STRESS AND HIPPOCAMPAL PLASTICITY

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ABSTRACT

The hippocampus is a target of stress hormones, and it is an especially plastic and vulnerable region of the brain. It also responds to gonadal, thyroid, and adrenal hormones, which modulate changes in synapse formation and dendritic structure and regulate dentate gyrus volume during development and in adult life. Two forms of structural plasticity are affected by stress: Repeated stress causes atrophy of dendrites in the CA3 region, and both acute and chronic stress suppresses neurogenesis of dentate gyrus granule neurons. Besides glucocorticoids, excitatory amino acids and N-methyl-D-aspartate (NMDA) receptors are involved in these two forms of plasticity as well as in neuronal death that is caused in pyramidal neurons by seizures and by ischemia. The two forms of hippocampal structural plasticity are relevant to the human hippocampus, which undergoes a selective atrophy in a number of disorders, accompanied by deficits in declarative, episodic, spatial, and contextual memory performance. It is important, from a therapeutic standpoint, to distinguish between a permanent loss of cells and a reversible atrophy.

INTRODUCTION

The hippocampal formation is an important brain structure in episodic, declarative, and spatial learning and memory and is a component in the control of autonomic and vegetative functions such as adrenocorticotropin secretion (Eichenbaum & Otto 1992, Jacobson & Sapolsky 1991). The hippocampus is also a plastic and vulnerable brain structure that is damaged by stroke and head trauma and susceptible to damage during aging and repeated stress (Sapolsky

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1992). Hippocampal neurons express receptors for circulating adrenal steroids (McEwen et al 1968). Two types of adrenal steroid receptors, type I (mineralocorticoid) and type II (glucocorticoid), mediate a variety of effects on neuronal excitability, neurochemistry, and structural plasticity (DeKloet et al 1996, 1998). Many of these hormone effects occur in the context of ongoing neuronal activity. In particular, excitatory amino acids and N-methyl-D-aspartate (NMDA) receptors, as well as serotonin, play important roles in the functional and structural changes produced in the hippocampal formation by steroid hormones. This chapter reviews the adaptive plasticity in the hippocampus produced by circulating adrenocortical, thyroid, and gonadal hormones acting, in many cases, in concert with excitatory amino acid neurotransmitters. It also considers some of the ways in which adaptive plasticity gives way to permanent damage.

STRUCTURAL CHANGES PRODUCED BY HORMONES IN THE HIPPOCAMPUS

Adrenal steroids are involved in three types of plasticity in the hippocampal formation. First, they reversibly and biphasically modulate excitability of hippocampal neurons and influence the magnitude of long-term potentiation. They also produce long-term depression (DeKloet et al 1998; Kerr et al 1994; Pavlides et al 1994, 1995a,b, 1996). These effects may be involved in biphasic effects of adrenal secretion on excitability, cognitive function, and memory during the diurnal rhythm and after stress (Diamond et al 1992, 1996; Dana & Martinez 1984; Barnes et al 1977). In particular, acute nonpainful novelty stress inhibits primed-burst potentiation and memory (Diamond et al 1994, 1996). Second, adrenal steroids participate along with excitatory amino acids in regulating neurogenesis of dentate gyrus granule neurons (Cameron & Gould 1996a), in which acute stressful experiences can suppress the ongoing neurogenesis (Gould et al 1997a, Galea et al 1996). 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 excitatory amino acids, in a reversible stress-induced atrophy of dendrites in the CA3 region of the hippocampus of male rats (McEwen et al 1995a) 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 1995a). The second and third aspects are described in more detail below.

