FIBROMYALGIA – FROM SYNDROME TO DISEASE.
OVERVIEW OF PATHOGENETIC MECHANISMS

Karl G. Henriksson

From the Department of Neuroscience and Locomotion Section of Medical Rehabilitation, Faculty of Health Sciences, Linköping University, Sweden

According to the classification criteria proposed by the American College of Rheumatology, fibromyalgia is a longstanding multifocal pain condition combined with generalised allodynia/hyperalgesia. It is the generalised allodynia/hyperalgesia that distinguishes fibromyalgia from other conditions with chronic musculoskeletal pain. Central sensitisation of nociceptive neurons in the dorsal horn due to activation of N-methyl-D-aspartic acid receptors and disinhibition of pain due to deficient function of the descending inhibitory system are probable pathogenic factors for allodynia/hyperalgesia. Furthermore, chronic pain is a chronic emotional and physical stressor. Chronic stress and chronic sleep disturbance are not specific for fibromyalgia but could be the causes of symptoms like fatigue, cognitive difficulties and other stress-related symptoms. They may also cause neuroendocrinological and immunological aberrations.

INTRODUCTION

Any long-standing or permanent change in function in an organ system is a disease. In fibromyalgia (FM), as we shall see, there is a constant pain hypersensitivity due to changes in the function of the nociceptive system, mainly in the central nervous system (CNS). Consequently, FM is a disease, not only a syndrome or an illness. Continuous pain of moderate or high intensity as in FM is both a physical and an emotional stressor, and stress-related symptoms are common in patients with FM. Pain disturbs sleep, and unrefreshing sleep causes fatigue and cognitive symptoms. Muscular pain inhibits full activation of motor units. FM sufferers experience reduced muscle strength and endurance. Constant pain and the symptoms that are associated with it reduce work capacity and quality of life. Psychological distress, including depressive symptoms, ensues.

This overview will deal with FM as a disease of the nociceptive system. A similar overview entitled "Is fibromyalgia a central pain state?" has recently been published in the Journal of Musculoskeletal Pain (1). Two books published in 2002 deal with the pathogenesis and treatment of symptoms in FM (2, 3).

DEFINITIONS AND DIAGNOSTIC CRITERIA

The classification criteria of the FM syndrome proposed and accepted by the American College of Rheumatology (ACR) in 1990 are often in practice also used as diagnostic criteria (4). The criteria consist of one symptom and one sign. The symptom is multifocal musculoskeletal pain; the sign is generalised allodynia/hyperalgesia. The pain in FM is usually not pain all over, and the pain sites are not strictly symmetrical. The pain is, however, multifocal and is experienced in both the upper and lower half of the body and on both sides. Axial pain is also a symptom. The pain is more or less continuous. Only about 30% of the patients have shorter pain-free periods or episodes. The pain intensity is usually moderate or high, and varies from time to time also during the same day (5). The pain locations may also change from one time to another.

The generalised allodynia/hyperalgesia is the sign that distinguishes FM from other conditions with widespread musculoskeletal pain. Allodynia is pain elicited by non-noxious stimuli that are not normally painful. Hyperalgesia is increased intensity and prolonged duration of pain caused by noxious stimuli. In the clinical setting, pressure allodynia is tested by determining whether moderate pressure from the tip of the thumb (around 4 kg) evokes pain. If it does, this is a tender point. The ACR criteria for FM require that allodynia should be tested at 18 specified locations and that there should be tender points at no fewer than 11 of these sites.

As will be discussed below FM should be suspected in any chronic musculoskeletal pain condition when localised or regional pain spreads to several sites, when temporary or intermittent pain becomes more or less continuous, when pain on movement becomes pain at rest, or when segmental allodynia/hyperalgesia becomes generalised. FM may be the end stage in a continuum that starts with chronic localised musculoskeletal pain. This in turn means that a pain drawing and a tender point examination ought to be performed in all patients with long-standing muscu-

loskeletal pain. Such an examination does not take long to perform.

