones, particularly glucocorticoids. In the short run, acute elevation of both glucocorticoids and catecholamines facilitates the formation of memories of events associated with strong emotions [102,125]. Chronically, however, stress hormones, and glucocorticoids, in particular, contribute to impairment of cognitive function and promote damage to brain structures such as the hippocampus [78,98,127].

The response of the brain to both acute and chronic stress must be regarded in terms of its capacity to show adaptive plasticity. The adult brain is more plastic than previously believed. Remodeling of synaptic contacts and dendrites in the hypothalamus with the onset of lactation [108,146] and growth and branching of dendrites of cerebrocortical neurons in an enriched environment and after training [54,155] are two examples of such plasticity. Recent studies on the hippocampal formation of the brain provides further examples of adult brain plasticity which is regulated by hormones in adult life and during brain development. The hippocampus is involved in episodic, declarative, contextual and spatial learning and memory, as well as a component in the control of autonomic and vegetative functions such as ACTH secretion [34,57,118]. The hippocampus is also vulnerable to damage by stroke and head trauma and susceptible to damage during aging and repeated stress [127].

Hippocampal neurons express receptors for circulating adrenal steroids [101], and work in many laboratories has shown that the hippocampus has two types of adrenal steroid receptors, Type I (mineralocorticoid) and Type II (glucocorticoid) which mediate a variety of effects on neuronal excitability, neurochemistry and structural plasticity [24]. These effects, which involve hormone-mediated effects on gene expression, include the regulation of branching and length of dendrites in the pyramidal cells of Ammon's horn and the replacement of nerve cells in the dentate gyrus. The hippocampus is also sensitive to gonadal hormones and expresses both intracellular androgen and estrogen receptors [63,154]. Gonadal and adrenal hormones participate in functional and structural changes in adult life, as well as in developmental events, which include sexual differentiation and influences of early stressful life experiences.

Many of these hormone effects do not occur alone but rather in the context of ongoing neuronal activity. In particular, excitatory amino acids and NMDA receptors, as well as serotonin, play an important role in the functional and structural changes produced in the hippocampal formation by steroid hormones. With regard to stress effects, two types of adaptive plasticity will be considered in this article, namely, the remodelling of dendrites of hippocampal pyramidal neurons in response to repeated stress and chronic elevation of glucocorticoids and the inhibition of neurogenesis of granule cells in the dentate gyrus (see Fig. 4).

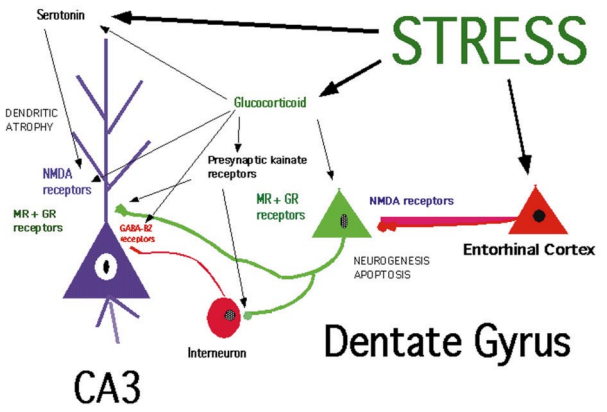

Fig. 4. Schematic diagram of the role of neurotransmitters and glucocorticoids in regulating neurogenesis and dendritic remodeling in the dentate gyrus-CA3 system of the hippocampal formation. Granule neurons are replaced in adult life, and neurogenesis, as well as apoptotic neuronal death, are regulated by stress as well as by seizure-like activity. Granule neurons send mossy fibers to both the CA3 pyramidal neurons and to interneurons in the hilus, which, in turn, send inhibitory projections to the CA3 pyramidal neurons. The balance between the excitatory input and the inhibitory tone from the interneurons is presumed to be very important to the excitability of CA3 neurons. Evidence summarized in the text indicates that excitatory amino acid release during repeated stress, aided by circulating glucocorticoids, leads to a reversible remodeling of apical dendrites over 3–4 weeks in rats and tree shrews. Serotonin also participates, possibly by aiding the excitatory amino acid activity at the NMDA receptor, and reduced GABA-benzodiazepine-mediated inhibitory activity at synapse from the interneurons on CA3 pyramidal neurons may also exacerbate the remodeling. Excitatory input to the dentate granule neurons from the entorhinal cortex acts via NMDA receptors in concert with circulating adrenal steroids to regulate the rate of neurogenesis and apoptotic cell death, and both acute and chronic stress appear to be capable of inhibiting neurogenesis in the dentate gyrus.

5. Remodelling of dendrites in hippocampal neurons

5.1. Role of excitatory amino acids

Remodelling of dendrites in hippocampal neurons was first described after treatment of adult male rats for 21 days with exogenous glucocorticoids [157] (reviewed in [96]). Subsequently, chronic restraint stress for 21 days in rats produced apical dendrites of CA3 pyramidal neurons to atrophy [104]. Stress- and CORT-induced atrophy were prevented by the anti-epileptic drug, phenytoin (Dilantin), thus implicating the release and actions of excitatory amino acids, since phenytoin blocks glutamate release and antagonizes sodium channels and possibly also T-type calcium channels that are activated during glutamate-induced excitation; this result was consistent with evidence that stress induces release of glutamate in hippocampus and other brain regions (see [72,110]). NMDA receptor

blockade is also effective in preventing stress-induced dendritic atrophy (see [96] for review).

5.2. Dendritic remodelling throughout the hippocampus?

A recent study using a multiple stress paradigm over 4 weeks has demonstrated that the remodelling of dendrites found in CA3 also occurs in the dentate gyrus and in CA 1, although the effects in the CA3 tend to be the greatest [141] (see Fig. 5). This important finding provides the basis for expecting that remodelling of dendrites could be a factor in the shrinkage of the hippocampus reported in a number of disorders such as recurrent major depression and aging with mild cognitive impairment (see [95,129] for review).

