Review

# Psychological stress and fibromyalgia: a review of the evidence suggesting a neuroendocrine link

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## Abstract

The present review attempts to reconcile the dichotomy that exists in the literature in relation to fibromyalgia, in that it is considered either a somatic response to psychological stress or a distinct organically based syndrome. Specifically, the hypothesis explored is that the link between chronic stress and the subsequent development of fibromyalgia can be explained by one or more abnormalities in neuroendocrine function. There are several such abnormalities recognised that both occur as a result of chronic stress and are observed in fibromyalgia. Whether such abnormalities have an aetiologic role remains uncertain but should be testable by well-designed prospective studies.

**Keywords:** fibromyalgia, hormone, neurotransmitter, psychological stress

## Introduction

Fibromyalgia is the second most common diagnosis made in rheumatology clinics [1], yet its aetiology remains a source of controversy. It has been suggested that fibromyalgia is a functional/psychological disorder and that the symptoms of fibromyalgia are simply due to somatisation of distress [2]. In support of this construct, there is definite evidence from population-based studies that psychological distress, particularly early-life trauma such as parental loss and abuse, can predict the future development of chronic widespread pain and fibromyalgia [3,4]. However, such observations leave unanswered the question of exactly how psychological factors translate into chronic physical pain.

The alternative hypothesis is that fibromyalgia has an organic basis [5]. The possible neuroendocrine origins of fibromyalgia have been extensively investigated, based on the specific hypothesis that abnormalities of various endocrine axes, and certain neurotransmitters, might be responsible for the development of the fibromyalgia syndrome [6–8].

The present review attempts to reconcile the conflict between psychological factors and physiological factors as a basis for fibromyalgia, by determining whether there are cogent neuroendocrine pathways that explain how psychological stress could lead to the symptoms of the fibromyalgia syndrome. Although these systems are clearly interconnected, the review will consider separately the potential role of the hypothalamic–pituitary–adrenal (HPA) axis, the role of the growth hormone axis, the role of sex steroids (both androgens and oestrogens), and the role of the neurotransmitters serotonin and substance P. Schematic representations of these systems are shown in Figs 1 and 2.

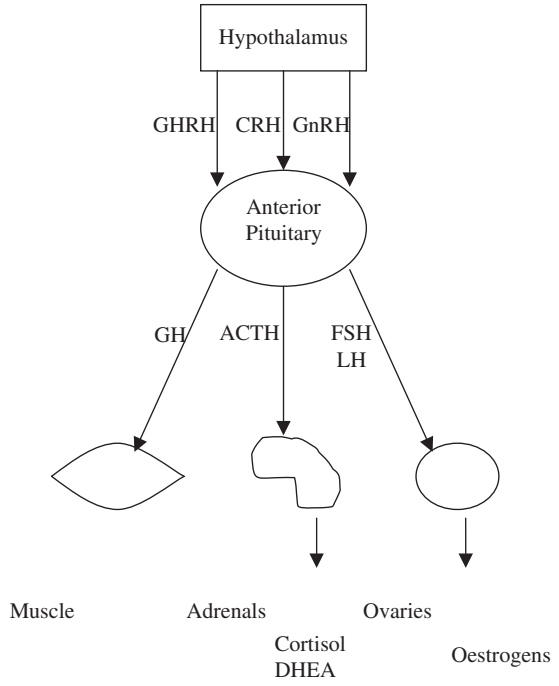
## The HPA axis

### Normal physiology and response to stress

The HPA axis, along with the sympatho-adrenal system, is the principal stress-response system in the human body. Acute stress causes the hypothalamus to release corticotrophin-releasing hormone (CRH) into the hypothalamic–hypophysial portal system. CRH releases adrenocorticotrophic hormone (ACTH) from the anterior

