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Review

The influence of glucocorticoids on neuronal survival and synaptic function

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Abstract

Glucocorticoids, recognized as stress-related steroid hormones secreted from adrenal glands, have multiple roles in brain function. The concentration of glucocorticoids is regulated by the hypothalamic-pituitary-adrenal axis, and chronically elevated levels of glucocorticoids are putatively involved in the pathophysiology of mental disorders, such as depression. As corticosteroids are also widely used as medical drugs (e.g., for chronic lung disease in infants), the developmental influence of glucocorticoids on neuronal survival and synaptic plasticity is a critical concern. Although many reports suggest a biological effect of glucocorticoids on neuronal populations of the central nervous system (CNS), some reports suggest a possibility that glial responses (including regulation of neurotrophic factor expression) to glucocorticoids are different from that of neurons. In the present review, we show an overview of the current knowledge concerning the impact of glucocorticoids on behavior in animal models of depression, and on cell survival and function in the CNS.

Keywords: brain-derived neurotrophic factor (BDNF); depression; glucocorticoids; glucocorticoid receptor (GR); growth factor.

Introduction

The hypothalamic-pituitary-adrenal (HPA) axis consists of numerous tightly regulated endocrinal steps that control the blood concentration of glucocorticoids. Several molecules and receptors control this system, including the glucocorticoid receptor (GR) located in neuronal regions of the HPA axis. It is speculated that intense and chronic stress results in HPA axis dysfunction with a consequent increase in glucocorticoids that may contribute to the onset of brain diseases including depressive disorders (1, 2). Therefore, the relationship between glucocorticoids and associated receptors and how they influence behavior in animal models of depression is an area of intense research interest. Furthermore, many reports indicate that exogenous glucocorticoid administration leads to depressive- and anxiety-like behaviors in rodent models (3, 4), corroborated by studies using GR gene mutant mice to show alternation in depressive- and anxiety-like behaviors (5, 6). In this review, we provide an overview of the behavioral changes of depressive animals after chronic stress and glucocorticoid administration.

Accumulating evidence including current reports indicate that glucocorticoids and GR exert multiple biological effects on central nervous system (CNS) neurons. In cell survival, glucocorticoid exposure during gestation increases caspase-3-immunoreactivity in the amygdala of rats, although postnatal exposure increases immunoreactivity in only female rats, suggesting sex-dependent differences (7). In addition to this apoptotic etiology, possible influences of glucocorticoids on synaptic plasticity have been shown. For example, it was reported that hippocampal long-term potentiation (LTP) can be modified through GR and mineralocorticoid receptor (MR) functions (8, 9). In the hypothalamic arcuate nucleus, synaptic inputs on proopiomelanocortin (POMC) or neuropeptide Y (NPY) neurons were differently affected by adrenalectomy (ADX) (10). Therefore, glucocorticoids also play a role in the development of synaptic connectivity. Furthermore, recent studies including ours, suggest a possible interaction between growth factors and glucocorticoids. In rat cerebral cortex, mecamylamine, an acetylcholine receptor antagonist, reversed glucocorticoid-stimulated downregulation of brain-derived neurotrophic factor (BDNF), a critical neurotrophin (11). In cultured neurons, acute application of glucocorticoids induced activation of TrkB, a critical BDNF receptor (12), whereas long-term pretreatment with glucocorticoids decreased BDNF-mediated synaptic function (13). In this paper, we also discuss the current knowledge concerning glucocorticoid/GR regulation of cell survival (including neurons and glia), synaptic function and expression of growth factors, as this will contribute to the overall understanding of glucocorticoid influence in the brain.

