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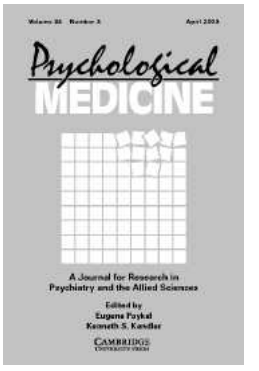
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Cutaneous glucocorticoid receptor sensitivity and pro-inflammatory cytokine levels in antidepressant-resistant depression

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ABSTRACT

Background. There is evidence to indicate that peripheral glucocorticoid receptor (GR) function is reduced in major depression, and a possible molecular explanation for this is the impact of raised pro-inflammatory cytokines. The topical steroid vasoconstriction assay provides a convenient probe of peripheral GR function. The present study sought to assess the sensitivity of peripheral GRs in antidepressant-resistant major depressives and investigate the association between GR sensitivity and circulating plasma cytokines.

Method. Nineteen antidepressant-resistant depressives together with age- and sex-matched healthy controls underwent the steroid vasoconstriction assay using three commercial preparations of corticosteroids containing clobetasol propionate 0·05%, betamethasone valerate 0·1%, and clobetasone butyrate 0·05%, corresponding to very potent, potent, and moderately potent steroid creams respectively. The pro-inflammatory cytokines, tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) were measured using enzyme-linked immunosorbent assays. The severity of the depressive episode was assessed using the Hamilton Depression Scale (HAMD).

Results. Depressed subjects had a significantly reduced vasoconstriction response across all three strengths of steroid. They also had significantly higher concentrations of TNF-α and IL-6. There was a significant inverse correlation between TNF-α concentration and vasoconstriction response and also between the HAMD score and vasoconstriction response.

Conclusions. These findings suggest that cutaneous GR function is abnormal in antidepressant-resistant depression, that circulating TNF-α may play a significant role in this abnormality and that the efficacy of topical steroids in antidepressant-resistant depressives is reduced.

INTRODUCTION

Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis in patients with major depression is one of the most consistent findings in biological psychiatry. Abnormalities include increased concentrations of cortisol in plasma, urine and cerebrospinal fluid (Gold *et al*. 1988), an exaggerated cortisol response to adrenocorticotropic hormone (Nemeroff, 1996), and a lack of suppression of cortisol in the dexamethasone suppression test (Carroll *et al*. 1981). It is postulated that these changes are due to an increase in the combined effects of the releasing factors, corticotrophin-releasing hormone and vasopressin, and a decrease in negative feedback control (Dinan *et al*. 2005). The latter may be due to a reduced sensitivity of the glucocorticoid receptor (GR), a view that is supported by the lack of cushingoid stigmata in hypercortisolaemic depressed patients (Murphy, 1991) and of abnormalities in GRs in peripheral

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blood cells (Yehuda *et al*. 1993). This suggests that GR dysfunction generalizes to tissues outside the HPA axis.

Corticosteroids influence vascular tone (Brenner *et al*. 1989) and cause blanching of the skin when topically applied. This cutaneous vasoconstrictor response has been used to compare the potency of topical steroids, as a high degree of blanching reflects high anti-inflammatory potency (Barry & Woodford, 1978). Vascular smooth muscle contains both GRs and mineralocorticoid receptors (MRs) (Scott *et al*. 1987) but only the GR is involved in cutaneous vasoconstriction (Gaillard *et al*. 1985).

A recent study has shown that patients with major depressive disorder have impaired sensitivity of peripheral GRs as demonstrated by reduced cutaneous vasoconstriction to topical steroids (Cotter *et al*. 2002). Although a significantly reduced response in depressives was found, no difference was observed between cortisol suppressors and non-suppressors.

It has been hypothesized that the altered GR function in major depression occurs via ligand-independent mechanisms involving signal-transduction pathways driven by compounds unrelated to steroids such as cytokines (O'Malley *et al*. 1995). Studies indicate that GR function can be influenced by pro-inflammatory cytokines via inhibition of GR translocation from cytoplasm to nucleus (Miller *et al*. 1999) and inhibition of GR-mediated gene transcription (Pariante *et al*. 1999). Patients with major depression have increases in pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) (Anisman *et al*. 1999; Maes, 1999). Moreover, pro-inflammatory cytokines are potent inducers of a syndrome of sickness behaviour that has many features in common with major depression, including anhedonia, anorexia, sleep disturbance and impaired cognition (Miller *et al*. 1999).