5.3. Importance of other neurotransmitters

Besides glutamate, other participating neurotransmitters include GABA and serotonin. As far as GABA, inhibitory interneurons have a significant role in controlling hippocampal neuronal excitability [39], and the involvement of the GABA-benzodiazepine receptor system is revealed by the ability of a benzodiazepine, adinazolam, to block dendritic atrophy [79]. Serotonin is released by stressors, and tianeptine, an atypical tricyclic antidepressant that enhances serotonin reuptake and thus reduces extracellular 5HT levels. Tianeptine prevented both stress- and corticosterone-induced dendritic atrophy of CA3 pyramidal neurons [149], whereas fluoxetine and fluvoxamine, inhibitors of serotonin reuptake, and desipramine, an inhibitor of noradrenaline uptake, failed to block atrophy [79]. Further evidence for serotonin involvement in dendritic atrophy comes from studies of psychosocial stress in rats, summarized below.

Because both phenytoin and tianeptine block corticosterone- and stress-induced atrophy of CA3 pyramidal neurons (see [96]), serotonin released by stress or by corticosterone may interact pre- or post-synaptically with glutamate released by stress or by corticosterone, and the final common path may involve interactive effects between serotonin and glutamate receptors on the dendrites of CA3 neurons innervated by mossy fibers from the dentate gyrus. There is evidence for interactions between serotonin and NMDA receptors, indicating that serotonin potentiates NMDA receptor binding as well as activity of NMDA receptors and may do so via 5-HT_2 receptors [107,120].

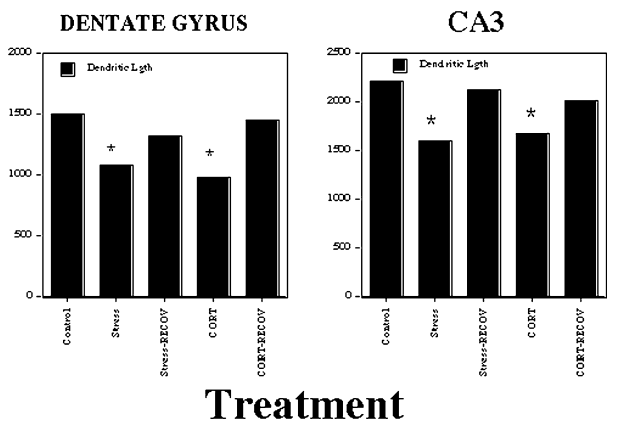

Fig. 5. One month of a multiple stress paradigm or daily corticosterone treatment causes dendrites in CA3 and dentate gyrus to become shorter in total length. Note that the effects of both stress and corticosterone treatment are reversible within several weeks. Data from [141].

5.4. Involvement of glucocorticoids

Glucocorticoid treatment causes dendritic atrophy, and stress-induced atrophy is blocked by treatment with an adrenal steroid synthesis blocker, cyanoketone (see [96]), indicating a role of endogenous glucocorticoids in stress-induced dendritic atrophy. There appear to be several ways in which glucocorticoids affect the excitatory amino acid system. First, adrenal steroids modulate expression of NMDA receptors in hippocampus [2,152], with chronic glucocorticoid exposure leading to increased expression of NMDA receptor binding and both NR2A and NR2B subunit mRNA levels [153]. Second, there are glucocorticoid effects on the expression of mRNA levels for specific subunits of GABAa receptors in CA3 and the dentate gyrus; both low and high levels of CORT have different effects on GABAa receptor subunit mRNA levels and receptor binding ([114], Orchinik, Weiland and McEwen, unpublished), suggesting corticosterone may alter the excitability of hippocampal neurons through regulation of GABAa receptor expression. However, it remains to be seen if the corticosteroid effects on neuronal morphology involve changes in the number or pharmacological properties of GABAa receptors.

Third, adrenal steroids regulate the release of glutamate, since adrenalectomy markedly reduces the magnitude of the EAA release evoked by restraint stress [72]. Mossy fiber terminals in the stratum lucidum contain presynaptic kainate receptors that positively regulate glutamate release [17]; these presynaptic kainate receptors are decreased in density by ADX and restored to normal by corticosterone replacement [151]. Moreover, repeated stress causes a reorganization of synaptic vesicles within mossy fiber terminals, as reported recently using electron microscopy [85]. Whereas mossy fiber terminals (MFT) from control rats were packed with small, clear synaptic vesicles, terminals from rats receiving 21 days of restraint stress showed a marked rearrangement of vesicles, with more densely packed clusters localized in the vicinity of active synaptic zones. Moreover, compared with controls, restraint stress increased the area of the mossy fiber terminal occupied by mitochondrial profiles, which implies a greater, localized energy-generating capacity. A single stress session did not produce these changes either immediately after or the next day following the restraint session [85].

6. Neurogenesis in the dentate gyrus

6.1. Effects of adrenalectomy and adrenal steroids

Neurogenesis in the dentate gyrus of adult rodents was reported [58,59] but never fully appreciated until recently, and the reactivation of this topic occurred in an unusual manner. First, bilateral adrenalectomy (ADX) of an adult rat was shown to increase granule neuron death by apoptosis [53,140]. Subsequently, neurogenesis was also found to increase following ADX in adults rats [11], as well as in the developing dentate gyrus [12]. In adult rats, very low levels of adrenal steroids, sufficient to occupy Type I adrenal steroid receptors completely blocks dentate gyrus neuronal loss [156]; but, in newborn rats, Type II receptor agonists protect against neuronal apoptosis [51]. This is consistent with the fact that dentate neuronal loss in the developing rat occurs at much higher circulating steroid levels than in the adult and it represents another example of the different ways that the two adrenal steroid receptor types are involved in hippocampal function [78].