PATHOGENESIS OF GENERALISED ALLODYNIA/HYPERALGESIA

Nociceptive signals from peripheral tissues can be modulated at several levels of the CNS, from the dorsal horn to the cortex. It is the balance between facilitation and inhibition that determines the pain sensitivity. In the spinal cord the focus of interest is on the Wide Dynamic Range (WDR) neurons in lamina V in the dorsal horn. These neurons receive input both from C fibres (pain) and A-beta fibres (touch) from peripheral tissues and input from descending inhibitory tracts from the brainstem. The descending tracts are in turn controlled by connections with the hypothalamus and cortex. In the WDR neurons, neuronal activity from the periphery and the brain is integrated. Long-standing bombardment of nociceptive neurons in the CNS by impulses in primary afferent nociceptive neurons induces neuronal plasticity changes.

The studies of FM that show that there is a changed function of the nociceptive system in patients with FM can be divided into studies showing ongoing activity in afferent nerves in FM, studies showing central sensitisation of nociceptive neurons, studies showing deficient function in the descending inhibitory system and, finally, studies that show changes in peripheral tissues like muscles. Examples will be given below.

Substance P in the cerebrospinal fluid (CSF)

The neuropeptide substance P is produced mainly in the cell bodies of primary afferent C fibres. It can also be produced in neurons in the CNS. In FM around 80% of patients have increased levels of substance P in CSF (7, 8). In the literature the origin of increased substance P in CSF in patients with FM has been attributed to release from neurons in the CNS. One can, however, not exclude that the increased content of substance P in CSF could be caused at least partly by release from primary afferent neurons. The substance P levels in CSF can, for example, increase in nociceptive pain due to arthrosis (6). The levels decrease after operation, concomitant to pain relief.

In FM findings in skin biopsies indicating neurogenic inflammation have been detected (9). Neurogenic inflammation is caused by release of neuropeptides, including substance P, from the peripheral endings of primary afferent nociceptive nerves.

Studies that show amplification of pain sensitivity

In a recent study published in Arthritis & Rheumatism, Gracely et al. (10) used functional magnetic resonance imaging to study the pattern of cerebral activation during application of painful pressure in patients with FM and healthy controls. The same pattern of brain activation was found in patients with FM and in healthy controls. The difference was that this pattern was elicited in the patients with FM by pressure that was about three times less than in healthy controls. Crofford & Clauw (11) commented on the results in an editorial from which I quote: 'Taken together the data on pain processing in FM demonstrate that the central representation of pain correlates with the patients' report on pain and that purely behavioural or psychological factors are not primarily responsible for the pain and tenderness in FM'.

Using single-photon emission computed tomography, Mountz et al. (12) found that regional cerebral blood flow in the left and right hemithalami and left and right heads of the caudate nucleus were lower in patients with FM than in healthy controls. Bradley et al. (13), discussing these findings in an overview of results obtained by brain imaging in patients with FM, maintained that the reduced blood flow is secondary to hypersensitivity in spinal and peripheral nociceptive neurons. Blood flow in these structures is increased in acute pain, whereas in chronic pain, such as cancer pain, neuropathic pain and FM, the blood flow is reduced.

Two studies (14, 15) show an increased amplitude of the cerebral somatosensory potentials evoked by laser heat stimuli to the dorsal surface of the hand in patients with FM compared with controls. Lorenz et al. (15) concluded that the effect on one component (N170) of the laser-evoked potential can best be explained by 'exogenous factors like peripheral and spinal sensitisation or reduced cortical or subcortical inhibition of nociception'. Abnormal responses to electrocutaneous stimulation in patients with FM have been reported by Arroyo & Cohen (16) and Vecciet et al. (17).

