Published in final edited form as:

Ann N Y Acad Sci. 2010 September ; 1204(Suppl): E38–E59. doi:10.1111/j.1749-6632.2010.05568.x.

Stress, sex and neural adaptation to a changing environment: mechanisms of neuronal remodeling

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Abstract

The adult brain is much more resilient and adaptable than previously believed, and adaptive structural plasticity involves growth and shrinkage of dendritic trees, turnover of synapses and limited amounts of neurogenesis in the forebrain, especially the dentate gyrus of the hippocampal formation. Stress and sex hormones help to mediate adaptive structural plasticity, which has been extensively investigated in hippocampus and to a lesser extent in prefrontal cortex and amygdala, all brain regions that are involved in cognitive and emotional functions. Stress and sex hormones exert their effects on brain structural remodeling through both classical genomic as well as non-genomic mechanisms, and they do so in collaboration with neurotransmitters and other intra- and extracellular mediators. This review will illustrate the actions of estrogen on synapse formation in the hippocampus and the process of stress-induced remodelling of dendrites and synapses in the hippocampus, amygdala and prefrontal cortex. The influence of early developmental epigenetic events, such as early life stress and brain sexual differentiation, is noted along with the interactions between sex hormones and the effects of stress on the brain. Because hormones influence brain structure and function and because hormone secretion is governed by the brain, applied molecular neuroscience techniques can begin to reveal the role of hormones in brain-related disorders and the treatment of these diseases. A better understanding of hormone-brain interactions should promote more flexible approaches to the treatment of psychiatric disorders, as well as their prevention through both behavioral and pharmaceutical interventions.

Keywords

hippocampus; prefrontal cortex; amygdala; HPA axis; glucocorticoids; estradiol; synaptogenesis; dendritic plasticity; neurogenesis; depression; aging; sex differences

Introduction

The adult brain possesses a remarkable ability to adapt and change with experience. Structural changes - neuronal replacement, dendritic remodelling, and synapse turnover - are a feature of the adult brain's response to the environment. Nowhere is this better illustrated in the mammalian brain than in the hippocampus, where all three types of structural plasticity have been recognized and investigated using a combination of morphological, molecular, pharmacological, electrophysiological and behavioral approaches. At the same time, new data on the amygdala and the prefrontal cortex, brain regions involved in emotions, cognitive function and behavioral control, have demonstrated that the adult brain is indeed a malleable and adaptable structure. Steroid hormones play an important role,

acting via both genomic and non-genomic mechanisms. In addition, a growing number of peptide hormones associated with metabolic control have been shown to be transported into the brain and to have important effects on cognitive function, mood and neuronal structure and function.

This review will summarize these various types of plasticity and the current knowledge of mechanisms and discuss them in the broader context of how the brain responds to environmental demands, including those related to stressful life events. The pathophysiological aspects of the adaptation to prolonged stress likely involve a loss of plasticity and an increased vulnerability to damage. These adaptations are discussed in relation to human psychiatric illness, aging and associated systemic comorbidities.

Examples of structural plasticity

Long regarded as a rather static and unchanging organ, except for electrophysiological responsivity such as long-term potentiation¹, the brain has gradually been recognized as capable of undergoing rewiring after brain damage² and also able to grow and change as seen by dendritic branching, angiogenesis and glial cell proliferation during cumulated experience³. More specific physiological changes in synaptic connectivity have also been recognized in relation to hormone action in the spinal cord⁴, and in environmentally directed plasticity of the adult songbird brain⁵. Seasonally varying neurogenesis in restricted areas of the adult songbird brain is recognized as part of this plasticity^{6;7}.

Rather than being isolated examples of plasticity in certain species, there are clear indications that many aspects of brain function are subject to structural plasticity, including respiratory and motor control regions during exercise training^{8;9}, the nucleus accumbens after repeated sodium depletion causing increased salt appetite and enhanced amphetamine self-administration¹⁰, the nucleus accumbens, hippocampus and orbitofrontal cortex after morphine, amphetamine or cocaine administration¹¹⁻¹³, and the hippocampus during hibernation^{14;15}.

The role of hormones in neuronal remodeling in the hippocampus

The hippocampal formation is an important brain structure in episodic, declarative, contextual and spatial learning, as well as a component of the control of vegetative functions, such as ACTH secretion¹⁶, cognition and mood^{17; 18;19}. It is also a plastic and vulnerable brain structure that is damaged by stroke and head trauma and is susceptible to damage during aging and repeated stress²⁰. In 1968, we showed that hippocampal neurons express receptors for circulating adrenal steroids²¹. Subsequent work in many laboratories has shown that the hippocampus has two types of adrenal steroid receptors which mediate a variety of effects on neuronal excitability, neurochemistry and structural plasticity²².

Hippocampal neurons also possess receptors for estrogens²³⁻²⁵ and androgens^{26;27} and show plasticity during sexual differentiation and in adult life in responses to gonadal steroids²⁸⁻³⁰. Recent work has revealed that adrenal and gonadal steroids are involved in four types of plasticity in the hippocampal formation. First, they reversibly and biphasically modulate the excitability of hippocampal neurons and influence the magnitude of long-term potentiation, as well as produce long-term depression³¹⁻³⁴. These effects may be involved in the biphasic effects of adrenal secretion on excitability and cognitive function and memory during the diurnal rhythm and after stress³⁵⁻³⁸. Second, adrenal steroids participate along with excitatory amino acids in regulating neurogenesis and neuronal replacement of dentate gyrus granule neurons, in which acute stressful experiences can suppress the ongoing neurogenesis³⁹. These effects are likely involved in fear-related learning and memory, given the anatomical connections between the dentate gyrus and the amygdala, a

brain area important in the memory of aversive and fear-producing experiences^{40;41}. Third, ovarian steroids regulate synaptic turnover in the hippocampus by a mechanism involving excitatory amino acids^{42;43}. These effects may underlie the impairment of hippocampal-dependent memory functions in women after loss or suppression of ovarian function. Finally, adrenal steroids participate along with excitatory amino acids in stress-induced remodeling of dendrites in the CA3 region of hippocampus, a process that affects only the apical dendrites and results in cognitive impairment in the learning of spatial and short-term memory tasks⁴⁴. Besides atrophy of neuronal processes, severe and prolonged stress causes neuronal loss⁴⁵. The relationship between reversible atrophy and permanent damage is an important issue that is relevant to recent reports showing that the human hippocampus undergoes shrinkage in Cushing's syndrome, normal aging, dementia, recurrent depressive illness, schizophrenia and post-traumatic stress disorder. The stress-induced remodeling seen in amygdala and prefrontal cortex will be discussed below.

Steroid hormones regulate gene expression via intracellular receptors that bind to DNA sequences known as "response elements". These hormones also act by tethering to other gene regulators that directly contact DNA response elements. In addition, growing evidence indicates that some steroid receptors directly regulate signaling pathways. This finding is particularly relevant in the context of estrogen regulation of synapse formation and turnover in the hippocampus, and it is also applicable to the actions of adrenal steroids, as will be discussed later in this review.