Stress and HPA axis disturbance

The CNS and several endocrine steps in vertebrates synergize to cope with both physical and psychological 'stressors'. It is well known that the HPA axis plays a key role in coping mechanisms via controlling plasma concentration of corticosteroids (cortisol in humans and corticosterone in rodents). Two neuropeptides, corticotropin-releasing hormone (CRH) and vasopressin (AVP), both secreted from the hypothalamus, stimulate the pituitary gland to secrete adrenocorticotrophic hormone (ACTH) which then induces corticosteroid (glucocorticoids and mineralocorticoids) secretion from the adrenals (Figure 1). Circulating corticosteroids which are assumed to penetrate the blood-brain barrier reach various brain regions, such as the hippocampus, hypothalamus, amygdala, cerebellum and cerebral cortex (14), and bind to their respective receptors including GR and MR. When 'stressors' fade away, feedback loops work to inhibit the HPA axis through GR and MR until corticosteroid levels reach a stable homeostatic point (Figure 1). Indeed, both GR and MR are ubiquitously expressed throughout mammalian brain tissue (14) with high levels of GR mRNA and protein observed in CA1 and CA2 regions of the hippocampus, dentate gyrus, paraventricular hypothalamus, lateral geniculate, amygdala and cerebellum, and high MR mRNA in hippocampal pyramidal cells, dentate gyrus granule cells, lateral septum and amygdala in the squirrel monkey. In addition, measurable amounts of GR and MR mRNA were also detected in the cerebral cortex (14). Interestingly, in the cerebral cortex, different distributions between these two receptors were evident, with GR in all cortical layers, particularly the pyramidal cell-rich layers II/III and V, and MR limited to superficial cortical layers (14). Importantly, MR has a 10-fold higher affinity for glucocorticoids compared to GR (15, 16). Hippocampal levels of GR mRNA are 3- to 5-fold lower than that of MR mRNA in rat (17), squirrel monkey (14) and human tissue (18). Given that a considerable amount of GR is observed in the prefrontal cortex, it is possible that GR in the prefrontal cortex plays a role in the corticosteroid-dependent negative feedback loop in the HPA axis (19).

Accumulating evidence indicates that HPA axis disturbance is strongly correlated with clinical depression. Furthermore, it is reported that the lifetime prevalence of a major depressive disorder with psychotic features is around 0.4% (20, 21),

