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Stress, Glucocorticoids, and Damage to the Nervous System: The Current State of Confusion

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An extensive literature demonstrates that glucocorticoids (GCs), the adrenal steroids secreted during stress, can have a broad range of deleterious effects in the brain. The actions occur predominately, but not exclusively, in the hippocampus, a structure rich in corticosteroid receptors and particularly sensitive to GCs. The first half of this review considers three types of GC effects: a) GC-induced atrophy, in which a few weeks' exposure to high GC concentrations or to stress causes reversible atrophy of dendritic processes in the hippocampus; b) GC neurotoxicity where, over the course of months, GC exposure kills hippocampal neurons; c) GC neuroendangerment, in which elevated GC concentrations at the time of a neurological insult such as a stroke or seizure impairs the ability of neurons to survive the insult.

The second half considers the rather confusing literature as to the possible mechanisms underlying these deleterious GC actions. Five broad themes are discerned: a) that GCs induce a metabolic vulnerability in neurons due to inhibition of glucose uptake; b) that GCs exacerbate various steps in a damaging cascade of glutamate excess, calcium mobilization and oxygen radical generation. In a review a number of years ago, I concluded that these two components accounted for the deleterious GC effects. Specifically, the energetic vulnerability induced by GCs left neurons metabolically compromised, and less able to carry out the costly task of containing glutamate, calcium and oxygen radicals. More recent work has shown this conclusion to be simplistic, and GC actions are shown to probably involve at least three additional components: c) that GCs impair a variety of neuronal defenses against neurologic insults; d) that GCs disrupt the mobilization of neurotrophins; e) that GCs have a variety of electrophysiological effects which can damage neurons. The relevance of each of those mechanisms to GC-induced atrophy, neurotoxicity and neuroendangerment is considered, as are the likely interactions among them.

Keywords: Stress, glucocorticoids, hippocampus, successful aging, necrotic neurologic insults

The body responds to perturbations with the stress-response, and the central tenet of stress pathophysiology is that while the stress-response is vital for surviving challenges to homeostasis, chronic mobilization of the stress-response can prove pathogenic. The pages of this new journal will no doubt be filled with reports of such deleterious effects of stress upon immunity, metabolism, cardiovascular function, or reproduction. These

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are vital topics—few of us will succumb to malaria, famine or cholera; instead, most will live well and long enough to slowly accumulate damage from Westernized diseases that are often markedly sensitive to stress.

Yet these pages of this first issue of *Stress* are devoted to reviewing the ability of stress to damage the nervous system. Not surprisingly, this prioritizing seems a good one to me. Woody Allen has stated, "My brain is my second favorite organ," and most of us would put our brains even higher on that list. If we lose a limb or our sight, if we are incapacitated by heart disease, we lose things that help make our lives worth living. But when it is our brains that are damaged, we may cease to exist as sentient beings. It seems essential to understand the ways in which stress might impair neural function, accelerate brain aging, or exacerbate neurologic disease.

The goals of this paper are two-fold: the first half reviews the evidence that stress and, in particular, glucocorticoids can damage or endanger the nervous system. (For lack of space, I will omit the literature showing that elimination of glucocorticoids can also damage neurons (Sloviter *et al.*, 1989), an observation which underlines the regulatory need to avoid both glucocorticoid hyposecretion, as well as hypersecretion.) The second half reviews the current state of confusion as to *how* such deleterious effects occur. In a recent review of this subject (Sapolsky, 1994), a model was proposed to explain such deleterious effects. More recent work has shown this model to be too simple, and the far more complicated current picture is discussed.

I. GLUCOCORTICOIDS AND THEIR DELETERIOUS NEURAL EFFECTS

Few readers will need an introduction to glucocorticoids (GCs) and their role in stress pathophysiology. GCs are central to the deleterious effects of stress upon the brain structure, particularly in the hippocampus, a site rich in corticosteroid receptors and markedly sensitive to GCs (McEwen *et al.*, 1986). Such deleterious effects have been documented in three ways. "Neuronal atrophy" will refer to the ability of stress and GCs to cause reversible loss of neuronal processes (without killing neurons themselves). "Neurotoxicity" refers to the neuronal killing. Finally, "neuroendangerment" refers to the ability of stress and GCs to make neurons vulnerable, impairing their capacity to survive coincident neurologic insults.

1. Glucocorticoids and Neuronal Atrophy

Recent papers, predominately from the laboratory of Bruce McEwen, have shown that as little as 3 weeks of stress and/or stress levels of GC can reversibly decrease the number of apical dendritic branch points and the length of apical dendrites in the CA3 region of the hippocampus (Wooley *et al.*, 1990; Watanabe *et al.*, 1992a). Other features of CA3 dendrites, and processes of neurons elsewhere in the hippocampus are spared. Such atrophy can be triggered by a variety of stressors (Magarinos and McEwen, 1995a), and is mediated by GC secretion, as it is blocked by a GC synthesis inhibitor (Magarinos and McEwen 1993). The atrophy is of sufficient magnitude to impair hippocampal-dependent cognition (Watanabe *et al.*, 1992b).

Importantly, this phenomenon might apply to primates and humans. Among tree shrews, social subordinance is associated with both GC hypersecretion (Fuchs and Flugge, 1995) and atrophy of CA3 apical dendrites (Magarinos *et al.*, 1996). Furthermore, magnetic resonance imaging (MRI) of Cushingoid patients has revealed selective decreases in hippocampal volume (Starkman *et al.*, 1992). That particular study suffered from the reliance on comparison with previously published norms, rather than with an actual control group; however, as an impressive finding that helped counteract this weakness, among the Cushingoid patients, more severe hypercortisolism correlated with smaller hippocampi. Importantly, this shrinkage appears to be reversible with the correction of the hypercortisolism (Starkman, pers. comm.), suggesting the reversible atrophy phenomenon seen in the animal studies.

2. Glucocorticoids and Neurotoxicity

It is now recognized that even more sustained GC exposure can lead to loss of hippocampal neurons.

