

PAPERS AND SHORT REPORTS

Glucocorticoid receptors and depression

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Abstract

The number of glucocorticoid receptor sites in lymphocytes was estimated and plasma cortisol concentrations measured in 17 depressed patients, 12 patients with chronic schizophrenia, and 31 healthy control subjects. The number of receptor sites was significantly lower in the depressed patients than in either the controls or the patients with chronic schizophrenia, but there were no differences between the groups in the dissociation constants of the glucocorticoid receptors or the plasma cortisol concentrations. When two control subjects were studied intensively over 28 hours a slight diurnal variation in the number of glucocorticoid receptors was detected.

The lower numbers of glucocorticoid receptors in the lymphocytes of depressed patients may explain why such patients, who often have hypercortisolaemia, do not show the clinical features of excess production of cortisol.

Introduction

Patients with severe depression, as well as other types of psychoses, may have plasma cortisol concentrations as high as those reported in patients with mild or moderate Cushing's syndrome.¹ Hypercortisolaemia in psychiatric patients is not, however, associated with the physical features characteristic of Cushing's syndrome. Thus the tissue of psychiatric patients with hypercortisolaemia may be fairly insensitive to raised cortisol concentrations. We performed a study to determine whether this apparent lack of sensitivity might be due to a decrease in the number or affinity of glucocorticoid receptors in depressed patients.

Patients and methods

We studied two groups of patients. We identified 29 inpatients from the routine admissions to this hospital, of whom 17 had depression and 12 chronic schizophrenia. The patients with depression (two men, 15 women; mean age 42.7 years (range 23-62)) were interviewed using the present state examination² and the severity of their depression estimated using the Hamilton rating scale.³ All 17 met the research diagnostic criteria for major depressive disorder⁴ and could be further classified as having psychosis (five patients) or endogenous depression (12). All but two had received psychotropic drugs—namely, amitriptyline or imipramine (seven, one in conjunction with a phenothiazine), a phenothiazine alone (five), mianserin (one), lofepramine (one), and flurazepam (one). A subgroup of seven depressed patients who had not received any antidepressant drugs was compared with control subjects matched for sex and age. Scores on the Hamilton rating scale were in the range 19-38 (mean 26.9 (SD 4.5)). The 12 patients with chronic psychosis (two men, 10 women; mean age 42.8 years (range 19-66)) met the research diagnostic criteria for schizophrenia and were receiving long term neuroleptic drugs either to control continuing symptoms or to prevent relapse. All had received psychotropic drugs for more than six months—namely, thioridazine (three), flupenthixol (three), fluphenazine (two), chlorpromazine (one), trifluoperazine (one), sulpiride (one), and haloperidol (one); three had received more than one neuroleptic.

We also studied a second group comprising 31 control subjects (mean age 41.5 years (range 19-62)) recruited from the general population; 29 of these were closely matched for age and sex with the 29 patients. None of the control subjects had a history of psychiatric disorder, and none were taking drugs (including oral contraceptives).

Samples of peripheral venous blood were collected in heparinised tubes from patients and controls within 40 minutes of each other between 1130 and 1230. Two controls (one man aged 29 and one woman aged 23) were studied intensively and separately over 28 hours; 2 ml blood samples for measurement of plasma cortisol concentration were taken every 20 minutes, and 10 ml blood samples for estimation of glucocorticoid receptors were taken at intervals of four hours.