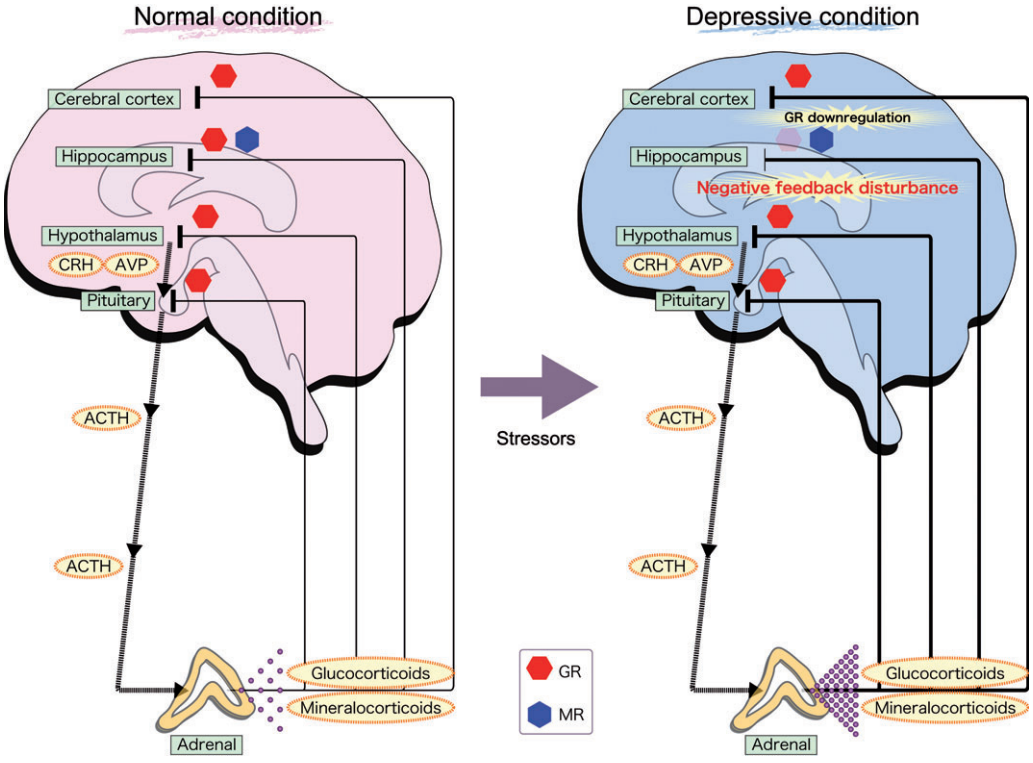

Figure 1 Disturbance in HPA axis feedback loop.
The hypothalamic-pituitary-adrenal (HPA) axis maintains a homeostatic balance in the blood concentration of corticosteroids (glucocorticoids and mineralocorticoids). The hypothalamus secretes corticotropin-releasing hormone (CRH) and vasopressin (AVP), which stimulate release of adrenocorticotrophic hormone (ACTH) by the pituitary. ACTH stimulates the adrenals to produce and secrete two corticosteroids. Increased levels of corticosteroids caused by stressors are returned to basal levels through their receptors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). GR expression was observed in broader regions than MR. The close correlation between chronic change in the plasma concentration of glucocorticoids and GR expression was reported particularly in the hippocampus. It is possible that chronic stress causes dysregulation of the HPA axis, resulting in increased glucocorticoid levels which contribute to the pathophysiology of depressive disorders. Furthermore, it is possible that GR downregulation (particularly in the hippocampus) is closely related to the dysregulation of the HPA axis and depression.

with symptoms including depressed mood, anhedonia and sleep abnormalities (22). When patients are pretreated with oral dexamethasone (DEX, a potent GR agonist) and given an infusion of CRH (namely the DEX/CRH test), a greater increase in ACTH and corticosteroid secretion is observed in those with depressive disorders (1, 2). Recently, Hinkelmann et al. showed that memory functions, such as verbal memory, visuospatial memory and working memory, are impaired in patients with depression whose cortisol levels were significantly higher than healthy subjects (23). Impairments in brain function, therefore, could be caused by HPA axis dysregulation.

Degeneration of hippocampal neurons is caused by sustained administration of glucocorticoids in non-human primates (24). Remarkably, several reports suggest an association between reduced hippocampal volume and depression in humans (25–27). Additionally, in rodents, a possible contribution of GR function in depression was revealed. GR knockout mice using a nestin promoter in which the GR gene was deleted during early development in whole brain tissue showed decreased anxiety-related behavior (5), whereas GR knockout mice with forebrain-specific disruption of GR displayed dysfunction in the negative feedback system of the HPA axis (28). Interestingly, in both GR heterozygous (50% down) and 2-fold GR overexpression mice, significant dysregulation of the HPA axis was revealed through use of the DEX/CRH test (6). As expected, upregulation of GR expression after antidepressant treatment was reported in rat primary cultured neurons (29). Such a positive effect of antidepressants on GR expression was confirmed in the hippocampus and the hypothalamus of rats (30–32). Furthermore, potential use of mifepristone (RU38486), a GR antagonist, for the treatment of major depression has been reported [for a review, see (33)]. Together, all these findings suggest that HPA axis disturbance substantially contributes to the pathophysiology of depression. Because both GR and MR can function as transcription factors, differences in glucocorticoid levels may reflect a change of structure/function of brain tissue after long-term exposure. This is especially true when considering stressful experiences in early life, as this exposure can impact mental health in adulthood (34). In the following sections, we offer an overview of glucocorticoid-induced behavioral changes in depressive animal models, supplemented with current knowledge concerning glucocorticoid regulation on cell survival and synaptic function.

