Neurochemical Research, Vol. 28, No. 11, November 2003 (© 2003), pp. 1735–1742

Stress and Plasticity in the Limbic System*

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(Accepted March 4, 2003)

The adult nervous system is not static, but instead can change, can be reshaped by experience. Such plasticity has been demonstrated from the most reductive to the most integrated levels, and understanding the bases of this plasticity is a major challenge. It is apparent that stress can alter plasticity in the nervous system, particularly in the limbic system. This paper reviews that subject, concentrating on: a) the ability of severe and/or prolonged stress to impair hippocampal-dependent explicit learning and the plasticity that underlies it; b) the ability of mild and transient stress to facilitate such plasticity; c) the ability of a range of stressors to enhance implicit fear conditioning, and to enhance the amygdaloid plasticity that underlies it.

KEY WORDS: Stress; hippocampus; glucocorticoids; amygdala; LTP; LTD.

INTRODUCTION

In 1967's *The Graduate,* Dustin Hoffman, embarking on life postcollege, was given some unwanted career advice—plastics. And the field of neural plasticity has yet to recover fully from this setback.

We all responded to that bit of advice with a snicker, based on the pejorative view of "plastic" as artificial, unnatural, cold, unyielding. And the problem is that neural plasticity traditionally implies anything but that. Instead, it is a good thing. Specifically, it is a field built around the fact that experience can alter the nervous system adaptively, enhancing function in self-perpetuating ways. At the level of the synapse, this is the world of long-term potentiation and related electrophysiological phenomena. At the cytoarchitectural level, it is the demonstration that neurons can respond to the proper stimuli by forming new synapses, by elaborating dendritic processes. At the cellular level, it is the truly revolutionary finding that learning, environmental enrichment, even exercise can stimulate neurogenesis. As perhaps the most important cornerstone of such plasticity, these instances of experience-dependent modification of the nervous system can occur throughout the lifetime.

Carl Cotman has made seminal contributions to this topic, helping to make it one of the most exciting branches of neuroscience. But neural plasticity has a dark side. It is not the banality of "plastics," but instead, the undesirable realm where "neural plasticity" means that experience is causing involution, impairment, and damage to the nervous system. This can include impairment of LTP, retraction of dendritic processes, inhibition of neurogenesis, and even the death of neurons.

In principle, this need not be particularly interesting, the fact that there can be "good" and "bad" aspects to neural plasticity. For example, there can be "good" and "bad" aspects to, say, the neurobiological consequences of things that we humans can ingest. Thus, ingest a well-balanced diet and you promote proper neural development; ingest a diet with vast excesses of alcohol and you promote neuron death. This is a fairly unsubtle contrast. What is fascinating in the realm of the adaptive and

* Special issue dedicated to Dr. Carl Cotman.

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maladaptive features of experience-dependent neural plasticity is how similar the experiences can be in bringing about quite contrasting outcomes. Depending on changes in the magnitude or duration of the stimulus, the individual who is experiencing the stimulus, or the part of the brain being considered, the outcome can be neural plasticity of the "good" kind or of the "bad."

In this review I will first consider the basic findings regarding how one aspect of experience—the experience of stress—can have adverse effects on neural plasticity. I will then consider some parameters in which stress does not always have such adverse effects and can even promote versions of the classically "good" forms of neural plasticity.

DISCUSSION

Glucocorticoids and Their Adverse Effects on Hippocampal-Dependent Cognition

Glucocorticoids (GCs) are the adrenal steroid hormones secreted in response to stress. The hormones are central to successfully coping with a major physical stressor (such as fleeing a predator), as they mobilize stored energy, increase cardiovascular tone, and suppress costly anabolism (such as growth, tissue repair, reproduction, digestion and immunity) for more auspicious times. However, if the exposure to GCs is prolonged, there are a variety of pathological outcomes that become more likely, including insulin-resistant diabetes, hypertension, immunosuppression, and reproductive impairments (1).

These deleterious consequences include adverse effects in the nervous system. The most dramatic ones occur in the hippocampus, a primary GC target, with ample quantities of corticosteroid receptors.

