

## Cortisol, serotonin and depression: all stressed out?†

P. J. COWEN

The fact that patients with major depression exhibit decreased brain serotonin (5-hydroxytryptamine, 5-HT) function and elevated cortisol secretion has reached the status of textbook truism. More recent formulations have suggested that elevated cortisol levels, probably caused by stressful life events, may themselves lower brain 5-HT function and this in turn leads to the manifestation of the depressive state (see Dinan, 1994). This elegant proposal neatly ties abnormalities of cortisol secretion and 5-HT function into a causal chain in which cortisol is the key biological mediator through which life stress lowers brain 5-HT function, thereby causing depression in vulnerable individuals.

The importance, and occasional discomfort, of testing cherished beliefs is shown in a ground-breaking study from the Manchester University Department of Psychiatry published in this issue of the journal (Strickland *et al*, 2002). In a large group of women the authors found no evidence of increased salivary cortisol levels in those with depression or in the majority of those vulnerable to depression through adverse social or personal circumstances. Moreover, in women with depression, brain 5-HT function (as judged by the prolactin response to the 5-HT releasing agent, d-fenfluramine) was increased rather than diminished. These findings pose serious problems for hypotheses linking hypercortisolaemia with lowered brain 5-HT function and depression.

### DEPRESSION, LIFE DIFFICULTIES AND CORTISOL

It is usually said that about 50% of patients with major depression hypersecrete cortisol, but the rate depends on the population sampled (Maes *et al*, 1994). The findings of Strickland *et al* (2002, this issue) suggest that increased cortisol secretion is not a characteristic feature of depression in the community. There are, however, some

caveats. In a cross-sectional study, it is not possible to know whether a proportion of depressed patients might, in fact, hypersecrete cortisol relative to their non-depressed state. In addition, more subtle abnormalities of the hypothalamic–pituitary–adrenal (HPA) axis could be missed by baseline sampling of salivary cortisol. That this could be the case is suggested by the finding that women with depression who had greater chronic difficulties did indeed have elevated salivary cortisol levels.

The authors did find elevated cortisol levels in a subgroup of participants who had experienced recent severe life events whether or not they were currently depressed. In addition, there is growing evidence that some specific kinds of chronic difficulty, for example caring for a relative with dementia, can be associated with increased cortisol secretion (Bauer *et al*, 2000; Da Roza Davis & Cowen, 2001). It therefore appears that life events and difficulties can result in cortisol hypersecretion but that this does not necessarily lead to the development of a depressive disorder. Indeed, some animal studies suggest that elevated cortisol levels may actually enhance 5-HT neurotransmission by decreasing the sensitivity of inhibitory 5-HT<sub>1A</sub> cell body autoreceptors (McAllister-Williams *et al*, 2001). From this viewpoint elevated cortisol levels may promote resilience to environmental adversity. Perhaps some subjects may respond to ‘stress levels’ of cortisol by developing depression, but in these cases cortisol hypersecretion must interact with other predisposing factors. In most moderately depressed patients in primary care, we may have to accept that increased cortisol secretion is not an important pathophysiological factor.

### TRYPTOPHAN, 5-HT AND DEPRESSION

The other intriguing finding in Strickland *et al*'s study is that women with depression

had elevated prolactin responses to d-fenfluramine, suggesting increased rather than decreased 5-HT neuroendocrine function. This is in contrast to nearly all previous studies of d-fenfluramine in major depression, although Maes *et al* (1989) reported a similar finding. What can explain this surprising observation?

The authors suggested that mild to moderate depression in the community may be associated with an increase in some aspects of 5-HT neurotransmission, particularly those mediated by post-synaptic 5-HT<sub>2C</sub> receptors. Deakin (1988) has suggested that these receptors are activated by adversity and mediate the symptoms of anxiety that often characterise this kind of depression. The prolactin response to d-fenfluramine is mediated via indirect activation of 5-HT<sub>2C</sub> receptors (Goodall *et al*, 1993), so an increased prolactin response would be consistent with increased neurotransmission at 5-HT<sub>2C</sub> synapses.

