The 'glucocorticoid cascade' hypothesis in man

Prolonged stress may cause permanent brain damage

JOHN T. O'BRIEN

Increased secretion of glucocorticoids such as cortisol, resulting from activation of the hypothalamic–pituitary–adrenal (HPA) axis, is a central feature of the stress response, serving to mobilise energy substrates and inhibit several 'non-vital' processes. While HPA axis activation is an essential adaptive response to stress, the deleterious effects of chronic glucocorticoid secretion, seen in Cushing's syndrome or during steroid therapy, have long been recognised. These include effects on the central nervous system such as ventricular dilatation, cerebral atrophy and impairments in cognition (Mauri *et al*, 1993). HPA axis activation is also a characteristic feature of several psychiatric disorders including depression, anorexia nervosa, schizophrenia and Alzheimer's disease (AD).

Although the effects of glucocorticoid secretion on mood are well recognised and have been reviewed (Dinan, 1994), there has recently been interest in the possibility that prolonged glucocorticoid secretion may cause deficits in memory and cognition through neurotoxic effects on hippocampal neurones. Most evidence comes from animal work, with relatively few studies examining this mechanism in humans, despite the potential relevance for normal human ageing and psychiatric disorders. This paper reviews evidence relating to the 'glucocorticoid cascade' hypothesis which proposes that prolonged HPA axis activation, however caused, can produce permanent brain damage.

ANIMAL WORK

Glucocorticoids, such as cortisol (man) and corticosterone (rats), act on receptors in the pituitary, hypothalamus and other brain regions to regulate the HPA axis by negative feedback, such that raised cortisol levels inhibit synthesis and release of corticotrophin releasing factor (CRH) and adrenocorticotrophin (ACTH). Two types of glucocorticoid receptor exist, mineralocorticoid (type I) and glucocorticoid (type II). The hippocampus has emerged as an important site of negative feedback as it contains high concentrations of both receptor types (Jacobson & Sapolsky, 1991), distinguishing it from other areas involved in feedback such as the pituitary and hypothalamus. Damage or isolation of the hippocampus in animals disinhibits the HPA axis and can result in hypercorticosalaemia both basally and after stress, as well as increasing the non-suppression of cortisol after oral dexamethasone (Jacobson & Sapolsky, 1991). In rats and primates, hippocampal neurones and glucocorticoid receptors are lost during ageing and dexamethasone resistance increases with advancing age (Sapolsky *et al*, 1986; Sapolsky & Plotsky, 1990). There is an association between high corticosterone levels in rats, hippocampal degeneration and impairments in memory and learning (Sapolsky *et al*, 1986). Cell loss in the hippocampus would be predicted to further activate the HPA axis by removing a site of negative feedback. Sapolsky and colleagues have proposed that a feed-forward loop may develop, with advancing age leading to hippocampal neuronal loss and disinhibition of the HPA axis. The resulting hypercortisolaemia would increase the rate of cell death, which would further disinhibit the HPA axis. This is the glucocorticoid cascade hypothesis of ageing (see Fig. 1).

This hypothesis is supported by the finding that reducing exposure to glucocorticoids (by adrenalectomy with low-dose steroid replacement) prevents both hippocampal degeneration and cognitive impairment in rats (Landfield *et al*, 1981), whereas young rats if stressed or given glucocorticoids exhibit both hippocampal changes and memory impairment characteristic of older animals (Levy *et al*, 1994). A naturalistic study of chronically stressed primates also demonstrated selective hippocampal cell loss (Uno *et al*, 1989) and chronic psychosocial conflict in primates causes down-regulation of hippocampal glucocorticoid receptors (Brooke *et al*, 1994). As well as ageing and stress, a simple environmental manipulation in early life, that of 'handling' (removing animals from their cage daily), can cause a permanent decrease in responsivity of the HPA axis to stress, with increased glucocorticoid receptor messenger RNA, lower glucocorticoid exposure during life and reduced cell loss in the hippocampus and less profound cognitive impairments with age (Meaney *et al*, 1981; O'Donnell *et al*, 1994). Although the significance of these observations outside the experimental setting is unclear, and parallel experiments in humans would be fraught with ethical as well as methodological problems, it is potentially of great interest in relation to psychiatric disorders associated with HPA axis changes that early life manipulations can permanently alter response to stress and ameliorate potentially deleterious effects of steroids on the brain.

While stress-induced neuronal and dendritic changes are probably initially reversible, cell death subsequently occurs (Landfield & Eldridge, 1994). The actual mechanism of cell loss remains unclear, hippocampal neurones (CA1–CA4) being most affected. They are among the most vulnerable in the brain to toxic insult and glucocorticoids appear to increase their vulnerability to a variety of stimuli, possibly interfering with energy pathways by inhibiting neuronal glucose uptake (Sapolsky *et al*, 1986) or increasing potentially toxic calcium influx to neurones (Landfield & Eldridge, 1994). Consistent with this, high doses of glucocorticoids, acting on type II receptors, reduce long-term potentiation in hippocampal neurones, a putative electrophysiological correlate of memory, and increase calcium-dependent after-hyperpolarisation (Landfield & Eldridge, 1994).

