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Mini-Review

Glucocorticoids, stress, and their adverse neurological effects: relevance to aging☆

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Abstract

Glucocorticoids, the adrenal steroids secreted during stress, while critical for successful adaptation to acute physical stressors, can have a variety of deleterious effects if secreted in excess. It has come to be recognized that glucocorticoid excess can have adverse effects in the nervous system, particularly the hippocampus. These effects include disruption of synaptic plasticity, atrophy of dendritic processes, compromising the ability of neurons to survive a variety of coincident insults and, at an extreme, overt neuron death. This review considers the current cellular and molecular bases underlying these adverse glucocorticoid actions, and their relevance to brain aging.

Keywords: Stress; Glucocorticoids; Hippocampus; Neuron death; Neurogenesis; Excitotoxins; Cerebral metabolism; Plasticity; Learning

1. Introduction

Gerontologists have long been interested in stress—whether aging impairs the ability to respond appropriately to stressful challenges, whether prolonged stress accelerates the aging process, and whether individual differences in coping with stress contributes to differences in "successful aging."

Despite stress causing the secretion of a dozen hormones, attention has focused on the adrenal steroids, glucocorticoids (GCs; cortisol in primates, corticosterone in rats). These hormones are essential for adapting to acute physical stressors; they divert energy to exercising muscle, enhance cardiovascular tone, suppress unessentials such as digestion, growth and reproduction, suppress immune responses that might otherwise spiral into auto-

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immunity, and sharpen cognition. In contrast, excessive GCs (as seen with chronic stress, exogenous administration, or with the GC hypersecretion of Cushing's disease) can cause or worsen various disorders, including myopathy, adult-onset diabetes, hypertension, amenorrhea and impotency, as well as be highly immunosuppressive (Munck et al., 1984). Because many of those disorders are the diseases of slow accumulation of damage of Western aging, the links between stress and aging have often been framed in the context of the pathogenic potential of GCs (Sapolsky et al., 1986).

Among the pathogenic effects of GCs is their ability to adversely affect the nervous system, even to the extent of being neurotoxic. In this review, I consider 1) the ways in which GCs and stress can impair the nervous system in rodents and non-human and human primates; 2) mechanisms implicated in mediating these GC actions; 3) their relevance to aging. Because of the brevity of this review and the limit on the number of references, in each section I will cite one or two more detailed reviews (which encompass all unreferenced statements) and a few key papers published since those reviews.

2. The deleterious effects of glucocorticoids in the nervous system

In this section, I review adverse effects of GCs on the brain, progressing from the most transient (i.e. reversible effects on function) to the most permanent (neuron loss). The effects are centered in (but not exclusive to) the hippocampus, a brain region rich in corticosteroid receptors, long recognized for its sensitivity to GC actions, and which plays a critical role in learning and memory.

2.1. Disruption of learning, memory and plasticity (reviewed in McEwen and Sapolsky, 1995)

An enormous literature suggests that hippocampal-dependent learning and memory depends upon the strengthening of synaptic communication called long-term potentiation (LTP). In contrast, long-term depression (LTD), basically the opposite process on a synaptic level, disrupts learning and memory.

A number of reports document GC effects on both LTP and LTD. Stress levels of GCs enhance LTD, whereas GC actions on LTP form an "inverse-U." Specifically, GC levels ranging from basal to those seen in mild stressors are needed for optimal LTP, whereas concentrations that are significantly lower (after adrenalectomy) or higher (as in major stressors) disrupt LTP. This inverse-U arises from a relatively unique feature of GC signal transduction in the hippocampus, namely, abundant levels of both a high-affinity (MR) and low-affinity (GR) receptor. Occupancy of the MR receptor mediates the salutary effects of basal GC levels, whereas GR occupancy mediates the disruptive effects of major stressors. Commensurate with receptor involvement (implying a genomic mechanism of action), these GC effects typically take a number of hours to emerge.

Few studies have examined the effects of GCs or of stress on learning and memory in laboratory animals, but these support a similar inverse-U profile; for example, in the rat, both adrenalectomy and stress levels of GCs impair hippocampal-dependent spatial learning.