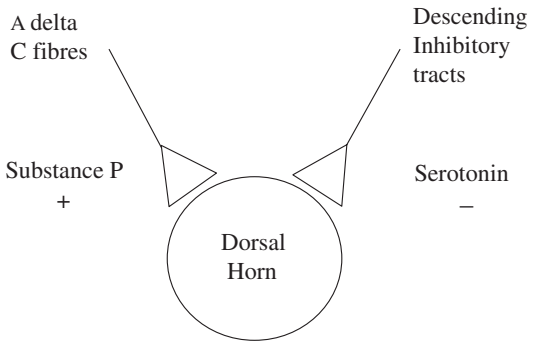
ACTH = adrenocorticotrophic hormone; CNS = central nervous system; CRH = corticotrophin-releasing hormone; CSF = cerebrospinal fluid; DHEA = dehydroepiandrosterone; FSH = follicle-stimulating hormone; HPA = hypothalamic–pituitary–adrenal; IGF-I = insulin-like growth factor I; LH = luteinising hormone.

**Figure 1**




Scheme showing the hormonal pathways implicated in stress and fibromyalgia. GHRH, growth hormone releasing hormone; CRH, corticotrophin releasing hormone; GnRH, gonadotrophin releasing hormone; GH, growth hormone; ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; DHEA, dehydroepiandrosterone.

**Figure 2**




Scheme showing the pain-modulating pathways in the dorsal horn of the spinal cord. Nociceptive A-delta fibres and nociceptive C fibres cause release of substance P in the dorsal horn. Serotonin released by the dorsolateral inhibitory tracts inhibits the release of substance P.

pituitary, which leads to cortisol being secreted from the adrenals. Elevated ACTH levels and elevated cortisol levels can be detected in the serum, which return to normal once the stressor has been dealt with.

Investigations of the HPA axis, like all endocrine axes, can be 'static' or 'dynamic'. Static tests include estimation of 24-hour free cortisol excretion in urine, and estimation of serum cortisol levels in the morning and the evening to detect the loss of normal diurnal variation. The most common dynamic test is the 'dexamethasone suppression test', which tests the suppressiblity of the HPA axis in response to an exogenous steroid. The ACTH response to exogenous CRH is a good indicator of the existing CRH 'tonus'. In CRH deficiency states there is an exaggerated ACTH response due to upregulation of CRH receptors in the anterior pituitary, while in conditions of CRH excess, such as classical depression, the ACTH response is muted.

Several studies, especially in animals, seem to suggest that the HPA axis becomes permanently hyperactive following exposures to early and severe stressors. Adult rats subjected to maternal deprivation as pups exhibit higher basal ACTH and higher ACTH response to stress [9], as well as a higher plasma cortisol response to stress [10]. This enhanced HPA responsivity to early life stress persisted throughout life [11].

Data from humans are less clearcut. Parental loss before the age of 17 years was only associated with higher basal levels of plasma cortisol in subjects who had abnormal psychiatric status as adults [12]. Even in children with a history of sexual abuse or other abuse the data are inconsistent, with both a decreased ACTH response to exogenous CRH [13] and an increased ACTH response to exogenous CRH [14] being reported. In the latter study, the abused children who had been selected for depression had a higher ACTH response compared with depressed but nonabused controls [14].

**Abnormalities in fibromyalgia**

Given the, albeit not completely clear, influence of stress on the HPA axis, there has been considerable research into the latter's role in fibromyalgia. In contrast to the stress data, available evidence suggests that the HPA axis is underactive in fibromyalgia. Several studies have shown reduced basal plasma cortisol or decreased 24-hour urinary free cortisol excretion [15–18]. Dynamic testing shows an exaggerated ACTH response but a blunted cortisol response to ovine CRH [7,18,19], and possibly reflects a CRH deficiency state and secondary atrophy of the adrenals due to chronic understimulation by reduced ACTH levels. This is consistent with a central abnormality of the HPA axis in fibromyalgia, resulting from the undersecretion of CRH by the hypothalamus.

