Abstract

There is increasing evidence that stress and depression may play a crucial role in the aetiology and pathophysiology of fibromyalgia (FM). We first review recent studies on the possible role of life stress, including childhood trauma, in FM. Subsequently we focus on clinical and aetio-pathogenetic links between stress, depression and pain. We put forward the hypothesis that chronic stress / depression may contribute to a dysregulation of neuro-endocrine, immune and central pain mechanisms in FM. Finally, we discuss some future directions, including the use of new conceptual models, research topics and strategies, as well as potential implications from recent studies in affective disorders for the treatment of FM.

Key words: Depression ; childhood trauma ; chronic fatigue syndrome ; fibromyalgia ; life events ; neurobiology ; stress ; treatment.

Introduction

Fibromyalgia (FM) is a syndrome characterized by medically unexplained, widespread musculoskeletal pain, hyperalgesia and/or allodynia, physical and mental fatigue and effort intolerance, non-restorative sleep, mood disturbance as well as other functional (e.g. gastrointestinal) complaints (Mease et al. 2005). The syndrome shows substantial symptomatic and diagnostic overlap with chronic fatigue syndrome (CFS) (Clauw and Chrousos 1997 ; Sullivan et al. 2002 ; Meeus et al. in press) and other functional somatic syndromes such as irritable bowel syndrome (IBS) (Wessely et al. 1999 ; Aggarwal et al. 2006).

In the following paragraphs, we discuss (1) the precipitating, predisposing and perpetuating role of physical and psychosocial stressors in FM ; (2) evidence concerning clinical and aetio-pathogenetic links between stress, depression and FM ; (3) a pathophysiological hypothesis on the role of chronic stress and depression in dysregulating neuroendocrine, immune and central pain mechanisms in FM ; (4) important methodological issues with regard to stress and depression research in FM ; (5) lessons from recent therapeutic studies in affective disorders that may also inform FM treatment ; and (6) new conceptual models, topics and strategies for future research in this domain.

Life stress and FM

Precipitating stressors

Although clinical experience and retrospective studies suggest that the onset of FM is frequently associated with various types of negative life events (Anderberg et al. 2000 ; Poyhia et al. 2001) and personally-relevant daily hassles (Van Houdenhove et al. 2002), prospective studies could only partially confirm these findings (Raphael et al. 2002 ; Williams et al. 2003 ; Kivimäki et al. 2004).

Whether traumatic stressors or posttraumatic stress disorder (PTSD) may precipitate FM still remains a controversial issue, although evidence for the frequent co-occurrence of PTSD and FM is increasing, in adult patients (Sherman et al. 2000 ; White et al. 2000 ; Cohen et al. 2002a ; Roy-Burne et al. 2004 ; Ciccone et al. 2005 ; Arguelles et al. 2006), as well as in children (Seng et al. 2005). The nature of the relationship remains unclear, but according to some authors, depression might be a mediating factor (Raphael et al. 2004a).

Predisposing stressors

Numerous retrospective case-control studies have shown that traumatic experiences (neglect, maltreatment or abuse) during childhood are more frequently reported by FM patients than by medically ill or healthy controls (for a review see e.g. Imbierowicz and Egle 2003 ; Davis et al. 2005 ; Van Houdenhove et al. in press). Although these findings suggest that early life stress may play a predisposing role in the aetio-pathogenesis of FM, such studies should be interpreted with caution due to confounding factors such as recall bias, response bias and health-care seeking bias (Hardt et al. 2004 ; Raphael 2005).

Traumatic experiences may augment vulnerability to FM via multiple and interacting mechanisms, notably psychophysiological mechanisms...
associated with pathological arousal, such as muscle hypertension, hyperventilation and sleep problems; hypothalamic-pituitary-adrenal (HPA-axis) dysfunction; and inadequate stress coping resulting from negative affectivity, low self-esteem, proneness to depression and abuse-related personality disorders (Van Houdenhove et al. 2001a; McLean et al. 2005; Weissbecker et al. 2006).

