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Chronic pain therapy and hypothalamic-pituitary-adrenal axis impairment

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Summary Opiates and/or nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most effective therapies for chronic pain, but their prolonged time of use can affect health conditions through physical and psychological side effects. They include the very common gastrointestinal effects and changes that can induce osteoporosis, depression, impaired cognition and a generally poor quality of life, which *per se* can induce and maintain a chronic painful condition. For this reason it is becoming imperative to expand our knowledge of the interaction of these substances with body functions apparently not directly involved in nociception and pain, such as neuroendocrine functions. The purpose of this study was to determine, in male and female patients suffering from chronic pain, the effect of conventional pain therapy (opiates, NSAIDs) on hypothalamic-pituitary-adrenal (HPA) axis function. This was assessed by measuring the blood levels of adrenal-related hormones (adrenocorticotrophin hormone, ACTH; cortisol; dehydroepiandrosterone, DHEA and dehydroepiandrosterone sulfate, DHEAS). The second purpose of the study was to test the hypothesis that these hormones are associated with the psychological profile shown by the chronic pain patients. The results showed significant changes induced by pain therapy on the HPA axis: ACTH, cortisol, DHEA and DHEAS blood levels decreased in all subjects taking opiates or NSAIDs to treat pain. Moreover these changes showed significant correlations with psychological features of the subjects depending on age and sex.
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1. Introduction

Pain, particularly chronic pain, requires treatment and, due to its chronicity, treatment is long-lasting. Several procedures and/or compounds can be used, mostly anti-inflammatories and/or opiates. When taking drugs, patients experience several 'adjustments' of their body functions, some expected and related to improvement of the health

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conditions (pain killers), others negative and included among the side effects. Examples of the latter category are well known to the general public, e.g. gastrointestinal effects (ulcer or constipation) taking anti-inflammatories or opiates. Other 'hidden adjustments' include changes in immune and neuroendocrine functions that are rarely considered by physicians in the evaluation of therapy outcome. Indeed endocrine impairment often does not cause acute health problems but slow changes related to hormone deprivation (Daniell, 2008; Aloisi et al., 2009) such as osteoporosis, depression, impaired cognition and a generally poor quality of life. These chronic dysfunctions can increase pain and are often attributed by patients to the lack of drug efficacy, leading them to change therapy and/or physician, with high personal and social costs. The clinical consequences of this are inadequate treatment and a higher probability of the pain becoming chronic.

The term OPIAD was introduced to refer to the opiate-induced effect on the hypothalamus—pituitary—gonadal (HPG) axis, namely a strong androgen deficiency. This particular form of hypogonadism affects male patients treated with opiates (Abs et al., 2000; Aloisi et al., 2005; Daniell, 2006). In these subjects, gonadal hormones are at very low levels and there are often clinical symptoms and signs such as increased weight, lower libido and gynecomasty. We have described the presence of OPIAD with different kinds of opiates and with different clinical procedures in which opiates were given in both acute and chronic forms (Aloisi et al., 2009). However, from the beginning, it was observed that the opiate-induced effects were not always comparable in the two sexes and at all ages.

Other axes have been reported to be affected by drugs, in particular the hypothalamic-pituitary-adrenal (HPA) axis. HPA-related hormones include products of the hypothalamus, pituitary and adrenal glands, the best known being corticotrophin-releasing hormone (CRH), adrenocorticotrophin hormone (ACTH), cortisol, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS); they are not commonly determined in pain patients although data exist to suggest their role in pain modulation. Indeed dysregulation of the HPA axis has been reported in several disease states, including chronic whiplash-associated disorders (Gaab et al., 2005), chronic widespread pain (McBeth et al., 2005), chronic myogenous facial pain (Galli et al., 2009) and various other conditions associated with chronic pain *per se*.

