The hypothalamic-pituitary-adrenal axis: a target for intervention in early psychosis?

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Since the first demonstrations of hypercortisolaemia in depression [1], our understanding of the hypothalamic-pituitary-adrenal (HPA) axis in health and in neuropsychiatric disease has increased in many ways. This has the potential to allow more sophisticated treatments, aimed at correcting HPA-axis dysfunction, in specific diseases and even particular phases of these diseases. The excellent paper by Phillips et al. [2] in this issue reviews the role of the HPA axis in psychosis and highlights the issue of changes in HPA-axis function at different stages of the disease. In this editorial, I will review recent developments in treatments based on modifying HPA-axis function, discuss, focused treatment trials in other neuropsychiatric conditions and suggest a role for such treatments in the early phase of psychotic disorders.

Specific abnormalities in specific diseases

The dexamethasone suppression test (DST) is the most widely researched biological test in psychiatry and the most commonly used test of HPA-axis function. It is believed to be a good indicator of glucocorticoid receptor (GR) mediated negative feedback in the HPA axis. Despite considerable early enthusiasm, however, it has not proven to be either sensitive or specific to depression [3] or indeed to any other neuropsychiatric condition. Part of the reason for this is that studies have usually investigated patients with a range of presentations and at a range of different stages within heterogeneous neuropsychiatric conditions. For instance, studies in depression show marked variation in the percentage of DST non-suppressors based both on clinical condition and on the stage of the illness. Psychotic depression [4] and bipolar depression appear to have higher rates of DST non-suppression [5] than unipolar, non-psychotic depression, while treatment-resistant, long-term depression is associated with a low rate of non-suppression [6].

Various factors also seem to affect the results of the DST in schizophrenia [2] while pituitary volume (which has been found to be closely correlated with post-dexamethasone cortisol in psychiatric inpatients [7]) is increased in first-episode psychosis [8] but reduced in chronic, treated schizophrenia [9]. Even more specifically, in patients at ultra high risk of psychosis (UHR) [10], pituitary volume predicts future transition to psychosis and in those who went on to develop psychosis, pituitary volume was greater than in control subjects while in those who did not develop psychosis, it was less than in controls. The volume of the hippocampus, an area particularly dense in glucocorticoid receptors and sensitive to increased cortisol levels, is reduced in first-episode psychosis [11] and there is also evidence of a reduction in volume in this region in the transition from UHR to psychosis [12]. The exact role in this process of an affective component to the illness is unclear at this point.

The HPA axis and existing treatments

Some existing treatments appear to have important effects on various aspects of HPA-axis function. For instance, in neuronal cultures, amitriptyline increases GR mRNA expression [13] while in mice, amitriptyline, desipramine, imipramine, lithium and electroconvulsive shock all increase the expression of GR mRNA in the brain (see [14] for review). In transgenic mice with reduced numbers of GRs, which show behavioural and neuroendocrine characteristics very similar to those seen in major depression in humans, antidepressants likewise...
increase GR mRNA and reverse at least some of the deficits [15]. However, these effects do not appear to occur with selective serotonin re-uptake inhibitors (fluoxetine and citalopram), suggesting that they may not be as effective in modifying HPA-axis feedback [16,17]. Interestingly, a recent clinical trial suggested that adding metyrapone (a cortisol synthesis inhibitor) to treatment with the serotonergic antidepressants fluvoxamine or nefazodone in the treatment of hospitalized depression improved response [18], suggesting that direct modulation of HPA-axis function was helpful in at least a subgroup of patients. There is also evidence that when antidepressants do not normalize HPA-axis function this may predict early relapse despite apparent resolution of symptoms [19].

Antipsychotics also have effects on HPA-axis function although evidence of a relationship between this effect and treatment effects is not as strong as it is for antidepressants (see [2] for review).

**HPA-axis interventions in specific neuropsychiatric conditions**

Early researches into treatment strategies altering the HPA axis have tended to use rather crude methods of manipulation such as the antiglucocorticoid ketoconazole or the GR agonist dexamethasone and have often focused on treatment-resistant depression which does not appear to have a high rate of HPA-axis abnormality [6]. Based on the more recent developments noted above, three main treatment strategies have been developed, some of which have been targeted to specific conditions or situations.

Corticotrophin releasing hormone (CRH) released from the paraventricular hypothalamus drives adrenocorticotropic hormone (ACTH) secretion from the pituitary which stimulates cortisol secretion. Not only does CRH secretion control the activity of the HPA axis but it is a neuropeptide with significant neurobehavioural effects which have been extensively studied in recent years. These include effects on anxiety and fear responses, sleep, sexual drive and appetite (see [20] for review). Receptors for CRH, of which there are two major subtypes, have also been identified leading to the development of antagonists at these receptors [21]. Studies of the behavioural effects resulting from stimulation of each group of receptors have led to a focus on the development of CRH1 receptor antagonists for the treatment of depression and anxiety. R121919, a CRH1 receptor antagonist has been trialled in depression [22]. While there was no clear effect on HPA-axis measures (probably because CRH2 receptors continue to mediate the pituitary effects of CRH), there were beneficial effects on the symptoms of depression presumably based on blockade of the direct neurobehavioural effects of CRH.

Dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S) are the most abundant steroid hormones in man, secreted by the adrenal cortex in response to ACTH as part of the stress response. They antagonize various of the effects of cortisol in the brain [23] and can be seen as an important factor in modulating the stress response. Dehydroepiandrosterone may also be an important protective hormone, mitigating the adverse effects of dysregulation of the HPA axis. Levels of DHEA increase rapidly during childhood, reaching a peak in the late teenage years and decline steadily thereafter to very low levels in late life [24].

There is some evidence of altered DHEA levels or DHEA/cortisol ratio in major depression [25] and DHEA has been investigated as a possible therapeutic agent specifically in midlife depression (a time when DHEA levels are naturally declining). Two placebo-controlled studies have been conducted in patients aged 45–65 and although they have included milder forms of depression not usually associated with HPA-axis abnormality, they have shown a significant improvement compared with placebo [26,27]. Later in life, DHEA has also been trialled in an attempt to offset age-associated cognitive impairment which may, at least in part, be related to altered HPA-axis function [28]. Results in this area are so far inconclusive [29].

Both the actions and control of cortisol secretion are mediated by two distinct receptors, the GR and the mineralocorticoid receptor which have distinct but complementary roles [30]. The GR function is necessary for HPA-axis feedback regulation at high levels of circulating corticosteroids and as discussed appears to be reduced by certain types of depression. Several recent studies have investigated specific GR antagonists, some targeting types of depression which are likely to have a high incidence of HPA-axis abnormalities. RU486 is a potent GR antagonist which has been trialled with some effect in psychotic depression [31,32] while a recent preliminary study suggests a beneficial effect on cognitive function in bipolar depression [33]. In later stage schizophrenia, RU486 had no effect on cognitive function or symptoms [34]. A larger study of RU486 in bipolar depression is ongoing in collaboration between groups in Newcastle, Christchurch and Vancouver.

The relationship between pituitary volume and progression to psychosis suggests that HPA activation may play a role in this process. The progression to reduced hippocampal volume in first-episode psychosis may also suggest adverse effects on the brain of the HPA axis over activity. Perhaps then, future research should include
trials of specific HPA-axis agents in ultra high-risk patients. These may modify the onset of psychosis and hippocampal changes in some patients.

Conclusion

As understanding of the HPA axis increases, there is once again interest in the role of therapeutic agents acting directly on it. A trial of specific treatment acting on the HPA axis in a group of subjects at ultra-high risk of psychosis is now warranted.

References