Besides what stress does to change hippocampal structure, there are other forms of plasticity in the hippocampus. These include (a) reversible synaptogenesis that is regulated by ovarian steroids and excitatory amino acids

via NMDA receptors in female rats and that occurs in the CA1 region (Gazzaley et al 1996; Woolley et al 1990, 1997) and (*b*) a reversible atrophy of dendrites of CA3 neurons during hibernation in ground squirrels and hamsters (Popov et al 1992, Popov & Bocharova 1992). The estrogen-regulated CA1 synaptic plasticity is a rapid event. In the female rat it occurs during the 5-day estrus cycle, with the synapses taking several days to be induced under the influence of estrogens and endogenous glutamic acid and then, under the influence of the proestrus surge of progesterone, disappearing within 12–24 h (McEwen et al 1995b). Blocking NMDA receptors blocks atrophy, and NMDA receptors are induced by estrogens on CA1 neurons (Gazzaley et al 1996, Weiland 1992). In contrast, the CA3 atrophy found in rats is a relatively slow process, taking at least 3 weeks to develop under daily stress and a week or so to disappear. However, dendritic atrophy in hibernating ground squirrels and hamsters develops as fast as the hibernating state and can be reversed rapidly within several hours (Popov et al 1992, Popov & Bocharova 1992; AM Magarinos, BS McEwen, P Pevet, unpublished data). Although anatomically similar to the stress-induced atrophy in rats and tree shrews, it is not yet clear whether this process involves the same mechanisms. If it does, the question becomes this: What factors make the atrophy process rapid in hibernation and slow in the case of repeated stress?

STRESS-INDUCED PLASTICITY

Reversible Atrophy of Dendrites

The detailed study of the process of dendritic atrophy in rats and tree shrews is useful for understanding cellular mechanisms and pharmacological means of intervening and either blocking or reversing hippocampal atrophy. In the hibernation and stress studies, dendritic length and branching is assessed by morphometry after silver staining neurons with the single-section Golgi technique. More recently, electron microscopy has revealed that stress and glucocorticoids alter morphology of presynaptic MFT in the stratum lucidum region of CA3 (Magarinos et al 1997). It was found that 21 days of corticosterone treatment or 21 days of 6 h of restraint stress per day caused atrophy of apical dendrites of CA3 pyramidal neurons (reviewed in McEwen et al 1995a). Psychosocial stress also causes apical dendrites of CA3 pyramidal neurons to atrophy in rats (McKittrick et al 1996) and in the tree shrew (Magarinos et al 1996).

PHARMACOLOGY OF DENDRITIC ATROPHY   Stress- and corticosterone-induced atrophy were prevented by the anti-epileptic 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 was consistent with evidence that stress induces release of glutamate in the hippocampus and other brain regions (see Taylor & Meldrum 1995, Magarinos et al 1996, McEwen et al 1995a). NMDA receptor blockade is also effective in preventing stress-induced dendritic atrophy (see McEwen et al 1995a).

A model of the cellular and neurochemical interactions involved in dendritic atrophy is presented in Figure 1. It emphasizes the interactions among
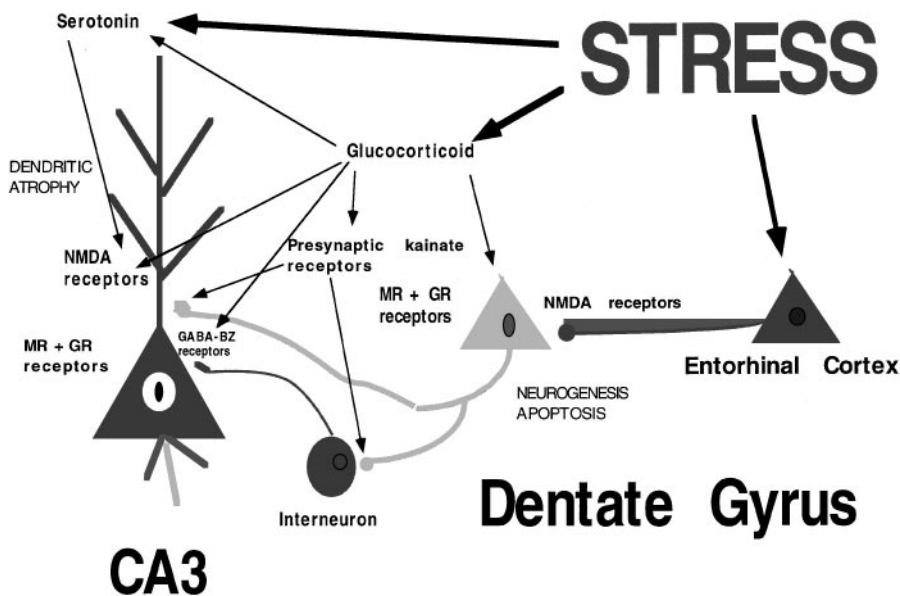
Figure 1   Schematic diagram of the postulated role of neurotransmitters and glucocorticoids in regulating neurogenesis and dendritic atrophy in the dentate gyrus–CA3 system of the hippocampal formation. (MR, mineralocorticoid or Type I adrenal steroid receptor; GR, glucocorticoid or Type II adrenal steroid receptor.) Granule neurons are replaced in adult life, and neurogenesis and apoptotic neuronal death are regulated by stress and by an enriched environment, 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 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 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-aspartate (NMDA) receptor, and reduced GABA-benzodiazepine–mediated inhibitory activity at synapse from the interneurons on CA3 pyramidal neurons may also exacerbate the atrophy. 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.

