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BRIEF COMMUNICATION

Biochemical stress of caring

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ABSTRACT

Background. Carers of patients with clinical dementia have increased rates of depressive illness but the biological mechanisms by which the stress of caring can lead to mood disorders is not well understood.

Methods. We recruited 30 full-time carers of patients with dementia and 28 age and gender-matched controls. None of the subjects were suffering from a significant depressive disorder. We measured salivary cortisol at four time points throughout a single day and also took a single fasting morning blood sample for plasma tryptophan.

Results. Salivary cortisol levels were significantly higher in carers than controls at 12.00 h and 22.00 h. Plasma total tryptophan but not free tryptophan levels were significantly lower in carers.

Conclusions. The changes found in these non-depressed carers were essentially similar to those in patients with major depression. We suggest that increased cortisol secretion and lowered tryptophan availability increase the risk of mood disorders in carers.

INTRODUCTION

Caring for a person with cognitive decline is stressful and carries a substantially increased risk of depressive illness (Ballard *et al*. l995). The biological mechanisms by which environmental stress is translated into clinical depression are not well understood but increases in plasma cortisol are likely to be involved (see Herbert, 1997). In addition, depressive illness is characterized by hypercortisolaemia and lowered plasma concentration of total tryptophan, the amino acid precursor of serotonin (5-HT) (Maes *et al*. 1987; Anderson *et al*. 1990*a*; Cowen, 1998). The aim of the present study was to assess salivary cortisol secretion and plasma tryptophan levels in non-depressed carers of people with dementia.

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METHOD

Subjects

We studied 30 subjects (18 women, 12 men), who were the main caregivers of patients with clinical dementia. They were recruited via Old Age Psychiatry teams in Oxfordshire and West Berkshire. Their mean age was 68·8 years (range 30–75 years). All but one of the female subjects were post-menopausal. On the basis of the Structured Clinical Interview for DSM-III-R (SCID) we determined that none met criteria for current major depression. One subject met criteria for social phobia, another had subthreshold major depression and a third had subthreshold generalized anxiety disorder. Five subjects had a past history of major depression. None was taking psychotropic drugs although 21 were taking regular medication, mainly antihypertensives and analgesics. Two of the carers were taking steroid inhalers for asthma

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Table 1. *Mean (±S.E.M.) plasma tryptophan and salivary cortisol in carers and controls*

	Tryptophan (μg/ml)	Cortisol† (μg/100ml)			
		08.00 h	12.00 h	16.00 h	22.00 h
Carer	9·1±0·3*	35·6±3·8	17·2±1·8**	11·4±1·5	7·8±1·0**
Control	10·2±0·3	28·8±2·4	11·0±1·2	11·9±1·2	4·7±1·4

** Significantly different from control: *$P < 0·05$, **$P < 0·005$, unpaired t test.
† ANOVA on log transformed data showed main effect of diagnosis ($F = 6·1$, $P = 0·017$) and time × diagnosis interaction ($F = 4·2$, $P = 0·008$). Cortisol values are antilog mean ± S.E.M.

and another was taking propanolol for hypertension. Apart from this no subject was taking medication known to interact directly with 5-HT mechanisms or the HPA axis. Subjects completed the Caregiver Burden Inventory (CBI) (Novak & Guest, 1989) and the Beck Depression Inventory (BDI) (Beck *et al.* 1961).

We also studied 28 control subjects (17 women and 11 men) who were non-caregivers. Their mean age was 68·1 years (range 35–84 years). All but one of the female subjects were postmenopausal. None met criteria for current major depression or any other Axis I disorder on the SCID but four had a past history of major depression. None was taking psychotropic drugs although 17 were taking other regular medication, again mainly antihypertensives and analgesics. Controls also completed the BDI. All subjects gave written informed consent to the study, which was approved by the relevant local ethics committees.

