UNIVERSITY HONORS PROGRAM

SENIOR PROJECT - APPROVAL

Name: Jennifer Powell

College: Arts and Sciences Department: College Scholars

Faculty Mentor: Laura Gagnon

PROJECT TITLE: Implications of Stress in the Fibromyalgia Syndrome

I have reviewed this completed senior honors thesis with this student and certify that it is a project commensurate with honors level undergraduate research in this field.

Signed: Laura Gagnon, Faculty Mentor

Date: 5/16/03

Comments (Optional): Excellent!!

Implications of Stress in the Fibromyalgia Syndrome

Jennifer Powell

Senior Thesis

May 16, 2003

Table of Contents

Abstract **3**

Introduction **4**

Fibromyalgia **4**

Epidemioloy 5

Symptoms 5

Diagnosis 6

Endocrinology **8**

Physiology of the Stress Response **9**

General Response to Stress 9

The HPA axis 11

Chronic Stress **12**

Chronic Hyper/Hypoactivation of the Stress System 12

Fibromyalgia and Stress **13**

Research Data 14

Discussion of Data 16

The Link Between Stress and Pain **18**

General Interactions 19

Specific Interactions 20

The influence of pain response on the stress system 20

The influence of stress response on pain perception 21

A Predisposition for Fibromyalgia **22**

Future Research and Conclusion **24**

References **26**

Abstract

Fibromyalgia Syndrome (FM) has been defined as a "specific, chronic, non-degenerative, non-progressive, non-inflammatory, systemic pain condition." It is a syndrome, not a disease, since it is characterized by a specific set of signs and symptoms that occur together. It is currently estimated that seven to ten million Americans are affected by this syndrome. Because FM has few symptoms that are outwardly visible and almost every part of the body can be affected, it has been termed "the invisible disability" or the "irritable everything" syndrome.

Because of the growing number of diagnosises being made and the wide spread physical abnormalities observed, FM has been studied extensively. Despite these many studies, no cause has been identified. However, these studies have provided insight into the complexity of this syndrome. There is now evidence for neuroendocrine abnormalities in Fibromyalgia patients as a result of the continued stress they encounter. These abnormalities seem to center around a dysfunction of negative feedback mechanisms within the hypothalamic-pituitary-adrenal axis. Furthermore, it seems as though there may be a link between the high levels of stress and pain experienced by these patients.

It is now being assumed that the solution to this syndrome may exist not in one single dysfunction, but rather in several abnormalities that feed off of each other to result in the symptoms of fibromyalgia. By examining these relationships, a clearer perspective may be obtained of the elusive cause of FM.

Introduction

As diagnosises for Fibromyalgia (FM) continue to increase at a drastic rate, researchers have responded accordingly with over 1000 articles appearing in the last decade. The two most prominent areas of study attempting to explain this syndrome's origin have surrounded the issues of stress and pain. In this work, FM and the stress response system will be reviewed, and the existing research linking this response to FM will be presented and discussed. As the current research is presented, abnormalities in the neuroendocrine response to stress will become apparent. In addition to this, an attempt will be made to demonstrate the relationship between neuroendocrine abnormalities and persistent pain in fibromyalgia patients. Finally, a possible genetic predisposition for such abnormalities and ideas for future research on this syndrome will be explored.

Fibromyalgia

Fibromyalgia Syndrome, while first described by physicians in 1816, was not officially recognized by the American Medical Association as a true illness until 1987. It has been defined as a specific, chronic, non-degenerative, non-progressive, non-inflammatory, systemic pain condition (1). Unlike a disease, which has known causes and understood mechanisms for producing symptoms, FM, which is of unknown etiology, has been characterized as a syndrome, or having a specific set of signs and symptoms that occur together.

Epidemiology

It is estimated that anywhere from 3 to 10 million people are affected by FM, and it is the third most commonly diagnosed rheumatic disorder after osteoarthritis and rheumatoid arthritis (2, 3). It is seen in all races and age groups with the median onset of the syndrome occurring from 29 to 37 years (3). Unfortunately the median age of formal diagnosis for FM is 34 to 53 years, meaning that most patients endure symptoms for many years before they receive an accurate diagnosis (2). This usually occurs because fibromyalgia is frequently misdiagnosed and often confused with other disorders such as myofascial pain syndrome, hypothyroidism, rheumatoid arthritis, and chronic fatigue syndrome (2). While this syndrome does not seem to be age specific, it does target by gender. Fibromyalgia affects women much more than men in an approximate ratio of 20:1 (3). In addition to this, 90% of the patients treated in rheumatology practices for fibromyalgia are women (2).

Symptoms

Because FM has few symptoms that are outwardly visible, it has been nicknamed "the invisible disability" or the "irritable everything" syndrome (4). The most common characteristic of fibromyalgia is that of pain. The pain of FM is profound, widespread and chronic. It knows no boundaries, migrating to all parts of the body and varying in intensity. It has been described as a deep muscular aching, throbbing, stabbing and shooting pain that defines the very existence of the fibromyalgia patient (3). While this extreme pain is a reality for many FM patients, others report a much lower pain intensity that is only a moderate in nature. Fatigue is a symptom that is also highly reported as problematic in 78 to

94% of FM patients (5). Interestingly, fatigue seems to be more prevalent in FM than in other rheumatological conditions. Furthermore, in a study examining daily fatigue and pain in FM, fatigue was reported to constitute a greater obstacle in the accomplishment of daily tasks than pain (5).