neurons and neurotransmitters. The role of adrenal steroids is discussed below. Besides glutamate, other participating neurotransmitters include GABA and serotonin. Inhibitory interneurons have a significant role in controlling hippocampal neuronal excitability (Freund & Buzsaki 1996), and the involvement of the GABA-benzodiazepine receptor system is strongly suggested by the ability of a benzodiazepine, adinazolam, to block dendritic atrophy (AM Magarinos, BS McEwen, unpublished data).

Serotonin is released by stressors and tianeptine, an atypical tricyclic antidepressant that enhances serotonin reuptake and, thus, reduces extracellular 5HT levels, preventing both stress- and corticosterone-induced dendritic atrophy of CA3 pyramidal neurons (Watanabe et al 1992a). However, several inhibitors of serotonin reuptake, fluoxetine and fluvoxamine, and desipramine, an inhibitor of noradrenaline uptake, failed to block atrophy (AM Magarinos, BS McEwen, unpublished data). Thus, the effect of tianeptine on CA3 pyramidal neuron morphology is not due to its reported ability to reduce corticosterone secretion (Delbende et al 1991) but may instead be related to its reported ability to enhance the reuptake of serotonin within the hippocampus (Whitton et al 1991). Further evidence for serotonin involvement in dendritic atrophy comes from studies of psychosocial stress in rats, in that both dominant and subordinate rats show dendritic atrophy as well as downregulation of 5HT transporter expression in the CA3 region. This indicates either a reduced density of serotonin terminals or a reduced expression of the transporter (7186). Moreover, repeated restraint stress and psychosocial stress in rats suppresses expression of the inhibitory 5HT1A receptor in the hippocampus in rats and tree shrews (Flugge 1995, McKittrick et al 1996, McEwen et al 1995a).

Because corticosterone- and stress-induced atrophy of CA3 pyramidal neurons are both blocked by phenytoin as well as by tianeptine (see McEwen et al 1995a), serotonin released by stress or corticosterone may interact pre- or postsynaptically with glutamate released by stress or 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 $5HT_2$ receptors (Rahmann & Neumann 1993, Mennini & Miari 1991).

