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PHARMACOLOGICAL MODULATION OF HPA AXIS IN DEPRESSION – NEW AVENUES FOR POTENTIAL THERAPEUTIC BENEFITS

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SUMMARY

One of the most consistent biological findings in major depression (MDD) is the altered activity of the hypothalamic-pituitary-adrenal (HPA) axis. It is not surprising that glucocorticoid receptor (GR), the common mechanism for stress-related changes in brain function, is a potential target of antidepressant drugs and therapies. All effective antidepressant treatments should trigger and maintain GR-related cellular processes necessary for recovery from MDD. Classic antidepressants act indirectly, by affecting the dynamic interplay between serotonin neurotransmission and HPA. On the other hand, certain compounds acting at supra-hypothalamic, HPA axis, glucocorticoid receptors, and post-receptor levels are being considered as new therapeutic options with the potential to modulate the aforementioned system in affective disorders directly.

Different classes of drugs pharmacologically modify the HPA axis. This article summarizes the efficacy of classic anti-depressants, as well as drugs classified as "antiglucocorticoids" (GR agonists, GR antagonists, dehydroepiandrosterone- DHEA, steroid synthesis inhibitors drugs, etc) in their capacity to heal glucocorticoid-mediated damage in depression. New avenues investigating the potential therapeutic benefits of antiglucocorticoids in affective disorders are at the proof-of-concept stage and future developments in this area deserve the full attention of psychiatrists and neuroscientists, as the current pharmacological treatment of MDD is far from perfect.

Key words: *depression – HPA – glucocorticoid – antiglucocorticoid - antidepressant*

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HPA AXIS, TRAUMA AND DEPRESSION

The HPA axis is an integral part of the endocrine system that regulates the response to external stressors by providing energy and focusing attention. The end products of HPA axis activity, glucocorticoids (GCs), regulate many physiological functions and play an important role in affective regulation and dysregulation. Events that sensitize the HPA axis in utero including maternal stress, and early bereavement or abuse in childhood, lead to a higher risk of developing MDD later in life. The potential mechanisms of the above mentioned processes include epigenetic factors such as methylation of the glucocorticoid receptor gene (NR3C1) which affects cortisol sensitivity (Oberlander et al. 2008, Perroud et al. 2011). Regarding behavioral phenotypes, negative childhood experiences are causally linked to later depression since they may lead to a negative evaluation of self (the personality trait of neuroticism - perhaps better understood as "negative emotionality" - is a well recognized risk factor of major depression) and difficulties with core relationships (Bifulco et al. 1998). According to Nater et al. (2010), higher scores in neuroticism were associated with higher levels of cortisol. Neuroticism is suggested to exert its effect via increased basal HPA axis activity (as indicated by high cortisol levels over a period of time), which might lead to allostatic load and, ultimately, to dysfunction not only in affective regulation, but also in metabolic, immune, and cardiovascular systems (Chrousos 2009).

This is in line with an illness model of depression in which the stimulus (i.e. time-dependent risk factor) continues to have an impact even when no longer present. In this model there is an immediate increase in the risk of illness following application of a stimulus; once ill however, removing the risk factor does not necessarily lead to restitution (Bottomley et al. 2010). Therefore, we need to look for treatment strategies that provide HPA functional restitution and promote resilience. Resilience is defined as the ability to maintain a state of normal equilibrium in the face of extremely unfavorable circumstances.

Clinical studies assessing the glucocorticoid receptor (GR) function with other cellular processes that influence the receptor gene expression and its action as a transcription factor are very scarce. Transgenic animals with partial impairment of GR function show behavioral changes consistent with MDD (Claes 2009a). This makes the GR gene a prime candidate for research into the genetic and epigenetic background of MDD. It is very important to evaluate how changes in GR activation and its modification induce and reflect depressive symptoms, and how alterations of receptor activity could be used as a “biomarker” of vulnerability to depression, depressive status and subtypes of

depression (Simic et al. 2013a,b, Freeborough & Kimpton 2011). On the other hand, question arises as to how GR related cellular dynamics modulate antidepressant effects, could they be used to predict drug or other treatment response, and whether there are possibilities to use HPA related parameters in regard to clinical prognosis, treatment outcome, etc.