Regulation of GR in an animal model of depression

Several lines of mice with a deficit in HPA axis-related genes show significant alterations in depressive- and anxiety-like behaviors. Both mice that overexpress CRH and are deficient in CRH receptor-2 display exaggerated anxiety-like behavior in the elevated-plus maze and light/dark box tests (35, 36). One of the characteristics of GR knockout mice is the reduced anxiety in the dark/light crossing task and the zero maze test (5). By contrast, depression-like behaviors in the learned-helplessness test are observed in heterozygous GR mutant ($GR^{+/-}$) mice with 50% GR expression levels (6). Time- and forebrain-specific GR knockout mice demonstrate depression-like behavior in the forced swim, tail suspension and sucrose preference tests (28). Interestingly, these three GR knockout mice described above exhibit higher blood concentrations of corticosterone, although their behavioral phenotypes are very different, respectively (5, 6, 28). These different behavioral phenotypes may be attributed to expression levels of GR (total deficient vs. reduced) or to the various brain regions in which GR functions.

Importantly, glucocorticoid administration has been shown to exacerbate depression- and anxiety-like behaviors in four different treatment scenarios: (i) 5 mg/kg prednisone (synthetic glucocorticoid) for 5 days (3), (ii) 20 mg/kg corticosterone for 20 days (4), (iii) 50 mg/kg prednisolone for 6–7 days (37) and (iv) 5 mg/kg corticosterone for 7 weeks (38). Remarkably, it is possible that long-term elevation of glucocorticoids reduces the expression of GR as discussed below leading to the manifestation of anxious and depressive behaviors.

The regulation of GR compounded by stress or glucocorticoid exposure is complex. A transient (less than 1 h) trend of upregulation and significant downregulation (at 2 h) of GR mRNA was found in the hippocampus of rats restrained for 30 min (39). Furthermore, Fujikawa et al. reported significant attenuation (at 30 min) and elevation (at 2 h) of GR mRNA in the dentate gyrus, followed by re-attenuation of GR levels at the end of a 7-h restrain stress exercise in the water (40). Another study lead by Herman and Spencer showed that exposure to 4-day corticosterone that reaches approximately 250 ng/ml in plasma of sham-operated rats caused downregulation of GR translation in the CA1 region of the hippocampus, whereas ADX induces consistent upregulation of GR in CA1, CA3 and dentate gyrus regions of the hippocampus (41). Furthermore, GR downregulation in the hippocampus was shown to occur at 8 h after single corticosterone (2 mg/kg) administration (42). Interestingly, Zhou et al. recently reported a possible role for neuronal nitric oxide synthase (nNOS) in the regulation of GR expression. They found that chronic mild stress enhances nNOS activity, which induces a consequent downregulation of GR via soluble guanylate cyclase/cGMP and peroxynitrite/extracellular signal-regulated kinase (ERK) pathways (43). A summarized list of changes in GR expression after stress or glucocorticoid administration is shown in Table 1.

Glucocorticoids and cell death

Considering that DEX is used for the treatment of chronic lung disease in preterm infants, the neurodevelopmental impairment after long-term treatment is a critical concern. Specifically, many recent studies clearly show that glucocorticoids, including synthetic DEX, induce apoptosis of neuronal populations. Yu et al. showed that DEX exposure causes apoptosis in immature hippocampal neurons via activation of GR, whereas exposure to RU38486, a GR antagonist, prevents the

Table 1 Regulation of GR by stress and corticosterone administration.