CONNECTIONS BETWEEN GLUCOCORTICOIDS AND EXCITABILITY   Glucocorticoid treatment causes dendritic atrophy, and stress-induced atrophy is blocked by treatment with an adrenal steroid synthesis blocker, cyanoketone (see McEwen et al 1995a). This indicates that endogenous glucocorticoids have a role 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 the hippocampus (Weiland et al 1995, Bartanusz et al 1995), with chronic glucocorticoid exposure leading to increased expression of NMDA receptor binding in both NR2A and NR2B subunit mRNA levels (Weiland et al 1997). Second, glucocorticoid affects the expression of mRNA levels for specific subunits of GABAa receptors in CA3 and the dentate gyrus. Both low and high levels of corticosterone have different effects on GABAa receptor subunit mRNA levels and receptor binding (Orchinik et al 1994; M Orchinik, NG Weiland, BS McEwen, unpublished data), which suggests corticosterone may alter the excitability of hippocampal neurons through regulation of GABAa receptor expression. However, whether the corticosteroid effects on neuronal morphology involve changes in the number or pharmacological properties of GABAa receptors remains to be seen. Third, adrenal steroids regulate the release of glutamate because adrenalectomy markedly reduces the magnitude of the excitatory amino acid (EAA) release evoked by restraint stress (Moghaddam et al 1994, Lowy et al 1993). Mossy fiber terminals (MFT) in the stratum lucidum contain presynaptic kainate receptors that postively regulate glutamate release (Chittajallu et al 1996). These presynaptic kainate receptors are decreased in density by adrenalectomy and restored to normal by corticosterone replacement (Watanabe et al 1995). Moreover, repeated stress causes a reorganization of synaptic vesicles within MFT, as reported recently from electron microscopy studies (Magarinos et al 1997). Although 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).

SYNAPTIC VESICLE REORGANIZATION IN MOSSY FIBER TERMINALS   There are several implications of the changes in MFT. First, 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. This possibility, however, remains to be tested directly by electrophysiology and microdialysis (Magarinos et al 1997). Second, the synaptic vesicle reorganization in MFT 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 MFT reside on the proximal regions of the apical dendrites, and their numbers are not reduced in number 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 (Li et al 1994, Ishizuka et al 1990). Moreover, CA3 neurons have a multiplicty of calcium channel types that contribute to the activation of calcium currents by low-voltage changes (Avery & Johnston 1996). In addition, pyramidal neurons in subregion CA3c, which lies closest to the hilus, send excitatory axons back to the hilar region and affect the dentate gyrus itself (Scharfman 1994, Kneisler & Dingledine 1995). Such feedback loops can presumably reactivate the mossy fiber system and sustain CA3 excitation, as in the so-called SPW (sharp waves) (Buzsaki 1986), and such an activation may drive the reorganization of vesicles within the MFT. Moreover, collateral activation of CA3 neurons by other CA3 neurons would help explain the blockade of dendritic atrophy by NMDA receptor blockade (Magarinos & McEwen 1995) because 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 & Cuthbertson 1980). The CA3 hippocampal sub-region is also damaged by epileptogenic stimulation of the perforant path, which involves the activation of the dentate gyrus (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 proned epileptic gerbils show MFT synaptic vesicle clustering, an effect that could be blocked by the disruption of the perforant pathway (Farias et al 1992).

ELECTROPHYSIOLOGICAL CONSEQUENCES OF REPEATED STRESS   In keeping with the reorganization of dendrites and the alteration of synaptic vesicles in MFT, repeated stress produces a variety of effects on the electrophysiological features of the hippocampus (C Pavlides, BS McEwen, unpublished data). At 48 h following 21 days of 6 h of repeated restraint stress per day, rats were studied under chloropent anesthesia. Compared with control animals handled briefly but not subjected to restraint stress, in rats repeatedly stressed there was an inhibition of long-term potentiation (LTP) in the laconosum/moleculare layer of CA3 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. High-frequency stimulation produced epileptic after-discharges in 38% of the repeatedly stressed rats, whereas among the nonstressed controls it produced epileptic after-discharges in only 15%. The rats showing seizures were removed from the analysis described above. The increased incidence of seizures is consistent with the possibility of stress-induced mossy fiber sprouting because in epilepsy there is sprouting of mossy fibers that generate a recurrent excitatory circuit involving aberrant granule cell–granule cell synapses (Sutula et al 1996, Parent et al 1997, Okazaki et al 1995). Moreover, LTP itself appears to be capable of inducing mossy fiber sprouting (Cameron et al 1998).

