

FIBROMYALGIA RESEARCH REVIEW

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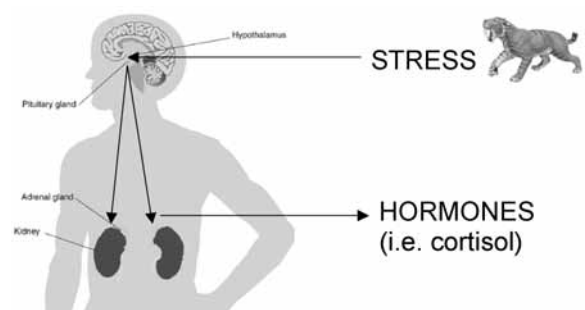
Given the growing interest in the role of stress in fibromyalgia development, the principal focus of this month's articles will be **stress and anxiety**. In the words of a recent review article from the Center for Research on Pain, McGill University Canada, "Despite the numerous cerebral alterations, fibromyalgia might not be a primary disorder of the brain but may be a consequence of early life stress or prolonged or severe stress, affecting brain modulatory circuitry of pain and emotions in genetically susceptible individuals."

STRESS RESPONSE AXIS IMPAIRED IN FIBROMYALGIA PATIENTS

A large proportion of fibromyalgia syndrome (FMS) patients report a worsening of their symptoms (a "flare-up") during periods of stress. A recent biochemical study has confirmed that FMS patients do in fact struggle to cope with stress. The body's stress response system, termed the hypothalamic-pituitary-adrenal axis (HPA axis), helps the body to remain stable under conditions of physical or psychological stress. The HPA axis actually describes the interactions between three different components of the body: the hypothalamus and the pituitary gland, both located in the brain, and the adrenal glands, located at the top of each kidney. In addition to its role in stress control, the HPA axis regulates a number of other functions of the body, including digestion, the immune system, mood, and energy usage. In response to changes in the environment, the hypothalamus and pituitary gland in the brain relay messages to the adrenal glands, which react by producing several crucial hormones (see diagram). For instance, if the "fight-or-flight" response is signalled by the hypothalamus in response to stress, the adrenal glands are instructed to produce hormones such as adrenaline and cortisol. Production of these "stress hormones" leads to an increase in blood sugar, heart rate and blood flow to the muscles, resulting in a sudden burst of strength. Although this "fight-or-flight" response was once vital for early man to escape from a saber tooth tiger, this system has become overstimulated in our modern-day, stressful environments! It is therefore not surprising that dysfunction of the HPA axis has been reported for many disorders associated with chronic stress, including chronic fatigue syndrome, gastrointestinal disorders, chronic pelvic pain and fibromyalgia. However, while a number of scientific studies have shown that the HPA axis is dysfunctional in fibromyalgia, there is considerable confusion as to exact nature of this abnormality. For every study that suggests the adrenal glands are overactive, one can find another stating that they are underactive! In addition to individual differences between patients, (and related factors such as the drugs they were taking, menstrual cycle phase etc.), the widely differing results may simply reflect the different tests used by different laboratories to measure adrenal gland function.

In order to shed some light on this perplexing topic,

researchers from Germany compared the functioning of the HPA axis in both female fibromyalgia and chronic pelvic pain patients. Chronic pelvic pain consists of persistent or recurring lower abdominal, pelvic and/or back pain, and like FMS, is associated with a number of other symptoms, including headache, fatigue, gastrointestinal disturbances, sleep problems, depression and anxiety. Chronic pelvic pain further resembles FMS in that many studies have failed to find any physical source of the symptoms. The German researchers recruited 17 female FMS patients, 18 chronic pelvic pain patients, and 24 healthy female controls for the study. Volunteers were first subjected to a "stress test", in which they were required to prepare and give a speech in front of an audience, and then made to sit an arithmetic test! The levels of stress hormones in blood and saliva samples from the volunteers were measured at 15 minute time intervals before, during, and after the stress test, in order to see how their HPA axis responded to stress. Interestingly, the total level of cortisol was reduced in FMS patients compared to chronic pelvic pain patients or the healthy controls. Cortisol is a hormone produced by the adrenal glands in response to stress, and plays an important role in glucose metabolism, blood pressure regulation and the immune system. Similarly, levels of cortisol in the blood were reduced in FMS patients (but not in chronic pelvic pain patients or in healthy controls), following direct stimulation of the HPA axis by drug treatment. Therefore this study seems to indicate reduced responsiveness of the adrenal glands specifically in FMS patients. FMS sufferers face a constant battle with chronic pain and stress, which may reduce the ability of their stress response system (the HPA axis) to appropriately respond to the "saber tooth tiger" when it appears. Further studies of adrenal gland biochemistry are now vital to build up a full picture of the impaired stress response in fibromyalgia.



