Effects of Adverse Experiences for Brain Structure and Function

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Studies of the hippocampus as a target of stress and stress hormones have revealed a considerable degree of structural plasticity in the adult brain. Repeated stress causes shortening and debranching of dendrites in the CA3 region of the hippocampus and suppresses neurogenesis of dentate gyrus granule neurons. Both forms of structural remodeling of the hippocampus appear to be reversible and are mediated by glucocorticoid hormones working in concert with excitatory amino acids (EAA) and N-*methyl-*D*-aspartate (NMDA) receptors, along with transmitters such as serotonin and the GABA-benzodiazepine system. Glucocorticoids, EAA, and NMDA receptors are also involved in neuronal damage and death that is caused in pyramidal neurons by seizures and by ischemia. A similar mechanism may be involved in hippocampal damage caused by severe and prolonged psychosocial stress. Studies using magnetic resonance imaging have shown that there is a selective atrophy of the human hippocampus in a number of psychiatric disorders, as well as during aging in some individuals, accompanied by deficits in declarative, spatial, and contextual memory performance. It is therefore important to appreciate how hippocampal dysfunction may play a role in the symptoms of the psychiatric illness and, from a therapeutic standpoint, to distinguish between a permanent loss of cells and a reversible remodeling to develop treatment strategies to prevent or reverse deficits. Remodeling of the hippocampus may be only the tip of the iceberg; other brain regions may also be affected.* Biol Psychiatry 2000;48: 721–731 © *2000 Society of Biological Psychiatry*

Key Words: Hippocampus, dendritic remodeling, neurogenesis, depression, posttraumatic stress disorder, glucocorticoids, hypothalamic–pituitary–adrenal axis

Introduction

The adult brain is more plastic than previously believed. Remodeling of synaptic contacts and dendrites in the hypothalamus with the onset of lactation (Michaloudi et al 1997; Stern and Armstrong 1998) and growth and branching of dendrites of cerebrocortical neurons in an enriched environment and after training (Greenough and Bailey 1988; Withers and Greenough 1989) 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 memory and in episodic, declarative, contextual, and spatial learning, as well as being a component in the control of autonomic and vegetative functions such as corticotropin secretion (Eichenbaum et al 1992; Jacobson and Sapolsky 1991; Phillips and LeDoux 1992). The hippocampus is also vulnerable to damage by stroke and head trauma and susceptible to damage during aging and repeated stress (Sapolsky 1992), and hippocampal atrophy has been reported in a number of psychiatric disorders, as will be discussed below.

Hippocampal neurons express receptors for circulating adrenal steroids (McEwen et al 1968), and work in many laboratories has shown that the hippocampus has two types of adrenal steroid receptors, Type I (mineralocorticoid) and Type II (glucocorticoid), that mediate a variety of effects on neuronal excitability, neurochemistry, and structural plasticity (DeKloet et al 1998). 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. This article reviews the adaptive plasticity in the hippocampus produced by circulating adrenocortical hormones acting in many cases in concert with excitatory amino acid neurotransmitters, and it also considers some of the ways in which adaptive plasticity gives way to permanent damage. The implications for hippocampal function and its role in the pathophysiology of psychiatric illnesses is discussed.

An Overview of Hormonally Regulated Plasticity in the Hippocampus

There are three types of plasticity in the hippocampal formation in which adrenal steroids play a role. First,

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Received March 17, 2000; revised June 14; accepted June 19, 2000.

0006-3223/00/$20.00
PII S0006-3223(00)00964-1

adrenal steroids participate along with excitatory amino acids in regulating neurogenesis of dentate gyrus granule neuron (Gould et al 2000) in which acute stressful experiences can suppress the ongoing neurogenesis (for reviews, see Gould et al 2000; McEwen 1999). We believe that these effects may be involved in fear-related learning and memory because of the anatomic and functional connections between the dentate gyrus and the amygdala (Ikegaya et al 1997), a brain area important in memory of aversive and fear-producing experiences (LeDoux 1995).

Second, adrenal steroids participate along with excitatory amino acids in a reversible stress-induced remodeling of dendrites in the CA3 region of hippocampus of male rats and tree shrews, a process that affects only the apical dendrites and results in cognitive impairment in the learning of spatial and short-term memory tasks (McEwen 1999; McEwen and Sapolsky 1995).