To determine the number of glucocorticoid receptors the blood samples were diluted with two volumes of phosphate buffered saline and a mononuclear cell fraction obtained by Ficoll-Hypaque density gradient centrifugation.⁵ Cells were washed twice with phosphate buffered saline and resuspended in RPMI-1640 medium. Cell suspensions (0.8 ml containing 1.5×10^6 cells) were added to 0.2 ml RPMI-1640 medium containing 50 mM *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulphonic acid (HEPES) and increasing amounts (final concentrations 1-40 nM) of [1,2,4,6,7-³H] dexamethasone (Amersham International). Control tubes for the determination of non-specific binding also contained a 200-fold excess of unlabelled dexamethasone. After incubation for 45 minutes at 37°C cold phosphate buffered saline (2 ml) was added to each tube and the cells harvested by centrifugation for five minutes at 500 g and then washed twice by suspension

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in 2 ml phosphate buffered saline and centrifugation as above. The cell pellets were suspended in 0.5 ml phosphate buffered saline, ethanol (1 ml) was added, and the suspension was transferred to phials for scintillation counting. After correction for non-specific binding, estimates of the number of binding sites per cell and the equilibrium dissociation constant were obtained.⁶ Plasma cortisol concentrations were measured by radioimmunoassay.⁷ The distribution of the data (expressed here as means (SD)) was about normal. Group results were compared by Student's paired *t* test and correlations between measures estimated by Pearson's method.

Results

Figure 1 shows the results of the intensive studies in the two control subjects (cases 1 and 2). As expected, plasma cortisol concentrations were highest during the early morning, and the number of glucocorticoid receptors varied over 24 hours. In both subjects the minimum number of glucocorticoid receptors occurred at 1600 and the maximum at 0800, the percentage differences between maximum and minimum values being 16.3% (case 1) and 8.3% (case 2).

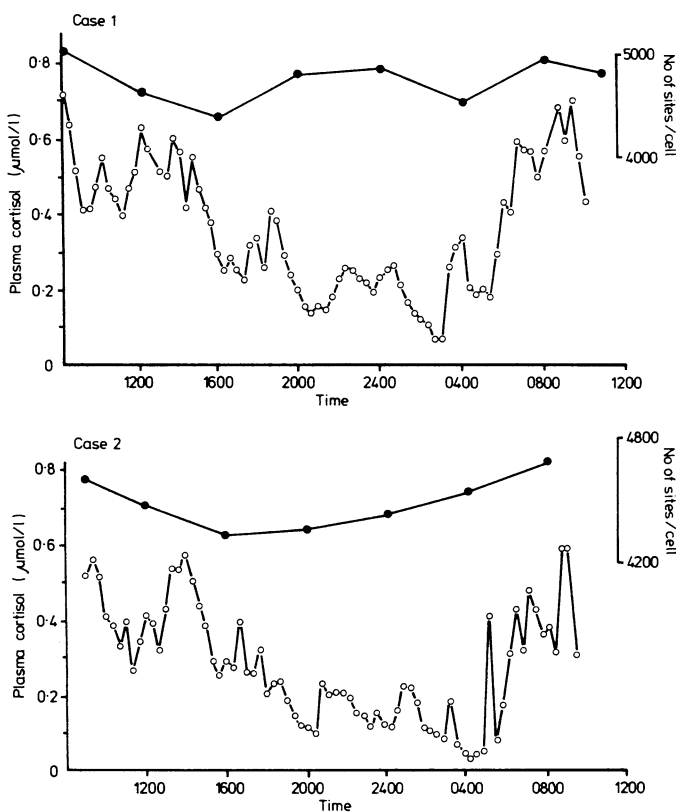


FIG 1—Plasma cortisol concentrations (○) and numbers of glucocorticoid receptors (●) in two healthy control subjects studied over 28 hours.

Conversion: SI to traditional units—Cortisol: 1 µmol/l ≈ 36 µg/100 ml.

The number of glucocorticoid receptor sites in lymphocytes from the 29 controls (means 4895 (826) sites/lymphocyte) was significantly higher ($p < 0.001$) than that in the 17 patients with depression (mean 3899 (528) sites/lymphocyte) (fig 2). The number of receptor sites per lymphocyte in the patients with chronic schizophrenia (mean 4886 (809)) was not significantly different from that in the controls. There were no significant differences between the groups in the dissociation constants for the interaction of the cellular receptor and ³H-dexamethasone, the mean values being 5.58 (0.73) mol/l in the controls, 5.47 (0.71) mol/l in the patients with chronic schizophrenia, and 5.42 (0.61) mol/l in the depressed patients.