There is indirect evidence supporting fibromyalgia as a low-cortisol state, in that it has several clinical features in common with other hypocortisolic states (namely, fatigue, somnolence, and muscle and joint pain). Fibromyalgia has indeed been reported to develop after hypophysectomy for Cushing's disease [20].

Some investigators have, confusingly, pointed out that fibromyalgia displays endocrine responses observed in the hypercortisolic state of Cushing's syndrome. These responses include blunting of the diurnal variation of serum cortisol [16,17] and a failure in approximately 35% of fibromyalgia patients to suppress serum cortisol levels with low-dose dexamethasone [21,22]. However, these abnormalities have been reported in clinical depression and alcohol abuse, and are therefore not specific to fibromyalgia [23,24].

The confounding effect of depression, a relatively frequent comorbidity associated with fibromyalgia, is an important consideration in hormonal studies. In particular, HPA axis abnormalities are often found in depression [25–27]. While there are certain similarities between depression and fibromylagia, as already mentioned, there are significant differences. Unlike fibromyalgia, plasma-free cortisol levels are increased in classical depression [24,28], and the ACTH response to exogenous CRH is blunted rather than increased [24,25]. Only one of these studies adjusted for coexistent depression, and none of them adjusted for alcohol use.

It is also relevant to consider whether these abnormalities are a feature of all chronic pain states or are a particular feature of the otherwise unexplained pain observed in fibromyalgia. Few studies have addressed this. In one study, compared with patients with rheumatoid arthritis, patients with fibromyalgia showed a significant loss of diurnal variation and a lack of suppression of serum cortisol with dexamethasone [16]. None of the subjects had clinical depression, and the depression rating scale was similar in both groups. Griep and colleagues [18] similarly reported that the exaggerated ACTH response to CRH challenge was significantly less in noninflammatory low back pain patients compared with fibromyalgia patients. There was, however, no difference between the two groups in 24-hour free cortisol excretion, both groups being lower than healthy controls.

In summary, animal studies would indicate that exposure to stress during childhood has the effect of raising the 'tonus' of the HPA axis, with exaggerated ACTH response and exaggerated cortisol response to stressors in later life. These findings contrast with the observed central deficiency of CRH in fibromyalgia, and thus the relationship between changes in the HPA axis in stress and in fibromylagia remain to be clarified.

## Growth hormone – insulin-like growth factor I

### Normal physiology and response to stress

Growth hormone is released from the anterior pituitary in response to a releasing hormone from the hypothalamus. Growth hormone causes release of insulin-like growth factor I (IGF-I) from the liver, which exerts its effect on target organs such as muscles.

The effects of acute and chronic stress on growth hormone secretion are diametrically different. Several authors have reported that acute stress has the effect of raising growth hormone levels in the plasma manifold [29–32].

Conversely, chronic psychosocial stress has the effect of lowering growth hormone levels. This phenomenon has been well studied in children and adolescents because of its implications in terms of growth failure [33–35]. Powell and colleagues [34] were the first to describe a syndrome of emotional deprivation and growth retardation associated with low growth hormone levels. Skuse and colleagues [35] more recently described a condition of growth failure and hyperphagia associated with low growth hormone levels in children who came from stressful homes. When the children were removed from their stressful home circumstances, growth hormone insufficiency resolved spontaneously.

### Abnormalities in fibromyalgia

Given the aforementioned, it is appropriate to consider evidence that fibromyalgia is associated with a growth hormone deficiency state. In support, several authors have demonstrated low serum growth hormone levels or low IGF-I levels in patients with fibromyalgia compared with controls [7,36–40].

