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Detrimental Effects of Chronic Hypothalamic–Pituitary–Adrenal Axis Activation

From Obesity to Memory Deficits

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Abstract

Increasing evidence suggests that the detrimental effects of glucocorticoid (GC) hypersecretion occur by activation of the hypothalamic–pituitary–adrenal (HPA) axis in several human pathologies, including obesity, Alzheimer's disease, AIDS dementia, and depression. The different patterns of response by the HPA axis during chronic activation are an important consideration in selecting an animal model to assess HPA axis function in a particular disorder. This article will discuss how chronic HPA axis activation and GC hypersecretion affect hippocampal function and contribute to the development of obesity. In the brain, the hippocampus has the highest concentration of GC receptors. Chronic stress or corticosterone treatment induces neuropathological alterations, such as dendritic atrophy in hippocampal neurons, which are paralleled by cognitive deficits. Excitatory amino acid (EAA) neurotransmission has been implicated in chronic HPA axis activation. EAAs play a major role in neuroendocrine regulation. Hippocampal dendritic atrophy may involve alterations in EAA transporter function, and decreased EAA transporter function may also contribute to chronic HPA axis activation. Understanding the molecular mechanisms of HPA axis activation will likely advance the development of therapeutic interventions for conditions in which GC levels are chronically elevated.

Index Entries: Glucocortioids; adrenal gland; hypothalamus; amygdala; hippocampus; chronic stress; excitatory amino acids; arginine vasopressin; cognitive deficits; obesity.

Introduction

Detrimental Effects of Chronic Hypothalamic–Pituitary–Adrenal (HPA) Axis Activation

The HPA axis plays an important role in many brain functions, including feeding, sexual behavior, cognition, and emotion, and alterations in the regulation of this axis are associated with impairments in these functions. Both HPA axis hypoactivity and hyperactivity with prolonged elevations in glucocorticoid (GC) levels can be detrimental. Increasing evidence suggests that the detrimental effects of GC hypersecretion occur by activation of the HPA

axis in several human pathologies, including obesity, Alzheimer's disease, AIDS dementia, and depression. This article will focus on the role of chronic HPA axis activation and GC hypersecretion in hippocampal function and in the development of obesity.

Regulation of the HPA Axis

The secretion of GCs, which are essential for adaptation to acute stressors, including infection and injury, is accomplished by the HPA axis. Activation of the HPA axis is a defensive response to stimuli that threaten homeostasis and is initiated by neurons in the hypothalamic paraventricular nucleus (PVN), which secrete the adrenocorticotrophic hormone (ACTH) secretagogs corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) into the pituitary portal circulation (Antoni, 1986; Whitnall, 1993). Subsequent release of ACTH from the pituitary stimulates the secretion of GCs from the adrenal gland. Normally, GCs secreted by the adrenal cortex interact with receptors in the hypothalamus, hippocampus, and pituitary to inhibit the release of CRF and ACTH via negative feedback (Keller-Wood and Dallman, 1984; Dallman et al. 1987) (Fig. 1). The hippocampus is the main site for negative feedback under basal conditions. The HPA axis is controlled by the high-affinity type 1 or mineralocorticoid receptor (MR) and the low-affinity type 2 or GC receptor (GR) (McEwen et al., 1968; Reul and De Kloet, 1986; Joels and De Kloet 1994). MRs, which constitute the majority of GC receptors in the hippocampus, mediate feedback inhibition under basal conditions. Stress levels of circulating GCs occupy the GRs which constitute the majority of GC receptors in the PVN and pituitary; GRs are also present at high levels in the hippocampus (Reul and De Kloet, 1986).

GCs are also thought to be involved in learning and memory. In rodents, the GR is proposed to be involved in the effects of GCs in the consolidation and retention of learned behavior (Oitzl and De Kloet, 1992). The MR is involved in anxiety-like behavior, explorations of novel environments, and search-escape strategies in locating a hidden platform in the water maze spatial learning task (Oitzl and De Kloet, 1992; Smythe et al., 1997).

Role of the Amygdala in HPA Axis Regulation

The amygdala plays a key role in the response to stress (Singh et al., 1990; Emoto et al., 1993; Koob et al., 1993), in emotional memory (Adolphs et al., 1994), and in HPA axis regulation (Dunn and Whitener, 1986; Beaulieu et al., 1989). The amygdala contains high levels of CRF (Gray et al., 1989) and has been implicated as a central site for the stress-related autonomic and behavioral responses associated with CRF (Koob et al., 1993), such as decreased locomotion and exploration in a novel environment (Britton et al., 1982; Sutton et al., 1982; Liang and Lee, 1988; Takahashi et al., 1989) and decreased investigative behavior during social interactions (Elkabir et al., 1990) in rodents. Restraint stress increases CRF release in the amygdala (Pich et al., 1995), and stimulation of the amygdala increases plasma corticosterone levels (Matheson et al., 1971; Redgate and Fahringer, 1973; Dunn and Whitener, 1986).

