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Editorial

Depression and the hypothalamic-pituitary-adrenal axis: increasing the scope

Several theories have been posited about the neurobiology of depressive disorder. The monoaminergic hypothesis has much supporting evidence, such as relapse induced by serotonin depletion (1), contributing to the foundation for the development of several antidepressant drugs. However, this theory has some drawbacks, such as the unexpected antidepressant effect of tianeptine, which reduces extracellular serotonin (2). Furthermore, this theory has not led to the development of antidepressant drugs with greater efficacy or a faster onset of action compared with older drugs. Thus, alternative hypotheses have been proposed, including those that involve molecular neurotrophy (3), glutamatergic hyperactivity (4) and glucocorticoid dysfunction (5–7). This latter hypothesis is the subject of the review by Von Werne Baes et al. (8) published in the current issue of *Acta Neuropsychiatrica*. Their review highlights two important but (relatively) poorly evaluated points in hypothalamic-pituitary-adrenal (HPA) axis-depression relationships, specifically early life stress and mineralocorticoid receptors (MRs).

The glucocorticoid dysfunction hypothesis proposes that depression is related to HPA axis dysfunction, leading to increased plasma cortisol levels, and antidepressant drugs exert their effects through HPA normalisation (5,9). Following the initial studies of Carroll et al. (10), numerous clinical studies correlated some aspects of changes in the HPA axis, such as increased plasma cortisol levels, with major depression. Preclinical findings also supported this association. Glucocorticoid administration appeared to induce depression-like behaviour in rodents (11), and antiglucocorticoids exert an antidepressant-like effect in animal models (12).

Functional neuroendocrine tests have been one of the most frequent strategies used to study HPA axis function in depression. The dexamethasone suppression test (DST) has been used in several studies and is based on the physiological negative feedback of glucocorticoids on the HPA axis. Normally, after dexamethasone [a synthetic corticoid that binds to glucocorticoid receptor (GRs)] administration, plasma cortisol levels decrease (i.e. are suppressed), but this suppression does not occur in some depressed patients (13).

The non-normalisation of altered HPA axis function after antidepressant treatment has been associated with non-responses to antidepressant treatment or a high percentage of relapse. For example, non-suppression in the DST after treatment is correlated with a poor prognosis (13). Antidepressant treatment leads to the reinstatement of corticosteroid receptors, which would result in the normalisation of HPA function. Thus, the degree of normalisation may be a biological marker for the clinical efficacy of antidepressant treatments.

Glucocorticoids bind to two different receptors: MRs (or type I receptors) and GRs (or type II receptors). These receptor types have some important differences. For example, MRs bind glucocorticoids with 10-fold higher affinity than GRs (7). Furthermore, GRs are widely distributed in the brain, but MRs are concentrated in specific brain areas, such as the hippocampus, where MRs and GRs may be co-expressed (9). MRs in the hippocampus exert inhibitory control over the HPA axis (14). MRs were initially proposed to be completely occupied at basal plasma corticosteroid levels, but more recently, these receptors have been suggested to mediate the initial phase of the stress response (15). GRs and MRs may interact synergistically because they can form heterodimers that act in gene regulation (16). These receptors also have opposing effects. 5-Hydroxytryptamine transmission is decreased by MR activity but increased by GR activity (16).

Several studies have implicated GR dysfunction in depression. However, some inconsistencies have emerged in clinical and preclinical studies. For example, exogenous administration of glucocorticoids (e.g. corticosterone, the main glucocorticoid in rodents) generally induces depressive-like behaviour (11), but an antidepressant-like effect has also been observed (17). Furthermore, mifepristone, a glucocorticoid and progesterone receptor antagonist, exerted antidepressant-like effects in animal models (12). However, although mifepristone showed a clinical antidepressant effect in some studies (18), these results have been criticised (19). Mifepristone may be effective specifically in psychotic depression, which has been associated with hypercortisolaemia.

Mifepristone treatment increases cortisol and decreases brain-derived neurotrophic factor levels in bipolar patients (20), and thus, the conflicting data about the clinical antidepressant effect of mifepristone may be attributable to its selective antagonism of GRs, which leads to increased cortisol that can activate MRs or act through non-genomic mechanisms. Alternatively, hypercortisolaemia may represent a consequence of a reduction in the effects of corticosteroid in the brain (6).

Homeostasis is related to a balance between MRs and GRs, with hippocampal MRs mediating the initial response to stress and GRs related to later phases of the stress response (15). Additionally, low-affinity membrane MRs may mediate glutamate release in the stress response (15).

It is interesting to note the progression of neuroendocrine tests: the evaluation of GRs in the DST, the evaluation of pituitary function in the dexamethasone/corticotropin-releasing factor test and prednisolone suppression test (PST), a drug which possesses similar pharmacokinetic parameters to cortisol and binds to both GRs and MRs. The PST results suggest the maintenance of MR activity and impaired GR sensitivity (21). Thus, an imbalance between these two corticoid-sensitive receptors may play an important role in the pathophysiology of major depression (7,16,21). The review published in the present issue of *Acta Neuropsychiatrica* is timely. Von Werne Baes et al. (8) provide a detailed and updated overview on this topic, suggesting that MRs can play an important role in the pathophysiology of depression.

In a case study series, lithium was successfully replaced by spironolactone, an MR antagonist, in bipolar patients (22). In a small-sample case series, spironolactone appeared to effectively improve residual symptoms in euthymic bipolar patients (23). However, a controlled add-on study found that fludrocortisone, an MR agonist, but not spironolactone accelerated the antidepressant response to escitalopram, although it did not increase the effectiveness of escitalopram (24).