In adult rats, newly-born neurons arise in the hilus, very close to the granule cell layer, and then migrate into the granule cell layer, presumably along a vimentin-staining radial glial network that is also enhanced by ADX [10]. Most neuroblasts labeled with [^{3}H] thymidine lack both Type I and Type II adrenal steroid receptors [10], indicating steroidal regulation occurs via messengers from an unidentified steroid-sensitive cell that may involve a signalling role for TGF alpha and the EGF receptor system [147].

6.2. Aging, glucocorticoids and neurogenesis

It has been reported that neurogenesis declines in the aging rodent [61] and rhesus monkey [36] dentate gyrus. Recent studies of aging rats showed that adrenalectomy could reverse the decline in dentate gyrus neurogenesis [15], suggesting that they are the result of age-related increases in HPA activity and glucocorticoid levels that have been reported [68,93,127,128].

6.3. Neurogenesis in different mammalian species

The question whether dentate gyrus neurogenesis is a widespread phenomenon among mammals was addressed recently by studies showing that neurogenesis occurs in the marmoset [52], a new-world primate, as well as in an old-world primate species, the rhesus monkey [36] and in the adult human dentate gyrus [35]. Thus, changes in size of the human hippocampus, described below, may include changes in neuron number in the dentate gyrus.

6.4. Regulation of neurogenesis

Granule neuron birth is accelerated by seizure-like activity [116] and the stimulus for this neurogenesis is likely to be apoptotic cell death because seizures kill granule neurons [3] and local increases in apoptosis simulate local neurogenesis [13]. Granule neuron birth is also accelerated by blocking NMDA receptors or lesioning the excitatory perforant pathway input from the entorhinal cortex [14]. Unlike ADX, these treatments do not increase granule neuron apoptosis, and a single dose of an NMDA-blocking drug results in a 20% increase in dentate gyrus neuron number several weeks later [14]. Thus, although increased apoptosis leads to increased neurogenesis [49], the two processes occur in different regions of the granule cell layer and can be uncoupled from each other. Nevertheless, the adrenal steroid suppression of neurogenesis is through an NMDA-receptor mechanism [50,111].

Very recently it was reported that serotonin may be a positive signal for neurogenesis in the adult dentate gyrus. Treatment with the serotonin-releasing drug, *d*-fenfluramine, increased neurogenesis [46]. Likewise, the 5HT1A agonist, 8-hydroxy-DPAT, stimulated neurogenesis, whereas blockade of 5HT1A receptors had the opposite effect and prevented the effect of *d*-fenfluramine treatment [46], as well as preventing increased neurogenesis caused by pilocarpine-induced seizures [119].

6.5. Role in learning and memory?

One reason for turnover of dentate gyrus granule neurons in adult life is to adjust needs for hippocampal function in spatial learning and memory to environmental demands [137]. Birds that use space around them to hide and locate food, and voles as well as deer mice that traverse large distances to find mates, have larger hippocampal volumes than closely-related species which do not; moreover, there are indications that hippocampal volume may change during the breeding season [41,137]. Indeed, the rate of neurogenesis in the male and female prairie vole varies according to the breeding season [42]. In contrast, an enriched environment has been found to increase dentate gyrus volume in mice by increasing neuronal survival without altering the rate of neurogenesis [60]. Thus, there are several ways to maintain the balance between neuronal apoptosis and neurogenesis.

Learning that involves the hippocampus also appears to affect the survival of newly-formed dentate granule neurons. When rats were trained in a task involving the hippocampus, the survival of previously labelled granule neurons was prolonged [47]. Changes in dentate gyrus volume appear to have consequences for cognitive functions subserved by the hippocampus. In the enriched environment studies [60], increased dentate gyrus volume was accompanied by better performance on spatial learning tasks. In contrast, decreased dentate gyrus volume in chronically stressed tree shrews is paralleled by impaired spatial learning and memory [112], although this might be as much due to atrophy of dendrites of CA3 pyramidal

neurons and dentate granule neurons (see above) as to reduced dentate gyrus neurogenesis.

7. Experimenter-applied stressors: restraint and multiple stress effects

A closer examination of the effects of stressors on structural plasticity in the hippocampus and neurochemical changes in other brain regions reveals some important properties of both experimenter-applied stressors and natural psychosocial stressors which emphasize the adaptive nature of these changes in brain structure and the complex interactions between circulating stress hormones and neurotransmitters.

Contrary to expectations, there is no consistent relationship between stress-induced dendritic remodelling in hippocampus and elevated glucocorticoid secretion or other signs of chronic stress such as thymus atrophy, adrenal hypertrophy and body weight reduction. As noted above, a recent study showed that a chronic multiple stress paradigm, which is designed to avoid habituation of glucocorticoid responses to the same stressor, produced dendritic remodelling not only in the CA3 region of the hippocampus but also in the dentate gyrus and CA1 [141]. Glucocorticoid treatment mimicked the effects of stress, and the effects of both treatments were largely reversible after termination of the treatment [141]. See Fig. 5.

We showed previously that a similar multiple stress paradigm, consisting of daily 1-h restraint, 1-h shaking, 30′ swim in body-temperature water, did indeed produce continued elevation of glucocorticoids throughout the 21-day paradigm, in contrast to 21 days of 6 h/day restraint stress which did produce habituation of the glucocorticoid stress response [80] (see Fig. 6). Yet both treatments caused similar degrees of dendritic remodelling in CA3 (Fig. 7) and both treatments produced non-significant atrophy of the thymus and hypertrophy of the adrenal gland and moderate decrease in body weight gain over 21 days (Table 1). In spite of the minimal changes in the expected parameters of chronic stress, blockade of glucocorticoid synthesis with cyanoketone prevented dendritic remodelling [81] and oral administration of glucocorticoids, which does not involve the stress of injection, causes dendritic remodelling [79,84].