GCs also have adverse effects on human cognition. Studies show hippocampal-dependent memory problems in Cushing's Disease, where the extent of GC hypersecretion predicts the extent of memory impairment (Starkman et al., 1992). Another literature

documents that GCs, when administered pharmacologically because of any of a number of peripheral diseases, disrupts cognition as well (with careful controls implicating the steroids in the cognitive dysfunction, rather than the disease itself) (5). Finally, administration of moderately elevated GC concentrations to healthy subjects causes mild impairments of hippocampal-dependent cognition within a few days (McEwen and Sapolsky, 1995).

Thus, exposure to elevated GC concentrations for relatively short periods of time will disrupt hippocampal-dependent cognition, and the synaptic phenomenon thought to underly such cognition.

2.2. Inhibition of dentate neurogenesis (reviewed in Gould, 1994; Reagen and McEwen, 1997)

The long-standing dogma of neurons in the adult brain being postmitotic has been challenged with reports of neurogenesis, most notably the dentate gyrus of the hippocampus (Gould et al., 1998; Eriksson et al., 1998). This has prompted interest in factors that modulate neurogenesis. Of great relevance is evidence that stress and GCs can inhibit the process. This has been shown in rodents, where GC concentrations in the stress range rapidly inhibits neurogenesis, whereas adrenalectomy stimulates the process; this implies that basal GC concentrations tonically inhibit neurogenesis. The same phenomenon is seen in New World monkeys, where an acute social stressor inhibits dentate gyrus neurogenesis within a few hours. The role of GCs in this primate example have not yet been proven.

2.3. Atrophy of neuronal processes (reviewed in Sapolsky, 1996a; Reagen and McEwen, 1997)

In the rodent, as few as 4 weeks of various stressors, or of stress levels of GCs reversibly decreases the number of apical dendritic branch points and the length of apical dendrites in the CA3 region of the hippocampus. Atrophy is substantial enough to disrupt hippocampal-dependent cognition. The stress effect is mediated by GCs (as it can be blocked by a GC synthesis inhibitor).

This phenomenon occurs in primates as well. Among tree shrews, a few weeks of social subordinance (which causes substantial GC secretion) atrophies CA3 apical dendrites, whereas sustained GC overexposure (for 1 year) causes dendritic atrophy (along with cell layer irregularity, soma shrinkage and condensation, and nuclear pyknosis) in the CA3 region in vervet monkeys. Among humans, hippocampal volume reduction is detectable by MRI in Cushing's Disease, where the extent of hypercortisolism predicts the magnitude of the volume loss (Starkman et al., 1992). Upon correction of the hypercortisolism, volume normalizes (Starkman, personal communication). Although this fits the profile of the reversible dendritic atrophy demonstrated in rodents, this has not been explicitly demonstrated in the Cushingoid brain (nor has it been shown that the volume loss is centered in CA3, as in rodents).

2.4. Endangerment of hippocampal neurons (reviewed in McEwen and Sapolsky, 1995; Sapolsky, 1996a)

GCs can "endanger" neurons, which is to say that the hormone can impair the ability of neurons to survive a co-incident insult. Such endangerment translates into the obser-

vation that the higher the levels of GCs at the time of an insult (or the more severe the stressor), the more neuron loss.

This has been shown for various insults by numerous research groups. Insults whose toxicity in the rodent hippocampus are exacerbated by GCs include exposure to excitotoxins (e.g., glutamate or kainic acid), hypoxia-ischemia, hypoglycemia, an electron transport uncoupler, cyanide, three oxygen radical generators, cholinergic and serotonergic toxins, the β-amyloid peptide, the gp120 glycoprotein of HIV, and by HIV-infected monocytes (Goodman et al., 1996; Brooke et al., 1997; Limoges et al., 1997). These effects occur throughout all cell fields of the hippocampus. In general, the exacerbation can occur over the course of only a few days, the magnitude of the exacerbation can be quite large (an order of magnitude increase in toxicity in some cases), and it is occupation of the GR that mediates the endangerment.

A number of these neurologic insults (e.g., hypoxia-ischemia or excitotoxic seizure) constitute stressors and cause substantial GC secretion. Preventing this stress-induced increase in GC exposure (either through surgical or chemical adrenalectomy) decreases the resulting hippocampal damage. Thus, the "typical" extent of damage after an insult reflects, in part, GC-induced endangerment.