In addition to pain and fatigue, a number of other symptoms are usually reported and associated with FM. Many patients also complain of sleep disturbances. Despite sufficient amounts of sleep, patients may awaken feeling unrefreshed as well as having difficulty falling asleep or staying asleep (4). Another major symptomatic problem of Fibromyalgia seems to be depression. Although reports are somewhat unclear on the true numbers affected by depression with estimates ranging from 14-76% (5). Typically patients also suffer from one or more of the following: body stiffness, increased headaches or facial pain, cognitive disorders including spaciness or memory lapses, paresthesia (numbness and tingling particularly in the hands and feet), myofascial trigger points, chest pain, dysequilibrium, restless leg syndrome (an irresistible urge to move the legs particularly when at rest), irritable bowel syndrome (includes abdominal pain, bloating, constipation and/or diarrhea), increased frequency of urination, hypersensitivity to light, sound, touch, and odors, and skin complaints such as itchy, dry, or blotchy skin (2, 4).

Diagnosis

Despite these numerous symptoms, a physician's diagnosis of FM is based on taking a careful history and finding tender points in specific areas of muscle (3). In 1990, the American College of Rheumatology concluded that fibromyalgia could be diagnosed by two specific criteria: a history of widespread

pain occurring for longer than 3 months in all four quadrants of the body, and identified pain in 11 or more of 18 specified bilateral tender points in muscular tissue (Figure 1) when approximately four kilograms of pressure was applied (2,3,4,6).

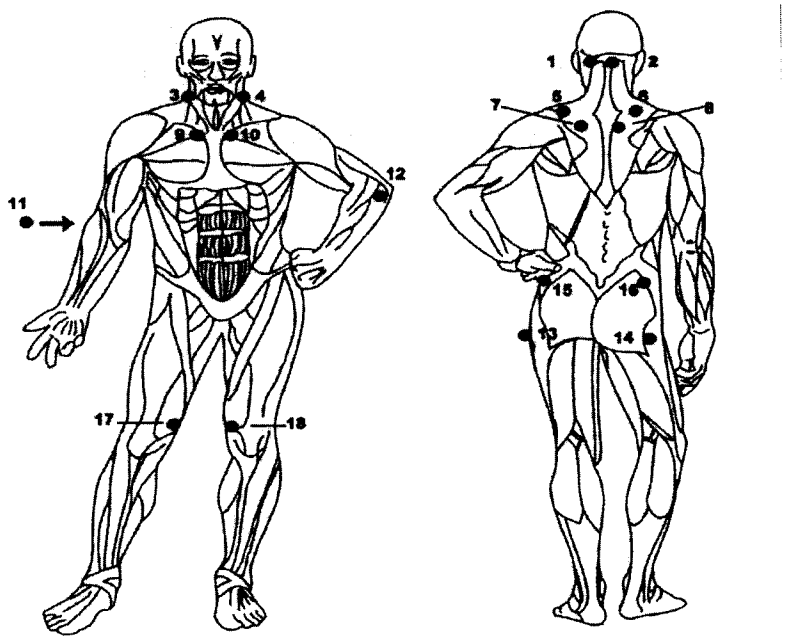


Figure 1: Fibromyalgia Tender Points Identified By The American College of Rheumatology in 1990 (4)

Tender points can occur in muscles, ligaments, or tendons and localize pain upon stimulation rather than referring it to an adjacent area as a trigger +point would (2). The presence of these many tender points has been correlated with depression, fatigue, anxiety, and other somatic symptoms as well as with pain (6). These set requirements for a diagnosis of FM provided a sensitivity of 88% and a specificity of 81% in distinguishing FM from other causes of chronic musculoskeletal pain (6).

Endocrinology

Throughout this work, some specific aspects of the endocrine and neuroendocrine system will be examined. The body can be affected either directly or indirectly by external changes and can only survive if the consistency of its environment can be controlled. The endocrine system is one way in which the body responds to reoccurring environmental changes. The word "endocrine" refers to the internal secretion of biologically active substances, which are commonly known as hormones. Hormones are released by endocrine glands and transported through the bloodstream to designated tissues. Once there, they act by binding to specific receptors on a target cell's surface or within the cell, which generally results in a cascade of intracellular reactions and therefore amplifies the original stimulus (7).

Traditionally the endocrine system is distinguished from the nervous system because the nervous system is connected to its target tissues through neurons that carry and transmit chemical signals (8). This is accomplished through neurotransmitters that mediate the synaptic transmission between two neurons. These chemical transmitters are synthesized in the cell body and travel down an axon where they are stored in synaptic vesicles and released upon depolarization. Unlike hormones, neurotransmitters act directly in the target's vicinity instead of traveling through the circulatory system and being distributed to all tissues. This allows the release of high concentrations of a transmitter to a particular target while preventing the release of that transmitter at other locations throughout the body (8). It is interesting to note that the same molecule may act either as a hormone or as a neurotransmitter depending on where it is being

released within the body (8). Sometimes both neurotransmitters and hormones are secreted by neurons, forming an interaction which is known as the neuroendocrine system (7). Both of these systems help maintain the body's internal environment and can cause important long-term changes in an organism's behavior that may or may not be beneficial.