We noted above that dendritic remodelling is reversible following the termination of stress or corticosterone treatment [19,141]. Moreover, we also noted that both Dilantin and tianeptine prevent dendritic remodelling caused by repeated restraint stress and glucocorticoid injections. Treatment with tianeptine is able to reverse the remodelling produced by 21 days oral corticosterone and to do so within 2 weeks even while the corticosterone treatment is continuing.

A final note on the structural plasticity produced by repeated restraint stress is that dentate gyrus neurogenesis

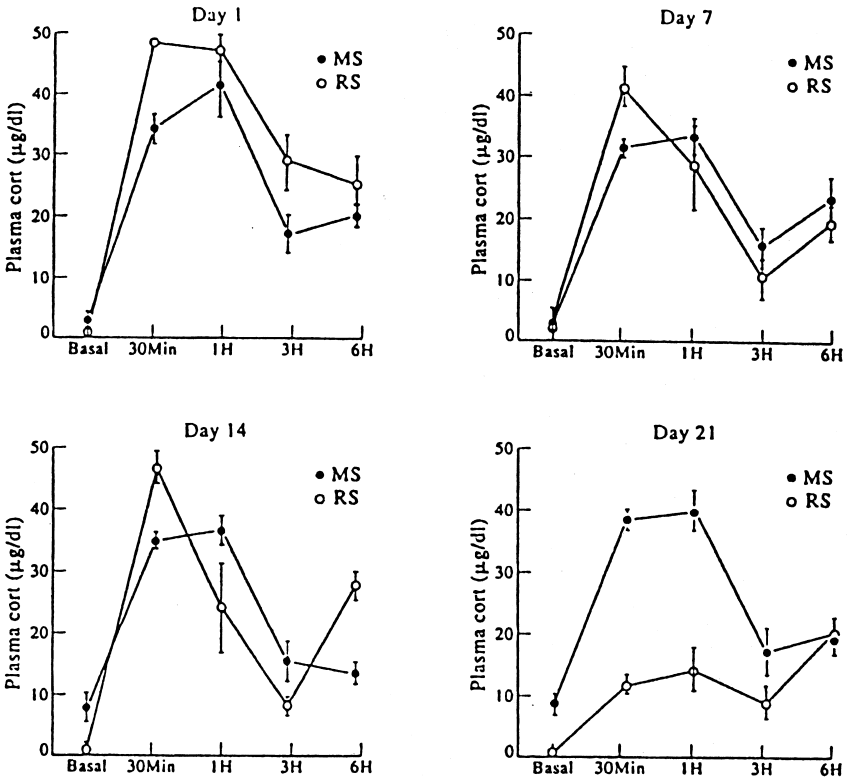

Fig. 6. Comparison of the elevation of corticosterone over repetitions in a multiple stress paradigm with the effects of repeated restraint stress. Note that the HPA response habituates with the restraint stress paradigm but not after multiple stress. Reprinted from [80] by permission.

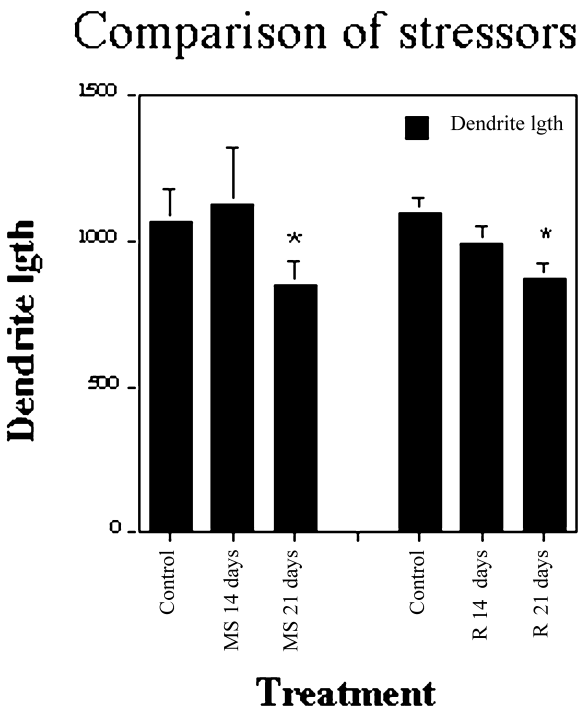

Fig. 7. CA3 apical dendritic length over 3 weeks of either a multiple stress paradigm or a repeated restraint stress paradigm. Note that both types of stress cause shortening of dendrites but only after 3 weeks. Data from [80].

is not inhibited by a single acute restraint stress but is impaired after 21 days of daily restraint [117]. The reduction in neurogenesis is not as large as has been reported in rats after natural predator odor [44] or in tree shrews after acute or chronic psychosocial stress [48]. We will return to this topic in the next section.

We interpret these effects as further evidence of the importance of endogenous neurotransmitters along with glucocorticoids in the regulation of structural plasticity in the hippocampus. As noted above, serotonin and NMDA receptors are both implicated as mediators of dendritic remodelling, and GABA-benzodiazepine receptors play an opposing role. Moreover, as noted earlier, in the regulation of neurogenesis, serotonin acting via 5HT1A receptors plays an opposing role to glucocorticoids and NMDA receptors.

The multiplicity of regulatory factors for structural plasticity in the hippocampus is consistent with the interpretation of these changes as reflecting adaptive plasticity, rather than as a pathway leading to damage. Behavioral changes accompanying repeated restraint stress fit with this view and provide additional surprises. In spite of the apparent habituation of the HPA response to repeated restraint stress, these animals develop increased fear in an open field apparatus and showed increased fear conditioning to both tone and contextual cues [19]. Moreover, repeatedly restrained rats show progressively increasing aggression towards their cage mates after they are released from their restrainers (G. Wood and B. McEwen, unpublished).