Intra-Amygdaloid Circuitry and HPA Axis Regulation

Within the amygdala, the lateral nucleus receives sensory inputs and, via internal connections, communicates with the central nucleus (for review, see Pitkanen et al., 1997). Although the basolateral nucleus of the amygdala is involved in mediating the β-adrenergic activation-dependent effects of GCs on memory storage (Quirarte et al., 1997), the central nucleus of the amygdala is involved in the expression of fear and anxiety (Moller et al., 1997). However, the distinction between these two nuclei may be too simple, since a role for the basolateral amygdala has recently been implicated in some types of fear-conditioned behavior (Killcross et al., 1997). Lesions in the central nucleus of the amygdala, unlike those

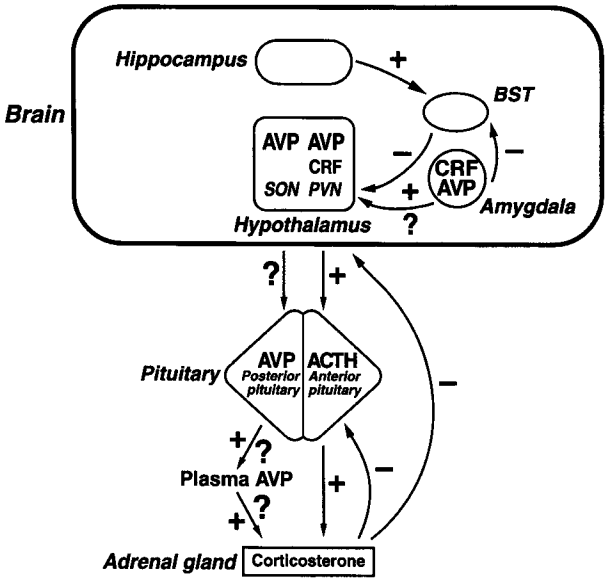

Fig. 1. Diagram of HPA axis modulation. Activation of the HPA axis is initiated by neurons in the hypothalamic PVN that secrete the ACTH secretagogus CRF and AVP into the pituitary portal circulation. Subsequent release of ACTH from the pituitary stimulates GC secretion from the adrenal gland. Increased plasma GC levels may contribute to hippocampal damage, which in turn could further enhance the HPA axis activation through decreased negative feedback. The adrenal gland could be sensitized to ACTH or directly activated by plasma AVP secreted from the posterior pituitary, possibly reflecting activation of magnocellular AVP neurons in the supraoptic nucleus (SON). The amygdala and bed nucleus of the stria terminalis (BST) may also be important for HPA axis activation (*see text*).

in the PVN, abolish some of the behavioral effects of exogenously administered CRF (Liang and Lee, 1988). Interestingly, GC receptors are colocalized in CRF cells in the central nucleus (Cintra et al., 1987a; Honkaniemi et al., 1992). GC receptors in the amygdala have been implicated in the regulation of body weight (Akana et al., 1997). These data suggest that there is also feedback regulation of GCs in the amygdala as well as in the hypothalamus.

The central and medial nuclei of the amygdala project directly to the lateral and medial PVN and, within the PVN, to AVP- and CRF-immunoreactive cells that modulate pituitary ACTH release (Gray et al., 1989). CRF-containing fibers have been traced from the amygdala to the lateral hypothalamus, suggesting a possible direct innervation of CRF- and AVP-containing neurons in the PVN that may be important for the regulation of ACTH-releasing neurons in the hypothalamus by the amygdala (Gray et al., 1989).

The central nucleus also projects to ventral regions of the lateral bed nucleus of the stria terminalis (BST) (Sakanaka et al., 1986; McDonald, 1987). Stimulation of the lateral BST increases corticosterone secretion (Dunn, 1987), and lesions in this region decrease expression of CRF mRNA in the PVN (Herman et al., 1994) and attenuate corticosterone secretion induced by conditioned fear (Gray et al., 1993). Both stimulatory (Matheson et al., 1971; Redgate and Fahringer 1973; Dornhorst et al., 1981) and inhibitory (Eleftheriou et al., 1972; Tannahill et al., 1991) effects of the amygdala on the regulation of the HPA axis have been reported. This discrepancy may be owing to species differences, differences in methodology, and differential effects of different amygdaloid nuclei on regulation of the HPA axis (Dunn and Whitener, 1986).

