

**REVIEW ARTICLE**

# The Role of Stress and Glucocorticoids in Pathogeny of Age-Related Neuropsychiatric Disorders

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## Abstract

An overview and commentary are presented on the role of stress and glucocorticoids in the pathogeny of age-related psychiatric and neurologic disorders, first of all depressive illness and Alzheimer's disease. The connections of these disorders with senescence-induced changes in bio-regulation of hypothalamo-pituitary-adrenal axis activity are discussed, focusing attention on biphasic glucocorticoid effects, gender differences, adverse effects of exogenous corticosteroids and the importance of stress and glucocorticoid effects on developing brain, as related to programming/imprinting and embedding phenomena. In addition, the interactions of neuropsychiatric disorders with diabetes mellitus and other chronic diseases, as well as of glucocorticoids with proinflammatory cytokines are briefly considered in relation to postnatal ontogeny and aging.

## Keywords

Stress, Glucocorticoids, Depression, Dementia, Ontogeny

## Abbreviations

ACTH: Adrenocorticotrophic Hormone; AVP: Arginine-Vasopressin; BDNF: Brain-Derived Neurotrophic Factor; CRF: Corticotropin-Releasing Factor; CRP: C-Reactive Protein; CNS: Central Nervous System; DOHaD: Developmental Origins of Health and Disease; DST: Dexamethasone Suppression Test; GC: Glucocorticoids; GR: Glucocorticoid Receptors; HPA: Hypothalamo-Pituitary-Adrenal (axis); HSP: Heat Shock Proteins; IL: Interleukin; MR: Mineralocorticoid Receptors; TSD: Posttraumatic Stress Disorder; PVN: Paraventricular Nucleus; RS: Rio Grande do Sul; SAMS: Sympathetic - Adrenomedullary System; SES: Socioeconomic Status

## Introduction

Earlier we have evaluated the role of stress hormones and proteins in ontogenetic bioregulation [1,2]

as well as in pathogeny of diabetes mellitus and metabolic disorders [3]. Here this work was continued for neuropsychiatric diseases, focusing on those disorders that occur in certain age categories, i.e. appear to be age-related.

In general, central nervous system (CNS) and especially the brain are the main components of reactions to various stressors. In endocrinologic literature the hypothalamo-pituitary-adrenal (HPA) axis is principally considered. It includes: 1) Paraventricular nucleus (PVN) of the hypothalamus, producing corticotropin-releasing factor (CRF) and arginine-vasopressin (AVP); 2) The corticotrophs of anterior pituitary gland secreting adrenocorticotropic hormone (ACTH); and 3) Adrenal cortex producing glucocorticoids (GC), cortisol in humans and corticosterone in rats - the widely used model species of laboratory animals in endocrine research. The established scheme of bioregulation for HPA axis includes stimulatory actions of CRF and AVP on ACTH secretion and of ACTH on GC production, as well as negative GC feedback actions on CRF and ACTH secretion.

However, during the last decades this scheme had an important expansion, involving some other brain regions, first of all the hippocampus [4]. At present this region is estimated as one of the principal parts of bioregulatory circuits for HPA axis and stress reactions, contributing also to the maintenance of circadian GC rhythms. For this task the hippocampus contains both types of corticosteroid receptors: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). MR have much higher affinity to GC and regulate mainly basal GC secretion, whereas GR respond to peak GC lev-

els, both in active phase of circadian rhythm and during stress reactions [5].

Fifty years ago, in 1968 Bruce McEwen and his colleagues have shown that 3H-corticosterone accumulated mainly in hippocampus, whereas one of synthetic GC 3H-dexamethasone - in pituitary gland (see discussion in [6]). Since that time the hippocampus has turned out to be the main focus of attention for researchers working in neuroscience and endocrinology, psychiatry and neurology. Whereas hippocampus contains both MR and GR, other brain regions possess mainly GR. From all of these regions, the amygdala and prefrontal cortex are the most important for regulation of stress responses. In a roughly simplified mode, it can be said that hippocampus and prefrontal cortex inhibit hypothalamic PVN activity, whereas amygdala stimulates it [7]. Later in this article we shall see that such interrelations between various parts of the brain are important for understanding the role of stress and GC in the pathogeny of neuropsychiatric disorders.

Although Hans Selye focused mainly on the role of GC in stress reactions, Walter Cannon and subsequently many other researchers underlined the importance of catecholamines in bioregulation of responses to stressors. In this sense, it is impossible to describe the pathogeny of neuropsychiatric disorders without evaluating the role of noradrenaline and adrenaline, as well as of sympathetic-adrenomedullary system (SAMS) in stress reactions. For example, it is important to mention Locus Coeruleus, a main source of noradrenaline in the brain that interacts with CRF produced in hypothalamic PVN and appears to have an especially important role in the pathogeny of posttraumatic stress disorder (PTSD) [8].

