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Hypothalamic–pituitary–adrenal axis function in patients with chronic depression

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ABSTRACT

Background. Hypothalamic–pituitary–adrenal (HPA) axis function in patients with chronic depression has previously been shown to be normal when measured using the dexamethasone suppression test (DST). We examined patients with chronic depression using the sensitive dexamethasone/corticotropin releasing hormone (dex/CRH) test and the dexamethasone suppression test (DST) to establish whether HPA axis abnormalities are present in this group. We also compared the sensitivity of the two tests and compared the results with previous studies in depression that have not specifically selected chronic patients.

Method. Twenty-nine patients with the chronic subtype of major depressive disorder and 28 matched controls underwent examination of HPA axis function.

Results. Neither the cortisol response to the DST or the dex/CRH test differed significantly between the patient and control groups. There was a trend in favour of more patients than controls having an abnormal response to the dex/CRH test ($P = 0{\cdot}052$). Neither the patients with an abnormally enhanced response, nor the magnitude of response could be predicted by any illness or demographic variable.

Conclusion. The HPA axis is not overtly abnormal in chronic depression. This contrasts with previous findings in acute depression and bipolar disorder and may suggest that the HPA axis abnormalities present in acute depression resolve, but are not accompanied by symptom resolution. Alternatively, a subgroup of depressives with less HPA dysfunction may progress to chronicity. This has implications for treatment and prognosis. The dex/CRH is a more sensitive test of HPA axis function than the DST in patients with chronic depression.

INTRODUCTION

Stress is thought to have an important role in determining both the onset and course of major depressive disorder. However, as yet we do not fully understand the effects that stress has on the brain, why it provokes major depressive disorder in some people and how we can use this understanding to develop effective treatments (Herbert, 1997).

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Many of the effects of stress are mediated via the hypothalamic–pituitary–adrenal (HPA) axis. Although basal cortisol levels are elevated in 25–50% of acutely depressed patients, activated tests of HPA axis function are more sensitive and reveal higher rates of disturbance. The dexamethasone suppression test (DST) measures HPA axis negative feedback sensitivity to glucocorticoids. The combined dexamethasone/corticotropin releasing hormone challenge (dex/CRH) is an integrated test of HPA axis function. Essentially it is a DST followed by CRH challenge. It is a sensitive test of HPA axis function and 75% of patients with depression

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can be discriminated from healthy controls on the basis of their response to this test (Heuser *et al*. 1994).

Chronic depression denotes the persistence of major depressive symptoms for at least 2 years and occurs in 15–20 % of patients with depressive disorders (Keller *et al*. 1992). Chronic depression tends to be under-recognized, under-treated, and associated with significant morbidity, disability and cost (Keller *et al*. 1982; Hays *et al*. 1995). It has been associated with particular interpersonal and cognitive styles, childhood adversity (Lara & Klein, 1999) and central nervous system abnormalities including reduced grey matter density in the left temporal cortex (Shah *et al*. 1998).

The vast majority of patients with depression entered into neuroendocrine studies have depression of a more recent onset. Previous studies of HPA axis function in chronic depression have shown a normal, i.e. suppressed cortisol response to the DST (Shah *et al*. 1998) and reduced urinary free cortisol levels (Oldehinkel *et al*. 2001). This may indicate either that the HPA axis is normal in this group, or that the abnormalities are such that they cannot be detected by these tests.

In this study, we examine patients with chronic depression using the sensitive dex/CRH test to establish if HPA axis abnormalities are present in this group, to compare the sensitivity of the two methods for assessing function and to compare the results with previous studies in depression which have not specifically selected chronic patients.

METHOD

Subjects

We recruited 29 patients (15 males and 14 females; mean age = 48·8, S.D. = 9·6; range 28 to 63 years) with the chronic subtype of major depressive disorder (MDD). Diagnosis was confirmed using the Structured Clinical Interview for DSM-IV (SCID) (First *et al*. 1997). All patients had been stable on medication for at least 6 weeks. Illness characteristics and clinical ratings are reported in Table 2. We excluded subjects with a history of head injury, neurological disorder or problem use of alcohol or drugs.