Biochemical measures

Subjects collected four saliva samples on a single day at 08.00 h, 12.00 h, 16.00 h and 22.00 h. Salivary cortisol was measured by a direct radioimmunoassay that used ^{125}I-cortisol (Amersham International) and Sac-Cel antibody (IDS). The intra- and inter-assay coefficients of variation over the range encompassed by the standard curve were 2·4% and 6·0% respectively. Venous samples for plasma tryptophan were taken after an overnight fast on a separate day from the saliva collection. Plasma total and free tryptophan were measured by automated high performance liquid chromatography with coulometric end-point detection. The free fraction of TRP was obtained by filtering plasma through a 10K cut-off filter using high-speed centrifugation. The resulting supernatant was injected into the HPLC system. The intra- and inter-assay coefficients of variation for total tryptophan over the range encompassed by the standard curve were 1·8% and 6·3% respectively. The corresponding values for free tryptophan were 6·6% and 6·2%.

Statistical analysis

The salivary cortisol data were log transformed to approximate to a normal distribution and analysed with a repeated measures analysis of variance (ANOVA) with 'time' (time of sampling) as a within-subject factor and diagnosis (carer *versus* control) as a between subject factor. Students unpaired *t* test was used as a *post-hoc* range test. Differences in plasma tryptophan levels between carers and controls were also analysed with an unpaired *t* test (two-tailed). Correlations were carried out using Pearson's product moment.

RESULTS

Salivary cortisol levels in the carers were significantly higher than controls. The ANOVA showed a significant main effect of diagnosis ($F = 6·1$; df = 1,56; $P = 0·017$), and a significant interaction between diagnosis and time ($F = 4·2$; df = 3,56; $P = 0·008$) (see Table 1). *Post-hoc* testing showed that cortisol levels were significantly higher in carers at 12.00 h and 22.00 h. Fig. 1 shows a scatterplot of the cortisol values for carers and controls at 12.00 h. Fasting plasma total tryptophan levels were slightly but significantly lower in carers (Table 1). There was no difference in free tryptophan levels. There were no significant differences in 12.00 h cortisol level and total tryptophan levels in subjects with a past history of depression and those without.

Depression scores, as measured by the BDI,

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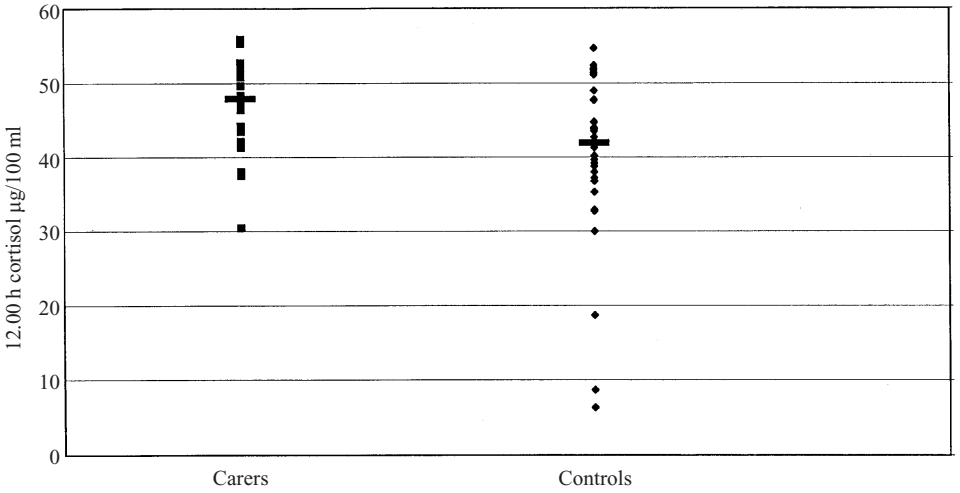


FIG. 1. Individual 12.00 h salivary cortisol concentrations in carers ($N = 30$) and controls ($N = 28$). Bars show median values. Median values in the carers are significantly higher than in the controls ($P = 0{\cdot}004$, Mann–Whitney test).

