Thus, it appears that behavioural experiences in early life permanently affect the stress response system, and the vulnerability to cognitive failure and mood disturbance. These permanent effects are mediated by brain corticosteroid receptors. This finding may open new leads towards neuropharmaceutical intervention in stress system disorders.

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STRESS, CORTICOSTEROIDS AND THE GENESIS OF DEPRESSION

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Abnormalities in the hypothalamic-pituitary-adrenal axis (HPA) have been the most consistently demonstrated biological markers in depressive illness. Numerous other endocrine disturbances have also been described, including blunted clonidine-induced growth hormone release and blunted fenfluramine-induced prolactin release. These abnormalities are generally interpreted in terms of monoaminergic receptor dysfunction. A theory will be presented which suggests that chronic stress, capable of activating the HPA, will in certain susceptible people produce changes in central monoamines. The high level of glucocorticoid receptors on such central neurones is postulated as mediating the alterations. Thus, monoamine abnormalities, rather than being a core aetiological feature of depression, are seen as secondary to HPA overdrive.

DEPRESSION IN LATE LIFE AND THE "GLUCOCORTICOID CASCADE" HYPOTHESIS

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It is well recognised that age modulates hypothalamic-pituitary-adrenal (HPA) axis activity in animals, with advancing age associated with raised corticosteroid levels. Accumulating data suggests the same is likely to be true in humans. If corticosteroids are implicated in the genesis of depression, an age related increase may explain, in part at least, the continued high prevalence of depression in late life despite the declining importance of other well established aetiological factors such as genetics.

Corticosteroids may also play an important role in mediating cognitive impairments, a prominent feature of depression and other conditions associated with raised steroid levels. Cognitive deficits correlate with steroid levels in a number of different disorders, while corticosteroid administration to controls induces impairments in memory and learning. An influential hypothesis suggests this effect on cognition may be via a specific, and potentially toxic, action on hippocampal neurones. The hippocampus inhibits the HPA axis, so any hippocampal damage due to raised steroids would itself elevate steroid levels, potentially leading to a feed-forward loop or "glucocorticoid cascade". Although this hypothesis requires further testing in humans, this presentation will demonstrate that studies of elderly patients with depression and Alzheimer's disease (which is associated with profound hippocampal changes) have started to unravel the intriguing and complex relationship between ageing, HPA axis changes, hippocampal cell loss, depression and cognitive impairments.

THE ROLE OF LIFE EVENTS IN SENILE DEMENTIA

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Dementia sufferers are highly sensitive to changes in their social environment because their impaired memory reduces their capacity to adapt to change. Earlier studies have indicated that relocation can lead to distress and confusion. Our study investigated the hypothesis that recent life events are related both to acute deterioration of senile dementia and to the patient's presentation to services, and that this may relate to life events involving change in routine and environment.

The study was a case-control comparison involving 70 patients with senile dementia admitted to a psychiatric unit. The informants were interviewed about life events in the six months before the patient's admission. The two control groups comprised of 50 dementia sufferers in the community and 50 age/sex matched fit elderly controls from a local general practice list. The principle instruments used were the Geriatric Mental State Schedule and the Bedford College Life Events and Difficulties Schedule. Additional measures to evaluate environment and routine change were developed. There was an excess of independent life events in the admitted dementia group but only when events were selected on the basis of routine and environment change rather than threat. However, in both groups of dementia sufferers severe threat events were strongly associated with depressive symptoms.

The results are interpreted in the context of potential social and neurobiological models of dementia, and in terms of the possible implications for clinical practice.

THE ACTIVITY OF CORTICOTROPIN RELEASING HORMONE (CRH) NEURONS IN THE HUMAN HYPOTHALMUS IN RELATION TO AGING, ALZHEIMER'S DISEASE AND DEPRESSION

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CRH neurons in the human paraventricular nucleus (PVN) are gradually slightly activated during the course of aging, moderately activated in Alzheimer's disease and strongly activated in depressed patients as appears from (i) the number of PVN neurons expressing CRH [1,3], (ii) the number of CRH neurons coexpressing vasopressin [2,3], and (iii) the total amount of CRHmRNA in the PVN [4].

A number of observations is not in agreement with the hypothesis that activation of the hypothalamo-pituitary-adrenal (HPA) axis results in elevated cortisol levels that would be neurotoxic and causal in the pathogenesis of Alzheimer's disease [5]. Recently we found arguments, however, that do suggest increased CRH activity might be causal in the development of depression [4].

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