

Neuro-endocrinology

5 BRIEFINGS

STRESS, HORMONES AND YOUR BRAIN

SUMMARY

As the Millennium draws to a close, 'stress' is a word on everyone's lips. Despite sixty years of intense research effort we are only just beginning to unravel the complex interactions between systems in the body which underlie this vital and yet tantalisingly obscure phenomenon. Failure to respond appropriately to stress risks the development of pathological conditions while advance in our understanding of what goes wrong raises real hopes for improving the quality of life for many.

Blue arrows in the diagram illustrate the brain-pituitary-adrenal stress axis and the 'feedback' actions of adrenal corticosteroids on the brain.

Under conditions of stress, illness or depression the axis can be profoundly altered.

Living on your nerves ?

We all know what stress is. We all know when we are stressed and the pressures that induce the condition. More elusive has been an understanding of the physiological mechanisms which characterise stress.

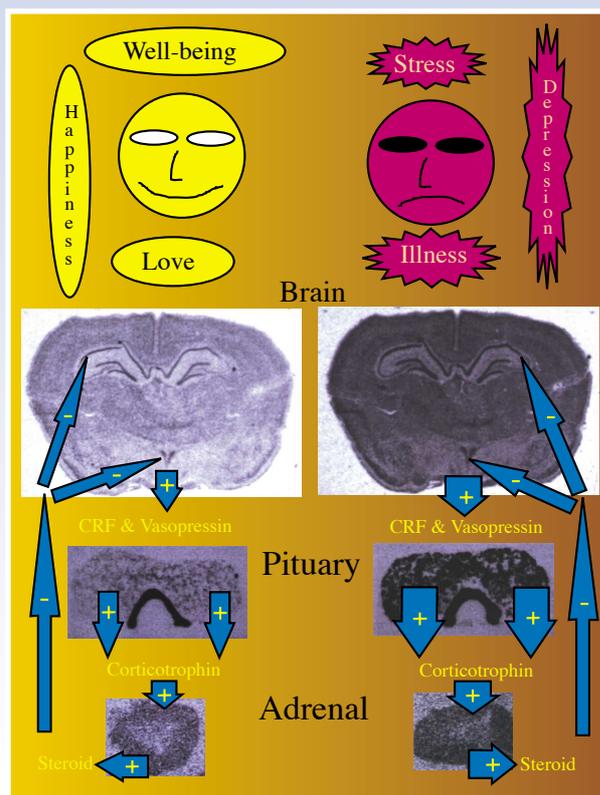
Stress, via control centres in the hypothalamus of the brain, sends signals to the pituitary gland which result in an increase in corticosteroid hormone release from the adrenal glands into the bloodstream. This activation of the hypothalamic-pituitary-adrenal (or stress) axis charac-

terises the response to stress and is essential to survival. Where the adrenals have been damaged, for instance by tuberculosis, cancer or following surgical removal to excise a tumour, failure to provide corticosteroid replacement can result in minor stressors or infections becoming life-threatening.

Stressors are able to differentially activate a variety of mechanisms in the brain. The response to predominantly psychological stressors differs from the response to physical or painful stimuli. In addition, other mechanisms mediate the response to immune challenges. The

paraventricular nucleus, located within the hypothalamus of the brain, contains nerve cells which co-ordinate these responses. Corticotrophin-releasing factor (CRF) is generally considered to be the main signal released from the hypothalamus controlling the stress response. However, under certain circumstances other substances such as vasopressin, which is co-synthesised with CRF, may take over this role.

Within the last few years the molecular cloning of receptors and binding proteins for CRF has allowed the distribution of these proteins to be deter-



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mined, and their functions to be assessed. The recent identification of urocortin, another CRF-like substance, in both humans and other animals, with a distribution distinct from CRF, has opened the possibility of a family of CRF-related peptides underlying different aspects of the response to stress.

Mind the baby . . .

It has become apparent that early life events have a major impact on the ability of adults to respond to stress. Removing rat pups from their mother for short periods, or mimicking infections by treatment with immune-activators, can produce different stress responsiveness in the adult offspring.

Increasing evidence suggests that in addition to the profound changes in stress responsiveness which result from early life events, there are also long-term changes in function associated with life events in adulthood. It has long been assumed that the loss of responsiveness seen following repeated exposure to a single stressor was due to the repeated nature of the stimulus. Recent studies have revealed that a single exposure to a particular stressor can reduce the response to that same stimulus several weeks later suggesting that prior history may be an important determinant of the response to stress.

When it all goes wrong: stress and pathology

Successful control of the hormonal response to stress is essential for normal function. For any particular stressor (be it psychological, physical or immunological), we need to be able to identify the stimulus, initiate

a response, respond to an appropriate level and then to terminate the response. Failure of any of these components risks the development of a pathological situation. Some conditions where there are profound alterations in the stress axis are outlined below.

“Failure to mount a steroid response can have profound implications for life expectancy”

Depression is associated with major changes in neurotransmitter concentrations in the brain and most antidepressant drugs are aimed at reversing these changes. In addition, a common feature of depression is an excess release of corticosteroids into the blood. With successful treatment these changes in corticosteroids are also reversed. Some psychiatrists have now suggested that the neurotransmitter changes may be secondary to the changes in the stress axis and are beginning to target this directly.

Despite evidence of depression in many patients suffering trauma, corticosteroid levels in **post-traumatic stress disorder** have generally been reported to be lower than those in patients with other psychiatric disorders. It has been suggested that the acute corticosteroid response to a trauma may be lower in those prone to post-traumatic stress disorder than in others who are not. This may be linked to prior history, as described above.

Autoimmune diseases such as **rheumatoid arthritis** are associated with profound neuroendocrine changes and these have implications for the ability of the individual to respond to acute stressors. Patients

with rheumatoid arthritis are unable to mount a corticosteroid response to the stress of joint-replacement surgery, whereas patients with osteoarthritis undergoing similar surgery can. This failure to release anti-inflammatory steroids may affect the disease process. As noted above, failure to mount a steroid response can have profound implications for life expectancy, although patients with rheumatoid arthritis are not unduly troubled by minor infections. Recent studies suggest other compensatory mechanisms stimulate the stress axis under these conditions.

Stress affects every aspect of life. Whether caused by bereavement, divorce, redundancy or other situations, it can determine our ability to cope with trauma and disease and even influence what we are likely to die of. The recent advances in our understanding of the stress response hold real hope for improving the quality of life in health and disease.

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Neuro-endocrinology Briefings are produced by the British Neuroendocrine Group

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