

Stress and hippocampal plasticity: implications for the pathophysiology of affective disorders

Bruce S. McEwen* and Ana Maria Magarinos

Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY, USA

The hippocampal formation, a structure involved in declarative, spatial and contextual memory, is a particularly sensitive and vulnerable brain region to stress and stress hormones. The hippocampus shows a considerable degree of structural plasticity in the adult brain. Stress suppresses neurogenesis of dentate gyrus granule neurons, and repeated stress causes atrophy of dendrites in the CA3 region. In addition, ovarian steroids regulate synapse formation during the estrous cycle of female rats. All three forms of structural remodeling of the hippocampus are mediated by hormones working in concert with excitatory amino acids (EAA) and *N*-methyl-D-aspartate (NMDA) receptors. EAA and NMDA receptors are also involved in neuronal death that is caused in pyramidal neurons by seizures and by ischemia and prolonged psychosocial stress. In the human hippocampus, magnetic resonance imaging studies have shown that there is a selective atrophy in recurrent depressive illness, accompanied by deficits in memory performance. Hippocampal atrophy may be a feature of affective disorders that is not treated by all medications. From a therapeutic standpoint, it is essential to distinguish between permanent damage and reversible atrophy in order to develop treatment strategies to either prevent or reverse deficits. In addition, remodeling of brain cells may occur in other brain regions. Possible treatments are discussed. Copyright © 2001 John Wiley & Sons, Ltd.

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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 provide 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 being a component in

the control of autonomic and vegetative functions such as regulation of adrenocorticotrophic hormone (ACTH) secretion (Jacobson and Sapolsky, 1991; Gazzaley *et al.*, 1996; Phillips and LeDoux, 1992). The hippocampus is also vulnerable to damage by stroke and head trauma and is susceptible to damage during aging and repeated stress (Sapolsky, 1992).

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), which mediate a variety of effects on neuronal excitability, neurochemistry and structural plasticity (DeKloet *et al.*, 1996; De Kloet *et al.*, 1998). The hippocampus is also sensitive to gonadal hormones and expresses both androgen and estrogen receptors (Kerr *et al.*, 1995; Weiland *et al.*, 1997b). 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 (McEwen and Alves, 1999; Meaney *et al.*, 1991).

*Correspondence to: Bruce S. McEwen, The Rockefeller University, Box 165, 1230 York Avenue, New York, NY 10021, USA. E-mail: mcewen@rockvax.rockefeller.edu

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Many of these hormone effects do not occur alone but rather in the context of ongoing neuronal activity. In particular, excitatory amino acids (EAA) and *N*-methyl-D-aspartate (NMDA) receptors, as well as serotonin, play an important role in the functional and structural changes produced in the hippocampal formation by steroid hormones and by stress. The reason for considering cellular mechanisms of the effects of stress on the hippocampus in animal models is that the human brain shows signs of atrophy as a result of elevated glucocorticoids and severe, traumatic stress (e.g. holocaust survivors, see Sapolsky, 1992). However, it has only been very recently that brain imaging techniques have allowed a regional analysis of the atrophy or shrinking 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 recurrent depressive illness, Cushing's syndrome, posttraumatic stress disorder (PTSD), schizophrenia and aging prior to overt dementia (Starkman *et al.*, 1992; Bogerts, 1993; Bremner *et al.*, 1995; Freund and Buzaki, 1996; Gurvits *et al.*, 1996; Sheline *et al.*, 1996, 1999).

This article reviews the adaptive plasticity in the hippocampus produced by circulating adrenal steroids acting in many cases in concert with EAA 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 are discussed, along with possible treatment strategies.

An overview of structural and functional changes produced by hormones in hippocampus

Adrenal steroids mediate both rapid and long-term delayed effects on hippocampal neuronal function and structure. Adrenal steroids reversibly and biphasically modulate excitability of hippocampal neurons and influence the magnitude of long-term potentiation, besides producing long-term depression (Pavlidis *et al.*, 1994, 1995a,b, 1996; De Kloet *et al.*, 1998; Gould *et al.*, 1999). 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.*, 1992, 1996b; Dana and Martinez 1984; Barnes *et al.*, 1997). In particular, acute non-painful novelty stress inhibits primed-burst potentiation and memory (Diamond *et al.*, 1994, 1996a).

