EDITORIAL

Irish Journal of Psychological Medicine 1996 March; 13 (1): 3-5

HPA axis overactivity and the pathogenesis of depression

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Normal physiology of the HPA axis

Neuro-endocrine systems are characterised by a feed forward limb, which results in the synthesis and release of hormones, and a negative feedback limb whereby these substances limit their own production.[1] Corticotropin-releasing hormone (CRH) has the majority of its cell bodies in paraventricular nucleus of the hypothalamus and is under the regulation of hormonal, neuronal and neurochemical inputs.[2] This neuropeptide is the most potent adrenocorticotropin (ACTH) secretagogue known and binds to specific membrane receptors on pituitary corticotropes. ACTH is responsible for promoting adrenal steroidogenesis and does so by acting at membrane specific adrenocortical receptors.[3]

Cortisol limits its own production by acting at a hypothalamic and pituitary level.[4] Feedback inhibition is mediated by two types of corticosteroid receptors, Type 1 and Type 2. Mineralocorticoid or Type 1 receptors, are principally located in the septo-hippocampal complex, have a high affinity for cortisol and are believed to be involved with tonic inhibitory activity within the Hypothalamic-pituitary-adrenal (HPA) axis; glucocorticoid (GC) or Type 2 receptors have widespread distribution throughout the central nervous system, have a lower affinity for their substrate and appear to 'switch off' the production of cortisol during times of overactivity of the HPA axis.[5]

HPA axis function in depression

Pathological overactivation of the HPA axis in patients with major depressive illness may reflect disruption of the feed-forward limb and/or the feedback limb.[6] The fact that cerebrospinal fluid concentrations of CRH are increased in depressives[7] suggests hyperactivity of the positive feed-forward limb with the HPA axis. Furthermore, administration of ACTH to depressives leads to a greater release of cortisol in depressives than in normal controls. Dexamethasone administration in control subjects leads to a suppression of plasma cortisol levels; the same is not true of depression which suggest a malfunctioning negative feedback system.[8] HPA axis disturbances have hithertofore been considered as secondary to monoaminergic dysfunction in depression. However, the evidence from basic science and clinical studies for the contrary is just as convincing.

Glucocorticoid-monoaminergic interactions

A glucocorticoid milieu analogous to depression in humans can be simulated by exposing animals to high levels of corticosterone. Such animals display deficits in serotonergic-dependent cellular and behavioural activity which may offer insights into the possible pathogenesis of depression. Central serotonergic activity is responsible for stimulating the release of the anterior pituitary hormone, prolactin (PRL).[10] Therefore, plasma levels of PRL indirectly reflect 5HT-dependent activity. A wealth of scientific literature exists regarding the effects of adrenal steroids on PRL release. Chronic exposure to glucocorticoids either in the form of persistent stress or exogenous corticosterone administration leads to a decrease in the number $5HT_1$ receptors in the hippocampus and raphe nuclei (neurones that contain the cell bodies of 5HT) and a decrease in PRL secretion.[11-14] Furthermore, suckling-induced PRL secretion, hind-limb abduction, forepaw treading and head weaving, all 5HT-dependent behaviours are markedly reduced in the presence of high levels of corticosterone.[15,16]

A similar interaction between GCs and serotonergic function has been reported in a human volunteer study[17] examining the role of cortisol on spontaneous and 5HT-mediated PRL release. Metyrapone (a steroid lowering agent) treatment of healthy controls resulted in enhanced d-fenfluramine (D-FEN) (a serotonergic agonist) induced PRL secretion and an increase in the nocturnal surge of PRL. In the second part of the study, thyrotropin-mediated PRL secretion (a pituitary-dependent process) was augmented following metyrapone treatment, indicating that cortisol-induced inhibition of PRL release is partly mediated at a pituitary level.

From a clinical perspective, blunted prolactin release in

response to a number of serotonergic agonists such as, D-FEN[18], d,l-fenfluramine[19], L-tryptophan[20] is a characteristic feature of depression. Strong evidence exists to indicate that high levels of cortisol may be responsible for reduced PRL release in depression.[18,21] Therefore, from the animal and human data presented so far, hypercortisolaemic-induced serotonergic hyporesponsivity may be responsible for the affective and biological features observed in depression.

The presence of noradrenergic synapses on the CRH-containing paraventricular neurones suggests the presence of significant interactions between the HPA and the noradrenergic system.[22] In fact, adrenalectomy results in a decrease in the number of α2-nordrenergic receptors, a process prevented by corticosterone replacement.[23] Suppression of noradrenergic-mediated cAMP (the principal second messenger involved with this receptor subclass) occurs in the cerebral cortex of rats exposed to adrenocorticoids.[12] A recent in vivo study has added further weight to these observations in that glucocorticoids reduce basal and stress-induced catecholaminergic activity in the paraventricular nucleus, implying that noradrenergic neurones are sites for adrenocorticoid action.[24]

Despite evidence that noradrenergic activity is grossly disturbed in depression,[25] there have been few if any studies examining the interaction between glucocorticoids and noradrenergic function in this condition. In health, stimulation of specific noradrenergic receptors results in the secretion of growth hormone from the anterior pituitary. Blunted desipramine/growth hormone responses are a characteristic feature of depressive illness, occurring more frequently in patients who show non-suppression to dexamethasone, indicating a link between abnormal functioning of the HPA axis and growth hormone secretion.[26,27] It would appear that serotonergic activity and perhaps noradrenergic function may be abnormal in depression as a consequence of primary HPA axis disturbance.