Such GC endangerment also occurs in models of these insults in primary cultures. As noted, GCs have numerous peripheral actions. As such, studying endangerment in vitro, in which those confounding actions have been eliminated, has aided identifying underlying mechanisms that mediate it.

This endangerment has also been demonstrated in other brain regions, although to a lesser extent, or with less consistency than in the hippocampus. In the striatum, GCs worsen the toxicity of excitotoxins, of gp120, hypoxia-ischemia, and of phencyclidine. In the cortex, the steroids worsen the toxicity of hypoxia-ischemia and of gp120 (Iyer et al., 1998). Finally, whereas heavy occupancy of MR and mild GR occupancy by GCs (i.e., what occurs basally) decreases *N*-methyl-D-aspartate-toxicity in the nucleus basalis (Abraham et al., 1997), heavier GR occupation worsens the toxicity (Abraham, personal communication).

Of note, GCs do not worsen zinc neurotoxicity in hippocampal cultures (Sunanda et al., 1998). Moreover, GCs lessen damage in neonatal hypoxia-ischemia in rats. Finally, megadoses of GCs (i.e., five orders of magnitude above the K_d of the GR) lessen the neuron loss after spinal cord trauma.

The demonstration of endangerment has not yet been extended to primates or humans, reflecting the expense of primate studies and the complexity of designing well-controlled human studies.

2.5. Neurotoxicity (McEwen, 1992; Sapolsky, 1996a)

The capacity of excessive GC exposure to kill hippocampal neurons was first hinted at in the late 1970s, with the demonstration (since replicated) that the extent of GC hypersecretion in aged rats predicts the magnitude of hippocampal neuron loss. Subsequent studies involved manipulation of GC exposure and have explicitly demonstrated GC neurotoxicity. In nearly a dozen studies, GC concentrations have been raised into the stress range for weeks to months. In about three quarters of those studies, this has resulted in significant hippocampal neuron loss, typically in the range of 15–20% and centered in the CA3 pyramidal cell layer.

Stress itself can cause CA3 neuron loss in rodents. In primates, social stress for one

month is insufficient to cause neuron loss (among tree shrews; Vollmann–Honsdorf et al., 1997), whereas more sustained or fatal social stress produces hippocampal degeneration in vervet monkeys and tree shrews.

Finally, four studies demonstrate that diminished GC exposure over the lifetime (by a manipulation [neonatal handling] that causes a life-long diminution in GC levels, adrenalectomy, or by pharmacological blockade of GRs) decreases the age-related loss of hippocampal pyramidal neurons.

Collectively, these studies show that prolonged stress or GC excess can damage the rodent hippocampus, whereas decreasing life-long exposure to the steroid can protect the hippocampus from senescent neuron loss. In these studies, endpoints have either been number of damaged/pyknotic neurons, neuron density per unit area of a hippocampal cell field, neuron density per unit area plus a measure of the overall size of the hippocampus, or total neuron count within the hippocampal cell field.

The reports of GC neurotoxicity, which have garnered a fair amount of attention, have been challenged in two ways. The first concerns individual differences in vulnerability to such neurotoxicity, and will be discussed below. The second concerns the emergence of unbiased stereology for counting neurons. The earlier literature had reported that the aged rodent hippocampus loses neurons in the CA3 region; the fact that GCs preferentially damage that region strengthened the stress/neurotoxicity/aging story. The stereological literature, however, has questioned whether there is actually loss of pyramidal neurons in the aging rodent hippocampus. Moreover, the basic premise of the unbiased counting technique challenges the validity of any prior study that relies solely on density measures of neurons.

Despite this revisionism, evidence for GC neurotoxicity remains. First, such neuron loss was reported in studies in which overall measures of hippocampal volume were controlled for, in addition to those merely using neuronal density measures. In addition, there has now been one abstract reporting GC-induced neuron loss in the CA3 region by using unbiased stereological techniques (Sousa et al., 1995).