However, we will not discuss this further and shall focus on the structural changes produced by hormones.

Adrenal steroids and gonadal steroids are involved in four types of plasticity in the hippocampal formation. First, estrogens induce synapse formation in the CA1 region by a process that requires NMDA receptors and involves the participation of inhibitory interneurons (Woolley *et al.*, 1990, 1997; Weiland, 1992; Gazzaley *et al.*, 1996). Second, adrenal steroids participate along with EAAs in regulating neurogenesis of dentate gyrus granule neurons (Cameron and Gould, 1996a), in which acute stressful experiences can suppress the ongoing neurogenesis (Galea *et al.*, 1996; Gould *et al.*, 1997a). We believe that these effects may be involved in fear-related learning and memory, because of the anatomical 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). Third, adrenal steroids participate along with EAAs in a reversible stress-induced atrophy of dendrites in the CA3 region of the hippocampus of male rats (McEwen *et al.*, 1995) and tree shrews (Magarinos *et al.*, 1996), a process that affects only the apical dendrites and results in cognitive impairment in the learning of spatial and short-term memory tasks (McEwen *et al.*, 1995). We shall now consider these latter two processes – the regulation of neurogenesis and atrophy of dendrites – as they may help us understand the atrophy of the human hippocampus that has been described in depressive illness (Sheline *et al.*, 1996; Sheline *et al.*, 1999).

Neurogenesis in the dentate gyrus

Turnover of dentate gyrus granule neurons in adult life. Neurogenesis in the dentate gyrus of adult rodents has been reported (Kaplan and Hinds, 1977; Kaplan and Bell, 1984; Kempermann *et al.*, 1998), 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 (Gould *et al.*, 1990; Sloviter *et al.*, 1989). Subsequently, neurogenesis was also found to increase following ADX in adult rats (Cameron and Gould, 1994), as well as in the developing dentate gyrus, (Cameron and Gould, 1996a). In adult rats, very low levels of adrenal steroids, sufficient to occupy type I adrenal steroid receptors, completely block dentate gyrus neuronal loss (Woolley *et al.*, 1991); but, in

newborn rats, type II receptor agonists protect against neuronal apoptosis (Gould *et al.*, 1997c). 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 ADX (Cameron *et al.*, 1993). Most neuroblasts labeled with [³H] thymidine lack both type I and type II adrenal steroid receptors (Cameron *et al.*, 1993), indicating that steroidal regulation occurs via messengers from an unidentified steroid-sensitive cell. Recent data suggest an important signaling role for the transforming growth factor α (TGF α) and epidermal growth factor (EGF) receptor system (Tanapat and Gould, 1997).

Dentate gyrus neurogenesis from rodents to humans.

The question as to whether dentate gyrus neurogenesis is a widespread phenomenon among mammals was addressed recently by studies showing that neurogenesis occurs in the marmoset (Gould *et al.*, 1998), a New World primate, as well as in an Old World primate species, the rhesus monkey (Gould *et al.*, 1999b), and in the adult human dentate gyrus (Eriksson *et al.*, 1998). Thus, changes in size of the human hippocampus, described below, may include changes in neuron number in the dentate gyrus.

Neurochemical control of neurogenesis. Granule neuron birth is accelerated by seizure-like activity (Parent *et al.*, 1997) and the stimulus for this neurogenesis is likely to be apoptotic cell death, because seizures kill granule neurons (Bengzon *et al.*, 1997) and local increases in apoptosis stimulate local neurogenesis (Cameron and Gould, 1996b). Granule neuron birth is also accelerated by blocking NMDA receptors or lesioning the excitatory perforant pathway input from the entorhinal cortex (Cameron *et al.*, 1995). 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 (Cameron *et al.*, 1995). Thus, although increased apoptosis leads to increased neurogenesis (Gould *et al.*, 1997b), the two processes occurred 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 (Gould *et al.*, 1997b; Noguchi *et al.*, 1990).

