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A SUBTLE DISTURBANCE IN THE FEEDBACK REGULATION OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS IN THE EARLY PHASE OF ALZHEIMER'S DISEASE

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SUMMARY

In an attempt to find if a disturbance in the function of the feedback regulation of the hypothalamic–pituitary–adrenal axis is an early feature in Alzheimer's disease (AD), 35 outpatients (mean age 76.8 years) with a mild to moderate AD were compared to 20 controls (mean age 73.8 years) in their response to different doses of dexamethasone. After 0.5 mg dexamethasone, serum cortisol levels were significantly less suppressed in patients with early AD ($p = .03$) and these patients were significantly more often dexamethasone nonsuppressors (serum cortisol ≥138 nmol/l) than controls (14/35 vs. 2/20; $p = .03$). Nonsuppression to 1 mg dexamethasone did not differ between groups (2/35 vs. 0/20). Plasma adrenocorticotropin levels were significantly lower in patients with Alzheimer's disease ($n = 16$) after 0.5 mg as well as after 1.0 mg dexamethasone ($p = .01$ and $p < .001$, respectively). The relationship between cortisol resistance to dexamethasone suppression and pathophysiology of AD is discussed.

Keywords—Alzheimer's disease; Cortisol; Adrenocorticotropin; Dexamethasone suppression.

INTRODUCTION

GLUCOCORTICOID HORMONES ARE essential for survival and the stress response including energy mobilization, increased cardiovascular tone, and suppressed growth and reproduction. In contrast, excessive glucocorticoid concentrations for longer periods are associated with diabetes mellitus, hypertension, osteoporosis, and impaired immune function. Increased glucocorticoid levels are also associated with changes in mood and memory in Cushing's syndrome and in healthy individuals given high dose of corticosteroids (Murphy, 1991; Wolkowitz et al., 1990). Furthermore, evidence has accumulated for toxic effects of glucocorticoids on neurons, especially in the hippocampus where there is high density of glucocorticoid receptors (Jacobson & Sapolsky, 1991).

A substantial number of patients with Alzheimer's disease (AD) have increased circu-

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lating levels of cortisol (Davis et al., 1986; Heuser et al., 1989). Dysregulation at several sites within the limbic–hypothalamic–pituitary–adrenal (LHPA) axis may theoretically contribute to this phenomenon but changes in the negative feedback exerted by glucocorticoids on the LHPA axis have been suggested to be the link between hippocampal atrophy and hypercortisolism in AD (Landfield et al., 1978; Sapolsky et al., 1986).

However, studies of the suppressibility of the cortisol axis by dexamethasone (DEX) in patients with AD have generated conflicting results (Gurevich et al., 1990; Molchan et al., 1990; Skare et al., 1990). In a recent study of patients with early AD, it was concluded that LHPA dysfunction is not a general feature of AD in its early stages (Franceschi et al., 1991). In most studies, a standard dose of 1.0 mg DEX was given late in the evening with analysis of serum cortisol levels the following day, mainly at 1600h (Carroll et al., 1981). This procedure has been used in the investigation of adrenocortical hypersecretion in Cushing's syndrome (Nugent et al., 1965) and in patients with major depression (Carroll et al., 1981). Patients with serum cortisol levels above 138 nmol/l (5 μg/dl) have been considered as "non-suppressors" to DEX (Carroll et al., 1981). However, since the administration of 0.5 mg DEX overnight is enough to suppress the subsequent early morning peak in serum cortisol in young and old healthy individuals (Kawamura et al., 1987; Krieger et al., 1971), the use of this lower dose of DEX might allow to discover minor abnormalities in LHPA axis feedback. Furthermore, it is important to consider other factors possibly influencing post-DEX cortisol levels, such as age, gender, body mass index (BMI), and basal serum cortisol levels (Maes et al., 1991; Olsson et al., 1989). The objective of this study was to determine if patients with mild to moderate AD have a subtle disturbance of glucocorticoid negative feedback.