There has been interest as to whether GC-induced neuron death is necrotic or apoptotic. One study failed to find evidence for GC-induced DNA laddering (a hallmark of apoptosis) (Masters et al., 1989). Another study reports that GCs can induce apoptosis in the striatum, although the hormone levels used greatly exceeded those used in the rest of this literature (Mitchell et al., 1998). Finally, the neurogenesis that occurs in the dentate is balanced with some degree of ongoing apoptosis. There is no evidence that such apoptosis can be caused by GCs and, in fact, there is evidence that it can be suppressed by the hormone (Gould, 1994; Hassan et al., 1996).

GC neurotoxicity might occur in humans as well (reviewed in Sapolsky, 1996b). Sustained major depression is associated with elevated GC concentrations in about half of patients, and two groups report that prolonged depression is associated with selective reduction in hippocampal volume (as assessed by magnetic resonance imaging). In one study, the extent of atrophy correlated with depression duration and persisted months to years after the depressions had abated; this would argue against the reversible shrinkage of neuronal processes discussed above. These findings contrast with earlier reports that failed to find such volume loss; however, those earlier papers relied on MRIs with one-tenth the anatomical resolution of these more modern ones (making it impossible to distinguish hippocampus from amygdala). Despite these exciting findings, it remains to be shown that volume loss occurs only among patients with elevated GC levels and whether it is due to actual loss of neurons.

A spate of papers also report selective hippocampal volume loss in post-traumatic stress disorder (PTSD) due to combat trauma or childhood abuse, even decades after the trauma (reviewed in Sapolsky, 1996b). This could be due to any of three causes. First, a small hippocampus might be a risk factor for PTSD (or depression, for that matter), rather than a consequence. Although there are some hints in favor of this idea (see Sapolsky, 1996b), this can only be answered with prospective studies of individuals before (or at the time of) trauma. As a second possibility, hippocampal damage could emerge as a result of the stressfulness of the trauma itself; were such the case, the volume loss would thus have persisted many decades later, suggesting an irreversible cause, such as cell loss or inhibition of neurogenesis. Assessing the likelihood of this possibility is hampered by the fact that it is not known to what extent GCs are secreted in humans during traumatic stressors. Finally, the damage could emerge as a result of the ongoing post-traumatic period; this possibility is complicated by the fact that PTSD (as opposed to the time of the trauma itself) is associated with GC hyposecretion, rather than hypersecretion, due to enhanced negative feedback sensitivity of the adrenocortical axis. Were the volume loss due to the ongoing post-traumatic period, it could involve neuron loss, inhibition of neurogenesis, or dendritic atrophy (which would, theoretically, reverse, should the PTSD abate). Thus, this constitutes a very preliminary literature that would be aided greatly by prospective studies and by postmortem examination of brains to determine the cellular basis of the volume loss.

3. Some mechanisms implicated in the adverse effects of glucocorticoids in the nervous system

3.1. Disruption of neuronal energetics (reviewed in Sapolsky, 1996a)

For most mammals, “stress” is an acute physical challenge to homeostasis, such as in escaping a predator. Under such circumstances, an adaptive feature of the stress-response is the diversion of energy to exercising muscle. This involves inhibition of energy uptake and storage throughout the body. Approximately a dozen reports have examined the effects of GCs upon glucose uptake and utilization in the brain, and nearly all report a 15–25% inhibition (including in humans), most markedly in the hippocampus (hippocampal cultures). In the periphery, GCs decrease glucose uptake by altering the distribution and number of glucose transporters; similar studies have not been carried out in the brain.

These GC actions seem to have consequences during a metabolic insult. For example, GCs accelerate the decline in ATP concentrations in hippocampal neurons and glia during necrotic insults. This is seemingly relevant to the phenomenon of endangerment as such endangerment is prevented if neurons are supplemented with excess energy, including glucose.

These energetic actions are posited to play out in the individual steps mediating neuron death. Necrotic neurological insults constitute energy crises (disrupting energy production, as in hypoxia-ischemia, or excessively consuming energy, as in a seizure). In such cases, hippocampal neurons fail in the costly task of maintaining synaptic glutamate concentrations in a safe range. This, in turn, leads to excessive mobilization of cytosolic calcium in the postsynaptic neuron, with the costly task of carrying out calcium efflux impaired. This leads to degenerative consequences, including cytoskeletal damage and oxygen radical generation. In this scenario, GCs, by disrupting energetics, exacerbate

various steps in this degenerative cascade during insults. More than a dozen studies show that GCs do so, augmenting extracellular glutamate concentrations, cytosolic calcium levels, cytoskeletal degradation and oxygen radical accumulation. As evidence implicating the energetic features of GC actions, these effects are lessened when GC-treated rats or cultures are supplemented with excess energy.