Chronic HPA Axis Activation

The Role of AVP in Chronic HPA Axis Activation

AVP is proposed to be important for maintaining the activity of the HPA axis after repeated stimulation (Hashimoto et al., 1988; Scaccianoce et al., 1991; Lightman, 1994). Single stressful stimuli (e.g., exposure to lipopolysaccharide (LPS), interleukin-1 (IL-1), brain surgery, or electric footshocks) increase the AVP stores in terminals of CRF neurons in the external zone of the median eminence (Schmidt et al., 1995, 1996). Chronic increases in GC secretion are not sufficient to block upregulation of hypothalamic CRF and AVP mRNA expression (Herman et al., 1995; Makino et al., 1995), and AVP

may maintain HPA axis activity after repeated stimulation (Lightman, 1994). During chronic or repeated stress, there is a shift from non-AVP-producing to AVP-producing CRF neurons, an increase in AVP vesicles in the median eminence (De Goeij et al., 1992a, b, c, Bartanusz et al., 1993), and a release of AVP, but not of CRF (De Goeij et al., 1992c, Aguilera, 1994).

HPA Axis Activation in Obesity

The development and maintenance of obesity are associated with profound endocrine disorders, including increased HPA axis activity (Dallman et al., 1993; Pasquali et al., 1993). The important role of HPA axis activation and GC hypersecretion in the development of obesity is demonstrated by the fact that adrenalectomy eliminates hyperphagia and excessive weight gain, which are restored with GC treatment, in obese *fa/fa* rats (Yukimara et al., 1978), in obese rats with ventromedial hypothalamic lesions (Mook et al., 1975, Bruce et al., 1982), and in obese *ob/ob* mice (Saito and Bray, 1984; Boston et al., 1997).

Obesity may depend on maladaptation to chronic stress, as proposed by Bjorntorp (1991) for the visceral obesity in premenopausal women, which is associated with HPA axis activation and characterized by an exaggerated hormone response to CRF, combined CRF and AVP, and ACTH (Pasquali et al., 1996). CRF acting at the PVN not only is involved in regulating the pituitary–adrenal axis (Antoni, 1986), but also is thermogenic and anorexogenic (Morley, 1987; Arase et al., 1988). Corticosteroids inhibit afferent input to the PVN (Saphier, 1987; Pacak et al., 1995), and the inhibitory actions of corticosteroids on hypothalamic CRF synthesis and/or release may play a role in the development of obesity.

Reduction in central CRF activity may contribute to the development of obesity (Rothwell, 1990). This suggestion is supported by numerous experimental observations. Hypothalamic CRF content was reported to be reduced in obese rats (Nakaishi et al., 1990; Fukushima et al., 1992), though no reduction of CRF mRNA was found in *fa/fa* rats (Richard et al., 1996). The expression of the CRF_2-receptor, which is particularly concentrated in the ventromedial hypothalamus (Richard et al., 1996), is reduced, and CRF responsiveness at the pituitary level diminished (Cunningham et al., 1986) in *fa/fa* rats. Intracerebroventricular (icv) infusion of CRF in genetically obese mice (*ob/ob*) and rats (*fa/fa*) or lean controls depresses food intake and stimulates the metabolic rate (Rohner-Jeanrenaud et al., 1989; Langley and York, 1990; Rothwell, 1990; Glowa et al., 1992). Treadmill running, restraint stress, tumorigenesis, or appetite-suppressing drugs, which increase hypothalamic CRF production, also diminish food intake (Shibasaki et al., 1988; Rivest and Richard, 1990; Appel et al., 1991; McCarthy et al., 1993; Spina et al., 1996). ICV infusion of ligand inhibitors of CRF binding proteins, which displace CRF or the recently characterized CRF-like peptide urocortin (Vaughan et al., 1995), increase extracellular levels of unbound CRF and significantly blunt excessive weight gain in obese *fa/fa* rats (Heinrichs et al., 1996). In anesthetized rats with high levels of corticosterone, portal secretion of CRF was lower in *fa/fa* rats and enhanced to a greater extent after pharmacological adrenalectomy (Plotsky et al., 1992) than in lean controls, suggesting that the CRF system in *fa/fa* rats might be more sensitive to the negative feedback of corticosterone. GC receptors are colocalized in CRF cells in the parvocellular region of the PVN of the hypothalamus (Cintra et al., 1987b), and the number of GC receptors in the hypothalamus and hippocampus is increased in obese *fa/fa* rats (Langly and York, 1990, 1992). These studies suggest that abnormalities in CRF synthesis, release, and/or bioavailability of extracellular free CRF might contribute to the development of obesity.