SUBJECTS AND METHODS

Patients (n = 35) were outpatients investigated at the Department of Psychogeriatrics, University Hospital of Northern Sweden and the Department of Geriatric Medicine, Huddinge University Hospital with a mild to moderate AD. Nineteen of the patients were admitted to hospital for investigation of their dementia during 3–10 days. Healthy age-matched controls (n = 20) were recruited from ongoing studies of healthy elderly at the Department of Geriatric Medicine in Umeå. Background data for patients and controls are given in Table I. All subjects underwent physical examination and routine laboratory screening, including serum B12, thyroid hormones, EEG, and CT scan. Serum albumin levels were normal in all subjects. All patients had two points or less on the Hachinski scale (Hachinski et al., 1975). Montgomery–Åsberg's Depression Scale was used to exclude concomitant depressive symptoms (Montgomery & Åsberg, 1979). The patients met the clinical criteria for probable AD according to NINCDS-ADRDA (McKhann et al., 1984). Cognitive function was assessed by neuropsychological assessment and Mini-Mental State Examination (MMSE) (Folstein et al., 1975). The Clinical Dementia Rating (CDR) scale was used as a global rating for staging of dementia (Hughes et al., 1982), range 0–3, where CDR = 1 is mild dementia, CDR = 2 moderate dementia and CDR = 3 severe dementia. Body mass index was calculated by dividing body weight (kg) with the square of height (m). Two patients were treated with benzodiazepines in low doses, i.e., 10 mg of oxazepam daily. No other medications were used. Exclusion criteria for patients and controls were: acute medical illness including infectious disease, endocrine disease, signs of liver disease or renal dysfunc-

TABLE I. BACKGROUND DATA OF PATIENTS AND CONTROLS

Variable	Controls	AD	*p* (two-sided *t*-test)
Age, mean (95% CI)	73.8 (70.4–77.2)	76.8 (74.7–78.9)	0.14
Sex (male/female), *n*	10/10	9/26	0.08
BMI, mean (95% CI)	25.3 (24.1–26.5)	22.6 (21.7–23.6)	0.001
MMSE, mean (95% CI)	29.4 (29.1–29.7)	18.3 (16.7–19.9)	<0.001
CDR 1, *n* (male/female)		18 (4/14)	
CDR 2, *n* (male/female)		17 (5/12)	

CDR = Clinical Dementia Rating Scale (Hughes, 1982).
BMI = Body mass index.
MMSE = Mini-Mental State Examination (Folstein, 1975).

tion, depression, prostatic disease, uterine disorders, smoking, excessive alcohol intake. The study was approved by the Ethics Committees of Umeaå University and the Karolinska Institute, Stockholm.

On the first day of study blood was drawn, after an overnight fast, at 0800h for hormone analyses. At 2200h the same day, 0.5 mg DEX was given orally (Decadron®, Merck Sharp & Dohme Internat., Rahway, NJ, USA). Blood was drawn on the following day at 0800h for hormone analyses. The same procedure was repeated with 1.0 mg DEX for patients and control subjects after an interval of at least 4 days. Blood for the determination of serum cortisol was collected into plain glass tubes after separation of serum, whereas blood for plasma ACTH was collected into chilled tubes containing EDTA, which were kept at 4°C before centrifugation. Tubes were centrifuged within 20 min of collection and plasma samples were stored at −70°C until assayed.

Serum concentrations of cortisol were determined by radioimmunoassay using a commercial kit obtained from Diagnostic Products Corp, USA. Plasma ACTH was determined in a subgroup of patients (n = 16 after 0.5 mg DEX and n = 14 after 1.0 mg DEX, respectively) and all controls by an immunoradiometric technique using a commercial kit (ACTH-fast IRMA [^{125}I]) obtained from Eurodiagnostics Ltd, Apeldoorn, The Netherlands). Detection limit and within and between assay coefficients of variation were 11 nmol/l, 4.5% and 7% for cortisol; and 0.8 ng/l, 4.5% and 5.4% for ACTH.

The data were analysed using a computerized statistical program, Systat® (Wilkinson, 1988). Data are given as means with confidence intervals (95%) unless otherwise stated. Differences between groups were assessed by two-tailed Students' *t*-tests or ANOVA unless otherwise specified in the text. Fisher's Exact Test and Pearson's correlation coefficients were used as specified in the text. In the multivariate analyses, the multiple general linear hypothesis (MGLH) module in Systat was used with hormonal parameters as dependent variables, gender and AD/healthy controls as independent factors and age, BMI and basal hormone levels as covariates. Dummy variables (0/1 corresponding to no/yes) were used when necessary and two-tailed *t*-tests were utilized to test the regression coefficients of each independent variable against the dependent variable. A p-value of $< .05$ was considered significant.