In summary, there is good evidence from animal work for the glucocorticoid cascade

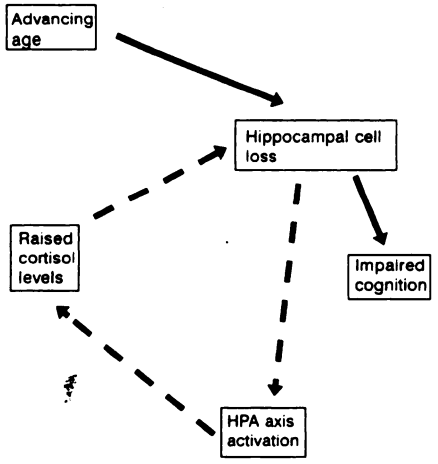

Fig. 1 The glucocorticoid cascade hypothesis

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hypothesis of ageing. However, the important clinical question is whether this mechanism applies to human ageing or disorders associated with both cognitive deficits and HPA axis activation, like depression and AD.

HPA AXIS FUNCTION IN HUMAN AGEING

A reduction in hippocampal cell loss of up to 40% occurs with advancing age, and an age-related decline in memory and cognition is well recognised, with some evidence that the two are linked (Golomb *et al*, 1993). The nature of HPA axis changes with age in humans is more controversial, although Sapolsky & Plotsky (1990) argue that few studies in humans have included truly elderly subjects and note that when subjects in their 80s and 90s are included, significant effects of ageing on HPA axis activation are seen. Many recent studies do find increasing HPA axis activity with age, possibly more pronounced in females (Heuser *et al*, 1994; O'Brien *et al* 1994). An age-related increase in paraventricular CRH and neurones co-localising vasopressin (Raadsheer *et al*, 1994) has also been reported, supporting increased activation of the axis with age. Of interest, O'Brien *et al* (1994) found an inverse correlation between post-dexamethasone levels and both age and cognitive test score in elderly subjects, suggesting that the association between increasing age, HPA axis dysregulation and cognitive impairments shown in animals may also be seen in humans. However, it cannot be determined from such cross-sectional work whether HPA axis activation causes or exacerbates age-related cognitive decline, although interestingly exogenous steroid administration causes deficits in declarative memory (Newcomer *et al*, 1994), and in one of the few prospective studies, Lupien *et al* (1994) found that cognitive decline over four years in 19 healthy controls was confined to those who had a combination of high basal cortisol levels and a significant increase in cortisol levels over time. There is a need for further longitudinal study of HPA axis function and cognition in 'truly' elderly subjects, with careful attention to possible gender differences that may exist (Heuser *et al*, 1994).

DEPRESSION

There has been extensive interest in HPA axis function in depression, a disorder known to be associated with both stress and multiple HPA axis changes, including hypercortisolism and dexamethasone resistance in up to 70% of cases (Dinan, 1994). Nearly all depressed subjects show multiple deficits on neuropsychological testing, including impairments in memory and learning. Previous formulations that these deficits were secondary to depressed mood, and so reversible on recovery from depression, have needed revision as cognitive impairments can persist on recovery from depression, particularly in the elderly (Abas *et al*, 1990), are associated with abnormalities on neuroimaging and may eventually progress to dementia in some cases. In contrast to normal ageing, it is well established that an age-related dysregulation of the HPA axis occurs in depression (Sharma *et al*, 1988). Correlations between raised cortisol levels and cognitive impairments in depressed subjects have been reported by many, but not all, authors (Mitchell, 1995), although few studies have used anything other than global and rather basic tests of neuropsychological function. Axelson *et al* (1993) found a relationship between hypercortisolaemia and reduced hippocampal volume on magnetic resonance imaging (MRI) in depressed subjects, an association which would be predicted by the glucocorticoid cascade hypothesis. However, there is no firm evidence that hippocampal cell loss occurs in depression; Coffey *et al* (1993) did not find a reduction in hippocampal volume, also assessed by MRI, in depressed subjects, neither did they replicate the positive findings of Axelson *et al* (1993) in relation to hypercortisolaemia and hippocampal size. Such contradictory findings indicate the need for further study of hippocampal size and HPA axis function in depression. It would also be of great interest to determine whether cognitive impairments remaining on recovery from depression are related to past or current HPA axis activation. Ferrier *et al* (1991) reported that dexamethasone non-suppression predicted cognitive deterioration among depressed but not demented subjects at three-year follow up. Whether such cognitive deterioration is a consequence of hippocampal cell damage due to high cortisol levels is unknown, but is clearly an important area for future research.