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 (Jacobs *et al.*, 1998). Likewise, the 5-HT_{1A} agonist, 8-hydroxy-2-(di-*n*-propylamine) tetralin (8-hydroxy-DPAT), stimulated neurogenesis, whereas blockade of 5-HT_{1A} receptors had the opposite effect and prevented the effect of D-fenfluramine treatment, as well as preventing increased neurogenesis caused by pilocarpine-induced seizures (Jacobs *et al.*, 1998; Radley *et al.*, 1998).

Age-related decline in neurogenesis. 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, 1998), suggesting that they are the result of age-related increases in HPA activity and glucocorticoid levels that have been reported (Sapolsky *et al.*, 1986; McEwen, 1992; Sapolsky, 1992; Landfield and Eldridge, 1994).

Possible role of neurogenesis in adaptive behavior and learning. One reason for turnover of dentate gyrus granule neurons in adult life is to adjust the needs for hippocampal function in spatial learning and memory to environmental demands (Sherry *et al.*, 1992). 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 that do not; moreover, there are indications that hippocampal volume may change during the breeding season (Galea *et al.*, 1994; Sherry *et al.*, 1992). Indeed, the rate of neurogenesis in the male and female prairie vole varies according to the breeding season (Galea and McEwen, 1999). 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 (Kempermann *et al.*, 1997). 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

labeled granule neurons was prolonged (Gould *et al.*, 1999a).

Acute and chronic stress effects upon neurogenesis. Another important effect 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). Acute psychosocial stress in the adult tree shrew, involving largely visual cues, inhibits neurogenesis (Gould *et al.*, 1997a). 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; moreover, the dentate gyrus is 30% smaller in the chronically stressed tree shrew, although granule neuron number only shows a trend towards reduction (Gould E. and Fuchs E., unpublished observations). This finding suggests that there may be other changes such as atrophy of dendritic branching to account for the decrease in dentate gyrus volume.

Changes in dentate gyrus volume appear to have consequences for cognitive functions subserved by the hippocampus. In the enriched environment studies (Kempermann *et al.*, 1998), 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 (Fuchs E., personal communication), although this might be as much due to atrophy of dendrites of CA3 pyramidal neurons and dentate granule neurons (see below) as to reduced dentate gyrus neurogenesis.

Reversible atrophy of dendrites

Modeling causes for changes in hippocampal volume. Investigating the process of dendritic atrophy in the hippocampus of rats and tree shrews provides a useful model for modeling and understanding hippocampal atrophy that is seen in human subjects using magnetic resonance imaging (MRI) (see below), including the investigation of possible cellular mechanisms and pharmacological means of intervening and either blocking or reversing hippocampal atrophy (see Figure 1). In the animal models using rats and tree shrews, dendritic length and branching are assessed by morphometry after silver staining neurons with the single section Golgi technique; furthermore, electron microscopy has revealed that stress and glucocor-

ticoids alter morphology of presynaptic mossy fiber terminals in the stratum lucidum of the hippocampal CA3 subregion (Magarinos *et al.*, 1997).

Role of excitatory amino acids. The first study in a rat model showed that 21 days of corticosterone treatment or 21 days of 6 hours/day restraint stress caused atrophy of apical dendrites of CA3 pyramidal neurons (reviewed in McEwen *et al.*, 1995). Subsequently, chronic restraint stress for 21 days in rats caused apical dendrites of CA3 pyramidal neurons to atrophy (McKittrick *et al.*, 1996), and psychosocial stress over 28 days was found to cause the same type of dendritic atrophy in the tree shrew (Magarinos *et al.*, 1996). Stress- and corticosterone-induced atrophy were prevented by the anti-epileptic drug phenytoin (Dilantin), thus implicating the release and actions of EAAs, 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 Lowy *et al.*, 1993, 1995; Moghaddam *et al.*, 1994). NMDA receptor blockade is also effective in preventing stress-induced dendritic atrophy (Magarinos and McEwen, 1995; McEwen *et al.*, 1995) (see Figure 1).