Our study sought to replicate the previous studies of altered steroid-induced vasoconstriction (SIV) major depression in a group of antidepressant-resistant depressives while also measuring their pro-inflammatory cytokine profiles using high-sensitivity assays. We hypothesized that reduced cutaneous blanching in patients with depression would correlate with increased levels of circulating pro-inflammatory cytokines.

Table 1. *Patient characteristics including final antidepressant dose which was sustained for at least 6 weeks*

Subject no.	Age (yr)	Sex	HAMD score	Medication	Dose (mg) daily)
1	57	F	31	Venlafaxine	225
2	44	F	35	Fluoxetine	60
3	55	F	28	Citalopram	60
4	64	F	25	Citalopram	60
5	46	F	23	Moclobemide	600
6	54	F	27	Venlafaxine	150
				Mirtazepine	30
7	25	F	20	Fluoxetine	40
8	59	F	14	Citalopram	60
9	41	F	12	Fluoxetine	60
10	38	F	25	Sertraline	200
11	57	F	20	Fluoxetine	40
12	56	F	31	Venlafaxine	150
				Mirtazepine	30
13	57	F	20	Paroxetine	40
14	41	M	20	Venlafaxine	225
15	63	M	13	Citalopram	40
16	22	M	10	Venlafaxine	150
17	34	M	27	Imipramine	150
18	32	M	18	Paroxetine	60
19	38	M	31	Venlafaxine	150
				Reboxetine	8

HAMD, Hamilton Depression Scale.

METHOD

Subjects

We recruited 38 physically healthy subjects between the ages of 25 and 65 years with the approval of the Ethics Committee of the Cork Teaching Hospitals. All participants gave fully informed written consent. The patient group comprised 13 females and 6 males with a mean $\pm$ S.E.M. age of $46{\cdot}4 \pm 2{\cdot}92$ years, all of who met the DSM-IV diagnostic criteria for major depression (without psychotic features). The Hamilton Depression Scale (HAMD) was used to measure severity of depression. All patients had been treated for at least 6 weeks with an adequate dose of antidepressants (see Table 1) but failed to reduce their HAMD score by at least 50%. Patients were age- and sex-matched within 5 years of controls (mean $\pm$ S.E.M. age of controls was $40{\cdot}1 \pm 2{\cdot}44$ years). Controls were recruited from a pool of known healthy volunteers.

Exclusion criteria were co-morbid psychiatric disorders in those with depression; current/past

psychiatric illness in controls or their first-degree relatives and, for both groups, the presence of inflammatory or allergic conditions, recent or current use of corticosteroids and concurrent physical illness.

Procedures

SIV assay

Three commercial preparations of corticosteroids containing clobetasol propionate 0·05%, betamethasone valerate 0·1%, and clobetasone butyrate 0·05%, corresponding to very potent, potent, and moderately potent steroid creams (Pardasani *et al.* 2000) were used to perform the vasoconstrictor assay. These widely available steroid creams provide a convenient probe of GR function and have been previously used in vasoconstriction studies (Marks *et al.* 1982). All steroid assays were carried out between 15:00 and 17:00 hours. In a single-blind random order, each of the creams was applied in 20-μl aliquots with the total amount sufficient to cover a well-circumscribed area of 2 cm diameter to the volar surface of the forearm of each subject. Non-reactive plastic guards with a circular diameter of 2 cm were used to ensure that each concentration was applied to a standardized area. After application, the forearm was wrapped in plastic clingfilm to enhance percutaneous absorption of the corticosteroid and protect the forearm from contamination. Subjects were instructed to keep the forearm free from water for the duration of the study.

The clingfilm was removed between 08:00 and 09:00 hours the next morning in order to allow resolution of any reactive hyperaemia before inspection. All examinations were carried out 18 hours after application of the creams under standardized conditions. A trained observer, blind to the potency of the steroid, assessed the degree of skin blanching using a 4- point scale to yield a SIV score: 0 = no blanching; 1 = faint blanching; 2 = obvious blanching extending to the boundary of application; 3 = intense blanching extending beyond the application site.