Stressor/glucocorticoid treatment	Animal	Affected area	Changes in GR expression	Reference
Restraint for 30 min	SD rat	CA1, CA3, DG	↓ 120 min after single restraint	Paskitti et al., 2000 (39)
Chronic intermittent stress	SD rat	CA3	↓ at 14 and 28 days during chronic stress exposure	Paskitti et al., 2000 (39)
Restraint in the water for 7 h	SD rat	DG	↓ at 30 min during stress exposure ↑ at 2 h during stress exposure ↓ at 7 h during stress exposure	Fujikawa et al., 2000 (40)
ADX and CORT supplement	SD rat	CA1, CA3, DG	↑ 4 days after ADX - 4 days after ADX and CORT supplement	Herman and Spencer, 1998 (41)
ADX and CORT administration	SD rat	Hippocampus	↑ 3 days after ADX ↓ at 8 h after CORT administration	Hügin-Flores et al., 2004 (42)
CORT administration	B6129SF2 mice	Hippocampus	↓ 7 days during chronic CORT administration	Zhou et al., 2011 (43)

ADX, adrenalectomy; CA, Cornu Ammonis; CORT, corticosterone; SD, Sprague-Dawley; DG, dentate gyrus.

DEX effect (44). Additionally, gestational or postnatal exposure to DEX was shown to activate caspase-3, which plays a pivotal role in mechanisms underlying cell death (7). DEX administration was performed either at late gestational age or at postnatal days 4–6. They found that prenatal DEX treatment increased cleaved caspase-3-immunopositive cells in the amygdala of both sexes, whereas postnatal treatment caused an increase of caspase-immunoreactivity of female rats only. An increase in *Bax* mRNA, a proapoptotic molecule, was also confirmed (7).

Generally, as it is difficult to treat patients with neurodegenerative disorders (including Alzheimer's disease and Parkinson's disease) where progressive neuronal cell death is occurring, the emphasis on prevention of such brain diseases is growing. Specifically, current research focuses on dietary restriction (DR) and its potential to reduce risk for neurodegenerative brain diseases (45). Kainic acid (KA), an excitotoxicity drug, stimulates maze learning deficits in rats which were ameliorated following an every-other-day fasting regimen for 14 weeks (46). ADX with a consequent decrease in corticosterone levels (to 30% below that of control) before the DR regimen remarkably enhanced the ameliorating effects of DR, suggesting a possible interaction between DR and glucocorticoids (46). In this system, the beneficial effects of DR were demonstrated in that KA-treated rats showed significant cell death in the hippocampal region, whereas rats with ADX+DR who were also exposed to KA exhibited an increase in neuroprotection and upregulation of pCREB (cAMP-responsive element binding protein) and BDNF expression (46).

The regulation of glial cells by glucocorticoids and the downstream effects on neurodegeneration are also important. ADX causes an increase in both glial fibrillary acidic protein (GFAP) and transforming growth factor-β1 (TGF-β1) mRNA in the dentate gyrus, and these glial genes ultimately play a role in ADX-dependent neuronal apoptosis (47). Recently, astrocyte function after glucocorticoid exposure has been shown. Yu et al. reported that *in vivo* application of DEX caused neuronal cell death but not astroglial cell death in the hippocampus of rats (48). They investigated possible changes in antiapoptotic and proapoptotic markers (activated caspase-3, Bax, Bcl-2, etc.) in both neuronal and astroglial cultures, finding that astrocytes are resistant to glucocorticoid-mediated apoptosis. Furthermore, both BDNF and basic fibroblast growth factor (bFGF) mRNA in astrocytes were increased after exposure to glucocorticoids, although mRNA of nerve growth factor (NGF) was decreased (48). Because it is well known that glial populations produce a variety of growth factors (49, 50) while playing a role in neuroprotection, further study concerning the detailed mechanisms underlying neurotrophic factor expression in glial cells after glucocorticoid administration is necessary.