Studies on thermogenesis and pyrogenesis support the involvement of an increased corticosterone-mediated negative feedback on the hypothalamic CRF system. Genetically obese rats and mice exhibit reduced thermogenesis, which has been ascribed to a reduction in either the synthesis or action of CRF within the hypothalamus. In addition, the GR blocker

RU486 prevents obesity and hyperphagia, and increases adipose tissue thermogenesis in obese rats (Hardwick et al., 1989); this effect on thermogenesis was blocked by the α-helical CRF antagonist. Finally, thermogenesis is restored and fat deposition markedly attenuated by either adrenalectomy (Marchington et al., 1983) or hypophysectomy (Holt and York, 1982). A reduction in CRF activity can lead to decreased sympathetic drive to brown adipose tissue, hyperphagia, and hypersecretion of insulin. The cytokine IL-1β, which activates the HPA axis, is dependent on hypothalamic CRF release for its actions on fever and thermogenesis. The reduced pyrogenic and thermogenic response to central injection of IL-1β in obese *fa/fa* rats is also restored by adrenalectomy (Busbridge et al., 1990), consistent with the observation that endogenous GCs downregulate the central effects of IL-1β on body temperature (Goujon et al., 1995).

Disturbed negative feedback could also contribute to the paradoxical effects of high levels of leptin (ob), a factor that suppresses appetite, increases metabolism and stimulates hypothalamic CRF release (Raber et al., 1997a; Fig. 2), in obese humans. It is important to note that the effects of GCs are complex, since they seem to have a dual dose-dependent effect on body weight and food intake. At high pharmacological doses, corticosteroids decrease food intake and body weight, which is correlated with the induction of *ob* gene expression by corticosteroids in adipose tissue (DeVos et al., 1995; Slieker et al., 1996). In contrast, administration of lower doses of corticosteroids stimulates food intake (Devenport et al., 1989), and obesity is a major side effect of GC therapy (Reid et al., 1996). The hypersensitivity to GC-stimulated feeding and hyposensitivity to GC-induced weight loss may exaggerate the weight gain in genetically obese rodents (McGinnis et al., 1987).

The amygdala also plays a role in the development of obesity. Electrolytic lesions of the posterodorsal amygdala result in hyperphagia and excessive weight gain (King et al., 1996a, b, 1997). Recent evidence indicated involvement of the amygdala in the effects of GCs on abdominal obesity. Corticosterone implants in the amygdala activate the amygdala and promote abdominal fat stores (Akana et al., 1997).

HPA Axis Activation and Hippocampal Function

In rodents, the hippocampus has a critical function in spatial learning and memory (for review, *see* Poucet and Benhanou, 1997) and in the response to novelty (Gray, 1982; Gray and McNaughton 1983). Disturbances in hippocampal functioning reduce spatial learning and memory performance and the ability to explore the environment adequately. The latter effect may not to be a problem of stimulus detection, but of altered reactivity to the stimulus (Gray, 1982). A role for GCs in the response to novelty is supported by the increased behavioral reactivity of rodents toward a novel object after adrenalectomy; GC treatment restores normal reactivity (Oitzl et al., 1994).

Chronic HPA axis activation and elevation of GC levels contribute to the onset of hippocampal pathology. Chronic stress or corticosterone elevation induces dendritic atrophy in hippocampal neurons, which is paralleled by cognitive deficits in spatial learning and memory (Woolley et al., 1990; Watanabe et al., 1992; Dachir et al., 1993; Magariños and McEwen 1995; Magariños et al., 1997). In turn, damage to the hippocampus (Feldman and Conforti 1976; Fischette et al., 1980; Jacobson and Sapolsky, 1991) or prefrontal cortex (Diorio et al., 1993) increases the basal and stress-induced corticosterone response. HPA activation and GC hypersecretion have also been implicated in hippocampal neuron loss during aging (Landfield et al., 1981; Sapolsky et al., 1985; Coleman and Flood, 1987; Issa et al., 1990). The combination of GC-mediated hippocampal damage and the decreased ability of the damaged hippocampus to inhibit corticosterone secretion has been proposed to cause a feed-forward cascade of hippocampal degeneration with age (GC cascade hypothesis) (Horel, 1978; Sapolsky et al., 1985).