Reduced activity of the HPA-related hormones, cortisol in particular, has been described for fibromyalgia and chronic fatigue syndrome (Gur et al., 2004; Parker et al., 2001; Valença et al., 2009), chronic pelvic pain (Heim et al., 1998), low back pain (Griep et al., 1998) and irritable bowel syndrome (Böhmelt et al., 2005; Chang et al., 2009; Zhou et al., 2010). However, little is known about the role of DHEA and DHEAS in pain. Harry Daniell's group (2006) reported an opiate-induced depressant effect on their plasma levels in chronic pain patients and Kibaly et al. (2008) demonstrated that P450c17 (DHEA-synthesizing enzyme) gene expression was suppressed in neuropathic rat spinal cord.

The primary aim of the present study was to evaluate the effect of pain therapy on HPA axis functions through the evaluation of ACTH, cortisol, DHEA and DHEAS blood levels in male and female chronic pain patients. The secondary objective was to test the hypothesis that changes in these hormones are associated with psychological dysfunctions such as anxiety, depression and poor quality of life, determined in chronic pain patients with dedicated questionnaires.

2. Methods

2.1. Subjects

Male and female subjects suffering chronic noncancer pain from a population of patients of the *Pain Medicine Unit* of the Salvatore Maugeri Foundation in Pavia were asked to participate in the study between September 2009 and June 2010. Inclusion criteria were as follows: (a) suffering persistent noncancer pain for more than 12 months and being treated with analgesics/anti-inflammatory drugs for at least 3 months; (b) agreement to sign the informed consent form; and (c) over 18 years old.

Controls were age-matched subjects not suffering chronic pain and not taking drugs continuously. All experiments were carried out according to the Declaration of Helsinki.

2.2. Procedure

During routine control visits, out-patients were asked to participate in the present study. After signing the informed consent form, the patients were asked to complete psychological questionnaires and to give blood samples for hormonal evaluation. Clinical and psychological assessments were carried out on the same morning as the blood collection. Four patients were asked to participate in the study twice due to the complete change of their therapy (i.e. from anti-inflammatories to opiates) with an interval of at least four months.

2.3. Hormone collection

Blood for hormone determinations was taken by venipuncture in the morning, between 08:00 h and 10:00 h. Blood for DHEA, DHEAS and cortisol assays was collected in tubes without gel barriers or clot-promoting additives and centrifuged at 3000 $\times$ *g* for 15 min at 4 °C. Blood for ACTH determination was collected in EDTA-Vacutainer tubes and immediately placed on ice and centrifuged. Aliquots were then frozen till hormonal determination of cortisol, ACTH, DHEA and DHEAS. All hormone determinations were carried out in the Laboratory of the S. Maugeri Foundation of Pavia.

2.4. Hormone assays

Quantitative measurements of cortisol and DHEAS serum levels were carried out with the IMMULITE 2000 Analyzer (a solid-phase, competitive chemiluminescent enzyme immunoassay). The analytical sensitivity of the DHEAS assay was 3 μg/dl, while the sensitivity of cortisol was 0.20 μg/dl (Siemens Healthcare Diagnostics Products Ltd. Llanberis, Gwynedd LL55 4EL, United Kingdom). The normal range for serum DHEAS is 35—430 μg/dl for females and 80—560 μg/dl for men. The normal range for serum cortisol is 5—25 μg/dl.

ACTH was measured with an RIA kit (DiaSorin, Minneapolis, MN) according to the manufacturer's instructions; this assay requires 200 μl plasma/RIA tube. The limit of detection

for this assay was 15 pg/ml. The normal value for plasma ACTH is 0—71 pg/ml. DHEA was also measured by RIA (Diagnostic System Laboratories and IMMUNOTECH). The analytical sensitivity, or minimum detection limit, is 0.3 ng/ml. The intra-assay and inter-assay coefficients of variation were $\leq$7.9% and 11.9%, respectively. The normal value of plasma DHEA for men and pre-menopausal women is 0.5—7.0 ng/ml and for menopausal women 0.2—2.5 ng/ml.

2.5. Questionnaires

For the determination of psychological parameters, all participants completed a set of self-report instruments consisting of:

Beck Depression Inventory-II (BDI-II; Beck et al., 1996) used as a primary measure of depression. The BDI-II is a 21-item self-report of the cognitive, affective, physiological and motivational symptoms of depression the individual experienced over the past two weeks. Each item is scored on a four-point scale (0—3), summed to provide a scale score and corrected to be compared with the normal population. Higher scores reflect greater severity. A score under 85 means a state of depression consistent with normality, a score between 85 and 90 means a light state of depression, a score between 91 and 95 means moderate depression and a score over 95 means grave depression.