Assays

On the morning the vasoconstriction assay was started 6 ml of whole blood was collected between 09:00 and 11:00 hours in ethylenediaminetetraacetic acid (EDTA) tubes. Samples were centrifuged immediately and plasma frozen at -80 °C. IL-6 and TNF-α were measured in duplicate by enzyme-linked immunosorbent assays (ELISA). The dynamic range of the IL-6 assay varies between 0·16 and 10·0 pg/ml with an intra-assay coefficient of variation of 8·33% and an inter-assay coefficient of variation of 10·00% at the 2·0-pg/ml level. The range of the TNF-α assay varies between 0·5 and 32·0 pg/ml with an intra-assay coefficient of variation of 6·7% and an inter-assay coefficient of variation of 8·2% at the 6·1-pg/ml level. Samples were also taken for measurement of plasma cortisol using an unextracted, non-chromatographic radioimmunoassay. The coefficient of variation at both 100 nmol/l and 1000 nmol/l was 6%.

Statistics

Parametric data (including pro-inflammatory cytokines and cortisol) were compared using two-tailed Student's t tests. SIV scores were compared using χ^2 tests. Spearman rank correlations were used to test for associations between cytokine levels, HAMD scores, and SIV scores. GraphPad Prism version 4 for Windows (GraphPad Software, San Diego, CA, USA) was used for statistical analysis.

RESULTS

SIV

There was a highly significant difference in the distribution of blanching scores between the depressives and controls across all steroid strengths, with depressives having decreased SIV compared to controls (see Fig. 1). One hundred per cent of the controls showed full (blanching to the periphery of the test ring) or greater blanching to all three topical steroid creams, while this was markedly reduced in the depressive sample. Seventy nine per cent (79%) of depressives showed full blanching to the very potent topical steroid; this decreased to 26·3% in response to moderately potent steroid; and none had full blanching to the potent topical steroid. The comparisons were as follows: very potent topical steroid ($\chi^2 = 38{\cdot}0$, df = 3, $p < 0{\cdot}001$); potent topical steroid ($\chi^2 = 23{\cdot}3$, df = 3, $p < 0{\cdot}001$) and moderately potent topical steroid ($\chi^2 = 16{\cdot}1$, df = 3, $p < 0{\cdot}001$).

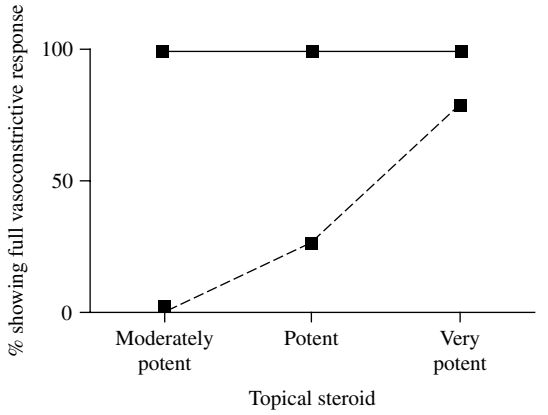


FIG. 1. Percentage of depressed subjects (--■--) and controls (—■—) displaying a full skin-blanching response to topical steroid application.

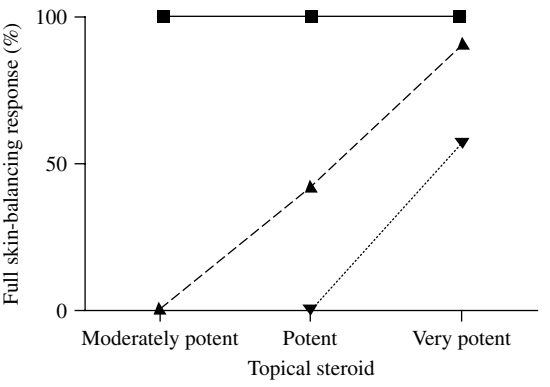


FIG. 2. Full skin-blanching response to topical steroid application in severe depression (····▼····), mild/moderate depression (--▲--) and healthy controls (—■—).