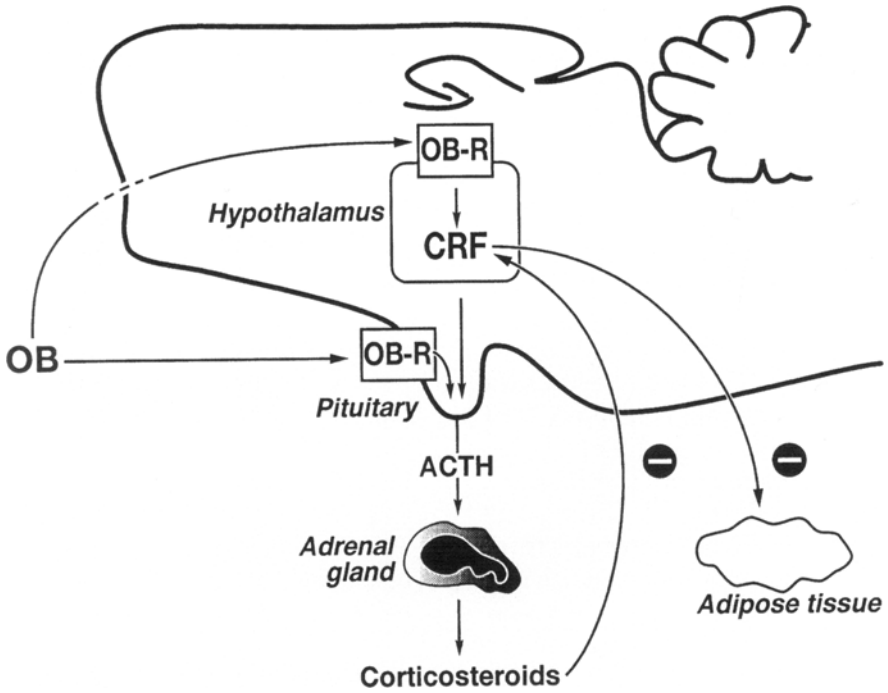

Fig. 2. Diagram of the possible role of HPA axis function in obesity. Recombinant OB can directly activate the hypothalamus and pituitary to induce CRF and ACTH release, respectively. CRF inhibits food intake, and its effect on adipose tissue might be mediated by the sympathetic nervous system. OB-induced ACTH release from the anterior pituitary might stimulate the adrenal gland to increase corticosterone levels in the systemic circulation, which could counterbalance the hypothalamic CRF effects. OB-R = OB receptor.

The GC cascade hypothesis is supported by the finding that adrenalectomy attenuates the neuronal loss observed in intact aged (12-mo-old) rats (Landfield et al., 1981). In addition, reducing GC secretion by behavioral modifications, such as neonatal handling, can improve neuronal morphology and learning in later life (Meany et al., 1988; McEwen et al., 1992). This reduction in GC secretion alters the regulation of the HPA axis, since it is paralleled by decreased hypothalamic CRF mRNA levels, reduced plasma ACTH and corticosterone responses to acute stress, and increased hippocampal GR mRNA levels and enhanced GC feedback sensitivity (Liu et al., 1997). However, the original findings of hippocampal neuron loss after sustained exposure to GC (Sapolsky et al., 1985) remain controversial, since they have been reproduced in some studies (Issa et al., 1990; Dachir et al., 1993; Arbel et al., 1994; Clark et al., 1995) but not in others (Bardgett et al., 1994; Bodnoff et al., 1995). The discrepancies may be owing to strain differences in (age-dependent) susceptibility to the effects of GCs, to differential effects of GCs on various hippocampal cell populations (McEwen et al., 1992; McLay et al., 1997), and to individual differences in stress response (Sapolsky, 1994), in structural alterations, and in cognitive function (Issa et al., 1990; Arbel et al., 1994; Rapp and Gallagher, 1996).

The significance of HPA axis activation in cognitive function in humans is illustrated in Table 1. In humans, HPA activation is associated with memory impairments in various conditions, including acquired immunodeficiency syndrome (AIDS), Alzheimer's disease, Cushing's disease, depression, and GC treatment.

Table 1
HPA Axis Activation, GC Treatments, and Cognitive Impairments in Humans

Disease/Treatment	Effect	Reference
AIDS	Increased plasma cortisol levels	Vago et al., 1994; Wilson et al., 1996; Sapse 1997; Norbiato et al., 1997; Oberfield et al., 1994
	Correlation of cortisol with hippocampal atrophy in pediatric patients	Oberfield et al., 1994
Alzheimer's disease	Plasma ACTH and cortisol levels are increased and correlate with severity of hippocampal atrophy and memory impairments	Jenike and Albert, 1984; De Leon et al., 1988; Gurevich et al., 1990; O'Brien et al., 1996; Nasman et al., 1996; Weiner et al., 1997
Cushing's disease	Plasma ACTH and cortisol levels are increased and correlate with memory impairments	Whelan et al., 1980; Starkman et al., 1986; Mauri et al., 1993
Schizophrenia	Plasma ACTH and cortisol levels are increased and correlate with memory impairments	Newcomer et al., 1991
Depression, post-traumatic stress disorder, aging preceding dementia	Plasma ACTH and cortisol levels are increased; hippocampal atrophy correlates with memory impairments	Reus, 1984 McEwen, 1997; Newcomer et al., 1994
GC treatment	Transient memory deficits in healthy volunteers and depressed patients	
	Memory impairments in asthmatic children who were treated with higher GC doses	Bender et al., 1991; Walkowitz et al., 1990