These GC actions are likely relevant to the other instances of adverse GC effects. The energetic actions of GCs could help explain GC-induced inhibition of neurogenesis and atrophy of neuronal processes, given the cost of cell division and remodeling. It has not been shown, however, that these GC effects are prevented by energy supplementation. It is also relatively easy to speculate about GC effects on energy being relevant to the slowly emerging neurotoxicity, given wear-and-tear models of neuron loss during aging. This has not been tested explicitly either, however.

3.2. Exacerbation of the glutamate/calcium cascade of damage (Reagan AND McEwen, 1997)

Thus GCs, through their energetic effects, worsen this cascade during insults. There are also nonenergetic GC effects on glutamate, calcium, and oxygen radical biochemistry. As evidence for the energy independence, either they are too rapid to be secondary to an energy problem, or there is no precedent for this endpoint being energy-dependent. In the studies to be cited, this remains speculative, as there has yet to be the critical test, namely, whether the GC effect still persists despite energy supplementation.

As one example, GCs and stress alter levels in the hippocampus of glutamate receptor binding, as well as mRNA levels for various receptor subtypes (reviewed in Sapolsky, 1996a). Although intriguing, this is still too sparse a literature to form a coherent whole. As another example, in some studies, the GC actions on extracellular glutamate levels or cytosolic calcium concentrations are quite rapid (Abraham et al., 1996). This is of obvious significance to the endangerment phenomenon. This might also be relevant to the atrophy of processes, in as much as such atrophy is prevented with drugs that inhibit glutamate release or block the *N*-methyl-D-aspartate subtype of glutamate receptors. Moreover, in the absence of an insult, GCs rapidly increase voltage-dependent calcium conductance, calcium spike duration, and calcium-dependent after hyperpolarizations (reviewed in Joels and de Kloet, 1994), in principle biasing toward neurotoxicity. Although these effects have been reported in CA1 neurons, something akin to this probably occurs in CA3, the best-documented site of GC neurotoxicity, as such toxicity is prevented with calcium channel blockers (Dachir et al., 1997). In addition, GCs induce the potent calcium binding protein calbindin D28K in CA1 neurons, which seems to have protective effects that partially outweigh GCs endangering actions (Rami et al., 1998). Finally, GCs blunt the activity of the antioxidant enzymes glutathione peroxidase and catalase in the hippocampus during an insult (but not of superoxide dismutase); there is little precedent for these effects being energy-dependent (McIntosh et al., 1998).

3.3. Disruption of cellular defenses

Neurons are not just passively buffeted by insults. There are numerous defenses mobilized, and their efficacies can determine a neuron's survival. Recent reports suggest that GCs are neuroendangering (and possibly neurotoxic) by impairing some of these

defenses. The first few instances to be discussed have already been presented and are restated briefly in this "defense" context.

On the most obvious level, glutamate removal from the synapse and calcium extrusion from the cytoplasm constitute defenses, and GCs worsen glutamate and calcium accumulation during insults, at least in part, by impairing these recovery processes. Moreover, mobilizing antioxidant defenses during an insult constitutes a defense, one disrupted by GCs. Furthermore, after necrotic insults, hippocampal neurons upregulate glucose transporter number. Although it has not been explicitly shown that GCs blunt this upregulation, the general effects of GCs on such transport will disrupt this defense.

GCs disrupt other defenses as well. Glutamate-mediated excitation can release "compensatory" neurotransmitters, which inhibit subsequent glutamate release. These include adenosine, released by postsynaptic neurons as retrograde, a neurotransmitter, and γ-aminobutyric acid (GABA), released via interneuronal feedback loops. Adenosine and GABA release are important, as antagonism of their receptors augments excitotoxic insults. GCs blunt the extracellular accumulation of both GABA and adenosine (Ravindran et al., 1994; Dash et al., 1995) and decrease the efficacy of GABA (reviewed in Sapolsky, 1996a).