Physiology of the Stress Response

General Response to Stress

As previously mentioned, the body is in a constant struggle to combat external changes and maintain homeostasis, or a dynamic steady state. Any adverse force that causes a series of reactions that alters the body's homeostasis is known as a stressor. When faced with excessive demands, a person's adaptive responses take on a stereotypic nature, a state known as "stress." More specifically, stress can be defined as a state in which the brain interprets the quantity of stimulation to be excessive or the quality of stimulation threatening with the brain subsequently responding in a generalized manner (10, 11). A good understanding of the systems that control the response to stress and their physiological consequences is necessary when examining the negative impact of stress.

During stress, attention is enhanced, and the brain focuses on the perceived stress. Cardiac output and respiration are enhanced, and blood flow is redirected to fuel the aroused brain, heart, and muscles. Furthermore, normal endocrine functions such as growth, reproduction, and pleasure are shut down to conserve needed energy (11).

The stress response, which is initiated by both the nervous and endocrine systems, is centrally controlled through systems located in the hypothalamus and brain stem (9, 12). These control systems include corticotropin-releasing hormone (CRH), arginine-vasopressin (AVP) neurons of the hypothalamus, and the locus ceruleus-norepinephrine (LC/NE) system (the central sympathetic system) (12). The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic system represent the effector limbs by which the brain influences all organs in the body throughout the duration of stressful stimuli (11, 12). In addition to this, there are interactions of these stress systems with three higher brain control areas that influence anticipatory response (mesocortical/mesolimbic systems); the initiation, propagation, and termination of stress system activity (amygdala/hippocampus); and the setting of pain sensation (arcuate nucleus) (12).

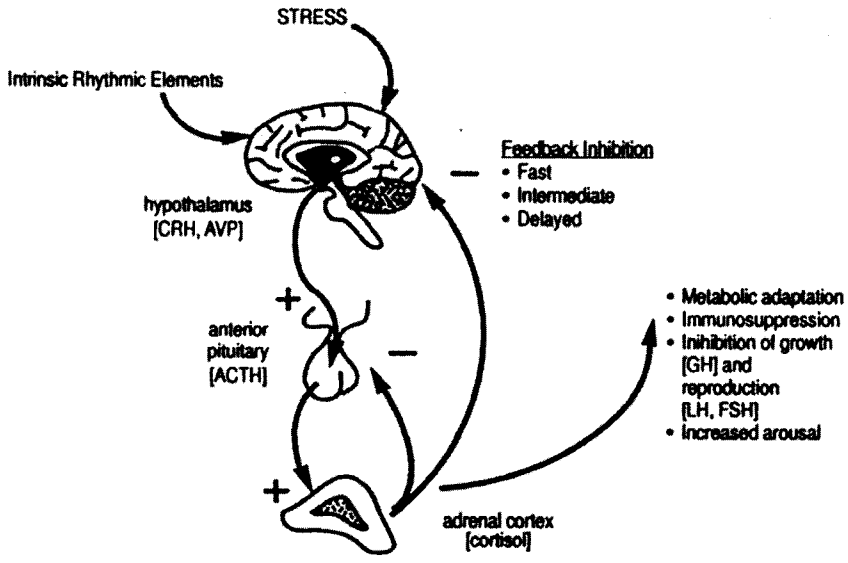


Figure 2: Hypothalamic-pituitary-adrenal axis (13)

The HPA axis

The HPA axis (Figure 2) is an example of a negative feedback system and mainly involves the synthesis and release of three hormones: adrenocorticotropic hormone (ACTH), corticotropin releasing hormone (CRH), and cortisol (10). The hypothalamus controls the secretion of ACTH from the anterior pituitary, which then stimulates the adrenal cortex to release glucocorticoid hormones (11, 12). The main glucocorticoid hormone secreted in humans is cortisol (11). An excessive amount of this hormone has long been known to mark subjects undergoing stress. After intensive research, the factor responsible for corticotropin secretion was isolated as a 41 amino acid peptide and named CRH (10-12).

After its release, CRH acts as the main hypothalamic mediator of HPA axis activation by regulating ACTH secretion (11, 13). Arginine vasopressin (AVP) has little ability to stimulate ACTH secretion on its own, but when combined with CRH, the two work synergistically to increase ACTH secretion (11-13). CRH and AVP control ACTH production and release through separate receptors and signaling pathways, allowing for a very rapid increase in ACTH secretion when circulating glucocorticoid levels become too low (10). This is made possible through reciprocal positive interaction where each neuropeptide is capable of stimulating the other (11).

Under nonstressful conditions, both CRH and AVP are secreted in a circadian (24 hour), pulsing fashion, with about two to three secretatory pulses per hour (12). Under resting conditions, the amplitude of these pulses increases in the early morning, which results in ACTH and cortisol bursts in the general

circulation (12). These are known as diurnal variations and can be disrupted by stress (11). During stress, the amplitude and frequency of CRH and AVP pulses increase, therefore resulting in a marked increase of ACTH and cortisol secretatory bursts (11, 12).

Glucocorticoids are the final products of the HPA axis and are involved in maintaining whole body homeostasis and the response to stress. They assist in regulating the basal level of the HPA axis as well as the termination of the stress response (12). Through inhibitory negative feedback on ACTH secretion, the time that tissues are exposed to glucocorticoids is limited (12). This minimizes their catabolic, immunosuppressive, and anti-inflammatory effects, which limits the possibility of tissue destruction (14).