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.

POSSIBLE MECHANISMS OF DENDRITIC PLASTICITY Following on 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 1995a for discussion). Some researchers report that stress also alters the expression of the neurotrophins, BDNF and NT-3, in the hippocampus (Ueyama et al 1997, Smith et al 1995). Others, however, report that conditions that cause dendritic atrophy, such as repeated restraint stress or psychosocial stress, do not appear to change neurotrophin expression in the hippocampus (Kuroda & McEwen 1998), which indicates 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).

Neurogenesis in the Dentate Gyrus

Adrenalectomy (ADX) of an adult rat causes increased granule neuron death by apoptosis (Gould et al 1990, Sloviter et al 1989). However, continuous birth of granule neurons occurs in the adult dentate gyrus, and neurogenesis also increases following ADX (Cameron & Gould 1994). A similar story applies to the developing dentate gyrus (Cameron & 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). Curiously, however, 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 & McEwen 1997).

Accelerated by ADX in both the adult and the developing dentate gyrus, newly born neuron-specific enolase cells arise in the hilus, 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 [^{3}H]thymidine lack both type I and type II adrenal steroid receptors (Cameron et al 1993), which indicates that steroidal regulation occurs via messengers from an unidentified steroid-sensitive cell. Recent data suggests an important signaling role for transforming growth factor alpha (TGFα) and the epidermal growth factor (EGF) receptor system (Tanapat & Gould 1997).

Granule neuron birth is accelerated by seizure-like activity (Parent et al 1997). 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 simulate local neurogenesis (Cameron & 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 & Tanapat 1997), 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 (Cameron et al 1998, Gould et al 1997a).

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 (Sherry et al 1992). Birds that use space around them to hide and locate food, as well as voles and deer mice that traverse large distances to find mates, have larger hippocampal volumes than do closely related species that do not engage in those activities. 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 & McEwen 1995). 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.

Another important effect is that of acute and chronic stress. Acute stress involving the odor of a natural predator, the fox, inhibits neurogenesis in adult

rats (Galea et al 1996). Acute psychosocial stress in adult tree shrews, involving largely visual cues, inhibits neurogenesis (Gould et al 1997a). Inhibition of neurogenesis is also seen in the dentate gyrus of marmosets after acute psychosocial stress (Gould et al 1997d). Chronic psychosocial stress in tree shrews results in a more substantial inhibition of neurogenesis than does a single acute stressful encounter. Moreover, the dentate gyrus is 30% smaller in chronically stressed tree shrews, although granule neuron number only shows a trend for reduction (Fuchs et al 1997). This finding suggests that there may be other changes, such as atrophy of dendritic branching, to account for the decrease in dentate gyrus volume.

Finally, what are the consequences for hippocampal function of altering dentate gyrus volume and the rates of neurogenesis and neuronal apoptosis? In the enriched environment studies (Kempermann et al 1997), increased dentate gyrus volume was accompanied by better performance on spatial learning tasks. In contrast, chronically stressed tree shrews display impaired spatial learning and memory (E Fuchs, personal communication). However, this might be as much due to atrophy of dendrites of CA3 pyramidal neurons (see above) as to reduced dentate gyrus neurogenesis.

ADRENAL STEROIDS, HIPPOCAMPAL ATROPHY, AND COGNITION

Stress and glucocorticoids are known to 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 (Lupien & McEwen 1997). However, repeated stress also impairs cognitive function in animal models, and repeated glucocorticoid elevation or treatment in humans is accompanied by cognitive dysfunction (McEwen & Sapolsky 1995). There are also declines in cognitive function in aging humans that are correlated with progressive elevations in hypothalamo-pituitary-adrenal (HPA) activity over 3–4 years (Seeman et al 1997, Lupien et al 1994).