Choice of an Appropriate Animal Model of Chronic HPA Axis Activation

There are different patterns of response of chronic HPA axis activation (Aguilera, 1994). This is important for the selection of an animal model to assess the role of the HPA axis in a particular disorder. In Table 2, the main patterns of chronic HPA axis activation are listed, which can be used as criteria for this selection. For instance, IL-6 has been reported to stimulate the HPA axis (Harbuz et al., 1992; Hu et al., 1993; Mastorakos et al., 1993) in humans chronically treated with IL-6 (Mastorakos et al., 1993 Spath-Schwalbe et al., 1994) and in patients with various disorders associated with elevated IL-6 levels in brain and cerebrospinal fluid, including Alzheimer's disease, multiple sclerosis, and depression (Gold et al., 1995; Hatzinger et al, 1995). Strikingly, the HPA axis exhibits a blunting of ACTH, but not cortisol responses, a pattern resembling the diminished ACTH responses during chronic stress (Aguilera, 1994). One appropriate model for studying the HPA axis under such conditions is a transgenic mouse model in which constitutive expression of IL-6 under the control of the glial fibrillary acidic protein (GFAP) promoter is targeted to astrocytes in the central nervous system (CNS) (Raber et al., 1997b). GFAP-IL6 mice heterozygous or homozygous for the IL-6 transgene had normal basal plasma corticosterone levels, but after restraint stress, showed abnormally increased levels in a gene dose-dependent fashion, whereas plasma ACTH levels and pituitary ACTH content were either not changed or decreased. The increased plasma corticosterone levels were associated

Table 2
Main Patterns of Chronic HPA Axis Activation

Pattern of ACTH response to repeated and novel stimulus[a]	Basal ACTH levels[a]	Basal corticosterone levels[a]	ACTH response to novel stressor[b]	Examples
Desensitization of ACTH response to a repeated stressor Hyperresponsiveness to a novel stimulus	Similar	Increased	Increased	Repeated stressor: restraint stress or cold stress; novel stressor: hypertonic saline injection (Hauger et al., 1988; Plotsky and Sawchenko, 1987; Hauger and Aguilera, 1992)
No desensitization of ACTH response to a repeated stressor Hyperresponsiveness to a novel stimulus	Similar	Increased	Increased	Repeated stressor: hypertonic saline, footshock, or hypertonic saline injection; novel stressor: restraint stress (De Goeij et al., 1992; Kiss and Aguilera, 1993) GFAP-gp120 transgenic mice, repeated stressor: chronic CNS HIV-1 gp120 expression; novel stressor: restraint (Raber et al., 1996)
No desensitization of ACTH response to a repeated stressor Normal responsiveness to a novel novel stimulus	Increased	Increased	Similar	Repeated stressor: chronic central administration of IL-2; novel stressor, restraint stress (Hanisch et al., 1994)
Diminished ACTH response to a novel stimulus	Increased	Increased	Decreased	Repeated stressor: water deprivation or adding 2% saline to drinking water; novel stressor: restraint stress (Dohanics et al., 1990; Jessop et al., 1990; Chowdrey et al., 1991; Aguilera et al., 1993)
	Similar	Similar	Decreased	GFAP-IL-6 transgenic mice, repeated stressor: chronic CNS IL-6 expression; novel stressor: restraint (Raber et al., 1997b)

[a]Plasma hormone levels as compared to control treatment or nontransgenic littermates controls. In this context, basal levels indicate hormone levels under conditions of the repeated stimulus/control treatment or hormone levels of nontrasgenic littermate controls.

[b]ACTH response as compared to repeated stimulus or nontransgenic littermates controls.

with increased adrenal corticosterone content and hyperplasia of both adrenal cortex and medulla. Interestingly, plasma AVP was increased as in humans treated with IL-6 (Mastorakos et al., 1994). The reduced ACTH response and the adrenal hyperplasia in the IL-6 transgenic mice suggest direct activation at the level of the adrenal gland, which may be directly activated by AVP or be sensitized to ACTH. A similar mechanism may play a role in the blunted ACTH response and elevated corticosterone levels under pathophysiological

conditions observed in humans with high brain levels of IL-6.