The hippocampus as a target of sex hormones, particularly estrogens

Estrogen-regulated synapse formation

Because of the paucity of cell nuclear estrogen receptors in the hippocampus, it was a huge surprise to find that hippocampal pyramidal neurons demonstrate reversible synaptogenesis in CA1 pyramidal neurons, a process that is regulated by ovarian steroids and excitatory amino acids via NMDA receptors in female rats^{42;46}. CA1 synaptic remodeling is a relatively rapid event, occurring during the female rats' 5 day estrous cycle: the synapses take several days to be induced under the influence of estrogens and activated NMDA receptors and then disappear within 12h under the influence of the proestrus surge of progesterone⁴².

Even though the hippocampus expresses few cell nuclear estrogen receptors and virtually no cell nuclear progesterone receptors, this structure displays a robust response to estrogen and progesterone treatment and to endogenous ovarian steroids during the natural estrous cycle. This was first presaged with the finding of cyclic variations in the threshold of the dorsal hippocampus to elicitation of seizures, with the greatest sensitivity occurring during proestrus⁴⁷. Mapping studies of [³H]-estradiol labeling of cell nuclei in hippocampus²⁵, and later immunocytochemistry with estrogen receptor antibodies^{24;48}, revealed estrogen receptors in cell nuclei of scattered interneurons in the CA1 region, as well as other regions of Ammon's horn²⁵.

Role of progesterone receptors

The hippocampus also expresses estrogen-inducible progesterone receptors, albeit at much lower levels than in the hypothalamus⁴⁹, as well as low levels of progesterone receptor mRNA in both the CA1 and CA3 regions of Ammon's horn⁵⁰. New evidence from electron microscopic immunocytochemistry reveals that the estrogen-inducible progesterone receptors in hippocampus are present in axons, dendrites and synaptic terminals, as well as glial cell processes⁵¹. The critical involvement of progesterone was indicated by the fact that progesterone administration rapidly potentiated estrogen-induced spine formation, but then triggered the down-regulation of spines on CA1 neurons. The down-regulation of dendritic

spines occurred over the course of days when estrogen was withdrawn, but took place within 8 to 12 hours when progesterone was administered. Moreover, the natural down-regulation of dendritic spines between the proestrus peak and the trough on the day of estrus was blocked by the progesterone antagonist, RU38486 Woolley, McEwen, 1993. This finding is compatible with a role for estrogen-inducible progesterin receptors in the CA1 region of the hippocampus^{49;51}. Yet these estrogen-inducible progesterin receptors are located in axons, dendrites, synaptic endings and glial cell processes and not in cell nuclei⁵¹. The significance of this localization will be discussed below.

Role of NMDA receptors

Besides progesterone, the single most novel feature of estrogen-induced spinogenesis on CA1 pyramidal neurons is that it is blocked by concurrent administration of NMDA receptor antagonists but not by cholinergic or AMPA-kainate receptor antagonists⁵². Spine synapses are excitatory and likely express NMDA receptors; one of the long-term effects of estradiol is to induce NMDA receptor binding sites in the CA1 region of the hippocampus⁵³. Estradiol also increases immunoreactivity for the NMDA R1 subunit in both the cell bodies and dendrites of CA1 pyramidal neurons while not altering NMDAR1 mRNA levels measured by *in situ* hybridization⁵⁴. Furthermore, the actions of estradiol on NMDA receptor expression are mimicked by enhancing cholinergic function, just as the actions of estradiol are blocked by antagonizing cholinergic activity⁵⁵. This cholinergic influence may occur through inhibitory GABAergic interneurons^{56;57}. Thus, activation of NMDA receptors themselves could lead to induction of new synapses, in which case estrogen/cholinergic induction of NMDA receptors would be a primary event leading to synapse formation. Moreover, NMDA-receptor gating of calcium ions may be an important factor in the extension and retraction of dendritic spines: for example, NMDA-receptor activation promotes dephosphorylation of MAP2 and alters the interaction of this cytoskeletal protein with actin and tubulin⁵², as will be discussed further below.

The *in vivo* studies summarized above have been supported by investigations of embryonic hippocampal neurons in cell culture, in which estradiol induces spines over a time course of 24 to 48 hours by a process that is blocked by the anti-estrogen tamoxifen and by the NMDA antagonist APV but not by the AMPA/kainate antagonist, DNQX⁵⁸. The phosphorylation of CREB has been implicated in this process⁵⁹, and a decrease in both BDNF and inhibitory GABA transmission are also implicated^{60;61}. Data from *in vivo* studies also support a role for a transient estrogen-induced inhibition of GABA levels in inhibitory interneurons in the CA1 region⁵⁶. These results point to the importance of inhibitory interneurons in estrogen signaling.

Role of inhibitory interneurons

Building upon the finding that estrogen receptors are present on inhibitory interneurons and not on CA1 pyramidal neurons where spine formation takes place, it was found that estradiol treatment induced an increase in GAD mRNA in inhibitory interneurons within the CA1 pyramidal cell layer Weiland, 1992b. This would potentially increase inhibitory activity within these neurons, although it is not clear whether they exert their inhibitory effect on the pyramidal neurons or on other inhibitory interneurons. Other studies point to the excitatory effects of estrogen on hippocampal CA1 pyramidal neurons, possibly through disinhibition⁶². One explanation of this finding is that estrogen acts on inhibitory interneurons that in turn disinhibit pyramidal neurons, allowing for removal of the magnesium blockade and allow activation of NMDA receptors⁵². These findings raise the question of how nuclear and non-nuclear actions of estrogen can work together in the hippocampus.

There is strong evidence both *in vivo* and *in vitro* supporting an indirect GABAergic mediation of estrogen actions on synapse formation involving interneurons that express estrogen receptor [α] ER α)⁶¹⁻⁶³. The *in vitro* evidence comes from studies of estrogen-induced synapse formation, in which estrogen induces spines on dendrites of dissociated hippocampal neurons by a process that is sensitive to NMDA receptor antagonism but not to AMPA/kainate antagonism⁵⁸. Furthermore, estrogen treatment was found to increase expression of phosphorylated CREB, and a specific antisense to CREB prevented both the formation of dendritic spines and the elevation in pCREB immunoreactivity IR⁵⁹. The location of ER α in the cultures, resembling the *in vivo* localization, was in putative inhibitory interneurons, i.e., glutamic acid decarboxylase GAD -immunoreactive cells that constituted around 20% of the total neuronal population⁶⁴. Estrogen treatment caused decreases in GAD content and the total number of neurons expressing GAD. Mimicking this decrease with an inhibitor of GABA synthesis, mercaptopropionic acid, caused an upregulation of dendritic spine density, paralleling the effects of estrogen⁶¹. Thus, estrogen induced synapse formation may involve the suppression of GABA inhibitory input to the pyramidal neurons where the synapses are being generated.