Table 1
Summary of changes in body weight, thymus and adrenal weights after repeated stress[a]

	Body weight 1	Adrenal wt. 2	Thymus wt. 3
Restraint stress, 21 days			
Control	100%	16±1	138±13
1 week	90*	n.d.	n.d.
2 weeks	88*	17±1	150±17
3 weeks	88*	16±1	122±15
Chronic multiple stress, 21 days			
Control	100%	11±0.4	176±11
1 week	93*	n.d.	n.d.
2 weeks	89*	14±0.7*	140±12
3 weeks	100	12±0.4	126±10*

[a] Data from [80].
*Significantly different from control, $P<0.05$.

8. Animal to animal stress

The theme of adaptive plasticity in the face of repeated stress is further documented by studies of more naturalistic types of stressors, and these studies provide additional clues as to the multiplicity of neurochemical pathways affected by chronic stressors. In the tree shrew, a resident–intruder paradigm was used to produce chronic psychosocial stress in the intruder over 28 days. This procedure caused the same type of dendritic remodelling of CA3 neurons in the tree shrew as was found in the rat; moreover the effects of this type of stress were prevented by concurrent treatment of intruder tree shrews with Dilantin [83]. Dilantin treatment did not prevent the stress-induced elevation in catecholamines and glucocorticoids, and the HPA response was very robust and showed no signs of habituating over time, in contrast to the story with repeated restraint stress (see above) [83].

Neurogenesis was inhibited by both acute and chronic psychosocial stress in the intruder tree shrew [48], and this effect was substantially larger than that seen in rats after chronic restraint stress (see above) (see Fig. 8). Moreover, the dentate gyrus is 30% smaller in the chronically-stressed tree shrew, although granule neuron number shows a smaller reduction (Gould, Fuchs and McEwen, unpublished). This finding suggests that there may be other changes such as atrophy of dendritic branching to account for the decrease in dentate gyrus volume. It should also be noted that neurogenesis is inhibited in the marmoset after acute psychosocial stress [48].

Another important animal model to study psychosocial stress is the visible burrow system (VBS) in the rat [4].

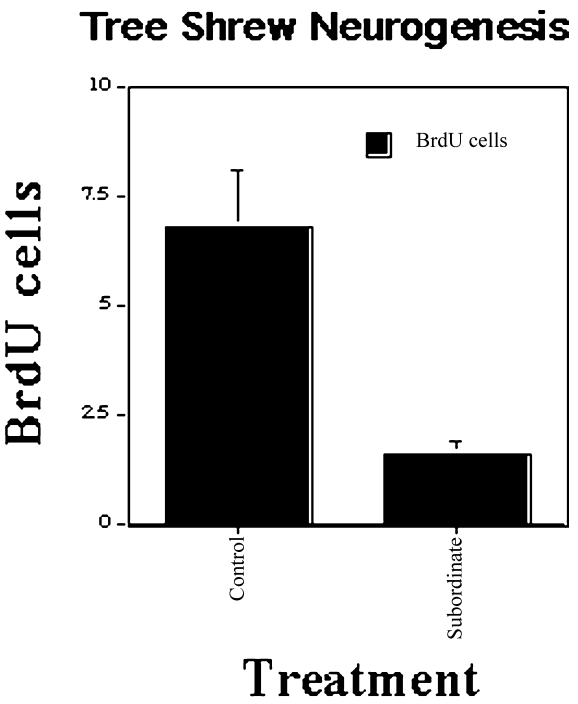

Fig. 8. Acute psychosocial stress inhibits neurogenesis in the dentate gyrus of an adult tree shrew. The stress consisted of putting a tree shrew into the territory of a dominant tree shrew. Data from [48].

Table 2
Summary of changes in dominant and subordinate rats under psychosocial stress in the visible burrow

Endocrine parameters:
Dominants and subordinates show:
Elevated CORT
Adrenal hypertrophy
Thymic involution
Subordinates show:
Progressive weight loss
Greater thymic involution
Decreased CBG
Decreased testosterone
Decreased insulin and glucose
Non-responsive subordinates show:
Largest body weight loss
Lowest testosterone
Lowest CBG
No response to novel stressor
Neural parameters:
Dominants and subordinates show:
CA3 dendritic remodelling
Down regulation of 5HTT in hippocampus
Down regulation of 5HT1a receptors in hippocampus
Decreased 5HT1A receptors
Increased CRF mRNA in hypothalamus
Dominants show:
Somewhat more dendritic remodelling
Somewhat greater down-regulation of 5HTT in hippocampus
Subordinates show:
Increased CRF mRNA levels in central nucleus of amygdala
Increased tyrosine hydroxylase mRNA and protein in locus coeruleus
Increased 5HT2A receptor binding in layer IV of parietal cortex
Down-regulation of GR and MR mRNA in CA1 of hippocampus
Non-responsive subordinates show:
Decreased CRF mRNA in hypothalamus
Somewhat less decrease of 5HT1A receptors in hippocampus
Somewhat less down-regulation of GR and MR mRNA in CA1 of hippocampus

Five males and two females are placed in an apparatus that has an open chamber and tunnels and compartments, and there is a videocamera to record the animals' behavior. A dominant male usual emerges within several days and controls access to the food and water cups and to the females. Within the 2-week span of this study, it is not uncommon for one or two of the subordinate males to die, usually not so much from wounds as from autonomic collapse related to defeat. A complex set of neuroendocrine and neurochemical changes has been found for the dominants and subordinates, which are both experiencing stress compared to control animals living in the normal cage environment (see Table 2). The most striking difference is among the subordinates, in which two types have been recognized. The non-responders are so identified because they show an attenuated HPA response to acute restraint stress and also show a reduced level of CRH mRNA in the hypothalamus [1].