Chronic Stress

Chronic stress can alter the body's normal response in a different manner than acute stress (15). The stress response is intended to be limited in duration with an appropriate initiation, amplitude, and termination (11). This limited nature of the response renders the effects beneficial rather than damaging (12). In contrast, chronic activation of the stress system can lead to a syndromal state described by Selye in 1936 (12).

Chronic Hyper/Hypoactivation of the Stress System

Because CRH is involved in almost every area of stress adaptation, the magnitude and duration of its production has been evaluated to help explain the pathogenesis of many syndromes (12). The best example of chronic hyperactivation is seen in melancholic depression. Here cortisol secretion is

increased, and ACTH response to CRH is decreased (11, 12). Another strong example of an overactive axis is demonstrated in Cushing's disease. This disease is characterized by a feedback abnormality, where CRH and ACTH secretion are only suppressed at inappropriately high circulating levels of cortisol, resulting in hypercortisolaemia (7, 8). Chronic hypoarousal, however, is characterized by chronically reduced secretion of CRH (12). This state has been consistently linked with atypical depression and chronic fatigue syndrome (11, 12). In this glucocorticoid-deficient state it is believed that the body remains relatively resistant to infections but has an increased susceptibility to autoimmune/inflammatory diseases (11, 12). While the above descriptions involving CRH levels are accurate, a more simplistic understanding of these two states is possible. In order to maintain sensitivity to new incoming stressors during chronic stress the body has two options: to increase the drive on hormone production and release resulting in a hyperfunctioning axis, or to become resistant to the effect of circulating glucocorticoids which would result in a hypofunctioning axis (14). In either case, the appropriate negative feedback within the HPA axis is lost (14).

Fibromyalgia and Stress

It has been frequently observed that the onset of FM symptoms occurs following a significant stress or period of stress, such as a death in the family or a serious illness (13). In addition to this, approximately 65% of patients report that the intensity of their symptoms directly correlates with their current stress level (16, 22). It is also important to remember that simply living with a syndrome such

as FM results in exposure to a chronic stressor. The reported rates of depression previously mentioned far exceed the rates in normal healthy populations, indicating a high degree of emotional distress as well (22). With this information, much of the research over the past decade has concentrated on examining the stress response system in fibromyalgia patients. Although some of the data and interpretations accumulated by researchers are conflicting, all agree that there are abnormalities in the FM patient's neuroendocrine response to stress. It is because of this that some researchers have started to consider FM as a "stress-related syndrome" (14-18).

Research Data

Studies performed by McCain and Tilbe on basal HPA axis function in patients with FM demonstrated low 24-hour urine free cortisol levels compared with normal subjects (13, 16-19, 21, 24, 25). Patients also showed normal morning (peak) and elevated evening (trough) cortisol levels, resulting in the loss of normal diurnal cortisol fluctuation. In this flattened diurnal cortisol pattern, the elevated cortisol levels could not be suppressed by dexamethasone, a potent glucocorticoid that normally suppresses pituitary ACTH and results in a decrease of plasma and urine corticosteroids (13, 16-19, 21, 24, 25). Furthermore, abnormal cortisol levels seem to predominate in patients who have suffered from FM for a duration greater than two years (13, 16). All of these results were confirmed in a later more expanded study by Ferraccioli et al. It should be noted however, that in one study by Adler et al. 24-hour urinary free cortisol, and the diurnal pattern were reported as normal (23).

In order to determine whether or not this abnormality originated at the hypothalamic or pituitary level, Griep et al. injected patients with CRH in the morning, when no significant difference in cortisol levels should exist. This test of the HPA axis's response to injected CRH is a fairly accurate measurement of its stress-induced activation. Results revealed a hyperactive ACTH release with a blunted cortisol response relative to the ACTH stimulation (18, 19, 24, 25). In a similar study by Riedel et al., basal values of ACTH and cortisol were shown to be higher prior to the CRH stimulation (19). A more recent study by Griep et al. comparing FM patients, patients with low back pain, and controls concluded that while pre-stimulation basal levels of ACTH appeared higher, the basal cortisol levels were significantly reduced (21). Despite the pre-stimulation discrepancies, both of the previously mentioned studies confirmed that following CRH injection only ACTH reached a higher level in FM patients, while no significant changes in cortisol concentrations were observed (19, 21). In addition to this, the latter study reported that not only was the ACTH response hyperactive in magnitude, it was also significantly more prolonged (21). The results of the Griep et al. study can be seen in Figure 3. Similar results to the previous studies were also confirmed in experimental data by Crofford (13, 16). Furthermore, Crofford observed low cortisol levels following exercise and an increase release of AVP, with five of the twelve patients achieving AVP levels more than two standard deviations above the highest control value (13, 16).