We also recruited 28 controls (15 males and 13 females; mean age = 49·0, S.D. = 9·4; range 24 to 60 years). There were 14 female patients: six were post-menopausal of whom, one was taking hormone replacement therapy (HRT); eight were pre-menopausal of whom seven were in the follicular phase (one was taking the oral contraceptive pill) and one in the luteal phase. There were 13 female controls: five were post-menopausal, two of whom were taking HRT; eight were pre-menopausal and all were in the follicular phase (one was taking the progesterone only pill). Patients and controls were matched for age ($F = 0{\cdot}51$, df = 1, 55, $P = 0{\cdot}48$), sex (Fisher's exact, $P = 1{\cdot}00$), menstrual and menopausal status ($\chi^2 = 3{\cdot}3$, df = 4, $P = 0{\cdot}50$). Controls were confirmed by full medical examination and the SCID to be free of neurological and psychiatric disorder.

Ethical approval

The Newcastle and North Tyneside Ethics Committee approved the study. All subjects gave written consent.

Neuroendocrine testing

We performed the dex/CRH test using the established protocol (Heuser *et al*. 1994). Subjects took 1.5 mg of dexamethasone orally at 23.00 h on the evening before neuroendocrine testing. They attended the research unit on the morning of the test day and had a light lunch at noon, following which they were canulated in the antecubital fossa at 13.00 h. Subjects fasted throughout the experiment, remained semi-supine and did not sleep. Human CRH (100 μg) (hCRH, Ufelfingen, Switzerland) was administered over 30 s via the canula at 15.00 h. Blood was taken serially for measurement of cortisol every 15 min until 17.00 h. Subjects lightly chewed a citric acid impregnated cotton wool salivette (Sarstedt Ltd, UK) at 08.00, 12.00, 16.00 and 20.00 h on the day prior to neuroendocrine testing to allow assessment of basal cortisol secretion. Subjects were permitted to smoke as usual to reduce the influence of nicotine withdrawal.

Power calculation

Based on the effect size seen in previous studies in depression (von Bardeleben & Holsboer, 1989) and the current sample size, this study had

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a power of greater than 99% at the 0·05 level of significance.

Biochemical measures

Blood was collected in EDTA and centrifuged at $1000 \times g$ for 10 min to prepare plasma, which was removed and immediately frozen at −20 °C until assayed. Dexamethasone was assayed at Emory University, Georgia using a method previously described (Ritchie *et al*. 1990). In this method, the 80%, 50% and 20% binding points have averaged to 0·07, 0·33 and 1·46 ng/ml respectively. At a level of 0·52 ng/ml, the inter-assay coefficient of variability (CV) was 8% and the intra-assay CV was 4%. Cortisol was determined using Corti-cote radioimmunoassay (RIA) kits (ICN Pharmaceuticals Inc, USA). The sensitivity of the plasma cortisol assay was 1·9 nmol/l the inter-assay and intra-assay CVs for the low (10·7 nmol/l), medium (25·1 nmol/l) and high (51·1 nmol/l) quality controls (QCs) were 5·9, 7·7; 7·8, 6·6; and 9·6, 9·4% respectively.

Saliva collected using the salivette system was extracted from the cotton wool swab by centrifugation and stored at −20 °C until analysis. Samples were analysed in-house for cortisol using RIA. The sensitivity of the saliva cortisol assay was 0·08 nmol/l at 98% binding, the inter-assay and intra-assay CVs for the low (8·6 nmol/l), medium (31·5 nmol/l) and high (87·5 nmol/l) QCs were: 17·2, 25·8; 10·3, 16·3; and 9·6, 9·1% respectively.

Statistical analysis

The area under the curve (AUC) for salivary and plasma cortisol was calculated using trapezoidal integration (baseline corrected). For statistical analysis we used SPSS version 9 (SPSS, 1988). AUCs were compared using one-way analysis of variance (ANOVA). Data were analysed non-parametrically (Mann–Whitney U) where violations of the assumptions of the ANOVA occurred. Correlations were carried out using Spearman's Rank (r_s) or Kendall's tau-b (τ) where appropriate. Categorical variables were analysed using Fisher's exact test.

