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Sex differences in hypothalamic-pituitary-adrenal axis function in patients with chronic pain syndrome

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Abstract

Chronic pain is often equated with chronic stress yet the relationship between chronic pain and hypothalamic-pituitary-adrenal (HPA) axis activity is poorly understood. The objective of this study was to examine diurnal functioning of the HPA axis in patients with clinically defined non-inflammatory chronic pain syndrome (CPS) compared to controls. The sample consisted of 37 adults with CPS and 47 healthy controls. All participants provided saliva samples at awakening, 1200h, 1800h, and 2100h on two consecutive days, as well as completing self report questionnaires relating to anxiety and depression. The CPS group had a significantly lower overall mean diurnal cortisol level compared to the control group (p<0.01) but no significant differences were found between the two groups for repeated cortisol sampling across the day. However, a three-way interaction of time of day by patient status by sex was found ($p<0.032$), with lower cortisol in male patients compared to female patients in the afternoon period. No significant group effect was found for the rate of cortisol circadian decline. These data demonstrate that CPS is associated with a degree of hypocortisolaemia, particularly in male patients. The altered dynamics of cortisol secretion in CPS in relation to the onset and duration of pain in patients remains to be determined.

Introduction

The hypothalamic-pituitary-adrenal (HPA) axis acts as a neuroendocrine stress response system and also plays an important role in the maintenance of homeostasis (Buckingham *et al.,* 1997). Stimulation of the HPA axis in man results in elevated release of the glucocorticoid cortisol from the adrenal cortex, while under basal, unstressed conditions, glucocorticoid secretion exhibits a robust circadian pattern. Glucocorticoids act through negative feedback pathways to minimize long term activation of the HPA axis (De Kloet *et al.,* 1998). Alteration of the HPA axis can lead to a form of allostatic load, or accumulated lifetime stress, in which an inadequate cortisol response is mounted to chronic noxious or adverse experiences, resulting in a hypocortisolaemic state (Sterling et al., 1988; McEwen, 1998). HPA axis activity has been reported to be dysfunctional in a range of syndromes such as inflammatory autoimmune diseases (Jessop and Harbuz, 2005; Heesen et al., 2007) and in conditions associated with chronic pain such as fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS) (Fries et al., 2005). However, in benign non-inflammatory chronic pain syndrome (CPS), HPA axis activity has been little investigated. This is surprising given that CPS is often associated with significant levels of distress and disability, both physical and psychological, which has the potential to impact on endocrine functioning (Chapman et al., 2008). Indeed, it has been proposed that the HPA axis may represent a therapeutic target for the treatment of chronic pain (Blackburn-Munro and Blackburn-Munro, 2003) but it is as yet unclear which types of chronic pain conditions are characterised by HPA axis dysfunction.

Of the studies which have examined the HPA axis in syndromes in which chronic pain has been reported as a clinical symptom, most relate specifically to FMS and reports are inconsistent. Some studies report hypocortisolaemia (Crofford et al., 1994; Greip et al., 1998), while others report elevated (McCain and Tilbe, 1989; Ferraccioli et al., 1990; Neeck and Riedelm, 1999; Crofford et al., 2004) or normal (Adler et al., 1999; McLean et al., 2005; Wingenfeld et al., 2007) basal cortisol levels. Basal total blood, but not free salivary, cortisol was lower in a group of predominantly female patients with FMS (Maceda et al., 2008) and blood (but not salivary) cortisol responses to a social

stressor task were found to be attenuated in female patients with FMS (Wingenfeld et al., 2008). Blood and salivary cortisol were normal in patients with chronic pelvic pain compared to controls (Wingenfeld et al., 2008). Regarding cortisol circadian rhythms in FMS, at least one study has reported elevated evening cortisol levels (Crofford et al., 2004), while others report a normal cortisol circadian rhythm (Klerman et al., 2001; Loevinger et al., 2007). Other conditions in which pain is a significant component have also been linked to disruptions in cortisol production, A flattened morning and evening salivary cortisol profile has been observed in patients with chronic widespread pain (CWP) (McBeth et al., 2005) and in healthy subjects defined as psychologically 'at risk' of developing CWP (McBeth et al., 2007). Blunted morning cortisol levels have also been reported in CFS which is often accompanied by widespread muscle pain (Crofford et al., 2004; Nater et al., 2008a; Nater et al., 2008b). These findings, over a range of syndromes associated with chronic benign pain, indicate intriguing albeit inconsistent evidence for alterations in cortisol secretion which warrant further investigation.