Glucocorticoids and neuronal plasticity

As mentioned above, in the case of preterm infants, DEX is useful to reduce the risk of chronic lung disease. Therefore, the possible influence of neonatal glucocorticoid exposure on synaptic plasticity is a critical issue and should be clarified. McEwen and colleagues reported that enhancement and reduction of LTP in hippocampal neurons were produced by MR and GR agonists, respectively (8). Furthermore, neonatal treatment with DEX impaired hippocampal LTP, which, in turn, increased long-term depression in adolescent rats (9). DEX administration ultimately induced phosphorylation of the α isoform of calcium calmodulin-dependent kinase II (CaMKII) as well as decreased levels of protein phosphatase 1 (9). Several reports indicate that neonatal DEX treatment induces slow-rate weight gain and impairs hippocampal synaptic plasticity (51, 52). Recently, Hsu and colleagues (53) found that rats reared in small litters consisting of four pups displayed an improvement in both neonatal DEX-induced growth retardation and hippocampal synaptic dysfunction during adulthood (including reduced basal glutamatergic transmission, decreased LTP and increased long-term depression), indicating a correlation between growth retardation and the effects of neonatal DEX treatment on adult synaptic function (53). Considering that CaMKII and protein phosphatase 1 play an essential role in hippocampal LTP regulation (54), discovering the mechanism underlying the function and/or

expression of synaptic molecules (e.g., CaMKII and protein phosphatase 1) throughout growth retardation is very lucrative. By contrast, potentiation of LTP by DEX exposure was reported. In LTP induction by tetanic stimulation using organotypic hippocampal slice cultures, spatiotemporal changes of signal transmission were enhanced by DEX treatment (55). In their system, Gongjin-dan, a multi-herbal formula, reversed DEX action on LTP. Furthermore, they found that significant secretion of NGF, a key neurotrophin in astroglial cells, is induced by the herbal formula (55). Because NGF contributes to the maintenance of CNS functions including regulation of the cholinergic system (56, 57), an investigation of how DEX influences the secretion of NGF is needed for future studies.

Interestingly, it has been shown that corticosterone regulates synaptic properties of POMC and NPY neurons in the hypothalamic arcuate nucleus. By using the electron micrograph technique, Gyengesi et al. examined synaptic input on POMC and NPY neurons following ADX and found that the number of putative 'inhibitory' synapses on POMC neurons was decreased whereas that of putative 'excitatory' synapses on NPY neurons was decreased (10). As a result of the reduced number of inhibitory synaptic inputs, the frequency of mIPSCs (miniature inhibitory postsynaptic currents) and mEPSCs (miniature excitatory postsynaptic currents) recorded from each POMC neuron was decreased and increased, respectively. Postsynaptic regulation by glucocorticoids has also been reported. Using a transcranial two-photon microscope, Liston and Gan observed an increase in spine turnover (formation and elimination of spine) in the barrel cortex of mice after single corticosterone injections as soon as 5 h post-treatment (58). Although it is established that chronic stress indeed alters dendritic morphology and induces spine loss (59, 60), such an acute spine turnover by glucocorticoids in the *in vivo* approach is remarkable.

Although GR and MR are well-known transcription factors regulating expression of many genes, growing evidence suggests that rapid nongenomic functions (without gene expression) of GR and MR are also involved in synaptic function. Di et al. reported that DEX suppressed glutamatergic transmission of magnocellular neurons in the hypothalamus within 10 min while γ-aminobutyric acid (GABA) release was facilitated (61). They also showed that retrograde release of endocannabinoids and neuronal nitric oxide (NO) contributed to the suppression of glutamate release and the facilitation of GABA release, respectively (62). Furthermore, it was reported that DEX rapidly potentiated GABAergic transmission in the CA1 region through membrane-bound GR and NO release from pyramidal neurons (63). The fast nongenomic function of MR that is involved in corticosterone-induced enhancement of glutamate release in CA1 pyramidal neurons was also suggested (64). Taken together, GR modulates synaptic connectivity via transcription regulation and/or nongenomic function.