Plasma cortisol concentrations did not differ significantly between the groups, being 0.33 (0.17) µmol/l (11.8 (6.1) µg/100 ml) in the depressed patients, 0.34 (0.19) µmol/l (12.3 (6.8) µg/100 ml) in the control subjects, and 0.39 (0.12) µmol/l (14.2 (4.4) µg/100 ml) in the patients with chronic psychosis. There was no significant correlation between the plasma cortisol concentration and the number of glucocorticoid receptors (depressed patients $r = -0.439$, control subjects $r = 0.088$, patients with chronic psychosis

$r = 0.059$) or between the number of glucocorticoid receptors and body weight ($r = 0.276$). Scores on the Hamilton rating scale did not correlate significantly with the number of glucocorticoid receptors ($r = -0.045$) or plasma cortisol concentrations ($r = 0.308$).

The numbers of glucocorticoid receptors were significantly lower ($p < 0.025$) in the seven depressed patients who had not received an antidepressant (mean 3724 (SD 395) sites/lymphocyte) than in the seven matched control subjects (mean 4738 (752) sites/lymphocyte), but there was no significant difference in plasma cortisol concentrations between these patients (mean 0.32 (0.13) µmol/l (11.7 (4.8) µg/100 ml)) and their controls (mean 0.26 (0.14) µmol/l (9.6 (5.2) µg/100 ml)) or in dissociation constants for glucocorticoid receptors (5.3 (0.3) mol/l *v* 5.4 (0.7) mol/l).

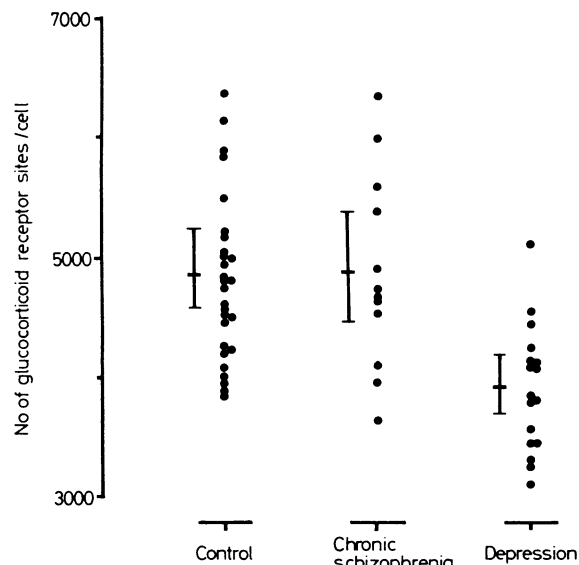


FIG 2—Mean numbers of glucocorticoid receptors (and 95% confidence intervals) in 29 controls, 12 patients with chronic schizophrenia, and 17 depressed patients.

Discussion

Our results show that the numbers of glucocorticoid receptors in lymphocytes from depressed patients are significantly lower than those in patients with chronic schizophrenia and in control subjects. These differences cannot be attributed to psychotropic drug treatment because the number of receptors in seven depressed patients who had not been treated with antidepressant drugs was also significantly lower than that in controls matched for age and sex, and the data from the schizophrenic patients show that neuroleptics do not affect the numbers of glucocorticoid receptors. The similarity between the numbers of receptors in lymphocytes from the patients with schizophrenia and from the control subjects also shows that the decrease in the number of receptors in the depressed patients could not be attributed to admission to hospital or non-specific factors associated with the illness. The difference between the depressed patients and control subjects could have arisen because of an abnormality in the diurnal variation of the number of glucocorticoid receptors in depressed patients. Disruption of the circadian rhythm of plasma cortisol concentration has been reported in depressed patients,⁸ but this is unlikely to explain our results because the maximal diurnal variation in the number of glucocorticoid receptors in our two controls (8.3% and 16.3%), though consistent in timing, seemed insufficient to explain the difference (25%) between the depressed patients and control subjects, even if the rhythm of the number of receptors in the lymphocytes was totally out of phase in these two groups.