At the most integrated level, sustained stress or exposure to GCs can impair aspects of hippocampal-dependent cognition. Memory is not a monolithic phenomenon; instead, there are a number of types of memory, with the medial temporal lobe, and particularly the hippocampus within it, playing a critical role in explicit memory (concerned with facts and events) (2). Thus stressors as different as a number of weeks of daily restraint stress, brief exposure to the smell of a predator (a cat), or months of rotating group membership disrupt spatial memory performance in rats (a classic hippocampal-dependent explicit memory task in a rodent) (3–5). The stress-induced GC secretion in these instances appears to mediate the disruptive effects. As evidence, similar time courses of administration of exogenous GCs producing circulating levels typical of the stress range also disrupt spatial memory performance (6–8). Such impaired performance could reflect impairment of the initial consolidation of the spatial information and/or the retrieval of it. Recent work suggests that it is the retrieval component that is most sensitive to the disruptive effects of GCs (9,10).

An emerging literature demonstrates that GCs can disrupt hippocampal-dependent declarative memory performance in humans as well. Some of these studies examine humans treated chronically with exogenous GCs to control an autoimmune, or inflammatory disorder, or an immune cancer (11,12). Moreover, declarative memory performance in Cushing's syndrome patients (in which GCs are hypersecreted secondary to any of a number of types of tumors) is impaired (13). A fascinating literature of aged humans demonstrate that those whose basal GC levels increase most dramatically with age over time, or increase most dramatically in response to an acute stressor, have the poorest declarative memory performance (14–21). Finally, treatment of healthy volunteers with exogenous GCs in the range used in clinical medicine impairs declarative memory performance as well (22–29). As with the rodent studies, the impaired performance in the hippocampal-dependent tasks could represent impairment of consolidation and/or retrieval; as with rodents, it appears as if the retrieval component is most sensitive (30). As important controls, a number of these studies demonstrating impairment of hippocampal-dependent cognition also demonstrated that hippocampal-independent cognition remained intact (11,29).

Thus stress and/or exposure to elevated GC concentrations disrupt hippocampal-dependent cognition while sparing hippocampal-independent cognition, in both rodents and humans.

Mechanisms Underlying These Adverse GC Effects

There is considerable information regarding the mechanisms contributing to these disruptive GC actions. As an initial critical observation, GCs and stress impair the synaptic plasticity essential to hippocampal-dependent cognition. Thus stress disrupts long-term potentiation (LTP) and primed burst potentiation (PBP) in a variety of hippocampal cell fields *in vivo* (31–37), with the suggestion that PBP is more vulnerable to this effect than is LTP (38). Moreover, administration of exogenous GCs in a regimen producing circulating concentrations typical of stress also disrupt LTP and PBP (36,39–42). In addition, both premortem stress and *in vitro* GC exposure disrupt LTP in hippocampal slices *in vitro* (38,43).

There are two receptors for GCs found in the brain (with ample concentrations of both in the hippocampus),

with the high-affinity mineralocorticoid receptor (MR) occupied heavily under basal conditions, and the low affinity glucocorticoid receptor (GR) occupied heavily only during major stressors. Heavy occupancy of GR mediates these disruptive effects of stress and GCs upon LTP (39,42,44). Such GR occupancy leads to increased calcium conductance in hippocampal neurons; this in turn leads to prolonged opening of calcium-dependent potassium channels, thereby prolonging afterhyperpolarizations. This results in decreased neuronal excitability (45–48).

It has come to be recognized that LTP can be counteracted by long-term depression (LTD). Not surprisingly, stress and GCs enhance LTD under conditions where they disrupt LTP (35,39,49).

These GC effects at the level of synaptic plasticity could readily explain the ability of the hormone to impair cognition. However, GCs have deleterious effects on the cytoarchitectural level in the hippocampus as well. Specifically, over the course of a few days to weeks, stress and/or exposure to elevated GC concentrations will cause retraction of dendritic processes in rats. Golgi staining reveals that the atrophy arises from a loss of apical dendritic branch points and decreases in the length of apical dendrities (6,50–53). Such regression occurs in CA1 and CA3 cell fields of the hippocampus (50,51,54) and can be caused by an array of stressors and, in those cases, the regression is GC dependent (55). Importantly, with the cessation of stress or GC exposure, the process is slowly reversible, with neuron rebuilding processes (52).