While there were prior hints of such neurotoxicity (Aus der Muhlen and Ockenfels, 1968), the strongest documentation came from the work of Phil Landfield beginning in the late 1970's. GC concentrations tend to rise with age in rats (cf Sapolsky, 1992a and b), and it was first shown that the extent of such hypersecretion predicted the magnitude of degeneration in the aged hippocampus, and the extent of cognitive decline (Landfield *et al.*, 1978; Issa *et al.*, 1990; see also Sirevaag *et al.*, 1991, showing that the magnitude of adrenal hypertrophy post-mortem predicts the extent of hippocampal degeneration). Critically, eliminating such prolonged GC exposure was then shown to protect the hippocampus from senescent neuron loss (Landfield *et al.*, 1981). Findings since then can be organized into three branches:

a) Sustained exposure to stress levels of GCs can damage the hippocampus. In the first demonstration of this, rats were exposed to high concentrations of corticosterone (the GC of rats) for approximately 12 hours/day for 3 months, producing a 20% loss of neurons specific to the CA3 region (Sapolsky *et al.*, 1985a). The broad features of this finding (the need for GC levels in the stress range for months) has been replicated in most (Xuming *et al.*, 1991; Levy *et al.*, 1994; Arbel *et al.*, 1994; Dachir *et al.*, 1993; Sousa and Paula-Barbosa 1995; Clark *et al.*, 1995) but not all (Bodnoff *et al.*, 1995; Bardgett *et al.*, 1994) studies. Most studies indicate that toxicity occurs in the CA3 region, although one study reports CA1 and CA4 damage (Levy *et al.*, 1994). This CA3 vulnerability echoes the pattern seen in GC-induced neuronal atrophy; the possible mechanistic links between the atrophy and the toxicity will be discussed below.

The anatomical and cytological features of degeneration strongly resembled that seen during aging; i.e., sustained GC exposure seemed to accelerate hippocampal aging. It was then reported that sustained GC exposure in mice will accelerate the electrophysiological features of hippocampal aging as well (Talmi *et al.*, 1993).

b) Stress itself will accelerate hippocampal aging. This was shown in a study where rats were exposed to six months of an aversive learning paradigm involving foot shock; both morphologic and electrophysiological indices of hippocampal aging were accelerated (Kerr *et al.*, 1991). In addition, sustained restraint or water immersion stress cause loss of CA3 and CA4 neurons (Mizoguchi *et al.*, 1992).

c) Interventions which *decrease* cumulative GC exposure delay hippocampal aging. In a first demonstration, mid-aged (12 month old) rats were adrenalectomized and given low levels of replacement GCs. A year later, the neuron loss, glial hypertrophy and cognitive deficits typical of aging had been prevented (Landfield *et al.*, 1981). In an elaboration, a behavioral manipulation which decreases life-long GC secretion (neonatal handling) was also protective (Meaney *et al.*, 1988, 1991). Moreover, pharamcologic antagonism of corticosteroid receptors beginning in mid-age prevents senescent electrophysiological changes in mice (Talmi *et al.*, 1996).

While these studies, individually, had some interpretative ambiguities, they collectively suggest that the extent of a rodent's lifetime exposure to stress and GCs predicts the extent of hippocampal decay in old age. The relevance of this is obvious to understanding "successful aging." Moreover, the aging hippocampus becomes increasingly vulnerable to the destructive effects of GCs or stress (Kerr *et al.*, 1991). (In an extension of this, Mizoguchi *et al.*, [1992] reported that chronic stress damaged the hippocampus only in castrated rats, and speculated that it is the declining androgen levels of old age which make the hippocampus more vulnerable to GCs. However, they offered no mechanistic explanation for this androgen dependency, which has since failed to be replicated [Clark *et al.*, 1995], and were not able to explain a similar GC neurotoxicity in the female rat [Meaney *et al.*, 1991]).

A few studies suggest that such GC neurotoxicity might also apply to the primate. In vervet monkeys and tree shrews, sustained and fatal social stress is linked to hippocampal degeneration similar to that of rodents (Uno *et al.*, 1989; Fuchs *et al.*, 1995). Moreover, sustained exposure to exogenous GCs causes hippocampal degeneration in vervet monkeys as well (Sapolsky *et al.*, 1990). Finally, a recent literature hints at the loss of hippocampal neurons in humans exposed to either severe, acute stress (such as PTSD), or sustained GC hypersecretion (as in a subset of depressives). While

quite exciting, there are numerous methodological complexities in interpreting this handful of studies, which are beyond the scope of this review.

3. Glucocorticoids and Neuroendangerment

A third type of deleterious GC actions has been recognized, initially as a result of work from my own group. Under circumstances where the stress or GC exposure is of an insufficient magnitude and duration to cause neurotoxicity or even neuronal atrophy, the steroids can nevertheless "endanger" neurons. By this I mean that they make the neurons less likely to survive a coincident insult, either increasing the numbers of neurons lost, or accelerating the emergence of damage.

The first case of such endangerment concerned excitatory amino acid (EAA) neurotransmitters, which produce seizures and damage the hippocampus. For example, the EAA kainate produces status epilepticus and preferential CA3 damage. Either stress or physiologic elevations of GCs around the time of kainate exposure exacerbates the kainate toxicity (Sapolsky 1985a and b, 1986a,b; Theoret *et al.*, 1985; Stein and Sapolsky, 1989; Stein-Behrens *et al.*, 1994a and b; Smith-Swintosky, *et al.*, 1996). Moreover, GCs lower the threshold for kainate-induced epileptiform activity (Talmi *et al.*, 1995). GCs also worsen the striatal damage caused by the EAAs quinolinic acid and NMDA (Uhler *et al.*, 1994; Supko and Johnston, 1994). A hallmark of these studies is the potency of this GC effect, where elevated GC exposure for as little as a few days can potentiate the toxicity of the insult as much as an order of magnitude.

Efforts were then made to establish such GC endangerment in vitro, to study its underlying mechanisms. As such, GCs were shown to augment the toxicity of EAAs in primary hippocampal cultures (Sapolsky *et al.*, 1988; Packan and Sapolsky, 1990; Behl *et al.*, 1995; Kito *et al.*, 1995; Goodman *et al.*, 1996; Rajan *et al.*, 1996).

As a second model, GCs worsened or accelerated global ischemic damage to the hippocampus (Sapolsky and Pulsinelli, 1985; Koide *et al.*, 1986; Hall, 1990; Morse and Davis, 1990; Miller and Davis, 1991). These studies indicated the broad nature of the GC endangerment—while the GC/seizure synergy was most pronounced in the CA3 cell field, the GC/ischemia synergy is centered in CA1. Moreover, GCs also worsened ischemic damage to the neocortex, and possibly to the striatum (Sapolsky and Pulsinelli, 1985; Koide *et al.*, 1986). GCs exacerbate injury in primary hippocampal cultures induced by combined hypoxia-hypoglycemia (i.e., an in vitro model of hypoxia-ischemia) (Tombaugh *et al.*, 1992; Tombaugh and Sapolsky, 1993). The effects of GCs on stroke damage caused by middle cerebral artery occlusion are less clear, with one report of protection by megadoses of GCs (de Courten-Myers *et al.*, 1994), one mention in the discussion of a paper of GCs failing to alter the outcome (Strijbos *et al.*, 1994), and one report of exacerbation of damage (Smith-Swintosky *et al.*, 1996).

