Evolving model of depression as an expression of multiple interacting risk factors†

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Our understanding of how stress alters our physiology to produce a state that resembles clinical depression is germane to the evolving model of depression as an expression of multiple interactive risk factors. The concept of depression has moved from one where 'endogenous', or genetic, risk factors and 'reactive', or environmental, risk factors were thought to be unrelated and to define a particular clinical syndrome to one where these risk factors are seen as additive, and interacting with developmental risk factors. The study published in this issue by Goodyer *et al* (2000) examines the contribution of developmental, environmental and physiological risk factors in adolescent depression.

HYPOTHALAMIC–PITUITARY–ADRENAL AXIS AND DEPRESSION

Different stressors activate selective stress responses in the body but the most commonly activated and the most researched of these systems is the hypothalamic–pituitary–adrenal (HPA) axis. Overdrive of this system is associated with the depressed state (Gold *et al*, 1988). There is a consensus that major depressive disorder (MDD), and particularly the melancholic subtype, is associated with corticotropin-releasing hormone (CRH) hypersecretion and subsequent HPA axis overdrive. Hypercortisolaemic states produce many of the symptoms and behaviours associated with depression, as demonstrated by the affective syndromes that generally accompany Cushing's syndrome (Dorn *et al*, 1995). These behavioural effects are brought about by the binding of cortisol to nuclear receptors in the brain, most densely concentrated in the hippocampus, and the subsequent activation of transcriptional activity (McEwan *et al*, 1992). Many biological and cognitive processes are modified by cortisol, including sleep, appetite, libido, energy, motivation, concentration and memory (Martignoni *et al*, 1992).

Little is known of the mechanism of activation of the HPA axis following psychological stress but it may involve the stress neurotransmitters 5-hydroxytryptamine (5-HT) or noradrenaline (NA). Stimulation of either of these neurotransmitter systems results in CRH release from the hypothalamus and subsequent release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. The mechanism of HPA axis activation following physical trauma involves cytokine-mediated stimulation of CRH (Raber *et al*, 1997). Cytokines are released following tissue injury and as part of the inflammatory/immune response. Some workers in the field of psychoimmunology, however, would invoke cytokines in the mechanism of activation of the HPA axis following psychological events (Mohr *et al*, 1999). That there are several means of activating the hypothalamic secretion of ACTH secretagogues goes some way to explaining an individual's diathesis to developing depressive syndromes following particular adverse events.

DEVELOPMENTAL, ENVIRONMENTAL AND GENETIC RISK FACTORS

There is evidence to suggest that this diathesis is associated with abnormal HPA axis responses. This may be a genetic vulnerability or may come about as a result of stress during critical periods of brain development. Experiments in rats demonstrate that adult rats that have been subjected as pups to psychological stress, such as maternal separation, non-handling or early immune challenge, demonstrate exaggerated HPA axis responses to stress (Ladd *et al*, 1996). The non-handled rats also demonstrate many of the behavioural characteristics associated with animal models of depression, such as reduced exploration of novel environments. These behavioural and endocrine responses to stress are stable over time and appear to be mediated by glucocorticoid receptor density in the hippocampus. HPA axis hypersecretion is inhibited by a negative feedback process, whereby the elevated cortisol levels act on glucocorticoid receptors, primarily in the hippocampus, to decrease the synthesis of CRH. Reduced receptor availability in the hippocampus thus leads to attenuated inhibition, and therefore hyper-responsivity, of the HPA axis. Glucocorticoid receptor density in the hippocampus is determined largely during the first 3 weeks of a pup's life and non-handling during this critical period leads to reduced glucocorticoid receptor density. These animal studies underlie the importance of examining HPA axis function in stressed young adults.

An animal model of psychological stress that approximates more closely to human social stressors involved housing the *Macaca fascilcularis* monkey in social groups that were either stable or were repeatedly destabilised by changing of group membership (Brooke *et al*, 1994). Animals from unstable groups were twice as likely as animals coming from the stable groups to have resistance to the suppressive effects of dexamethasone. Dexamethasone-resistant animals had significantly fewer glucocorticoid receptors in their hippocampi. These results suggest a model linking sustained stress with hypercortisolaemia and consequent reduction of glucocorticoid receptors in the hippocampus.

There are few experiments in humans examining the effects of stress in childhood on HPA axis responses. A recently published study has demonstrated that HPA axis responses to stress are altered by the mode of delivery (Taylor *et al*, 2000). This study found that salivary cortisol responses to the stress of inoculation at 8 weeks post-delivery were increased in neonates who had assisted deliveries compared to those delivered by elective caesarean section. De Bellis *et al* (1994) compared ACTH and cortisol responses to CRH in teenage girls who had been sexually abused in childhood to age-matched control girls. The test

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group had relatively blunted CRH/ACTH responses: a finding similar to that in depressed adults and thought to indicate CRH hypersecretion. Abnormal HPA axis stress responses may also be genetically determined. Holsboer *et al* (1995) have demonstrated that first-degree relatives of probands with MDD who have never themselves had an episode of major depression have HPA axis responses similar to their affected relative and different from healthy controls.

ADOLESCENT RISK FACTORS AND DEPRESSION

The study published in this issue by Goodyer *et al* is a rare human study that attempts to unravel the contribution and interaction of the various risk factors involved in the evolution of depression. This study builds on prior work done by this group and others that has identified risk factors for depression in adolescents and, through questionnaires, identifies an at-risk subgroup. This population was then examined prospectively over a period of 1 year for adverse events and psychopathology using DSM–IV (American Psychiatric Association, 1994) caseness and morning and evening cortisol and dehydroepiandrosterone levels. Specific HPA axis abnormalities and adverse events were associated with the occurrence of MDD.

The authors' findings reflect the complexity and detail of the study design. This sort of design is of immense scientific value but rarely realised. Implicit in this design is a knowledge base encompassing complex epidemiology data, neurodevelopmental physiology and psychology, and subtle pathophysiological alterations known to predate the depressed state.

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CONCLUSION

Our knowledge of the interaction of risk factors in adolescent depression has been advanced by this study. Following this group into adulthood will provide invaluable information on the evolution of these stress syndromes in these vulnerable individuals. Whether psychological interventions, such as cognitive–behavioural therapy, could modify these responses in a sustainable way is one of the key questions that remains to be answered. Studies such as this, spanning the disciplines of neuroendocrinology, epidemiology and psychology, are required if we wish to advance our understanding of depression. It is not always possible to measure these risk factors in such an exact way but future studies should attempt to incorporate measurement of these variables in study designs. Examining depression from a purely epidemiological, psychological or biological viewpoint can only yield a limited view on the complex and diverse syndrome of MDD.

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