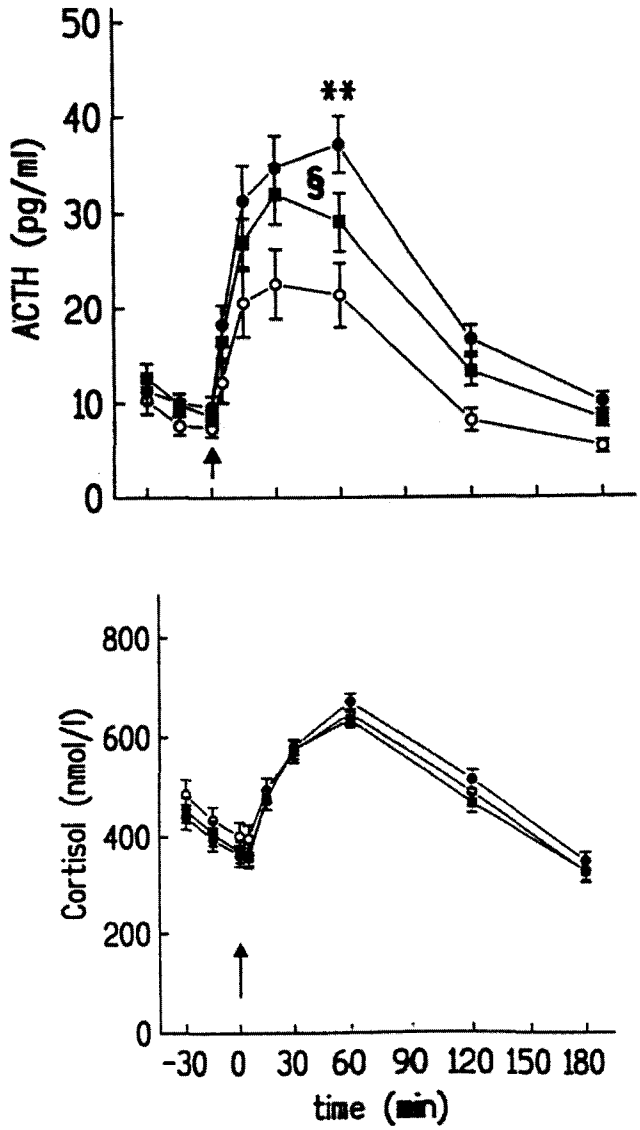


Figure 3: Response of ACTH and cortisol to patients with FM (closed circle), with low back pain (closed square), and healthy controls (open circle); arrow indicates the time of injection (20).

Discussion of Data

The results demonstrating low 24-hour urine free cortisol, which reflects the time-integrated plasma free cortisol concentrations over 24 hours, seem incongruent with the corresponding occurrence of higher cortisol levels in the evening but normal morning levels. A plausible explanation provided by Crofford hinges on the pulsing nature of cortisol secretion. There are normally eight to

nine peaks of cortisol over a 24-hour period, with the highest secretion occurring during the nighttime (8). These theoretically should be in response to basal surges of CRH and ACTH. It is possible that in FM, the height of the cortisol peaks might be normal or elevated, but the frequency of the peaks could be decreased, resulting in a low cortisol output over a 24 hour period (13, 16, 18, 24).

The results of the experiments involving CRH become much more difficult to explain. Although many researchers found similar data, there have been several different interpretations concerning the implications of those results. Earlier studies by Crofford et al. explain the blunted cortisol response to ACTH release as the result of a hyporesponsive adrenal gland due to hypoactivity of the adrenal cortex or through chronic understimulation from deficiencies of CRH or ACTH (13, 16). This interpretation has been linked to similar findings in patients with CFS, as both syndromes are permeated by fatigue (13). Interestingly, in Crofford's latest published work the conclusion made from the same data is characterized by a hyperactivity of the stress system, instead of the previously mentioned hyporesponsive system. In this work Crofford correlates the results to comparable findings in patients with depression or Cushing's syndrome (18). Similarly, Neeck interprets the data as a hyperfunctioning system resulting as an adaptive mechanism of a chronically stimulated adrenal cortex with a decrease in receptor regulation (19). In Griep's most recent study he explains the results as the apparent hyporesponsiveness of cortisol secretion to increased ACTH stimulation, which is known as hypocortisolemia (21). This is in direct conflict with Crofford's correlation of FM to Cushing's syndrome, which is characterized

by hypercortisolaemia (8). In addition to this Griep also states that the HPA activity in FM is clearly different from that of depression, which is characterized by a hyperactivity of all parts of the HPA axis (21). He argues that in depression the feedback abnormality is found at the corticosteroid level, while it is more probable that in FM the feedback resistance exists at the glucocorticoid level (21). This conclusion is based on his findings that the ACTH response to CRH is more prolonged, suggesting a defect in cortisol control. This impaired feedback may be a result of glucocorticoid receptor function, instead of the adrenal receptor function suggested by Neeck (21).

The Link Between Stress and Pain

Two of the major systems affected by fibromyalgia are the stress-regulating system and the nociceptive system. While the stress response has been extensively reviewed thus far, the primary complaint of these patients is still pain related. There are generally two types of pain described by FM patients: Allodynia, pain from normally non-painful stimuli and Hyperalgesia, an increase in pain intensity and prolonged pain duration from normally painful stimuli (27). In accordance with this, studies have shown that pain thresholds in these patients are two to three times lower than the levels in healthy controls (25).

