Involvement and role of antidepressant drugs of the hypothalamic-pituitary-adrenal axis and glucocorticoid receptor function

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Abstract

Changes in the hypothalamic-pituitary-adrenal (HPA) axis are characteristic of major depression. Because the effects of glucocorticoids are mediated by intracellular receptors including, most notably, the glucocorticoid receptor (GR), several studies have examined the number and/or function of GR's in depressed patients. Review scientific evidences have consistently demonstrated that GR function is impaired in major depression, resulting in reduced GR-mediated negative feedback on the HPA axis and increased production and secretion of corticotropin-releasing hormone (CRH) in various brain regions postulated to be involved in the causality of major depression. Hyperactivity of HPA axis is the main biochemical change, besides disturbed monoaminergic neurotransmission, observed in the patients suffering from a major depression. High incidence of depression in Cushing's syndrome as well as antidepressant effects of adrenocortical enzyme inhibitors in major depression support hypothesis that hyperactivity of HPA axis may be involved in pathogenesis of depression. Major alterations of the HPA axis that can be reversed by successful antidepressant therapy are often seen in depressed patients. A possible explanation for this is that the antidepressant-induced increase in GR's renders the HPA axis more sensitive to glucocorticoid feedback. This new insight into antidepressant drug action suggests a novel approach to the development of antidepressant drugs.

REVIEW

INTRODUCTION

The main driving force for HPA activation is hypothalamic corticotropin-releasing hormone (CRH) acting in synergy with vasopressin, which is produced in either the same or distinct neurons of the paraventricular nucleus, to enhance release of pituitary pro-opiomelanocortin (POMC)-derived peptides (corticotropin [ACTH] and endorphins). Adrenal glucocorticoid hormone secretion (corticosterone in rodents, cortisol in humans) is stimulated mainly by ACTH, although adrenocortical sensitivity to ACTH may be modified by sympathetic innervation of the adrenal gland (Jasper & Engeland, 1994). Different regulatory forces are superimposed on this system to coordinate adrenal secretions during periods of inactivity and stress. The first of these is a circadian rhythm of basal activity derived from the suprachiasmatic nucleus (Casio *et al*. 1987). Stress-induced responses of the HPA axis involve afferent inputs from numerous other brain regions including noradrenergic innervation from the brainstem A1 and A2 cell groups and the pontine locus coeruleus (Szafarczyk *et al*.

1985), the amygdale (Beaulieu *et al.* 1987; Beaulieu *et al.* 1989), cerebral cortex and hippocampus (Jacobson & Sapolsky, 1991). In general, the septum and hippocampus have inhibitory actions on HPA axis activity, whereas the effect of the amygdala is largely permissive. Another regulatory force on HPA axis activity is provided by inhibitory feedback actions of adrenal steroids exerted through corticosteroid receptors located in different brain areas.

Glucocorticoid hormones terminate the stress response by negative feedback action at the level of the pituitary, hypothalamus and limbic brain areas, including the hippocampus, amygdala and septum. This action is mediated by 2 types of corticosteroid receptor that have been identified (Reul & de Kloet, 1985): the type I or mineralocorticoid receptor (MR) and the type II or glucocorticoid receptor (GR). The MR is mainly expressed either alone or together with the GR in hippocampal neurons, whereas the GR is more ubiquitously distributed in the brain (Cintra *et al.* 1994), particularly in neurons. This dual system may be necessary to cope with corticosteroid concentrations ranging from 0.5 nmol/L to 50 nmol/L during the diurnal cycle and up to 100 nmol/L or more in response to stress (de Kloet, 1991). An adequate physiologic response to a wide hormone concentration range can be achieved by these 2 receptors, because the MR mediates the effects of, and possibly controls, low basal circadian levels of circulating glucocorticoids, and the GR appears to mediate the effects of high-stress levels of glucocorticoids and to be responsible for the negative feedback effects of glucocorticoids on the HPA axis (Reul & de Kloet, 1985; de Kloet, 1991; Funder, 1994; Ratka *et al.* 1989; Bradbury *et al.* 1991; Dallmann *et al.* 1989).