Nevertheless, we need to consider here that specifically GC (and not catecholamines) became one of the principal classes of pharmacotherapeutic agents, widely used as anti-inflammatory and immunosuppressive drugs. Perhaps, highly lipophilic nature and relative chemical stability partly explain this GC potential, as compared to catecholamines. However, as we shall see later, adverse effects are characteristic not only for endogenous GC in excessively elevated concentrations, like those during prolonged and intensive stress, but also for exogenous GC used in various areas of modern medicine, especially in the cases of their chronic utilization, and in many of these cases adverse effects include GC actions on CNS.

Before advancing to the main part of this article, we must discuss briefly the difficulties and complexities of exploring the role of CNS in regulation of stress reactions involving GC. Really, in spite of tremendous success of investigations in this area during the last decades, we are still far from firmly established theories and concepts. First of all, this is related to enormous complexity of the brain, especially in humans. Many years ago, it was already underlined that biochemical approaches do

not always work well for studying the brain and other CNS parts, since the information loss may occur already during the first steps in biochemical procedures [9].

In addition, even mammals including primates are quite different from humans, as referred to CNS. On the other hand, bioethics strictly prohibits various invasive approaches in humans, especially in perinatal period. Therefore, laboratory animals, principally rats serve as important sources of evidence on the role of CNS in regulation of stress reactions, despite of strong interspecies differences. However, it is not a surprise that psychometric tests in humans became quite essential for studies in this area, although the definitions of cognitive functions including memory and attention are far from being firmly established and moreover, it is difficult to compare the results of psychometric tests in humans with the data obtained in experiments for studying neurobehavior on laboratory animals.

And finally, at least developing brain consists of quite soft, vulnerable tissues that preclude their easy handling, e.g. for isolating and weighing the brain and its different parts. Because of this peculiarity, from the whole brain in our previous studies we used only pituitary gland for investigating the effects of exogenous GC administered to rats in neonatal period. Nevertheless, fortunately there are some data on brain growth under the influence of exogenous GC in the literature (see later in this article). For us these data are essential, in order to discuss the role of GC in programming/imprinting phenomena in the framework of Developmental Origins of Health and Disease (DOHaD), the principal area investigating connections between development and aging, as well as age-related diseases.

## **Role of Stress and Glucocorticoids in Pathogeny of Psychiatric Disorders**

From the whole spectrum of psychiatric diseases, the depressive illness (first of all, major depressive disorder of melancholic or psychotic type) has attracted principal attention of researchers, and this is quite understandable: as a matter of fact, affective disorders including depression and bipolar disorder have very significant contribution to the burden of morbidity on global scale. In addition, depressive illness is age-related, being more frequent in the intermediate age categories [10]. On the other hand, the role of stress and GC in pathogeny of depressive illness is fairly well established, much more than in other neuropsychiatric disorders. Really, acute and chronic stressors can potently augment the risk of depressive illness [8]. Moreover, in accord with modified double-hit model, especially a combination of chronic and acute stress is able to induce the episodes of depression [11].

It is important to note that stress-related anxiety disturbances, first of all panic syndrome, frequently occur before depression [12]. On the other hand, depressive

illness can accompany many chronic diseases, such as the components of metabolic syndrome, largely enhancing the risk of mortality associated with them [13]. As will be discussed later, there is also important link between depression and cognitive disturbances including Alzheimer's disease.

The role of HPA axis in depression began to be revealed already in the second half of the last century, especially with the introduction of dexamethasone suppression test (DST). In this test, cortisol concentration in patient's blood is measured after dexamethasone administration, and normally, due to negative feedback, principally on the level of pituitary gland, there occurs a suppression of cortisol level, but in a large percentage of depressed patients a non-suppression phenomenon is evident, indicating a lower efficacy of GC feedback [14].

This inadequate efficacy of GC feedback action is revealed also in flattened form of circadian biorhythm of cortisol, with higher GC level especially at night, when normally there should be quiescent phase of cortisol rhythm in humans [15]. And since the hippocampus is also involved in negative feedback GC action, the present consensus considers, first of all, adverse action of chronically excessive GC levels on hippocampal structures, especially dentate gyrus and CA regions. In this sense, it is well known already that chronic stress or exposure to excessive GC treatment may result in hippocampal atrophy that is explained (depending on the duration of stress or chronic GC exposure) by neuronal apoptosis and loss of neurons or perhaps by inhibition of neurogenesis, dendritic atrophy and decrease in tissue hydration [16,17]. In addition, noxious GC action on hippocampus may be related to a decrease in content of brain-derived neurotrophic factor (BDNF) [18].

