SHORT REPORT

ACTH and cortisol secretion in patients with Alzheimer's disease

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Abstract

The "glucocorticoid cascade hypothesis" for pathological ageing of the brain is supported by strong experimental data, but the clinical correlates are far less clear. The basal ACTH and cortisol secretion have been studied before and after the dexamethasone suppression test in patients in the early stages of clinically probable Alzheimer's disease and in controls, and the results were all normal. These findings do not support the hypothesis that the pathological brain ageing of Alzheimer's type is caused by hyperactivity of the pituitary-adrenal axis.

Alzheimer's disease (AD) is the most prevalent degenerative disorder causing dementia. The possible causes of AD are currently being extensively investigated, particularly the roles of heredity, viruses, environmental toxic agents and immunological factors. The aetiology of the disease, however, is still unknown. One of the less frequently investigated, though challenging, hypotheses for pathological brain ageing, is the "glucocorticoid cascade hypothesis",¹ based on evidence that increased secretion of glucocorticoids and/or prolonged exposure to hypercortisolism can damage the hippocampal neurons.^{2,3}

The hippocampus is the site of early pathological lesions of AD. This brain region, critical for memory performance, mediates the inhibition of glucocorticoid secretion arising at the end of the stress.⁴ Since hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been described in AD patients,⁵⁻⁸ hippocampal degeneration has been proposed as either the cause or the effect of HPA hyperactivity.

Adrenal hyperactivity in AD patients is not universally accepted, however, and normal activity of HPA axis has been reported.⁹⁻¹¹ Our study was performed to evaluate the clinical equivalent of the "glucocorticoid cascade hypothesis" in view of the conflicting results of previous studies. Dexamethasone suppressibility of plasma ACTH and cortisol

and the circadian rhythm of cortisol in patients with mild to moderate AD were compared with those of normal controls.

Subjects and methods

Fourteen patients with AD, 10 women and four men, aged 59-79 years, were studied. All had clinically probable AD, according to standard research criteria.¹² They had had mild to moderate dementia for two to four years.

The controls were 13 age matched subjects, four women and nine men, with normal neurological examination and history, admitted to hospital for minor medical problems. Patients and controls had been admitted to hospital for at least one week and were free of drugs when tested. The controls and 10 patients gave their consent to the study; permission was given by the next of kin for the other four patients.

Exclusion criteria were: history or clinical evidence of depression, as evaluated by the Hamilton Depression Scale; obesity and endocrinopathy; infectious and neoplastic disorders.

After an overnight fast, a blood specimen was taken at 8.00 am for basal hormone determinations. Blood samples for ACTH determination were collected in siliconised tubes containing EDTA and aprotinin, immediately centrifuged and stored in aliquots at -20°C. Blood samples for cortisol determination were collected in heparinised tubes, aliquoted and stored at -20°C.

An overnight suppression test was performed administering 1 mg of dexamethasone IM, at 11.00 pm. Blood samples were collected at 8.00 am and 4.00 pm the following day (normal inhibition of plasma cortisol < 7 µg/dl).¹³

Circadian rhythm of cortisol was evaluated at 8.00 am (normal range 6-23 µg/dl) and 11.00 pm (normal < 7 µg/dl), in seven patients, two men and five women.

Plasma ACTH was measured by an IRMA method (Nichols Institute, San Juan Capistrano, CA); normal range 9-52 pg/ml; intra-assay CV 3.0%; inter-assay CV 7.8%; sensitivity 1 pg/ml. Plasma cortisol was measured in unextracted plasma by solid phase RIA (Sorin, Saluggia, Italy).

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Results

Basal plasma ACTH and cortisol concentration, mean (SD), were similar in AD patients [23.4 (3.3) pg ACTH/ml and 15.5 (5) µg cortisol/dl] and controls [21.9 (9.3) pg/ml and 14.8 (6.1) µg/dl].

After dexamethasone administration, normal inhibition of plasma cortisol was observed in 13/14 patients and in 12/13 controls. Cortisol levels in the AD group were 1.2 (1.1) [versus 2.0 (1.3) in controls] at 8.00 am and 3.0 (5.3) [versus 2.4 (1.6) in controls] at 4.00 pm.

After dexamethasone administration, both patients and controls showed significant reductions of ACTH plasma concentrations: 8.4 (2.1) versus 7.5 (1.5) at 8.00 am and 9.2 (6.2) versus 7.8 (1.7). The degree of ACTH reduction was similar for the two groups.

The circadian rhythms of plasma cortisol were normal for the seven AD patients in whom it was studied: 16.6 (3.3) at 8.00 am, and 3.9 (1.2) at 11 pm. There was no correlation in the AD patients between severity of dementia or duration of the disease and basal and post-dexamethasone levels of ACTH or cortisol.

Discussion

This study of AD patients in early stages of their disease demonstrated normal secretory dynamics of circulating ACTH and cortisol.

The dexamethasone suppression test has been widely used to study demented patients,⁵⁻¹¹ mainly to differentiate organic dementia from depressive pseudodementia.^{5,8} Conflicting results have been reported and this test is considered to be of limited usefulness for diagnostic purposes.^{7,8}

The prevalence of non-suppressor demented patients after dexamethasone administration have differed: 7/15,⁵ 12/21,⁶ 3/18,⁷ or 7/27.⁸ The probability of being a non-suppressor correlated sometimes with age,⁸ sometimes with severity of dementia,^{6,8} sometimes with no clinical features.⁹ However, in agreement with this study, normal responses to dexamethasone inhibition in all the patients have also been reported by others.⁹⁻¹¹

Increased basal plasma cortisol was found in demented patients¹¹ and Raskind *et al*⁵ also reported blunted cortisol circadian rhythms in non-suppressor demented patients. In seven of our 14 patients, all inhibited by dexamethasone, we found normal circadian cortisol

rhythm, supporting previous reports.^{8,10}

The discrepancies among the results of various studies may have different explanations. First, earlier studies may have suffered from methodological bias due to inadequate diagnostic criteria for differentiation of primary dementia of Alzheimer's type from other types of dementias.

Moreover, some of these studies did not adequately describe the clinical features of the patients investigated. Patients included in previous studies also differed widely in age, duration and severity of disease, all parameters reported to influence the neuroendocrine profile. Finally, other methodological differences in these studies may be important: inpatient or outpatient, control groups, concomitant therapy, affective or clinical disorders. This study which supports previous research, excludes adrenal hyperactivity or HPA dysfunction as a general feature of AD at least in its early stage.

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