Psychoneuroendocrinology (2006) 31, 900–904

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SHORT COMMUNICATION

The cortisol awakening response is blunted in psychotherapy inpatients suffering from depression

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Received 1 February 2006; received in revised form 20 March 2006; accepted 24 March 2006

KEYWORDS
Cortisol;
Saliva;
Stress;
Depression;
Psychotherapy;
HPA axis

Summary Determining the salivary awakening cortisol response (ACR) is a non-invasive, reliable method to detect changes in the hypothalamus–hypopituitary–adrenal (HPA) axis. Although a role of the HPA axis in depression is widely recognized, data on the ACR in depressive patients are still scarce and inconsistent. The present study assessed the ACR in depressed patients admitted for inpatient psychotherapy and a comparison group of other psychiatric diagnoses under the same conditions. The ACR was found to be attenuated in depressed as compared to non-depressed patients. This finding is in contrast to previous studies in healthy subjects or depressed outpatients and suggests a blunted rather than an excacerbated HPA reactivity. Further studies will be needed to disentangle the complex relationship between depression and the ACR.

1. Introduction

Alterations of the hypothalamus–hypopituitary–adrenal (HPA) axis in chronic stress and major depression have repeatedly been demonstrated, the most consistent findings being elevated cortisol levels in the peripheral blood and non-suppression in the dexamethasone test (Holsboer, 2003). The awakening cortisol response in saliva (ACR) has been identified as a non-invasive and reliable method to detect subtle changes in the HPA axis. It allows repeated assessment and has been shown to have a high intra-individual stability (Pruessner et al., 1997) and to be more consistent between studies than absolute cortisol values (Clow et al., 2004).

An enhanced ACR has been demonstrated in healthy subjects under chronic stress either manifested as high work load or social stress (Wüst et al., 2000); in contrast, teachers suffering from burn-out exhibited a blunted morning cortisol rise (Pruessner et al., 1999). A community study showed 74 subjects with chronic health problems—

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doi:10.1016/j.psyneuen.2006.03.005

seven of which were classified as 'psychiatric'—to have a trend for a blunted ACR as compared to 103 healthy volunteers (Kudielka et al., 2003). In healthy college students, higher levels of self-reported depressive symptomatology were associated with a higher ACR (Pruessner et al., 2003a) and acutely depressed subjects in the community were also shown to have an enhanced ACR as compared to controls (Bhagwagar et al., 2005). However, other studies found an unchanged salivary cortisol or blunted response to a stressor in association with depressive symptoms (Strickland et al., 2002; Burke et al., 2005a). In summary, data on the influence of psychosocial variables and psychiatric illness on the ACR are still scarce and inconsistent (Clow et al., 2004) and comparison is difficult due to different methodologies and study designs.

The present investigation used the ACR to determine alterations of the HPA axis in depressed inpatients admitted for psychotherapy. In order to control for the undoubtedly stressful experience of the admission itself, this group was compared with subjects in the same psychotherapy program not suffering from depressive symptoms.

2. Methods

With approval of the local ethics committee and adequate understanding and written consent of 72 subjects admitted to participate in an inpatient psychotherapy program, free salivary cortisol levels were assessed at 15-min intervals for half an hour directly after waking. Patients were asked to remain in bed for the first 15-min interval and to refrain from drinking and eating for the entire sampling period. Waking took place by a member of the hospital staff between 07.00 and 07.15 h on the day after admission; all participants were reminded of all three saliva samples, samples were collected under supervision and subjects were asked to fill in a protocol stating subjective sleep quality on a 10 point scale, time of going to bed, waking up and collecting the samples to ensure adherence. In the case of non-adherence (i.e. awakening before the waking, rising before the second sample was collected), the procedure was repeated on the following day, which happened in less than 10% of patients. Saliva was collected using Salivette collection devices (Sarstedt, Nümbrecht, Germany). Free cortisol was measured using a commercially available immunoassay (IBL, Hamburg, Germany). Inter-assay and intra-assay variations were $<15\%$.