However, chronic stress or excessive GC treatment can adversely affect other brain regions, resulting sometimes in general brain atrophy. Nevertheless, these same stress- or GC-related factors result paradoxically in hyperactive amygdala. Here we must remember that amygdala stimulates HPA axis, thereby creating a vicious cycle of positive feedback actions [7].

Very important aspect of hippocampal involvement in depression and other psychiatric disorders is related to aging. Indeed, the senescence results in hippocampal atrophy also and moreover, a combination of depression and aging has especially adverse actions on hippocampal structures, provoking apoptosis and loss of neurons, inhibiting neurogenesis and activity of pyramidal neurons, as expressed in diminished long-term potentiation (LTP) phenomenon [19,20]. Here it is necessary to mention that both neurogenesis and LTP neurophysiologic phenomenon are considered as essential mechanisms of memory and learning [21]. Obviously enough, both these cognitive functions suffer significant decline in aging and at least in some depressed patients.

Of course, all the facts described above do not mean exactly that depressive illness is equivalent to senescence, as referred to GC actions on brain structures [22]. Nevertheless, rather strong connection between them appears to be warranted, being based on the contribution of stress and GC. The depressive illness is associated also with increased sizes of pituitary and adrenal glands that correspond to hyperactive HPA axis. However, in bipolar disorder hypophyseal size may be decreased, probably as related to down-regulation of CRF receptors on corticotrophs [23].

Hippocampal atrophy and non-suppression phenomenon in DST are also present in schizophrenia [24], however in PTSD, despite of accompanying atrophy of hippocampal structures, there occurs paradoxical increase in GC negative feedback sensitivity revealed by higher suppression of cortisol in DST. Moreover, basal levels of cortisol in patients with PTSD may be decreased [25]. Nevertheless, at least partially, these paradoxical data may be explained by selective increase in the levels of noradrenaline and hyperactive SAMS, probably related to increased activity of Locus Coeruleus [26].

## Role of Stress and Glucocorticoids in Neurologic Disorders

From the whole spectrum of neurologic disturbances, moderate cognitive decline progressing to dementia have attracted major attention of researchers, showing their age-related character, with Alzheimer's disease being much more frequent in advanced age categories [27]. First of all, both the augment of basal cortisol levels in blood and non-suppression phenomenon in DST were registered in patients with Alzheimer's disease. Moreover, hippocampal atrophy is characteristic to patients with dementia [28]. There are some data that implicate also an important role of GC in abnormal tau hyperphosphorylation and enhanced production of amyloid-beta peptide from amyloid precursor protein. In addition, there exist data showing that depressive illness can augment the risk of dementia. This is quite understandable, if to consider the common pathogenic mechanisms, based on stress and GC, in both of these disorders [29].

However, the most interesting evidence, on our opinion, is related to the role of glucose and insulin in cognitive disturbances. In fact, pathogenic pathways of adverse GC effects on neurons include the inhibition of glucose transport, resulting in lower ATP reserve and the consequent increase in glutamate excitotoxicity via receptors of NMDA type that in turn provokes excessive accumulation of intracellular calcium ions [20,30]. In order to explain better how it is possible, we should remember that intracellular levels of glutamate in neurons are very high, close to 10 mM, so malfunctioning and death of only a small proportion of neurons may provoke an increase in extracellular glutamate from 0.6 to 2-5 micromole/L, resulting in excitotoxicity [31].

The present consensus on the mechanisms of adverse GC actions on neurons is the following: in excessive concentrations GC do not kill neurons directly but may enhance the actions of neurotoxins and other adverse factors, first of all ischemia/hypoxia and hypoglycemia, i.e. ATP/energy-restricting agents, thereby greatly potentiating the vulnerability of neurons to other toxic insults [18].

In this sense, the Italian research group of Maurizio Popoli has established quite recently that not only chronic stress, but also acute stress of sufficient intensity may potentiate excitotoxicity in some brain regions [32,33]. Here it is pertinent to remember that hippocampus normally inhibits HPA axis, and its atrophy provoked by stress or GC excess can result in vicious cycle of higher GC and consequently, glutamate impact (a so called "death spiral") [31], perhaps even on various brain regions.