RESULTS

There was a close relationship between serum cortisol levels before the 0.5 and the 1.0 mg DEX suppression test ($r = .51$; $p < .001$). Basal serum cortisol levels were identical in healthy controls and patients with early AD; 432 nmol/l (383–481 nmol/l) vs. 437 nmol/l (388–486 nmol/l). There were no significant differences in serum cortisol levels before or after DEX between patients investigated during a short hospital stay and those investigated without admission to hospital (data not shown). Therefore, the data from these groups have been analyzed as one group.

The results from the serum cortisol analyses before and after 0.5 and 1.0 mg, respectively, are shown in Figs. 1 and 2. Serum cortisol levels were significantly higher in AD patients after 0.5 mg DEX than in control subjects; 143 nmol/l (90–195 nmol/l) vs. 77 nmol/l (40–112 nmol/l), $p = .03$. After 1.0 mg DEX serum cortisol levels were higher in AD patients, although not significantly so; 60 nmol/l (31–89 nmol/l) vs. 33 nmol/l (29–36 nmol/l), $p = .06$. If the conventional cut-off limit of a postDEX level of $\geq$ 138 nmol/l at 0800h was used (Carroll et al., 1981), 14/35 patients with AD vs. 2/20 healthy elderly were nonsuppressors after 0.5 mg DEX ($p = .03$; Fisher's Exact Test). After 1.0 mg DEX, 2/33 were nonsuppressors among AD patients and 0/20 among healthy elderly ($p = .52$, Fisher's Exact Test).

The basal plasma ACTH levels were lower in patients with AD compared with healthy elderly, although not significantly so: 7.3 ng/l (5.3–9.2 ng/l) vs. 9.8 ng/l (7.8–11.7 ng/l), $p = .06$. After 0.5 mg DEX, plasma ACTH levels were significantly lower in patients with AD: 2.9 ng/l (2.4–3.3 ng/l) vs. 4.4 ng/l (3.3–5.5 ng/l), $p = .01$. This difference persisted after 1.0 mg DEX: 2.1 ng/l (1.8–2.4 ng/l) vs. 3.4 ng/l (2.9–3.8 ng/l), $p < .001$ (Fig. 3). Basal plasma ACTH levels before the 0.5 and 1.0 mg DEX suppression tests were closely correlated ($r = 0.79$; $p < .001$).

Patients with mild dementia, that is, CDR = 1, had slightly lower post-DEX serum cortisol levels after 0.5 mg DEX [95 nmol/l (53–137 nmol/l)] than patients with moderate dementia, that is, CDR = 2 [193 nmol/l (101–285 nmol/l)].

Within the patient group, an analysis comparing suppressors and nonsuppressors after 0.5 mg dexamethasone was performed in 16 patients. Age and Mini-Mental State Examination results did not differ significantly between groups (data not shown). Nonsuppressors had higher basal serum cortisol levels [524 nmol/l (458–590 nmol/l) vs. 379 nmol/l (318–440 nmol/l), $p = .002$], but basal plasma ACTH levels between these groups did not differ [7.7 ng/l (4.8–10.5 ng/l) vs. 5.9 ng/l (3.1–8.7 ng/l), $p = .30$]. However, plasma ACTH levels after 0.5 mg dexamethasone were significantly higher in nonsuppressors compared to suppressors [3.6 ng/l (2.8–4.3 ng/l) vs. 2.5 ng/l (2.0–3.0 ng/l), $p = .01$]. There were no significant differences in plasma ACTH levels after 0.5 mg DEX between nonsuppressors and healthy controls.

Due to intercorrelations between clinical variables, multiple regression was used to determine the independent predictive values of age, gender, BMI, and basal cortisol levels besides AD per se on hormone levels. Basal serum cortisol levels were included to adjust for possible influence of basal hyperactivity in the cortisol axis. Serum cortisol levels after 0.5 mg DEX were best predicted by basal cortisol levels (standardized regression coefficient, $St.c. = .48$, $p < .001$) followed by AD ($St.c. = .23$, $p = .10$). After 1.0 mg DEX independent significant predictors for high postDEX cortisol levels were basal levels of cortisol ($St.c. = .41$; $p = .004$), AD ($St.c. = .40$; $p = .009$) and male sex ($St.c. = .37$; $p = .01$).