Third, adrenal steroids reversibly and biphasically modulate excitability of hippocampal neurons and influence the magnitude of long-term potentiation, as well as producing long-term depression (DeKloet et al 1998; Kerr et al 1994; McEwen and Sapolsky 1995; Pavlides et al 1996). These effects on neuronal responses may be involved in biphasic effects of adrenal secretion on excitability and cognitive function and memory during the diurnal rhythm and after stress (Diamond et al 1996; McEwen and Sapolsky 1995). In particular, acute nonpainful novelty stress inhibits primed-burst potentiation and memory (Diamond et al 1994, 1996).

Reversible Remodeling of Dendrites

Investigating the process of dendritic remodeling in the hippocampus of rats and tree shrews (formerly called atrophy; see next paragraph for explanation) provides one potential explanation of the hippocampal shrinkage that is seen in human subjects using magnetic resonance imaging (MRI; see below). Furthermore, the neurochemistry and neuroendocrinology of this process offers possibilities for pharmacologic intervention and either blocking or reversing hippocampal atrophy. In animal models using rats and tree shrews, dendritic length and branching are assessed by morphometry after silver staining of neurons with the single section Golgi technique. Furthermore, electron microscopy has revealed that stress and glucocorticoids alter morphology of presynaptic mossy fiber terminals in the stratum lucidum region of CA3 (for a review, see McEwen 1999; Figure 1).

The first study in a rat model showed that 21 days of corticosterone treatment or 21 days of 6-hour-per-day restraint stress caused remodeling of apical dendrites of CA3 pyramidal neurons (for a review, see McEwen and Sapolsky 1995). Subsequently, chronic restraint stress for 21 days in rats caused apical dendrites of CA3 pyramidal neurons to decrease in length and branching, and psychosocial stress over 28 days was found to cause the same type of dendritic remodeling (which we previously called "atrophy") in the tree shrew. In the rat, recent evidence indicates that dendritic remodeling is reversible within 7 to 10 days after the termination of 21 days of daily restraint stress (Conrad et al 1999). Hence, we have dropped the term "atrophy" and refer to this process as "dendritic remodeling." Nonetheless, shrinkage of the human hippocampus in depressive illness and other disorders will be referred to as "atrophy."

Pharmacology and Neurochemistry of Dendritic Remodeling

Stress- and corticosterone-induced remodeling were prevented by the antiepileptic drug, phenytoin (Dilantin), thus implicating the release and actions of excitatory amino acids because phenytoin blocks glutamate release and antagonizes sodium channels and possibly also T-type calcium channels that are activated during glutamate-induced excitation. This result is consistent with evidence that stress induces release of glutamate in hippocampus and other brain regions, and NMDA receptor blockade is also effective in preventing stress-induced dendritic remodeling (for reviews, see McEwen 1999; McEwen and Sapolsky 1995).

Glutamate is not the only transmitter involved in dendritic remodeling. Other participating neurotransmitters include GABA and serotonin, and the evidence thus far for their involvement may be summarized as follows (for a review, see McEwen 1999; McEwen and Sapolsky 1995). First, inhibitory interneurons have a significant role in controlling hippocampal neuronal excitability (Freund and Buzsaki 1996), and the involvement of the GABA-benzodiazepine receptor system is implicated by the ability of a benzodiazepine, adinazolam, to block dendritic remodeling (Magarinos et al 1999). Second, serotonin is released by stressors; and tianeptine, an atypical tricyclic antidepressant that enhances serotonin reuptake and thus reduces extracellular 5HT levels, prevents both stress- and corticosterone-induced dendritic remodeling of CA3 pyramidal neurons. In contrast, the inhibitors of serotonin reuptake, fluoxetine and fluvoxamine, failed to block remodeling (Magarinos et al 1999). Other antidepressant treatments have not yet been tried.

Further evidence for serotonin involvement in dendritic remodeling comes from studies of psychosocial stress in rats and tree shrews. Repeated restraint stress and psychosocial stress in rats and in tree shrews suppresses expression of the inhibitory 5-HT1A receptor in the hippocampus. Moreover, in the visible burrow model of