Furthermore, whilst the influence of sex is considered to be important within the pain context (Unruh, 1996; Berkley, 1997; Holdcroft and Berkley, 2005; Keogh, 2006; Bernardes et al., 2008) sex differences in endocrine functioning are rarely considered directly in pain. For example, there are sex differences in pain prevalence rates, analgesic use (Antonov and Isacson, 1998), and different responses to pain management approaches (Fillingim, 2002; Keogh et al., 2005), effects which tend to be more pronounced in female patients. Sex differences in HPA axis activity in normal healthy subjects are well-described although not necessarily consistent (al'Absi et al., 2004; Zimmer etal., 2003; for review see Kudielka et al., 2009). Therefore we hypothesised that sex dimorphism in cortisol secretion may occur in CPS.

The principal aim of the current study was to compare the diurnal pattern of salivary cortisol levels in male and female patients diagnosed with CPS, inclusion criteria being predominantly benign low back pain or musculoskeletal pain and excluding primary diagnoses of CFS or FMS. This category of CPS patients has not been previously characterised for HPA axis dysfunction in a controlled study. We

hypothesised that abnormalities in cortisol secretion would be observed in CPS patients compared to healthy controls, with a flattened diurnal rhythm associated with a hypocortisolaemic state consistent with CPS as a model of allostatic load.

Methods

Recruitment

Participants (n = 84) consisted of 37 adult CPS patients recruited from a hospital based pain clinic and 47 healthy controls. Controls were recruited using opportunistic sampling via a flyer displayed at the hospital requesting participation from healthy members of the public and staff. Ethics approval was obtained from a National Health Service Research Ethics Committee and the University of Bath Departmental Committee. Patients were initially approached during their regular clinic visit, and provided with study information. Those who agreed to participate completed a consent form and were provided with the questionnaire and saliva sampling kit to take home. All participants gave informed written consent to the study.

Inclusion criteria for patient participation was based on having been diagnosed with CPS for at least one year and being over 18 years of age, on the diagnostic criteria of the International Association for the study of Pain (IASP, 1994). A diagnosis of CPS was defined as pain that had persisted for more than six months and was not related to ongoing peripheral disease. Pain experienced in this population of CPS patients was predominantly musculoskeletal or benign low back pain. Therefore this group could also be defined as having chronic benign musculoskeletal pain syndrome. Patients with primary diagnoses of CFS or FMS were excluded from the study group. Patients were also excluded if they had experienced a psychiatric episode including severe depression. The clinical consultant involved in the study employed a pre-screening process of patients suitable for the researcher to approach on clinic day. This pre-screening involved an assessment of patient records to exclude anyone who had experienced contact with inpatient psychiatric services over the previous two years. In essence this excluded anyone who had a significant and overwhelming episode of depression or psychosis that required clinical treatment in the previous two years.

Although our CPS group is not a strictly homogeneous group due to the well-known clinical difficulties of diagnosis in chronic pain, it is representative of a patient population regularly seen in out-patient clinics and clinically defined as CPS in terms of diagnosis, referral, and importantly in respect to treatments offered. The average amount of time that patients had experienced chronic pain was 8.83 years (SD 8.36 years) and ranged from 1.25 yrs to 32.41 years. Patients were not taking steroidal medication or opioids.

Measures

Participants completed a range of self report assessments including demographic details (age, sex, marital status and educational level of attainment), medical status (duration of patient illness, medication, anxiety/depression), and pain experience, and provided saliva samples for cortisol assessment.