Beck Anxiety Inventory (*BAI*; Beck et al., 1988) is a 21-item self-report instrument for the evaluation of anxiety symptoms. Each item is a descriptor of the most common symptoms of anxiety. Each answer (none, a little bit, enough, a lot) is evaluated on a four-point scale (0—3), summed to provide a scale score and corrected to be compared with the normal population. Higher scores reflect greater severity. A score under 85 means a minimal level of anxiety, a score between 85 and 90 means a light level of anxiety, a score between 91 and 95 means a moderate level of anxiety and a score over 95 means a grave condition of anxiety.

SF-12 (Ware et al., 1996) is the brief version of the SF-36 questionnaire. It consists of 12 of the 36 items of the original questionnaire and investigates only the two general indexes, PCS (Physical Component Summary) and MCS (Mental Component Summary), the former for Physical Health, the latter for Mental Health. It can be used during an interview or can be self-completed. Lower scores mean a worse perception of physical and mental state.

QUID (De Benedittis et al., 1988) is the Italian equivalent of the McGill Pain Questionnaire (MPQ). It represents the first Italian semantic questionnaire for the evaluation of pain. QUID is composed of a 5-point scale for the assessment of pain intensity (Present Pain Intensity-PPI) and a semantic interval scale consisting of 42 pain descriptors divided into 4 categories (sensory, affective, evaluative and mixed) and 16 subclasses, similar to the minor classes of the MPQ. Each subclass is scored on an interval scale. Higher scores mean greater importance of a particular subscale in the perception of pain.

2.6. Statistical analysis

Statistical analyses were performed with the SPSS statistical package. Hormone data were analyzed by three-way analysis of variance (ANOVA) with the factors Sex (2 levels: male and female), Age (2 levels: >55 and <55) and Therapy (3 levels: controls, opiate and anti-inflammatory). Post hoc analysis was carried out with the Tukey and Bonferroni tests. Questionnaire data were correlated with hormone levels by the Spearman rank test. Significance was accepted at $p < 0.05$. Data are reported as mean $\pm$ SEM.

3. Results

3.1. Subjects

In total, 126 patients suffering from noncancer chronic pain were included in the study. The most commonly diagnosed pain disorders were: failed back surgery, fibromyalgia, postherpetic neuralgia, low back pain, unspecified neuropathic pain and radiculopathy. The most common drugs used were: opiates (fentanyl, oxycodone, tramadol, codeine, morphine, hydromorphone), nonsteroidal anti-inflammatory agents (NSAIDs; ibuprofen, aspirin, nimesulide) and anticonvulsants (gabapentin, pregabalin and carbamazepine). Since the number of subjects undergoing anticonvulsant therapy was too low, they were not considered further.

As reported in Table 1 the opiates and NSAIDs group consisted of 18 males (14 opiates users, 4 NSAIDs users) and 96 females (71 opiates users, 25 NSAIDs users); both sexes were divided into younger (<55) or older (>55) subjects. For the women, this corresponded to those in reproductive age and in menopause, respectively.

3.2. Hormones

3.2.1. ACTH

As shown in Fig. 1A, male and female control subjects showed comparable levels of ACTH. Three-way ANOVA (factors: Sex, Age and Therapy) revealed a significant effect of Therapy [$F(2,150) = 3.5$ $p < 0.03$] independently of age and sex. This was due to the fact that subjects treated with opiates or NSAIDs had lower levels than control ($p < 0.001$ and $p < 0.003$, respectively). Although no significant interactions were found, opiate-treated females under 55 years showed a much higher difference (−53%) from controls than opiate-treated females over 55 (−28%). In males the changes were also different: in the opiate-treated group the decrease was more evident in the younger subjects while the older group values remained at control levels. Similarly, in males the NSAID-treated patients showed lower levels only in the younger group.