Other insults worsened by GCs include hypoglycemia and antimetabolite toxins (Sapolsky 1985a, b, 1986a and b; Sapolsky *et al.*, 1988; Tombaugh *et al.*, 1992), oxygen radical generators (Sapolsky *et al.*, 1988; McIntosh and Sapolsky, 1996; Goodman *et al.*, 1996), and cholinergic or serotonergic toxins (Amoroso *et al.*, 1994; Hortnagl *et al.*, 1993; Johnson *et al.*, 1989). Recent reports indicate that GCs also worsen the toxicity of the β-amyloid fragment of Alzheimer's disease (Behl *et al.*, 1995; Goodman *et al.*, 1996), and of the gp120 glycoprotein of HIV (Brooke *et al.*, 1995). The relevance of these observations to either Alzheimer's disease or AIDS is, obviously highly speculative.

The GC endangerment might be relevant to clinical neurology, given how often GCs are administered to control post-stroke edema (Sapolsky and Pulsinelli, 1985). Moreover, seizure and hypoxia-ischemia cause vast endogenous GC secretion, and this stress-response appears to add to the brain damage. As evidence, chemical or surgical adrenalectomy after hypoxia-ischemia or seizure decreases hippocampal damage (Sapolsky and Pulsinelli, 1985; Stein and Sapolsky, 1988; Morse and Davis, 1990; Smith-Swintosky *et al.*, 1996). In an elaboration on this (Krugers *et al.*, 1995), rats were treated with GCs until a day before an ischemic insult; because of the exogenous GC's inhibitory effects on the adrenocortical axis, endogenous GC secretion was attenuated at the time of the ischemia, resulting in less hippocampal damage.

Given the broad list of neurological insults wors-

ened by GCs, it is important to note two neurologic insults that are not. First, the neonatal rodent brain appears to be somewhat resistant to GC/insult synergies; while GCs worsen the toxicity of EAAs (Barks, 1991; Supko and Johnson, 1993), they do not augment ischemic damage (Barks *et al.*, 1991; Tuor *et al.*, 1993a,b, 1995; Chumas *et al.*, 1993). In contrast, GCs worsen in vitro ischemia of cultured fetal neurons (Tombaugh *et al.*, 1992), and worsen ischemic damage to one-month old rats (Tuor *et al.*, 1995).

As a second exception, GCs protect against spinal trauma in both experimental models and clinical trials (Young and Flamm, 1982; Braughler and Hall, 1985; Bracken *et al.*, 1990). This phenomenon relies upon untraditional GC actions, in that the steroids appear to intercalate into membranes and protect against lipid peroxidation; thus, the effect is not receptor mediated, and requires supraphysiologic GC levels. Moreover, non-GC steroids such as progesterone or the synthetic 21-aminosteroids protect at least as well (Betz and Coester, 1990; Hall *et al.*, 1987).

II. MECHANISMS UNDERLYING THE DELETERIOUS EFFECTS OF GCS

Thus, stress and GCs can compromise the ability of neurons to survive some of the most common and devastating neurological insults, atrophy the processes essential to neuronal communication and plasticity, and can play a role in the aging of a vital brain region. The remainder of this review considers the mechanisms underlying these GC actions, concentrating on recent findings that show the story to be more complex and multifaceted than previously appreciated. To begin, three points must be clarified. The first concerns "apoptosis," once an obscure topic and now the trendiest in biology. GCs trigger programmed cell death in the immune system (Evans-Storms and Cidlowski, 1995), and an immunologist, if informed that GCs also damage neurons, might readily predict that such death would also be apoptotic. An explosion of recent papers indicates that necrotic neuron death can trigger apoptotic elements of DNA fragmentation; the relevance of this to the eventual cell death remains unresolved. Amid this burgeoning literature, there are no reports to my knowledge, that GCs, in either being neurotoxic or neuroendangering, cause or exacerbate any apoptotic endpoints, while one paper explicitly reports there being no GC-induced DNA fragmentation in the hippocampus (Masters *et al.*, 1989).

As a second point, however GCs are deleterious, it is via a traditional steroidal mechanism. Of the two types of corticosteroid receptors in the brain (Reul and de Kloet, 1985), the effect is mediated by the low-affinity glucocorticoid (GR) receptor (Packan and Sapolsky 1990; Mizoguchi *et al.*, 1992; Talmi *et al.*, 1995; 1996). As such, synthetic GR ligands (such as methylprednisolone, RU28362 or dexamethasone) can cause atrophy, endangerment or toxicity (Koide *et al.*, 1986; Hall, 1990; Mizoguchi *et al.*, 1992; Uhler *et al.*, 1994; Supko and Johnston, 1994; Hortnagl *et al.*, 1993; Brooke *et al.*, 1995), while non-GC steroids are not deleterious (Packan and Sapolsky 1990; Monyer *et al.*, 1990; Behl *et al.*, 1995; Goodman *et al.*, 1996).

Finally, however GCs are disruptive, there may now be a few reasons why they are particularly so in the hippocampus. Traditionally (i.e. until a few months ago), the hippocampal vulnerability was thought to derive exclusively from its high concentrations of corticosteroid receptors. A recent paper may add an additional mechanism, concerning 11β-hydroxysteroid dehydrogenase, an enzyme which degrades GCs (thus allowing aldosterone to have access to MR receptors [Funder *et al.*, 1988]). The enzyme occurs in the hippocampus, prompting speculation that it protects neurons from deleterious GC actions (Monder, 1991). A bi-directional isoform of the enzyme exists, acting as a dehydrogenase to deactivate GCs, or as a reductase to convert GC catabolites back to GCs. In cultured hippocampal neurons, the reductase activity dominates, and blockade of this enzyme lessens GC neuroendangerment (Rajan *et al.*, 1996). Therefore, should this in vitro observation apply in vivo, it would suggest that rather than serving as a protective buffer in the hippocampus, this enzyme regenerates GCs from catabolites, amplifying the deleterious GC signal.

Thus, GC-induced damage appears to be necrotic, rather than apoptotic, is receptor-mediated, and may target the hippocampus both because of the local

regeneration of GCs and the high concentration of corticosteroid receptors. I will now review five themes that have emerged concerning the mechanisms of the deleterious GC actions; as will be seen, this division is somewhat arbitrary. I will consider whether each theme is relevant to GC-induced atrophy, neurotoxicity, and/or neuroendangerment, and how it might interact with the other themes.

1. The Disruptive Effects of GCs Upon Energetics in the Brain

GCs inhibit glucose uptake by as much as 70% in adipocytes and fibroblasts as a means to divert energy from storage sites to muscle during physical stressors (Munck, 1971). Within hours, GCs do this by translocating glucose transporters from the cell surface to intracellular storage sites (Carter-Su and Okamoto, 1985), while over days, GCs decrease levels of transporter mRNA (Garvey *et al.*, 1989).