Wingenfeld, K., Heim, C., Schmidt, I., Wagner, D., Meinlschmidt, G., Hellhammer, D.H. 2008. "HPA axis reactivity and lymphocyte glucocorticoid sensitivity in fibromyalgia syndrome and chronic pelvic pain." *Psychosom Med.* 70, 65-72.

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COPING STRATEGIES IN FIBROMYALGIA AND THE EFFECT OF POST-TRAUMATIC STRESS DISORDER.

Post-traumatic stress disorder (PTSD) is a chronic disorder that follows a major stressful or traumatic experience such as an injury, assault, rape or warfare. Sufferers of PTSD re-experience the traumatic event and display an exaggerated response to reminders of the initial trauma. In common with fibromyalgia syndrome (FMS), PTSD patients also describe disturbed sleep and anxiety. There is a strong association between FMS and PTSD, since the prevalence of PTSD is significantly higher among FMS patients than in the general population. Post-traumatic stress disorder and fibromyalgia further overlap, as FMS is frequently triggered by a physical or emotional trauma. Researchers from Israel proposed that the ability of individuals to cope with a severe psychological trauma may affect the development of FMS. A total of 77 FMS sufferers, a proportion of whom also had PTSD, were questioned regarding previous traumatic experiences, and compared with 48 healthy controls. Volunteers were asked to describe their "coping styles". "Coping" (the processes by which the individuals attempted to manage their emotions), was divided into "active" or "avoidant" coping. In active coping, the individual attempts to alter the stressful situation, or their reaction to it, whereas in avoidant coping the individual distances him/herself from the stressful situation. The results, published in *Rheumatology International*, demonstrated that FMS patients were more likely to use avoidant coping strategies compared with the healthy controls. Interestingly, FMS patients that also suffered from post-traumatic stress disorder were more likely to suppress emotions, (avoided thinking about unpleasant events), than FMS patients without PTSD. Suppression as a coping style has previously been associated with increased pain, thus it is possible that the way a person perceives and responds to stress influences FMS development. Alternatively, living with chronic pain may hinder the ability of FMS patients to cope with stress and trauma. Either way, these recent findings suggest that therapies aimed at enhancing coping skills and managing stress may be beneficial for fibromyalgia sufferers.

Ablin, J.N., Cohen, H., Neumann, L., Kaplan, Z. and Buskila, D., 2007. "Coping styles in fibromyalgia: effect of co-morbid posttraumatic stress disorder." *Rheumatol Int.* (E.pub ahead of print). Institute of Rheumatology, Tel-Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel-Aviv University, 6 Weizman St., Tel-Aviv, 64239, Israel.

THE EFFECT OF PREGABALIN (LYRICA) ON DEPRESSION AND ANXIETY.