Growth factor regulation by glucocorticoids

BDNF has been linked to the pathophysiology of depression as well as the mechanism of antidepressant action [for a review, see (65–67)]. As expected, several reports indicate possible glucocorticoid regulation on expression/function of growth factors including BDNF. Regarding the effect on the neurotrophin family and their receptors, early postnatal corticosterone administration in rats results in both NGF and neurotrophin-3 mRNA level increases as well as increases in receptors TrkA, TrkB and TrkC in hippocampal tissue (68). Specifically, glucocorticoid-mediated regulation of BDNF expression *in vivo* is well known. In 1995, Smith et al. found a decrease in BDNF after 2-h restraint stress exposure (69). Upregulation of BDNF mRNA after ADX was also demonstrated in the CA3 field of hippocampal tissue (70). In a later study, ADX-induced upregulation, as well as corticosterone-induced downregulation, of BDNF mRNA in hippocampal subfields was also documented (71). The attenuation of BDNF transcription seems to be most obvious 4 h after corticosterone administration (72). Recently, Park et al. discovered DEX-induced anxiety-like behavior followed by beneficial recovery effects by mecamylamine, an antagonist of nicotinic acetylcholine receptors (11). They clearly showed that rats injected with DEX exhibit increased anxiety-like behavior and decreased levels of BDNF signaling, including phosphorylated extracellular signal-regulated protein kinase (pERK) and pCREB in cerebral cortex, which was ameliorated by mecamylamine administration (11). Using cultured cortical neurons, we recently reported that pretreatment with glucocorticoids inhibits neurotransmitter release and upregulation of synaptic proteins stimulated by BDNF (13, 73). It is well established that BDNF mainly triggers three intracellular pathways following TrkB stimulation, including ERK, phosphoinositide 3-kinase (PI3K) and phospholipase Cγ (PLCγ), and exerts its biological influence on the neuronal population via these intracellular signaling cascades (74, 75). We confirmed that BDNF enhances expression levels of synaptic proteins including glutamate receptors, such as NR2B, and that upregulation of synaptic proteins after BDNF application is dependent on the ERK pathway. Furthermore, BDNF-dependent ERK activation is attenuated by glucocorticoids in cultured cortical neurons (73). In our cortical cultures, marked downregulation of GR protein is induced after chronic DEX application (24–48 h). We observed that BDNF-induced neurotransmitter release is attenuated after such GR downregulation, suggesting that GR plays a role in BDNF-mediated synaptic function (13). We also confirmed that interaction between GR and TrkB plays an important role in BDNF-induced neurotransmitter release from cortical neurons, suggesting an involvement of nongenomic function of GR (13). By contrast, increased activity of TrkB is induced by acute glucocorticoid application. In rats, 6 h after DEX injection and 3 h after corticosterone treatment, activation of TrkB in both hippocampal tissue and cultured cortical and hippocampal neurons occurs, respectively (12). By contrast, the receptor for FGF was not activated by corticosterone stimulation (12). Possible involvement of bFGF in mood disorders is also suggested, in that elevated levels of bFGF may decrease the risk for mood disorder vulnerability including depression (76). As expected, FGF also exerts antidepressant-like effects (77), making the specificity of glucocorticoids on Trk receptor stimulation more interesting.

Recently, BDNF regulation of CRH homeostasis has been reported (78). As mentioned above, CRH is an essential regulator of the HPA axis, regulating levels of ACTH in the anterior pituitary and of glucocorticoids in the adrenal cortex. BDNF induces CRH expression via CREB signaling, whereas glucocorticoids deactivate the CRH increase via neutralizing the function of CRTC2, a CREB coactivator (78).

In multiple sclerosis (MS), in which chronic inflammation of the CNS occurs, corticosteroids are used for treatment. Because demyelination is involved in the pathophysiology of MS, the glial response to glucocorticoids is imperative. Recently, Clarner et al. discovered that DEX and methylprednisolone increase myelin basic protein and proteolipid protein in cultured oligodendrocyte progenitor cells (79). They also showed that DEX induces upregulation of bFGF and platelet-derived growth factor-α in astrocytes, although insulin-like growth factor 1 is downregulated (79). Considering that inflammation is also suggested to contribute to the pathophysiology of depression (80), it may be valuable to investigate how these growth factors (derived from glial cells) influence the HPA axis in depression.