An abnormal DST was defined as a 15.00 h cortisol measurement above the standard cut-off of 4·0 μg/dl (110 nmol/l) (Rush *et al*. 1986) and an abnormal dex/CRH response as a peak cortisol level above the 95% of the peak cortisol control response (Rybakowski & Twardowska, 1999). Basal hypercortisolaemia (saliva) was defined as a response > 1 standard deviation above the mean of the control group. Cortisol levels are reported as nmol/l and cortisol AUCs as nmol/l/min unless otherwise specified. Parametric data are reported as means and standard deviation and non-parametric data as median with 95% CI of the median. All statistical tests are reported with the mean or median difference and the 95% CI of the difference (Altman *et al*. 2000).

Medication

Twenty-seven of the 29 patients were on antidepressants, 18 were on mood stabilizers and 10 were on antipsychotics.

RESULTS

Neuroendocrine responses

Neuroendocrine data are presented in Table 1.

Cortisol response to the dex/CRH challenge

Dex and hCRH were well tolerated by all subjects and other than a transient facial flushing, no side effects were experienced. The plasma cortisol response (AUC) did not significantly differ between patients and controls (median difference = 203·5, 95% CI = −74·2 to 644·3; $U = 324$, $N = 57$, $P = 0{\cdot}19$) (see Fig. 1). There was a trend in favour of more patients (7/29, 24·1%) than controls (1/28, 3·6%) having

Table 1. *Neuroendocrine results: median* (95% *CI*) *cortisol response to the DST and dex/CRH test* (*AUC*), *and basal salivary cortisol levels* (*AUC*) *for chronically depressed patients and controls*

	Controls	Patients
Dex/CRH		
Median (nmol/l/min)	−55·9	144·0
95% CI	−168·8 to 121·5	−156·0 to 1758·0
N	28	29
DST		
Median (nmol/l)	18·5	18·8
95% CI	12·1 to 20·8	12·4 to 23·8
N	28	29
Basal salivary cortisol		
Mean (nmol/l/h)	97·8	142·4
95% CI	77·7 to 117·9	42·2 to 242·0
N	22	19

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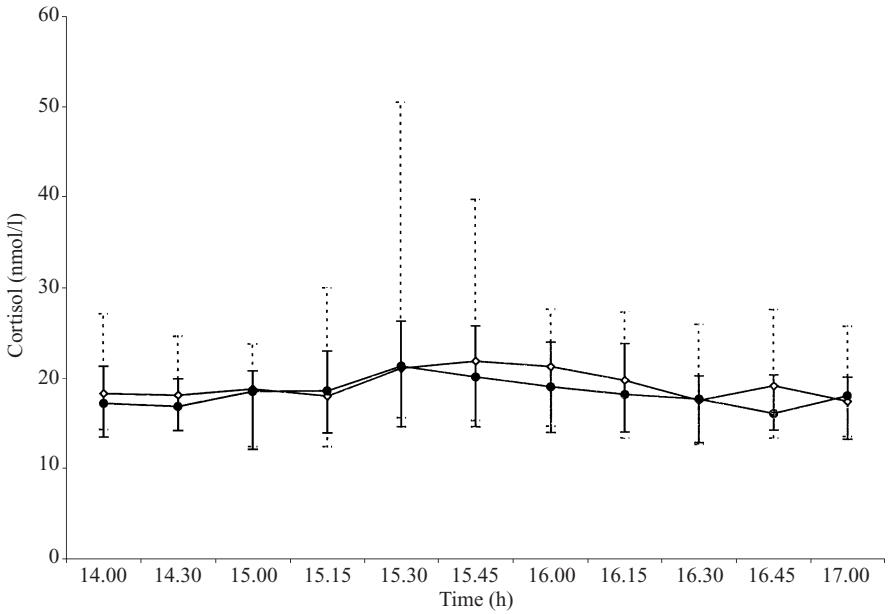


FIG. 1. Median cortisol response to combined dexamethasone/corticotropin releasing hormone challenge test (◇, patients; ●, controls). Error bars show the 95% confidence intervals with the patients error bars shown as dotted line.