HPA AXIS DISTURBANCES IN AFFECTIVE DISORDERS

Hypersecretion of ACTH and glucocorticoids at baseline and several neuroendocrine function tests convincingly indicate profound alterations of the HPA axis in patients with severe depression. Features of affective disorders, secondary to Cushing's syndrome, are also frequently indistinguishable from those of patients with primary psychiatric illness (Regestein *et al.* 1972). This role of the HPA axis in both stress, a major problem of modern-day (and probably past) lifestyles, and its deregulation in mood disorders, which may, at least once during their lifetime, disrupt the lives of up to 15% of the population, underlies the importance of an understanding of the integrated central nervous system mechanisms responsible for HPA axis regulation.

In addition, it is now becoming apparent that many of the beneficial effects of antidepressants could be exerted through their actions on the HPA axis. It is thus imperative to understand how normal HPA axis regulation is disturbed in affective disorders and how antidepressants modulate the HPA axis.

In certain depressed patients, cortisol secretion may be increased and may show an abnormal 24-hour secretory pattern and, unless exogenous CRH is administered, this pattern may be resistant to suppression by exogenous steroids (Carroll *et al.* 1976; von Bardeleben & Holsboer, 1989; Murphy, 1991). Somewhat surprisingly, very similar changes are also seen in the manic phase of bipolar illness (Linkowski *et al.* 1994). Lack of cortisol suppression by dexamethasone in depressed patients could indicate a primary hyperactivity of the adrenal glands rather than a central defect, but recent studies using CRH have eliminated this possibility (Holsboer *et al.* 1984; Holsboer *et al.* 1985; Holsboer *et al.* 1986; Gold *et al.* 1984). A key role of elevated CRH secretion in the development of depression is indicated by both clinical (Holsboer *et al.* 1992) and preclinical (Dunn & Berridge, 1990; Owens & Nemeroff, 1991) studies. In patients with depression, elevated concentrations of CRH in the cerebrospinal fluid (Nemeroff *et al.* 1984), increased numbers of CRH-containing cells in the paraventricular nucleus (Raadsheer *et al.* 1994), decreased CRH binding in the frontal cortex (Nemeroff *et al.* 1988) and a blunted ACTH response to an intravenously administered test dose of CRH (Holsboer *et al.* 1986; Gold *et al.* 1986) have been seen. These results are thought to reflect the desensitization of CRH receptors at corticotrophic cells and/or a restricted secretory response of ACTH to CRH caused by elevated basal cortisol levels. The latter mechanism is probably the most important, underscored by a normalized net ACTH output in patients with depression pretreated with metyrapone (von Bardeleben *et al.* 1988; Lisansky *et al.* 1989). Despite a blunted ACTH response to CRH, the associated cortisol response is unchanged, because ongoing HPA overactivity gradually produces adrenocortical hyperplasia rendering the gland hypersensitive to ACTH. Other non-ACTH mechanisms such as neural sympathetic factors or humoral factors from the immune system may also contribute to the dissociation between ACTH and cortisol in depression.

INVOLVEMENT OF HPA AXIS HYPERACTIVITY IN PATHOPHYSIOLOGY OF DEPRESSION

Some changes observed in depression, especially those affecting noradrenergic, serotoninergic and excitatory amino acid neurotransmission may be evoked or enhanced by the elevated concentrations of glucocorticoids and/or CRH. For example in rats, corticosterone-induced changes in serotonin receptors (decreases in 5-HT_{1A} receptor level and function, increases in 5-HT_{2A} receptor function) are similar to the changes observed in depression, and opposite to the effects induced by antidepressant drugs (Bagdy *et al.* 1989; Coppen & Doogan, 1988; Kuroda *et al.* 1992; Meijer & de Kloet, 1994; Young *et al.* 1992). It has been also found that high level of corticosterone increased concentra-

tion and action of glutamate, especially enhancing glutamate-induced atrophy of the hippocampal CA3 pyramidal neurons (Elliott & Sapolsky, 1991; Lowy *et al*. 1993; Magarinos *et al*. 1997; Watanabe *et al*. 1992). This fact deserves special consideration since recently it has been postulated that progressive neuropathological alterations may be responsible for the development of depression. Moreover, in HPA-hyperactive transgenic mice (with reduced glucocorticoid receptors expression mainly in neuronal tissue), some behavioural changes such as impairments in food consumption, sleep, learning and memory are observed (Montkowski *et al*. 1995; Pepin *et al*. 1992a; Rousse *et al*. 1997).