Other neurotransmitter systems. Besides glutamate, other participating neurotransmitters include gamma-aminobutyric acid (GABA) and serotonin, and the evidence thus far may be summarized as follows.

- Inhibitory interneurons have a significant role in controlling hippocampal neuronal excitability (Freund and Buzaki, 1996), and the involvement of the GABA-benzodiazepine receptor system is implicated by the ability of a benzodiazepine, adinazolam, to block dendritic atrophy (Magarinos *et al.*, 1999) (see Figure 1).
- Serotonin is released by stressors. Tianeptine, an atypical tricyclic antidepressant that enhances serotonin reuptake and thus reduces extracellular 5-HT levels, prevents both stress- and corticosterone-induced dendritic atrophy of CA3 pyramidal neurons (Watanabe *et al.*, 1992), whereas several inhibitors of serotonin reuptake, fluoxetine and fluvoxamine, failed to block atrophy (Magarinos *et al.*, 1999). The effectiveness of tianeptine and ineffectiveness of fluoxetine is illustrated in Figure 2. Further evidence for serotonin involvement

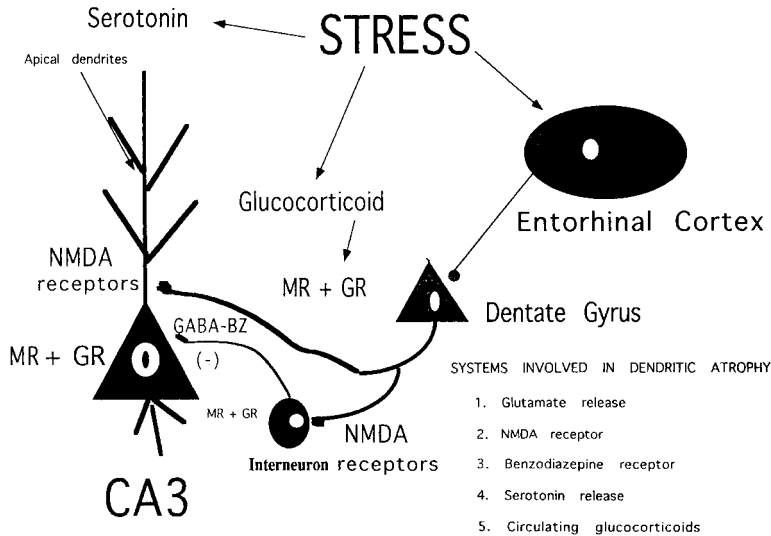


Figure 1. CA3 region of the hippocampus showing schematically the innervation of apical dendrites of CA3 pyramidal neurons by mossy fiber projections from dentate granule neurons. Granule neurons also send mossy fibers to interneurons in the hilus, which, in turn, send inhibitory projections to the CA3 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. Excitatory amino acid release during repeated stress, aided by circulating glucocorticoids, leads to a reversible atrophy 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 *N*-methyl-D-aspartic acid (NMDA) receptor, and reduced γ -aminobutyric acid–benzodiazepine-mediated inhibitory activity at synapse from the interneurons on CA3 pyramidal neurons may also exacerbate the atrophy. Prolonged psychosocial stress in primates is known to cause a permanent loss of CA3 pyramidal neurons, which may reflect another and more dangerous stage of the actions of the mediators that cause the atrophy shown in the diagram. We envision that the process that is so intense in the CA3 region occurs to some extent throughout the hippocampus, which might help explain why the entire human hippocampus undergoes atrophy of 10–15% in various conditions described in the text. The figure also summarizes the neurochemical systems that are implicated in dendritic atrophy, for which pharmacological treatment alters the course of dendritic atrophy, as summarized in the text. Modified from McEwen (1999), reproduced by permission

in dendritic atrophy comes from studies of psychosocial stress in rats, in that both dominant and subordinate rats show both dendritic atrophy as well as down-regulation of 5-HT transporter expression in the CA3 region, indicating either a reduced density of serotonin terminals or a reduced expression of the transporter (McKittrick *et al.*, 1996). Moreover, repeated restraint stress and psychosocial stress in rats suppresses expression of the inhibitory 5-HT_{1A} receptor in the hippocampus in rats and tree shrews (McKittrick *et al.*, 1996; Flugge, 1995; McEwen *et al.*, 1995).