An additional role of estrogen is to mobilize the movement of synaptic vesicles in ER α -containing presynaptic boutons of inhibitory interneurons that have the cholecystokinin neurochemical phenotype and which also express neuropeptide Y NPY, a modulator that inhibits excitatory activity⁶⁵. Estrogen treatment has also been shown to increase expression of NPY in a subset of inhibitory interneurons in hippocampus⁶⁶. Estrogen treatment may effect NPY expression via BDNF⁶⁷. These effects of estrogen via NPY may be relevant not only to synapse formation but also to the neuroprotective effects of estrogens in relation to stroke⁶⁸. Another important effect of estrogen is on mitochondria, where estradiol promotes calcium sequestration and thus attenuates free radical formation that is involved in excitotoxic cell damage and death⁶⁹. Indeed, mitochondria are one of the intracellular sites that express estrogen receptors.

Membrane-associated estrogen receptors

Besides cell nuclear ER, there is increasing evidence for non-nuclear ER that interact with second messenger pathways⁷⁰. A seminal study reported that transfection of ER α and ER β into Chinese hamster ovarian cells resulted in expression of both ERs in a form that couples to second messenger systems that are stimulated by estrogen and blocked, at least partially, by non-steroidal estrogen antagonists⁷¹. Previous studies had indicated that non-nuclear ERs can be seen at the light microscopic level in cultured cells⁷² and also at the electron microscopic level in hypothalamus⁷³. The proliferation of articles on non-nuclear actions of estrogen via membrane ER and membrane-associated ER e.g.,⁷⁴; see above has reinforced the importance of investigating non-nuclear actions of estrogens in the hippocampus.

Stimulated by this evidence, we used electron microscopy to examine ER α localization in rat hippocampal formation⁷⁵. We were able to see at the electron microscopic level the cell nuclear labelling seen by light microscopy in some GABAergic interneurons. In addition, some pyramidal and granule neuron perikarya have small amounts of ER α IR in the nuclear membrane, which is consistent with a recent report that 125I estradiol labels a small number of estrogen binding sites in cell nuclei of hippocampal principal cells⁷⁶. In CA1stratum radiatum, we found half of the total ER α -IR in unmyelinated axons and axon terminals containing small synaptic vesicles. This has potential functional relevance, since estrogen can influence neurotransmitter release e.g. see^{77,78}. The synaptic ER α -IR was found in terminals that formed both asymmetric and symmetric synapses on dendritic shafts and spines, suggesting that both excitatory and inhibitory transmitter systems are associated with ER α -IR⁷⁵ and further studies showed that cholinergic terminals express ER α -IR⁷⁹. Around 25% of the ER α -IR was found in dendritic spines of principal cells, where it was

often associated with spine apparatus and/or postsynaptic densities, suggesting that estrogen might act locally to regulate calcium availability, phosphorylation or protein synthesis. Finally, the remaining 25% of ER α -IR was found in astrocytic profiles, often located near the spines of principal cells.

A similar story applies to ER β -IR⁸⁰, where the presence of this form of the estrogen receptor was detected in largely extra-nuclear locations in synapses, dendrites, and glial cell processes. More than for ER α -IR, ER β -IR was evident in association with mitochondria⁸⁰. That these membrane-associated forms of ER α and ER β are likely to be functional is supported by recent evidences that they bind 125I estradiol⁸¹.

The association between the ER α -IR and ER β -IR and dendrites supports a possible local, non-genomic role for this ER in regulation of dendritic spine density via second messenger systems. Hippocampus studies performed both *in vivo* and *in vitro* examined one second messenger pathway, the phosphorylation of CREB, have indicated that estrogen has rapid effects that are evident within as little as 15 minutes to increase pCREB immunoreactivity in cell nuclei of hippocampal pyramidal neurons⁸². One related estrogen-sensitive pathway involves phosphoinositol-3 PI3 kinase, and the phosphorylation of Akt,^{83;84} and another, the phosphorylation of LIM kinase⁸⁵. The importance of both pathways has been revealed by *in vitro* cell models.

Contributions of *in vitro* models of estrogen action

While neuronal hippocampal systems have been important in understanding estrogen effects, the NG108-15 cell has also been very helpful in elucidating the role of estradiol in regulating mechanisms that may contribute to excitatory spine synaptogenesis because it expresses both ER α and ER β and, furthermore, responds to estradiol through activation of signaling pathways. In one series of studies, estradiol was shown to regulate Akt phosphorylation and the rapamycin-sensitive phosphorylation of a binding protein, leading to activation of translation of PSD-95 and *de novo* synthesis of this protein, a key anchoring protein in dendritic spines⁸⁶. A parallel study of phosphoAkt immunoreactivity in the rat hippocampus⁸⁴ revealed that the density of pAkt-IR in CA1 stratum radiatum was significantly higher in proestrus rats or in estrogen-supplemented ovariectomized females compared to diestrus, estrus or male rats. Ultrastructurally, pAkt-IR was found throughout the shafts and in select spines of stratum radiatum dendrites. Moreover, proestrus rats compared to diestrus, estrus and male rats contained a significantly more pAkt-IR associated with: dendritic spines, spine apparatus located within 0.1 μ m of dendritic spine bases, endoplasmic reticula and polyribosomes in the cytoplasm of dendritic shafts, and the plasmalemma of dendritic shafts. These findings suggest that estrogens may regulate spine formation in CA1 pyramidal neurons via Akt-mediated signaling events.

NG108-15 cells have also been useful to show a possible role of the phosphorylation of LIMK-1 and a downstream target, cofilin, in events related to actin polymerization. Estradiol regulates the phosphorylation of both targets. Parallel studies on young and aging rat hippocampus revealed that pLIMK-IR occurred primarily in perikarya within the pyramidal cell layer of CA1 and in dendritic shafts and spines in stratum radiatum. Post-embedding quantitative analysis of SR showed that pLIMK had a predominantly post-synaptic localization, preferentially within the postsynaptic density PSD where the percentage of pLIMK-labeled synapses increased 30% with E treatment in young animals and decreased 43% with age, without any effect of estrogen treatment in aged animals⁸⁵. This is consistent with a previous finding that estrogen treatment fails to induce spine synapses in aged female rat hippocampus⁸⁷ and with evidence of a deficit in ER α -IR in the spines of aged female rat hippocampus⁸⁸.

Exploiting the power of the mouse for studies of estrogen action

Estradiol regulates expression of pre- and postsynaptic proteins in the female mouse hippocampus, although it does not appear to alter the number of spine-like processes assessed by Golgi staining ⁸⁹. We, therefore, hypothesize that estrogen causes the maturation of spines rather than the net formation of connections in the mouse hippocampus ^{89;90}. As in the rat, the mouse hippocampus shows an ovarian hormone-dependent cycle of pAkt and pLIMK1 IR ⁹¹. Moreover, as in the rat where there is ovarian hormone-dependent variation in BDNF IR in hippocampus ⁹², the mouse hippocampus shows an ovarian cycle-dependent phosphorylation of the BDNF receptor, trkB ⁹¹. Therefore, future studies can exploit the genetics of the mouse to further investigate estrogen-regulated synaptogenesis.