GCs turn out to have a similar, if less dramatic effect in the brain, decreasing local cerebral glucose utilization (LCGU) throughout it (Kadekaro *et al.*, 1988; Bryan and King, 1988; Freo *et al.*, 1992; Doyle *et al.*, 1993). In apparent contradiction, two groups failed to see this effect (Seckl *et al.*, 1991); however, in the first case, GCs were applied 15 minutes prior to measuring LCGU, a time insufficient for the genomically-mediated GC effects on glucose transport (Munck, 1971).

GCs also inhibit glucose uptake in primary neuronal cultures (Horner *et al.*, 1990; Virgin *et al.*, 1991). In contrast to the inhibition of LCGU throughout the brain, this in vitro effect was hippocampal culture specific (Horner *et al.*, 1990). A likely explanation is the two-step process of glucose transport in the brain. Circulating glucose is transported across the blood/brain endothelial barrier to the extracellular space via the Glut-1 transporter, and then into neurons and glia via the Glut-3 transporter. GCs probably inhibit trans-endothelial transport throughout the brain, as they do peripherally (Olgemoller *et al.*, 1985), while the inhibition of Glut-3 transport appears to be hippocampal specific. Therefore, the in vivo picture likely reflects inhibition of trans-endothelial transport throughout the brain, coupled with further inhibition at hippocampal neurons and glia; supporting this, the magnitude of suppression of LCGU by GCs is greatest in the hippocampus (Doyle *et al.*, 1993).

The 20–30% inhibition of glucose transport in the hippocampus is milder than in the periphery. While insufficient to kill a neuron, this is enough to metabolically endanger, causing a suppression of glycogen content (Tombaugh *et al.*, 1992). Moreover, under conditions where GCs do not suppress basal ATP content or cytochrome oxidase activity, they nonetheless accelerate their decline in response to necrotic insults (Tombaugh and Sapolsky 1992; Lawrence and Sapolsky 1994; Bennett *et al.*, 1993); finally, GCs worsen the effects of necrotic insults on hippocampal lactate and proton efflux (Krugers *et al.*, 1992; Ajilore *et al.*, 1994).

Is this inhibition of glucose uptake relevant to understanding GC-induced atrophy, endangerment or toxicity? The strongest support for this concerns endangerment. Neurons are almost exclusively dependent upon glucose and have little capacity to store it. Necrotic insults are ultimately energetic crises (Beal, 1992; Sapolsky, 1992b; Turski and Turski, 1993); energy production is either disrupted (as in ischemia or hypoglycemia) or consumption is pathologically elevated (as in seizure). In either case, ATP stores decline, and glucose uptake can become rate limiting (Auer and Siesjo, 1988). Moreover, in necrotically endangered tissue, there is up regulation of glucose transport, in an apparent attempt to compensate for the energy crisis (McDougal *et al.*, 1992; Lee and Bondy, 1993). Thus, one can readily speculate that GCs worsen necrotic insults by making neurons energetically vulnerable and less capable of the costly containment of the insult's consequences. As support, energy supplementation lessens the endangering effects of GCs (Sapolsky, 1986a; Sapolsky *et al.*, 1988; Tombaugh *et al.*, 1992), and (discussed below), lessens some of the endangering effects of GCs on likely mediators of necrotic cell death. (It is important to note that pre-ischemic energy supplementation *worsens* outcome, probably by augmenting anerobic acidosis; however, post-ischemic energy supplemen-

tation lessens damage [cf Tombaugh and Sapolsky, 1993], and the studies showing GC exacerbation of ischemic injury predominately involved post-ischemic GC manipulations.)

There is good reason to think that neuron death during aging is inherently energetic in nature, given the vulnerability of aging neuronal mitochondria to oxidative damage (cf Stadtman, 1992). As such, inhibition of glucose transport may well play a role in GC neurotoxicity. However, no study has shown that energy supplementation prevents GC neurotoxicity, a critical test of this idea. Finally, there is little evidence that GC-induced dendritic atrophy arises from an energetic problem, and no demonstration that it is prevented by energy supplementation.

To summarize, the GC inhibition of glucose transport appears relevant to GC neuroendangerment and, perhaps, to neurotoxicity. Two caveats must be emphasized. First, inhibition of transport may not be the only way that GCs disrupt energetics, a point demonstrated by Koide *et al* (1986); as an example discussed below, GCs can inhibit the expression of glucose-regulated proteins. Second, the deleterious effects of GCs, even in the case of neuroendangerment, cannot be *exclusively* due to effects on energetics. Prior reviews of this subject (Sapolsky, 1992b, 1994) made the assumption that all the endangering, or even neurotoxic GC effects were outwards ripples of the basic energy problem. As will be seen, this view is no longer tenable.

2. Glucocorticoid Interaction with the Glutamatergic Cascade of Neuronal Injury

The most exciting development in cellular neuropathology in the last decade has been the elucidation of the glutamatergic cascade of necrotic neuronal injury; GCs appear to exert some of their deleterious effects by exacerbating this cascade.

I will assume some familiarity on the part of readers with this cascade. Glutamate and related EAA neurotransmitters are the most excitatory in the brain, and their predominance in synapses in the hippocampus attests to the explosive excitability needed for hippocampal plasticity. As a prerequisite to hippocampal LTP, EAAs bind to both NMDA and non-NMDA receptors, mobilizing postsynaptic cytosolic calcium which causes changes in both post- and pre-synaptic elements that strengthen subsequent synaptic communication. This cascade spirals out of control during ischemia, seizure and hypoglycemia; all involve an overabundance of synaptic EAAs and excessive mobilization of cytosolic calcium. This, in turn, causes promiscuous overactivation of calcium-dependent proteases, nucleases and lipases, resulting in cytoskeletal damage and, probably of greatest pathophysiologic significance, generation of oxygen radicals (reviewed in Dugan and Choi, 1994).

There is now at least plausible evidence that GC-induced atrophy, neurotoxicity and neuroendangerment all involve an interaction with this cascade.

As evidence for the relevance to *GC-induced atrophy*, the anti-seizure drug phenytoin (which reduces EAA release [Taft *et al.*, 1988; Potter *et al.*, 1991]) prevents GC-induced atrophy in both rats and primates (Watanabe *et al.*, 1992b; McEwen, pers. comm.). Moreover, use of EAA receptor antagonists indicates that this EAA-dependent GC-induced atrophy is mediated by NMDA-, rather than non-NMDA receptors (Magarinos and McEwen, 1995b). It is not clear at present *how* activation of EAA-triggered pathways causes reversible regression of apical dendrites.