Recently many researchers have concluded that the origin of fibromyalgia exists within abnormal processing of the Central Nervous System (20, 25, 27, 28). Proponents of this theory believe that the long-standing excitation of nociceptors may initiate and maintain a constant hyper-excitability in pain response (27). These same researchers believe that abnormalities seen in the

stress response system result only from chronic pain. It is believed that since pain is both a chronic and emotional stressor, it exists as the sole trigger of hormonal abnormalities. At the same time, there are those that still believe that the primary cause of FM symptoms is a result of other stressors, which in turn trigger abnormal pain behavior to perpetuate the cycle (13, 16, 17).

General Interactions

Regardless of whether or not stress or pain is the initial activating factor, these two systems are intertwined through a myriad of various feedback loops. Their interaction exists on such a level in which the alteration of one system will inevitably have some effect on the components of the other. This is demonstrated by the fact that a temporary increase in pain and allodynia is almost always correlated to an increase in the patient's stress level (27). Additionally, patients who score higher on all pain scales also score higher on tests for anxiety, depression, and general distress (28). It is also interesting to note that some of the most successful treatments of pain involve a reduction in stress. Patients who are most successful in lowering their pain levels have at least one of three characteristics in common: a high level of self-efficacy (the belief in one's ability to engage in actions sufficient to attain a desired health outcome), a belief that they personally posses the ability to control and decrease their pain, and a frequent use of adaptive coping strategies and support groups (25). Each of these characteristics demonstrates an obvious and direct reduction in personal stress.

Specific Interactions

It has been proposed that CRH may be the crucial link between the pain and stress responses. CRH activity may determine not only the symptoms of FM, but may also be the cause of many hormonal deviations previously discussed. Since altered levels of CRH have been observed in situations that are initiated and driven by either pain or stress, it is possible that this hormone plays a role in resetting endocrine and nociceptive mechanisms (20).

The influence of pain response on the stress system

The pain response system has a direct effect on the HPA axis by changing CRH levels. The change in CRH levels has been linked to two specific factors: Neuropeptide Y (NPY) and Serotonin (5-HT) (16, 19, 20). NPY co-localizes with norepinephrine and its levels represent sympathetic adrenal output (13). In FM patients, plasma NPY levels are much lower than controls (16). This is significant since the presence of NPY has been reported to increase concentrations of CRH (16). 5-HT plays an important role in the pain response system since one of its functions is to block the brain's perception of painful stimuli. Studies have found significantly lower serum levels of 5-HT in FM patients (19, 20). As would be expected, a highly inverse relationship was found between 5-HT levels and the intensity of perceived musculoskeletal pain (20). It is possible that low 5-HT levels may decrease antinociceptive mechanisms within the spinal cord, explaining allodynia in FM patients. In addition to this, 5-HT is linked to the regulation of the HPA axis through CRH. CRH containing neurons receive synaptic input from 5-HT neurons, which is one of the mechanisms by

which CRH is released (19). Here an abnormality in pain processing influences the stress response system to also respond in an irregular manner.

The influence of stress response on pain perception

In other mechanisms, altered levels of CRH may result in increased pain perception. As chronic stress persists, there seems to be a loss of negative feedback as previously discussed. As CRH levels increase, the release of somatostatin occurs, which serves to inhibit the release of growth hormone (GH) and insulin-like growth factor (IGF-I) (19). Studies have shown that both GH and IGF-I have low 24-hour levels in FM patients (14). Some have speculated that impaired GH secretion may disturb normal muscle homeostasis and therefore induce muscular pain (20). Additionally, it has been shown that decreased levels of IGF-I are associated with lower pain thresholds. In a study on rats, administration of IGF-I resulted in an increase in nociceptive threshold, and chronic administration resulted in a halted progression of hyperalgesia (14).

As levels of CRH rise there tends to be a blunted response of glucocorticoids in FM patients as previously discussed. Since glucocorticoids serve as powerful anti-inflammatory agents, a decreased response should theoretically result in increased inflammation. Interestingly, pain researchers have found that hyperalgesia can result from increased inflammation with a result almost identical to persistent pain conditions (25). Following inflammation, nociceptive neurons often have an increased excitability and an increased response to mechanical, thermal, and chemical stimuli. This hyperexcitability leads to increased activity at higher brain centers and is perceived as more intense and prolonged pain as seen in Figure 4 (14, 25). This possible

mechanism could serve to explain both the allodynia and hyperalgesia exhibited by fibromyalgia patients.