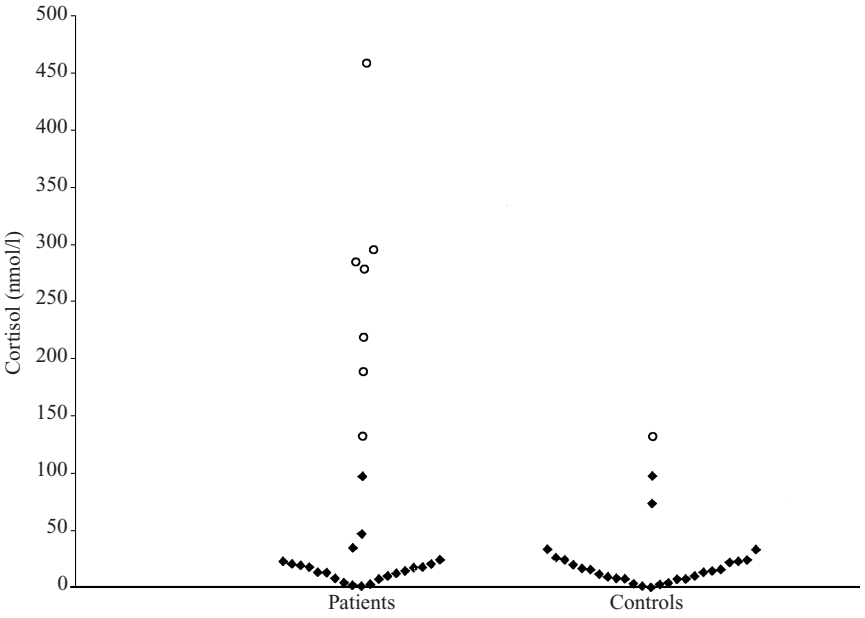


FIG. 2. Peak cortisol levels during combined dexamethasone/corticotropin releasing hormone challenge test (◆, non-responders; ○, responders).

an abnormally enhanced response (Fisher's exact test, $P = 0{\cdot}052$) (see Fig. 2). Neither responder status nor the magnitude of the cortisol response could be predicted by basal (salivary) cortisol AUC or any illness characteristic or demographic variable (see Table 2).

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Table 2. *Correlation of demographic and illness variables with cortisol response to the dex/CRH (AUC) for patients*

	Mean	(S.D.)	r_s*
Age (years)	48·8	(9·6)	0·34
Body mass index (kg/m²)	28·7	(4·6)	0·37
Previous episodes of depression	3·3	(6·6)	0·06
Lifetime months of depression	102·5	(69·3)	−0·03
Current duration (months)	83·5	(63·4)	0·34
Age at onset (years)	33·0	(10·9)	0·07
Number of hospitalizations	4·4	(6·2)	0·12
BDI	28·7	(11·6)	−0·18
MADRS	31·3	(8·0)	−0·26
HAM-D (21)	23	(7·0)	−0·19
CORE	8·8	(6·4)	−0·32
GAF	48·9	(12·2)	0·00
Basal salivary cortisol (nmol/l/h)	142·4	(206·7)	0·11

* $P > 0.05$ for all.

Cortisol response to challenge with dexamethasone

Plasma cortisol at 15.00 h did not differ between patients and controls (median difference = 1·05, 95% CI = −3·5 to 7·1; $U = 375{\cdot}5$, $N = 57$, $P = 0{\cdot}63$). One patient (3·4%) and no controls failed to suppress cortisol on the DST component of the test.

Comparison of the DST with the dex/CRH test

To examine the relative sensitivity of the dexamethasone suppression and dex/CRH tests in chronic depression, we compared the proportion of responders (non-suppressors) to the DST with the proportion responding to the combined dex/CRH test. There was one non-suppressor on the DST (3·4%), this patient and six others had an abnormal response to the dex/CRH test (24·1%). The dex/CRH test is therefore a more sensitive measure of HPA axis dysfunction in this group (difference = 20·7%, 95% CI = 3·6 to 38·6%). There was no difference in the proportion of controls who responded to dex/CRH than to the DST (difference = 3·6%, 95% CI = −8·8 to 17·7%).