McGill Pain Questionnaire (MPQ).

The MPQ is one of the most widely used measures for assessing pain (Melzack, 1975). It consists of a list of adjectives that can be divided into sensory (10 items), affective (5 items), evaluative (1 item) and miscellaneous subscales (3 items). Two main measures are created from the adjective list: 1) number of words chosen and the pain-rating index. The pain rating index adds the ranking of all words chosen (higher scores denoting more pain) according to their rank values to produce a total score.

Hospital Anxiety and Depression Scale (HADS).

The HADS (Zigmund and Snaith, 1983) consists of 14 items, 7 relating to the anxiety subscale and 7 to the depression subscale and utilises a 4 –point response scale from 0 – 3 (where 0 represents the absence of the symptom). Scores can range from 0- 21 on each subscale, a higher score indicating greater depression or anxiety, with cut-off points between 8 – 10 for borderline and 11-21 for probable clinical cases (Pallant and Bailey, 2005).

Saliva collection.

Saliva was collected using Salivettes with a sterile cotton swab held inside a plastic tube (Sarstedt, Germany). Each kit provided to participants comprised of 10 Salivettes, colour coded for time of sampling. Saliva was sampled four times per day across two consecutive days at 1) awakening; 2) 1200h; 3) 1800h; and 4) 2100h in order to obtain diurnal assessment of cortisol. The two day protocol for each time point was followed as recommended in order to obtain reliability and validity of assessment (Clow et al, 2004). There were no significant differences in cortisol values observed between testing days so samples were averaged across the two days at each time point. The saliva kits were accompanied by a sampling booklet, containing information on how to collect the sample, questions about medication taken leading up to or on the day of sample collection, duration (hours) and quality of sleep (number of times participant awoke during the night), final time of waking, sample collection time and any problems regarding sampling. Information regarding menopausal status was not requested as this does not significantly alter cortisol levels or circadian rhythm (Pataccioli et al., 2006; Kalleinen et al., 2008). Participants were instructed to choose two consecutive routine week days on which to provide their samples within seven days of being given the kits. Samples were stored in participants' home freezers until completion of the two sampling days when samples were returned by post to the researchers and were stored at -20 C prior to cortisol assay.

Cortisol assay.

Salivettes were thawed and centrifuged and then subjected to an in-house radioimmunoassay in sodium citrate/sodium orthophosphate buffer at pH 3 (Jessop et al., 2001; Turner-Cobb et al., 2008). Saliva samples were diluted 1:1 in buffer and assayed in duplicate with radiolabelled iodine 125-cortisol and antiserum. Total assay tube volume was 0.3ml. Cortisol antiserum is a rabbit polyclonal antibody raised against cortisol-3-BSA (B391, Acris Antibodies, Hiddenhausen, Germany). Cross-reactivities are: prednisolone 36%, 11-deoxycortisol 10%, corticosterone 3.2%, cortisone 0.9%. After 24h incubation at 4 C, activated charcoal was added to each tube and tubes were centrifuged for 15min. Supernatants were discarded and radioactivity in the pellets was

measured on a gamma counter. Limit of detection was 0.2ng/ml; intra- and interassay coefficients of variation were <10%.

Data transformation and statistical analyses

Cortisol values exhibited a positively skewed distribution requiring logarithmic transformations (log_{10}) prior to analysis. Cortisol variables of diurnal output consisted of the four time points across the day (mean across the two days calculated for each assessment time). From these were calculated three cortisol outcome variables of diurnal output and change in cortisol across the day. Rate of change in cortisol across the day was obtained by calculating the 'slope' of the regression line (beta value obtained from regressing cortisol on time of sample collection) (Sephton et al., 2000; Turner-Cobb et al., 2000; Abercrombie et al., 2004). Diurnal output and slope assessment were both calculated using all cortisol points. Non-transformed, raw values of cortisol in ng/ml are used for graphical illustration only. Given the established link between cortisol and age, and a significant age difference between patient and control groups, this variable was entered as a covariate in group comparisons. Differences in cortisol levels between patients and controls across the day were analysed using a split-plot ANCOVA. Patient status and sex were entered as the between group variables and cortisol time points across the day as the within-group IV. The dependent variable of cortisol slope was examined using between group ANCOVA and post-hoc t-tests.