A case control study of 500 patients with fibromyalgia and 152 controls (74 healthy subjects, 26 patients with regional pain and 52 patients with other rheumatic diseases) found significantly lower mean serum IGF-I levels in those with fibromyalgia [36]. The low levels of IGF-I in the fibromyalgia group were not explained by depression, tricyclic antidepressants, nonsteroidal anti-inflammatory medications, poor aerobic conditioning, obesity or pain levels. Controls with regional pain had normal IGF-I levels, as did most subjects with other rheumatic disorders, unless they had concomitant fibromyalgia.

The low growth hormone levels in fibromyalgia may be a consequence rather than a cause: the hormone is largely secreted during stage 3 and stage 4 of nonrapid eye movement sleep, which are known to be disrupted in fibromyalgia [41]. It was thus of interest that patients with fibromyalgia with initially normal IGF-I levels followed-up over 2 years often showed a rapid decline [36]. The majority of patients with fibromyalgia who had low IGF-I levels had markedly reduced stimulation of growth hormone secretion with secretagogues. The authors performed a similar study on a separate subset of patients, controlling for concomitant therapy, weight and disease

severity, and again reported significantly lower levels of IGF-I in fibromyalgia patients compared with controls. Overall, one-third of subjects with fibromyalgia had low IGF-I levels [37].

Support for a causal role for growth hormone deficiency, however, comes from observations that such deficiency in adults has been associated with many of the symptoms described by fibromyalgia patients. These symptoms are poor general health [42], low energy, reduced exercise capacity, cold intolerance, dysthymia [43,44], muscle weakness [45], impaired cognition [46] and reduced lean body mass [47]. Growth hormone is important in maintaining muscle homeostasis [48], and it has been suggested that low levels of the hormone may be responsible for delayed healing of muscle microtrauma in fibromyalgia [36].

Further evidence that growth hormone deficiency may have a role to play in fibromyalgia comes from a randomised, double-blinded, placebo-controlled study in which subjects with fibromyalgia, who gave themselves daily subcutaneous injections of growth hormone over 9 months, showed significant improvement in overall symptoms and tender points [49].

## Androgens

### Normal physiology and response to stress

Dehydroepiandrosterone (DHEA) is the major androgen produced by the adrenal glands, both in women and men. Up to 20% of DHEA in women is produced by the ovaries. The adrenal gland is also the major source of testosterone in women, where it is directly responsible for the production of the hormone. Testosterone is also produced peripherally in women by conversion from adrenal steroids. DHEA is present in high concentrations in the blood, lacks diurnal variation and has a long half-life [50]. Accordingly, serum DHEA levels are a good marker of adrenocortical function and are probably a more sensitive indicator of adrenocortical hypofunction than glucocorticoid secretion [51].

Serum DHEA levels are inversely related to perceived stress [52]. DHEA production and cortisol production vary inversely, and DHEA antagonises the physiological effects of corticosteroids [53]. This is illustrated by the existence of low levels of DHEA in depression [54], which, in its classical form, is now known to be a high cortisol state. Levels of DHEA have similarly been found to be low in anorexia nervosa relative to cortisol [55]. Testosterone levels also seem to be similarly lowered by stress. However, most studies on androgens (DHEA and testosterone) have been of acute stress, such as that resulting from military endurance courses [56–58]. Interestingly, many of these studies involved sleep deprivation, which was consistently associated with lower testosterone.

### Abnormalities in fibromyalgia

There have been few studies on clinic patients. In one study involving 56 women with fibromyalgia, serum DHEA and testosterone levels were markedly decreased in fibromyalgia patients compared with healthy controls [50]. Interestingly, low DHEA levels were significantly correlated with pain. The authors adjusted for important confounders such as age, menopausal status, body mass index and oral contraceptive use, and they excluded those who had recently taken glucocorticoids or other medications. No adjustments were made for levels of physical activity, however, which have been known to raise androgen levels [59].

There is indirect evidence that fibromyalgia may be a consequence of low androgens. Fibromyalgia has many anti-anabolic features, such as muscle pain and fatigue, typically seen in androgen-deficiency states. Androgens exert anabolic effects, particularly on muscle. They promote muscle growth and healing, and androgens have been used for this purpose after trauma, after prolonged immobilisation and in individuals with debilitating illness [60]. However, no therapeutic trials of androgens have been conducted in fibromyalgia.

