50 Increased Hypothalamo-pituitary–Adrenal Axis Activity is not Pivotal in the Pathogenesis of Alzheimer’s Disease


INTRODUCTION

Endocrine studies indicate that the hypothalamo-pituitary–adrenal (HPA) axis is activated in Alzheimer’s disease (AD) (1–4). Approximately 50% of patients with dementia have a non-suppression of plasma cortisol following dexamethasone administration (1,4–7). Interestingly, the degree of hyperactivity of the HPA axis in dementia was found to be correlated with the severity of cognitive impairment and hippocampal atrophy (4,8). Animal experiments suggested that these correlations might even be causal since hippocampal lesions, on the one hand, lead to hyperactivity of corticotropin-releasing hormone (CRH) neurons and, on the other hand, increased levels of corticosteroids may be neurotoxic and lead to irreversible hippocampal damage (9,10). According to the ‘glucocorticoid cascade hypothesis’, hippocampal damage by elevated corticosteroid levels would result in the diminishment of the normal inhibition of corticosteroids by the hippocampus and, thus, in a feedforward cascade that is supposed to be essential in the pathogenesis of AD (10).

Our recent research on the human hypothalamic CRH neurons and cerebrospinal fluid (CSF) cortisol levels has shown that the HPA axis is moderately activated, but does not seem to be relevant for the pathogenesis of AD. The activated HPA axis may be instrumental in the development of depression instead.

ACTIVATION OF CRH NEURONS IN ALZHEIMER’S DISEASE

The total number of CRH-expressing neurons in the human paraventricular nucleus (PVN) appeared to increase with age in controls and AD to the same
degree (11). Also, a second parameter for the activity stage of CRH neurons, i.e. the co-localization of vasopressin (AVP) within CRH neurons, did not show any difference between controls and AD patients. In both groups a similar increase with age in the number of CRH neurons that co-localize AVP was observed (12). However, the total amount of CRH mRNA, as determined by quantitative in situ hybridization histochemistry, was higher in AD patients than in age-matched controls (13). In conclusion, CRH neurons in AD patients were moderately activated as compared to normal controls merely due to a difference in CRH mRNA.

CEREBROSPINAL FLUID CORTISOL

The endpoint of the activation of the HPA axis in AD, i.e. cortisol production, was determined by measurement of its levels in postmortem ventricular CSF. In AD patients the mean CSF cortisol level was 83% higher than in controls. In presenile AD patients the CSF cortisol level was five times higher than in presenile controls. In contrast, senile AD patients and controls over 65 years of age did not show a significant difference in CSF cortisol levels (15), which is in agreement with similar cortisol blood levels found in these groups (1,14). This difference was due to increasing levels in controls in the course of aging. In controls over 65 years of age CSF cortisol levels were 3.5-fold higher than in controls under 65 years of age (15).

The increase of ventricular CSF cortisol with aging in control subjects supports earlier reports on age-related activation of the HPA axis (1,16,17) and also agrees with the observation that during aging the number of CRH neurons increases and starts to express AVP (11,12). The lack of a difference in CSF cortisol between senile AD patients and controls, keeping in mind the difference found in CRH mRNA in the PVN between these two groups (18), indicates that also on the pituitary and adrenal level differences between AD patients and controls are present.

IMPLICATIONS FOR THE CORTICOSTEROID NEUROTOXICITY CASCADE HYPOTHESIS

A number of observations are not in agreement with the hypothesis that activation of the HPA axis results in elevated cortisol levels that are neurotoxic and causal in the pathogenesis of AD.

If cortisol neurotoxicity would be a major component in the pathogenesis of AD, no explanation can be given for other disorders in which at least similar degrees of hypercortisolism are found that do not result in AD changes in the brain. Cushing's syndrome is characterized by hypercortisolism, memory dysfunction, cortical and hippocampal atrophy (19). However, no AD changes were reported in the brain of those examined at autopsy (20).

In addition, depressed patients showed a much stronger CRH neuron
activation than AD patients (13,18). Endocrinologically, depressed patients also have an activated HPA axis as judged from, for example, the dexamethasone suppression test (21–23). On the other hand, we were unable to find any sign of AD neuropathology in the hippocampus of the depressed patients in our study, although the oldest depressed patient was 80 years of age (18).

Moreover, if cortisol neurotoxicity would be a major factor in the development of AD pathology one cannot explain why AD patients and multi-infarct dementia (MID) patients show similar urinary cortisol levels (2), whereas MID patients do not have AD neuropathology. Multiple sclerosis (MS) patients also have a strongly activated HPA axis without the presence of AD neuropathology (24,25).

On the basis of the cortisol neurotoxicity hypothesis it is also not clear why in some AD patients, despite extensive AD neuropathology, the ventricular CSF cortisol levels are not elevated (15) and why the dexamethasone suppression test is only disturbed in 50% of the AD patients (1,3,4,6,7,26,27). Nor does the lack of a difference in CSF ventricular cortisol levels between senile AD patients and controls (15) and the similar plasma cortisol levels in these groups (1,14) tally with a pivotal role of cortisol in the pathogenesis of AD.

A last argument pleading against the idea of a crucial role for cortisol in the pathogenesis of AD is that in the early stages of the disease basal adrenocorticotropic hormone (ACTH), cortisol and the dexamethasone suppression test were all normal (28).

CONCLUSIONS

Combining all observations described in this chapter, it seems that cortisol levels are increased in AD as a result of the hippocampal damage that will diminish hippocampal inhibition of the HPA axis (29) rather than that cortisol plays a crucial role in the pathogenesis of AD. It is interesting to note that in all disorders in which an increased HPA axis activity has been reported an increased prevalence of depression was found as well. This holds true, for example, for AD (30–33), Cushing’s syndrome (20), MS (24) and depression (see above).

At present there are arguments suggesting that CRH might be causal in the development of depression: (i) the strong increase of CRH activity in major depression (13,18); (ii) the fact that symptoms resembling depression can be induced in experimental animals by intracerebroventricular injection of CRH (23); (iii) the observation that antidepressant drugs attenuate the synthesis of CRH (34–37); and (iv) the recent observation that the transgenic mouse model which has an overproduction of CRH appeared to have symptoms relating to major depression which can be counteracted by injection of CRH antagonist (38).

In conclusion, we want to propose that the HPA axis is involved in the development of depression rather than in the pathogenesis of AD.
Acknowledgements

We are grateful to the Netherlands Brain Bank (coordinator Dr R. Ravid) for brain tissue and CSF samples and to Ms T. Eikelboom for secretarial assistance. Part of this study was supported by the Amsterdam Neuroscience Network (F. C. Raadsheer) and by Mrs E. J. M. Stevens.

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