Basal cortisol

Basal salivary cortisol levels were obtained for 19 patients and 22 controls. Comparison between patients and controls revealed a significant effect of time ($F = 15{\cdot}4$, df = 3, 117, $P < 0{\cdot}0005$) but no main effect of diagnosis or time by diagnosis interaction ($P > 0{\cdot}4$). There was no difference in the proportion of hypercortisolaemic patients compared with controls (Fisher's exact test, $P = 0{\cdot}66$).

Dexamethasone levels

Plasma dexamethasone levels were taken on all subjects before administration of hCRH. There was no difference in mean levels between patients (mean = 2·0, S.D. = 1·4 ng/ml) and controls (mean = 1·9, S.D. = 1·0 ng/ml); (mean difference = 0·031, 95% CI = −0·6 to 0·7; $F = 0{\cdot}01$, df = 1, 55, $P = 0{\cdot}93$). Plasma dexamethasone levels correlated negatively with plasma cortisol response (AUC) ($\tau = -0{\cdot}32$, $P < 0{\cdot}0005$).

Prediction of responders to the dex/CRH test in patients

A number of variables were examined for their effects on response to the dex/CRH. Fisher's exact test confirmed that there was no significant difference in the number of responders to the dex/CRH after patients were grouped by: recent weight loss ($P = 0{\cdot}08$), previous ECT ($P = 0{\cdot}67$), family history of affective disorder ($P = 0{\cdot}22$), history of parasuicide ($P = 0{\cdot}59$), melancholic subtype ($P = 0{\cdot}68$), or hospitalization ($P = 0{\cdot}59$). There was also no significant difference after grouping by DST response ($P = 0{\cdot}24$).

As patients were receiving a heterogeneous range of psychotropic medications, we examined the proportion of responders *versus* non-responders across general categories: there was no significant difference in the proportion of responders grouped by use of antipsychotics ($P = 1{\cdot}00$), mood stabilizers ($P = 0{\cdot}20$) or mirtazapine ($P = 0{\cdot}38$).

DISCUSSION

Chronically depressed patients do not differ from controls in the group median cortisol response. There are a number of subjects with a clearly enhanced response. Using the criteria of Rybakowski & Twardowska (1999), 24·1% of patients and 3·6% of controls have an abnormal response. These findings contrast to previous studies in patients with depression of a more recent onset, where 75% of patients are classified as abnormal responders and the group mean response is enhanced (Heuser *et al.* 1994).

The seminal study using the dex/CRH test in patients with depression demonstrated a large

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effect size and a significant difference from controls (von Bardeleben & Holsboer, 1989). This finding has subsequently been replicated in studies from the same and other centres (Heuser *et al*. 1994; Rybakowski & Twardowska, 1999; Zobel *et al*. 2001). The present study replicated the methodology of these studies. Power calculations based on the effect size seen in previous studies in depression of recent onset indicated that this trial had sufficient power to reveal a difference in the primary outcome measure, i.e. the median cortisol response to challenge with the dex/CRH test, however we did not find a significant difference. The observed effect size seen in this study appears to be considerably smaller than that of previous studies in depression of recent onset. It is possible that a larger sample size may have revealed a difference compared with controls, however it appears that the high incidence of abnormalities previously seen in patients with acute depression are not seen in patients with chronic depression.

The rate of metabolism of dexamethasone has previously been shown to be a confounding factor in DST studies (Lowy & Meltzer, 1987). Dexamethasone levels did not differ between patients and controls. This suggests that variability in the rate of metabolism of dexamethasone is not a confound in this study, although the negative correlation between cortisol response and dexamethasone levels suggests that some of the variability within each group may have been accounted for by dexamethasone function.

A possible criticism of the present study is that we did not measure the ACTH response to the dex/CRH test. Previous studies have measured ACTH as well as cortisol, however ACTH responses tend to parallel cortisol responses and therefore add little to the overall sensitivity of the test (defined as the number of correctly classified cases in the patient population; Heuser *et al*. 1994).