Expert opinion

Considering that dysfunction of the HPA axis is assumed to play a central role in the pathogenesis of depression, understanding the basic mechanisms underlying the negative influence of glucocorticoids on brain function is critical for the development of effective treatments. There are, however, two major barriers impeding progress of this field. First, 'pulsatile' activity of the HPA axis, which produces an hourly 'ultradian rhythm' of oscillatory glucocorticoid secretion and changes its blood concentration periodically (81), may make it more difficult to stably determine exact levels of circulating glucocorticoids. The second problem is sex differences. Although circulating sex steroids, such as estrogen influence HPA axis function, most studies on stress and glucocorticoids on brain function and behavior have been determined by using male animals or humans (82). Ultimately, better understanding of the physiological meaning behind glucocorticoid release and sex differences in HPA axis regulation are required to launch a successful intervention alleviating depressive symptomatology in all individuals.

Stress and the resultant increase of glucocorticoids suppress GR expression in the animal model of depression (Table 1). The marked reduction of GR is also confirmed in an *in vitro* model (13). Thus, the attenuation of GR function and/or GR-inducible genes in the neuronal population may contribute to disease progression, although further studies are necessary. Furthermore, one of the drawbacks of previous studies regarding the role of GR in depression is the lack of anhedonia in the phenotypic milieu of all subjects, as it is a core symptom of major depressive disorder (83). The pioneering studies that reveal a relationship between GR in dopaminoceptor neurons and reward have been reported (84, 85).

The relationship between GR and synapse-related molecules has been a popular topic of current research. Specifically, BDNF function has been extensively studied, as BDNF is essential for synaptic plasticity. Recently, it has been reported that expression of CRH, which influences downstream glucocorticoid levels, is regulated by BDNF (78). Such an *in vivo* approach concerning growth factor contribution in HPA axis regulation is necessary for further understanding of glucocorticoid-related brain diseases. Furthermore, other growth factors, including bFGF, are expected to have beneficial effects against depression (76). In the near future, a functional association between bFGF (derived from glial cells) and glucocorticoids/HPA axis should be clarified to understand the varied presentations of the depressive phenotype.

Outlook

Although we have focused on GR/glucocorticoid function in this review, future research should investigate the biological etiology for the functional differences between GR and MR using both *in vivo* and *in vitro* rodent models. These two types of receptors have different affinities for glucocorticoids and diverse distributions within the brain. Furthermore, new techniques to monitor circulating corticosteroids and growth factors in rodents will allow us to illustrate detailed relationships among these key molecules and changes in brain function which are related to depressive behaviors. Although the role of GR and BDNF in animal models of depression has been elucidated, further study into their interaction is necessary to discover links between these molecules and behavioral outcomes.

Highlights

- A close relationship exists between HPA axis dysfunction and depression. It is possible that resultant increases in glucocorticoid levels due to HPA axis dysfunction play a role in the onset of depressive behavior, and GR contribution is speculated to be highly integral to this process.
- Glucocorticoids influence neuronal survival and synaptic function in the CNS. Generally, long-term exposure with glucocorticoids has a negative impact on survival and synaptic function.
- Glucocorticoid regulation of growth factor expression, including neurotrophins, is very important, as growth factors contribute to cell survival and function in the CNS.
- We suggest that in addition to neurotrophin BDNF, possible interplay between other growth factors and glucocorticoids/HPA axis may be important to fully understand the depressive phenotype.

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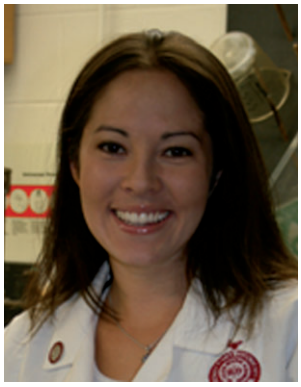

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