Using the three parameters for every subject, the mean free cortisol (mean) and the increase between baseline and 30-min-sample (delta) were determined. As suggested by several authors (Pruessner et al., 2003b; Clow et al., 2004), the area under the curve relative to zero (AUC_G) and the area under the curve with respect to increase (AUC_i) were computed as well. As correlations between AUC_G and mean free cortisol and between AUC_i and delta were high ($r>0.9$), only the mean and delta are given with emphasis on the delta because focus of the present article is the sensitivity of the system and the relation to perceived stress rather than physical complaints (see Pruessner et al., 2003a).

The group of 57 depressed subjects fulfilled criteria for a major depressive episode according to DSM-IV and ICD-10. None of the subjects were classified as 'with melancholic features' or 'somatic syndrome', which has previously been suggested to be associated with HPA overdrive as opposed to atypical depression having been linked to hypoactivity of the HPA axis (Antonijevic, 2006). The depressed subjects were compared with a group of 15 patients suffering from other than depressive symptoms (nine personality disorder (two comorbid with anxiety disorder), six anxiety disorder, two somatoform disorder). Thirty-nine patients received different antidepressants on admission (24 selective serotonine reuptake inhibitors, 9 mirtazepine, 6 trimipramine or amitryptiline) for a mean duration of 7.44 weeks, whereas 33 subjects were medication free (24 in the depressed group and 9 in the mixed diagnostic group).

Statistical analysis was performed using non-parametrical tests (Mann–Whitney-*U*-test and Spearman rank order correlations) because of the scewness of data. The level of probability was set at $p<0.05$.

3. Results

Of the 72 participants 57 (79.2%) suffered from depression as stated above, 21 (29.2%) from an anxiety disorder, 9 (12.5%) from obsessive–compulsive disorder with some overlap because of more than one diagnosis. Axis II comorbidity was high with 39 patients (54.2%). The subjects—of whom 43 (59.7%) were female—were between 20 and 69 years of age. There were no significant differences in age or gender ($\chi^2=1.459$) or subjective sleep quality ($p=0.786$), but depressed subjects reported a longer duration of symptoms in concordance with the often chronic course of this disorders in the sample presented. 49.1% (28 subjects) reported recurrent depressive episodes. Table 1 gives an

Table 1 Demographic and cortisol awakening response (CAR) information of the psychiatric patients participating in this study.

	Entire study population	Depressed subgroup	Non-depressed subgroup	*p*
Age (years)	40.54 (11.87)	41.40 (12.4)	37.27 (9.3)	0.232
Percent female	59.7	56.1	73.3	0.227
HAMD score	20.26 (5.73)	20.33 (5.93)	20.0 (4.99)	0.835
Duration of symptoms (months)	52.41 (76.16)	44.51 (73.05)	84.62 (83.0)	0.005
Cortisol increase (delta)	4.28 (9.0)	3.47 (9.6)	7.66 (4.7)	0.049
Mean cortisol	19.01 (8.4)	19.42 (8.5)	17.32 (8.2)	0.194

Age, gender distribution, HAMD scores and duration of symptoms (months) for the entire study population and the depressed and non-depressed subgroup; increase of free cortisol between wake up and 30 min (delta), mean free cortisol of the three collected samples (mean; nmol/l; standard deviation in brackets). p=level of probability for a difference between the depressed and non-depressed group.

overview of the relevant data on both subgroups and the entire study population.

The mean baseline total free cortisol directly after waking was 16.93 nmol/l. A significant number of subjects ($n=26$) did not show the typical awakening cortisol response seen in healthy volunteers, but according to Wüst and colleagues can be defined as non-responders (increase of free cortisol after waking less than 2.5 nmol/l). In the entire group, free cortisol increased to a mean of 20.87 nmol/l 30 min after waking. The delta (AUC_i, respectively) as primary focus was 4.28 (4.69) nmol/l (Table 1). The literature data suggest a delta in healthy subjects of roughly 9 nmol/l (Clow et al., 2004).