## Oestrogens

### Normal physiology and response to stress

Oestrogens in women are produced by the ovaries in response to the gonadotrophic hormones, namely follicle-stimulating hormone (FSH) and luteinising hormone (LH). FSH and LH are themselves released from the anterior pituitary by the gonadotrophin-releasing hormone, a product of the hypothalamus. Oestrogen levels vary throughout the menstrual cycle in response to fluctuations in LH levels, and the levels peak just before ovulation.

It has been known for some time that stress has a profound effect on the female reproductive system. The development of functional amenorrhoea in response to psychological stress is termed ‘hypothalamic’ amenorrhoea [61]. Animal studies have shown that socially subordinate macaques have impaired ovarian function, resulting in low oestrogen levels [62]. The effect is not confined to premenopausal females. Ballinger [63] found that stress lowered oestrogen levels in women in the early postmenopausal phase.

Oestrogens have also been shown to ameliorate the physiological response to stress. In perimenopausal women exposed to time-restricted mental arithmetic as a stressor, supplementation with oestradiol significantly blunted the increases in both systolic blood pressure and diastolic blood pressure, and in levels of plasma cortisol, of ACTH, of epinephrine and of norepinephrine in response to the challenge [64]. Oestradiol has also been

shown to lower the cardiovascular response to stress in young women [65].

### Abnormalities in fibromyalgia

Given the effect of stress on oestrogens, it is logical to consider whether oestrogen levels are lower in women with fibromyalgia, and whether this might contribute to the pathogenesis of this condition. There are indeed several lines of evidence suggesting that oestrogen deficiency may be relevant. Women with fibromyalgia report more pain perimenstrually compared with the ovulatory phase, consistent with the fact that oestrogen levels peak during the ovulatory phase and then nadir around menstruation [66,67]. Female fibromyalgia patients have significantly lower oestrogen levels than controls during the follicular phase despite elevated FSH levels [7]. None of these subjects were on hormones such as oral contraceptives at the time of the study nor had coexistent rheumatic conditions.

In another study, 65% of female patients with fibromyalgia experienced menopause prior to the onset of the condition [68]. In this study, 30% of fibromyalgia patients between the ages of 24 and 45 years were found to be prematurely menopausal. Despite these findings, however, Macfarlane and colleagues [69] failed to find an association between sex hormonal factors, including oestrogen levels, and chronic widespread pain in a large unselected population.

The relationship of oestrogen deficiency with pain is not confined to fibromyalgia. Rheumatoid arthritis tends to improve during pregnancy, during oestrogen replacement therapy and during treatment with oestrogen-containing oral contraceptives [70].

If lower oestrogen levels do predispose to pain, what are the pathways involved? Changes in oestrogen levels in the plasma are accompanied by changes in a variety of neurotransmitters, particularly serotonin and substance P [71,72]. Both of these neurotransmitters are closely involved in the pathogenesis of nociception. Increased serotonin levels suppress the production of substance P within the central nervous system (CNS) [8]. It has also been shown that oestrogens upregulate serotonin [73]. It is therefore possible that serotonin production in the CNS is decreased in low oestrogen states, thereby leading to increased substance P levels and to more pain.

## Serotonin

### Normal physiology and response to stress

Serotonin (5-hydroxytryptamine) acts as an antinociceptive transmitter in the descending tracts located in the dorsolateral funiculus of the spinal cord [74] (Fig. 2). These descending tracts inhibit input from pain receptors in deep tissues in preference to input from cutaneous nociceptors. Serotonin is thought to exert its antinociceptive effect by suppressing the production of substance P, a nociceptive neurotransmitter. In the spinal cord, substance P acts on the neurokinin-1 receptors located in the dorsal horn [75]. Loss of pain modulation by the descending inhibitory tracts subserved by serotonin may result in spontaneous pain and tenderness, mainly in the deep tissues. As the terminations of the descending neurones have a widespread distribution in the spinal cord, a dysfunction of the descending system due to a lack of serotonin is likely to cause widespread pain [74].