Furthermore, many FM patients appear to have created their own lifestyle stress – often since their early youth – by physically or mentally overexerting themselves, being too perfectionistic or overcommitted at work, or engaging in disproportionate self-sacrificing behaviour (Van Houdenhove et al. 1995, 2001b; Smith et al. 2006).

Perpetuating stressors

Not accepting their condition and failing to adjust to their functional limitations (Viane et al. 2003), low positive affect (Davis et al. 2001), high negative affect (Geenen & Middendorp 2006), illness uncertainty (Reich et al. 2006), perceptual biases such as somatic hypervigilance (Crombez et al. 2004; Carillo-de-la-Pena et al. 2006) and dysfunctional cognitive coping such as catastrophizing (Edwards et al. 2006) undoubtedly enhances the patients’ stress level and may lead to amplification and further persistence of FM symptoms.

Finally, not being accepted by significant others as suffering from a real and legitimate illness (lack of social support) can also be considered an important stress-generating factor that decreases quality of life and makes recovery from FM less probable (Schoofs et al. 2004).

Stress, depression and pain: what is the evidence?

The clinical and aetio-pathogenetic relations between pain and depression have since long been recognized, but recently this issue has received renewed attention (Schatzberg 2004; Peveler et al. 2006; Kennedy et al. 2006). Assuming that mood disorders and FM are both stress-related conditions (Van Houdenhove and Egle, 2004; Hammen 2005), it is hardly surprising that there is high comorbidity between both (White et al. 2002; Thieme et al. 2004; Kassam et al. 2006; Tennen et al. 2006; Michielsen et al. 2006).

Studies have found comorbidity rates from 30 to 80 percent, depending on variations in definition and measurement of depression (Henningen et al. 2003). A particular case is atypical depression, which is characterized by profound lethargia, daytime sleepiness and overeating, but also frequently involves diffuse somatic pain complaints and has been linked to stress-system underactivity (Gold and Chrousos 2002).

In FM patients, lifetime depression has been found to be much higher than in medical control groups and, moreover, to co-aggregate with mood disorders in family members (Arnold et al. 2004; Raphael et al. 2004b). Likewise, parents of children with primary juvenile FM reported higher levels of anxiety and depression than parents of healthy children or children with arthritis (Conte et al. 2003).

Thus, pain sensitivity, stress vulnerability and mood regulation may share common familial-genetic factors and FM may be categorized among the, genetically related, ‘affective spectrum disorders’ (Hudson et al. 2003, 2004).

More specifically, several recent studies have revealed genetic polymorphisms, i.e. in the serotonergic system (Offenbaecher et al. 1999; Cohen et al. 2002b), the dopamine receptor (Buskila et al. 2004), the norepinephrine system (Gursoy et al. 2003) and the substance P receptor gene regulatory region (Ablin et al. 2005). However, it can be assumed that no single gene will be identified as the sole cause of FM. Much more likely, a combination of genetic traits coupled with a chain of environmental (physical and/or psychosocial) events will gradually emerge as an explanation (Ablin and Buskila 2006; Buskila and Sarzi 2006).

Stress, depression and the pathophysiology of FM

Stress-system dysfunction

The available evidence suggests that in FM the stress response system – notably the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system – is dysregulated (Okifuji and Turk 2002; Gupta and Silman 2004; Crofford et al. 2004; Gur et al. 2004; Adler and Geenen 2005; McBeth et al. 2005). Clinical observation and careful listening to patients’ history, suggests that this abnormal functioning seems to occur mostly in the aftermath of a long period of overburdening by physical and/or emotional stressors, often associated with one or more depressive episodes. Eventually, the illness seems to be precipitated by an additional trigger in the shape of an acute physical or emotional event (Wentz et al. 2004; Van Houdenhove and Egle 2004; McLean et al. 2005).