The mechanisms underlying this phenomenon are being revealed. GC-induced atrophy is NMDA-receptor mediated, because it is blocked by receptor antagonists (51), or by drugs that decrease the release of glutamate, such as dilantin (56,57). There appears to be a serotonergic involvement as well, because the atypical antidepressant tianeptine, which decreases serotonergic tone, is also protective (52,58). As would be expected, stress- or GC-induced atrophy of dendritic processes also leads to the cognitive deficits described above and, importantly, pharmacological interventions that block the former can prevent the latter (59).

The effects of stress upon dendritic arborization have also been demonstrated in the nonhuman primate (60) and may extend to the human as well. Magnetic resonance imaging of Cushing's syndrome patients has revealed selective decreases in hippocampal volume (13), where more severe hypersecretion of GCs correlated with smaller hippocampi and more impairments of hippocampal-dependent cognition. Importantly, this shrinkage is reversible with the correction of the GC excess (61), suggesting the reversible atrophy of processes seen in the animal studies.

Another somewhat controversial route by which stress and GCs may impair cognition has emerged in recent years. The acceptance by the neuroscience community that the early, heretical reports of adult neurogenesis in the hippocampus are true represents a revolution in the field. Environmental enrichment, exercise and estrogen all promote such neurogenesis. Conversely, stress inhibits hippocampal neurogenesis in rodents and nonhuman primates (62). The mechanisms underlying this fascinating phenomenon are poorly understood at present, but may well be related to the effects of GCs upon neurotrophins and cell cycle genes (62). At least some newly born neurons in the adult hippocampus appear to form functional connections with other neurons (63). Far more controversial, however, is whether such neurogenesis is necessary or sufficient to explain any instances of learning and memory (64). Thus, it is not clear whether inhibition of neurogenesis by stress has cognitive consequences.

Finally, an excess of stress and/or GCs can affect the viability of hippocampal neurons. Specifically, both compromise the ability of such neurons to survive a variety of coincident neurological insults, such as seizure, hypoxia-ischemia, and hypoglycemia (65). Moreover, truly prolonged exposure to either can kill hippocampal neurons outright (66–68); it has been suggested that the atrophy of dendritic processes that would precede any such neuron death can be viewed as an involutional defense, a cellular hibernation, in effect, decreasing the risks of neuron death (69). However, it should be noted that the direct neurotoxic effects of stress and GCs rarely occur, and require unphysiological extremes of GC exposure.

Thus, excessive stress or GC exposure can impair hippocampal-dependent cognition, and there are an array of mechanisms that seemingly mediate this; these findings clearly fall under the rubric of stress having "bad" effects upon neural plasticity. I now consider two striking exceptions to this.

Stress, Stimulation and Inverse-U's

Whether considering childhood, old age, or any point in between, optimal function does not arise from a life without challenge. Instead, it involves the optimal amounts of challenge, what we typically refer to as "stimulation." Virtually by definition, what we view to be stimulatory is transient exposure to a mild stressor. A sufficiently severe challenge, no matter how transient, is aversive. Moreover, a truly prolonged

challenge, no matter how mild, is also aversive (in this regard, it is not by chance that roller coaster rides are 3 minutes, rather than 3 weeks in duration). Stimulation not only is not aversive, but is reinforcing, as shown by the capacity of transient exposure to mildly elevated GC levels to enhance dopaminergic transmission in the ventral tegmental/nucleus accumbens "pleasure" pathways (70).