Role of Excitatory Amino Acid (EAA) Neurotransmission in the Central Effects of GCs

Possible Mechanisms Mediating the Central Effects of GC

The mechanisms that are proposed to mediate the detrimental effects of GCs are summarized in Table 3. GCs can exert detrimental effects by directly inducing neurotoxicity, reversible loss of neuronal processes, or impaired ability of neurons to survive a neurological insult (for review, *see* Sapolsky, 1996). An example of the latter is GC-mediated inhibition of glucose transport into hippocampal neurons, which makes them more sensitive to kainic acid and metabolic toxins (Sapolsky, 1992). Increased neuronal vulnerability could also result from altered neurotrophin expression. GCs reduce the expression of brain-derived neurotrophic factor (BDNF) (Smith et al., 1995; Segal et al; 1995), but increase the expression of fibroblast growth factor (FGF), nerve growth factor (NGF), and neurotrophin-3 (NT-3) (for review, *see* McLay et al., 1997). These alterations in neurotrophin expression are complex, since NGF can activate the HPA axis (Otten et al., 1979), and altered expression of a particular neurotrophin can modulate the expression of the other neurotrophins (Lindholm et al., 1994). Furthermore, GC response elements are found in diverse genes, including those encoding cytokines and other mediators of the immune response (for review, *see* Wilckens, 1995). Type I and type II GC receptor complexes can also directly interact with various transcription factors, including AP-1 and NF-κB (Wilckens, 1995). GCs can also induce the IκB inhibitory protein, which traps activated NF-κB (Scheinman et al., 1995; Auphan et al., 1995). Finally, GCs can affect EAA neurotransmission.

Role of EAA in HPA Axis Activation

The amino acids L-glutamate and L-aspartate are the main excitatory neurotransmitters in the CNS (Fagg and Foster, 1983; Robinson and Coyle, 1987). Glutamate has been suggested to be important for neuroendocrine regulation (Reyes et al., 1990) and to be the predominant excitatory transmitter used for control of hypothalamic AVP cells (Meeker et al., 1993). The importance of glutamate in neuroendocrine regulation is illustrated in rodents that are treated neonatally with glutamate. This treatment damages the arcuate nucleus of the hypothalamus and decreases proopiomelanocortin (POMC) peptides, resulting in obesity, attenuation of leptin effects, and neuroendocrine dysfunction (Caputo et al., 1996; Dawson et al., 1997; Ribeiro et al., 1997). The potent effect of EAAs on the release of ACTH and, consequently, GCs seems to be mediated mainly by *N*-methyl-D-aspartate (NMDA) receptor activation (Gay and Plant, 1987; Jezova et al., 1991; Jacobs and Johnson, 1994). Direct administration of glutamate into the PVN stimulates ACTH release, suggesting a hypothalamic site of action for EAA stimulation of the HPA axis. Notably, NMDA receptor agonists have been reported to stimulate the release of AVP directly, but not of CRF, from hypothalamic explants (Patchev et al., 1994). However, anti-CRF antibodies block NMDA- and kainate-mediated stimulation of the HPA axis (Chautard et al., 1993), and EAA may act at extrahypothalamic sites to induce hypothalamic CRF release. For example, stimulation of the amygdala by glutamate increases CRF release from the median eminence and activates the HPA axis (Gabr et al., 1995).

The facilitation of HPA axis activation by glutamate-induced stimulation of the amygdala is likely to be important during chronic stress. Glutamate-mediated neurotransmission in the amygdala is involved in the stress response (Falls et al., 1992; Koch and Ebert, 1993), and has been implicated in emotional learning (Farb et al., 1992) and conditioned fear (Davis, 1992).

Table 3
Main Possible Mechanisms Mediating Detrimental GC Effects

Possible GC target	Effect	Reference
Glucose transport	Decreased	Horner et al., 1990; Virgin et al., 1991; Doyle et al., 1993
Neurotrophin expression	Reduction BDNF; increase FGF, NGF, and NT-3	Lindholm et al., 1994; Kononen et al., 1994; Chao and McEwen, 1994; Scully and Otten, 1995a,b; Smith, 1996; McLay et al., 1997
GC response elements in diverse genes and GC–receptor complex interactions with transcription factors, like AP-1 and NF-κB	Modulation of immune response; regulation of cytokine and cytokine receptor expression	Wilckens, 1995; Almawi et al., 1996; De Boscher et al., 1997
IκB inhibitory protein	Induction of IκB	Scheinman et al., 1995; Auphan et al., 1995
EAA neurotransmission EAA transporters	Increased extracellular EAA levels in brain	Stein-Behrens et al., 1992, 1994; Moghaddam, 1993; Moghaddam et al., 1994; Lowy et al., 1994, 1995; Chou et al., 1994; Magariños and McEwen, 1995
	Decreased EAA transporter activity	
	Increased EAA levels mediate hippocampal atrophy	
Cytosolic calcium levels	Increased	Joels and Kloet, 1989; Elliott and Sapolsky, 1992, 1993; Kerr et al., 1992