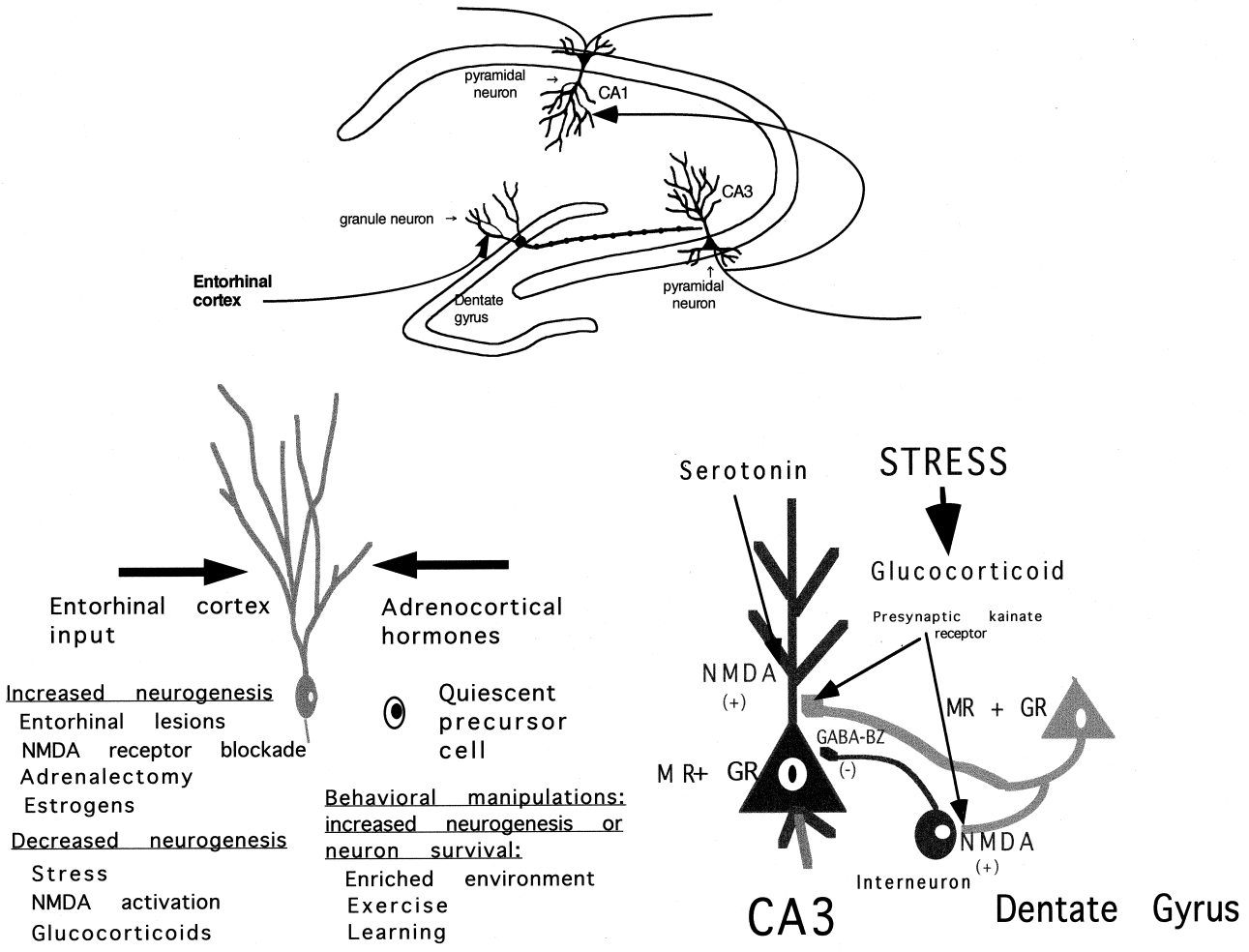

Figure 1. Schematic diagram of the role of neurotransmitters and glucocorticoids in regulating neurogenesis and dendritic remodeling in the dentate gyrus–CA3 system of the hippocampal formation. Granule neurons are replaced in adult life, and neurogenesis and apoptotic neuronal death are regulated by stress as well as by seizurelike 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 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 to 4 weeks in rats and tree shrews. Serotonin also participates, possibly by aiding the excitatory amino acid activity at the *N*-methyl-D-aspartate (NMDA) receptor, and reduced γ-aminobutyric acid (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. MR, mineralocorticoid receptor; GR, glucocorticoid receptor.

psychosocial stress in rats, both dominants and subordinates show dendritic remodeling as well as downregulation of 5HT transporter expression in the CA3 region (McKittrick et al 1996).

Because both phenytoin and tianeptine block corticosterone- and stress-induced remodeling of CA3 pyramidal neurons (McEwen and Sapolsky 1995), serotonin released by stress or by corticosterone may interact pre- or postsynaptically 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 (Mennini et al 1991; Rahmann and Neumann 1993; Figure 1).

Following upon the widespread activation of NMDA receptors, the increased levels of intracellular calcium may

make the dendritic cytoskeleton become depolymerized or undergo proteolysis (McEwen and Sapolsky 1995) thus accounting for the dendritic remodeling. This, along with evidence that glucocorticoids enhance calcium currents in the hippocampus (Joels and Vreugenhil 1998; Kerr et al 1992), suggest that calcium channel blockers might also be effective in regulating dendritic remodeling. This possibility has not yet been tested.