were modestly increased in the carers relative to the controls ($8{\cdot}3 \pm 0{\cdot}9$ *v.* $4{\cdot}3 \pm 0{\cdot}6$, $P = 0{\cdot}001$). In the carers there was no significant correlation between the BDI and 12.00 h cortisol level ($r = -0{\cdot}01$, $P = 0{\cdot}97$) or BDI and total tryptophan ($r = 0{\cdot}09$, $P = 0{\cdot}66$). The CBI correlated significantly with the BDI ($r = 0{\cdot}48$, $P = 0{\cdot}004$) but again in the patients CBI failed to correlate with 12.00 h cortisol ($r = 0{\cdot}039$, $P = 0{\cdot}84$) or total tryptophan ($r = 0{\cdot}34$, $P = 0{\cdot}07$). There was also no significant correlation between 12.00 h cortisol and total tryptophan ($r = -0{\cdot}15$, $P = 0{\cdot}42$).

DISCUSSION

Carers of patients with clinical dementia have elevated salivary cortisol levels and diminished total plasma concentrations of the serotonin precursor, tryptophan. These abnormalities are essentially similar to those seen in groups of patients with major depression (Maes *et al.* 1987: Anderson *et al.* 1990*a*). However, the carers in this study were chosen to be free of significant depressive disorder. In addition, there was no correlation between the BDI and 12.00 h cortisol level or plasma tryptophan concentration. This makes it unlikely that our findings can be accounted for by the presence of mild depressive symptomatology.

Indeed, in depressed patients elevated cortisol levels are more likely to be seen in severely ill subjects, particularly those who are hospitalized (Maes *et al.* 1994). Thus the relationship between the increased cortisol secretion we have found in non-depressed carers and that observed in some depressed patients may not be straightforward. It is possible for example that some of the carers may have been acutely stressed by events around the time of the salivary sampling. We did not record stress levels on the day of sampling and therefore cannot exclude this possibility.

Our finding of elevated cortisol levels in carers of dementia patients is consistent with some but not all previous investigations (Mills *et al.* 1997; Bauer *et al.* 2000). In addition, we found moderately lowered levels of plasma total tryptophan. In depressed patients plasma total tryptophan concentrations are also lowered but plasma levels of other large neutral amino acids are unchanged. This means that the plasma ratio of total tryptophan to other neutral amino acids (TRP: NAA) is decreased, which diminishes the availability of tryptophan for brain 5-HT synthesis (Maes *et al.* 1987; Anderson *et al.* 1990*a*). In the present study it was not possible, for technical reasons, to measure the concentration of other neutral amino acids but this will be an important assessment in future investigations, The modest decrease in plasma total tryptophan also requires replication.

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Plasma free tryptophan was not lowered in the carers. Both free tryptophan and the TRP: NAA ratio contribute to brain 5-HT synthesis but the relative importance of each process probably depends on the prevailing physiological circumstances (see Curzon, 1979). In subjects who lose weight by dieting, for example, plasma free TRP is not altered but plasma total tryptophan is lowered resulting in a diminished TRP:NAA ratio and changes in brain 5-HT function (Anderson *et al*. 1990*b*). We did not record weight changes in the carers and therefore cannot exclude recent weight loss as an explanation for their lowered total tryptophan levels.

It is possible that low plasma tryptophan in carers is secondary to elevated cortisol secretion. Cortisol can induce hepatic tryptophan pyrolase, which shunts tryptophan towards the kynurenine pathway (Green & Curzon, 1968). It is also possible that diminished tryptophan availability could be secondary to the changes in immune function that have been reported in dementia carers (Bauer *et al*. 2000). Elevated cortisol secretion could further compromise brain 5-HT function by decreasing expression and function of 5-HT receptors (see Deakin & Graeff, 1991; Dinan, 1994; Chaouloff, 1995).

We suggest that the abnormalities in cortisol secretion and plasma tryptophan levels found here could act as biological risk factors which increase the likelihood of depressive disorders in dementia carers, particularly those who are vulnerable to mood disorders for other reasons (see Smith *et al*. 1987). Follow-up studies will be needed to test this proposal adequately.

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