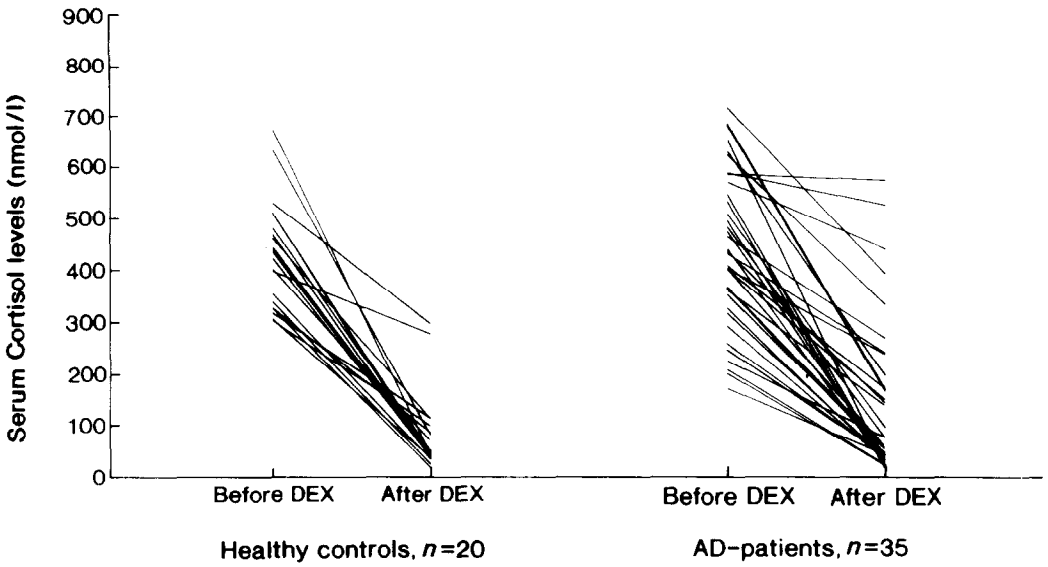

FIG. 1: Serum cortisol levels at 0800h in healthy elderly subjects (n = 20) and in patients with Alzheimer's disease (AD) (n = 35) before and after the administration of 0.5 mg dexamethasone at 2200h the evening before.

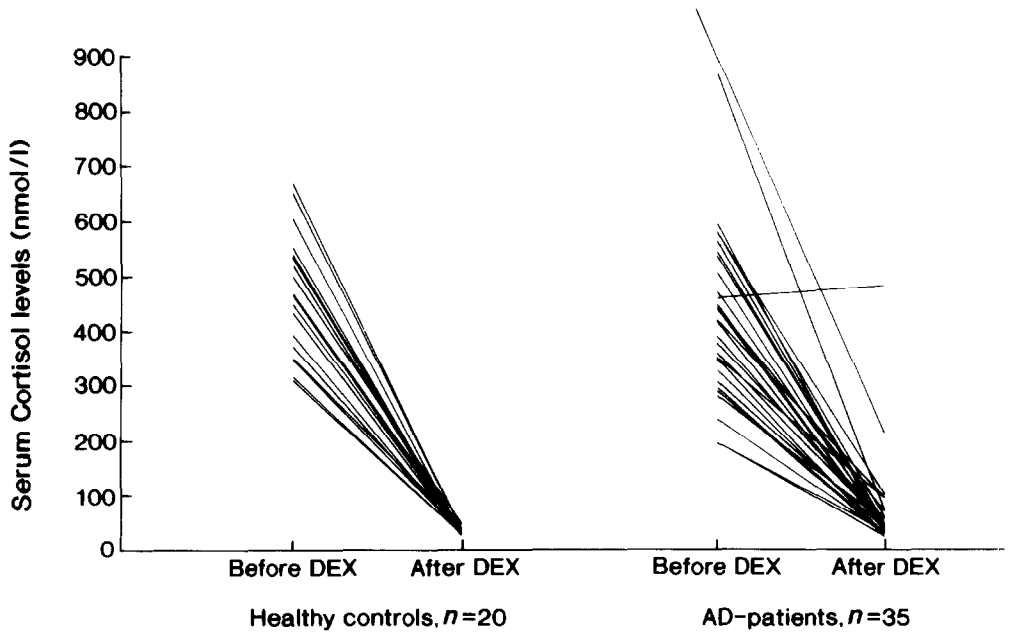

FIG. 2: Serum cortisol levels at 0800h in healthy elderly subjects (n = 20) and in patients with Alzheimer's disease (AD) (n = 35) before and after the administration of 1.0 mg dexamethasone at 2200h the evening before.