The link between *GC neurotoxicity* and the EAA cascade is more indirect, in that there has yet to be a report that blockade of EAA synapses prevents the toxicity. However, both stress and GCs increase extracellular EAA concentrations in the hippocampus, as measured by microdialysis (Moghaddam 1993; Moghaddam *et al.*, 1994; Lowy *et al.*, 1994, 1995; Bagley and Moghaddam, 1995), and stimulate NMDA-mediated lactate efflux (Krugers *et al.*, 1992). As a complication, in these studies, stress elevated extracellular EAA concentrations in the striatum and pre-frontal cortex to at least the same extent as in the hippocampus, yet only the latter appears to undergo GC neurotoxicity. These studies should be thought of as showing that GCs augment the EAA response to the acute insult of insertion of the microdialysis probe; as evidence, if probes are implanted a few days in advance of dialysis, GCs fail to enhance basal EAA levels (Lowy *et al.*, 1995). As another complication, GCs *decrease* EAA toxicity in cultured spinal neu-

rons (Ogata *et al.*, 1993). However, this is a facet of the generic protective effects of steroids in the spinal cord already discussed.

GCs also influence postsynaptic sensitivity to EAAs, i.e., EAA receptor profiles. One might predict that stress would cause an autoregulatory decrease in EAA receptors, secondary to the enhanced concentrations of ligands. However, amid the current confusion, the only thing clear is that something occurs other than mere secondary down-regulation (Table I). One can only state the obvious, that the differing paradigms and time courses for enhancing GC exposure is no doubt relevant to these discrepancies (without even considering the issue of *which* cell fields within the hippocampus were implicated in each study).

Insofar as stress raises extracellular EAA levels, it should then mobilize post-synaptic calcium; this has yet to be shown. However, GCs raise basal cytosolic calcium levels in cultured hippocampal neurons (Elliott and Sapolsky, 1992, 1993), increase voltage-dependent calcium conductance, calcium-dependent afterhyperpolarizations and prolong calcium spike duration (Kerr *et al.*, 1992; Joëls and de Kloet, 1989a, b; Porter *et al.*, 1995) (It should be noted that the electrophysiological studies just noted were primarily carried out with CA1 neurons, limiting the relevance of the observation to understanding GC neurotoxicity in CA3; the elevation of cytosolic calcium concentrations by GCs in cultured neurons, however, was likely to have occurred in all hippocampal neuron types). Moreover, the elevated basal GC concentrations in aged rats appears to worsen these features (Landfield and Pitler, 1984; Pitler and Landfield, 1990; Landfield *et al.*, 1986; Joëls and de Kloet, 1989a, b). As noted, basal GC concentrations do not enhance EAA tone, and are unlikely to be the means by which basal GC levels enhance postsynaptic calcium tone. As a possible route, GCs inhibit EAA-induced, metabotropic-mediated hydrolysis of phosphoinositide (Kolasa *et al*, 1992), an essential step for feedback inhibition of calcium currents (Sahara and Westbrook, 1993). GCs also induce the calcium binding protein calbindin in the hippocampus (Iacopino and Christakos, 1990); as a result, less calcium is bound by other binding proteins which mediate feedback inhibition of subsequent calcium currents (see below). As evidence for this, calbindin overexpression enhances subsequent calcium currents and EAA toxicity (Abdel-Hamid and Baimbridge 1995).

Finally, given that GCs are likely to mobilize cytosolic calcium, calcium-dependent degenerative events should also be mobilized. Chronic stress can worsen one such endpoint, namely peroxidative lipid damage (Liu *et al.*, 1996). The neuroanatomical specificity of this effect and the specific involvement of GCs is not yet clear. GCs might cause oxidative damage through an additional route, independent of the EAA cascade; specifically, GCs inhibit the activities of a number of anti-oxidant enzymes in the hippocampus (McIntosh and Sapolsky, 1995).

To sum, stress will bias components of the EAA cascade towards neurotoxicity. While no studies have shown that this is sufficient to actually cause neurotoxicity, it seems plausible that repeated activation of this cascade by stress throughout the lifetime could contribute to the gradual neuron loss of the aging hippocampus.

GC neuroendangerment also appears to involve the EAA cascade. As the broadest evidence, the endangerment is decreased by NMDA receptor antagonists (Armanini *et al.*, 1990). As more detailed support, beginning with the first step of the cascade, GCs augment EAAs accumulation in the hippocampus during necrotic insults without effecting non-EAA amino

TABLE I Effects of GCs and Stress on Glutamatergic Receptor mRNA and Binding.

Insult	NMDA Binding	NR2A NMDAreceptor Subtype mRNA	Non-NMDA Binding	Source
Single stressor	Increase		Decrease	Krugers *et al.*, 1993
			Increase	Tocco *et al.*, 1991
Sustained stressor or sustained GCs	No change		No change	Clark & Cotman, 1992; Watanabe *et al.*, 1995
	Increase	Increase		Wieland *et al.*, 1995

acids (Stein-Behrens *et al.*, 1992, 1994a); raising GC levels from the low to high basal range approximately doubled post-seizure glutamate concentrations, while elevation of GC levels into the stress range caused a 4-fold increase. Lowy *et al.* (1995) then showed that aged rats (with their elevated GC levels) have a prolonged recovery of extracellular EAA levels after a necrotic insult. GCs also increase extracellular EAA accumulation in ischemic hippocampal cultures, probably due to disruption of EAA reuptake (Chou *et al.*, 1994).

Moving to the next step, GCs also augment the mobilization of calcium induced by insults (Elliott and Sapolsky 1992, 1993; Goodman *et al.*, 1996); this appears to be mostly due to disruption of calcium efflux, rather than enhancement of influx. Finally, GCs and stress worsen calcium-dependent degenerative events triggered by insults, including cytoskeletal proteolysis, tau immunoreactivity, and oxygen radical generation (Elliott *et al.*, 1993; Stein-Behrens *et al.*, 1994b; McIntosh and Sapolsky, 1996). The GC effect on oxygen radical generation (as well as the worsening by GCs of neuronal killing by a pro-oxidant [McIntosh and Sapolsky, 1996]) suggest that GCs should also worsen insult-induced damage to lipids, proteins or nucleic acids. In the sole test of this, GCs did not augment ischemic lipid peroxidation (Koide *et al.*, 1986); whether the other components of oxidative damage are worsened is under study.

To summarize, the ability of GCs to trigger or worsen the EAA cascade seems relevant to atrophy, neurotoxicity and neuroendangerment. How do these findings intersect with the energetic effects of GCs discussed above? As noted, some (Sapolsky, 1994), but not all previous reviews (McEwen, 1992; Joëls and de Kloet, 1994) essentially labeled all the effects of GCs on the EAA cascade as merely secondary to the energetic endangerment—EAA reuptake, calcium efflux, and repair of oxidative damage are all expensive and decline during necrotic insults. By accelerating the depletion of ATP stores, GCs should obviously impair these costly containment steps. Supporting this, energy supplementation blunts the effects of GCs on the EAA accumulation, calcium mobilization, and calcium-dependent degeneration (Stein-Behrens *et al.*, 1992; Elliott and Sapolsky, 1993; Elliott *et al.*, 1993). However, many of the newer steps in this story—GC effects on calcium afterhyperpolarizations, EAA receptor profiles, calbindin levels, or activity of antioxidant enzymes—do not seem to be merely secondary to disrupted energetics. Moreover, as noted, there is little reason to think that GC-induced atrophy is an "energy crisis." The energetic and glutamatergic components of GC actions appear to be only partially overlapping.