3.2.2. Cortisol

As shown in Fig. 1B, cortisol plasma levels in controls did not show sex differences in either age group. Three-way ANOVA revealed a significant effect of Age [$F(1,150) = 3.67$ $p < 0.05$] and Therapy [$F(2,150) = 3.6$ $p < 0.03$] due to higher cortisol levels in older subjects than younger ones independently of sex. The significance of the effect of Therapy was due to the lower plasma levels in the opiates ($p < 0.04$) and NSAIDs groups ($p < 0.001$) than in controls.

3.2.3. DHEA and DHEAS

As shown in Fig. 2A, there was no sex difference in DHEA in the control groups in either age group, although there was a

Table 1 Demographic characteristics of male and female patients.

Groups	Opiates		NSAIDs	
Sex (*n.*)	Women (71)	Men (14)	Women (25)	Men (4)
Mean age ± SD	52.74 ± 11.97	54.08 ± 10.47	53.53 ± 12.09	56.81 ± 10.16
Age range	30—77	45—75	35—73	42—70
Employment (*n.*)				
Student	5	0	0	0
Employed	30	4	10	2
Housewife	15	0	9	0
Retired	14	5	3	1
Retired with invalidity	6	0	1	1
Unemployed	0	5	0	0
Marital status (*n.*)				
Never married	17	2	4	2
Married	43	9	15	2
Separated	10	3	3	0
Diagnosis (*n.*)				
Algodistrophy	7	2	3	0
Radiculopathy	47	8	19	4
Fibromyalgia	4	0	0	0
Neuropathy	5	4	2	0
Other	8	0	1	0

clear age-dependent decrease in both sexes; indeed ANOVA showed a significant effect of Age [$F(1,174) = 15.2$ $p < 0.001$] and Therapy [$F(2,174) = 2.65$ $p < 0.05$] due to lower plasma levels in older subjects than in younger ones. Moreover the opiates and NSAIDs groups had lower plasma levels than controls ($p < 0.002$ and $p < 0.04$, respectively).

As shown in Fig. 2B the DHEAS levels showed a significant sex difference in controls, with higher levels in men than women in both age groups; indeed ANOVA revealed a significant effect of Sex [$F(1,201) = 10.1$ $p < 0.002$], Age [$F(1,201) = 27.2$ $p < 0.0001$] and Therapy [$F(2,201) = 49.6$ $p < 0$]. This was due to higher values in men than women,

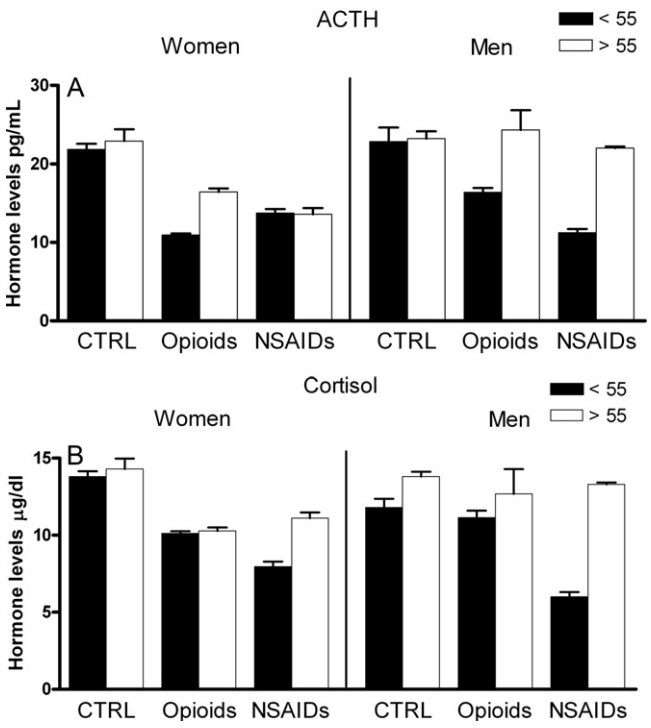

Figure 1 Histograms of ACTH (A) and cortisol (B) levels in the three groups: opiate users, NSAID users and controls (CTRL). Data are mean ± SEM.