Stimulus (pressure)-response (pain) function

When noxious stimuli activate high-threshold mechanosensitive neurons, the stimulus-response function is a power function. Activation by non-noxious stimuli gives a linear function. Bendtsen et al. (18) found that patients with FM display a linear stimulus (pressure)-response (pain) function in contrast to normal controls, who showed a power function. The authors interpret their findings as support for the notion that there are 'aberrant central pain mechanisms' in FM.

Decreased inhibition of pain

Tonic inhibition of pain caused by activity in the descending inhibitory tracts is an important part of our pain defence system, especially for the inhibition of musculoskeletal pain (19). The origin of these tracts is in the periaqueductal grey in the mesencephalon and the raphe magnus nucleus in the medulla. The end station is dorsal horn neurons. The degree of activity in the descending inhibitory tracts depends both on nociceptive input from the periphery and influences from the cortex and hypothalamus. One way of testing the descending inhibitory system is to test

diffuse noxious inhibitory control (DNIC). Kosek & Hansson (20) have used the DNIC test in patients with FM. A blood pressure cuff was placed around the left upper arm and inflated to 200 mmHg. The test subject then performed submaximal muscle contractions by the wrist extensors. The ischaemic pain was the heterotopic noxious conditioning stimulus. Quantitative sensory testing was performed in the right thigh. In the controls the pressure pain threshold increased. No increase was seen in patients with FM. This indicates a disturbance in the function of the descending inhibitory tracts.

Kosek et al. (21) have also studied pressure pain thresholds during isometric muscle contractions. In healthy controls, the thresholds increased in the contracting muscles. In FM patients, the thresholds decreased.

Central sensitisation

Besides depression of tonic inhibition, a central sensitisation due to activation of N-methyl-D-aspartic acid (NMDA) receptors on nociceptive neurons in the dorsal horn may be a pathogenetic factor for the generalised allodynia/hyperalgesia in FM. This statement is based on results from pharmacological pain analyses, determination of degree of temporal summation, and response to experimentally induced muscle pain.

Pharmacological pain analysis refers to the effect on pain of infusion of placebo, morphine, lidocaine or ketamine. Pain is estimated by a visual analogue scale (VAS). The test subject is considered responsive if the pain is reduced by 50% or more. With respect to activation of NMDA receptors, the response to ketamine, which is a non-competitive NMDA-receptor antagonist, is particularly of interest. In our studies, a total of 58 patients with FM were tested. Thirty-three (57%) were ketamine responders (22, 23, 24), experiencing decreased resting pain.

In collaboration with the Institute for Sensory-Motor Interaction at Aalborg University, Denmark, we performed studies in patients with FM where intramuscular pain was induced by infusion of hypertonic saline (25). The infusion was computerised to keep the amount of saline infused and the rate of infusion constant. The test subject recorded the experimental pain intensity continuously on an electronic VAS scale. The test muscle was the anterior tibialis muscle where neither the patients nor the healthy controls had ongoing pain. Pain intensity, pain duration and area of referred pain were recorded. Pain duration was longer and the area of referred pain was larger in patients compared with controls. The degree of temporal summation of electrical stimuli of the same intensity was tested. The summation pain threshold was defined as the stimulus intensity causing the 5th stimulus in a train of stimuli (2Hz) to be painful. In the controls the summation pain threshold was 89% of the threshold for a single stimulus. In patients with FM, the corresponding figure was 72%. Staud et al. (26) found that temporal summation was greater in patients with FM than in controls. They used repetitive thermal stimulation to induce temporal summation, which is equivalent to the 'wind up'

phenomenon. Temporal summation, which is not the same as central sensitisation but may initiate it, is caused by activation of NMDA receptors.

In one study we tested the effect of placebo and ketamine on the pain induced by intramuscular infusion of hypertonic saline (24). The test subjects were patients with FM who had previously been labelled as ketamine responders. In comparison with the placebo, ketamine reduced pain intensity, allodynia and the area of referred pain.