For rats in the VBS and the intruder tree shrew there is a parallel involvement of serotonin. In the VBS, both dominant and subordinate rats show both dendritic remodelling, and they also show a down-regulation of 5HT transporter expression in the CA3 region, indicating either a reduced density of serotonin terminals or a reduced expression of the transporter [65]. Moreover, repeated restraint stress and psychosocial stress in rats suppresses expression of the inhibitory 5-HT1A receptor in the hippocampus, and this is also true in the intruder tree shrews described above [38,96,104]. These stress-induced changes are relevant to the suspected role of 5HT1A receptors in anxiety disorders and depression [71]. For example, deletion of the 5HT1A receptor in mice results in increased anxiety, due in part to an impairment of the GABA-benzodiazepine system [122,138].

In the VBS, there is also an up-regulation of 5HT2A receptors in the cerebral cortex [103]. This also has relevance to depressive illness, since the inactivation of the 5HT2A receptor by antisense induces an antidepressant-like effect in mice [139]. Thus, animal models involving severe psychosocial stress of one animal by other conspecifics produce brain changes that are relevant to human psychiatric conditions such as anxiety and depression. And there are other aspects of the findings described above that

are relevant to human psychiatric and neurological disorders.

9. Implications for cognitive function and human psychiatric disorders

We have seen that the serendipitous discovery of adrenal steroid receptors in hippocampus led to findings about the vulnerability of the hippocampus in relation to stress, aging, seizures and head trauma in animal models of these conditions. The advent of magnetic resonance imaging (MRI) and positron emission tomography (PET) has opened the door for translating information based upon animal models of neurological and psychiatric disorders to directly studying patients with those disorders. In particular, changes in hippocampus in animal models provide insights into altered human hippocampal structure and function in depression and aging. First, we will consider the effects of stress and glucocorticoids on cognitive function and then review some of the evidence from brain imaging for structural changes in the hippocampus, amygdala and prefrontal cortex.

9.1. Stress, glucocorticoids and cognition

Stress and glucocorticoids have specific effects on cognitive function in humans and in animal models. Adrenal steroids and stressful experiences produce short-term and reversible deficits in episodic and spatial memory in animal models and in humans [78], whereas repeated stress also impairs cognitive function in animal models and repeated glucocorticoid elevation or treatment in humans is accompanied by cognitive dysfunction [98]. There are also declines in cognitive function in aging humans that are correlated with progressive elevations in HPA activity over 3–4 years [76,132].

Acute effects of stress or glucocorticoid administration are evident within a time span ranging from a few hours to a day and are generally reversible and quite selective to the task or particular situation [66,78]. Adrenal steroid effects are implicated in both selective attention as well as in memory consolidation [78], and such actions are consistent with the effects of adrenal steroids on the modulation of long-term potentiation and primed-burst potentiation (see above). However, some acute actions of stress may involve other mechanisms than glucocorticoids, including endogenous opioid neuropeptides in the case of painful stressors like shock (see [96] for summary). With regard to non-painful stressors, exposure of rats to a novel environment resulted in a rapid and reversible impairment of plasticity in vivo in the CA1 region and this effect may involve the actions of glucocorticoids [31].

Repeated stress that produces dendritic atrophy in the CA3 region impairs hippocampal-dependent learning. Rats that received 21 days of restraint stress were impaired in performance on an eight-arm radial maze when they were trained starting one day after the end of stress but not when trained 18 days later [74]. We now know that dendritic atrophy is reversible within 7–10 days after the end of stress [19]. The impairment was in the same direction, but not as great as, impairment found in aging rats. Moreover, stress effects were prevented by prior treatment of rats with phenytoin or with tianeptine under the same conditions in which both drugs prevented the stress-induced atrophy of CA3c pyramidal neurons [74,149,150]. A subsequent study showed that 21 days of repeated restraint stress impaired the short-term (4 h) retention of a spatial recognition memory in a hippocampus-dependent Y-maze task; again, stress impairment was prevented by tianeptine treatment during the stress regimen [18].

9.2. Atrophy of the human hippocampus and other brain structures

The human brain shows signs of atrophy as a result of elevated glucocorticoids and severe, traumatic stress (e.g., holocaust survivors, see [127]). However, it has been very recently only that brain-imaging techniques have allowed for a regional analysis of the atrophy of various brain structures to see which ones are most affected. Recent evidence indicates that the human hippocampus is particularly sensitive in this respect and tends to show greater changes than other brain areas, in particular in Cushing's syndrome, recurrent depressive illness, post-traumatic stress disorder (PTSD, schizophrenia and aging prior to overt dementia [5,40,55,126,135,136,143,144]).

For example, declines of hippocampally-related cognitive functions, such as spatial and episodic memory, occur in human subjects and are correlated with increases in HPA activity over 4–5 years [76,132]. Recent evidence has revealed that the most severely impaired individuals have a significantly smaller hippocampal volume compared to the least impaired individuals [75]. This result is consistent with other findings of individual differences in cognitive function correlated with hippocampal volume reductions in elderly humans [20,45].

In women with recurrent depressive illness, the magnitude of hippocampal atrophy is related to the duration of the symptoms of the disorder and not the age of the individuals [135].

The diversity of conditions in which atrophy occurs raises the question whether they reflect a common mechanism and whether the atrophy is permanent or reversible. Based upon what we have summarized above, the atrophy might be due to reduced volume of Ammon's horn or dentate gyrus due to reduced dendritic branching, to a reduction in dentate gyrus neuron number due to a suppression of neurogenesis or a decreased rate of neuron survival, or to permanent neuron loss. In addition, it is noteworthy that atrophy of other brain regions has been reported in depressive illness, e.g, prefrontal cortex [33]

and amygdala [134]. Moreover, new evidence suggests that glial cell depletion may contribute to atrophy of brain regions like the prefrontal cortex and amygdala [32,113,121,134,135] and the contribution of glial cell changes must now be considered in the hippocampus.