NORMALIZATION OF HPA AXIS ACTIVITY AND GR CONCENTRATION BY ANTIDEPRESSANTS

A dysfunction of the HPA axis is corrected during a clinically effective therapy with antidepressant drugs (Heuser *et al*. 1996; Holsboer & Barden, 1996; Nikisch *et al*. 2005b), while persistence of dexamethasone non-suppression is often associated with the risk of relapse or the lack of improvement. To explain the mechanism responsible for such a normalizing effect of antidepressant drugs, the modulation of the corticosteroid receptor system in the brain regions involved in the control of the HPA axis activity has been postulated (Pepin *et al*. 1989). The hypothesis suggesting that antidepressant drugs may exert their clinical effects (at least on HPA axis) through direct modulation of GR is supported by the fact that most of these drugs increase the level of GR in CNS.

Also the effect of antidepressant drugs on GR and MR concentration was studied in rodents, especially in rats. It has been found that long-term administration of some antidepressant drugs increases the GR mRNA and GR protein level mainly in the hippocampus (Pariante & Miller, 2001). Up-regulation of GR was observed also *in vivo* in other brain structures, e.g. in the hypothalamus, anterior pituitary and locus coeruleus (Pariante & Miller, 2001) and *in vitro* in the cerebral cortex and amygdala (Pepin *et al*. 1989), but the hippocampus remains the most thoroughly examined structure in which GR up-regulation occurs. This region is known to contain the highest levels of corticosteroid receptors, which are involved in negative feedback inhibition of the HPA axis activity, in learning and memory processes and in hippocampal neuronal survival. Chronic treatment with tricyclic antidepressants (imipramine, amitriptyline), the selective noradrenaline reuptake inhibitors (reboxetine, desipramine), electroconvulsive shock (a non-drug therapy of depression) and lithium (which is known to augment the clinical effects of medication in depressed patients) increases GR expression in the rat hippocampus (Pepin *et al*. 1989; Budziszewska *et al*. 1994; Peiffer *et al*. 1991; Przegaliński *et al*. 1993a,b; Seckl & Fink, 1992). In contrast, selective serotonin reuptake inhibitors (fluoxetine, citalopram, zimelidine) and a new antidepressant drug, tianeptine (an enhancer of serotonin reuptake) have no effect on GR level (Holsboer & Barden, 1996; Pariante & Miller, 2001; Holsboer, 2000). Tianeptine potently inhibits HPA axis activity, but not by increasing GR level or enhancing feedback mechanism, but probably by direct action on CRH synthesis and/or secretions. Selective serotonin reuptake inhibitors also seem to act on HPA axis activity not *via* GR up-regulation, but by other mechanism, e.g. by increasing MR level, by enhancing corticosteroid receptor function or by direct action on CRH release. The majority of studies evaluating the effect of antidepressants on corticosteroid receptors have been focused on GR, but the involvement of MR cannot be completely excluded. It is known that MR regulate the corticosterone release not only under basal conditions, but they are also involved in the stress-induced feedback mechanism (Ratka *et al*. 1989). The elevated level of the functional MR was found after electroconvulsive shock, while antidepressant drugs usually increased MR mRNA, but not MR protein (Budziszewska *et al*. 1994; Przegaliński *et al*. 1993b; Seckl & Fink, 1992). This fact suggests that antidepressants increase not only the biosynthesis of MR, but also their degradation and turnover. Selective serotonin reuptake inhibitors (fluoxetine, citalopram), which are without effect on GR level, have been shown to increase MR mRNA in the rat hippocampus (Pariante & Miller, 2001).