From the above studies it can be concluded that central sensitisation of nociceptive neurons due to activation of NMDA receptors, probably on WDR neurons in the dorsal horn, is part of the pathophysiology of allodynia/hyperalgesia in a majority of patients with FM.

Musculoskeletal pain generators (for overview, see 27)

Localised musculoskeletal pain often precedes the multifocal pain in FM. It is possible that muscle pain of different origins initiates neuroplastic changes in nociceptive neurons in the CNS. It is also possible that minor pathological changes in muscles can maintain pain when generalised allodynia is established. The pain-provoking factors in the muscle may not be the same at all pain sites, and at the same site the cause of pain may differ from one time to another. In patients with FM the tissue oxygen pressure, measured with an oxygen electrode directly on the muscle surface of the trapezius muscle, showed changes that indicated a disturbed regulation of intramuscular microcirculation (28). In another study it has been shown that in a subgroup of patients with FM there was insufficient relaxation between contractions, which means that there could also be hypoxia during dynamic muscle work (29). Hypoxia may sensitise intramuscular nociceptors.

A reduced amount of energy-rich phosphates has been found in the muscles of patients with FM (30, 31).

In a study of 10 patients with FM, pain and allodynia were recorded during lumbar epidural blockade by lidocaine (32). Pain and allodynia vanished completely in the lower extremities during the blockade, indicating that the prerequisite for pain in these particular patients, at least, was ongoing impulse traffic in primary afferent nociceptive and/or non-nociceptive neurons. In patients with FM where allodynia/hyperalgesia has already been established, it is possible that activity in afferent nerves during normal muscle contractions or tension could be enough to elicit pain.

WHAT CAN CAUSE OR INCREASE THE DEGREE OF ALLODYNIA/HYPERALGESIA?

All the above-mentioned studies taken together not only indicate, but also confirm, that there is a long-standing or permanent hypersensitivity in FM to pain that has a biological cause. How-

ever, it is possible that several different factors contribute to the development of generalised allodynia/hyperalgesia. These factors will be discussed below.

Long-standing musculoskeletal localised pain

In one of our studies (33), 87% of the patients with FM reported initial localised pain. For example, 55% had low back pain before they developed widespread pain. In another study (34), comprising 191 patients with FM, more than 80% reported that localised pain had gradually developed into widespread pain. Lapossy and co-workers (35) found that 25% of women with chronic low back pain developed FM. Around 20% of patients with inflammatory joint diseases also fulfil the criteria for FM (11). All these studies were retrospective. In a prospective study Buskila and co-workers (36) followed 102 persons who had been subjected to a neck injury. They found that no less than 21% met criteria for FM three months after the trauma. In a follow-up study three years later, 50% of the patients who contracted FM after injury still had FM (37). All the patients were still employed.

In summary, it can be stated that patients with long-standing localised musculoskeletal pain, be it myofascial pain, osteoarthrosis, painful inflammatory joint disease or pain due to malignancy, risk developing generalised allodynia and widespread pain. Genetic factors, stress-related factors and female gender may increase the vulnerability for acquiring generalised allodynia/hyperalgesia.

Female sex and oestrogen

The majority of patients with FM are women. The cause or causes of the predominance of women is not fully known. Factors that have been discussed as possibly contributing to more muscle pain in women than in men are lower muscle strength and greater exposure to static muscle work. Moreover, women have lower pain thresholds than men (38). Animal experiments have shown that there are oestrogen receptors in enkephalinergic neurons in the spinal cord (39). Oestrogen is one factor that regulates pain sensitivity. Low oestrogen levels could be a factor that contributes to allodynia/hyperalgesia.

Stress

In the literature, several articles examine neuroendocrinological aberrations in FM. These aberrations are similar to those observed in chronic stress (40, 41). The changes are not found in all patients with FM and are not, as a rule, pronounced (41). A disturbance in serotonin metabolism has been described (42, 43). The clinical impression is that pain and allodynia can be exacerbated by a temporary increase in stress.