Sex differences in response to estrogens

Male rats castrated as adults do not exhibit hippocampal synaptogenesis in response to estrogens ⁹³ unless the process of sexual differentiation has been blocked by aromatase inhibitors right after birth ⁹⁴. Yet castrated male rats show a decrease in spine density in hippocampus that is restored by treatment with testosterone or dihydrotestosterone ⁹³. Along with evidence that spatial memory processes show sex differences programmed by the aromatization of estrogens early in neonatal life ⁹⁵, these results indicate that the hippocampus undergoes sexual differentiation.

Summary

Estradiol exerts important regulatory effects on synapse formation in the hippocampus of rat and mouse as well as rhesus monkey ⁹⁶ by acting via both non-genomic and genomic estrogen receptors found in diverse locations: inhibitory interneurons, cholinergic synapses, dendrites and spines of excitatory neurons. Estrogen regulation of synapse formation has also been demonstrated in prefrontal cortex ⁹⁷ and in hypothalamus ^{98;99}. Besides enhancing aspects of cognitive function ¹⁰⁰, estrogen effects also include neuroprotection in relation to stroke ¹⁰¹. Cell nuclear ER in interneurons plays a role in regulating the inhibitory tone on pyramidal cells that helps to regulate synapse formation and, furthermore, may reduce neuronal excitability in relation to seizures and seizure-related damage. Concurrently, ER in dendrites and dendritic spines may be associated with the activation of mRNA translation from polyribosomes ¹⁰² or the endomembrane structures found in spines ¹⁰³. In addition, other second messenger signaling effects might include the phosphorylation of neurotransmitter receptors or ion channels. ER in certain presynaptic terminals might modulate neurotransmitter release or reuptake see ⁴³ for references. Moreover, ER-mediated activation of second messenger systems in dendritic spines and presynaptic endings might lead to retrograde signal transduction to the cell nucleus, perhaps via Akt or CREB, providing another pathway through which estrogen could regulate gene expression.

The hippocampus as a target of stress

Intracellular mechanisms of hormone action

Because the hippocampus was the first higher brain center that was recognized as a target of stress hormones ²¹, it has figured prominently in our understanding of how stress impacts brain structure and behavior. The hippocampus expresses both Type I mineralocorticoid, MR and Type II glucocorticoid, GR receptors, and these receptors mediate a biphasic response to adrenal steroids in the CA1 region although not in the dentate gyrus ¹⁰⁴, which, nevertheless, shows a diminished excitability in the absence of adrenal steroids ¹⁰⁵. Other brain regions, such as the paraventricular nucleus, lacking in MR but having GR, show a monophasic response ¹⁰⁴. Adrenal steroids exert biphasic effects on excitability of hippocampal neurons in terms of long-term potentiation and primed burst potentiation ^{31;33;37} and show parallel biphasic effects upon memory ¹⁰⁶.

In considering possible mechanisms for the biphasic responses, the co-expression of MR and GR in the same neurons could give rise to heterodimer formation and a different genomic activation from that produced by either MR or GR homodimers¹⁰⁴. In addition, deletion of the Type I MR receptor by genetic means has revealed that MR are required for non-genomic regulation of glutamatergic transmission by glucocorticoids¹⁰⁷, a phenomenon that involved glucocorticoid enhancement of extracellular levels of glutamate¹⁰⁸ that plays an important role in both modulatory and excitotoxic effects of glucocorticoids. Although beyond the scope of this review, the subject of non-genomic actions of adrenal steroids has taken on increasing importance in view of the discovery of adrenal steroid receptors that are G protein coupled in the amphibian brain¹⁰⁹ and the connection of this process to endocannabinoid release¹¹⁰, as well as glucocorticoid receptor immunoreactivity in post-synaptic and other non-nuclear regions of neurons in the rodent brain^{111;112} and a large number of reported rapid, non-genomic actions of adrenal steroids^{113;114}. These actions include the role of MR in the rapid, non-genomic actions of glucocorticoids on excitatory amino acid release¹⁰⁷. Hence, it is perhaps not surprising that there are conditions involving neural transmission that favor either rapid positive or negative actions of adrenal steroids on processes, such as learning and memory, as will be discussed later in this article.

Although much of the work on MR and GR has been done on rat and mouse brains, it is important to note that the rhesus monkey hippocampus has a predominance of MR and relatively less GR compared to rodent species¹¹⁵. This finding may have important implications for the effects of adrenal steroids on learning and vulnerability to stress and excitotoxicity, as well as age-related changes as discussed earlier.

Structural remodeling in the hippocampus

Stress hormones modulate function within the brain by changing the structure of neurons. As already noted, the hippocampus is one of the most sensitive and malleable regions of the brain. Within the hippocampus, the input from the entorhinal cortex to the dentate gyrus is ramified by the connections between the dentate gyrus and the CA3 pyramidal neurons. One granule neuron innervates, on the average, 12 CA3 neurons, and each CA3 neuron innervates, on the average, 50 other CA3 neurons via axon collaterals, as well as 25 inhibitory cells via other axon collaterals. The net result is a 600-fold amplification of excitation, as well as a 300 fold amplification of inhibition, that provides some degree of control of the system⁴⁴.

The circuitry of the dentate gyrus-CA3 system is believed to play a role in the memory of sequences of events, although long-term storage of memory occurs in other brain regions¹¹⁶. But, because the dentate gyrus DG -CA3 system is so delicately balanced in its function and vulnerability to damage, there is also adaptive structural plasticity, in that new neurons continue to be produced in the dentate gyrus throughout adult life, and CA3 pyramidal cells undergo a reversible remodeling of their dendrites in conditions such as hibernation and chronic stress, including a combination of food restriction and increased physical activity^{14;15;44;117;118}. The role of this plasticity may be to protect against permanent damage, or it may enhance vulnerability to damage, a topic that will be discussed below. Whatever the physiological significance of these changes, the hippocampus undergoes a number of adaptive changes in response to acute and chronic stress.

Replacement of neurons in dentate gyrus

One type of structural change that occurs in the hippocampus involves replacement of neurons. The subgranular layer of the dentate gyrus contains cells that have some properties of astrocytes e.g. expression of glial fibrillary acidic protein and which give rise to granule neurons^{119;120}. After BrdU administration to label DNA of dividing cells, these newly born

cells appear as clusters in the inner part of the granule cell layer, where a substantial number of them will go on to differentiate into granule neurons within as little as 7 days. In the adult rat, up to as many as 9000 new neurons are born per day and survive with a half-life of 28 days¹²¹. There are many hormonal, neurochemical and behavioral modulators of neurogenesis and cell survival in the dentate gyrus, including estradiol, IGF-1, antidepressants, voluntary exercise and hippocampal-dependent learning^{122, 123;124}. Neurochemical systems that regulate neurogenesis include excitatory amino acids, serotonin, noradrenalin, benzodiazepines, endogenous opioids, BDNF and IGF-1, as well as glucocorticoids. With respect to stress, certain types of acute stress and many chronic stressors suppress neurogenesis or cell survival in the dentate gyrus, and the mediators of these inhibitory effects include excitatory amino acids acting via NMDA receptors and endogenous opioids¹²⁵.