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 & McEwen 1997, Kirschbaum et al 1996). Adrenal steroid effects are implicated in selective attention as well as in memory consolidation (Lupien & McEwen 1997), 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 mechanisms other than glucocorticoids, including endogenous opioid neuropeptides in the case of painful

stressors such as shock (see McEwen et al 1995a for summary). 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 atrophy in the CA3 region impairs hippocampal-dependent learning. Rats that received 21 days of restraint stress were impaired in performance on an 8-arm radial maze when they were trained starting 1 day after the end of stress but not when trained 18 days later (Luine et al 1994). Dendritic atrophy is reversible within 7–10 days after the end of stress (CD Conrad, AM Magarinos, JE Ledoux, BS McEwen, submitted for publication). The impairment was in the same direction as, but not as great as, impairment found in aging rats. Moreover, stress effects were prevented by the 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 (Luine et al 1994; Watanabe et al 1992a,b). 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 (Conrad et al 1996).

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 3–4 years (Seeman et al 1997, Lupien et al 1994). Recent evidence has revealed that the most severely impaired individuals have a significantly smaller hippocampal volume than the least impaired individuals (Lupien et al 1996). This result is consistent with other findings of individual differences in cognitive function correlated with hippocampal volume reductions in elderly humans (Convit et al 1995, Golomb et al 1994).

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 loss of hippocampal pyramidal neurons (Kerr et al 1991). An important factor may be the enhancement by glucocorticoids of calcium currents in the 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).

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.

HUMAN HIPPOCAMPAL ATROPHY

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 is only 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 do, in particular in Cushing's syndrome, recurrent depressive illness, posttraumatic stress disorder (PTSD), schizophrenia, and aging prior to overt dementia (Table 1). The diversity of conditions in which atrophy occurs raises the question of whether they reflect a common mechanism and whether the atrophy is permanent or reversible.

It is tempting to attribute the occurrence of hippocampal atrophy to gluco-corticoids. This is because the hippocampus is a primary target area for adrenal steroids in the brain, and adrenal steroids have been shown to have effects on hippocampal neuronal plasticity and on the loss of hippocampal neurons in con-ditions such as ischemia and aging (McEwen et al 1995a; Landfield & Eldridge 1994; Sapolsky 1986, 1992). However, as discussed above, other factors play a role, including the endogenous excitatory amino acid neurotransmitters. More-over, 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 aging individuals, but this is probably not the

Table 1   Atrophy of the human hippocampus[a]

Disorder	References
Cushing's syndrome	Starkman et al 1992
Recurrent depressive illness	Sheline et al 1996
Posttraumatic stress disorder	Gurvits et al 1996, Bremner et al 1995
Schizophrenia	Fukuzako et al 1996, Bogerts et al 1993
Aging, preceding dementia	Convit et al 1995, Golomb et al 1994
Dementia	de Leon et al 1993

[a]See also Sapolsky (1996) for another recent overview of hippocampal atrophy in the human brain.

case for any of the other disorders listed in Table 1, 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 because 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. For example, 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 (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 do those 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 distinct pathways of selective and repeated elevations of glucocorticoid hormones in relationship to the individual experiences and reactivities. In the case of PTSD, the stress responses and neurochemical changes accompanying the initial trauma, which may have taken place 10–20 years previously, are unknown, as are the ongoing stress responsiveness and neurochemical activity (e.g. brain glucose metabolism) of traumatized individuals. Likewise, for recurrent depressive illness, the history of the depressed individual in terms of endocrine function and neurochemical activity is largely unknown, as too are the 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 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 (M Starkman, personal communication). On the other hand, there may be irreversible loss of hippocampal neurons, and some of the evidence in the magnetic resonance imaging of recurrent depressive illness is consistent with this possibility (Sheline et al 1996). Insofar 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 animals. 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.

CONCLUSIONS

Adrenal steroids participate with excitatory amino acids and NMDA receptors in regulating structural plasticity in the adult hippocampus. At the same time, excitatory amino acids 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.

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