Disturbed sleep

Sleep in patients with FM is non-restorative (40). Patients rarely feel refreshed when they wake up in the morning. Deep sleep is affected (40). Disturbed deep sleep can cause low levels of growth hormone, which has been found in FM (44).

Immunological changes

Chronic stress and disturbed sleep can affect the function of the immune system (41). Recently the importance of the release of proinflammatory cytokines both in peripheral tissues and in the CNS has been discussed as a factor that can cause or contribute to allodynia/hyperalgesia (45, 46). Wallace et al. (47) found increased levels in serum of IL-6 and IL-8 in patients with FM. Zachrisson et al. (48) found that a treatment program aiming at immune stimulation in patients, who met criteria for both FM and Chronic Fatigue Syndrome, gave reduced fatigue and better sleep. The treatment consisted of repeated injections of staphylococcus toxoid.

Autonomic nervous system

Symptoms indicating dysautonomia are reported by patients with FM. Studies show that sympathetic hyperactivity and hyporeactivity in response to stress are found in patients with FM (49).

Glial activation

Not only activation of neurons but also activation of microglia and astrocytes may lead to allodynia/hyperalgesia. Watkins et al. (50) presented results from animal experiments that support this statement. Whether these results have any bearing on pain conditions like FM is presently not known.

Psycho-social factors

FM is not a psychiatric disease, but psychological distress and depressive symptoms are common. These symptoms are most likely secondary to continuous pain, stress, fatigue and sleep disturbances. Henriksson & Liedberg (51) have studied the factors that are of importance for work disability in women with FM. The study comprised 176 patients with FM, half of whom were employed. Fifteen percent worked full time. In the non-working group 47% considered FM as the main cause for not being able to work.

CONCLUSION

For the majority of patients the development of FM is preceded by localised long-standing muscle pain that gradually spreads to

multiple sites and becomes continuous. Segmental allodynia becomes generalised. It is then that the diagnosis of FM can be made. There is strong support for the notion that generalised allodynia/hyperalgesia in FM is due to a possibly permanently disturbed function in the nociceptive system, especially in the CNS. Consequently FM is a disease. The many symptoms besides pain in FM are probably due to changes that are secondary to chronic pain.