Results

Means and standard deviations for demographic data for patients and controls are shown in Table 1. The patient group was significantly older than the control group (t (82) = 3.72; p<0.001) but did not differ in any other variable. Means and standard deviations for pain intensity, sleep variables, anxiety and depression are shown for patients and controls in Table 2. Pain intensity was comparable with that reported for other chronic pain states (Nicholas et al., 2008). Female patients reported higher levels of pain than male patients (F (1,33) = 6.15; p <0.005). Whilst reported nocturnal sleep quantity was not significantly different in patients compared to controls, quality of sleep

was found to be poorer in patients than controls (F(1,32) =15.81; *p*<0.001). However, correlational analyses revealed that neither patient sleep quality nor quantity were significantly associated with cortisol variables. Pain duration was not significantly correlated with cortisol outcome measures. Patients scored significantly higher than controls on measures of depression and anxiety (F(1,77) = 55.34/23.97; *p's*<0.001). Of the chronic pain patients a total of six (16.2%) scored in the borderline range on HADS-depression, and nine (24.3%) as 'probable cases'. On the HADS-anxiety subscale, seven patients (18.9%) were border-line for clinical anxiety, and 16 (43.2%) as 'probable cases'. Of the control group, only one scored in the borderline range for depression, with four (8.5%) scoring borderline for anxiety and 3 (6.3%) as 'probable cases'. Thus the patient group were presenting with significantly greater anxiety and depression than controls on a number of measures, reflecting the chronic nature of their condition. There were no significant interactions between sex and patient status on anxiety or depression. Anxiety and depression scores were not significantly correlated with cortisol values for patients or controls.

Tables 1 and 2 inserted about here

Average saliva collection times recorded in the sampling diary were 0713h (± 8 min) for the awakening sample, 1205h (± 2 minutes) for the noon sample, 1759h (± 5 minutes) for the 1800h sample and 2103h (± 6 minutes) for the 2100h sample. Figure 1 shows mean salivary cortisol values for CPS patients and controls across the five diurnal measurement points. The between subjects effect at individual time points of the diurnal profile revealed a significant difference between patients and controls at 1200h (F(1,75) = 7.25; p <0.01), and 1800h (F (1,75) = 7.94; p <0.01), with lower cortisol in patients compared to controls being observed at both these time points. A split-plot ANCOVA revealed a significant main effect for the within group factor of time (F (2,167) = 10.67; *p* <0.001), with cortisol typically declining across the day but no significant between group effect was observed across time. Overall mean cortisol across the day was significantly lower in patients compared to controls, as determined from the significant between group main effect of patient status (F (1,71) = 8.50; *p* <0.01).

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Insert figure 1 about here

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Although neither two-way interactions were significant (time x status or time x gender), the three-way interaction of time x patient status x sex was significant (F (2, 169) = 3.19; p <0.05. Separate follow-up ANOVA's conducted for the two groups revealed significant time x sex effects in the CPS patients (F(2, 65) = 3.00; $p<0.05$). Post hoc t-tests within CPS patients revealed a significant sex difference at noon (t(27) = -2.68; p <.05) and 6pm (t(29) = -2.83; p <.01) (Figure 2). There were no significant time x sex differences in the healthy controls (Figure 3).

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A similar analysis was conducted on the diurnal slope of cortisol, but no significant effects were found.

Discussion

We report novel evidence for an altered HPA axis in CPS patients compared to healthy controls, with lower cortisol levels in male compared to female patients in the afternoon period. This is the first report of sex differences in HPA axis activity in CPS. Significant differences relate to diurnal cortisol levels rather than to diurnal slope or CAR. Patients of both sexes scored more highly on depression and anxiety than controls but these psychological factors were found to be independent of cortisol levels and sex.