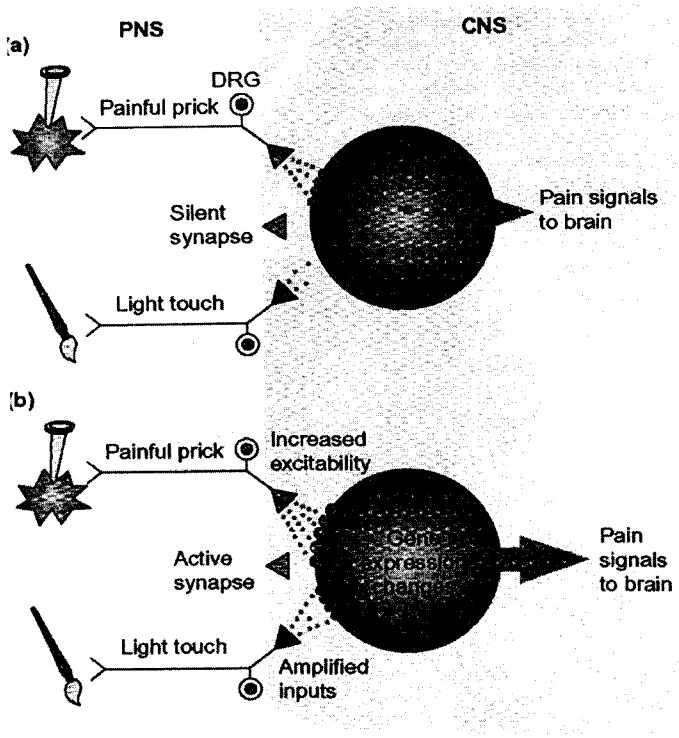


Figure 4: (a) Under normal conditions, low frequency activation of nociceptors by mild noxious stimuli results in an appropriate pain response. Activation of non-noxious mechanoreceptors also results in a response but at a level insufficient to initiate a pain response. (b) Following increased inflammation, the same noxious stimulus is correlated with persistent noxious input to the brain. There is also recruitment of the previously silent synapse and the activation of the mechanoreceptors is now sufficient to result in a pain response (14).

A Predisposition for Fibromyalgia

Due to the nature of this syndrome and the possible neuroendocrine involvement in its pathogenesis, it seems highly probable that fibromyalgia patients have some sort of vulnerability to the onset and continuation of symptoms. Additional support for this idea exists, as FM has been shown to have a high occurrence in more than one member of a family (27). Genetic and

environmental factors work together throughout development to shape the specific phenotype of an individual. Therefore the HPA axis is variable among individuals and can be determined by a number of different factors (13).

The importance of genetic variability has been demonstrated in studies of various rat strains. For example, Lewis rats have been shown to have a blunted HPA axis response when exposed to a variety of stressors, while Fischer rats display an exaggerated HPA axis response when exposed to the same stressors (17, 22). Lewis rats also show differences in levels of CRH and AVP peptide hormones as well as receptors for serotonin (26). In addition to this, these various strains also demonstrate differences in diseased susceptibility, vigilance, exploration, and apparent fear, which may all be related to differences in the central components of the HPA axis (17).

In another study, the importance of neonatal environmental factors was observed. Here male Long Evans rats were exposed to either repeated pain or maternal separation in the first two weeks of life (25). After exposure, the rats demonstrated enhanced central neurocircuit activity and HPA axis responsiveness as well as extreme anxiety and a reactivity of the dopaminergic system (24, 25). These alterations were perpetuated into adulthood where HPA axis function, central gene expression, and pain threshold abnormalities were exhibited (25). This study suggests that adverse early experiences, such as neglect or abuse, can significantly modify the body's response to major stressors encountered later in life.

These studies give some insight into a possible origin of fibromyalgia, which otherwise seems to have an unexplainable onset. It is therefore possible

that genetics and experience may contribute to a vulnerability of stress-related syndromes that have classic physical and psychological symptomology. However, the specific mechanisms by which a proceeding acute stress is translated into a syndrome of chronic pain still remain to be determined.

Future Research and Conclusion

Despite the various interpretations of data previously stated, it is obvious that neuroendocrine abnormalities do exist throughout the HPA axis. Whether the result is of a hyper or a hypo functioning stress response, there is agreement that negative feedback systems are impaired. More progress may be made when researchers cease trying to categorize FM under broad categories like the hyper/hypo functioning HPA axis, therefore linking it to other disorders. It seems clear that FM is not identical to any other syndrome or illness and therefore should not be similarly categorized. By viewing this syndrome as its own distinct entity, more options may present themselves concerning the syndrome's etiology.

Those who have started to view FM as a disorder of pain processing in the Central Nervous System have been able to examine the syndrome without consistently linking it to other disorders. However, much of the research in this field blatantly ignores pertinent research on stress induced neuroendocrine abnormalities. In 1997 a small conference workshop was held inviting experts in the fields of pain and neuroendocrine function in FM patients. After sharing their acquired knowledge, a combined work was written concluding that the integration of neuroendocrine and pain research was imperative to the future research and

understanding of FM (24). Unfortunately, to this date no such work can be found linking these two most pursued research fields. It is highly probable that the etiology of the syndrome will not be discovered until an interdisciplinary approach is taken, and the interactions of these systems are fully examined.

Specifically, more research is needed on the psychosocial factors involved in pain vulnerability and expression, which may demonstrate a genetic predisposition to chronic pain conditions. This possibility could help prove the theory that the syndrome originates as a pain disorder, which is perpetuated by the stress of pain. Similarly, those supporting the stress origin need to investigate a way to distinguish neuroendocrine vulnerability leading to the development of FM from abnormalities that might result from the syndrome. Since many studies are done on patients who have been ill for several years, it is difficult to know whether or not the observed abnormalities in the HPA axis represent a pre-existing, intrinsic defect, or if the abnormalities are acquired as a result of FM symptoms.

Finally, in FM research there seems to be a pervasiveness of inconsistent findings. A possible explanation and direction for future research has been proposed involving the groups of patients being examined. It could be that while researchers tend to view FM as if it was comprised of a homogeneous set of patients, a more heterogeneous approach should be taken (22). Although many symptoms are common, FM patients seem to be a group with diverse characteristics and responses. In order to better understand the syndrome, it might be profitable to look for commonalities that would divide FM patients into multiple subgroups under a larger diagnosis.