REFERENCES

1. Henriksson KG. Is fibromyalgia a central pain state? J Musculoskeletal Pain 2002; 10: 45–47.
2. Bennett RM. The clinical neurobiology of fibromyalgia and myofascial pain: Therapeutic implications. J Musculoskeletal Pain, 2002: 10: HMP, The Haworth Medical Press, Inc New York.
3. Bennett RM. Rheumatic disease clinics of North America. Rational Management of fibromyalgia. W.B. Saunders Company 2002: 28: 2.
4. Wolfe F, Smythe HA, Yunus MB, Bennet RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: Report of the Multicenter Criteria Committee. Arthritis Rheum 1990; 22: 160–172.
5. Henriksson Ch, Qvarsebo Å, Carlberg U, Henriksson KG, Kjällman M, Lundberg G. Eight day diary in fibromyalgia. Abstract in 10th World Congress on Pain, IASP Press Seattle; 2002: p. 536.
6. Lindh C, Liu Z, Lyrenäs S, Ordeberg G, Nyberg F. Elevated cerebrospinal fluid substance P-like immunoreactivity in patients with painful osteoarthritis, but not in patients with rhizopatic pain from a herniated lumbar disc. Scand J Rheumatol 1997; 26: 468-472.
7. Vaeroy H, Helle R, Forre O, Kass E, Terenius L. Elevated CSF levels of substance P and high incidence of Raynaud's phenomenon in patients with fibromyalgia: new features for diagnosis. Pain 1988; 32: 21–26.
8. Russell IJ, Orr MD, Littman B, Vipraio GA, Alboukrek D, Michalek JE, et al. Elevated cerebrospinal levels of substance P in patients with fibromyalgia syndrome. Arthritis Rheum 1994; 37: 1593–1601.
9. Eneström S, Bengtsson A, Frödin T. Dermal IgG deposits and increase of mast cells in patients with fibromyalgia – relevant findings or epiphenomena? Scand J Rheumatol 1997; 26: 308–313.
10. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002; 46: 1333–1343.
11. Crofford LJ, Clauw DJ. Fibromyalgia: Where are we a decade after the American College of rheumatology classification criteria were developed? Arthritis Rheum 2002; 46: 1136–1138.
12. Mountz JM, Bradley LA, Modell JG, Alexander RW, Triana-Alexander M, Aaron LA, et al. Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. Arthritis Rheum 1995; 38: 926–938.
13. Bradley LA, McKendree-Smith NL, Alberts KR, Alarcon GS, Mountz JM, Deutsch G. Use of neuroimaging to understand abnormal pain sensitivity in fibromyalgia. Current Rheumatology Reports 2000; 2: 141–148.
14. Gibson SJ, Littlejohn GO, Gorman MM, Helme RD, Granges G. Altered heat pain thresholds and cerebral event-related potentials following painful CO_2 laser stimulation in subjects with fibromyalgia syndrome. Pain 1994; 58: 185–193.
15. Lorentz J, Grasedck K. Bromm B. Middle and long latency somatosensory evoked potentials after painful laser stimulation in patients with fibromyalgia syndrome. Electroencephal Clin Neurophysiol 1996; 100: 165–168.
16. Arroyo JF, Cohen ML. Abnormal responses to electrocutaneous stimulation in fibromyalgia. J Rheumatol 1993; 20: 1925–1931.
17. Vecchiet L, Giamberardino MA, de Bigontina P, Dragani L. Comparative sensory evaluation of parietal tissues in painful and nonpainful areas in fibromyalgia and myofascial pain syndrome. In: Gebhart GF, Hammond DL, Jensen TS, editors. Progress in Pain Research and Management. IASP Press, Seattle, 1994; 2: p. 177–185.
18. Bendtsen L, Norregaard J, Jensen R, Olesen J. Evidence of qualitatively altered nociception in patients with fibromyalgia. Arthritis Rheum 1997; 40: 98–102.
19. Mense S. Neurobiological concepts of fibromyalgia – the possible role of descending spinal tracts. Scand J Rheumatol 2002; 29 suppl 113: 24–29.
20. Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 1997; 70: 41–51.
21. Kosek E, Ekholm J, Hansson P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. Pain 1996; 64: 415–423.
22. Sörensen J, Bengtsson A, Bäckman E, Henriksson KG, Bengtsson M. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine and ketamine. Scand J Rheumatol 1995; 24: 360–365.
23. Sörensen J, Bengtsson A, Ahlner J, Henriksson KG, Ekselius L. Fibromyalgia – Are there different mechanisms in the processing of pain? J Rheumatol 1997; 24: 1615–1621.
24. Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, Bengtsson M, Sörensen J, Johnson A, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain 2000; 85: 483–491.
25. Sörenson J, Graven-Nielsen T, Henriksson KG, Bengtsson M, Arendt-Nielsen L. Hyperexcitability in fibromyalgia. J Rheumatology 1998; 25: 152–155.
26. Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 2001; 91: 165–175.
27. Bengtsson A. The muscle in fibromyalgia. Rheumatol 2002; 41: 721–724.
28. Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen pressure in primary fibromyalgia. Scand J Rheumatol 1986; 15: 165–173.
29. Elert J, Kendall-A S, Larsson B, Månsson B, Gerdle B. Chronic pain and difficulty in relaxing postural muscles in patients with fibromyalgia and chronic whiplash associated disorders. J Rheumatol 2001; 28: 1361–1368.
30. Bengtsson A, Henriksson KG, Larsson J. Reduced high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia. Arthritis Rheum 1986; 29: 817–821.
31. Park JH, Phothimat P, Oates CO, Hernanz-Schulman M, Olsen NJ. Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia. Arthritis Rheum 1998; 41: 406–413.
32. Bengtsson M, Bengtsson A, Jorfeldt L. Diagnostic epidural opioid blockade in primary fibromyalgia at rest and during exercise. Pain 1989; 39: 171–180.
33. Bengtsson A, Henriksson KG, Jorfeldt L, Kågedal B, Lennmarken C, Lindström F. Primary fibromyalgia. A clinical and laboratory study of 55 patients. Scand J Rheumatol 1986; 15: 340–347.
34. Henriksson Ch, Carlberg U, Henriksson KG, Kjällman M, Lundberg G. Fibromyalgi. Rapport Stimulansbidrag för habilitering och rehabilitering. Socialstyrelsen, 2000; ISSN 1403–3348.
35. Lápossy E, Maleitzke R, Hrycaj P, Mennet W, Muller W. The frequency of transition of chronic low back pain to fibromyalgia. Scand