Because both phenytoin and tianeptine block corticosterone- and stress-induced atrophy of CA3 pyramidal neurons (see McEwen *et al.*, 1995), 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-HT₂ receptors (Mennini and Miari, 1991; Rahman and Neumann, 1993).

Role of glucocorticoids. Glucocorticoid treatment causes dendritic atrophy, and stress-induced atrophy is blocked by treatment with an adrenal steroid synthesis blocker, cyanoketone (see McEwen *et al.*, 1995), indicating a role of endogenous glucocorticoids in stress-induced dendritic atrophy. There appear to be several ways in which glucocorticoids affect the EAA system.

- First, adrenal steroids modulate expression of NMDA receptors in hippocampus (Bartanusz *et al.*, 1995; Weiland *et al.*, 1995), with chronic glucocorticoid exposure leading to increased expression of NMDA receptor binding and both

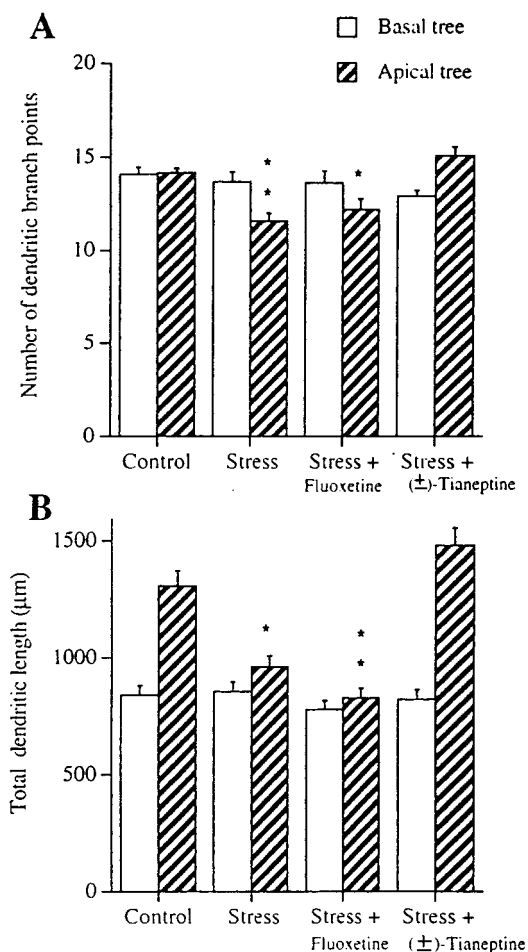


Figure 2. Effect of repeated stress, fluoxetine (10 mg/kg) and (±) tianeptine (10 mg/kg) on the number of branch points (A) and the length (in µm) of CA3 dendritic arbors (B). After 3 weeks of daily restraint stress, animals showed a decrease in the total length of CA3 apical dendrites. The antidepressant fluoxetine, a serotonin reuptake blocker, was without effect, whereas the serotonin reuptake enhancer (±) tianeptine prevented the hippocampal atrophy induced by stress. * $p < 0.05$, ** $p < 0.01$, compared with controls. One way ANOVA, Tukey post-hoc test. From Magarinos *et al.* (1999), reproduced by permission

NR2A and NR2B subunit mRNA levels (Weiland *et al.*, 1997a).

- Second, there are glucocorticoid effects on the expression of mRNA levels for specific subunits of GABA_A receptors in CA3 and the dentate gyrus; both low and high levels of corticosterone have different effects on GABA_A receptor subunit mRNA levels and receptor binding (Orchinik *et al.*, 1994; Orchinik, Weiland and McEwen, unpublished),

suggesting corticosterone may alter the excitability of hippocampal neurons through regulation of GABA_A receptor expression. However, it remains to be seen if the corticosteroid effects on neuronal morphology involve changes in the number or pharmacological properties of GABA_A receptors.