OTHER DISORDERS

Cushing's syndrome is associated with excess glucorticoid secretion and cognitive impairments which improve when steroid levels are lowered (Mauri *et al*, 1993). Starkman *et al* (1992), studying 12 patients with Cushing's syndrome, found reduced volume of the hippocampal formation in these patients and this was negatively correlated with plasma cortisol levels. Hippocampal size also correlated with a verbal paired associate memory test and tests of verbal recall. No control group was studied but this preliminary report provides some evidence in humans of a link between hypercortisolaemia, memory impairment and reduced hippocampal size. Post-traumatic stress disorder, another condition in which both HPA axis and cognitive changes are seen, may also be associated with decreased hippocampal size (Bremner *et al*, 1995).

Alzheimer's disease is associated with profound hippocampal cell loss and HPA axis activation (O'Brien *et al*, 1996). Are the two related, as the glucocorticoid cascade hypothesis would predict? Correlations between HPA axis changes and severity of cognitive impairment have been reported by many (though not all) studies, and O'Brien *et al* (1996) reported an association between hippocampal atrophy on MRI and HPA axis activation. In contrast, hippocampal glucocorticoid receptor gene expression is unaltered or even increased in AD (Wetzel *et al*, 1995), appearing to argue against the glucocorticoid hypothesis, which would predict that hippocampal neurones containing glucocorticoid receptors would be the most vulnerable and so their loss, combined with raised glucocorticoid levels, would be expected to result in lowered gene expression. It is possible that this paradox may reflect loss of normal receptor downregulation in response to elevated cortisol levels in AD, and this decreased plasticity may actually allow glucocorticoids to exert more potent deleterious effects (Seckl & Olsson, 1995). Alternatively, it is known that neurotransmitter systems affect glucocorticoid receptor binding, for example combined serotonergic and cholinergic lesions elevate hippocampal glucocorticoid gene expression (Seckl & Olsson, 1995). As both transmitters are profoundly depleted in AD, this mechanism may also explain why glucocorticoid receptors are not reduced.

As before, cause and effect cannot be determined from cross-sectional studies and so HPA axis changes in AD may purely be secondary to hippocampal damage. The important question is whether elevated glucocorticoids actually accelerate hippocampal damage, as predicted by the glucocorticoid cascade hypothesis. Amyloid

deposition in AD may ultimately cause cell death by altering calcium homeostasis, and the presence of high levels of glucocorticoids would be predicted to accelerate this process (Landfield & Eldridge, 1994), allowing an integration between the glucocorticoid cascade and 'amyloid cascade' hypotheses (Orrell & O'Dwyer, 1995). Weiner *et al* (1993) found a correlation between midday baseline cortisol level and cognitive decline, as measured by difference in Alzheimer's Disease Assessment Scale–Cognitive, over 12 months in 12 subjects with AD. While this preliminary study supports the role of glucocorticoids in exacerbating cognitive decline, larger studies investigating the role of hypercortisolaemia in relation to progression of impairment in AD are required.

CONCLUSION

As yet there is only limited evidence to support the hypothesis that in humans, as with animals, prolonged HPA axis activation causes neuronal, particularly hippocampal, damage with consequent impairments in cognition. However, the influence of ageing and stress, as well as changes in the HPA axis, cognitive deficits and cerebral abnormalities revealed by neuroimaging, are features shared by several psychiatric disorders and the prospect that they are closely linked merits further examination. There are several ways in which this could be achieved. Firstly, longitudinal studies in normal ageing, depression, dementia and other disorders are needed to build on cross-sectional work showing associations between hippocampal volume on MRI, hypercortisolaemia and psychological deficits. Secondly, effects of exogenous steroid administration and both acute and long-term stress on memory and cognition require further clarification. Thirdly, follow-up of cases to autopsy is needed so that clinicopathological correlations can be examined, as it would be predicted that those subjected to prolonged stress and HPA axis activation would show selective neuronal damage to hippocampal pyramidal cells and dendrites and loss of glucocorticoid receptors. Finally, the effects of anti-glucocorticoid agents on cognition should be determined. The demonstration that increased secretion of glucocorticoids in man, as in animals, may accelerate cognitive decline would have important clinical implications. It would allow early identification of those at risk of developing cognitive decline and, more importantly, allow new therapeutic strategies to be developed to slow cognitive decline in AD, depression or normal human ageing.

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JOHN T. O'BRIEN, MRCPsych, Department of Psychiatry and Institute for the Health of the Elderly, University of Newcastle

Correspondence: Dr John O'Brien, Castleside Unit, Institute for the Health of the Elderly, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE. Fax: 0191 219 5040

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