Depressed patients exhibited a significantly lower rise in free cortisol levels than non-depressed subjects ($p=0.049$) with a delta of 3.47 nmol/l in the depressed and of 7.66 nmol/l in the non-depressed subgroup. This appeared in correlation (Spearman rank $r=-0.46$, $p<0.001$) with a trend for higher baseline free cortisol levels in the depressed patients ($p=0.072$). For the significant differences in the ACR delta as well as for the trend in differences in the wake up value Cohen's d for pooled variances were calculated (Cohen, 1988). The effect size for the delta was -0.47, which is indicative of a medium sized effect. The effect size for the differences in wake up levels was similar (0.47). As displayed in Fig. 1 both groups did not differ in their cortisol levels at 15 min ($p=0.49$) or 30 min ($p=0.85$) or in their mean cortisol levels ($p=0.39$).

Nearly all of the non-responders (25 out of 26) were in the depressed subgroup. Thus, although subjects suffering from depression constituted only 79.2% of all patients, they accounted for 92% of the non-responders, which represents a statistically significant connection (Pearson $\chi^2=7.329$; $p=0.007$). The non-responders showed higher basal cortisol levels of 20.52 (SD 10.32) nmol/l as compared to the responders with 13.56 (SD 7.61) nmol/l ($p=0.003$), comparable levels at 15 min ($p=0.959$), but lower cortisol levels at 30 min with 17.05 (SD 8.93) nmol/l as compared to the responders with 24.33 (SD 8.34) nmol/l ($p=0.003$). There were no differences between non-responders and responders regarding Hamilton Depression Rating Scale scores ($p=0.245$) or Beck Depression Inventory scores ($p=0.707$), but the non-responders were significantly older at 43.85 (SD 12.72) years than the responders at 36.06 (SD 10.02) years. When analysing only responders, the observed significant difference of the ACR between depressed and non-depressed subjects was reduced to a trend ($p=0.083$). The ACR did not differ

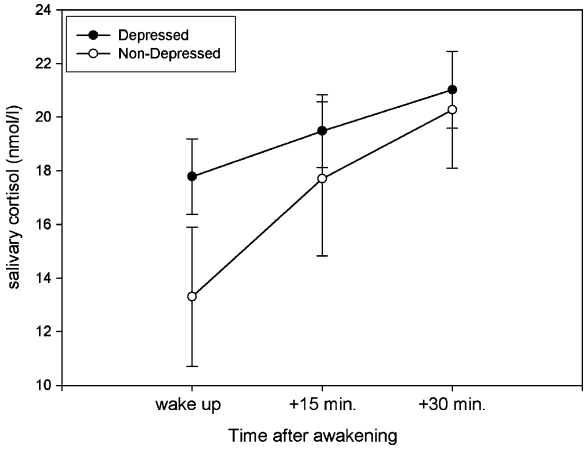

Figure 1 Cortisol awakening response (CAR) in depressed and non-depressed psychiatric patients admitted to an inpatient psychotherapy program. Depressed patients tended to have a higher wake up level ($p<0.10$) and had a significantly lower CAR delta increase ($p<0.05$). For additional analyses see result section. Error bars represent standard error of the mean (SE).

significantly between patients on and off medication. This was the case for the entire sample as well as for the depressed group only ($p > 0.1$).

4. Discussion

The awakening cortisol response (ACR) is increasingly regarded as a useful measure to detect subtle changes in the HPA axis. Although the importance of the HPA axis in psychiatric disorders, particularly in depression, is recognized, data on the ACR in psychiatric patients are still scarce and conflicting.

The present study investigated salivary free cortisol levels and the ACR in a sample of 72 patients admitted to an inpatient psychotherapy program. In comparison with literature data for healthy subjects, all patients exhibited a blunted response to awakening (Clow et al., 2004).