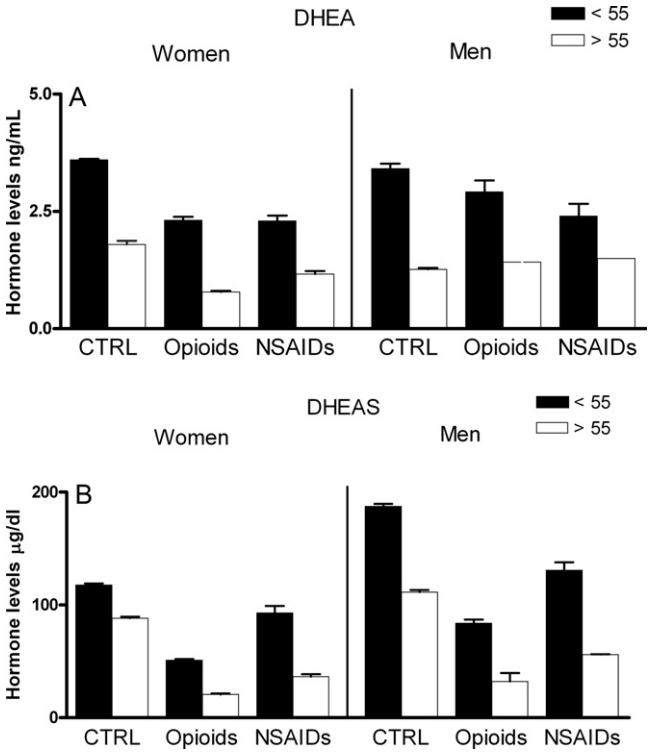

Figure 2 Histograms of DHEA (A) and DHEAS (B) plasma levels in the three groups: opiate users, NSAID users, controls. Data are mean ± SEM.

higher values in younger subjects than older ones and significant differences among all three groups: both opiates and NSAIDs groups had lower values than controls ($p < 0.001$ both) and there were lower values in the opiates group than the NSAIDs one ($p < 0.003$).

3.3. Questionnaires

3.3.1. BDI-II

As reported in Table 2, this questionnaire showed different scores depending on sex, age and therapy. The highest levels (>95) were found in men, particularly in men younger than 55. In this group all the measures of BDI-II reached 90 in total, cognitive and affective scores, suggesting severe depression. In the older men the levels were still very high but with lower scores. In contrast the scores in the women were close to 85 or less.

3.3.2. BAI

The BAI values were higher than the lower threshold (85) only in the two groups of men under 55. In both treatment groups these men showed a moderate level of anxiety. In women and in older men the scores were all under 85, i.e. control levels of anxiety.

3.3.3. SF12

In this questionnaire, higher scores represent a better quality of life. Most patients had quite low values on both scales (physical, PCS; mental, MCS). In particular, women treated with opiates showed very low values on the physical scale (i.e. <55: 26.3 ± 1.15) while men always had higher values than women in the respective groups. In contrast the lowest values in the MCS were presented by men under 55 (30 ± 4.02) treated with opiates. On this scale, younger women had higher values than older ones (see Table 2).

3.3.4. QUID

As shown in Table 2, the QUID data indicate that women over 55 and treated with opiates felt more severe overall pain. Similar values were present in all the other groups treated with opiates, including men. All the male and female groups treated with NSAIDs showed lower values. On the affective scale (QUID-A), men under 55 treated with opiates had the highest values, while on the sensorial scale (QUID-S) the highest values were in women under 55.

3.4. Correlations

HPA-related hormone levels were correlated with the questionnaire data to study the interactions among hormones and psychological dysfunction such as anxiety, depression and quality of life. In males older than 55, ACTH was positively correlated with Present Pain Intensity-PPI ($n = 5$; $R = 0.94$; $p < 0.01$), while in younger men (<55) ACTH was positively correlated with QUID-A ($n = 9$; $R = 0.68$; $p < 0.04$). In females, ACTH plasma levels were not correlated with the questionnaire data.