Another defensive response to insults is the induction of heat shock proteins (hsps), whose effects include preventing protein malfolding and aggregation. Such hsp overexpression can protect neurons from necrotic insults. Some studies show that GCs augment insult-induced or constitutive hsp expression, whereas others suggest that GCs blunt their expression. This confusion may reflect 1) the relevance of particular hsps to survival (i.e., their function is unknown); 2) whether the endpoint measured is mRNA or protein levels; 3) whether an antibody recognizes the constitutive or inducible version of the hsp; and 4) whether the endpoint differentiates between neurons vulnerable to or resistant to the insult. Collectively, there is thus some evidence for GCs disrupting the heat shock response to an insult.

Insofar as neurotrophins aid neuronal survival and the compensatory elaboration of surviving neurons postinsult, their induction by some insults constitutes a defense. The effects the GCs and stress on neurotrophins are also quite contradictory (Sapolsky, 1996a). In addition to the issues just noted with respect to the hsp literature, there is the added complexity that GCs can have opposite effects on the levels of a neurotropin (or its message) and on its receptor, potentially canceling each other out.

3.4. Electrophysiological effects (reviewed in Joels and de Kloet, 1994)

As noted, GCs have an inverse-U effect on synaptic plasticity, with basal levels (via MR occupancy) enhancing LTP, and stress levels (via GR) disrupting it. The electrophysiological bases of the disruptive effects understood. Although beyond the scope of this review, they involve both the previously mentioned GC effect on calcium-dependent afterhyperpolarization and complex effects on serotonin.

This section has reviewed mechanisms underlying the deleterious effects of GCs. In this final section, I will cite the relevance of these effects to aging of the hippocampus.

4. Relevance to aging

The interest of gerontologists in GCs has been strengthened by the demonstration in most studies that GC exposure increases somewhat linearly from late middle age (approximately 20 months) on in rodents ("exposure" meaning increases in basal concentra-

tions, in the time until levels normalize poststress or in feedback resistance), and in late old age (late 70s to 80s) in humans. Does this increased GC load explain some dysfunctions of the aged hippocampus? Some studies explicitly address this possibility. They have taken any of the following approaches: 1) the "replication" approach: will generating the GC-milieu of aged organisms in young organisms replicate the degenerative features of the hippocampus? 2) the "prevention" approach: will generating the GC milieu of a young organism in an aged one prevent those degenerative features? 3) the "correlative" approach: among aged organisms, do individual differences in the severity of GC exposure predict the severity of some degenerative endpoint?

4.1. Disruption of learning, memory, and synaptic plasticity

Such disruptions are typical of the aging hippocampus. Thus, the numerous studies discussed in which an excess of GCs or of stress disrupts such plasticity or cognition (McEwen and Sapolsky, 1995) constitute "replicating" these features of the aged hippocampus. As examples of the "preventative" approach, the studies cited in which the life-long GC load is decreased (by adrenalectomy, GR blockade or neonatal handling) all spared cognitive and electrophysiological abnormalities of the aged hippocampus (Landfield et al., 1981; Meaney et al., 1988; Talmi et al., 1996). Finally, as "correlative" evidence, among aged rats, those with more prolonged GC secretion postinsult are more cognitively impaired (Issa et al., 1990). Similarly, aged humans with the heaviest GC exposure (e.g., highest levels in anticipation of an acute stressor, highest basal levels, or the greatest increase in basal GC concentrations over the previous few years) have the most impaired hippocampal-dependent cognition (for example, see Lupien et al., 1994; Seeman et al., 1997).

4.2. Inhibition of dentate neurogenesis

In the single relevant study, aged rats had less dentate neurogenesis than young animals; in something resembling a "prevention" approach, neurogenesis rates in both age groups rose to equal levels after adrenalectomy (McKay, personal communication).

4.3. Atrophy of neuronal processes

To my knowledge, this has not been studied.