Stress is also reported to alter the expression of the neurotrophins, brain-derived neurotrophic factor (BDNF) and NT-3, in the hippocampus (Smith et al 1995; Ueyama et al 1997). In our hands, however, conditions that cause dendritic remodeling, such as repeated restraint stress or psychosocial stress, do not appear to change neurotrophin expression in hippocampus (Kuroda and McEwen 1998), indicating that neurotrophins are probably not directly involved in the mechanism of dendritic remodeling. This does not exclude the possibility that neurotrophin depletion or suppression might be involved in permanent neuronal loss resulting from more severe and prolonged stress (Uno et al 1989).

Along the same line, a number of antidepressant treatments, including selective serotonin reuptake inhibitors (SSRIs), increase the levels of BDNF messenger RNA (mRNA) in hippocampus of unstressed rats (Nibuya et al 1995), but these treatments have not been tried in conjunction with repeated stress. We noted above that SSRIs fail to prevent dendritic remodeling; yet tianeptine, which does prevent dendritic remodeling, did not increase BDNF mRNA in hippocampus of unstressed or stressed rats (Kuroda et al 1998). Therefore, the relationship with the ability of a treatment or drug to increase BDNF mRNA levels in hippocampus and the ability of that same treatment to alter stress-induced changes in BDNF mRNA levels or to affect dendritic remodeling remain important and unresolved topics in sorting out the relevance of these findings to the treatment of depressive illness.

Role of Glucocorticoids in Dendritic Remodeling

What is the role of glucocorticoids in dendritic remodeling in the hippocampus? Glucocorticoid treatment causes dendritic remodeling, and stress-induced remodeling is blocked by treatment with an adrenal steroid synthesis blocker, cyanoketone (McEwen and Sapolsky 1995), indicating a role for endogenous glucocorticoids in stress-induced dendritic remodeling. Nonetheless, treatment with agents such as Dilantin and tianeptine do not exert their effects in preventing dendritic remodeling by altering glucocorticoid secretion during stress because these same agents prevented glucocorticoid-induced dendritic remodeling (McEwen et al 1995). Thus, glucocorticoids can drive the remodeling of dendrites via a mechanism that involves activation of excitatory amino acid and serotonin release (Figure 1).

Corticosterone dissolved in the drinking water at a concentration of 400 μg/mL is able to do this (Magarinos et al 1998), and this allowed us to demonstrate in a "therapeutic" model that tianeptine treatment could reverse, over several weeks, the dendritic remodeling caused by corticosterone treatment even while the treatment was continued along with the tianeptine (Magarinos et al 1999). Yet the studies with oral corticosterone revealed another, unresolved paradox, namely, that when corticosterone treatment was combined with repeated stress for 21d, no remodeling of CA3 dendrites was observed (Magarinos et al 1998). Clearly, stress and oral corticosterone are doing somewhat different things, and the two pathways block each other proximally to the reorganization of dendrites.

Because of the diversity of neurotransmitter systems involved in stress- and glucocorticoid-induced dendritic remodeling, as noted above, it is not so surprising that there are multiple ways in which glucocorticoids affect the excitatory amino acid system (for a review, see McEwen 1999). In general, stress and glucocorticoids seem to tip the balance from inhibition toward excitation. First, 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. Second, adrenal steroids modulate expression of NMDA receptors in hippocampus, with chronic glucocorticoid exposure leading to increased expression of NMDA receptor binding and elevation of both NR2A and NR2B subunit mRNA levels. Third, adrenal steroids regulate extracellular levels of glutamate, in that adrenalectomy markedly reduces the level of extracellular glutamate following restraint stress. One possible mechanism for this effect is that mossy fiber terminals in the stratum lucidum contain presynaptic kainate receptors that positively regulate glutamate release, and kainate receptors in the CA3 stratum lucidum are decreased in density by adrenalectomy and restored to normal by corticosterone replacement (for reviews, see McEwen 1999; McEwen and Sapolsky 1995).