Remodeling of dendrites and synapses

Another form of structural plasticity is the remodeling of dendrites in the hippocampus, amygdala and prefrontal cortex. In hippocampus, chronic restraint stress CRS; daily for 21 days causes retraction and simplification of dendrites in the CA3 region of the hippocampus^{44;126}. Such dendritic reorganization is found in both dominant and subordinate rats undergoing adaptation to psychosocial stress in the visible burrow system and it is independent of adrenal size¹²⁷. It also occurs in psychosocial stress in intruder tree shrews in a resident-intruder paradigm, with a time course of 28 days¹²⁸, a procedure that does not cause a loss of pyramidal neurons in the hippocampus¹²⁹. The mossy fiber input to the CA3 region at the stratum lucidum appears to drive the dendritic remodeling as the apical dendrites above this input that retract⁴⁴.

Moreover, the thorny excrescences giant spines upon which the mossy fiber terminals form their synapses show stress-induced modifications¹³⁰. CRS caused retraction of thorny excrescence that was reversed after water maze training. In restrained rats that were water maze trained, PSD volume and surface area increased significantly, and the proportion of perforated PSDs almost doubled after water maze training and restraint stress. Moreover, the numbers of endosome-like structures in thorny excrescences decreased after restraint stress and increased after water maze training¹³⁰. The number of active synaptic zones between thorny excrescences and mossy fiber terminals is rapidly modulated during hibernation and recovery from the hibernating state¹⁵. The thorny excrescences are not the only spines affected by CRS. Dendritic spines also show remodeling, with increased spine density reported after chronic restraint stress on apical dendrites of CA3 neurons¹³¹.

Mechanisms of structural remodeling

Exploration of the underlying mechanism for this remodeling of dendrites and synapses reveals that it is not adrenal size or presumed amount of physiological stress per se that determines dendritic remodeling, but a complex set of other factors that modulate neuronal structure⁴⁴. Indeed, in species of mammals that hibernate, dendritic remodeling is a reversible process and occurs within hours of the onset of hibernation in European hamsters and ground squirrels, and it is also reversible within hours of waking of the animals from torpor^{14;15;118;132}. This implies that reorganization of the cytoskeleton is taking place rapidly and reversibly and that changes in dendrite length and branching are not “damage” but a form of structural plasticity.

Cellular and molecular mechanisms involving steroids contribute to structural remodeling. Specifically, adrenal steroids are important mediators of remodeling of hippocampal neurons during repeated stress, and exogenous adrenal steroids can also cause remodeling in the absence of an external stressor^{126;133}. The role of adrenal steroids in the hippocampus

involves many interactions with neurochemical systems including serotonin, endogenous opioids, calcium currents, GABA-benzodiazepine receptors and excitatory amino acids⁴⁴¹³⁴. Central to all of these interactions is the role of excitatory amino acids, such as glutamate. Excitatory amino acids released by the mossy fiber pathway play a key role in the remodeling of the CA3 region of the hippocampus, and regulation of glutamate release by adrenal steroids may play an important role⁴⁴.

Among the consequences of restraint stress is the elevation of extracellular glutamate levels, leading to induction of glial glutamate transporters, as well as increased activation of the nuclear transcription factor, phosphoCREB¹³⁵. Moreover, 21d of CRS leads to depletion of clear vesicles from mossy fiber terminals and increased expression of presynaptic proteins involved in vesicle release^{136;137}. Taken together with the fact that vesicles which remain in the mossy fiber terminal are near active synaptic zones and that there are more mitochondria in the terminals of stressed rats, this suggests that CRS increases the release of glutamate¹³⁶.

Extracellular molecules also play a role in remodeling. Neural cell adhesion molecule NCAM and its polysialated-NCAM PSA-NCAM, as well as L1, are expressed in the dentate gyrus and CA3 region. The expression of NCAM, L1, and PSA-NCAM are regulated by CRS¹³⁸. Tissue plasminogen activator tPA is an extracellular protease and signaling molecule that is released with neural activity and is required for chronic stress-induced loss of spines and NMDA receptor subunits on CA1 neurons¹³⁹.

Within the neuronal cytoskeleton, the remodeling of hippocampal neurons by CRS and hibernation alters the acetylation of microtubule subunits that is consistent with a more stable cytoskeleton¹⁴⁰ and alters microtubule associated proteins, including a soluble form of tau that undergoes phosphorylation that is increased in hibernation and reversed when hibernation is terminated¹³². Another cytoskeletal molecule is called M6a, a transmembrane glycoprotein belonging to the PLP family¹⁴¹. Although the PLP family is the most abundant protein of CNS myelin, M6a is a neuronal protein, and its knock-down by siRNA results in decreased filopodial number and decreased synaptophysin expression, whereas overexpression of M6a has the opposite effect¹⁴¹. Repeated stress decreases M6a expression in both rodents and tree shrews; this effect was prevented by the antidepressant tianeptine by preventing stress-induced remodeling of dendrites in the CA3 region of the hippocampus¹⁴². Chronic psychosocial stress in the tree shrew also down-regulated a number of other gene transcripts associated with neurotrophic effects and cytoskeletal plasticity, including nerve growth factor, NGF¹⁴³.

Dendritic branching and length are impacted by neurotrophic factors. For example, BDNF +/- mice show a less branched dendritic tree and do not show a further reduction of CA3 dendrite length with chronic stress, whereas wild-type mice show reduced dendritic branching after chronic stress [A.M. Magarinos, B. McEwen, unpublished observations]. At the same time, overexpression of BDNF prevents stress-induced reductions of dendritic branching in the CA3 hippocampus and results in anti-depressant-like effects in a Porsolt forced-swim task¹⁴⁴. However, there is contradictory information thus far concerning whether CRS reduces BDNF mRNA levels in hippocampus,¹⁴⁵ but see^{146;147}. These conflicting reports may reflect the balance of two opposing forces, namely, that stress triggers increased BDNF synthesis to replace depletion of BDNF caused by stress¹⁴⁸. BDNF and corticosteroids appear to oppose each other – with BDNF reversing reduced excitability in hippocampal neurons induced by stress levels of corticosterone¹⁴⁹.

Corticotrophin releasing factor CRF is a key mediator of many aspects related to stress¹⁵⁰. CRF in the paraventricular nucleus regulates ACTH release from the anterior pituitary

gland, whereas CRF in the central amygdala is involved in control of behavioral and autonomic responses to stress, including the release to tPA that is an essential part of stress-induced anxiety and structural plasticity in the medial amygdala ¹⁵¹. CRF in the hippocampus is expressed in a subset of GABA neurons Cajal-Retzius cells in the developing hippocampus, and early life stress produces a delayed effect that reduces cognitive function and the number of CA3 neurons, as well as decreased branching of hippocampal pyramidal neurons ^{152;153}. Indeed CRF inhibits dendritic branching in hippocampal cultures *in vitro* ^{154 155}.