In younger women (<55), DHEA was positively correlated with PPI ($n = 39$; $R = 0.31$; $p < 0.05$) and negatively with PCS12 ($n = 37$; $R = -0.32$; $p < 0.05$). Moreover DHEA was negatively correlated with MCS12 ($n = 37$; $R = -0.44$;

Table 2 Descriptive statistics for psychological questionnaires.

	Opioid users				NSAID users			
	Women		Men		Women		Men	
	<55	>55	<55	>55	<55	>55	<55	>55
BDI-II cogn ± SEM	80.31 ± 3.79	80.69 ± 4.92	92.75 ± 1.97	88.25 ± 6.92	69.85 ± 6.62	66.67 ± 6.84	94.32 ± 1.45	72.67 ± 1.46
BDI-II som-aff. ± SEM	85.23 ± 3.81	87.00 ± 6.33	98.38 ± 0.49	93.25 ± 3.47	74.92 ± 5.21	81.78 ± 9.27	97.70 ± 0.88	90.33 ± 0.88
BDI-II ± SEM	84.23 ± 3.49	85.62 ± 6.63	97.25 ± 1.11	90.75 ± 4.87	71.62 ± 6.47	78.89 ± 8.34	96.45 ± 1.56	85.33 ± 0.88
BAI ± SEM	84.04 ± 3.71	84.46 ± 6.01	91.25 ± 3.39	77.00 ± 16.29	68.38 ± 5.96	81.67 ± 4.25	92.65 ± 1.46	54.00 ± 2.08
QUID-S ± SEM	16.38 ± 0.59	15.31 ± 1.08	12.63 ± 1.51	13.50 ± 1.85	13.69 ± 1.19	12.56 ± 1.09	6.30 ± 0.88	12.67 ± 1.20
QUID-A ± SEM	7.00 ± 0.68	7.69 ± 0.76	8.38 ± 0.88	6.00 ± 1.08	5.38 ± 0.79	6.00 ± 0.76	5.30 ± 0.88	4.33 ± 0.88
QUID-E ± SEM	9.54 ± 0.71	10.46 ± 1.12	8.50 ± 1.08	8.00 ± 2.00	8.38 ± 1.21	6.22 ± 0.78	7.23 ± 1.56	2.33 ± 0.88
QUID-M ± SEM	4.92 ± 0.45	7.54 ± 0.94	5.00 ± 1.10	5.50 ± 0.87	5.15 ± 1.04	4.78 ± 0.89	5.30 ± 0.88	3.00 ± 0.58
QUID-T ± SEM	37.65 ± 1.70	41.08 ± 2.92	34.50 ± 4.15	33.00 ± 5.21	32.62 ± 3.68	29.56 ± 2.39	21.30 ± 1.76	20.00 ± 1.16
PPI ± SEM	2.77 ± 0.21	2.62 ± 0.31	2.25 ± 0.25	2.00 ± 0.41	1.77 ± 0.23	1.38 ± 0.26	2.30 ± 0.88	2.00 ± 0.58
PCS12 ± SEM	26.26 ± 1.15	28.64 ± 2.49	31.06 ± 2.14	35.26 ± 2.57	33.86 ± 2.66	33.93 ± 1.58	35.20 ± 0.79	43.09 ± 0.94
MCS12 ± SEM	38.74 ± 3.23	35.41 ± 3.40	30.04 ± 4.02	41.18 ± 6.23	44.46 ± 3.83	36.11 ± 2.89	38.14 ± 0.82	32.27 ± 0.87

$p < 0.006$) in younger women and with QUID-E ($n = 22$; $R = -0.50$; $p < 0.01$) in older ones. Similarly, in younger men (<55), DHEA was positively correlated with BDI-II ($n = 9$; $R = 0.78$; $p < 0.01$).

In younger women (<55), cortisol was positively correlated with BDI-II ($n = 39$; $R = 0.32$; $p < 0.04$) and negatively with PCS12 ($n = 37$; $R = -0.31$; $p < 0.05$).

4. Discussion

The main result of this study is the significant effect of pain therapy on hypothalamus–pituitary–adrenal (HPA) axis hormones. The levels of ACTH, cortisol, DHEA and DHEAS were significantly decreased in subjects taking opiates or nonsteroidal anti-inflammatory drugs (NSAIDs) to treat pain, moreover these hormones appeared to be correlated with psychological features of these subjects.