Reorganization and Depletion of Synaptic Vesicles in Mossy Fiber Terminals

In this connection, repeated stress causes a reorganization of synaptic vesicles within mossy fiber terminals, as determined using electron microscopy (Magarinos et al 1997). 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 depletion and rearrangement of vesicles, with more densely packed clusters localized in the vicinity of active synaptic zones. Moreover, compared with control subjects, rats undergoing 21 days of repeated 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 on the day following the restraint session (Magarinos et al 1997). In MFT from stressed rats, the redistribution of vesicles and their localization near the active synaptic zones, together with more mitochondria, suggests that more vesicles may be available for glutamate release, although this possibility remains to be tested directly by electrophysiology and microdialysis. Furthermore, the synaptic vesicle reorganization in MFT may be useful in future studies to provide insights into possible molecular mechanisms of the effects of stress and stress mediators on glutamate release, involving expression and phosphorylation of synaptic vesicle docking proteins such as synapsin I (Magarinos et al 1997).

Does Dendritic Remodeling Play a Protective Role in CA3 Apical Dendrites?

The mossy fiber terminals reside on the proximal regions of the CA3 apical dendrites that are remodeled by chronic stress, and chronic stress does not reduce their numbers (Magarinos et al 1997). If, indeed, chronic stress makes these giant synapses more efficient in releasing glutamate, then what is the significance of the remodeling of the apical dendrites? To answer this question, it is important to understand some key features of the CA3 region. In terms of circuitry, there are a series of recurrent feedback loops within the CA3 region that reactivate the mossy fiber system and sustain CA3 excitation, as in the so-called SPW or "sharp waves" (Buzsaki 1986). The SPW waves are postulated to be part of a circuit subserving memory of sequences of events (Lisman 1999). As reviewed in McEwen (1999), CA3 pyramidal neurons send axon collaterals to nearby CA3 neurons; moreover, CA3 neurons have a multiplicity of calcium channel types that contribute to the activation of calcium currents by low voltage changes, and pyramidal neurons in subregion CA3c that lies closest to the hilus send excitatory axons back to the hilar region and affect the dentate gyrus itself. Thus the CA3 region has an intrinsic instability that can be driven by stimulation via the perforant pathway, and the CA3 apical dendritic remodeling might be a protective adaptation to limit the increased excitatory input via the recurrent feedback loops. Moreover, the synchronized firing of the SPW waves during chronic stress or seizures may drive the reorganization of vesicles within the mossy fiber terminals. Indeed, collateral activation of CA3 neurons by other CA3 neurons would help explain the blockade of dendritic remodeling by treatment with antagonists to NMDA receptors because the stratum lucidum of the CA3 region does not express NMDA receptors (for a review, see McEwen 1999).

As reviewed in McEwen (1999), chronic stress may produce a graded response that is less drastic than that produced when seizures are elicited either by kainate treatment or perforant pathway stimulation. CA3 pyramidal neurons display a high vulnerability to kainic acid administration, an effect that requires the integrity of the mossy fiber pathway. The CA3 hippocampal subregion is also damaged by seizures evoked by stimulation of the perforant path, and this involves the activation of the dentate gyrus (DG)–MFT–CA3 pathway. In epilepsy, an interesting parallel exists with synaptic vesicle clustering found in the chronic stress model (see above). That is, gerbils that are genetically prone to epilepsy show MFT synaptic vesicle clustering that could be blocked by the disruption of the perforant pathway (Farias et al 1992).

Stress activation of the hippocampus also shows a strong trend to increase seizure susceptibility. In a recent electrophysiologic study of the effects of stress on long-term potentiation in the hippocampus (C. Pavlides et al, unpublished data), high-frequency stimulation (HFS) of the commissural/associational and MF inputs to CA3 produced epileptic afterdischarges in 56% of acutely stressed animals 48 hours after the stress, and 29% of the chronically stressed animals 48h after the last stress, but in only 9% of the non-stressed control animals. No epileptic afterdischarges were seen in the medial perforant path to DG input. The rats showing seizures were removed from the analysis of long-term potentiation (LTP) that is described below. The increased incidence of seizures is consistent with the possibility of stress-induced mossy fiber sprouting, since in epilepsy there is sprouting of mossy fibers that generate a recurrent excitatory circuit involving aberrant granule cell-granule cell synapses; see McEwen (1999) for references. Moreover, long-term potentiation itself appears to be capable of inducing mossy fiber sprouting (Noguchi et al 1990).