There are considerable discrepancies between reports of HPA axis activity associated with various conditions of chronic pain. Variations in sampling times for cortisol, the type of sample taken (blood, urine or saliva), recruitment of mixed-sex patient groups, and use of treatment regimens which affect the HPA axis, may have contributed to conflicting reports in the literature. Cortisol was elevated in hair samples from patients with severe chronic pain (van Uun et al., 2008) but this was a clinically heterogenous and mixed-sex group, all of whom were receiving opioid treatment.

Diurnal levels of salivary cortisol were lower in women with chronic pelvic pain associated with endometriosis (Petrelluzzi et al., 2008) but were normal in women with chronic pelvic pain not associated with endometriosis (Wingenfeld et al., 2008). Elevated salivary cortisol was reported in men with chronic pelvic pain associated with chronic prostatitis (Anderson et al., 2008). In contrast, no difference in blood cortisol was reported in a similar group of patients compared to controls (Dimitrakov et al., 2008). Our data are consistent with a report of hypocortisolism in patients with chronic low back pain or FMS (Greip et al., 1998) but contrast with other reports of elevated (McCain and Tilbe, 1989; Ferraccioli et al., 1990; Neeck and Riedelm, 1999; Crofford et al., 2004) or normal (Adler et al., 1999; McLean et al., 2005; Wingenfeld et al., 2007) basal cortisol in FMS. A flatter diurnal slope of cortisol, in the form of lower morning and higher evening levels, has been reported in CFS patients (Nater et al., 2008a; Nater et al., 2008b). Our study excluded patients with CFS and therefore the lower cortisol observed in our CPS sample is not due to a confounding influence from this condition.

We found that the overall differences in cortisol levels between patient and control groups were largely due to hypocortisolism in male patients. Whilst it is well established that pain-related conditions are more prevalent in females (Berkley, 1997; Mogil and Clark, 2005) with increased sensitivity to pain (Keogh and Herdenfeldt, 2002; Keogh, 2006), endocrine related mechanisms underlying sex differences in pain have not been systematically addressed and few human studies have examined sex-related dimorphism in the neuroendocrinology of chronic pain. In one of the few studies to examine sex effects in pain patients, Nater et al. (2008a) report a difference in the morning profile of cortisol where female CFS patients had a significantly lower cortisol profile than female controls, but no difference was observed in corresponding groups of males. In groups of predominantly female patients with FMS or non-inflammatory lower back pain, urinary free cortisol was moderately lower than the healthy control group (Greip et al., 1998) but the few male patients in each group may have skewed the data. Other studies have controlled for sex differences rather than examining the differences themselves (McBeth et al., 2007) but this approach can run the risk of overlooking important influences of sex on pain. Our observation that diurnal cortisol concentrations

are higher in female (i.e. more 'normal') than in male patients with CPS may in part be explained by the higher self reported pain in our female patients, on the basis of evidence from a study which showed a strong positive correlation between salivary cortisol and pain perception in women with FMS, although no abnormality was observed in the diurnal pattern of cortisol secretion (McLean et al., 2005). Of note, the diurnal cortisol sex differences found in our CPS population were related to the afternoon period (noon and 6pm measures), whereas in studies in CFS patients, it is the awakening cortisol response that has revealed sex differences (Nater et al., 2008a) or the early morning/late evening cortisol levels which have driven the diurnal flattening (Nater et al., 2008b). Therefore our patient group differs from CFS in both clinical diagnosis and endocrine profile.