It is not surprising that GR, the common mechanism for stress-related changes in brain function, is an important target of antidepressant drugs and therapies. All effective antidepressant treatments should trigger and maintain GR-related cellular processes necessary for recovery from MDD, as literature suggests that hyperactivity of the HPA-axis predicts a worse treatment outcome (Brouwer et al. 2006). The action of classic antidepressants on the HPA axis is considered indirect, as it is based on the dynamic interplay between serotonin neurotransmission and HPA axis. Additionally, certain compounds acting at supra-hypothalamic, HPA axis, glucocorticoid receptor and post-receptor levels are being considered as new therapeutic options which operate more directly on HPA-axis related domains to reduce vulnerability to depression and increase cellular (molecular) resilience.

PHARMACOLOGICAL MODIFICATION OF HPA AXIS

Antidepressants

Interaction between brain serotonergic systems and the HPA axis may be relevant to the outcome of therapy in depression (Maric & Adzic 2013).

Preclinical research has shown that antidepressants can enhance glucocorticoid sensitivity in rat brains and may restore GR-mediated feedback inhibition of the HPA-axis (Peiffer et al. 1991, Okugawa et al. 1999). The results from Anacker et al. (2011) demonstrated a bidirectional influence of antidepressants i.e. both a decrease and increase of GR-mediated gene transcription, and such changes were dependent on the cell type. The authors explained these findings by different second-messenger signaling mechanisms affected by antidepressants in different experimental conditions, which opens the question as to how the aforementioned groups of pharmacological agents regulate GR-related phenomenology. In addition, the authors noticed that short-term in vitro incubation with antidepressants leads to activation of GR translocation, which in turn leads to acute downregulation of GR expression, which can then be measured functionally as reduced GR function (Pariante et al. 1997, Pariante et al. 2003a,b). Therefore, it is possible that short-term antidepressant treatment leads to GR downregulation and concomitant reduction in its function. However, such GR downregulation was transient, and was followed by GR upregulation upon chronic treatment (Lai et al. 2003, Yau et al. 2001). The potential mechanisms included a number of receptor mechanisms, ranging from nuclear translocation, phosphorylation dependent differences in co-factor recruitment and gene transcription.

It is not surprising therefore that the latest research on antidepressive effects is being devoted to mechanisms involved in the regulation of GR function. A recent study from Italy, in which an animal model was used to evaluate the effect of an antidepressant on GR-FKBP (FK506 binding protein) and on receptor phosphorylation in the hippocampus (ventral and dorsal) and prefrontal cortex of rats exposed to chronic mild stress (CMS), showed that while animals exposed to CMS had increased expression of FKBP5 as well as enhanced cytoplasmic levels of GR, chronic treatment with the antidepressant duloxetine normalized these alterations, mainly in the prefrontal cortex (Guidotti et al. 2013). These results clearly indicate that GR-related changes could be relevant to depressive symptomatology, but also point out the ability of antidepressants to correct some of these alterations which in turn may contribute to the normalization of HPA axis dysfunctions associated with stress-related disorders, FKBP5 is protein involved in immunomodulation; interestingly, its SNPs - single nucleotide polymerphisms - interact with childhood trauma to predict the severity of adult PTSD (Binder et al. 2008).

When similar research has included human subjects (Pariante et al. 2012), results suggest that GR activation by antidepressants and the subsequent decrease in GR-mediated effects in the presence of GR agonists does indeed occur in the human brain. Namely, pretreatment with citalopram decreased the ability of cortisol to impair working memory: cortisol-induced increases in working memory errors were higher after placebo than after citalopram. The authors concluded that the results were consistent with the notion that citalopram treatment activated GR translocation, inhibiting the functional consequences of subsequent cortisol administration.