Stress-Induced Changes in Hippocampal Electrophysiology

The stress-induced changes in morphology within the hippocampus are reflected by electrophysiologic alterations within specific synaptic pathways (C. Pavlides et al, unpublished data). Rats were studied under chloropent anesthesia 48 hours following 21 days of 6-hour-per-day repeated restraint stress or following a single 6-hour restraint session. Chronic stress produced an inhibition of

LTP in the laconosum–molecular layer of CA3 after stimulation of the commissural–associational pathway. This inhibition was significant compared with that in animals receiving a single stress session and to control animals that were briefly handled but not subjected to the restraint stress. Chronic, but not acute, stress produced an inhibition of LTP in the dentate gyrus granule cell layer with stimulation of the medial perforant pathway. Mossy fiber LTP was not affected by repeated stress or by acute stress. In a second experiment, animals were subjected to a similar stress paradigm, and a current source density analysis was performed that revealed significant chronic stress-induced shifts in the current sources and sinks in the apical dendrites and pyramidal cell layers of the CA3 field, but not in the DG. These findings are consistent with the morphologic findings for effects of stress on dendrites of CA3 neurons. Furthermore, they suggest that chronic stress produces changes in the input–output relationship in the hippocampal trisynaptic circuit, which could affect information flow through this structure (C. Pavlides et al, unpublished data).

Gender Differences in Dendritic Remodeling

All of the experiments described above were carried out on male rats. We previously reported that female rats subjected to repeated restraint stress failed to show the remodeling of apical dendrites of CA3 pyramidal neurons (Galea et al 1997). The mechanism for this gender difference is unclear. It may reflect a protection by ovarian hormones or a developmentally programmed difference in hippocampal neuroanatomy. Gender differences in hippocampal neuroanatomy are known to exist (Juraska 1991). There also are reported gender differences in vulnerability of the hippocampus to damage in rats undergoing cold swim stress (Mizoguchi et al 1992) and in vervet monkeys undergoing psychosocial stress (Uno et al 1989). As discussed above, however, the relationship of dendritic remodeling to permanent hippocampal damage is too complex at this stage to make a simple link of these findings to each other.

Neurogenesis in the Dentate Gyrus

Neurogenesis in the dentate gyrus of adult rodents was reported several decades ago (for a review, see Gould et al 2000) but never fully appreciated until recently, and the reactivation of this topic occurred in an unusual manner (McEwen 1999). First, bilateral adrenalectomy of an adult rat was shown to increase granule neuron death by apoptosis (Gould et al 1990). Subsequently, neurogenesis was also found to increase following adrenalectomy in adults rats, as well as in the developing dentate gyrus. In adult rats, very low levels of adrenal steroids, sufficient to occupy Type I adrenal steroid receptors, completely blocks dentate gyrus neuronal loss; but in newborn rats, Type II receptor agonists protect against neuronal apoptosis (for reviews, see Gould et al 2000; McEwen 1999; Figure 1). 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 (Lupien and McEwen 1997).

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 adrenalectomy (Gould et al 2000). Most neuroblasts labeled with [3H] thymidine lack both Type I and Type II adrenal steroid receptor, indicating steroidal regulation occurs via messengers from an unidentified steroid-sensitive cell (Gould et al 2000). It has been reported that neurogenesis declines in the aging rodent (Kempermann et al 1998) and rhesus monkey (Fallah et al 1998) dentate gyrus. Recent studies of aging rats showed that adrenalectomy could reverse the decline in dentate gyrus neurogenesis (Cameron and McKay 1999), suggesting that they are the result of age-related increases in hypothalamic–pituitary–adrenal (HPA) activity and glucocorticoid levels that have been reported (Landfield et al 1994; Sapolsky et al 1986). Besides glucocorticoids, excitatory amino acids acting through NMDA receptors inhibit ongoing dentate gyrus neurogenesis, whereas other neurochemical and hormonal agents are known that stimulate neurogenesis, including serotonin and estrogens (Gould et al 2000).

The question of whether dentate gyrus neurogenesis is a widespread phenomenon among mammals was addressed by studies showing that neurogenesis occurs in the marmoset, a New World primate, as well as in an Old World primate species, the rhesus monkey and in the adult human dentate gyrus (Gould et al 2000). Thus changes in size of the human hippocampus, described below, may include changes in neuron number in the dentate gyrus.

One reason for turnover of dentate gyrus granule neurons in adult life is to adapt to needs for increased hippocampal function in spatial learning and memory to environmental demands (Sherry et al 1992). Learning that involves the hippocampus 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 labeled granule neurons was prolonged (Gould et al 1999). Another important influence on dentate gyrus neurogenesis and survival is that of acute and chronic stress. Acute stress involving the odor of a natural predator, the fox, inhibits neurogenesis in the adult rat

(Galea et al 1996), although acute restraint stress does not inhibit neurogenesis (K. Pham et al, unpublished data). Acute psychosocial stress in the adult tree shrew, involving largely visual cues, inhibits neurogenesis (Gould et al 1997). Inhibition of neurogenesis is also seen in the dentate gyrus of the marmoset after acute psychosocial stress (Gould et al 1998).