3. GCs and the Disruption of Neuronal Defense Mechanisms

The brain is not just passively buffeted by torrents of glutamate, calcium and oxygen radicals during an insult. Instead, neurons and glia mobilize a variety of defenses. Some have been long-recognized, but may rarely be conceptualized as "defenses." Others are more novel. The previous section demonstrates that GCs, in effect, make insults more "insulting." Recent evidence suggests that GCs, in addition, impair the mobilization of some of these defenses.

—During necrotic insults, defenses are mobilized to halt EAA release and to remove EAAs already in the synapse. Removal involves the well-known high-affinity reuptake system. The former involves the release of adenosine, GABA and taurine by postsynaptic neurons, local interneurons and glia, respectively. These all function as retrograde neurotransmitters to inhibit presynaptic EAA release, and have neuroprotective potential (Huxtable, 1989; Dragunow *et al.*, 1985). Adenosine seems particularly interesting, as it is generated in part from the breakdown of ATP. As such, its retrograde release is a signal of energy depletion (Auer and Siesjo, 1988).

GCs disrupt some of these steps. As noted, they inhibit EAA reuptake during ischemia in cultured neurons (Chou *et al.*, 1994). GCs also decrease the mobilization of adenosine and GABA (but not taurine) during insults (Ravindran *et al.*, 1994; Dash *et al.*, 1995). Pre-insult levels of both neurotransmitters were lowered by GCs, and the rise in response to EAAs was blunted. If such diminutions were chronic, one would predict compensatory up-regulation of receptor sensi-

tivity. However, GCs attenuate GABA communication postsynaptically, decreasing benzodiazepine and neurosteroid binding to the GABA complex (both of which potentiate GABAergic communication), as well as GABA binding itself (Acuna *et al.*, 1990; Orchinik *et al.*, 1995). Electrophysiological studies support this picture. With repeated stimulation of EAA pathways in the hippocampus, there is increasing inhibitory GABAergic tone, eventually causing habituation of the EAA response. Such slowly emerging inhibitory postsynaptic potentials (IPSPs) are blocked by stress levels of GCs (Joëls and de Kloet, 1992, 1993). Furthermore, even higher GC concentrations block the more rapid IPSPs mediated by the GABA-a receptor (Zeise *et al.*, 1992). These effects could reflect GC actions upon extracellular GABA levels, on receptor binding profiles, or on receptor-coupled ionic events. Therefore, in summary, GCs impair the protective activation of inhibitory neurotransmitter systems during insults.

—Defenses are also mobilized to decrease postsynaptic sensitivity to EAAs and the subsequent calcium mobilization. EAAs trigger intracellular acidification secondary to ATP hydrolysis (Irwin *et al.*, 1994), as well as generation of nitric oxide. In a negative feedback loop, both protons and nitric oxide inhibit NMDA receptor activation (Traynelis and Cull-Candy, 1990; Lipton *et al.*, 1993). Moreover, calcium influx inhibits subsequent calcium currents through a number of mechanisms, including feedback inhibition of voltage-gated calcium channels, of NMDA-gated calcium channels via calcium-dependent phosphatase, and metabotropic-mediated hydrolysis of phosphoinositide, which then inhibits calcium currents (Sahara and Westbrook, 1993; Armstrong, 1989; de Leon *et al.*, 1995; Lieberman and Mody, 1994). Finally, the complex calcium sequestering and efflux mechanisms can be viewed as defenses against necrotic insults.

GCs impair some of these steps, inhibiting calcium efflux during insults (Elliott and Sapolsky, 1993), and metabotropic-mediated phosphoinositide hydrolysis (Kolasa *et al.*, 1992). They also induce calbindin D28K (Iacopino and Christakos, 1990), whose overexpression can disrupt calcium negative feedback, increase calcium currents and enhance excitotoxicity (Abdel-Hamid and Baimbridge, 1995).

—The induction of antioxidant enzymes following necrotic insults represents an obvious cellular defense against oxidative damage. As noted, we observe that GCs decrease the activity of Cu-Zn-superoxide dismutase and glutathione peroxidase in the hippocampus and cortex (McIntosh and Sapolsky, 1995). Moreover, ascorbate uptake into peripheral tissues appears to be mediated by the glucose transporter (Padh *et al.*, 1985; Washko and Levine, 1992), and insofar as GCs decrease the availability of such transporters, they should decrease uptake of this antioxidant. However, this has not been tested directly, nor is it demonstrated yet whether ascorbate uptake in the brain is also mediated by the glucose transporter.

—Finally, an array of protective "stress proteins" are induced by insults. These include, of course, the heat shock proteins (HSPs), whose relevance to neuronal survival remains controversial (cf. Sloviter and Lowenstein, 1992), as well as glucose regulated proteins (GRPs) and glucose transporters (Lee and Bondy, 1993), whose expressions have obvious metabolic implications.

GCs are likely to impair some of these defenses. Whether GCs specifically antagonize the post-insult induction of glucose transporter expression is not known, but seems likely, given that GCs inhibit basal transcription of that gene (Garvey *et al.*, 1989). Moreover, GCs block the induction of GRPs by glucose starvation in L929 cells (Kasambalides and Lanks, 1983); whether the same occurs in the brain is not known. Finally, recent studies demonstrate GC effects on HSP expression and levels; "effects" is, of course, a euphemism for findings being inconsistent. GCs augment excitotoxin-triggered induction of HSP70 in the hippocampus and cortex (Lowy *et al.*, 1994) and heat shock-triggered induction of mRNA for HSP32 (heme oxygenase-1 and 2) (Maines *et al.*, 1995). However, GCs decrease HSP32 protein levels in the hippocampus (Weber *et al.*, 1994); finally, GCs decrease the expression of some, and increase that of other, unidentified heat-shock responsive proteins in hippocampal slices (Barr and Dokas, 1995). This confusion is reflected in how these findings can be interpreted. Were GCs to block expression of some HSP

during an insult, one might readily view this as the steroids impairing a potentially protective defense. At this preliminary stage, the opposite observation, that GCs augment some insult-induced HSP expression, is just as plausibly interpreted as indicating endangerment as well—in effect, GCs must really be adding to problems if neurons have to make even more HSPs when the steroids are around (Maines *et al.*, 1995).