It is possible to conjecture that differing psychotropic medication regimes between patients in the present study and those in previous studies may explain the difference in cortisol response. Heuser and colleagues have demonstrated that successful treatment with amitriptyline reduces the ACTH response on the dex/CRH test (Heuser *et al*. 1996) and mirtazapine has been shown to lower plasma cortisol levels in healthy volunteers (Laakmann *et al*. 1999). Patients in previous studies have been drug free (Heuser *et al*. 1994), on a range of psychotropic drugs (Zobel *et al*. 2001) or medication has not been reported (Rybakowski & Twardowska, 1999). Patients in this study were taking a heterogeneous range of psychotropics, however the medication regime did not predict response. A drug free study would be desirable, but impractical in this population.

The control group in our study exhibited relatively blunted cortisol responses in comparison to those seen in previous studies (Heuser *et al*. 1994). This could be attributable to many factors, for example variation in assay sensitivity between laboratories. Demographic differences such as the age and sex of participants may also be important. The average age of controls in the Heuser *et al*. (1994) study was 57 years (range, 23 to 85) while in the present study subjects were 48·8 years (range, 28 to 63). A recent study by Rybakowski & Twardowska (1999) with a control group aged 30 years (range, 22 to 52) also demonstrated a more attenuated response. To minimize the effects of this potential confound, we used a carefully matched control group.

There are a number of potential explanations for the apparently paradoxical finding in patients with chronic depression of persistent symptoms in the absence of HPA axis dysfunction, the biological system most closely linked with depression (Steckler & Holsboer, 1999). First, the initially dysfunctional HPA axis may have been normalized by chronic antidepressant treatment (Steckler & Holsboer, 1999; McQuade & Young, 2000). At the same time, symptoms and chronic disability may have been maintained by social and cognitive dysfunction, which have been shown to persist in chronic depression (Judd *et al*. 2000; Scott *et al*. 2000). This explanation would be in keeping with the demonstration that patients in partial remission have predominantly psychological rather than biological symptoms (Paykel, 1998) and has implications for the treatment of chronic depression. For instance, it is noteworthy that cognitive behavioural therapies have been shown to be efficacious in the treatment of chronic treatment resistant depression (Fava *et al*. 1997; Keller *et al*. 2000). Secondly, the HPA axis dysfunction of acute depression may persist but

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evolve with time. This may result in patients having a normal cortisol response to the dex/CRH challenge but having, for instance, abnormalities in other facets of HPA axis regulation, such as the function of vasopressin, a hormone which appears to have a particular role in the response to chronic stress (Scott & Dinan, 1998) or dehydroepiandrosterone (DHEA), which possesses antiglucocorticoid properties (Gallagher *et al*. 2001). Thirdly, the patients in this study may have been characterized at illness onset by their normal HPA axis and it was this that predicted the chronic course of their illness and explained the lack of response to physical treatment. This explanation is supported by the demonstration in depressed patients that DST suppressors have more personality dysfunction than DST non-suppressors (Schweitzer *et al*. 2001). These three explanations could be further examined with a large, well designed longitudinal study.

HPA axis dysfunction is greatest in bipolar affective disorder (Rush *et al*. 1997; Rybakowski & Twardowska, 1999). Up to 46% of patients initially diagnosed as having unipolar depressive disorder will later fulfil criteria for bipolar disorder (Goldberg *et al*. 2001). Bipolar disorder was an exclusion factor for this study, patients were relatively old with a prolonged duration of depression and therefore there was a low risk that patients in this study had undiagnosed bipolar disorder. Previous studies in acute depression will probably have included some as yet undiagnosed bipolars and thus compounded the degree of HPA dysfunction.

Although as a group the chronically depressed patients did not differ significantly from controls in their cortisol response to the dex/CRH challenge, the data revealed that seven individuals had an abnormal cortisol response similar to that seen in depression of a more recent onset. These patients could not be predicted by any illness variable or demographic factor, including age, gender, body mass index, illness duration or severity, a history of parasuicide or the presence of a diagnosis of melancholia. The dex/CRH test was more sensitive than the DST.

The response of patients with chronic depression to the combined dex/CRH test is very different from that previously reported in depression of more recent onset despite similar severity of symptoms. Further research is warranted into the role of HPA axis function in the pathophysiology of chronic depression, with particular focus on the role of AVP and DHEA.

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