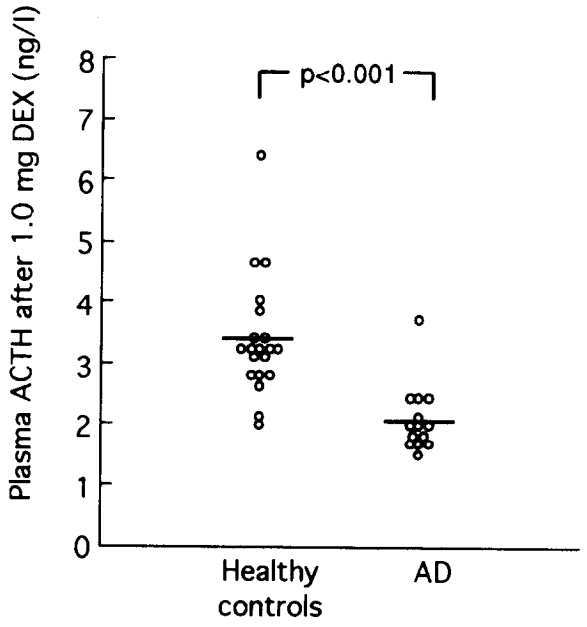

FIG. 3: Plasma adrenocorticotropin (ACTH) levels at 0800h after the administration of 1.0 mg dexamethasone in healthy elderly controls (n = 20) and in patients with Alzheimer's disease (AD) (n = 14). Mean levels are indicated by the horizontal bar. Two-tailed t-test used in the statistical calculation.

In similar multivariate models, low plasma ACTH levels after 0.5 mg DEX were best predicted by AD and basal ACTH levels (*St.c.* = .40, p = .04 and *St.c.* = .30, p = .06, respectively). After 1.0 mg DEX, the only significant independent predictor for low plasma ACTH was AD (*St.c.* = .38, p = .04).

DISCUSSION

The present results indicate that patients in the early phase of (i.e., mild to moderate) Alzheimer's disease display cortisol excessive levels after dexamethasone suppression. This is a consistent finding when possible confounding factors such as age, gender, BMI and basal hormone levels are taken into account.

In a recent study, the aim of which was to find if dexamethasone (DEX) nonsuppression was an early feature of AD, no difference was found between patients and controls; all patients were considered to be suppressors to 1.0 mg DEX (Franceschi et al., 1991). A lowering of the DEX dose might increase the probability of detecting subtle/early abnormalities in the cortisol axis feedback in AD. It is of interest that in a study of patients with major depression, who were administered 0.5 mg DEX overnight, plasma cortisol levels were strongly associated with cognitive disturbances (Siegel et al., 1989). In two earlier studies, 0.5 mg DEX was used in AD patients with different stages of dementia but there was no control group (Gurevich et al., 1990; Oxenkrug et al., 1989). In these studies, a correlation between the severity of dementia and postDEX cortisol levels was found, in one study only in females (Oxenkrug et al., 1989). The numbers of

patients showing nonsuppression to DEX was not given in these studies, and the lack of control subjects makes the interpretation of data difficult. However, our study also emphasizes the importance of considering basal serum cortisol levels as well as using hormone levels as a continous variable (Maes et al., 1991; Rose, 1987) in these analyses.