Given these effects of mild, transient stressors, it is not surprising that such "stimulatory" stressors also enhance hippocampal-dependent cognition. When combined with the disruptive effects of more severe or prolonged stressors upon such cognition, this forms an "inverse-U" pattern (71); the transition from subphysiological or basal GC concentrations into the mild stress range enhances cognition, and elevations beyond that disrupt cognition. This inverse-U pattern has been shown with enhancement with mild stressors and disruption with more severe ones (3,5,59,72–77). It has also been demonstrated in rodents exposed to exogenous GCs, rather than to stress regimens (78,79). Moreover, a similar inverse-U pattern holds at the electrophysiological level. Thus, whereas severe stressors or GC exposure disrupt LTP and PBP, milder exposure enhances it (41,47,74,80,81).

Some elegant studies have revealed the mechanisms underlying such inverse-U patterns. As noted, the hippocampus contains ample quantities of both MR and GR, with the former heavily occupied basally, while the latter, with its order of magnitude lower affinity, is only heavily occupied in response to major stressors. This suggests a relatively straightforward scenario: the transition from basal to mild stress levels of GCs, and the resulting transition from heavy to saturating MR occupancy, is responsible for the enhancing effects upon synaptic plasticity and cognition. The transition to major stress levels of GCs and the resulting heavy GR occupancy then mediates the deleterious effects.

There is considerable evidence supporting this picture. Thus MR occupancy enhances LTP and PBP (39, 41,79,80,81), as well as hippocampal-dependent spatial memory tasks (82). As an explanation for the enhanced excitability, MR occupancy reduces 5HT-1a receptor-mediated, calcium-independent potassium currents, thereby shortening afterhyperpolarization duration (45). And completing the two-receptor mediation of an inverse-U pattern, heavy GR occupancy enhances LTD (39) and disrupts spatial memory (83,84).

More recent studies suggests that this dichotomy between MR and GR actions is oversimplified. Specifically, the enhancing effects of mild, transient GC elevations are not only mediated by MR (and the transition from heavy to saturating occupancy), but by GR as well (with the transition from very low to moderate occupancy) (83–88). Thus, the inverse-U that contrasts stimulation with major stress is not merely due to a contrast between MR and GR, but rather between MR plus moderate GR occupancy, on one hand, versus heavy GR occupancy on the other.

Stress, Implicit Memory, and Flashbulb Memory

I now discuss a second realm in which stress can facilitate, rather than disrupt, memory. As noted, there are multiple types of memory, and whereas explicit memory is concerned with facts and events, "implicit" memory covers an array of non-declarative processes. These include classical Pavlovian conditioning of autonomic responses, procedural memory concerned with nonconscious skills and habits, and reflex pathways. This is the realm of conditioned responses to fear. The learned, nonconscious, and autonomic nature of such memory is shown when one's heart begins to race when in a setting similar to where some trauma occurred, even before one is consciously aware of the similarity of the setting.

Stress is particularly effective at *enhancing* aspects of implicit memories related to autonomic conditioning, implicit reflexes, and fear. For example, many (but not all) stressors will enhance subsequent classical Pavlovian eyeblink conditioning in a rat (89–91); specifically, the enhancement takes the form of more and larger magnitude eyeblinks in response to the conditioned stimulus. Similarly, stress enhances Pavlovian conditioning of freezing responses in rats (84,92). While stress-induced GC secretion is required for such cases of enhancement, the GCs seem to be permissive, in that stressors that do or do not enhance such conditioning do not differ in the magnitude of GC secretion they provoke.

The amygdala, another limbic structure rich in corticosteroid receptors, plays a critical role in fear conditioning and in its potentiation by stress (71,92,93). Thus, under circumstances where prolonged stress disrupts the cognition that is mediated by the hippocampus, it facilitates amygdala-dependent cognition. A fascinating literature is now documenting this polarity on a more reductive level. Specifically, under circumstances in which stress impairs hippocampal LTP, it facilitates amygdaloid LTP (93). Even more remarkably, a recent report demonstrates that under circumstances in which stress causes atrophy of dendritic processes in the hippocampus, the same stressor causes extension of processes by neurons in the amygdala (94) and in the bed nucleus of the stria terminalis, an amygdaloid projection site central to anxiety (95). The mech-

anisms underlying these opposing effects remain to be uncovered.