References

1 Starlanyl, Devin and Copeland, Mary E. (2001) *Fibromyalgia and Chronic Myofascial Pain: A Survival Manual* (2nd ed.). New Harbinger Publications, Inc.

2 Krsnich-Sheiwise, Susan (1997) Fibromyalgia syndrome: An overview. *Physical Therapy* 77, 68 – 75

3 Bennet, Robert (2001) *National Fibromyalgia Association Website*, (Online), Available: http:/www.fmaware.org/fminfo/overview.htm (27 November 2002)

4 National Fibromyalgia Partnership (2001) *National Fibromyalgia Partnership Website*, (Online), Available: http:/www.fmpartnership.org (27 November 2002)

5 Nicassio, Perry M. *et al.* (2002) The contribution of pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. *Pain* 100, 271 – 279

6 Goldenberg, DL (1999) FM a decade later - What have we learned? *Archives of Internal Medicine* 159, 777 – 785

7 Brook, Charles GD. and Marshall, Nicholes J. (2001) *Essential Endocrinology* (4th ed.). London: Blackwell Science Ltd.

8 Greenspan, Francis S. and Gardner, David G. (2001) *Basic and Clinical Endocrinology* (6th ed.). New York: McGraw Hill Co.

9 McCance, Kathryn L. and Huether, Sue E. (1994) *Pathophysiology: The Biological Basis for Disease in Adults and Children* (2nd ed.). St. Louis: Mosby

10 Miller, Diane B. and O'Callaghan, James P. (2002) Neuroendocrine Aspects of the Response to Stress. *Metabolism* 51, 5-10

11 Habib, Kamal E. *et al.* (2001) Neuroendocrinology of Stress. *Neuroendocrinology* 30, 695 – 723

12 Tsigos, Constantine and Chrousos, George P. (2002) Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research* 53, 865 – 871

13 Crofford, Leslie J. (1996) The Hypothalamic-Pituitary-Adrenal Stress Axis in the Fibromyalgia Syndrome. *Journal of Musculoskeletal Pain* 4, 181 – 200

14 Blackburn-Munro, Gordon and Ruth (2003) Pain in the brain: are hormones to blame? *Trends in Endocrinology and Metabolism* 14, 20 – 27

15 Kioukia-Fougia, Nassia *et al.* (2002) The effects of stress exposure on the hypothalamic-pituitary-adrenal axis, thymus, thyroid hormones and glucose levels. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 26, 823 – 830

16 Crofford, Leslie J. and Demitrack, Mark A. (1996) Evidence that abnormalities of central nerohormonal systems are key to understanding fibromyalgia and chronic fatigue syndrome. *Rheumatic Disease Clinics of North America* 22, 267 – 282

17 Crofford, Leslie J. (1998) Neuroendocrine Abnormalities in Fibromyalgia and Related Disorders. *The American Journal of the Medical Sciences* 315, 359 – 366

18 Neeck, Gunther and Crofford, Leslie J. (2000) Neuroendocrine Pertubations in Fibromyalgia and Chronic Fatigue Syndrome. *Rheumatic Disease Clinics of North America* 26, 989 – 1001

19 Neeck, Gunther (2002) Pathogenic Mechanisms of Fibromyalgia. *Ageing Research Reviews* 1, 243 – 255

20 Neeck, Gunther and Riedel, Walter (1999) Hormonal Pertubations in Fibromyalgia Syndrome. *Neuroendocrine Immune Basis of the Rheumatic Diseases* 876, 325 – 339

21 Griep, Edward N. *et al.* (1998) Function of the Hypothalamic-Pituitary-Adrenal Axis in Patients with Fibromyalgia and Low Back Pain. *The Journal of Rheumatology* 25, 1374 – 1380

22 Okifuji, Akiko and Turk, Denis C. (2002) Stress and Psychophysiological Dysregulation in Patients with Fibromyalgia Syndrome. *Applied Psychophysiology and Biofeedback* 27, 129 – 141

23 Adler, Gail K. *et al.* (1999) Reduced Hypothalamic-Pituitary-and Sympathoadrenal Responses to Hypoglycemia in women with Fibromyalgia Syndrome. *The American Journal of Medicine* 106, 534 – 543

24 Demitriack, Mark A. and Crofford, Leslie J. (1998) Evidence for and Pathophysiologic Implications of Hypothalamic-Pituitary-Adrenal Axis Dysregulation in Fibromyalgia and Chronic Fatigue Syndrome. *Annals of the New York Academy of Sciences* 840, 684 – 697

25 Pillemer, Stanley R. *et al.* (1997) The Neuroscience and Endocrinology of Fibromyalgia. *Arthritis and Rheumatism* 40, 1928 – 1938

26 Tsigos, Constantine, and Chrousos, George R, (1994) Physiology of the Hypothalamic-Pituitary-Adrenal Axis in Health and Dysregulation in Psychiatric and Autoimmune Disorders. *Endocrinology and Metabolism Clinics of North America* 23, 451 – 461

27 Henriksson KG, (2002) Is Fibromyalgia a Central Pain State? *Journal of musculoskeletal pain* 10, 45 – 57

28 Malt, Eva A. *et al.* (2002) Factors explaining variance in perceived pain in women with fibromyalgia. *BMC Musculoskeletal Disorders* 3, 1471 – 1480