The depressive group was subdivided according to HAMD scores into a mild-moderate depression group (HAMD scores from 18 to 25) and a severe depression group (HAMD <25), and comparison was made between their group status and SIV scores (see Fig. 2). None of the mild-moderate depressives exhibited a full skin-blanching response to application of the moderately potent topical steroid; this increased to 42% in response to the potent steroid, and 91% showed full skin-blanching to the very potent topical steroid. For the severely depressed group, however, there was a marked reduction in skin-blanching response with none exhibiting a full vasoconstriction response to either the moderately potent or potent strength steroid, and only 57% displaying full skin-blanching to the very potent steroid ($\chi^2 = 21{\cdot}1$, df = 2, $p < 0{\cdot}001$).

Cytokines and cortisol

The mean ± S.E.M. TNF-α level in the depressives was $22{\cdot}02 \pm 3{\cdot}62$ pg/ml and in the controls was $12{\cdot}10 \pm 2{\cdot}56$ pg/ml ($t = 2{\cdot}255$, df = 36, $p = 0{\cdot}03$). The mean ± S.E.M. IL-6 level in the depressed was $1{\cdot}18 \pm 0{\cdot}12$ pg/ml and in the controls was $0{\cdot}73 \pm 0{\cdot}11$ pg/ml ($t = 2{\cdot}712$, df = 36, $p = 0{\cdot}01$) (see Fig. 3). There was no statistically significant difference between the serum cortisol concentrations of the depressives ($325{\cdot}5 \pm 26{\cdot}4$ nmol/l) and the controls ($294{\cdot}6 \pm 28{\cdot}3$ nmol/l) ($t = 1{\cdot}47$, df = 33, $p = 0{\cdot}15$).

Correlations

Relationships between SIV ratings in response to the moderately potent topical steroid (the lowest dose steroid which best discriminated the groups), HAMD scores and cytokine levels were explored using Spearman rank correlations. There was a significant inverse correlation between TNF-α concentrations and SIV scores in the depressives ($\rho = -0{\cdot}46$, $p = 0{\cdot}04$), as well as a significant negative correlation between HAMD and SIV scores ($\rho = -0{\cdot}66$, $p = 0{\cdot}0018$). No relationship was established between serum cortisol and either IL-6, TNF-α or SIV scores.

DISCUSSION

The main findings in this study are that depressed subjects who fail to respond to an antidepressant show a reduced vasoconstrictor response to topical application of steroids when compared to healthy matched controls, while also having significantly higher circulating pro-inflammatory cytokines. Our finding of a decreased vasoconstrictor response is in keeping with the results of Cotter *et al.* (2002) but not those of Coupland *et al.* (2003). The contrast with the latter may be due to the fact that in their study only female patients were recruited, were drug free and less severely ill than in our study.

We established a relationship between TNF-α levels and vasoconstrictor response whereby the higher the concentration of circulating TNF-α, the lower the score on the vasoconstriction

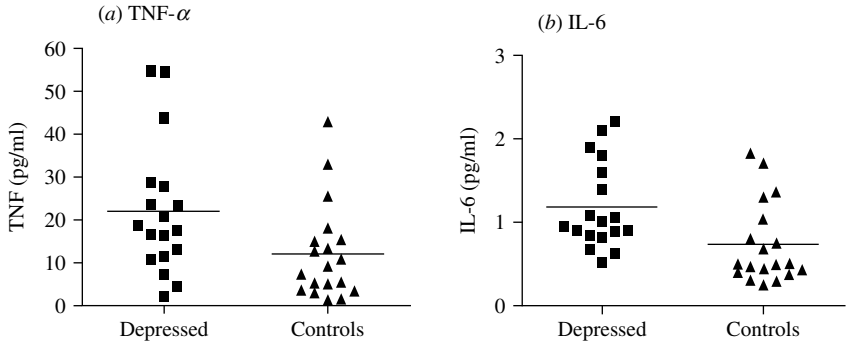


FIG. 3. (*a*) TNF-α and (*b*) IL-6 levels in patients with major depression (■) compared to healthy controls (▲).

assay (implying the less sensitive the cutaneous GR). The negative correlation found between HAMD scores and vasoconstrictor response implies that there is an inverse relationship between the severity of the depressive episode and the sensitivity of peripheral GRs.