In regards to different types of antidepressants, it is useful to consider work from the UK group (Carvalho et al. 2010). Firstly, the authors demonstrated that antidepressants with different mechanisms of action (clomipramine, amytriptiline, sertraline, paroxetine and venlafaxin) all inhibited glucocorticoid receptor function in whole blood cells in a group of healthy volunteers. Additionally, when compared to actions of antipsychotics (haloperidol and risperidone), only antidepressants had an effect on GR function. Similar findings demonstrating a lack of influence of most antipsychotics on cortisol in patients with depression were recently reviewed by Sagud et al. (2011).

In summary, evidence that antidepressants modulate GR is mainly taken from animal studies and there is little direct evidence of such modulation in humans. How antidepressants actually induce changes in GR function in patients, and how these changes affect brain function, mood and cognition needs to be evaluated further. The importance of HPA axis dysregulation for the short-term efficacy of antidepressants is still a

matter of debate. The most important question arises from the field of personalized medicine: which GR activity-related parameter or combination of parameters, easily accessible from peripheral blood, might be a valid and relevant predictor of response to a particular antidepressant and its short as well as long-term efficacy?

According to Brouwer et al. (2006), the first to investigate GR polymorphisms in relation to both treatment outcome and HPA activity in MDD, carriers of Bcll polymorphism (one of three GR gene polymorphisms of clinical relevance) with high ACTH after CRH in DEX/CRH test (the dexamethasone-suppressed CRH test) have less decrease in HAMD scale scores and lower response rates to paroxetine than patients with lower ACTH levels. The study lasted 8 weeks and the results suggested that a combination of high ACTH levels after CRH, and the presence of Bcll polymorphism predicted non-response to antidepressant drugs better than either of these factors alone. Similar evidence for a role of HPA, GR activity, GR polymorphism and its methylation status in the neurobiology of MDD and in response to available drugs should accumulate rapidly.

GR antagonist – Mifepristone

Mifepristone (RU-486) blocks progesterone and, at higher doses, glucocorticoid receptors. It is a "specific glucocorticoid receptor antagonist" and partially or completely inhibits (antagonizes) the binding of GR agonists. After administration of mifepristone, GR numbers increased rapidly (within hours), which may restore normal feedback, thus 'resetting' the HPA axis. A brief period of treatment with the antagonist may be adequate for restoring normal HPA axis function (McIsaac et al. 2009).

Mifepristone has been evaluated both as augmenttation and as monotherapy in the treatment of major depression, mostly the psychotic subtype (PMD). In a group of in-patients with psychotic depression and HAMD-21 scores of 18 or greater, one week augmenttation of current medications with 600 or 1200 mg RU-486 produced only mild and sporadic side effects, and significant reductions in the Brief Psychiatric Rating Scale and HAMD-21 were evident. Eight of the 19 patients had a 50% decline in the HAMD-21, compared with 2 of 11 in the 50-mg group (Belanoff et al. 2002). Similar findings were replicated in a study in which a group of patients was taking neither conventional antidepressant nor antipsychotic medications. A seven day course of mifepristone followed by usual treatment appears to be effective and well tolerated in the treatment of psychosis in PMD (DeBattista et al. 2006).

In the pilot study (Young et al. 2004) for treatment-resistant bipolar disorder, a selective improvement in neurocognitive functioning and significant improvements in mood symptoms were observed following treatment with RU-486 compared with placebo. The improvement in cognition was inversely correlated with basal cortisol levels, adding to the plausibility that this was an antiglucocorticoid effect. This data requires replication.

Mifepristone may be efficacious in part by reducing glucocorticoid enhancement of CRH action in neurons in the central nucleus of the amygdala and other structures outside the neuroendocrine hypothalamus. Interestingly, mifepristone has been proposed for the treatment of delirium and its efficacy is under evaluation (Belanoff 2012).