Stress facilitates another aspect of the interactions between fear and memory. Fear-evoked memory formation is not merely about autonomic reflexes. Our hearts do not merely race when we consider planes piloted into skyscrapers. Instead, in addition to these implicit, conditioned memories, we have explicit memories as well of where we were, for example, when hearing the news on September, 11th, 2001. Such "flashbulb" memories are characterized by their vividness and, amid the vividness, their relatively low level of accuracy. Flashbulb memories related to stress and trauma reflect the fact that we not only form implicit memories about such events, but form explicit memories centered around contextual cues about the event. As such, stress enhances conditioning to contextual cues of a stressor (83,92,96,97). In a classical and fascinating demonstration of this phenomenon in humans, subjects were read one of two 12-sentence stories. Both had identical beginning and last four sentences; however, in one case, the middle four sentences described a strongly emotional and disturbing scene, whereas in the other case, those middle four sentences were affectively neutral. It was then shown that some weeks later, recall of the middle four sentences was superior in individuals who had heard the disturbing scene, compared with those who heard the neutral one; recall of the first and last four sentences did not differ between the groups (98).

Such explicit memories are the purview of the hippocampus, and this is initially quite puzzling, given the extensive literature reviewed above showing stress to disrupt hippocampal-dependent cognition. This paradox can be resolved with the view that during stress, the hippocampus is less able to perform its traditional role of the processing of objective, neutral declarative information, and instead is recruited into a more amygdala-like role. In effect, the highly affective, often inaccurate process of forming a flashbulb memory seems like what would be produced were the amygdala to "attempt" to take on the task of forming a declarative memory, rather than if the job were done by the more steady hippocampus.

Remarkably, this nonscientific framing is actually quite accurate, in that the hippocampus forms declarative flashbulb memories during stress only when driven by amygdaloid arousal. This is shown with an elegant and detailed series of studies (reviewed in [96,99]) demonstrating that stress-induced enhancement of contextual memory consolidation by the hippocampus is blocked by lesions of the amygdala, specifically of the basolateral amygdala. Activation of the amygdala during stress requires arousal by the sympathetic nervous system. During stress, circulating catecholamines stimulate the afferent branch of the vagus nerve, which stimulates the nucleus of the tractus solitarius (NTS). This in turn causes the NTS to stimulate the amygdala via a major noradrenergic input. Furthermore, the normal recruitment by the amygdala of the hippocampus into this cognitive role during stress requires GC action within the hippocampus, amygdala, and NTS; as evidence, microinfusion of GR antagonists into any of those structures disrupts stress-induced enhancement of contextual learning. Thus the phenomenon requires cooperation between the adrenocortical branch of the stress-response (i.e., the secretion of GCs) and the adrenomedullary/sympathetic branch.

CONCLUSION

The classical work in the early 1960s showing that environmental enrichment during infancy could cause lasting and beneficial effects upon the brain helped usher in a view of use-dependent plasticity in the nervous system. This stance has formed a strong scientific rationale behind a number of basically optimistic interventions in humans, ranging from the Head Start program in children to rehabilitation strategies poststroke in elderly individuals. In this context, the adverse effects of stress upon the nervous system—the capacity of stress to impair synaptic plasticity in the hippocampus, to involute the processes of hippocampal neurons, to hasten the death of such neurons, and to impair neurogenesis—have always been viewed as the dark side of plasticity.

Given that, the discovery that stress could do essentially opposite things in the amygdala, namely enhancing plasticity and arborization of dendritic processes, seems initially like a welcome counter to the grim effects of stress in the hippocampus. To a biologist purely concerned with the function of synapses or neural networks, perhaps it is. Nonetheless, it must be recalled that these "good" effects of stress upon function of amygdaloid neurons are ultimately highly deleterious. This is because of the relevance of potentiated amygdaloid function to fear, anxiety and posttraumatic stress disorder (PTSD). As but one example of the relevance of this, two recent and very nonsensationalist papers (99, 100) generate credible estimates of up to 500,000 excess cases of PTSD emerging in the New York City area as a result of the occurrences on September, 11th, 2001. In that staggering context, the ability of stress to enhance the function of synapses and neurons is anything but salutary, and underlines the pressing need to understand these effects more fully.

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