- Third, adrenal steroids regulate the release of glutamate, since adrenalectomy markedly reduces the magnitude of the EAA release evoked by restraint stress (Lowy *et al.*, 1993; Moghaddam *et al.*, 1994). Mossy fiber terminals (MFTs) in the stratum lucidum contain presynaptic kainate receptors that positively regulate glutamate release (Chittajallu *et al.*, 1996); these presynaptic kainate receptors are decreased in density by ADX and restored to normal by corticosterone replacement (Watanabe *et al.*, 1995). Moreover, repeated stress causes a reorganization of synaptic vesicles within MFTs, as reported recently 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 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 MFT 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 (Magarinos *et al.*, 1997).

Implications of stress-induced MFT reorganization.

There are several implications of the changes in MFTs. First, in MFTs 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 (Magarinos *et al.*, 1997). Second, the synaptic vesicle reorganization in MFTs provides 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). It is possible that the effect of repeated stress causing clustering of vesicles close

to the active zones could involve an increased expression of phosphorylated synapsin I.

The MFTs reside on the proximal regions of the apical dendrites, and their numbers are not reduced by chronic stress (Magarinos *et al.*, 1997). Therefore, the CA3 apical dendritic atrophy might be an adaptation to limit the increased excitatory input from recurrent axonal collaterals that are known to project from neighboring CA3 pyramidal neurons (Ishizuka *et al.*, 1990; Li *et al.*, 1994). Moreover, CA3 neurons have a multiplicity of calcium channel types that contribute to the activation of calcium currents by low voltage changes (Avery and Johnson, 1996). In addition, pyramidal neurons in subregion CA3c that lie closest to the hilus send excitatory axons back to the hilar region and affect the dentate gyrus itself (Kneisler and Dingledine, 1995; Scharfman, 1994). Such feedback loops can presumably reactivate the mossy fiber system and sustain CA3 excitation, as in the so-called SPW or 'sharp waves' (Buzsaki, 1986), and such an activation may drive the reorganization of vesicles within the MFTs. Moreover, collateral activation of CA3 neurons by other CA3 neurons would help explain the blockade of dendritic atrophy by NMDA receptor blockade (Magarinos and McEwen, 1995), since the stratum lucidum of the CA3 region does not express NMDA receptors (Monaghan *et al.*, 1983).

CA3 pyramidal neurons display a high vulnerability not only to chronic stress but also to kainic acid administration, an effect that requires the integrity of the mossy fiber pathway (Nadler and Cuthbertson, 1980). The CA3 hippocampal subregion is also damaged by epileptogenic stimulation of the perforant path, which involves the activation of the DG-MFT-CA3 pathway (Sloviter, 1983). Furthermore, in the epilepsy model, another parallel exists with the chronic stress model in the clustering of synaptic vesicles in that genetically prone epileptic gerbils show MFT synaptic vesicle clustering, an affect that could be blocked by the disruption of the perforant pathway (Farias *et al.*, 1992).

Electrophysiological effects of repeated stress. In keeping with the reorganization of dendrites and alteration of synaptic vesicles in MFTs, repeated stress produces a variety of effects on the electrophysiological features of the hippocampus (Nivon, McEwen and Pavlides, unpublished). Forty-eight hours following 21 days of 6 hours/day of repeated restraint stress, rats were studied under chloroform anesthesia. Compared with control animals that were briefly handled but not subjected to the restraint stress,

there was an inhibition of LTP in the lacunosum/molecule layer of CA3 of repeatedly stressed rats after stimulation of the commissural/associational pathway. The same inhibition of LTP was seen in the dentate gyrus granule cell layer with stimulation of the medial perforant pathway. The mossy fiber LTP was not affected by repeated stress.