In the depressed subjects, the cortisol rise after awakening was significantly lower than in the non-depressed participants. Taking into account the literature data, this was not due to an enhanced ACR in the latter. There was a trend for higher basal free cortisol levels in the depressed subjects and both groups achieved similar 30-min levels. An association of higher wake up cortisol levels with an attenuated ACR has previously been reported in healthy subjects (Williams et al., 2005).

There are some limitations to the study presented: firstly subjects were not medication free. A possible influence of antidepressants on HPA activity (Schule et al., 2003) and the ACR has been reported (Laakmann et al., 2004), particularly for mirtazepine, which was taken by nine of the depressed patients; the sample size does not allow for statistical analysis of medication free patients only. However, we did not see significant differences in the ACR between patients on and off medication. Secondly, the sleep quality in the depressed subgroup may be different from that in the non-depressed subgroup; the depressed patients might have woken up spontaneously earlier and have slept only superficially thereafter, thus explaining the observed changes in the ACR and the high percentage of non-responders in the depressed group resulting from higher basal cortisol levels. However, when excluding the non-responders from the analysis, there was still a trend for an attenuated ACR in depressed patients and subjective sleep quality ratings did not differ between the two groups rendering this explanation unlikely.

One of the strengths of the study is that its design allowed to control for the stress of hospital admission, so that the observed blunted ACR in the depressed subgroup seems to be dependent on the depressive symptomatology rather than on situational factors. Another advantage is the use of an everyday stimulating influence (waking) on the HPA axis. Challenge studies with dexamethasone are designed to test the negative feedback of the axis in response to a very strong glucocorticoid signal. Thus they may not reflect the magnitude of endogenous HPA responses and suprahypothalamic (e.g. limbic) influences (Burke et al., 2005b).

Taking into account the current literature, psychotherapy inpatients appear to be distinct from acutely depressed outpatients as well as healthy subjects with depressive symptomatology, in whom an increased ACR has been demonstrated (Pruessner et al., 2003a). However, a recent meta analysis on cortisol stress reactivity in depression revealed a blunted reactivity pattern (Burke et al., 2005b), which would fit to the findings of this study.

The results of this investigation have to be interpreted cautiously due to the limitations mentioned. However, this first study on the ACR in depressed patients admitted for an inpatient psychotherapy programme revealed a pattern that seems unlike that seen in other studies on depressed inpatients or outpatients and more similar to that of teachers suffering from burn out (Pruessner et al., 1999) and chronically ill patients (Kudielka and Kirschbaum, 2003) in spite of the fact that all patients were acutely depressed fulfilling criteria for a major depressive episode. Most studies using dexamethasone challenge in depression revealed a non-suppression and therefore a hyperactivity of the HPA axis in contrast to the results presented. This might be explained by the mentioned maximal impact of dexamethasone on the HPA axis, which possibly does not mimic physiological conditions as well as the ACR does. Another possibility is that different subtypes of depression are associated with distinct alterations of the HPA axis as suggested by Antonijevic (2006), and that the patient sample presented reflects more the hypoactive state seen in atypical depression as opposed to melancholic subtypes.

The pathophysiological processes underlying this hyporeactivity in some depressed inpatients can only be speculated on. A possible mechanism could consist in a stress-related hippocampal atrophy in the studied patients. Depression associated volume reductions of the hippocampus have been demonstrated in multiple structural imaging studies (Videbech and Ravnkilde, 2004). A missing ACR similar to that seen in the sample presented has been shown in patients with selective hippocampal damage (Buchanan et al., 2004), in patients suffering from amnesia associated with brain injury

(Wolf et al., 2005) and in PTSD patients (Rohleder et al., 2004), in whom also a reduced hippocampal volume has been reported. Future neuroendocrine studies in psychiatric patients would benefit from the inclusion of structural volumetric measurements.

In summary, our study found a blunted ACR in depressed patients admitted to an inpatient psychotherapy program. Further studies of salivary cortisol in depression on more extensive samples seem necessary in order to be able to relate this finding to other observed HPA abnormalities in depression and to control for the possible effect of medication and sleep quality.

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