Early life stress can trigger long-term changes in the HPA axis, resulting in an altered response to stress in adulthood (25) and alteration in the biological vulnerability to depression. Alternatively, stressful life events in childhood can be continuously actualised by some reminders, resulting in the maintenance of changes in HPA stress reactivity.

This is consistent with a preclinical study, in which early life stress decreased hippocampal GR levels and increased corticosterone levels after stress in adulthood (26). Glucocorticoids may mediate changes in hippocampal neurogenesis induced by stressful life events. Von Werne Baes et al. (8) found that early life stress likely affects the HPA axis, but the results are not conclusive regarding the direction of change.

In summary, the article by Von Werne Baes et al. (8) in the present issue highlights some interesting lines of research on the HPA axis and depressive disorder. However, a significant proportion of depressed patients do not exhibit hypercortisolaemia or HPA axis alterations, indicating that other neurobiological changes are also related to depressive symptoms.

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References

1. Aan H, Rot M, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. CMAJ 2009;**180:**305–313.
2. McEwen BS, Chattarji S, Diamond DM et al. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Mol Psychiatry 2010;**15**:237–249.
3. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry 1997;**54:**597–606.
4. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 2006;**7:**137–151.
5. Barden N. Implication of the hypothalamic-pituitary-adrenal axis in the physiopathology of depression. J Psychiatry Neurosci 2004;**29:**185–193.
6. Pariante CM. The glucocorticoid receptor: part of the solution or part of the problem? J Psychopharmacol 2006;**20(Suppl. 4)**:79–84.
7. Oitzl MS, Champagne DL, van der Veen R, De Kloet ER. Brain development under stress: hypotheses of glucocorticoid actions revisited. Neurosci Biobehav Rev 2010;**34**:853–866.

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8. Von Werne Baes C, Tofoli SMC, Martins CMS, Juruena MF. Assessment of the hypothalamic-pituitary-adrenal axis activity: glucocorticoid receptor and mineralocorticoid receptor function in depression with early life stress – a systematic review. Acta Neuropsychiatr 2011;**24**:4–15.
9. Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 2000;**23**:477–501.
10. Carroll Curtis GC, Mendels J. Neuroendocrine regulation in depression. I. Limbic system-adrenocortical dysfunction. Arch Gen Psychiatry 1976;**33**:1039–1044.
11. Gregus A, Wintink AJ, Davis AC, Kalynchuk LE. Effect of repeated corticosterone injections and restraint stress on anxiety and depression-like behavior in male rats. Behav Brain Res 2005;**156**:105–114.
12. Wulsin AC, Herman JP, Solomon MB. Mifepristone decreases depression-like behavior and modulates neuroendocrine and central hypothalamic-pituitary-adrenocortical axis responsiveness to stress. Psychoneuroendocrinology 2010;**35**:1100–1112.
13. Ribeiro SC, Tandon R, Grunhaus L, Greden JF. The DST as a predictor of outcomein depression: a meta-analysis. Am J Psychiatry 1993;**150**:1618–1629.
14. Kellner M, Wiedemann K. Mineralocorticoid receptors in brain, in health and disease: possibilities for new pharmacotherapy. Eur J Pharmacol 2008;**583**:372–378.
15. Joëls M, Karst H, Derijk R, De Kloet ER. The coming out of the brain mineralocorticoid receptor. Trends Neurosci 2008;**31:**1–7.
16. Young EA, Lopez JF, Murphy-Weinberg V, Watson SJ, Akil H. Mineralocorticoid receptor function in major depression. Arch Gen Psychiatry 2003;**60:**24–28.
17. Stone EA, Lin Y. An anti-immobility effect of exogenous corticosterone in mice. Eur J Pharmacol 2008;**580**:135–142.
18. Debattista C, Belanoff J, Glass S et al. Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. Biol Psychiatry 2006;**60:** 1343–1349.
19. Carroll BJ, Rubin RT. Mifepristone in psychotic depression? Biol Psychiatry 2008;**63:**e1.
20. Mackin P, Gallagher P, Watson S, Young AH, Ferrier IN. Changes in brain-derived neurotrophic factor following treatment with mifepristone in bipolar disorder and schizophrenia. Aust N Z J Psychiatry 2007;**41:**321–326.
21. Juruena MF, Cleare AJ, Papadopoulos AS, Poon L, Lightman S, Pariante CM. Different responses to dexamethasone and prednisolone in the same depressed patients. Psychopharmacology (Berl) 2006;**189**:225–235.
22. Hendler NH. Spironolactone prophylaxis in manic-depressive disease. J Nerv Ment Dis 1978;**166**:517–520.
23. Juruena MF, Gama CS, Berk M, Belmonte-de-Abreu PS. Improved stress response in bipolar affective disorder with adjunctive spironolactone (mineralocorticoid receptor antagonist): case series. J Psychopharmacol 2009;**23**: 985–987.
24. Otte C, Hinkelmann K, Moritz S et al. Modulation of the mineralocorticoid receptor as add-on treatment in depression: a randomized, double-blind, placebo controlled proof-of-concept study. J Psychiatr Res 2010;**44**:339–346.
25. Faturi CB, Tiba PA, Kawakami SE, Catallani B, Kerstens M, Suchecki D. Disruptions of the mother-infant relationship and stress-related behaviours: altered corticosterone secretion does not explain everything. Neurosci Biobehav Rev 2010;**34:**821–834.
26. Uys JD, Muller CJ, Marais L, Harvey BH, Stein DJ, Daniels WM. Early life trauma decreases glucocorticoid receptors in rat dentate gyrus upon adult re-stress: reversal by escitalopram. Neuroscience 2006;**137**:619–625.

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