Serotonin has been implicated in various psychiatric disorders such as depression and anxiety. Its association with stress has also been studied, as part of the paradigm of stress-induced depression. Several studies indicate that acute stress results in activation of the brain serotonergic system. Various forms of stressors (namely, physical stressors, metabolic stressors, psychological stressors or immunological stressors) cause a rise in extracellular serotonin in most regions of the brain [76], and increase serotonin synthesis and turnover [77]. For example, levels of brain tryptophan, the amino acid precursor of serotonin, is markedly increased by exposure to insulin injection in fasted rats (metabolic stressor), by running (physical stressor) and by immobilisation (psychological stressor) [77].

However, chronic stress affects the brain serotonergic system quite differently from acute stress. Sustained stress is thus accompanied by diminution of serotonin turnover [78,79]. An inverse relation has been found between the plasma corticosterone level in rats and serotonin turnover in the CNS [80]. In subordinate (chronically stressed) rats, serotonin receptor binding throughout the entire hippocampus was decreased [81].

### Abnormalities in fibromyalgia

Consistent with the data on the influence of chronic stress, most studies of serotonin in serum of fibromyalgia patients reveal lower levels than in controls [82–85]. The association between pain and low serum serotonin levels is not limited to fibromyalgia. Both patients with fibromyalgia and those with rheumatoid arthritis have thus been shown to have low serum levels of serotonin compared with healthy controls [84,86]. However, serum concentrations of serotonin were significantly lower in patients with fibromyalgia compared with arthritis sufferers [86].

Serum serotonin levels do not simply reflect CNS serotonin levels, however, since serotonin does not cross the blood–brain barrier and since CNS serotonin makes up less than 2% of total body serotonin. Moreover, serum serotonin is obtained from platelets, and therefore can vary with the platelet count [87]. Serotonin levels have not been measured in the cerebrospinal fluid (CSF), but levels of its immediate precursor (5-hydroxytryptophan) and its

metabolite (5-hydroxy indoleacetic acid) were found to be lower than normal concentrations in the CSF of fibromyalgia patients [83,88].

Serotonin levels are, however, altered in psychiatric disorders, particularly in depression and in those patients receiving antidepressant therapy [89,90]. These factors are of relevance in interpreting most of the aforementioned studies, which were based on fibromyalgia patients from rheumatology clinics who are more likely to have associated depression and anxiety, resulting in healthcare-seeking behaviour [91,92]. The only population-based study found that serotonin levels were significantly lower in subjects with fibromyalgia compared with a composite group with no pain, regional pain or nonfibromyalgia chronic widespread pain [85]. However, serotonin levels were not significantly different between fibromyalgia subjects and the pain-free group, considered alone. Unexpectedly, serum serotonin levels rose correspondingly with depression scores, contrary to what has been reported in clinic patients [83,84]. Concurrent antidepressant therapy did not alter the relationship between fibromyalgia and serotonin levels, or that between depression and serotonin levels.

## Substance P

### Normal physiology and response to stress

Substance P is an 11-amino acid neuropeptide that plays an important role in nociception [93]. Activated, small, thinly myelinated A-delta afferent neurons release substance P into lamina I and lamina V in the dorsal horn of the spinal cord. Activated C fibres similarly release substance P into lamina II. Substance P exerts its action through neurokinin-1 receptors. Substance P probably acts by alerting spinal cord neurons to incoming nociceptive signals from the periphery [8] (Fig. 2). Substance P released into the spinal cord diffuses out into the CSF, where it can be measured.