In the therapy of chronic pain, the main therapeutic classes are opiates, NSAIDs and antiepileptics. Nevertheless, together with analgesia, these drugs too often produce side effects. Impaired digestive functions (gastritis, constipation) as well as psychological and behavioral effects very often lead to disturbed or depressed states. Indeed pain patients can suffer psychological and social discomfort such as depression, anxiety, somatoform disorders and other pathological conditions in which pain only represents the tip of a huge iceberg, even though the pain clinician often focuses only on pain. Unfortunately this partial therapeutic action can be one of the causes of the lack of efficacy and pain chronicization in these patients (Manchikanti et al., 2002).

We have shown the ability of opiate drugs to decrease blood steroid hormone levels (Aloisi et al., 2009), as described previously by other research groups (Abs et al., 2000; Finch et al., 2000; Daniell, 2007). In particular, morphine was shown to decrease testosterone via its decreased production and increased metabolism (Aloisi et al., 2010). Fewer data are available for other steroids such as those from the adrenals (i.e. cortisol, DHEA and DHEAS). These hormones are thought to be involved in a number of chronic pain disorders (Heim et al., 1998; Griep et al., 1998; Parker et al., 2001; Gur et al., 2004; Gaab et al., 2005; McBeth et al., 2005; Böhmelt et al., 2005; Chang et al., 2009; Galli et al., 2009; Valença et al., 2009; Zhou et al., 2010) but it is still not clear if their 'not normal' blood levels are the cause or the consequence of the painful syndrome.

ACTH is an important hormone modulated by the hypothalamic corticotrophin-releasing hormone and secreted by the pituitary. In the present experiment, opiates appeared to inhibit its production, probably through an inhibitory effect on the pituitary. An ACTH reduction is often accompanied by a decrease of the hormones produced by the adrenals. Indeed ACTH activity on the adrenals is mostly related to stimulation of the production and release of cortisol, although an aspecific activity on all adreno-cortical cells, resulting in modulation of all adrenal hormones, is known. The strong ACTH decrease observed in opiate-treated patients suggests a direct responsibility in the decrease of all the other hormones (cortisol, DHEA and DHEAS), particularly in females. Lower levels of ACTH were also found in the anti-inflammatory-treated chronic pain patients, suggesting dysregulation of the HPA axis possibly related to pain itself more than to treatment. This hypothesis must still be tested.

The positive correlation in male subjects between pain parameters (PPI and QUID-A) and ACTH shows that the hypothalamus–pituitary axis was more active in male patients who reported more pain, i.e. those subjects had higher stress levels. Indeed, particularly in the older subjects the correlation with pain intensity was highly significant (higher/lower ACTH, higher/lower pain), suggesting that when therapy is able to improve pain it is often accompanied by significant depression (lower than normal) of the hypothalamus. In general, this indicates that if a chronic pain patient is responsive to a treatment this is also because his CNS is still able to respond to that treatment, as indicated in this case by the lowering of HPA activity.

The positive correlation in the younger men between ACTH and QUID-A strongly indicates that the affective component of pain is more important in these subjects than in the older men and plays a much more important role in HPA axis modulation. These subjects (young men) had higher scores in the depression and anxiety scales (BDI-II, BAI), suggesting a hyperstimulated and still active affective system. These characteristics were not present in the older men and women, in whom the coping strategies appeared to be different and/or no longer active.

Differently from ACTH, we confirmed that cortisol levels in chronic pain patients are not high (Tanriverdi et al., 2007; Riva et al., 2010). Although a higher utilization rate can be hypothesized, there is more likely a higher inhibitory effect, possibly mediated by exogenous drugs as well as by endogenous opiates acting directly on the adrenals. Circulating cortisol is involved in many body functions including effects on glucose metabolism and mobilization in different tissues, regulation of immune and inflammatory responses, cardiovascular effects, neuroendocrine actions and effects on cognition.