J Rheumatol 1995; 24: 29–53.

36. Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F. Increased rates of fibromyalgia following cervical injury. A controlled study of 161 cases of traumatic injury. Arthritis Rheum1997; 40: 446–452.

37. Buskila D, Neumann L. The development of widespread pain after injuries. J Musculoskeletal Pain 2002; 10: 261–267.

38. Vecchiet L. Muscle pain and aging. J Musculoskel Pain 2002; 10: 5–22.

39. Amandusson A, Hermanson O, Blomqvist A. Colocalization of oestrogen receptor immunoreactivity and preproenkephalin MRNA expression to neurons in the superficial laminae of the spinal and medullary dorsal horn of rats. Eur J Neurosci 1996; 8: 2440–2445.

40. Pillemer SR, Bradley LA, Crofford LJ, Moldofsky H, Chrousos GP. The neuroscience and endocrinology of fibromyalgia. Arthritis Rheum 1997; 40: 1928–1939.

41. Geenen R, Jacobs JWG, Bijlsma JWJ. Evaluation and management of endocrine dysfunction in fibromyalgia. Rheum Dis Clin N Am 2002; 28: 389–404.

42. Russell IJ, Vipraio GA. Serotonin (5HT) in serum and platelets (PLT) from fibromyalgia patients (FS) and normal controls (NC). Arthritis Rheum 1994; 37 (suppl): S214.

43. Russell IJ. Neurochemical pathogenesis of fibromyalgia syndrome. J Musculoskel Pain 1997; 7: 183–191.

44. Bennett RM, Clark SR, Campbell SM, Burckhardt CS. Low levels of somatomedin C in patients with the fibromyalgia syndrome. A possible link between sleep and muscle pain. Arthritis Rheum 1992; 35: 1113–1116.

45. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, et al. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001; 410: 471–475.

46. Ek M, Engblom D, Saha S, Blomqvist A, Jakobsson PJ, Ericsson-Dahlstrand A. Pathway across the blood-brain barrier. Nature 2001; 410: 430–431.

47. Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH. Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. Rheumatol 2001; 40: 743–749.

48. Zachrisson O, Regland B, Jahreskog M, Jonsson M, Kron M, Gottfries CG. Treatment with staphylococcus toxoid in fibromyalgia / chronic fatigue syndrome - a randomised controlled trial. Eur J Pain 2002; 6: 455–466.

49. Martinez-Lavin M. The autonomic nervous system and fibromyalgia. J Musculoskel Pain 2002; 10: 221–228.

50. Watkins LR, Mair SF, Goehler LE. Immune activation; the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain 1995; 63: 289–302.

51. Henriksson Ch, Liedberg G. Factors of importance for work disability in women with fibromyalgia. J Rheumatol 2002; 27: 1271–1276.