Corcept Therapeutics Inc. has been developing mifepristone (as C-1073, Corlux), an orally available progesterone and glucocorticoid antagonist originally launched as an abortifacient by Aventis Pharma AG, for the potential treatment of the psychotic features of psychotic major depression (PMD) and for Alzheimer's disease (AD). However, in 2006-2007, some trials failed to meet their endpoints (Nihalani & Schwartz 2007), but phase III trials for the treatment of the psychotic features of psychotic major depression (PMD) began in 2009 and is ongoing.

GR-agonists – Dexamethasone

The synthetic glucocorticoid dexamethasone (Dex) blocks stress-induced hypothalamic-pituitary-adrenal (HPA) activation primarily at the level of the anterior pituitary. Findings from deKloet group (Karssen et al. 2005) suggest that treatment with small amounts of Dex can produce a hypocorticoid state selectively in the brain with a concomitant modestly increased glucocorticoid action in the periphery. This finding supports the concept that, using the right conditions, the partial exclusion of Dex from the brain combined with the suppression of peripheral pituitary-adrenal activity can create the state of a central hypocorticoid condition.

In male Wistar rats a low dose of Dex reverted anhedonia, normalized adrenal gland weight and body weight, corticosterone and ACTH levels, and decreased memory impairment, demonstrating that low doses of Dex for moderate periods may be beneficial for depressive-like parameters and memory impairment, at least in animals (Cassol-Jr et al. 2010).

In a clinical study from Arana et al. (1995) 37 outpatients meeting DSM-III-R criteria for major depressive disorder were randomly assigned to receive either placebo or 4 mg/day oral Dex for 4 days, baseline HAM-D scores were compared with scores obtained 14 days after. Seven (37%) of the 19 patients given Dex, and only one (6%) of the 18 patients given placebo responded positively. No adverse events or side effects were reported. Authors concluded that a brief course of oral Dex is effective and safe for the treatment of depression. According to the authors, Dex given at doses of 3-4 mg for 4 days has putative antidepressant effects. This effect is exerted at the level of the pituitary gland, as at this dose Dex does not enter the CNS and central GR (Karssen et al. 2005, McIssac et al. 2009).

Similarly to mifepristone, Dex was evaluated for its efficacy in preventing delirium. In a cardiac surgery unit setting, one group of patients (dexamethasone group) took 8 mg Dex before induction of anesthesia, followed by 8 mg every 8 hours for 3 days. The other group received placebo in the same way. Results showed that in the first post-operative day delirium, extubation time, and intensive care unit length of stay significantly decreased in the dexamethasone group without an increase in any serious complications (Mardani & Bigdelian 2012).

Selective modulators of GR actions

Recently, a high-affinity GR ligand C108297 with a selective modulation role in rat brain was discovered. C108297 treatment induces a unique interaction between GR and its downstream effector molecules, the nuclear receptor coregulators, compared with the full agonist dexamethasone and the antagonist RU486 (Zalachoras et al. 2013). C108297 displays partial agonistic activity by suppressing hypothalamic corticotropin-releasing hormone (CRH) gene expression and potently enhances GR-dependent memory consolidation of training on an inhibitory avoidance task. Conversely, it lacks agonistic effects on the expression of CRH in the central amygdala and antagonizes GR-mediated reduction in hippocampal neurogenesis after chronic corticosterone exposure and does not lead to disinhibition of the HPA axis. In summary, C108297 belongs to a class of ligands that have the potential to more selectively reduce pathogenic GR-dependent processes in the brain, while retaining beneficial aspects of GR signaling (Zalachoras et al. 2013). These preliminary findings shed light on a promising field in GCs therapy, however preclinical and clinical research in depression and stress related disorders is urgently needed.