4.4. Neuroendangerment

To my knowledge, it has not been studied whether there is an age-related increase in neuronal vulnerability to a necrotic insult because of increasing GC exposure. However, some of the mechanistic steps implicated in the endangerment have been studied in an aging context. Pharmacological GC levels inhibits glucose utilization in the brain of aged humans, particularly in the hippocampus (De Leon et al., 1997). In addition, aged rats, with their elevated GC levels, have prolonged accumulation of extracellular glutamate in the hippocampus postinsult (Lowy et al., 1995).

4.5. Neurotoxicity

Amid the debates concerning stereology, there does seem to be some degree of neuron and volume loss in the aging hippocampal complex. The rodent and primate studies showing that chronic stress or GC overexposure leads to hippocampal neuron loss thus represent "replicating" degenerative features of a hippocampal aging (Sapolsky, 1996a). As a caveat, in such studies, it is probably most informative to test whether GCs accelerate the emergence of some degenerative feature in a young or middle-aged animal, rather than worsen that feature in an aged animal. This is because any such damage might already be maximal in the aged; this might account for a reported lack of hippocampal neuron loss when GCs were administered to aged monkeys (Leverenzl et al., 1999). As discussed, more studies are needed to evaluate whether the hippocampal volume loss in prolonged major depression or PTSD really match the changes in aging.

Support for the relevance of GC neurotoxicity comes from "prevention" studies as well; neonatal handling or adrenalectomy (with replacement at low basal concentrations), by decreasing life-long GC load, also prevents the neuron loss of the aging hippocampus (Landfield et al., 1981; Meaney et al., 1988). "Correlative" studies show that aged rodents with the most sluggish recovery of GC concentrations postinsult have the most loss of hippocampal neurons (Issa et al., 1990), whereas aged humans whose basal GC concentrations have risen the most over the previous years have sustained the most hippocampal atrophy during that time (Lupien et al., 1998).

A model was proposed concerning interactions between GC toxicity and hippocampal function during aging (Sapolsky et al., 1986). This was centered on the well-documented role of the hippocampus as a negative-feedback mediator of GC secretion (via its inhibitory projections to CRH neurons in the hypothalamus). As such, hippocampal damage causes at least transient GC hypersecretion, as does down-regulation of hippocampal GR. In this model, the ability of stress or GCs to cause such down-regulation or, if sufficiently sustained, to cause neurotoxicity, was thought to cause feedback resistance and GC hypersecretion, thereby worsening the subsequent adverse effects of GCs on the hippocampus. This "feedforward cascade" was thought to explain the parallel emergence of hippocampal neuron loss and rising basal levels of GCs in the aged rat. Although the broad features of this model have held up, it has had to be modified by more recent findings concerning individual differences in the extent to which neuron loss or GC hypersecretion actually occurs during aging (McEwen, 1992).

5. Conclusions

We now view stress and key hormones secreted during stress as being relevant to many facets of health. Increasing evidence links stress and GCs to the health and functioning of the nervous system, particularly the aging hippocampus. Arguably, the two most exciting datasets in this field that have emerged in recent years concern the individual differences in GC/hippocampal interactions that can begin to explain neurobiological realms of "successful aging" and the (still tentative) hints that GCs or stress can cause significant volume loss in the human hippocampus. Future research would be most helpful in:

1) Providing further insight into the cellular and molecular mechanisms underlying these adverse GC effects. For example, the most such insight is currently available regarding GC neuroendangerment, and it is appealing to hypothesize that GC-induced

neurotoxicity during aging is, in fact, the small identified steps of the neuroendangerment repeatedly activated over the lifetime. In such a model, it would have to be shown that neuron loss during aging reflects, in part, microinsults (such as a transient of hypoglycemia in an animal fed late, transient ischemia after a vasospasm), and that GCs exacerbate these events. These will be extremely difficult studies and speak to the issue of the extent to which normative aging reflects the rate of "external hits" from the environment.

2) Determining, through postmortem studies, whether the instances of hippocampal volume loss in humans are due to dendritic atrophy, suppression of neurogenesis, or overt cell loss.

3) Working through the dose-response studies that would determine precisely what regimes of GC overexposure are most damaging, especially in the context of the neurologically compromised or aged hippocampus. This final approach would pave the way for clinicians to make more informed decisions as to how best to balance the potentially adverse central nervous system effects of GCs with their beneficial effects in treating inflammatory or autoimmune disorders.

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