A decreased sensitivity to DEX may be due to functional alterations of glucocorticoid receptors at the hippocampus level or more likely at the pituitary level (Miller et al., 1992). It is possible that decreased sensitivity of the pituitary to DEX is related to an abnormal central control from higher brain centres responding to cortisol. Hippocampal neurons are an early and major target of damage during the course of AD (Arriagada et al., 1992; Hyman et al., 1984). A consistent finding after hippocampal lesions in both rats and primates is resistance to DEX-mediated lowering of endogenous corticosteroid levels (Jacobson & Sapolsky, 1991; Sapolsky & Altman, 1991). However, hippocampal or fornix lesions do not produce complete resistance to corticosteroid feedback; only the glucocorticoid dose required to achieve inhibition increases (Jacobson & Sapolsky, 1991). Our findings in patients with early AD emphasize the subtlety of this effect and demonstrate the need to use graded doses of DEX to characterize feedback sensitivity. Furthermore, bilateral lesions of the hippocampus or bilateral transection of the fornix of the rat produces hypersecretion of glucocorticoids, primarily by raising trough corticosteroid level (Jacobson & Sapolsky, 1991). In contrast, peak levels of corticosteroids are unchanged or even slightly reduced. This fits well with our data on equal morning basal serum cortisol levels among patients and controls.

In this study, we found two healthy individuals (males aged 83 and 84 years with body mass indices 20.9 and 25.4, respectively) who were nonsuppressors to 0.5 mg DEX by conventional criteria, but showed a normal suppression after 1.0 mg DEX. This was a consistent finding with repeated testing, and could be due to altered DEX pharmacokinetics. It would be of interest to take into account plasma DEX measurements in further studies of this patient group as differences between patients and controls in DEX metabolism might influence the results as has been suggested for patients with major depression (Lowy & Meltzer, 1987). However, it has been shown repeatedly that plasma DEX is a minor contributor to cortisol levels after DEX in patients with major depression (Maes et al., 1991). Furthermore, two earlier studies of AD patients in which plasma DEX levels after 1.0 mg DEX were analyzed revealed no differences between patients and controls (Ferrier et al., 1988; Molchan et al., 1990).

The lower plasma ACTH levels in the subgroup of AD patients in which this alteration was investigated may indicate multiple causes for an increased HPA axis activity in early AD. Earlier studies have reported equal or increased levels of plasma ACTH before or after DEX compared to controls in AD (Ferrier et al., 1988; Franceschi et al., 1991; Leake et al., 1990). However, in two of these studies inpatients with dementia were included and the majority of patients were treated with different drugs, including medications for physical illness (Ferrier et al., 1988; Leake et al., 1990). In patients with major depression, a similar disturbance of cortisol feedback is common. In these patients, some studies have shown increased circulating ACTH levels, but more often normal or low levels of ACTH have been reported (see for a review Murphy, 1991). This could be due to an increased central drive by CRH with downregulation of pituitary ACTH receptors with concomitant inhibition of corticotrophs by increased cortisol levels secondary to an increased peripheral sensitivity of the adrenal gland to ACTH (Amsterdam et al., 1989; Gold et al., 1988). Studies with CRH stimulation tests in AD have suggested a decrease in ACTH response in these patients (Dodt et al., 1991; Lesch et al., 1990). It

would thus be of interest to study adrenal sensitivity to ACTH in early AD. However, recent data from our study group suggest no increase in the cortisol response to exogenous ACTH in early AD (Näsman et al., 1995).

In the glucocorticoid cascade hypothesis, put forward by Sapolsky et al. (1986), changes in the function and/or number of glucocorticoid receptors in the hippocampus can lead to a disturbance of the negative feed-back, that is, a failure of the shut-off mechanism of glucocorticoid steroids. Thus, an early change in the hippocampus due to impairment of receptor function(s) may lead to a vicous circle where hypercortisolism is created, possibly augmented by an increased sensitivity of the adrenal glands to ACTH, causing further damage to hippocampal neurones. Glucocorticoids may accelerate neuron damage in AD through exacerbation of the cascade of injury associated with activation of exitatory amino acids and production of various neurotoxic substances and/or neurotoxins (Hortnagel et al., 1991; Kowall et al., 1991; Sapolsky, 1992). Recently, close similarities between demented and nondemented elderly individuals in the hierarchical topographic distribution of neurofibrillary tangles and senile plaques has been demonstrated (Arriagada et al., 1992). Thus, it is of considerable interest to identify possible factors that might accelerate preexisting abnormalities potentially leading to AD. We suggest that hypercortisolism, at least partly due to a disturbance of the negative feedback system, can be such a factor.

In summary, we have demonstrated cortisol resistance to DEX suppression and lower levels of plasma ACTH in early phase of AD, a phenomenon that may be of pathophysiologic importance in this disease.

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