Ketoconazole and metyrapone

Among agents that are expected to potentiate the efficacy of ADs are inhibitors of glucocorticoid synthesis. The 11-HSD (11-hydroxylase) inhibitors are a very interesting class of drugs, since they can treat the over-production of cortisol both at central (hippocampal) and peripheral (splanchnic) sites (Martocchia et al. 2013). These compounds act by decreasing cortisol synthesized in hepatic and adipose tissue and therefore reduce tissue-specific gluconeogenesis and fatty acid metabolism. However, there is concern that a reduction in tissue-generated cortisol might decrease feedback to the hypothalamic-pituitary-adrenal (HPA) axis resulting in an upregulation of cortisol. Theoretically, a combination of a glucocorticoid synthesis inhibitor and an antidepressant drug could help reduce the required doses of 11 HSD inhibitors and consequently their side-effects.

Ketoconazole (KTZ) is a widely used antifungal agent. KTZ inhibits various enzymes in adrenal cortisol synthesis and is effective in treating hypercortisolemia, but its use is limited due to toxicity. Side effects of the drug include nausea, pruritus, and transient elevations of liver enzymes, with occasional severe hepatotoxicity (Sonino 1987).

There is some evidence suggesting KTZ use to modify the activity of the HPA axis in MDD. Sovner and Fogelman (1996) presented a case report of two patients with atypical depression that responded to ketoconazole 400 mg/day after proving resistant to, or intolerant of, several conventional antidepressants. In contrast to those findings, Amsterdam and Hornig-Rohan (1993) observed no responders in 10 patients with refractory depression treated with KTZ. However, Wolkowitz et al. (1999a) found that KTZ (compared to placebo) was associated with improvements in depression ratings in hypercortisolemic, but not in non-hypercortisolemic patients. The authors also reported that ketoconazole was generally well tolerated and did not cause any significant side effects or laboratory abnormalities during this 4-week long trial. The hormonal changes found (decreased dehydroepiandrosterone and testosterone levels and increased pregnenolone and pregnenolone-sulfate levels) were consistent with enzymatic blockade of C17,20-lyase, 11-hydroxylase (11 HSD), and 17-hydroxylase.

Metyrapone is a drug used in the diagnosis of adrenal insufficiency and occasionally in the treatment of Cushing's syndrome (hypercortisolism), with moderate side effects on gonadal hormone levels. It blocks cortisol synthesis by inhibiting the steroid 11HSD. Side effects are primarily gastrointestinal, and long-term use can be associated with hirsutism (due to accumulation of androgens) and hypertension (due to accumulation of mineralocorticoids) (Miller & Crapo 1993).

In an animal study of metyrapone with fluoxetine, it was shown that this drug combination significantly increased the levels of extracellullar DA metabolites (3,4-dihydroxyphenylacetic acid, homovanillic acid) and a 5-HT metabolite (5-hydroxyindoleacetic acid) than fluoxetine alone (Rogóż & Gołembiowska 2010). Among other mechanisms, increased levels of extracellular DA and 5-HT metabolites may play a role in the enhancement of fluoxetine efficacy by metyrapone, and may be of crucial importance to the pharmacotherapy of drug-resistant depression.

In a study evaluating the effects of adding metyrapone to standard SSRI regimens, it was shown that this combination of drugs induced a more rapid, efficacious and sustained treatment response in MDD than SSRI alone (Jahn et al. 2004). Patients with major depression received metyrapone for 3 weeks (during a 5-week trial) in addition to nefazodone or fluvoxamine. Metyrapone accelerated the onset of antidepressant action, and its efficacy was sustained during the period of observation.

In the future, we can expect more from clinical trials with metyrapone (500 mg twice daily), that recruit depressed patients not responding to standard treatment (Martocchia et al. 2013).

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a hormone produced by the body's adrenal glands. The body uses DHEA to make androgens and estrogens, the male and female sex hormones. Because levels of DHEA decline with age, the question arises if DHEA could work as an anti-aging treatment. DHEA can produce unwanted side effects such as lowering levels of HDL "good" cholesterol in the body, and raising levels of testosterone as well as estrogen. In addition, DHEA exerts numerous other functions including the modulation of multiple neurotransmitter systems, and the regulation of pro-inflammatory cytokines such as tumor necrosis factor alpha and interleukin-6 which have been shown to be involved in MDD (Claes 2009b). Long-term exposure to DHEA affects the transcriptional activity of the glucocorticoid receptor (Saponaro et al. 2007).