The cause of the decreased number of glucocorticoid receptors in depressed patients is not clear. Although an increased plasma concentration of some hormones such as insulin⁹ and progesterone¹⁰ may result in a decrease in the number of receptors (receptor "down-regulation"), this is unlikely to be the case for glucocorticoid receptors as the numbers of receptors in lymphocytes from patients

with Cushing's syndrome and Addison's disease are similar to those in healthy control subjects.¹¹ The number of glucocorticoid receptors in lymphocytes is, however, significantly reduced in patients with anorexia nervosa.¹² Although dietary restrictions cannot be excluded as a possible cause of the reduced number of receptors in anorexia nervosa and in some cases of depression, it is equally plausible that the similar decline in the numbers of receptors in both conditions points to a biological link between them.

Resistance to glucocorticoids in man and other species is associated with a decrease in the number of glucocorticoid receptors in lymphoid tissue^{13, 14}; this might also explain why the clinical features of hypercortisolaemia are usually absent in severe depression and anorexia nervosa. Resistance to glucocorticoids in depression may also be related to changes in the function of glucocorticoid receptors; this is suggested by the fact that the absence of cortisol suppression in response to dexamethasone in depression is associated with a failure of dexamethasone to decrease the immunoproliferative response to mitogens in the same patients.¹⁵

Though our results and those of Kontula *et al* and Lowy *et al* might explain the apparent resistance of depressed patients to the effects of hypercortisolaemia,^{12, 14} it remains a matter for speculation whether changes in peripheral glucocorticoid receptors reflect a generalised change in numbers of glucocorticoid receptors including those in the brain. If the number of receptors decreased in the hippocampus, an area of the brain associated with control of the hypothalamic pituitary adrenal system¹⁶ and in which tricyclic antidepressants affect glucocorticoid receptors,¹⁷ this could partly explain the increased output of adrenocorticotrophin and cortisol in depression.

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Role of drugs in fractures of the femoral neck

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Abstract

To investigate the role of drugs in the rising incidence of fractures of the femoral neck in the elderly a case-control study inquiring about the use of prescribed drugs was carried out. The drug histories of 102 patients with femoral neck fractures were obtained from general practice records and compared with those of 204 controls matched for age and sex from the same practices. At the time of fracture 41 patients with fractures and 126 controls were receiving at least one prescription (relative risk of fracture of the femoral neck in patients taking drugs=0.42, $p=0.0006$). For all types of prescribed drugs except antibiotics the risk of fracture of the femoral neck was less in patients taking drugs than in those not doing so, and this was true at all times in the year before fracture. Six patients with fractures were receiving

thiazide diuretics compared with 37 controls (relative risk 0.28, $p=0.004$).

These results indicate that, contrary to popular belief, drugs that sedate or that impair postural control are not important factors in fractures of the femoral neck. The results are consistent with the hypothesis that the hypocalcaemia induced by thiazides protects against fracture, but the degree of protection is not significantly greater than that associated with other drugs.

Introduction

Several British studies have found that the incidence of fractures of the femoral neck in the United Kingdom is increasing at a much greater rate than can be accounted for by the increasing numbers of elderly people.^{1,3} Though osteoporosis is regarded as being the most important risk factor, the relation between severity of osteoporosis and risk of fracture is controversial.⁴ No change in other risk factors has been shown to account for the increase, but one study implicated use of barbiturates and others have suggested that thiazide diuretics might be protective.^{5,7} We therefore carried out a case-control study to investigate whether fracture of the femoral neck is associated with the use of various drugs that might disturb postural stability and increase any tendency to fall or might modify the development of osteoporosis.

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