We can only speculate why the diurnal cortisol profile was higher in our female patients compared to males. Basal HPA axis activity is slightly higher in normal females than in males, partly due to oestrogens stimulating the HPA axis through oestrogen response elements upstream of the corticotrophin-releasing hormone gene within the hypothalamus (Vamvakopoulos and Chrousos, 1994). However, since on the basis of their age a significant proportion of the female patients in our study were probably post-menopausal, elevated oestrogens are unlikely to have contributed to increased cortisol secretion. Also, in a small group of female FMS patients, blood oestrogen concentrations were found to be significantly lower than controls (Reidel et al., 1998). Therefore, at least in FMS, oestrogens are unlikely to be responsible for elevated cortisol, although we did not measure oestrogens in our CPS patients. Furthermore, recruitment in our study of post-menopausal women would not influence cortisol patterns since menopause does not significantly alter cortisol levels or circadian rhythm (Kalleinen et al., 2008). A small but significant increase in cortisol in post-menopausal women has been reported (Patacchioli et al., 2006) but this study was not age-controlled. Anxiety and depression scores were similar in male and female patients, and therefore sex differences in cortisol secretion could not be related to these variables. The differences in cortisol observed between male and female CPS patients in our study may be a differential response of HPA axis activity specific to chronic pain. It is

interesting to note in this context that salivary cortisol was correlated with self-reported pain following a noxious stressor in men only (al'Absi et al., 2002).

The patients in our study were experiencing symptoms of chronic pain which are largely refractory to treatment, of unknown aetiology, and are not related to any known underlying pathology. It may therefore be the case in this specific group of patients, most notably in male patients, that allostatic systems have become overtaxed and the HPA axis has been reset at a lower level of activity, thereby contributing to the pathology of CPS since low glucocorticoid levels may induce a hyperalgesic state. Indeed, glucocorticoids are commonly used as therapeutic analgesic agents (for review see Romundstad et al., 2007). Our data could be interpreted as evidence for the cumulative effect of the chronic affective burden experienced by CPS patients and it is possible that female patients may be more used to coping with pain than male patients. The simultaneously 'wound up' and 'run down' experience of these patients accurately articulates the physiological strain on allostatic systems reflected in allostatic load. Anxiety and depression, whilst significantly greater in the CPS group, were not directly associated with the cortisol profile, indicating that allostatic load may not always be operationalised into self-reported expression of stress. That HPA axis abnormalities can be independent of reported psychological stress in chronic pain is consistent with the findings of McBeth et al (2005).

There are some areas in this study which could be addressed and strengthened in future investigations of this nature. Firstly, we did not measure body mass index as a measure of obesity in our CPS patients. We have observed decreased blood cortisol concentrations in conventionally obese males (Jessop et al., 2001), an observation which has the potential to confound the data from our present study if a significant number of male CPS patients were obese. However, another study reported lower blood cortisol in obese women but not men (Strain et al., 1982). The reasons for this discrepancy are not clear, but it is apparent from the literature that there is no clearcut sex dimorphism in cortisol in obesity which might explain the lower cortisol in male CPS patients. Secondly, we did not ascertain at which stage of the menstrual cycle saliva

samples were provided by women. Although there have been reports that basal cortisol fluctuates slightly during the menstrual cycle (reviewed in Baker and Driver, 2007), the effects are small (Kirschbaum et al., 1999).

It is important to determine in future studies when hypocortisolaemia first becomes manifest in CPS patients, and whether it is involved in the etiology, or is a consequence of, onset of pain. In this context it is interesting that McBeth et al. (2007) observed a flattened cortisol circadian rhythm in pain-free healthy subjects who later developed chronic wide-spread musculoskeletal pain. Therefore HPA axis dysfunction may be predictive of predisposition to development of chronic pain. Cortisol was not measured in this study after the onset of symptoms but in an earlier study patients with established chronic pain had lower salivary (but higher serum) cortisol (McBeth et al. 2005). In the light of this discrepancy between total blood cortisol and free salivary cortisol, also observed in other studies (Maceda et al., 2008; Anderson et al., 2008; Dimitrakov et al., 2008; Wingenfeld et al., 2008), simultaneous blood and saliva sampling for cortisol and corticosteroid binding globulin measurements may shed further light on the pattern of cortisol secretion in chronic pain. It may also be instructive to study the history of stressful episodes in patients with CPS to determine whether any correlation exists which might be related to the etiology of CPS through resetting of the HPA axis, as has been proposed for chronic inflammatory diseases (Straub and Besedovsky, 2003). Greater understanding of the altered dynamics of cortisol secretion in CPS, and the adaptive role of the HPA axis in CPS, may assist clinical intervention and may also help some patients to reassess their pain in the context of an underlying pathophysiology.

