Neuro-endocrinology
19 BRIEFINGS

DEPRESSION, STRESS AND THE ADRENAL AXIS

SUMMARY

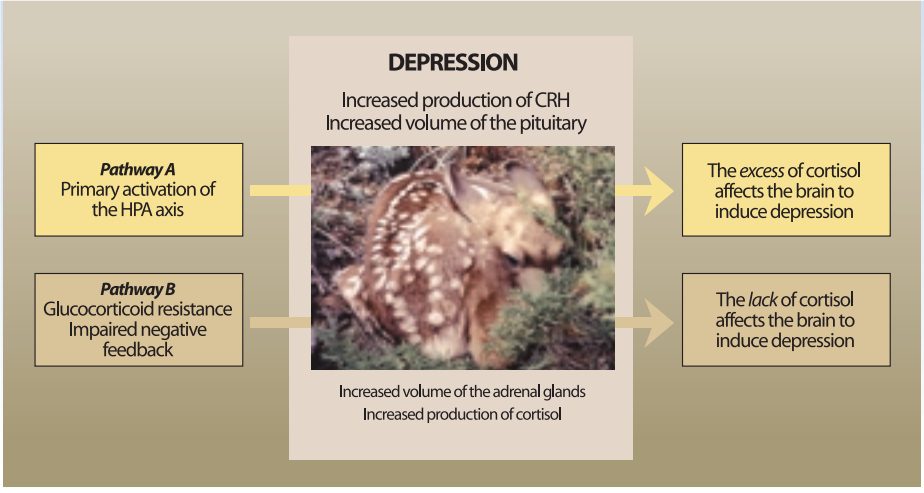
Depression is characterised by an over activity of the hypothalamic-pituitary-adrenal (HPA) axis that resembles the neuro-endocrine response to stress. These HPA axis abnormalities participate in the development of depressive symptoms. Moreover, antidepressants directly regulate HPA axis function. These novel findings are reshaping our understanding of the causes and treatment of this disabling disorder.

Major depression – major importance

Costing more than 30 billion pounds every year in the UK and the US alone, major depression is a significant cause of disability and the most important cause of suicide worldwide. Why should neuro-endocrinologists bother with depression? Depression is characterised by an over activity of the hypothalamic-pituitary-adrenal (HPA) axis that resembles the neuro-endocrine response to stress. In this Briefing I will claim that HPA axis hyperactivity is not a mere epiphenomenon of depression, but rather a crucial biological mechanism in the pathogenesis of this disorder and a fundamental target for its successful treatment.

HPA axis activity is governed by the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH activates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH, in turn, stimulates the secretion of glucocorticoids (cortisol in humans) from the adrenal glands. Glucocorticoids interact with their receptors – the corticosteroid receptors – in almost every tissue in the body, and the best known effect is the regulation of energy metabolism. By binding to corticosteroid receptors in the brain, glucocorticoids also inhibit the further secretion of CRH from the hypothalamus and ACTH from the pituitary (negative feedback).

Three lines of evidence demonstrate the link between stress, depression and the HPA axis. First, depression, in its core symptoms of dysphoric or low mood, inability to take pleasure and low energy, is a universal cross-cultural response to stressful events, particularly when the stress is chronic or the individual



Two hypothetical pathways by which the activation of the HPA axis participates in the development of depression. In Pathway A, the elevated levels of cortisol induce the depressive symptoms (as in Cushing's disease). In Pathway B, the lack of effects of cortisol induces the depressive symptoms (as in Addison's disease). See text.

has no control over the situation. Second, stress activates the HPA axis, leading to a powerful release of glucocorticoids into the bloodstream; depression, especially when severe, is also characterised by over activity of the HPA axis. Third, treatments that modify the stress response, like 'talking therapies' improving the ability to cope with stress, have an antidepressant effect; moreover, known antidepressants directly decrease HPA axis activity.

Facts and questions

The HPA axis abnormalities in patients with major depression are remarkably similar to those present in animals experiencing chronic stress. Depressed patients have an increased drive to the HPA axis, as shown by the larger production of CRH in the brain. They also have an impaired negative feedback by glucocorticoids. Finally, they have an increased volume of the adrenal and pituitary glands. One accepted explanation for the HPA axis over activity in depression is that, because of the reduced function of the corticosteroid receptors, circulating cortisol is unable to successfully inhibit HPA axis activity ('glucocorticoid resistance'). Consistent with this, antidepressants directly increase the expression and function of corticosteroid receptors in the brain, thus enhancing the negative feedback and reducing HPA axis activity.

There is, however, a big unanswered question (see Figure). Does the fact that depressed patients have a hyperactive HPA axis actually mean that a lot of cortisol is flooding their brain, and that the depressive symptoms are consequence of this putative 'toxic' effect of cortisol (Pathway A)? Or is the opposite true: that patients have a hyperactive HPA axis as a compensatory mechanism, because their brain is resistant to the effects of circulating cortisol (Pathway B)? The question is not trivial, especially in our quest for a more effective treatment. In the first scenario, our recommendation should be the lowering of cortisol levels. In the second scenario, our recommendation should be the administering of more cortisol. The situation is complicated by the fact that increased cortisol levels in the bloodstream do not necessarily translate into increased effects of glucocorticoids on the brain, because the brain sensitivity to cortisol is also regulated by the function of the corticosteroid receptors as well as by efflux systems at the blood-brain barrier. In what seems to be a clear effort of nature to tease us all, depression has been described in endocrine disorders characterised by elevated cortisol levels, like Cushing's disease, but also in disorders characterised by low cortisol levels, like Addison's disease. Moreover, high and low levels of cortisol give similar functional and morphological changes in the brain. Even more strikingly, both the lowering of cortisol levels and the administering of cortisol have antidepressant effects in depressed patients.

> *'One way to conceptualise depression is a pathological stress response gone awry'*
>
> Charles B. Nemeroff, 1996

Hero or villain?

Why should the stress-induced activation of the HPA axis, a biological system that is life saving and enables us to fight or escape our enemy, lead to such a bad thing as depression? The answer, from an evolutionary point of view, is that depression – if you are a fawn in a cold barren land, or a defeated gorilla that has fallen in the dominance hierarchy – is an adaptive response. Depression stops you dispersing energy in the pursuing of unavailable goals, prevents further aggressive behaviour from the dominant animals, and signals your difficulty. Today, an increasing number of researchers believe that the stress-induced HPA axis activation directly causes depressive symptoms, by interacting with the brain neurotransmitter systems regulating these behavioural changes. This idea is further supported by clinical studies showing that normalization of HPA activity by antidepressants precedes the therapeutic effects on the depressive symptoms. While the exact mechanism of this effect is still unknown – and we are divided on whether cortisol is a hero or is a villain – the galloping development in this research field is already changing our understanding of neurobiology and our clinical practice.

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