Functional consequences of structural remodeling in hippocampus

CRS for 21 days causes impairments in memory in a radial arm maze and in a Y maze that can be prevented by agents, such as Dilantin and the antidepressant, tianeptine, which prevents stress-induced remodeling of CA3 dendrites ¹⁵⁶⁻¹⁵⁸. In another study using a one month chronic variable stress paradigm, stressed rats took longer to train in the initial Morris water maze trial the day after the last stress session and they also were impaired in learning a new platform location in a probe trial ¹²⁶. The effects of chronic stress on both morphology and learning disappeared within 1-2 weeks after cessation of the daily stress regimen ^{126;159}, suggesting that it serves an adaptive function and does not constitute “damage”. This notion, discussed above in relation to the dendritic remodeling during hibernation, is supported by the fact that dominant rats in a social hierarchy have somewhat larger reductions of CA3 dendritic length and branching compared to subordinate rats in the hierarchy, with both groups showing shorter dendrites than rats housed in groups in ordinary cages, with adrenal size larger in the subordinate rats! ¹²⁷.

Thus, it is attractive to suppose that remodeling of dendrites in hippocampus is not only an adaptation to a behavioral situation but also possibly a protective strategy to reduce excitatory input and prevent permanent damage ⁴⁴. Yet, there is evidence for enhancement of ibotenic acid induced excitotoxic damage in the CA3 region in rats given 21d of chronic restraint compared to unstressed rats ¹⁶⁰. Interestingly, ibotenic acid damage to CA1 is not enhanced by chronic stress and female rats do not show the stress-induced sensitization of damage in either CA3 or CA1 ¹⁶⁰, nor do female rats show stress-induced remodeling of CA3 dendrites ¹⁶¹. Thus, it is tempting to conclude that the remodeling of dendrites enhances excitotoxicity ¹⁶², but the only way to test that is to prevent remodeling and determine whether this makes damage less or worse. It is conceivable that damage would be much worse if dendritic remodeling was prevented, due to increased sensitivity to glucocorticoids see below along with undiminished excitatory input.

In spite of the focus on dendritic remodeling after repeated stress, it is apparent that chronic stress causes other changes in the brain besides dendritic remodeling in CA3, including affects on dentate gyrus neurogenesis ¹⁶³, dentate gyrus dendritic remodeling ¹²⁶ and dentate gyrus long-term potentiation LTP ¹⁶⁴. Moreover, 21d chronic restraint alters the ability of acute stress to affect hippocampal functions, such as spatial memory, and here a change in sensitivity to glucocorticoids is involved ¹⁶². Using metyrapone to acutely reduce corticosterone levels in rats given 21 days of CRS resulted in prevention of the impairment of spatial memory seen in chronically stressed animals ¹⁶⁵. Yet, corticosterone levels in chronically stressed rats were only marginally higher during spatial maze training than in control rats during the maze training, indicating that there had been either a shift in sensitivity of the hippocampus to corticosterone or a qualitative change towards inhibition of the spatial task ¹⁶⁵. Whatever the mechanism, these results also highlight the fact that stress-induced dendritic retraction, which was unlikely to have reversed itself in a matter of several hours during Y maze training and metyrapone treatment, is not a sufficient condition for impairment of hippocampal dependent spatial memory ¹⁶². Rather, increased sensitivity to glucocorticoids is also a factor.

Variable glucocorticoid involvement in structural plasticity

There are a number of examples of altered responses to glucocorticoids in relation to structural plasticity. For neurogenesis in dentate gyrus, elevated glucocorticoid levels in an enriched environment or during physical activity are associated with increased neurogenesis and/or cell survival, even though there are other conditions in which glucocorticoids suppress neurogenesis¹⁶⁶. Chronicity of glucocorticoid elevation may play a role, with acute glucocorticoid elevation suppressing cell proliferation and prolonged glucocorticoid exposure ceasing to have this effect¹⁶⁶. Chronic restraint stress is known to reduce dentate gyrus proliferation, whereas acute restraint does not have any measurable effect¹⁶⁷. In contrast, the ability of physical activity to elevate neurogenesis depends on the social housing environment; that is, individual housing of rats that results in elevated corticosterone levels prevented running from acutely increasing neurogenesis. Yet, reducing corticosterone levels by adrenalectomy and supplementation with corticosterone in the drinking water reinstated the positive effect of exercise on neurogenesis¹⁶⁸.

This implies a shift in glucocorticoid sensitivity and a possible factor may be excitatory neurotransmission. NMDA receptors play a role in regulation of neurogenesis, having both positive and negative effects in different experimental settings¹⁶⁹, and blocking NMDA receptors prevents acute glucocorticoid effects on neurogenesis¹⁷⁰, indicating that the role of excitatory amino acids is a primary one. In this connection, it is important to recall the different effects of stress on memory that depend on the state of arousal and the timing with the learning situation¹⁷¹. Moreover, the possible involvement of non-genomic effects of adrenal steroids must be considered.

Hormone regulated structural plasticity in other brain regions

Prefrontal cortex and amygdala

Acute and repeated stress 21 days of CRS also causes functional and structural changes in other brain regions, such as the prefrontal cortex and amygdala. CRS and chronic immobilization caused dendritic shortening in medial prefrontal cortex^{126;172;172-174;174-178} but produced dendritic growth in neurons in amygdala¹⁷⁸, as well as in orbitofrontal cortex¹⁷⁹. These actions of stress are reminiscent of recent work on experimenter versus self-administered morphine and amphetamine, in which different, and sometimes opposite, effects were seen on dendritic spine density in orbitofrontal cortex, medial prefrontal cortex and hippocampus CA1¹⁸⁰. For example, amphetamine self-administration increased spine density on pyramidal neurons in the medial PFC and decreased spine density on OFC pyramidal neurons¹¹.

Along with many other brain regions, the amygdala and prefrontal cortex also contain adrenal steroid receptors^{181;182}; however, the role of adrenal steroids, excitatory amino acids and other mediators has not yet been studied in detail in these brain regions, in contrast to the hippocampus. Nevertheless, glucocorticoids do appear to play a role, since 3 weeks of chronic corticosterone treatment was shown to produce retraction of dendrites in medial prefrontal cortex¹⁷⁴, although with subtle differences in the qualitative nature of the effect from what has been described after chronic restraint stress¹⁸³. Another study determined the effect of adrenalectomy or either chronic treatment for 4 weeks with corticosterone or dexamethasone on volume and neuron number in the prefrontal cortex¹⁸⁴. Dexamethasone treatment at a dose that may have been high enough to enter the brain although this was not directly measured caused a loss of neurons in Layer II of the infralimbic, prelimbic and cingulate cortex, whereas corticosterone treatment reduced the volume, but not the neuron number of these cortical regions¹⁸⁴. The dexamethasone treatment was particularly effective in impairing working memory and cognitive flexibility using working memory task in a Morris water maze¹⁸⁴. Effects of chronic stress were not investigated in this study.