As previous studies have demonstrated that the reduction in peripheral GR sensitivity in depression may not be the result of hypercortisolaemia (Cotter *et al.* 2002), the finding of an association between pro-inflammatory cytokines and GR sub-sensitivity in this study suggests a possible causal mechanism for altered peripheral GR sensitivity in major depressives. We were unable to establish a relationship between cortisol and GR response, which supports the conclusion of Cotter *et al.* (2002) that cortisol is not directly responsible for the sub-sensitivity. However, a limitation of our study is the fact that only one sample was taken for cortisol estimation which provides a crude measure of cortisol production. No measure of cortisol level following the application of the steroid cream is available. Furthermore, we did not complete a dexamethasone suppression test, which would have yielded interesting data on the response of a separate population of GRs.

The molecular mechanisms through which cytokines can influence the GR have been explored in previous studies (Miller *et al.* 1999; Pariante *et al.* 1999). These found that cytokines can exert their effects on GR function by one of two ways. First, through binding to specific membrane receptors and activation of secondary messenger cascades, they inhibit GR-mediated gene transcription, and furthermore, they inhibit GR translocation from cytoplasm to nucleus via possible interactions with heat-shock proteins, one of the constituents of the cytoplasmic GR complex. Wang *et al.* (2004) demonstrated that pro-inflammatory cytokine inhibition of GR function is associated with activation of the p38 mitogen-activated protein kinase signal transduction pathway. This may explain the current findings.

The skin-blanching assay is a well established method for ranking the efficacy of corticosteroids, with the degree of vasoconstriction correlating well with the clinical efficacy of the steroid (Barry & Woodford, 1978). It has been shown to be sensitive, precise and reproducible (Place *et al.* 1970; Barry & Woodford, 1978). The inference from our study is that the efficacy of topical steroids in patients with inflammatory skin disorders and co-morbid depression is markedly reduced, with impairment in efficacy being correlated with the severity of depression. This would be of importance in conditions such as eczema and psoriasis, which are known to have significant co-morbidity with depression (Jowett & Ryan, 1985) and for which topical steroids are often the first-line treatment.

It has previously been shown that depressed mood can impact negatively on the course of inflammatory bowel disorder (IBD) (Mittermaier *et al.* 2004). Patients with IBD and co-morbid depression have been found to require higher doses of steroids than those with IBD alone (Szigethy *et al.* 2004). Depressive symptoms in asthmatics predict worse asthma outcomes (Mancusso *et al.* 2001) and, interestingly, limited data suggest that administration

of antidepressants to asthmatics can improve asthmatic symptoms as well as depression (Zielinski *et al.* 2000).

The findings of our study suggest the link between depression and inflammatory disorders may be found in the expression of pro-inflammatory cytokines which can produce symptoms of depression, render the GR receptor sub-sensitive and thereby potentially result in inflammatory disorders requiring higher doses of steroids for effective treatment.

However, it is inappropriate to suggest that a sub-sensitive cutaneous GR necessarily means that peripheral GRs in general are also sub-sensitive as there is data suggesting that glucocorticoid sensitivity in depressed patients remains intact in some tissues or compartments. Specifically, depressed patients have been found to exhibit increased intra-abdominal fat deposition (Thakore *et al.* 1997) and decreased bone mineral density (Michelson *et al.* 1996) suggesting that GRs in these tissues may maintain their sensitivity to glucocorticoids, although this view is rejected by Raison & Miller (2003) who argue that such changes are due to insufficient glucocorticoid signalling. Future studies should examine GR function in different tissues in the same patients whilst provided a more in-depth analysis of cortisol production.

Chronic antidepressant use in animal studies has been reported to up-regulate GRs (Seckl & Fink, 1992), a finding which could not explain our results of reduced sensitivity to topical steroids. However, such up-regulation may not occur in antidepressant-resistant depression. It is also of note that in previous clinical studies, no difference in lymphocyte GRs has been shown between medicated and non-medicated depressed patients (Yehuda *et al.* 1991). It is possible however, that SIV may be influenced by effects of antidepressants on vascular tone downstream to GRs. For example, glucocorticoids potentiate noradrenaline-induced vasoconstriction (Walker & Williams, 1992), and noradrenergic function may be increased by antidepressants (Checkley *et al.* 1986). Replication of this study in drug-free depressives would be of interest in controlling for this effect.

In conclusion, this study suggest that cutaneous GR function is abnormal in antidepressant-resistant depression, that circulating TNF-α may play a significant role in this abnormality and that the efficacy of topical steroids in antidepressant-resistant depressives is reduced.

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DECLARATION OF INTEREST

None.

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