This final confusion indicates how tentative these recent findings are. Nonetheless, GCs may well compromise some of the defenses mobilized by the endangered hippocampus. There do not yet appear to be any organizing patterns for the cellular mechanisms by which GCs accomplish this. However, this does not disturb me, given what a hodgepodge of mechanisms the defenses themselves are.

Do these GC effects help explain GC-induced atrophy, toxicity or endangerment? I detect few means to tie these effects to the atrophy phenomenon. The relevance to neuroendangerment is obvious, given that the effects concern the responses of the brain to insults. Some of these GC effects concern defenses studied under conditions where no insult was occurring—for example, GCs decreasing basal activity hippocampal antioxidants (McIntosh and Sapolsky, 1995). For an observation like this to be relevant to neuroendangerment, it must be shown that GCs also blunt the induction of these enzymes during insults. And to be relevant to neurotoxicity, it must be shown that, in effect, daily life entails small oxidative challenges for a neuron, and that basal levels of activity of antioxidant enzymes can be viewed as small defenses against these challenges; there is much to suggest that for antioxidants (cf Liu *et al.*, 1996). Similar assumptions must be met for the other disruptions by GCs of neuronal defenses in the absence of a coincident insult.

How do these GC effects overlap with effects on energetics and the EAA cascade? Obviously, the effects upon glucose transport constitute both a route of making neurons energetically vulnerable, and a disruption of a metabolic defense of neurons. Moreover, once such metabolic disruption occurs, costly defenses are likely to be impaired (e.g., EAA reuptake). However, all of these GC effects upon defenses are not merely secondary to the energetic disruption (e.g., the induction of calbindin). Even more explicitly, if the GC effects on energetics were the only point of regulation in this story, the demonstrated acceleration of ATP depletion by GCs during an insult should generate *more* adenosine, rather than less. Moreover, the GC disruption of some defenses is not merely the outcome of the GC potentiation of the EAA cascade either. For example, the enhanced accumulation of EAAs by GCs should increase, rather than inhibit, the subsequent mobilization of adenosine and GABA. This suggests that these disparate cases of GCs disrupting neuronal defenses are not the passive outcome of the effects of GCs on energetics or the EAA cascade, but can reflect independent points of regulation and endangerment.

4. Glucocorticoids and Neurotrophin Profiles in the Hippocampus

One of the most exciting areas of current neurobiology research concerns neurotrophins and their role in neural development, remodeling and survival of injury (cf. Thoenen, 1995). GCs regulate the expression of both neurotrophins and their receptors, and modulate their regulation by other factors. These are very recent findings and there is, at present, far from consensus. To minimize confusion, I will only consider studies of the hippocampus, or hippocampal cultures (Table II). There is some consistency regarding BDNF, where five of six studies suggest that GCs decrease BDNF mRNA levels, and blunt the induction of BDNF during necrotic insults. Three caveats should be noted, however. First, as indicated, the effects of stress need not be exclusively GC-mediated. Second, levels of mRNA do not equal levels, let alone activity of the protein itself. Finally, it is often the case that a change in the level of a messenger (such as a neurotrophin) is more than offset by a compensatory change in the opposite direction in the level or sensitivity of the receptor for that messenger. However, as shown in Table II, there is no consensus as to the effects of stress or GCs on mRNA levels for the BDNF (TrkB) receptor (despite each of those groups also reporting that stress or GCs decrease BDNF mRNA levels themselves).

The picture with NGF is even murkier, with no con-

TABLE II The Effects of Stress or GCs on Levels of mRNA for Neurotrphins and their Receptors

Manipulation	BDNF mRNA	Trk B mRNA	NGF mRNA
Effects of stress or GCs on:	Decrease (1–3)	Increase (3) Decrease (2) No change (1)	Increase (4,5) Decrease (2,6) No change (7)
Effects of GCs on the EAA-triggered induction of:	Block (8,9) Augment (10)		
Effects of GCs on cytokine-triggered induction of:			Block (7, 11)

References: 1: Smith *et al.*, 1995; this study showed both GC-dependent and independent effects on BDNF mRNA; 2: Ueyama *et al.*, 1995; 3: Duman, pers. comm. 1996; 4: Foreman *et al.*, 1993; 5: Scully & Otten, 1993 (in immortalized hippocampal neurons); 6: Niu *et al.*, 1995; 7: Pshenichkin *et al.*, 1994; 8: Lauterborn *et al.*, 1995; 9: Cosi *et al.*, 1993; 10: Barbany & Persson, 1993; 11: Yoshida *et al.*, 1993.

sensus regarding the effects of stress or GCs on its mRNA levels, and some indication that GCs block the induction by cytokines of NGF mRNA (Table II). Adding to the confusion, the induction by stress reported by Foreman *et al.* (1993) was not GC-dependent.

The suggestion that GCs inhibit basal and post-insult BDNF mRNA levels might be relevant to atrophy, toxicity and endangerment. The first case would probably be the strongest, as there is every reason to think that dendritic remodeling involves neurotrophins. The induction of neurotrophins by necrotic insults and by inflammatory cytokine cascades, and the neuroprotective potential of neurotrophins after necrotic insults (Cheng and Mattson, 1994; Mattson *et al.*, 1995), makes the GC effects relevant to neuroendangerment. Finally, it is plausible to extend the relevance of this GC/neurotrophin relationship from the dramatic and acute scenario of a necrotic crisis to GC neurotoxicity and gradual degeneration over time.

There are likely to be a few mechanistic overlaps between this section and previous ones. Given the protective potential of neurotrophins and the triggering of their expression by some insults, this constitutes a special case of GCs disrupting a defense. There is little reason to think that the GC effects on neurotrophins are merely secondary to the energetic disruption. Finally, there is an obvious relationship between the EAA cascade and mobilization of neurotrophins after an insult; however, to my knowledge, there is not yet sufficient information about how tightly those two branches are coupled as to guess whether, for example, a 30% increase in extracellular EAA concentrations during an insult (as would be caused by GC exposure) would increase the extent of neurotrophin induction.

5. Glucocorticoids and Hippocampal Electrophysiology

Numerous studies over the decades have shown GCs to effect electrophysiology, ionic conductance or receptor profiles relevant to electrophysiology. These generated considerable confusion. This has been resolved in the last decade because of the seminal contribution of Ron de Kloet and Marian Joëls, beginning with the demonstration that there are two corticosteroid receptors in the hippocampus (Reul and de Kloet, 1985), and that they typically mediate precisely opposite electrophysiological effects (cf. Joëls and de Kloet, 1994). Some of these effects may be relevant to understanding the deleterious actions of GCs.