The increased level of glucocorticoid receptors in CNS should lead, by enhancing feedback mechanism, to the inhibition of HPA axis activity, e.g. to a decrease in blood ACTH and corticosterone level. However, acute administration of most antidepressant drugs leads to the activation of the HPA axis in humans as well as in laboratory animals. Tianeptine is the only antidepressant drug, which inhibits HPA axis activity just after single administration (Watanabe *et al*. 1992; Holsboer & Barden, 1996). In contrast to acute effects, long-term administration of antidepressans decreases ACTH and corticosterone level in blood and CRH concentration in the hypothalamus (Holsboer & Barden, 1996; Brady *et al*. 1991; Fadda *et al*. 1995). Such suppressive effect on HPA axis activity was demonstrated in rats both under basal and stress conditions for the most of antidepressant drugs, e.g. tricyclic antidepressants, MAOI, tianeptine. Selective inhibitors of serotonin reuptake (fluoxetine, citalopram) did not change corticosterone level in rats, but in men fluoxetine and citalopram decreased CRH and AVP levels in the cerebrospinal fluid (de Bellis *et al*. 1993; Nikisch *et al*. 2005a). The effects observed after acute and long-term administration of antidepressant drugs are sometimes opposite. Since therapeutic effects of these drugs can be observed only after 2–3 weeks of treatment, long-term adaptive changes are more important for their mechanism of action. An increase in GR level and inhibition of HPA axis activity are observed only after their long-term

administration, so they are probably more important for therapeutic action of antidepressants.

MECHANISM OF ANTIDEPRESSANT DRUG ACTION ON GR GENE TRANSCRIPTION

Mechanism of antidepressant-induced changes in GR concentration remains unknown as yet. Antidepressants are known to modify noradrenergic and serotoninergic neurotransmission, and both these systems have been found to influence the hippocampal GR density. Serotonin and agonists of 5-HT_{2A} receptor increase density of GR in the hippocampal cell culture (Mitchell *et al*. 1990). Moreover, *in vivo* experiments have shown that a lesion of the 5-HT system decreases corticosterone binding in the rat hippocampus (Siegel *et al*. 1983). Sparse and inconsistent data show that noradrenaline also increases GR number (Maccari *et al*. 1990). Therefore, the increase in the GR level induced by antidepressant drugs may be connected with their actions on the monoaminergic systems. On the other hand, some recent data have indicated that the action of antidepressants on GR number is independent of their action on monoaminergic neurotransmission. The lack of effect of a selective inhibitor of noradrenaline uptake (+)-oxaprotiline and selective inhibitors of serotonin uptake (citalopram, fluoxetine) indicates that the action of tricyclic antidepressants on GR level is rather not connected with their influence on monoamine concentrations (Pariante & Miller, 2001). Moreover, amitriptyline, desipramine and maprotiline have been shown to increase the GR mRNA level also in cell cultures, which do not contain monoaminergic neurons (Pepin *et al*. 1989). Rossby *et al*. have demonstrated that desipramine induces GR up-regulation both in the control and in the rats after noradrenergic neuron lesion (Rossby *et al*. 1995). Furthermore, since desipramine increases the activity of GR gene promoter, it has been suggested that antidepressant drugs can act directly at the genomic level (Pepin *et al*. 1989).