There was another significant finding, namely, that high-frequency stimulation (HFS) produced epileptic after-discharges in 38% of the repeatedly stressed rats, while in the nonstressed controls, HFS produced epileptic after-discharges in only 15% of the animals. The rats showing seizures were removed from the analysis described in the previous paragraph. 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 (Okazaki *et al.*, 1995; Parent *et al.*, 1997; Sutula *et al.*, 1996). Moreover, long-term potentiation itself appears to be capable of inducing mossy fiber sprouting (Noguchi *et al.*, 1990).

In a second experiment, animals were subjected to a similar stress paradigm and a current source density analysis was performed. In each of the hippocampal subfields, significant shifts were observed in the sources and sinks, between the control and stressed animals (Nivon, McEwen and Pavlides, unpublished).

Possible role of neurotrophins. Following on from the widespread activation of NMDA receptors, the increased levels of intracellular calcium may make the dendritic cytoskeleton become depolymerized or undergo proteolysis (see McEwen *et al.*, 1995 for a discussion). Stress is also reported to alter the expression of the neurotrophins brain-derived neurotrophic factor (BDNF) and NT-3 in hippocampus (Smith *et al.*, 1995; Ueyama *et al.*, 1997). However, in our hands, conditions that cause dendritic atrophy, 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 atrophy. 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 (e.g. see Uno *et al.*, 1989). Indeed, studies are currently underway to find out if mice showing reductions in BDNF expression respond to repeated stress by showing permanent damage to the hippocampus.

Human hippocampal atrophy

We have noted above that atrophy of the human hippocampus has been reported in conditions such as Cushing's syndrome, recurrent depressive illness, post-traumatic stress disorder (PTSD), schizophrenia and aging prior to overt dementia (Starkman *et al.*, 1982; Bogerts *et al.*, 1993, 1995; Fukuzako *et al.*, 1996; Gurvits *et al.*, 1996; Sheline *et al.*, 1996, 1999). The diversity of conditions in which atrophy occurs raises the question as to whether they reflect a common mechanism and, secondly, whether the atrophy is permanent or reversible. Based on 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 (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 like the prefrontal cortex and amygdala (Drevets *et al.*, 1998; Ongur *et al.*, 1998; Sheline *et al.*, 1998) 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 (Sapolsky *et al.*, 1986; Sapolsky 1992; Landfield and Eldridge, 1994; McEwen *et al.*, 1995). 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 when there are elevations in glucocorticoids associated with the diurnal rhythm and stressful experiences that take place on a daily basis.

Sustained stress levels of cortisol or cushingoid elevations of adrenal steroids are not required for atrophy of hippocampal neurons, since 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, 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 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 the stress responses and neurochemical changes accompanying the initial trauma, which may have taken place 10–20 years previously, 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 are concerned, as well as responses to stressful life experiences, although a recent study has made it clear that it is the duration of the depressive illness and not the age of the individual that is most salient for hippocampal volume decrease (Sheline *et al.*, 1999). In both PTSD and recurrent major depression, a long-term pattern of increased neurochemical, autonomic and hypothalamus–pituitary–adrenal (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 mechanisms 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 (Starkman, personal communication). 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 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.

A model of reversible atrophy of hippocampal neurons involving the effects of chronic glucocorticoid elevation has revealed that the antidepressant tianeptine is effective in reversing the atrophy of dendrites of CA3 pyramidal neurons produced by 3 weeks of treatment with elevated glucocorticoids, even while the glucocorticoid treatment continues (Magarinos *et al.*, 1999) (see Figure 3). This finding encourages the use of tianeptine and other agents such as phenytoin (see above) in the treatment of human hippocampal atrophy. In the case of depressive illness, it may be that treatments that relieve the symptoms of depression are only part of the therapeutic regimen needed to provide long-term benefit to those suffering from depressive illness. Rather, treatments that also prevent or reverse neuronal atrophy and permanent brain damage may be needed to arrest or slow the long-term progression of the disease and the long-term decline in cognitive function and other aspects of behavior.