Few significant advances have been made therapeutically for fibromyalgia syndrome (FMS), and indeed the best current treatment for FMS is multidisciplinary, combining exercise and lifestyle changes. However a milestone was passed in 2007, with the licensing by the US Food and Drug Administration of the first drug treatment for fibromyalgia, Lyrica or pregabalin (see last month's front cover of *FaMily*). Although Lyrica was originally designed for treatment of neuropathic pain (pain from damaged nerves), the pharmaceutical company Pfizer recently completed clinical trials in adult FMS patients, demonstrating that Lyrica also reduces fibromyalgia pain. A team of researchers from the US confirmed these findings, demonstrating that 450mg pregabalin/day significantly reduced pain severity compared to a placebo drug (1). This group recently published a follow-up study in the *Pain Medicine* journal, which aimed to analyse the potential impact of anxiety and depression on the response of 529 fibromyalgia patients to pregabalin treatment (2). Questionnaires revealed a higher incidence of moderate to severe

anxiety (45%), compared to depression (31%), among FMS patients. Anxiety disorders have previously been neglected in chronic pain studies, however there is growing awareness of the strong link between anxiety and chronic pain, and further attention should be given to the effect of anxiety on FMS. A quarter of patients reported pain relief following improvements in anxiety or depression, which the researchers suggest may be indirectly linked. However the majority (75%), experienced pain relief with no accompanying change in anxiety or mood symptoms. Although the mechanism of action of pregabalin in humans is currently unknown, studies in animals suggest that pregabalin acts by dampening down the response of over-excited nerve cells, reducing the release of chemicals responsible for transmitting pain signals (neurotransmitters). It is hoped that licensing of the first drug for FMS will encourage further research into how pregabalin works, and improve our understanding of exactly why FMS sufferers experience a low pain threshold.

1. Crofford, L.J., Rowbotham, M.C., Mease, P.J., Russell, I.J., Dworkin, R.H., Corbin, A.E., Young, J.P Jr, LaMoreaux, L.K., Martin, S.A., Sharma, U. ; Pregabalin 1008-105 Study Group, 2005. "Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial." *Arthritis Rheum.* 52, 1264-73.

2. Arnold, L.M., Crofford, L.J., Martin, S.A., Young, J.P and Sharma, U., 2007. "The Effect of Anxiety and Depression on Improvements in Pain in a Randomized, Controlled Trial of Pregabalin for Treatment of Fibromyalgia." *Pain Med* 8, 633-638.

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GROWTH HORMONE TREATMENT FOR FIBROMYALGIA.

It has previously been suggested that a proportion of fibromyalgia syndrome (FMS) patients have a deficiency of growth hormone. Growth hormone is produced by the pituitary gland situated in the brain (see previous diagram), and stimulates the liver to produce a chemical known as "insulin-like growth factor 1" (IGF-1). IGF-1 is important for regulating the growth and development of cells in our body, and has a particularly important role in the growth of nerve cells. Researchers from Barcelona thus decided to analyse the effect of growth hormone drug treatment in a group of 24 female patients with both severe FMS (16 or more tender points), and abnormal blood insulin-like growth factor levels. The FMS patients were randomly split into two groups: treatment group 1, treated with growth hormone in addition to three standard FMS drugs (amitriptyline, fluoxetine and tramadol), and treatment group 2, treated with the three standard FMS drugs only. Patients were assessed at 3, 6, and 12 months following the start of treatment, and the average number of tender points, severity of FMS symptoms and quality of life determined by questionnaires. The findings, reported in the *BMC Musculoskeletal Disorders* journal, revealed that patients receiving the growth hormone treatment demonstrated an improvement in all aspects measured. Compared to the control group 2, the average number of tender points per patient decreased by 60% in the growth hormone-treated group 1. However, the ability of growth hormone to improve FMS symptoms over standard drug therapy treatment requires further research. The authors do not suggest exactly how growth hormone treatment acts to reduce pain levels in fibromyalgia patients, and it is also not known whether growth hormone could effectively treat FMS symptoms if taken alone, without the other drugs administered in this study.

Cuatrecasas, G., Riudavets, C., Guell, M.A. and Nadal, A., 2007. "Growth hormone as concomitant treatment in severe fibromyalgia associated with low IGF-1 serum levels. A pilot study." *BMC Musculoskeletal Disord* 8, 119. Servicio de Endocrinología y Nutrición, Centro Médico Teknon, Vilana 12, E-08022 Barcelona, Spain.