These data notwithstanding, the cautions expressed above concerning differences between chronic stress and chronic glucocorticoid treatment must be kept in mind for the prefrontal cortex, as well as the amygdala, that has not been studied yet in this regard.

Behavioral correlates of CRS-induced remodeling in the prefrontal cortex include impairment in attention set shifting, possibly reflecting structural remodeling in the medial prefrontal cortex¹⁷⁹. Attention set shifting is a task in which a rat first learns that either odor or the digging medium in a pair of bowls predicts where food reward is to be found; then new cues are introduced and the rat needs to learn which ones predict the location of food¹⁸⁵. There is also a report that chronic restraint stress impairs extinction of a fear conditioning task¹⁸⁶. This is an important lead since the prefrontal cortex is involved in extinction, a type of learning¹⁸⁷, but much more research is needed to explore the complex relationship between stress, fear conditioning, extinction and possible morphological remodeling that may well accompany each of these experiences.

Regarding the amygdala, chronic stress for 21 days or longer not only impairs hippocampal-dependent cognitive function⁴⁴, but it also enhances amygdala-dependent unlearned fear and fear conditioning¹⁵⁹, that are consistent with the opposite effects of stress on hippocampal and amygdala structure. Chronic stress also increases aggression between animals living in the same cage, and this is likely to reflect another aspect of hyperactivity of the amygdala¹⁸⁸. Moreover, chronic corticosterone treatment in the drinking water produces an anxiogenic effect in mice¹⁸⁹, an effect that could be due to the glucocorticoid enhancement of CRF activity in the amygdala^{190;191}.

As for mechanism of remodeling, besides the possible role of glucocorticoids and excitatory amino acids, tissue plasminogen activator tPA is required for acute stress to activate not only indices of structural plasticity, but also to enhance anxiety¹⁹². These effects occur in the medial and central amygdala and not in basolateral amygdala and the release of CRF acting via CRF-1 receptors appears to be responsible¹⁵¹. Nothing is yet known about the role of tPA, if any, in the prefrontal cortex, although tPA does appear to play a role in stress-induced reductions of spine synapse number in the CA1 region of the mouse hippocampus¹³⁹, as noted earlier.

BDNF may also play a role in amygdala, since overexpression of BDNF, without any applied stressor, enhances anxiety in an elevated plus maze and increases spine density on basolateral amygdala neurons and this occludes the effect of immobilization stress on both anxiety and spine density¹⁴⁴. As noted above for hippocampus, BDNF overexpressing mice also show reduced behavioral depression in the Porsolt forced-swim task and show protection against stress-induced shortening of dendrites in the CA3 region¹⁴⁴.

Interactions between amygdala, prefrontal cortex and hippocampus

The prefrontal cortex, amygdala and hippocampus are interconnected and influence each other via direct and indirect neural activity^{40;193-196}. For example, inactivation of the amygdala blocks stress-induced impairment of hippocampal LTP and spatial memory¹⁹⁷ and stimulation of basolateral amygdala enhances dentate gyrus field potentials¹⁹⁸, while stimulation of medial prefrontal cortex decreases responsiveness of central amygdala output neurons¹⁹⁹. The processing of emotional memories with contextual information requires amygdala – hippocampal interactions^{16, 200} whereas the prefrontal cortex, with its powerful influence on amygdala activity¹⁹⁹ plays an important role in fear extinction^{201;202}. Because of these interactions, future studies need to address their possible role in the morphological and functional changes produced by single and repeated stress.

Additional factors involved in structural remodeling

Metabolic hormones affect the hippocampus

Besides glucocorticoids and excitatory amino acids, a number of protein hormones have been shown to affect the hippocampus. The hippocampus has receptors for IGF-1 and insulin²⁰³ and it responds to circulating insulin to translocate glucose transporters to cell membranes²⁰⁴. Circulating IGF-1 is a key mediator of the ability of physical activity to increase neurogenesis in the dentate gyrus of the hippocampal formation^{123;205}. IGF-1 is taken up into brain via a transport system different from that which transports insulin, although there is some overlap^{206;207}. IGF-1 is a member of the growth hormone family, and growth hormone is implicated in cognitive function and mood regulation^{208, 209}. Growth hormone is expressed in the hippocampus where it is up-regulated by acute stress and also, in females, by estradiol²⁰⁹. Interestingly, although growth hormone mRNA is expressed in hippocampus²¹⁰, growth hormone also enters the brain in small amounts from the circulation, although not by a specific transport system²¹¹.

Furthermore, circulating ghrelin, a pro-appetitive hormone, has been shown to increase synapse formation in hippocampal pyramidal neurons and to improve hippocampal-dependent memory²¹². Ghrelin is transported into brain via a saturable system²¹³ and receptors for ghrelin are expressed in hippocampus, as well as in other regions of the brain²¹⁴.

Another metabolic hormone, leptin, has been found to exert anti-depressant effects when infused directly into the hippocampus.²¹⁵ Leptin is transported into the brain, and both glucose and insulin mediate the ability of fasting to increase leptin transport into the brain²¹⁶. Leptin receptors are found in hippocampus among other brain regions and leptin has actions in hippocampus that reduce the probability of seizures and enhance aspects of cognitive function²¹⁷.

Thus far, there is little information that would indicate the cellular and molecular mechanisms by which these hormones produce their effects and whether they interact with some of the other factors that will be discussed below in connection with mechanisms of structural plasticity in the hippocampus. Nevertheless, it is clear that metabolic factors involving glucose regulation play a role in hippocampal volume change in the human hippocampus in mild cognitive impairment with aging²¹⁸. In rodents, fatty Zucker rats have poorer hippocampal dependent memory than lean Zucker rats, as well as impaired translocation of an insulin dependent glucose transporter to hippocampal membranes²¹⁹. Moreover, a diet rich in fat has been shown to impair hippocampal dependent memory²²⁰ and a combination of a high fat diet and a 3 week predator exposure causes retraction of dendrites in the CA3 hippocampus, even though neither treatment alone had this effect²²¹.

Sex differences in stress effects

There are sex differences in the effects of stress on the hippocampus and amygdala, whereas nothing is yet known about the prefrontal cortex in this regard. Chronic foot shock stress for 3 weeks caused a decrease in proliferation in dentate gyrus in singly housed male rats, but caused an increase in proliferation in female rats, and both effects were prevented by group housing²²². Chronic restraint stress-induced retraction of dendrites in the CA3 region of hippocampus is found in males, but not in females unless the females are ovariectomized¹⁶¹. G. Wood, B. McEwen, unpublished observations. Chronic restraint stress for 21d has been reported to either enhance or have no effect on performance of female rats in a spatial learning task, while having an inhibitory effect in males^{156;223-226}. Interestingly, as noted above, females did not show the chronic stress-induced enhancement of ibotenic acid-induced damage in the CA3 region, in contrast to chronically stressed male rats¹⁶⁰. In

basolateral amygdala, chronic restraint stress increased dendritic length in males and in estradiol treated females, but not in ovariectomized females G. Wood, B. McEwen, unpublished observations. In prefrontal cortex, the ability of stress to cause shortening of dendrites is evident in males but not in females, whereas female rats with estrogen treatment show an enhancement of dendritic outgrowth under stress in neurons that project to the amygdala Shansky, McEwen, Morrison, unpublished. Furthermore, as another example of a sex difference, acute tail shock restraint stress produces opposite effects on classical eye blink conditioning, enhancing performance in males and reducing it in females ²²⁷, and both developmental and adult activation effects of gonadal hormones are involved ²²⁸. Further discussion of sex differences is beyond the scope of this article and the reader is referred to reviews on why sex differences are important for the study of brain function ²²⁹⁻²³¹.