### Biphasic Glucocorticoid Effects on the Brain

Of course, the bioregulatory mechanisms are quite complex, and surely there exist data confirming a neuroprotective action of GC in some situations [34]. It is important to discuss this topic, since the essential task is to clarify if normal, basal levels of circulating GC can have adverse actions on CNS. As for hippocampus, the present consensus is that low (but not extremely low) levels, and up to intermediate GC levels, are beneficial for hippocampal structures, since via MR they enhance LTP, favoring better memory and learning [35], whereas elevated GC concentrations, as in prolonged and intensive stress, may have adverse impact via GR, decreasing LTP, inhibiting neurogenesis and worsening cognitive functions [36]. But where is a threshold, above which GC and stress become adverse factors for the brain? Till the present moment this important question, unfortunately, remains without an adequate answer, considering not only GC levels, but also the duration of GC exposure. The opinions of researchers in this sense are numerous. Some of them suggest that even basal GC levels can result in cumulative damage to the brain and especially to hippocampus [37], whereas others suggest that only adverse environmental conditions are able to provoke neuronal damage by means of chronic stress and excessive GC exposure [18]. In this regard, an important contribution was made by Bruce McEwen, together with Teresa Seeman and their collaborators by developing a concept of allostatic load. They supposed and at least partially proved that GC and catecholamines are involved in adverse impact of cumulative exposure to undesirable life conditions, as referred especially to low socioeconomic status (SES) [38].

### Gender Differences in the Role of Stress and Glucocorticoids

A vast literature largely affirms the existence of gender differences in neuropsychiatric disorders. In fact,

there is a female predominance in depressive illness, Alzheimer's disease and PTSD (see discussion in [29]). Earlier we have partially confirmed this peculiarity, showing female predominance in affective disorders and male predominance in schizophrenia, as evaluated in three Brazilian states of Southern region [39]. Moreover, we have observed also the decrease and even reversion of gender differences for many disorders of various pathologic groups with the onset of menopause [40]. Finally, we have shown a clear-cut gender difference in psychotropic drug consumption in the population of North-Western region of Brazilian state of Rio Grande do Sul (RS), with female predominance in consumption of benzodiazepines and antidepressive drugs [41].

What for the role of stress and GC as related to gender differences, this theme is far from being clear, although many data confirm higher GC reactions to stress in females, as well as higher protection by estrogens and some other reproductive hormones in females of fertile age groups (see discussion in [42]). Of course, with the onset of menopause this female advantage is no longer possible, what probably explains some of our epidemiologic data mentioned above [40].

### Effects of Exogenous Glucocorticoids on Central Nervous System

The paradox of modern situation is quite obvious: although GC were introduced to clinical practice long time ago, at the end of fifties of the last century and presently are widely used in many areas of medicine, especially in rheumatology, oncology and for the treatment of asthma and other respiratory disorders, their adverse effects in general and specifically on CNS are well known, but "tolerated", since there exist scarce possibilities to diminish them.

What for actions of exogenous GC on the brain, it is firmly established that chronic GC pharmacotherapy can provoke various mental disturbances, from decline in memory and learning [23] to steroid psychosis [37]. Moreover, the attempts to administer GC on alternate days can result in iatrogenic bipolar disorder with rapid cycling that persists even after the end of GC treatment [43]. So, in many cases of chronic GC pharmacotherapy the physicians are obliged to prescribe several psychotropic drugs, such as lithium salts, neuroleptics and benzodiazepines, in order to diminish adverse GC effects on mental health [44]. Especially important is utilization of antidepressant drugs that serve as neuroprotectors and even as anti-inflammatory agents [45]. In addition, experimental data on laboratory animals suggest that phenytoin and tianeptine can diminish adverse effects of stress and excessive GC on hippocampus [46].

Particularly problematic may be weaning of patients from the course of chronic GC treatment, since at least in some cases the consequence of such weaning ap-

pears to be like a chemical dependence, similar to that of drugs of abuse. Especially serious is a problem of adverse GC actions in pediatric patients [47].

## The Importance of Stress and Glucocorticoid Effects on Developing Brain

Previously we and others have shown growth retardation caused by dexamethasone and other GC administered to rats in neonatal period [48]. Later we reconsidered this phenomenon as a modeling of pharmacotoxicologic programming/imprinting in the cases of perinatal GC treatment in humans [49]. Moreover, we have demonstrated an impressive growth-inhibitory GC action on rat pituitary gland both *in vivo* and *in vitro*, especially in neonatal period [50,51]. And although we did not study yet the impact of exogenous GC on brain growth, earlier this topic was already investigated by other researchers showing GC-induced brain growth retardation in experimental models on laboratory animals [6,9] - the evidence that probably corresponds to diminution of head circumference in human neonates treated with dexamethasone, with consequent decrease in hippocampal volume, at least, in adolescence [49,52].