Affective disorder and excess glucocorticoids

Neurotransmitter considerations aside, the administration of exogenous steroids has long been associated with psychiatric disturbance which can range from subtle personality changes, cognitive defects, dysphoria and elation to frank psychosis, with reported incidence of such adverse-effects varying from 1.8 to 57.0%.[28-31] Over production of endogenous cortisol as in Cushing's syndrome can lead to psychiatric symptoms not unlike those found in depression.[33]

Dorn and his colleagues[34] have provided us with one of the most detailed accounts of the psychiatric status of Cushing's syndrome patients. They found that 66.7% of their patients fulfiled DSM-IIIR criteria for various psychiatric diagnoses with half of these suffering from a major depressive disorder and longer duration of illness placing them at an increased rick of such psychopathology. Though the precise processes underpinning these disorders are unknown, glucocorticoids are known to affect neural activity and alter the activities of certain neurotransmitters.[32] Reduction of ambient cortisol levels by surgery or pharmacotherapy leads to an amelioration of physical and psychiatric symptomatology in the majority of patients.[35,36]

These observations together with the fact that patients with major depression who have abnormal pre-treatment dexamethasone suppression tests are less likely to respond to placebo and that an an abnormal post-treatment result signifies a poor prognosis, have provided a major stimulus for using steroid lowering agents in patients with affective disorders.[37]

Antidepressant response and normalisation of HPA axis function

Certain clinical studies have shown a close correlation between conventional antidepressant action and the normalisation of the HPA axis disturbances observed in depressive disorders.[38-41] As mentioned earlier, major depression is characterised by abnormal negative feedback, reflecting dysfunctional corticosteroid receptor function. Direct evidence of receptor defects has come from various investigators who have observed that Type 2 receptors are either not present in sufficient number or lack plasticity (ie: the ability to up and down regulate in response to differing steroid milieus) leading to a reduced capacity in 'switching off' the HPA axis.[42]

Experimental studies have shown that the effectiveness of traditional antidepressants may lie in their ability to manipulate the corticosteroid receptor milieu in major depression. Preclinical studies, using mostly in vitro preparations, indicate that antidepressants increase Type 1 and Type 2 receptor number thereby restoring negative feedback and allowing HPA axis homeostasis to be regained in depression.[43] For instance, Montokowski *et al*[44] have shown that treatment with conventional antidepressants can reduce many of the abnormalities found in transgenic mice that have impaired Type 2 receptor activity. Furthermore, the time course (3 weeks) of receptor changes paralleled the time frame within which patients respond to conventional antidepressant therapy.

From a clinical perspective, drugs with effects on the HPA axis have been used with some benefit in the treatment of major depressive disorder. The earliest series of studies was by Murphy and her colleagues.[45,46] With trials lasting on average eight weeks, they used varying doses of either aminogluthemide, ketoconazole or metyrapone in treatment refractory patients and found response rates approaching 50%. Wolkowitz et al[47] used ketoconazole in hypercortisolaemic patients with major depression over a three to six week period and found that Hamilton Depression Rating Scale (HAMD) levels decreased by 30%.

Thakore and Dinan[48] used ketocanozole in non-refractory patients with major depressive disorder and found HAMD reductions of 63% and an increase in D-FEN-induced prolactin release, indicating an augmentation of serotonergic function. O'Dwyer et al[49] used metyrapone and placebo in a single-blind, cross-over paradigm and found a response rate of 63%. However, their results are confounded by the fact that they used hydrocortisone in order to prevent hypadrenalism, potentially induced by metyrapone. Krishnan et al[50] and Murphy et al[51] using mifepristone had smaller response rates and a greater number of treatment discontinuations due to side-effects.

To-date no large, double-blind placebo-controlled study has been undertaken with steroid lowering agents in major depression. In contrast to the above mentioned studies, Arana and his colleagues[52-54] have used either intravenous dexamethasone in an open fashion or oral dexamethasone in a randomised, double-blind placebo-controlled manner and found active treatment to be more effective than placebo. The exact mechanisms underlying dexamethasone's effectiveness are unknown; however, supraphysiological doses of dexamethasone as used by Arana et al[52-54] may serve to

'switch off' the HPA axis at either a hypothalamic or hippocampal site.

Conclusions

Hyperactivity of the HPA axis may be a core feature rather than an epiphenomenon of major depressive illness. Many of the deficits in serotonergic and noradrenergic activity observed in depression could be secondary to HPA axis over-activity. Furthermore, classical antidepressant treatments upregulate brain glucocorticoid receptors and normalise HPA dysfunction. For these reasons, the development of drugs that directly or indirectly modulate glucocorticoid receptor function could provide exciting and novel strategies for the treatment of depression.

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Original manuscript received November 1, 1995.
Final revision accepted February 10, 1996.