One randomized controlled trial with 22 MDD subjects (Wolkowitz et al. 1999b) reported that DHEA (maximum dose=90 mg/day, treatment duration 6 weeks) is an effective antidepressant, and its efficacy was confirmed later on by Schmidt et al (2005). Schmidt and coauthors (2005) also conducted a 6-weeks trial of DHEA administration and found a significant improvement in the HAMD-17 compared with placebo treatment. A 50% or greater reduction in HAMD-17 was observed in 23 subjects after DHEA and in 13 subjects after placebo treatments.

There is limited evidence on the safety or long-term effectiveness of DHEA. Acne and hirsutism have both been described in women participating in long-term trials of DHEA.

More evidence in this field is expected after administration of 7-keto DHEA alone or in combination with other psychiatric drugs (such as anticonvulsants, anti-anxiety agents, antidepressants, antipsychotic agents, mood stabilizers). The efficacy of the aforementioned combinations and their safety in psychiatry is under evaluation (Sageman & Brown 2012).

Statins

Low cholesterol is almost always associated with increased risk of death from various causes, including suicide and violence. It is not surprising that statins, cholesterol synthesis inhibitors, have been reported to be associated with an increased incidence of behavioural and personality disorders that may be hormonally influenced (Huffman & Stern 2007). Lowering cholesterol levels may actually be attributed to an increase in depressive symptoms.

Despite this, cholesterol synthesis inhibitors (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have been studied as potential means of reducing available adrenal steroids. In a prospective study of almost 200 subjects representative of a broader Australian community, Stafford and Berk (2011) showed that the use of statins was associated with a significant reduction in the risk of depression in individuals following a cardiac event. They concluded that their data supported the role of oxidative and inflammatory processes in depression and opened the door to rational and novel pathophysiologically based therapies distinct from conventional antidepressants. Decreased risk of depression in cardiac patients was replicated and confirmed even in a larger sample recruited by Otte et al. (2012). Finally, when 7 randomized controlled trials were evaluated which represented 2,105 participants, a test for overall effect of statin demonstrated no statistically significant differences in psychological well-being between participants receiving statins (simvastatin, lovastatin, provastatin) or a placebo, but sensitivity analyses conducted to separately analyze depression and mood outcomes showed that statins were associated with statistically significant improvements in mood scores (95% CI -0.61 to -0.24) (O'Neil et al. 2012).

Nevertheless, future studies in psychiatric, rather than general medicine patients are necessary to observe and understand the potential efficacy and risk of statin use in depression.

CONCLUSION

HPA axis hyperactivity has been demonstrated in chronic diseases affecting endocrine (abdominal obesity with metabolic syndrome, type-2 diabetes mellitus), cardiovascular (atherosclerosis, essential hypertension) and nervous system disorders (depression). New journeys venturing to discover antidepressant drugs other than monoamines are recognizing the hypothalamic–pituitary–adrenal (HPA) axis as a valid target. McIssac et al. (2009) recently reviewed the physiology of the HPA axis. Based on evidence of its dysfunction in psychiatric illnesses and the role that this dysfunction might play in pharmacological treatment resistance, they have identified the following agents as potentially useful in the treatment of mood disorders: GR agonists, GR antagonists, and steroid synthesis inhibitors (ketokonazole and metyrapone). The results in some diagnostic subtypes of depression are promising and warrant further investigation.

However, at present, the available clinical trials according to Claes (2009b) still do not support claims that antiglucocorticoids are superior to existing treatments. New avenues investigating potential therapeutic benefits of direct HPA regulation in depression are at the proof-of-concept stage and future developments in this area deserve the full attention of psychiatrists and neuroscientists, as the current pharmacological treatment of major depressive disorder is far from perfect.

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