Chronic psychosocial stress in the tree shrew results in a more substantial inhibition of neurogenesis than after a single acute stressful encounter (Gould et al 2000); moreover, the dentate gyrus is 30% smaller in the chronically stressed tree shrew, although the granule neuron number only shows a trend for reduction (E. Gould et al, unpublished data). This finding suggests that there may be other changes such as remodeling of dendritic branching to account for the decrease in dentate gyrus volume. On the other hand, repeated restraint stress does not reduce dentate gyrus neuron number or alter the survival of granule neurons formed before the beginning of chronic stress (K. Pham et al, unpublished data). This indicates that not all stressors will alter dentate gyrus neuron number, even though they may cause remodeling of dendrites in CA3 neurons.

Changes in dentate gyrus volume appear to have consequences for cognitive functions subserved by the hippocampus. In the enriched environment studies (Kempermann et al 1997), increased dentate gyrus volume was accompanied by better performance on spatial learning tasks. Chronic stress, on the other hand, impairs spatial learning and memory in the tree shrew (Ohl and Fuchs 1999). This may be due to the decreased dentate gyrus volume as well as to remodeling of dendrites of CA3 pyramidal neurons and dentate granule neurons (see above).

Chronic stress has another interesting effect on the dentate gyrus. In the restraint stress model in the rat, 21 days of repeated stress increased expression of cells with polysialic acid neural cell adhesion molecule (PSA-NCAM) in the inner granule cell layer of the dentate gyrus while at the same time decreasing the rate of neurogenesis found in the dentate; a single acute stress did not produce either effect (K. Pham et al, unpublished data). The number of cells expressing PSA-NCAM was 10-fold larger than the number of newly BrdU labeled neurons, indicating that chronic stress has an effect on the subsequent properties of DG granule neurons. Glucocorticoids may be involved in regulating the process that adds polysialic acid to NCAM, and because PSA-NCAM is associated with the movement of cells and their processes, these findings are consistent with the overall increased plasticity produced by repeated stress in the DG-CA3 region of the hippocampus (K. Pham et al, unpublished data).

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 (de Quervain et al 2000; Lupien and McEwen 1997), whereas repeated stress also impairs cognitive function in animal models and repeated glucocorticoid elevation or treatment in humans is accompanied by cognitive dysfunction (McEwen and Sapolsky 1995). There also are declines in cognitive function in aging humans that are correlated with progressive elevations in HPA activity over 3 to 4 years (see below).

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 (Lupien and McEwen 1997).Adrenal steroid effects are implicated in both selective attention, as well as in memory consolidation (Lupien and McEwen 1997) and retrieval, and such actions are consistent with the effects of adrenal steroids on the modulation of long-term potentiation and primed-burst potentiation (see above). Nonetheless, some acute actions of stress may involve other mechanisms than glucocorticoids, including endogenous opioid neuropeptides in the case of painful stressors such as shock (for a summary, see McEwen et al 1995). With regard to nonpainful 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 (Diamond et al 1996).

Repeated stress that produces dendritic remodeling 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, whereas a subsequent study showed that 21 days of repeated restraint stress impaired the short-term (4-hour) 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 (McEwen 1999). We now know that dendritic remodeling is reversible within 7 to 10 days after the end of stress (Conrad et al 1999). 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 remodeling of CA3c pyramidal neurons (for a review, see McEwen and Sapolsky 1995).

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 3 to 4 years (for a review, see McEwen et al 1999). Recent evidence has revealed that the most severely impaired individuals have a significantly smaller hippocampal volume compared with the least impaired individuals (Lupien and McEwen 1998).

An important aspect of stressful experiences is the developmental influence of early stress and of neonatal handling on the life course of aging and age-related cognitive impairment. As discussed elsewhere (Meaney et al 1988, 1994), 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 overreact in animals subject to early unpredictable stress or underreact in animals exposed to the neonatal handling procedure.

Long-term stress also 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 an apparent loss of hippocampal pyramidal neurons (Kerr et al 1991). An important factor may be the enhancement by glucocorticoids of calcium currents in hippocampus (Kerr et al 1992), in view of the key role of calcium ions in destructive as well as plastic processes in hippocampal neurons (Mattson 1988, 1992). Another aspect making the aging hippocampus more vulnerable may be the persistence of excitatory amino acid release after the termination of a stressful experience (Lowy et al 1995).

