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Cortisol, stress and depression

Strickland *et al* (2002) are to be congratulated for their Herculean task of testing the elegant hypothesis that cortisol is the biological link between stressful life events and the onset of depression. In a large community sample they found that cortisol was not elevated in currently depressed or vulnerable subjects, but was increased after recent life events, and hence concluded that 'the hypothalamic–pituitary–adrenal [HPA] axis is sensitive to social stress but *does not mediate vulnerability to depression*' (italics added). However, it is possibly premature to bury the 'HPA-hypothesis' under this evidence alone.

The rationale for a community study is that it captures the effects of life events, but this exclusive approach misses the other naturalistic event in depression, namely admission to hospital. Thus, the proportion of patients in the 'depressed' group showing severe illness was less than 10% (9 out of 94), leaving more than 90% with mild (51%, n=48) to moderate (41%, n=37) illness. Given the well-replicated finding of elevated cortisol in major depression (Harris *et al*, 2000) it would be helpful to provide a subgroup analysis for the severely depressed sample. Nevertheless, it is particularly interesting that there was significantly elevated cortisol in a subgroup of women who had experienced recent life events, whether or not they were currently depressed. It is possible that exposure to life events is a watershed in the evolution of depression, some people showing enhanced serotonin activity and avoiding depression, and others showing reduced serotonin function and becoming depressed, as suggested by animal studies (McAllister-Williams *et al*, 2001).

Moreover, the investigation of state and trait abnormalities in major depression by Bhagwagar *et al* (2002) shows that recovery from depression is accompanied by a restoration of HPA-axis function, suggesting that cortisol is a trait marker for depression. One inference of these combined findings is that life events preceding depression lead to raised cortisol and lowered serotonin, whereas life events not leading to depression are associated with raised cortisol and normal or even enhanced serotonin function (in what might be described as the 'depression-resistant' subgroup). In order to disentangle these apparently disparate findings it seems that a longitudinal study including a subgroup analysis of people with major depression is inevitable, and I am sure that Strickland's group will not disappoint us.

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The study of Strickland *et al* (2002) underpins the considerable inconsistency in the literature that addresses the area of peripheral markers in depression.

It has been argued that neuroendocrine challenge tests (such as the prolactin response to dexfenfluramine used by the authors) is not a valid probe of central neuronal function (for discussion see Weiss & Coccaro, 1997) and this may account for the negative findings of the study. More perplexing is the lack of association between depression and a reliable index of hypothalamic–pituitary–adrenal (HPA) axis activation, late-night salivary cortisol (reviewed by Kirschbaum & Hellhammer, 1994). In both humans and animals various models of acute and chronic stress (e.g. physical trauma, public speaking, caregiver stress in carers of people with Alzheimer's disease) are reliably associated with hypercortisolaemia (Kirschbaum & Hellhammer, 1994). If depression is considered to be an extreme form of chronic stress, why is there so little consistency between studies examining cortisol in populations with depression (Haskett, 1993)?

Strickland *et al* may have serendipitously discovered a crucial, if seemingly trivial, psycho-biological 'co-factor' in depression that dramatically distinguishes between cases with or without HPA axis activation: perceived stress (as measured by the Life Events and Difficulties Schedule (LEDS), see Strickland *et al*; p. 170, Fig. 1c). Equally depressed patients may not be equally 'stressed' and this may have biological as well as clinical consequences. The increased cardiac (Carney *et al*, 1997) and oncological (Persky *et al*, 1987) morbidity and mortality associated with depression may particularly apply to the depressed–stressed–hypercortisolaemic subgroup. Clearly more research is needed to explore this possibility.

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