It is tempting to attribute the occurrence of hippocampal atrophy to glucocorticoids. This is because the hippocampus is a primary target area for adrenal steroids in brain, and adrenal steroids have been shown to have effects on hippocampal neuronal plasticity and on the loss of hippocampal neurons in conditions like ischemia and aging [68,96,127,128]. However, we have seen earlier in this article that other factors play a role, including the endogenous excitatory amino acid neurotransmitters. Moreover, changes in dentate gyrus neuron number may be involved along with atrophy of dendritic processes. Nevertheless, the role of glucocorticoids should not be ignored. Glucocorticoids are elevated in Cushing's syndrome and may also be somewhat elevated in depressive illness, but this is probably not the case for PTSD, at least at the time they are studied, except as there are elevations in glucocorticoids associated with the diurnal rhythm and stressful experiences that take place on a daily basis.

Sustained stress-level of Cushingoid elevations of adrenal steroids are not required for atrophy of hippocampal neurons, since we have already noted above that in the animal models of stress-induced atrophy, ordinary, periodic adrenocortical stress responses are all that is needed for the process to occur with daily stress. With regard to human hippocampal atrophy, individual differences in stress responsiveness may play a role in making some people more vulnerable to their own stress hormones: e.g., some individuals who are exposed to repeated psychosocial stress (e.g., public speaking) fail to habituate their cortisol elevation; these individuals lack self-esteem and self-confidence [65]. Therefore, one could imagine that individuals with a more reactive stress hormone profile will expose themselves to more cortisol and experience more stress-elevated neural activity, than other people who can more easily habituate to psychosocial challenges.

In this regard, events related to trauma leading to PTSD and the course of illness in recurrent depressive illness may involve very distinct pathways of selective and repeated elevations of glucocorticoid hormones in relation to the individual experiences and reactivities. In the case of PTSD, we are ignorant of stress responses and neurochemical changes accompanying the initial trauma, which may have taken place 10–20 years ago, as well as the ongoing stress responsiveness and neurochemical activity (e.g., brain glucose metabolism) of traumatized individuals. Likewise, for recurrent depressive illness, we are largely ignorant of the history of the depressed individual as far as endocrine function and neurochemical activity, as well as responses to stressful life experiences. In both disorders, a long-term pattern of increased neurochemical, autonomic and HPA reactivity to experiences may underlie a progression of neuronal structural changes, involving atrophy that might lead to permanent damage, including neuronal loss.

Regarding reversibility, treatment with drugs like phenytoin or tianeptine, both of which block stress-induced atrophy, is a potential means of testing both the mechanism and at the same time, demonstrating the reversibility of human hippocampal atrophy. There is already some indication that hippocampal atrophy in Cushing's syndrome is reversible [144]. On the other hand, there may be irreversible loss of hippocampal neurons, and some of the evidence from MRI concerning hippocampal abnormalities in recurrent depressive illness is consistent with this possibility [136]. In so far as atrophy of the hippocampus and accompanying cognitive impairment are signs of reversible neuronal atrophy, they may be treatable with agents that block the neuronal atrophy in animal models. On the other hand, where atrophy involves neuronal loss, treatment strategies should focus on the earlier traumatic or recurrent events, and it may be possible to devise strategies to reduce or prevent neuronal damage.

10. Future directions

Research on the hippocampus in animal models and human disorders has established that the brain is a resilient structure that is capable of adaptive plasticity but is also vulnerable to damage. While illuminating many aspects of mechanisms underlying plasticity and opening the door for therapeutic interventions, recent research on this topic has also raised some important questions that form the basis of future studies. First, what are the conditions that determine whether brain structures will respond with adapative plasticity or show permanent damage? Second, how does the vulnerability to permanent damage change in the aging brain? And third, how do gender differences in the response to stressful challenges influence the brain's response in terms of resilience or damage?

10.1. From protection to damage

The concept of allostasis and allostatic load imply that normal attempts of the body to adapt to stressful challenges and a changing environment exact a cost on the body in terms of wear and tear on tissues and organs that impair their normal function, as well as a progressive failure of the systems that mediate allostasis to operate efficiently. An example of wear and tear is the stress-induced remodelling of hippocampal dendrites and reduction of dentate gyrus neurogenesis, described above, in which the combined actions of circulating glucocorticoids and excitatory amino acids are involved in changes that lead to cognitive impairment and other behavioral alterations.

As far as the progressive failure of the mediators of

allostasis, the aging process provides several good examples as far as the hippocampus is concerned. Aging is accompanied in some individuals by an elevated level of glucocorticoids and a failure of the HPA axis to shut off efficiently in the aftermath of activation [67,93,105,127,128]. According to the glucocorticoid cascade hypothesis of stress and aging [130], the progressive failure of the hippocampus to exercise its role in shutting off the HPA axis leads to further elevation of glucocorticoids and further damage to the hippocampus during the aging process. We have seen that evidence for individual differences in human hippocampal aging is consistent with this model [77].

Long-term stress accelerates a number of biological markers of aging in rats, including increasing the excitability of CA1 pyramidal neurons via a calcium-dependent mechanism and causing loss of hippocampal pyramidal neurons [64]. An important factor may be the enhancement by glucocorticoids of calcium currents in hippocampus [62], in view of the key role of calcium ions in destructive as well as plastic processes in hippocampal neurons [91,92]. Another aspect making the aging hippocampus more vulnerable may be the persistence of excitatory amino acid release after the termination of a stressful experience [73].