Atrophy of the Hippocampus and Other Brain Structures in Psychiatric Disorders

The human brain shows signs of atrophy as a result of elevated glucocorticoids and severe, traumatic stress (e.g., holocaust survivors; Sapolsky 1992). Advances in brain imaging techniques have allowed for a regional analysis of the atrophy of various brain structures. Recent evidence indicates that the human hippocampus is particularly sensitive in this respect and tends to show greater changes than do other brain areas, especially in Cushing's syndrome, recurrent depressive illness, posttraumatic stress disorder (PTSD), schizophrenia, and aging before overt dementia (Bogerts et al 1993; Bremner et al 1995; Fukuzako et al 1996; Gurvits et al 1996; Lupien et al 1998; Sheline et al 1996, 1999; Starkman et al 1992).

The diversity of conditions in which atrophy occurs raises two questions, namely, whether there is a common mechanism and whether the atrophy is permanent or reversible. Based on what we have summarized above, the atrophy might be due to one of at least four different processes: 1) a reduced volume of Ammon's horn or dentate gyrus due to reduced dendritic branching, 2) a reduction in dentate gyrus neuron number due to a suppression of neurogenesis, 3) a decreased rate of neuron survival, 4) permanent neuron loss. In addition, it is noteworthy that atrophy of other brain regions has been reported in depressive illness (e.g., prefrontal cortex; Drevets et al 1997) and amygdala (Sheline et al 1998). Moreover, new evidence suggests that glial cell depletion may contribute to atrophy of brain regions such as the prefrontal cortex and amygdala (Drevets et al 1998; Ongur et al 1998; Rajkowska et al 1999; Sheline et al 1998), and the contribution of glial cell changes must now be considered for the hippocampus.

Because of the high density of intracellular receptors for adrenal steroids in hippocampus, it is tempting to attribute the occurrence of hippocampal atrophy solely to the actions of glucocorticoids. As summarized above, the hippocampus shows influences of adrenal steroids on plasticity, as well as on the loss and damage to hippocampal neurons in conditions such as ischemia and aging (Landfield and Eldridge 1994; McEwen and Sapolsky 1995; Sapolsky 1992; Sapolsky et al 1986); however, adrenal steroids produce their effects on plasticity (see earlier discussion) and on damage in ischemia and aging (see above references) by acting in concert with neuromodulators and neurotransmitters, in particular the endogenous excitatory amino acids. Nonetheless, 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 the PTSD subjects are studied, except as there are elevations in glucocorticoids associated with the diurnal rhythm and stressful experiences that take place on a daily basis.

In this connection, it is important to emphasize that sustained stress levels, or Cushings-like elevations, of adrenal steroids are not required to produce structural changes in hippocampus. For example, in animal models of stress-induced remodeling of CA3 apical dendrites, periodic adrenocortical stress responses over 21 days are all that are needed, and even those responses tend to habituate and show an earlier shutoff with the repetition of the daily stressor (McEwen and Sapolsky 1995). 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; for example, some individuals who are exposed to repeated psychosocial stress, such as public speaking, fail to habituate their cortisol elevation, and these individuals lack self-esteem and self-confidence (Kirschbaum et al 1995). 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 will other people who can more easily habituate to psychosocial challenges.

In this regard, events related to the course of illness in recurrent depressive illness may involve distinct pathways of selective and repeated elevations of glucocorticoid hormones in relation to the individual experiences and reactivities. 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 the neurochemical aspects, there is need to measure the activity of excitatory amino acids in the brain during recurrent depressive illness because neural activity is likely to be a major factor in the long-term atrophy of key brain regions such as hippocampus, amygdala, and prefrontal cortex.

Regarding reversibility or irreversibility of these structural changes, treatment with drugs such as phenytoin or tianeptine, both of which block stress-induced dendritic remodeling in the CA3 or rats and tree shrews, 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 at least partially reversible (Starkman et al 1999). On the other hand, there may be irreversible loss of hippocampal neurons, and some of the evidence in the MRI of recurrent depressive illness is consistent with this possibility (Sheline et al 1996). In so far as atrophy of the hippocampus and accompanying cognitive impairment are signs of reversible neuronal remodeling, they may be treatable with agents that block the neuronal remodeling 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.

Research in the author's laboratory on the topic of this article is supported by National Institutes of Health Grant Nos. MH 41256 and Center Grant No. MH58911, as well as by funding from the Health Foundation (New York) and Servier (France).

Aspects of this work were presented at the conference "Depression in the Twenty-First Century: New Insights into Drug Development and Neurobiology," February 21–22, 2000, Dana Point, California. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided jointly by Pharmacia & Upjohn and Janssen Pharmaceutica.

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