Role of EAA Neurotransmission in the Detrimental Effects of GCs

Increasing evidence suggests that excess extracellular levels of EAA may play an important role in neuronal death associated with several conditions (for review, *see* Lipton and Rosenberg, 1994) including cerebral ischemia (Benveniste et al., 1984; Globus et al., 1988), hypoglycemia (Sandberg et al., 1986), cerebral trauma (Faden et al., 1989), Alzheimer's disease (Greenamyre and Young, 1989; Mattson and Rychlik, 1990; Olney et al., 1997), and Huntington's disease (Coyle et al., 1983; Kremer et al., 1993). The increased extracellular EAA levels could be owing to altered EAA metabolism, increased EAA release, or impaired EAA reuptake by EAA transporters (Nicholls and Attwell, 1990). Increased extracellular EAA levels could cause cell death by altering neuronal calcium homeostasis (Olney, 1990; Porter and Greenamyre, 1995; Rothstein, 1996).

Together with GCs and serotonin, EAAs mediate hippocampal atrophy during chronic stress (McEwen et al., 1997). Importantly, chronic stress and aging increase extracellular glutamate levels in the hippocampus (Moghaddam, 1993; Moghaddam et al., 1994; Lowy et al., 1994,1995; Arias et al., 1995; Bagley and Moghaddam, 1997). A role for GCs in the increased EAA levels is indicated by the reported lower basal and stress-induced increases in extracellular glutamate levels in the hippocampus of adrenalectomized rats (Lowy et al., 1993). There is more direct evidence for GC modulation of extracellular EAA levels. GCs increase extracellular concentra-

tions of glutamate and, to a lesser extent, of aspartate in the hippocampus and increase the magnitude of these EAAs in response to kainic acid (Stein-Behrens et al., 1992; 1994).

GCs may increase extracellular EAA levels by impairing EAA reuptake. Most of the EAA uptake, which is crucial for clearing EAA from the synaptic cleft, is mediated by astroglial transporters (Nicholls and Attwell, 1990; Balcar and Li 1992; Kanai et al., 1993; Greenamyre and Porter, 1994; Rothstein et al., 1996). Modulation of EAA transporter activity has been proposed to play an important role in disease, since decreased EAA transporter activity has been associated with neurodegeneration (Silverstein et al., 1986; Rothstein and Kuncl, 1995; Scott et al., 1995; Masliah et al., 1996; Rothstein et al., 1996). Little is known about possible direct effects of GCs on EAA transporters. Interestingly, GCs were shown to increase extracellular EAA in hippocampal cultures by disrupting EAA reuptake (Chou et al., 1994), which supports the involvement of GC-mediated deficient uptake in the increase in extracellular EAA levels and subsequent neuronal damage (Massieu and Tapia, 1997). The regulation of EAA transporter activity may be complex, since many factors influence this activity. These factors include arachidonic acid (Zerangue et al., 1995), free radicals (Dowd and Robinson, 1996), substance P (Johnson and Johnson, 1993), cytokines, such as TNF-α, IFN-γ, and IL-1β (Fine et al., 1996; Ye and Sontheimer, 1996), HIV-1 gp120 (Vesce et al., 1997), and amyloid β-peptide (Aβ) (Butterfield, 1997; Keller et al., 1997), all of which reduce EAA transporter activity, and glutamate and phorbol esters (Dowd and Robinson, 1996), which activate EAA transporter activity (Gegelashvili et al., 1996).

Decreased EAA transporter function might also contribute to HPA axis activation. The hypothalamus and amygdala are implicated in HPA axis activation by EAA (Gabr et al., 1995; Joanny et al., 1997), and increased extracellular EAA in these brain regions may contribute to HPA axis activation. Thus, these brain regions, unlike the hippocampus, would not be susceptible to EAA toxicity. The specific vulnerability of the hippocampus to increased extracellular EAA levels would be consistent with the lack of GC-mediated toxicity in the striatum and prefrontal cortex, in which stress-induced extracellular EAA levels were similar to those in the damaged hippocampus (Moghaddam, 1993; Moghaddam et al., 1994; Lowy et al., 1994).

Significance

In humans, HPA activation is associated with memory impairments in various conditions, including AIDS, Alzheimer's disease, Cushing's disease, depression, and GC treatment (Table 1), as well as with obesity. Increasing evidence suggests an important role for EAA neurotransmission in (chronic) HPA axis activation. This is important to our understanding of HPA axis function in health as well as in diseases characterized by GC hypersecretion. Understanding the molecular mechanisms involved in HPA axis activation will likely advance the development of interventions for chronically elevated GC levels, including chronic GC treatment.

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