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Figure legends

Figure 1. Salivary cortisol concentrations (mean $\pm$ SEM) in CPS patients (n=37) and controls (n=47) across four diurnal sampling points. Overall mean cortisol concentration across the day was significantly lower in patients compared to controls (between group main effect of patient status ($F_{(1,71)} = 8.50$; $p < 0.01$)).

Figure 2. Salivary cortisol concentrations (mean $\pm$ SEM) in male (n=18) and female (n=19) CPS patients. Salivary cortisol concentrations in male patients were lower than in females at noon ($p < 0.05$) and 6pm ($p < 0.01$).

Figure 3. Salivary cortisol concentrations (mean $\pm$ SEM) in healthy male (n=17) and female (n=30) controls. No significant sex differences in cortisol concentrations were observed at any time point.
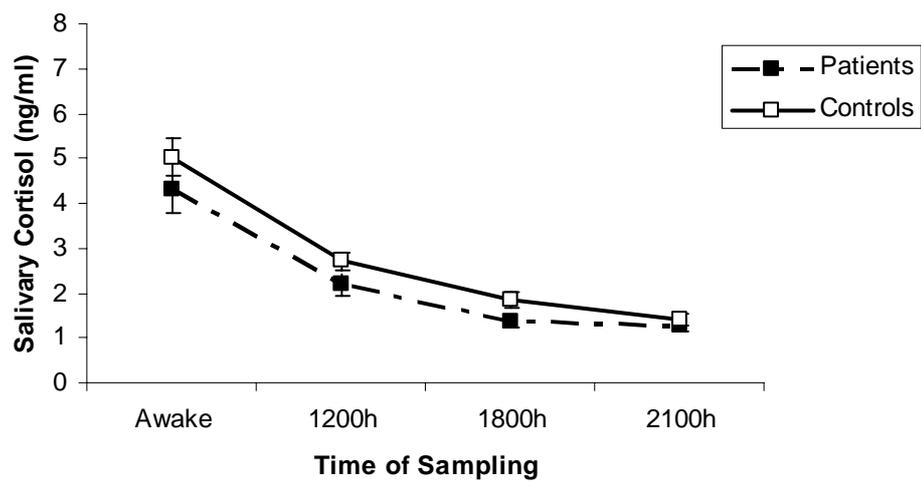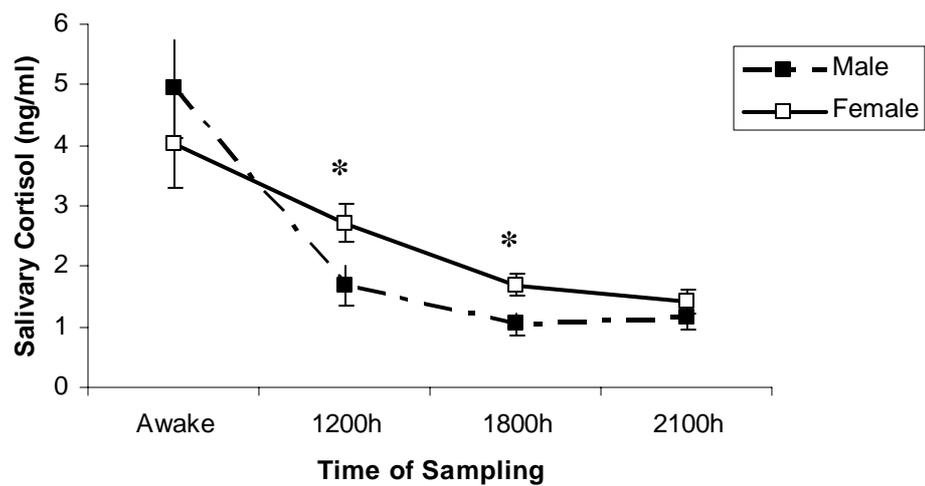
Table 1. Demographic data for chronic pain syndrome (CPS) patients and healthy controls