We and others have proposed that this might imply a neurobiological ‘switch’ from hyper(re)activity to hypo(re)activity of the HPA-axis, based on functional or even structural receptor changes, and followed by a cascade of disturbances in neurotransmitter functions, immunological and central pain processing mechanisms (Van Houdenhove and Egle 2004; Fries et al. 2005). In line with this, HPA-axis hypo-function following chronic stress has been found to lead to an inadequate neurohormonal stress response and impaired habituation to subsequent physical or psychosocial challenges.
Deficient HPA-axis functioning might foster pathological immune activation with release of pro-inflammatory cytokines, provoking the so-called sickness response (lethargia and malaise, social withdrawal, flu-like symptoms, concentration difficulties, mood lowering and pain threshold lowering), all of which characterize the symptom picture of FM (Wallace et al. 2001; Raison and Miller 2003).

Alternatively, stress system hypo-function might be considered a preceding ‘trait’ factor in some FM patients (Glass et al. 2004), possibly related to early adversities (Gunnar and Vazquez 2001). Interestingly, in this respect, recent population-based prospective investigative studies showed that HPA-axis hypo-function helped to predict the development of new chronic widespread pain in a group of psychologically ‘at risk’ subjects (Gupta et al. in press; McBeth et al. in press).

Taken together, however, the exact significance of neuroendocrine dysfunction for the pathophysiology of FM remains to be elucidated (Cleare 2004).

**Abnormal pain processing**

Several recent studies strongly suggest that central pain processing is disturbed in FM. Indeed, ‘generalized pain hypersensitivity’ is now considered an important hallmark of the syndrome and has recently been confirmed by brain imaging studies (Gracely et al. 2002, 2004). Stress-related, cytokine-mediated activation of the inflammatory system may contribute to this central sensitization (Maier 2003; Khasar et al. 2005), but other factors such as inadequate descending pain inhibition (Mense 2000), including disturbed endogenous opioid system functioning (Kennedy et al. 2006), and low corticotropin releasing factor (CRF) (Larivière and Melzack 2000; Vit et al. 2006), may also play a role.

Furthermore, increasing evidence points towards peripheral tissues as relevant contributors to central sensitization, via neuroplastic changes in the spinal cord and brain. After central sensitization has been established, only minimal nociceptive input is required for the maintenance of the chronic pain state. Additional emotional and behavioural factors, such as pain-related negative affect and poor sleep may also play a role in pain threshold lowering (Price and Staud, 2005; Chiu et al. 2005; Staud 2006; Vierck 2006).

**Studying the role of stress / depression in FM**

The stress concept is rather vaguely defined and difficult to operationalize, which undoubtedly hampers its application in research (Van Praag 2004). Moreover, investigators on chronic pain disorders are not always aware of major methodological advances in the area of modern life stress studies. One example is the use of sophisticated interview-based strategies that may reveal not only external but also internal stressors associated with personality features and life history, and that focus on contextual features (and not only on stressors as such). Another example is the use of ecological momentary assessment methods and multivariate time series analyses that allow a detailed longitudinal view on the impact of daily life stressors on symptoms (Luyten and Van Houdenhove 2005).

Researchers should further recognize that causal relationships between FM and stress / depression are not linear, but recursive – so that patients often become trapped in a vicious cycle. Hence, future research should move away from simple linear etio-pathogenetic models but instead use ‘multi-wave’ studies to investigate recursive interactions between (pre- and post-morbid) stressors, coping styles / personality factors, and affective disorders in FM (Luyten and Van Houdenhove 2005).

Finally, FM researchers should study the relationship between stress, pain symptoms and HPA-axis functioning using objective stress measures and controlling for associated depression. By focusing on both biologic and psychosocial mediators and moderators, the complex interactions between these factors in the aetio-pathogenesis of FM may be unravelled (McLean et al. 2005b; Luyten and Van Houdenhove 2006).