Strickland *et al*'s data could suggest another possibility. The synthesis of 5-HT in the brain is dependent on the availability of its amino acid precursor tryptophan from plasma. Tryptophan competes with branched-chain amino acids (BCAA) for transport across the blood–brain barrier and therefore the ratio of tryptophan to BCAA in plasma is a critical determinant of the availability of tryptophan for brain 5-HT synthesis (Fernstrom & Wurtman, 1971). Patients with depression have been reported to have low plasma levels of tryptophan, and the women with depression in the Strickland *et al* study had a lower plasma tryptophan:BCAA ratio.

The effect of a chronic decrease in tryptophan availability is to increase the prolactin response to d-fenfluramine, particularly in women (Walsh *et al*, 1995). The likely mechanism here is an upregulation of 5-HT<sub>2C</sub> receptor sensitivity, providing an adaptive response in the presence of diminished brain 5-HT synthesis (Cowen *et al*, 1995). Both basic and clinical studies have shown that this adaptive response can manifest itself as an increased prolactin response to fenfluramine (see Walsh *et al*, 1995). Thus, the women with depression in this study might have lowered brain 5-HT neurotransmission despite having an increased prolactin response to fenfluramine. Strickland *et al* do not favour this explanation, on the basis that the decrease in plasma tryptophan availability was not a significant covariate of the prolactin responses. However, the fact that there is

†See pp. 168–173, this issue.

not a linear correlation between a single plasma measure of tryptophan availability and an adaptive cellular change is not particularly surprising.

Interestingly, the women who were not depressed despite the experience of recent severe life events also had lowered plasma tryptophan availability, but their prolactin response to d-fenfluramine was not increased relative to the women without such life events (personal communication, J. F. W. Deakin, 2001). This suggests that in some of these participants, brain 5-HT function is less sensitive to compromise by precursor deficit and that these women might be less likely to develop depressive disorders.

### CORTISOL, TRYPTOPHAN AVAILABILITY AND VULNERABILITY TO DEPRESSION

Why should tryptophan availability be decreased in women with depression and in those who have suffered recent severe life events? Increased cortisol secretion may play a role by inducing tryptophan 2,3-dioxygenase (tryptophan pyrrolase), the main metabolising enzyme of tryptophan. Elevated cortisol levels could therefore explain lowered plasma tryptophan levels in women with recent severe life events. Consistent with this we have recently found lowered plasma tryptophan levels in association with increased cortisol secretion in carers of patients with clinical dementia (Da Rosa Davis & Cowen, 2001). However, Strickland *et al* found that women with depression demonstrated a decreased tryptophan:BCAA plasma ratio despite having normal cortisol levels. This makes it important to explore other mechanisms by which life events and difficulties could lower tryptophan availability; activation of the immune system is one possibility (Van West & Maes, 1999).

The evidence that brain 5-HT function is lowered in unmedicated patients with depression has grown with the development of specialised imaging technologies (see Sargent *et al*, 2000). More pertinent to the present discussion is the finding that patients who have recovered from major depression respond to acute diet-induced tryptophan depletion with a temporary re-appearance of depressive symptomatology (Smith *et al*, 1997). This effect is not seen in subjects who lack vulnerability factors for the development of depression. This

P. J. COWEN, FRCPsych, University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK

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makes it possible that even modest degrees of tryptophan depletion, presumably through impairment of brain 5-HT neurotransmission, might be sufficient to cause clinical depressive symptomatology in vulnerable individuals. Thus, although tryptophan availability to the brain might be compromised to some extent in any of us who experience life events and difficulties, this might lead to clinical depression only in the presence of other predisposing factors.

### CONCLUSION

The findings of Strickland *et al* (2002, this issue) suggest that some patients with depression (for example, those reporting recent severe life events) do hypersecrete cortisol. However, elevated cortisol levels after life events are not necessarily associated with the development of depressive disorder. Furthermore, the majority of patients with moderate depression in the community probably do not hypersecrete cortisol. It seems more likely that people with depression in the community exhibit abnormal brain 5-HT function, although the cause of this abnormality requires further study. Decreased tryptophan availability is one possibility, but the same change is seen in women who have experienced recent severe life events but who are not depressed. Through studies like that of Strickland *et al* we know significantly more about the neurobiological correlates of life stress and difficulties. What we do not know is why these changes are associated with the development of depressive disorders in some people but not in others. At the root of this problem lies the need to understand individual differences in response to stress and adversity. Only models providing an integration of biological, personal and social factors are likely to have sufficient explanatory power for this difficult task.

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### DECLARATION OF INTEREST

None.

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P.J. COWEN

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