Conclusions

This review summarizes research showing that the adult brain undergoes adaptive plasticity in its circuitry and that stress, sex and metabolic hormones play an important role in some of this plasticity by acting in synergy with neuronal activity and other cellular processes. Moreover, sex differences exist in at least some of these actions and sex hormones have widespread effects on many regions of the brain. Therefore, hormonal influences must be considered along with the effects of experience in understanding how the brain adapts to challenges, as well as how pathophysiological processes overcome the normal resilience of the nervous system and also how pharmacological and other treatments produce their effects.

The actions of hormones on structural plasticity involve both direct and indirect genomic actions, as well as hormonal regulation of signaling pathways that directly affect neuronal excitability, metabolism and neuronal survival. The actions of membrane-associated forms of classical steroid hormone receptors to regulate signaling pathways is one of the new frontiers of the study of hormone action [e.g., see ^{70;74}]. The identification of membrane-associated steroid hormone receptors has expanded the number of brain regions, cell types and subcellular compartments that are likely to respond to hormones ⁷⁰. Rather than just the cell nucleus, we now know that synaptic terminals, dendritic spines, dendritic shafts, mitochondria and glial cell processes express receptors for estrogens, androgens, progestins and glucocorticoids and are likely to respond to these hormones. Likewise, ongoing studies of how metabolic hormones such as leptin, ghrelin and insulin gain access to and affect brain function add to the picture of hormonal influences on the nervous system. Underlying all of this new information is the need to better understand how stressful experiences and lifestyle affect brain and body and how this changes over the lifecourse.

A major theme of this review is that stress affects brain circuits in ways that promote adaptive plasticity. Although repeated stress can cause deleterious effects on the brain and body, it must be re-emphasized that the primary role of the stress response is to promote adaptation by a process referred to as “allostasis” ²³². The overuse of adaptive systems of the body gives rise to “allostatic load”, which can contribute to accelerated aging ^{233;234}. In neuroscience and neuroendocrinology, the studies of Landfield ²³⁵ and Sapolsky ²³⁶ were among the first to call attention to how aging and adrenal stress hormones impact the hippocampus, the brain region that has been a major focus of this review. The hippocampus also plays a role in shutting off the HPA stress response, and damage or atrophy of the hippocampus impairs the shut off and leads to a more prolonged HPA response to psychological stressors ^{19;237}. This led to the “glucocorticoid cascade hypothesis” of stress and aging ²³⁶. Longitudinal studies on aging human subjects support this model, e.g., the work of Lupien and colleagues revealed that progressive increases in salivary cortisol during

a yearly exam over a 5 year period predicted reduced hippocampal volume and reduced performance on hippocampal-dependent memory tasks ²³⁸.

While the initial view of aging in the hippocampus favored the notion of a loss of neurons, subsequent studies on animal models of aging have favored a loss of synaptic connectivity or impairment of synaptic function, although with some indication that the aging human hippocampus may lose neurons ²³⁹⁻²⁴². A likely mechanism for these changes is the synergistic interactions between glucocorticoids and excitatory amino acids in the hippocampus ²⁰, as well as metabolic hormones this review. Yet, as summarized in this article, these same players are involved in the reversible adaptive plasticity. We, therefore, need to better understand where allostasis gives rise to allostatic load.

There are enormous individual differences in the response to stress, based upon the experience of the individual, early in life and in adult life, and some of the mediators described above may be involved. As for the role of experiences, positive or negative, in school, at work or in romantic and family interpersonal relationships, experiences can bias an individual towards either a positive or negative response in a new situation. For example, someone who has been treated badly in a job by a domineering and abusive supervisor and/or has been fired, will approach a new job situation quite differently than someone who has had positive experiences in employment.

Yet, early life experiences perhaps carry an even greater weight in terms of how an individual reacts to new situations. Early life, physical and sexual abuse, carry with it a life-long burden of behavioral and pathophysiological problems ^{243;244}. Moreover, cold and uncaring families produce long-lasting emotional problems in children ²⁴⁵. Some of these effects are seen on brain structure and function and in the risk for later depression and post-traumatic stress disorder ²⁴⁶⁻²⁴⁸. Recent studies in animal models reinforce the notion that increased levels of anxiety throughout life are associated with a shorter lifespan ^{249;250}.

One view of adaptive plasticity in the face of stress is that depression and anxiety are a natural reaction to major life events, as long as there is also resilience ²⁵¹. When the individual fails to “bounce back”, treatment for anxiety or depression is in order. In other words, major psychiatric disorders of mood and anxiety are likely to be due, at least in part, to a failure of the natural capacity for resilience of the brain and body. Treatments may be pharmacological or behavioral, or both. Since mood and anxiety disorders have cumulative effects over the lifecourse, what we need to know much more about is the extent to which the aging process deprives the brain of its capacity for adaptive plasticity. It is believed that depression is accompanied by hippocampal atrophy over many years ²⁵². Cushing's Disease is also accompanied by hippocampal shrinkage, albeit over much shorter time frames, accompanied by cognitive impairment and depressive symptoms; these changes are at least partially reversible with successful treatment of the hypercortisolism ^{253;254}. However, longitudinal studies of treatment effects on brain changes in mood and anxiety disorders, as well as in related problems of chronic pain, are in their infancy, and yet a few show some promise ²⁵⁵⁻²⁵⁷.

It should also be remembered that there is comorbidity of mood and anxiety disorders with diabetes and metabolic disorders ^{258;259}, and that diabetes is also accompanied by hippocampal atrophy ²⁶⁰. This reinforces the need to better understand the role of metabolic hormones in brain function, over and above hypothalamic control of food intake and metabolism. This is particularly so, since leptin is reported to have mood elevating and procognitive effects, acting in part on the hippocampus ^{215;261}. This leads to a further consideration of interventions: moderate physical activity not only increases glucose utilization, even in people with insulin resistance ^{262;263}, but also has antidepressant effects

²⁶⁴ and increases neurogenesis in dentate gyrus ²⁶⁵ and enhances executive function and activity in the prefrontal cortex ²⁶⁶.

In conclusion, the study of hormone action on the brain, as well as the study of how the brain regulates endocrine function, is prompting a re-evaluation of the more traditional views of the separation between psychiatric and systemic medical disorders. The new viewpoint should promote new and more flexible approaches to both treatment, as well as the all important aspect of prevention.

Acknowledgments

Supported by NIH Grants NS07080, MH41256, 5P01 AG16765, 5P50MH58911.

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