**Treating FM : lessons from depression treatment research**

Recent therapeutic guidelines for affective disorders emphasize the benefits of long-term maintenance / continuation treatment in preventing relapse, and recommend that therapists should aim at enduring changes in personality functioning and life style, as well as customize treatment to the patient’s individual needs (Luyten et al. 2006). These guidelines are congruent with recent recommendations regarding the treatment of stress-related somatic syndromes such as CFS (Van Houdenhove, 2006) and FM (Dabadhoy & Clauw, 2006; Morley & Williams, 2006).

Moreover, depression treatment research has provided a compelling case for the importance of non-specific factors (such as the therapeutic alliance, and patient and therapist factors) in explaining outcome, beyond specific psychotherapeutic techniques and biological agents (Luyten et al. 2006). Treatment studies in FM should therefore consider these factors as well.

Finally, on a more general level, it may be expected that the growing interface between fundamental and treatment research in the study of affective disorders may inform a similar interface in FM research.
Future directions

Several new conceptual models may advance our understanding of the aetio-pathogenesis of various stress-related somatic syndromes, such as FM. Excellent examples are the concepts of ‘stress system disorders’ (Chrousos and Gold 1992), and ‘allostasis / allostatic load’ (McEwen 1998) that have recently been formulated within the ‘bridging’ sciences of psychoneuro-endocrinology and psychoneuro-immunology.

Furthermore, there is growing attention in stress research for ‘nature-nurture’ relationships (Meaney 2001; Moffit et al. 2005) including epigenetic mechanisms (Champagne and Meaney 2006); the role of positive and negative affect regulation (Zautra et al. 2005; Geenen and Middendorp 2006); and factors protecting against the impact of stressors (Champagne and Curley, 2005; Detert et al. 2004) including psychobiological determinants of resilience and vulnerability (Charney 2004) and consequences of childhood trauma and disordered early attachment (Waldinger et al. 2006) – all of which will open exciting heuristic avenues to study recursive interactions between life stress, personality, and genetic dispositions in stress-related illnesses.

Particularly growing insights in the role of the inflammatory response system, its links with the stress response system and its two-way relationships with the brain will augment our knowledge about cytokine-mediated pathological pain, fatigue, cognitive disturbances and mood disorders (Watkins and Maier, 2005; Glaser and Kiecolt-Glaser 2005).

It can be expected that these promising new developments will lay the groundwork for novel medications that will correct stress system dysregulations and abnormal pain processing (see e.g. Hendriksson and Sørensen 2002; Ledeboer et al. 2005; Crofford et al. 2005; Wood et al. 2005; Wallace 2006), and complement present pharmacological, cognitive-behavioural, rehabilitative and lifestyle interventions (Goldenberg et al. 2004; Jackson et al. 2006).

Conclusions

During the last years, evidence has accumulated that FM can be best understood psychologically as well as neurobiologically against the background of modern stress and depression research.

Nonetheless, our insights in the exact conditions under which stress and depression may play a predisposing, precipitating and / or perpetuating role in this syndrome remain fragmentary. Many uncertainties also remain with regard to the interference of physical and psychosocial stressors in the neurobiological processes giving rise to pain hypersensitivity, mood disturbance, fatigue and other FM symptoms.

On the other hand, it has become clear that FM treatment could benefit from lessons learned by recent research in depression, suggesting that therapeutic strategies in these patients should be personalized and maintained in the long run.

All these issues should be further investigated, based on new methodologies and theoretical concepts, and hopefully leading to more effective psychological and psychopharmacological therapies for those who suffer from FM.

REFERENCES


CHARNEY D. S. Psychobiological mechanisms of resilience and vulnerability: implications for


Clauw D., Chrousos G. P. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *Neuroimmunomodulation*, 1997, **4**: 143-153.


LUTTEN P., BLAUF S. J., VAN HOUĐENHOVE B., CORVELEYN J. Depression research and treatment: are we skating to where the puck is going to be? Clin. Psychol. Rev., 2006, 26: 985-999.


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