Most data investigating the substance P response to stress have been based on acute stress. Mapping studies indicate that the substance P-preferring neurokinin-1 receptor is highly expressed in brain regions that are critical for the regulation of affective behaviour and neurochemical responses to stress [94]. Neurochemical experiments in rats revealed changes in substance P content in the hippocampus, the septum, the periaqueductal grey and the ventral tegemental areas of the midbrain after stressors such as inescapable foot shock, immobilisation and social isolation [95]. In guinea pigs, central infusion of substance P agonists causes locomotor activation [96], accompanied by pronounced and long-lasting vocalisations [97]. This observation is of particular interest because exposure to stress induces vocalisations in many mammalian species [98]. The data suggested that psychological stress causes release of substance P in the limbic system of the brain, and that pharmacological blockade of substance P receptors is capable of inhibiting behavioural responses to such stress [97].

### Abnormalities in fibromyalgia

Although there is little data on chronic stress, it is reasonable to hypothesise that substance P may be elevated in fibromyalgia. Several studies have reported that CSF concentrations of substance P in fibromyalgia are around twofold to threefold higher than those in healthy controls [85,99–101]. However, nonfibromyalgia subjects suffering from chronic pain can display similar levels of CSF substance P as is found in fibromyalgia [8].

Increased levels of substance P in the dorsal horn of subjects with fibromyalgia would result in amplification of nociceptive signals from the periphery and would be a mechanism leading to widespread pain.

## Conclusions

The aim of the present review is not to consider what neuroendocrine abnormalities occur in fibromyalgia *per se*, but rather to evaluate whether such abnormalities could explain the relationship between chronic stress and fibromyalgia. We have shown that activities of several endocrine axes and neurotransmitters change in parallel in both fibromyalgia and stress. In particular, there are decreased basal levels of growth hormone and IGF-I, androgens and oestrogens both in stress and fibromyalgia. Serotonin levels are reduced in both fibromyalgia and chronic stress, while levels of substance P are increased. Available evidence would favour diminished function of the HPA axis in fibromyalgia. The HPA axis is of course one of the major stress-response systems of the body and, in this respect, there seems to be divergence between fibromyalgia and stress. Nevertheless, similar changes in most other hormones and neurotransmitters would favour a role for stress in fibromyalgia.

There are large areas of uncertainty, however. For several hormones, the response to stress has been mainly studied in animals and there are very few reports on the response in humans. Even where human studies do exist, they may not be representative of the general population (e.g. military endurance exercises).

Also, for the present review, we are mainly interested in the effects of chronic psychological stress on various hormones and neurotransmitters, as this is more relevant for fibromyalgia than acute stress. It is, however, difficult to replicate conditions of chronic stress in experimental conditions. As a result, in many instances, the only data that could be found were from conditions mimicking acute stress.

Finally, an inherent difficulty with the study of hormones and neurotransmitters in both stress and fibromyalgia is to

determine whether an effect is primary or secondary. All the studies discussed have been cross-sectional in nature, and do not allow conclusions on temporality. Thus, for example, low androgen levels in fibromyalgia could well be a result of chronic pain rather than the cause of it.

While the central theme of the present review is that chronic stress may lead to changes in various hormones and neurotransmitters, resulting in various manifestations of fibromyalgia such as pain and fatigue, it is not inconceivable that the chronic pain present in fibromyalgia can give rise to psychological stress, and thereby cause changes in neuroendocrine axes. Well-designed prospective studies are needed to resolve these issues.

To address this in relation to the HPA axis, our group is conducting a population study where we initially identified psychologically stressed subjects in the community through well-validated questionnaires. These subjects have had their HPA axis function assessed [102] and are now being followed-up after a period of 15 months to help resolve the issue of whether derangements of the HPA axis in psychologically stressed subjects predict the future development of, as opposed to being a consequence of, chronic widespread pain.

## Competing interests

None declared.

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