CONCLUSIONS

Understanding the cellular and molecular basis of hormonally and environmentally regulated structural remodeling of the hippocampus provides a new window into processes that are undoubtedly involved in the etiology and treatment of major psychiatric illnesses, as well as providing yet another link between organic brain dysfunction and behavior. We have seen that not all of these changes are irreversible and that there is considerable latitude for treatment that may either reverse or prevent structural changes and functional impairment. In the case of the hippocampus, there are three major contributions to brain function made by this structure: first, the well-known role in declarative, spatial and contextual memory; second, the role of the hippocampus in shutting off the HPA response to stress and in maintaining the normal diurnal rhythm (Herman and Cullinan, 1997; Jacobson and Sapolsky, 1991), third, the role of the hippocampus in the processing of emotional information (Gray, 1982). Impairment of each of these functions can be seen in psychiatric illnesses such as depression, schizophrenia and PTSD, in which hippocampal atrophy is also reported.

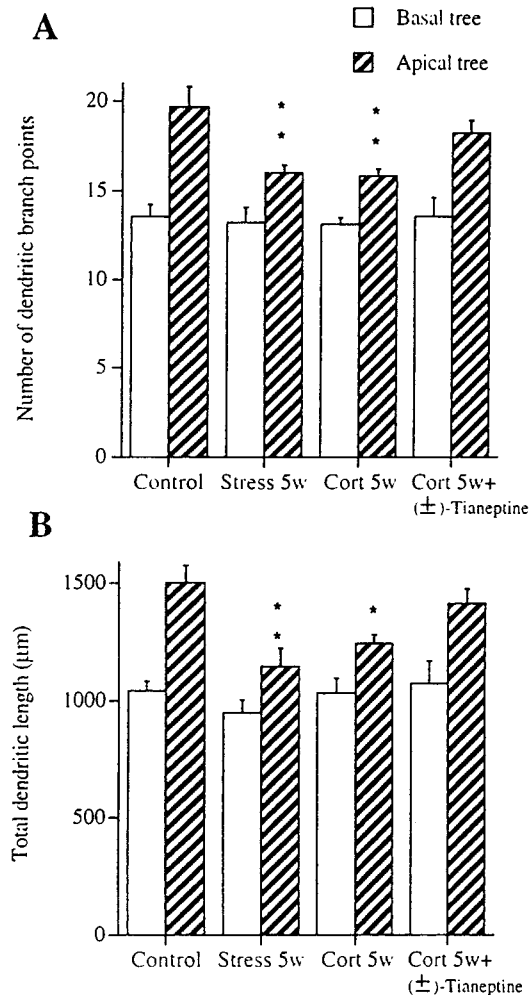


Figure 3. Effect of repeated stress, corticosterone (CORT) administration and cotreatment with (±) tianeptine on the number of branch points (A) and length (in μm) of CA3 dendritic arbors (B). After 5 weeks of daily administration of exogenous corticosterone in the drinking water (400 $\mu\text{m}/\text{ml}$, CORT 5w), animals showed a CA3 apical atrophy similar in magnitude to that obtained after 5 weeks of restraint stress (stress 5w). The antidepressant (±) tianeptine (10 mg/kg) administered for weeks 4 and 5 (CORT 5w + TIA) reversed the dendritic atrophy induced by corticosterone. ** $p < 0.01$, compared with controls. One way ANOVA, Tukey post-hoc test. From Magarinos *et al.* (1999), reproduced by permission

Thus, hormone actions on the hippocampus during adult life alter the neural substrate upon which experience exerts its effects on brain structure and function, as has already been demonstrated in studies of the effects of an enriched environment on the rat hippocampus and cerebral cortex (Juraska *et al.*, 1989; Juraska, 1991; Kempermann *et al.*, 1997). Adrenal

steroids participate with EAAs and NMDA receptors in regulating structural plasticity in the adult hippocampus. At the same time, EAAs and NMDA receptors are involved in the destructive actions of stress and trauma on the hippocampus. One of the challenges for future research is to understand what triggers the transition from adaptive plasticity to permanent damage. Studies of this type may help us understand and ultimately treat affective disorders not only in terms of their effects on mood but also in terms of the degeneration of brain function.

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