The significant correlations between cortisol and the depression index (positive) and quality of life (negative) in women strongly indicate that this hormone is involved in the modulation of these states, independently of the kind of therapy used. Since in women there is no correlation of these parameters with ACTH but there is with cortisol, it appears that women have higher reactivity at the adrenal level, as recently reported (Turner-Cobb et al., 2010).

DHEA and DHEAS levels were found to be much lower in patients suffering chronic pain and being treated with either opiates or NSAIDs. The presence of these hormones in the blood requires particular attention because of their role as prohormones supplying steroid hormones in both women and men. In women, more than 50% of active androgens are generated by peripheral conversion from DHEA, while in men, despite the testicular production, about 50% of androgens are made locally from DHEA (Labrie et al., 2005). All the enzymes required to transform DHEA into androgen are expressed in a cell-specific manner in a large series of peripheral target tissues, permitting all androgen-sensitive and estrogen-sensitive tissues to make sex steroids locally and to control their intracellular levels according to local needs. In post-menopausal women, all estrogens and almost all androgens are made locally in peripheral tissue from DHEA which indirectly exerts effects on bone formation, adiposity, muscle, insulin and glucose metabolism, skin, libido and well-being. Serum DHEAS is also of value due to its stability in the blood; indeed it does not vary with the day, most likely because of its

longer half life. DHEA and DHEAS were found to be particularly correlated with PPI, the pain intensity at that moment. The positive correlations between these hormones and pain intensity indicate that when the levels of these hormones are high the subjects feel more pain and perceive a poor quality of life. Several hypotheses can be advanced to explain these results. Firstly higher pain is probably accompanied by higher stress and the activation of the HPA axis is followed by an increase of all adrenal hormone levels since ACTH stimulates not only the corticotropic cells but also the other adrenocortical hormones. However due to the lower hormone levels in pain patients under chronic therapy, it can also be hypothesized that the lower hormone levels/lower pain correlation could be the result of a more efficient pharmacological therapy, i.e. when the drug decreases pain, lower DHEA levels ensue. Confirmation of this has been found in unresponsive opiate patients in which the normal hormone values were accompanied by high pain levels. DHEAS is a relatively weak androgen and due to its high serum concentration (even higher than DHEA) it is a good marker of androgen production. Once in the general circulation, these hormones reach their target sites where they initiate action after being processed by specific enzymes. Indeed the synthesis of active steroid hormones from adrenal-secreted precursors allows for the local production of specific steroid hormones within the target cell. There are numerous tissues that express 3βHSD, 17HSD and aromatase enzymes, and thus have the capacity to synthesize active steroid hormones from circulating steroid precursors (Garcia-Segura et al., 2003). The expression of these enzymes in target tissues is of particular importance in humans, in which the adrenal glands secrete high amounts of DHEA and DHEAS.

DHEA has neuroprotective properties (Arlt, 2004) and together with other sex steroid precursors (pregnenolone and its sulfate derivative) enhances memory and cognitive functions in different animal models and increases neurogenesis in the adult rat hippocampus (Vallée et al., 1997, 2001; Darnaudéry et al., 2002). DHEA and DHEAS have been shown to protect neurons from other degenerative stimuli as well, including neurotoxic effects of corticosterone, oxidative stress, ischemia and amyloid-beta protein toxicity (Bologa et al., 1987; Kimonides et al., 1999; Bastianetto et al., 1999; Cardounel et al., 1999; Kaasik et al., 2001; Tomas-Camardiel et al., 2002).

On the whole it appears that most of these chronic pain patients do not adequately produce hormones strongly involved in anti-inflammatory and neuroprotective actions. The question is merely to evaluate the possibility that the use of several kinds of pain killers can *per se* support and/or increase the gravity of the original painful condition; data from addicted people support this hypothesis (i.e. Camı et al., 1992). In this study involving a large cohort of patients suffering from nonmalignant pain, we were able to clearly demonstrate that long-term NSAIDs or oral, intrathecal and epidural opiate therapy can have profound effects on endocrine functions, especially the HPA axis; thus adequate hormone-replacement therapies need to be considered.

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Conflict of interest

All authors declare no conlflict of interest.

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