On the other hand, prenatal stress and infections can result in the tendency to HPA axis hyperactivity in offspring, probably resulting in acceleration of brain and especially, hippocampal aging, as well as increasing the predisposition to various neuropsychiatric disorders, particularly to depression and schizophrenia [17,24,53]. All these data are extremely important for DOHaD paradigm and moreover, to public health, so quite recently we have launched an idea of not only pharmacotoxicologic programming/imprinting, but also cumulative pharmacotoxicologic embedding, as referred to the ontopathogeny of various disorders [54]. Of course, nobody can imagine present-day clinical medicine without GC pharmacotherapy. On our opinion, the principal question is how to optimize such treatment by adjusting GC dosage and duration of exposure, as well as by finding ways to diminish GC adverse effects.

## Conclusion

At present an important role of stress and GC in pathogeny of many neuropsychiatric diseases appears to be well established, however a lot of topics remain to be explored in a more detailed manner. One of these topics is the interaction of diabetes mellitus and other metabolic disorders with neuropsychiatric diseases, especially depressive illness and Alzheimer's disease [38,55]. Indeed, our recent review article has already described the role of stress and GC in the pathogeny of metabolic disturbances [3], however there may be a triple interaction of stress-related mental disorders, diabetes mellitus of type 2 and senescence. It means that ontopathogenic model offered by us earlier [56] has many perspectives for further elaboration already in near future.

Another important topic to be considered includes the interactions of GC with cytokines, especially those of interleukin (IL) group. In this sense, it is already clear that proinflammatory cytokines, first of all IL-1beta, tumor necrosis factor (TNF) of type alpha and IL-6, are able to cause GC resistance that explains concomitant increase in both GC and cytokines in many chronic disorders, considering well-known stimulatory action of proinflammatory cytokines on HPA axis activity, as well as GC-induced inhibition of proinflammatory cytokine production [45,57]. The resistance to negative GC feedback action may be explained also by a relative increase in AVP production by hypothalamic PVN, as well as by increased generation of neurotoxic products of tryptophan metabolism, also under the influence of pro-inflammatory cytokines, both in depression and senescence [13].

In accord with principal focus of this article, we shall discuss here only neuropsychiatric disorders, especially depression. A simultaneous increase in both GC and proinflammatory cytokines in depressive illness can explain higher tendency to metabolic disturbances, sarcopenia and osteoporosis in such patients [58]. Nevertheless, many aspects should be clarified further in this interesting theme, especially as referred to the possibility of subclinical infections resulting in the augment of C-reactive protein (CRP) and positive components of acute phase reaction [56]. Unfortunately, the contribution of exosomal release of heat shock proteins (HSP) to pathogeny of neuropsychiatric disorders still has not attracted due attention, as compared to metabolic diseases [3].

In conclusion, in spite of existing lacunes in our knowledge about the pathogeny of neuropsychiatric disorders, the role of stress and GC in at least some of them, like depression and dementia, may be considered as quite firmly established. There are also some data on the role of stress in pathogeny of other diseases of this group, but their proportion in the whole discussion is much lower, as compared to depression and dementia. On our opinion, both earlier review article [3] and the present one add important dimensions to the role of stress and GC in aging and age-related pharmacotherapy [59].

Nevertheless, we should express here our preoccupation on somewhat slow incorporation of certain ideas to present paradigms governing the discussion on the role of stress and GC in pathogeny of neuropsychiatric disorders. In fact, already at the end of the last century we and others have considered the role of ultradian biorhythms of hormonal secretion in the mechanisms of ontogenetic transitions and tissue growth regulation [60,61]. However, only just recently the discussion began on possible disruption of pulsatile release of endogenous GC due to adverse actions of exogenous GC, as well as in some age-related diseases [62]. It appears

that concepts of allostasis and allostatic load [16,38] should be adjusted, according to new data concerning ultradian GC secretion. An important contribution of mathematical models [63] in such adjustment is highly desirable. Unfortunately, we must underline here that on our opinion, the problem is in the whole biomedical paradigm that should be transformed from homeostatic to homeodynamic one.

And finally, an essential recent review written by an international group of researchers [64] has largely supported the concepts on neuropathology of stress described in the present article, although it suggested their future refinement, especially as referred to the data obtained by means of the latest neuroimaging techniques. On the other hand, another important paper [65] recently discussed the interrelationship between stress and aging, focusing on the necessity of differentiation between "good" and "bad", or hormetic and toxic stress on the basis of establishing the "inflection point" or switch between these two types of stress, thus corroborating in part to a discussion in presented article.

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