We have seen earlier in this article that, besides glucocorticoids, excitatory amino acids are also important players in the structural remodelling of the hippocampus. The same is true for hippocampal damage produced by ischemia, seizures and head trauma [127]. The release of glutamate as a neurotransmitter is a good example of allostasis that leads to transmission of nerve impulses and learning and memory, and the failure to efficiently terminate this release and/or recapture the glutamate after release leads to an example of allostatic load. Such a situation has been encountered in the aging rat brain. Under restraint stress, rats show increased extracellular levels of glutamate in hippocampus, as determined by microdialysis, and adrenalectomy markedly attenuates this elevation [72]. Glucocorticoids appear to be involved in potentiating the increased extracellular levels of excitatory amino acids under stress [110]. Similar results have been reported using lactography, a method that is based upon the stimulation of glucose metabolism by increased neuronal activity [23,131]. In aging rats, hippocampal release of excitatory amino acids during restraint stress is markedly potentiated [73], and this constitutes an example of allostatic load in the brain, representing a failure to shut off the production and/or removal of a mediator of neuronal activation.

In considering the resilient brain that shows reversible remodelling of dendrites in the hippocampus after repeated stress, we must consider the mechanisms that protect the brain and counteract the potential for permanent damage. Glucose availability is a key factor, and Sapolsky has referrred to an ‘energy crisis’ in which inability to obtain sufficient glucose leads to excitotoxic cell death. Sapolsky and coworkers have had some success in reducing excitotoxic damage by introducing glucose transporters in viral vectors [115]. Diabetes is a condition in which tissues may be unable to obtain sufficient glucose. The streptozotocin (STZ) model of Type I diabetes has provided a model in which the absence of insulin creates a hyperglycemic state as well as an elevation of glucocorticoids. STZ diabetes results in an acceleration of the remodelling of dendrites in the hippocampus, in that diabetic animals without additional stress display within 10 days the same morphological changes that non-diabetic rats show after 21 days of stress or glucocorticoid treatment; moreover, restraint stress causes additional dendritic remodelling within 7 days [82]. In addition, there are signs of astroglial reactivity and the appearance of damaged synapses and neuron cell bodies that suggest the beginning of permanent damage (Magarinos, unpublished). Studies are underway to evaluate the levels of glucose transporter proteins and mRNA in the hippocampus [124], as well as insulin-like growth factor expression [123].

10.2. Determinants of individual differences in stress reactivity in early development

Individual differences in rates of brain aging and hippocampal atrophy are evident in longitudinal studies on human subjects (see above and [76,77,132]). Individual differences in stress reactivity are also seen in rats, and this reactivity can be increased by early maternal deprivation and decreased by separating pups from their mothers for brief periods of time, resulting in increased maternal care when the pups are reunited with their mothers [8,9,70]. As discussed elsewhere [105,106], such early experiences can either increase or decrease the rate of brain aging through a mechanism in which the activity of the HPA axis appears to be involved. The early experiences are believed to set the level of responsiveness of the HPA axis and autonomic nervous system in such a way that these systems either over-react in animals subject to early unpredictable stress or under-react in animals exposed to the neonatal handling procedure.

There are situations in both the animal model literature and in studies of children exposed to early trauma or neglect in which alterations in emotionality and HPA axis functioning have been described. In studies on infrahuman primates, maternal deprivation and peer rearing and the variable foraging demand model have both been linked to later increases in psychopathology [21,22,56]. In children exposed to physical and sexual abuse, there are indications of later life problems such as substance abuse, hostility and antisocial behavior, suicide and a host of physical illnesses reflecting a general systemic disregulation [37].

10.3. Sex differences in response to stress and glucocorticoids

Sex differences in response to stress have been noted

above and imply that either the sexual differentiation of the hippocampus or the presence of circulating hormones affects how the hippocampus responds to stress. Stress effects on dendritic atrophy occur in males but not in females [43]. Moreover, pyramidal neuron loss was evident in subordinate male vervet monkeys, but not in females, after prolonged psychosocial stress [148], and evidence of neuronal damage in rats undergoing cold-swim stress was evident in males, but not in females [109]. However, after estrogens are absent, the female hippocampus may be vulnerable to functional impairment, judging from the report that women who showed an increase in overnight urinary cortisol over 2.5 years showed declines in cognitive performance on hippocampal-related memory tasks [132].

11. Conclusions

Studies of how acute and repeated stress affect the hippocampus and immune system reveal a degree of resilience that is not normally appreciated. The protective and adaptive effects of the mediators of allostasis are capable of promoting adaptive plasticity. In the case of the immune system, this takes the form of the movement of immune cells to sites where they are needed to respond to a challenge. Where the immune response is to a pathogen, the enhancement of the response is beneficial; where an autoimmune response is involved, the outcome may by deleterious. Glucocorticoids and catecholamines play an important role but act in concert with other tissue-specific regulators such as cytokines and cell surface molecules.

In the case of the brain, the enhancement of fear-related learning is generally beneficial to an individual's ability to remember danger and act accordingly. Even the stress-induced remodelling of hippocampal dendrites and suppression of neurogenesis may serve a protective function in the short run against outright excitotoxic damage, and it also appears to go hand-in-hand with the adjustments of the animal's behavior to a long-term change in the social and physical environment. For these changes, circulating glucocorticoids and catecholamines act together with local tissue mediators such as the excitatory amino acids and serotonin, among other neurotransmitters.

The findings of plasticity, as well as damage, in hippocampus after prolonged psychosocial stress in animal models have encouraged investigations of the human hippocampus in stress-related disorders such as depressive illness, post-traumatic stress disorder and schizophrenia, as well as in relation to individual differences in human cognitive aging. These investigations have uncovered the phenomenon of atrophy, not only of the hippocampus, but also of structures such as the amygdala and prefrontal cortex in some of the conditions. Other studies have provided initial suggestions that the human hippocampus may increase in volume as a result of spatial information processing [86]. The cellular basis of these changes in volume remains to be determined, but it is the continuing work in animal models on processes such as neurogenesis, dendritic remodelling, glial cell plasticity and neuron loss that will continue to provide the essential information for interpreting changes in the living human brain seen by imaging procedures.

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