The two receptors differ markedly in their affinity for GCs; high-affinity MRs are occupied heavily under basal conditions, whereas the low-affinity GRs require stress levels of GCs to be heavily occupied. Under basal conditions, the preferential MR occupancy enhances hippocampal excitability (as well as LTP [Diamond *et al.*, 1992]). Serotonin binding to its 1a receptor is decreased, lessening serotonin-mediated hyperpolarization of neurons (Joëls *et al.*, 1991). Moreover, calcium-dependent, potassium-mediated afterhyperpolarizations are lessened, allowing for more action potentials (Joëls and de Kloet, 1989).

In contrast, stress concentrations of GCs and heavy

occupancy of GRs blunt hippocampal excitability (and disrupt LTP and cognition [Diamond *et al.*, 1992; McEwen and Sapolsky, 1995]). As causes, GR occupancy enhances serotonin 1a binding and serotonin-mediated hyperpolarization of neurons (Joëls *et al.*, 1991) and lengthen calcium-dependent, potassium-mediated afterhyperpolarizations (Joëls and de Kloet, 1989a; Kerr *et al.*, 1992). The latter could be due to GCs effecting the potassium and/or the calcium component of that phenomenon; as discussed, GCs enhance calcium currents (Kerr *et al.*, 1992) and increase cytosolic calcium concentrations (Elliott and Sapolsky, 1992, 1993). As another consequence of this enhanced calcium current, GR occupancy decreases the amplitude of the population spike (Rey *et al.*, 1987; Joëls and Fernhout, 1993; Talmi *et al.*, 1992).

Therefore, both extremely low and high GC levels disrupt hippocampal excitability and LTP, while intermediate, basal levels do the opposite; this "inverse-U" pattern agrees with the salutary effects of mild stimulation on cognition, and the disruptive effects of extreme stress. The GR-mediated electrophysiological effects are hard to fit into a framework of neuronal injury. The enhanced serotonin-mediated hyperpolarization, and the augmented afterhyperpolarizations decrease EAA tone and excitablity and can be viewed as protective. In contrast, two actions can readily be viewed as deleterious—the increased calcium currents and the ability of GCs, as discussed in the section on neuronal defenses, to decrease GABAergic IPSPs, allowing for more prolonged excitatory glutamatergic volleys. When coupled with the ability of high GC concentrations to increase extracellular EAA content, one is left with a seeming paradox—how does one integrate the excitatory consequences of increased EAA tone and damped GABAergic input with what is, overall, an inhibitory effect of high GC concentrations on hippocampal excitability?

Part of the explanation might be anatomical, in that most of the electrophysiological studies showing decreased excitability after GC treatment concern the CA1 region, whereas the microdialysis studies showing elevated extracellular EAA levels were likely to be more responsive to CA3/CA4 inputs. In addition, a possible explanation is that the different GC effects might occur to differing extents in different contexts. Surprisingly, GCs have virtually no electrophysiolo-gical effects on neurons at resting potentials (Kerr *et al.*, 1989; Karst *et al.*, 1993); the effects discussed occur only when neurons are stimulated (or, as restated within the framework of this review, are "challenged") (Joëls and de Kloet, 1994). The authors speculate that when heavy GC secretion coincides with challenges—heavy EAA exposure or energy deprivation—the pro-excitotoxic components predominate. This extremely interesting idea must be tested experimentally. If true, it would represent the very essence of GC endangerment, the deleterious and synergistic interactions between GCs and an insult. The extent to which these effects apply to atrophy or to neurotoxicity depends on how much each represents a "challenge" for a neuron. As discussed, there is little reason to think of the atrophy as being the outcome of a desperate excitotoxic challenge (despite the involvement of EAAs) or severe energy shortage. In contrast, as discussed, it is plausible to think that the progressive neuron loss of aging reflects "mini-challenges"—transient vasospasms causing mild ischemia, brief periods of hypoglycemia, and so on—which could well bias towards the deleterious electrophysiological events.

The overlaps between conceptualizing the disruptive effects of GCs within an electrophysiological framework and within the other four categories are fairly obvious. Many of the GC effects on the EAA cascade are the electrophysiological ones discussed here; furthermore, these effects are likely to interact with energy status. Moreover, the electrophysiological effects that involve compromising GABAergic IPSPs represent the failure of a potent defense. The links between the electrophysiology and neurotrophin stories seem less clear.

III. CONCLUSIONS

This paper aimed to review the solid evidence that GCs can be deleterious in the hippocampus, as well as to review the considerable confusion as to how this occurs. The reader most likely needs little convincing now as to the confusion. In theory, one could view the exacerbation of the EAA cascade and the disruption of defenses as simple outcomes of the energetic disrup-

tion, with the electrophysiological effects as subsets of both the defensive component and the EAA cascade, and with the neurotrophins being shoe-horned as a failure of defenses as well. However, this review has demonstrated how the picture is not that simple, and the five broad categories of mechanisms are at least partially independent of each other.

On a different level of analysis, endangerment, atrophy and toxicity could be viewed as on a continuum—whatever GCs do to enhance the lethality of insults over the a day or two will cause atrophy if extended for weeks and, over months, will cause death. This is possible, and I suspect that there are strong mechanistic links between endangerment and toxicity—one could exacerbate neuron death by coupling GCs with a massive insult for a few days, or with tiny, micro-insults for a lifetime. However, I suspect that the atrophy is a different phenomenon. It has even been suggested that it represents a means of *protecting* neurons from GC neurotoxicity; specifically, dendritic atrophy will decrease excitatory EAA-tone and, at the cost of transiently impaired cognition, neurons become less likely to succumb to a GC/EAA synergy (Magarinos and McEwen, 1995a). This is a novel and interesting possibility.

Another issue that needs resolving is the anatomical specificity of the GC actions. GC-induced atrophy and neurotoxicity appear, at present, to be specific to only certain subregions of the hippocampus, while GC neuroendangerment occurs throughout the hippocampus and, to a lesser extent, has also been documented in cortex and striatum. As a further complication, there is not always an anatomical match between where a particular reductive action of GCs occur and where GCs do or do not exert their deleterious effects.

In short, much more work is needed, particularly to understand how and when the transition occurs between when GCs cease to have their normal, often critically salutary effects and when they begin to exert their deleterious actions. The first half of this review should hopefully have convinced the reader of the value of such an understanding. The evidence that GCs, in the broadest sense, can be deleterious to the brain in general and the hippocampus in particular seems unassailable by now. The implications of this may prove enormous, should this apply to the primate and human brain, as an emerging literature suggests. (Sapolsky, 1996) At the least, it may explain why our students, at the end of a stressful week of studying and with atrophic dendritic processes, might have a dramatic failure of explicit memory as they sit down to our finals. These findings may be of greater significance to the hundreds of thousands of individuals who sustain necrotic neurologic damage annually, as GCs may potently influence the extent of damage caused, or for those individuals who take long-term high-dose GCs to control any of a variety of disorders. Finally, these studies may well be of significance to those of us who plan to age, and who would prefer to do so successfully.

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