RATIONALE AND THE EFFECT OF ANTIDEPRESSANT DRUGS ON GR FUNCTION

Apart from increasing GR concentration, antidepressant drugs have been shown to affect GR function. Effects of antidepressants and glucocorticoids are often opposite. They regulate some neurotransmitter receptors (5HT_{1A} and 5-HT_{1B}; ß-adrenergic) in different way. Moreover, corticosterone or stress decrease the level of brain-derived neurotrophic factor (BDNF) which has antidepressant effect, while antidepressant drugs stimulate this neurotrophin and block the effect of stress (Holsboer, 2000; Nibuya *et al*. 1995). Antidepressant drugs also inhibit some other changes evoked by glucocorticoids or stress, e.g. neurodegenerative changes in the rat hippocampus and increased TRH content in the hypothalamic neurons (Watanabe *et al*. 1992; Jackson & Luo, 1998). Since antidepressant drugs have been shown to act on gene transcription (Schwaninger *et al*. 1995), recently their effect on GR-mediated gene transcription was evaluated. GR is a hormone-activated transcription factor which binds to the specific DNA sequence (*glucocorticoid responsive element, GRE*) and acts as regulator of genes expression. The GR-mediated gene transcription can be modulated by cAMP/protein kinase A-, phospholipase C/protein kinase C and the Ca^{2+}/calmodulin-dependent protein kinase-mediated signal transduction pathways, whose activities are affected by antidepressant drugs. The action of GR *via* binding to GRE is the most important, classic effect of glucocorticoid hormones, yet some their effects on gene transcription are due to the action of GR on transcription factors bound to other DNA sequences (CRE, AP-1, NF_KB). Glucocorticoids inhibit the effect of cAMP/protein kinase. A pathway activation on the CRH gene by feedback mechanism, acting on transcription factor bound to *cAMP-responsive element* (fosfo-CREB) (Itoi *et al*. 1996; Legradi *et al*. 1997).

Decreasing effect of antidepressants on the CRH level in the PVN of the hypothalamus is belived to be evoked by increasing the density of GR in the hippocampus and enhancing feedback mechanism. However, the effect of antidepressants on the action of glucocorticosteroids on CRH gene regulation was not determined yet. Instead, the effect of antidepressant drugs on GR-mediated gene transcription, produced by influencing the sequence specific for glucocorticoid hormones (e.g. *via* binding to GRE) was examined. The first two studies showed that an antidepressant drug, desipramine, could directly affect GR-mediated gene transcription (Pariante *et al*. 1997; Pepin *et al*. 1992b). However, this drug acts in both directions, depending on experimental conditionits, e.g. on the concentration and time of it's and dexamethasone presence in the medium and on the presence or absence of steroids in serum added to the incubation medium. More recently, we have demonstrated that various antidepressants (imipramine, amitriptyline, desipramine, fluoxetine, tianeptine, mianserin, moclobemide), inhibit the corticosterone-induced gene transcription in a concentration- and a time-dependent manner (Budziszewska *et al*. 2000). These data show that antidepressant drugs inhibit the HPA axis activity in two different, independent ways. They increase the GR level in the CNS and enhance the GR-mediated feedback inhibition, which leads to a decrease in the corticosterone level. Apart from lowering the corticosterone level, they are able to inhibit corticosterone receptor-mediated transcription of some genes.

Antidepressant drugs capable of affecting the GR-induced gene transcription can act on different processes connected with GR action, such as the binding of hormones with receptors, dissociation of the steroid-receptor complex from other cytosol proteins, translocation the hormone-GR complex from cytoplasm to

the nucleus, phosphorylation of GR, binding to DNA and modulation of the transcription complex. The data on the effects of antidepressant drugs on these processes are sparse. Pariante *et al*. found that desipramine induced GR translocation and potentiated the dexamethasone induced GR translocation (Pariante *et al*. 1997), but effects of other antidepressant drugs have not been determined. Budziszewska *et al*. indicated with their study that imipramine inhibited the binding of the corticosterone-receptor complex to DNA (Budziszewska *et al*. 2000). Moreover, the mechanism of antidepressant drug action on GR-mediated gene transcription has been studied mainly in fibroblast cell line, so it is unknown if similar mechanism operates also in neurons. Inhibition of corticosterone receptor mediated gene transcription by antidepressants could explain some effects of these drugs on genes with GRE sequence (e.g. $ß_1$-adrenergic receptor, TRH, GH and prolactin).

Further studies of the mechanism of HPA axis disturbance and antidepressant drug action on GR and CRH functions can lead to improvement of treatment of major depression. Some recent clinical studies revealing that the inhibitors of cortisol synthesis (metyrapone, ketoconazole, aminoglutetimide) and CRH_{1R} receptor antagonist show antidepressant effect (Murphy, 1997; Holsboer, 2000; Holsboer & Ising, 2008; Binnemann *et al*. 2008; Erhardt *et al*. 2009), may pave the way for the development of still more effective pharmacotherapies of depression.

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