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...
Depression, stress and the adrenal axis

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 hyperac-

‘One way to conceptualise depression is a pathological stress response gone awry’

Charles B. Nemeroff, 1996

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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