	CPS patients (n = 37)	Controls (n = 47)
Age (yrs) Mean (SD)	50.59 (15.68)*	39.11 (11.72)
Male Patients – 22-50 yrs = 8		
51-77 yrs = 10		
Controls – 22-50 yrs = 4		
51-77 yrs = 13		
Female Patients – 23-50 yrs = 11		
51-72 yrs = 8		
Controls – 23-50 yrs = 12		
51-72 yrs = 18		
Sex n (%)		
M	18 (48.6)	17 (35.2)
F	19 (51.4)	30 (63.8)
Marital Status n (%)		
Single	6 (16.2)	22 (46.8)
Married/co-habiting	25 (66.6)	19 (40.4)
Separated/Divorced	6 (16.2)	6 (16.5)

*p<0.05 compared to controls

Table 2. Mean (SD) for pain, sleep, anxiety and depression scores in patients with chronic pain syndrome (CPS) and healthy controls

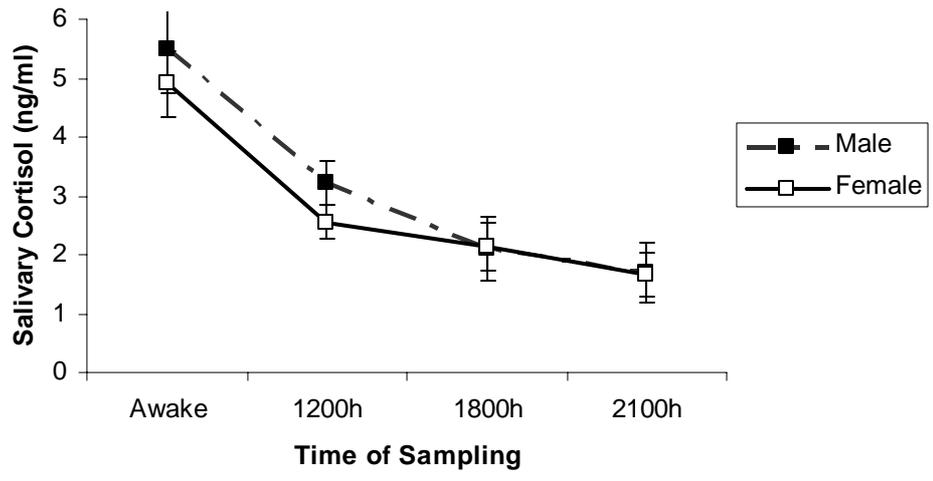|	CPS patients (N = 37)			Controls (N = 47)		
	Male	Female	Total	Male	Female	Total
Pain rating index (MPQ)	20.63(12.93)	31.84(13.65)*	26.71(14.30)	-	-	-
Sleep quantity (hours) (mean days 1 & 2)	7.46(.87)	7.78(1.22)	7.62(1.06)	6.72(1.49)	7.34(1.06)	7.15 (1.22)
Sleep quality (awakenings)	1.50(1.40)	3.92(2.04)	2.78(2.13)**	1.29(1.56)	1.48(1.18)	1.43(1.29)
Depression & anxiety						
Depression (HADS)	7.56(4.75)	8.17(4.91)	7.88(4.77)**	1.56(1.68)	2.13(2.31)	1.93(2.13)
Anxiety (HADS)	8.38(5.90)	11.11(4.27)	9.86(5.19)**	4.53(4.0)	5.43(3.10)	5.13(3.41)

*p<0.005 compared to male patients
**p<0.001 compared to total controls

Figure 2

Figure3