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Neurochemical pathogenesis of fibromyalgia

Neurochemische Pathogenese der Fibromyalgie

Summary In contrast with the situation just a few years ago, the most widely accepted model for the pathogenesis of FMS now invokes CNS mechanisms like nociception and allodynia rather than pathologically painful muscles. The levels of platelet serotonin and CSF substance P appear to be abnormal in directions that could logically amplify pain perception. The extent to which these mechanisms are unique to FMS will be critical in determining the direction that future research should take. Certainly, a better understanding of the cause of FMS could represent an important step toward the development of more effective therapy.

Zusammenfassung Im Gegensatz zur Situation vor wenigen Jahren ist das heute international weitestgehend anerkannte Modell in der Pathogenese des Fibromyalgie Syndroms (FMS) eher das einer Störung zentralvenöser Schmerzverarbeitung als das einer peripheren Muskelerkrankung. Abnormalitäten der Serotoninspiegel aus Thrombozyten sowie von Substanz P im Liquor deuten auf Mechanismen der Erniedrigung der Schmerzschwelle hin. Inwieweit diese Mechanismen spezifisch für das FMS sind, wird die weitere Forschungsrichtung in der Zukunft bestimmen. Ein besseres Verständnis der Ursachen des FMS bedeutet auch einen Schritt vorwärts in der Therapie dieser Erkrankung.

Key words Fibromyalgia – allodynia – pathogenesis – substance P –serotonin

Schlüsselwörter Fibromyalgie – Pathogenese – Serotonin

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Introduction

Fibromyalgia syndrome (FMS) is a painful clinical disorder characterized by chronic wide-spread body pain and tenderness to four kilograms of deep pressure at anatomically-defined tender points (TPs) (35). Since that amount of pressure does not cause pain among healthy normal individuals, the findings in FMS indicate a lower than normal average pressure pain threshold. The International Association for the Study of Pain (IASP) has defined the term "allodynia" as the situation in which pain is caused by a stimulus which should not normally cause pain (i.e., a non-noxious stimulus) (3). This contrasts with the definition of "hyperalgesia" where the finding is an increased response to a stimulus which would cause pain in normal individuals (i.e., a noxious stimulus). The low pain threshold in FMS can be viewed as a human model for chronic, widespread allodynia to deep pressure. It may also extend to heat-induced cutaneous pain perception in FMS (7). The fact that some people with FMS also exhibit hyperalgesia is another issue and not really relevant to this discussion.

The term *nociception* refers to the physiological process of transmitting a painful stimulus from the periphery to the cerebral cortex where its effect and location are consciously interpreted. The process of nociception is accomplished by a series of electrical and chemical neurotransmission steps involving excitatory amino acids, neuropeptides, prostaglandins, biogenic amines, nitrous oxide, mineral ions, and endogenous opioids. Some of those agents are *pro-nociceptive*, meaning that they carry or amplify the signal induced by the stimulus, while others are *anti-nociceptive*, meaning that they inhibit transmission of the nociceptive signal or reduce its amplitude.

The roles of neurotransmitters in allodynia have been studied extensively in animals (15), and the findings are now theoretically relevant to human FMS (22). This line of reasoning has led to the measurement of neurotransmitter levels in biological fluids obtained from FMS patients. This report will focus on animal and human data regarding two neuroactive chemicals, serotonin, and substance P.

Serotonin and Substance P in Animal Studies

Animal studies have shown that dietary tryptophan (TRP) is transported across the blood brain barrier by an energy-dependent process for delivery to the brain stem raphe nucleus. Oxidation of TRP forms 5-hydroxytryptophan (5HTP), which can then be decarboxylated to form serotonin. In the central nervous system (CNS), the newly formed serotonin is packaged into vesicles and made available for axonal delivery to synapses in brain (2) and spinal cord locations (5). Like norepinephrine and dopamine, serotonin is a biogenic amine with the capacity to influence many central nervous system functions. In the spinal cord, serotonin inhibits the release of substance P by afferent neurons in response to peripheral stimuli (6). In rodents, there is a recognized inverse relationship between serotonin in the brain and substance P levels at the spinal cord (19, 28, 32), so low brain serotonin would be associated with high cord-level substance P.

Substance P is an 11 amino acid neuropeptide which has several important roles in the process of nociception (15). Activated, small, thinly myelinated A-delta and C-fiber afferent neurons release substance P into laminae I and V (A-delta) and laminae II (C-fiber) of the spinal cord dorsal horn. With random interstitial diffusion, substance P or its C-terminal peptide fragment makes contact with its effector NK1 receptors. It may facilitate nociception by "arming" or "alerting" spinal cord neurons to incoming nociceptive signals from the periphery. Substance P released into neural tissue can presumably diffuse out into the cerebrospinal fluid (CSF) where it can be measured (10).

The levels of substance P can be manipulated to induce allodynia in animal models (9). When substance P was administered intrathecally to rats, the animals exhibited a dose-dependent increase in the number of peripheral nerves and/or fiber types that were effective in driving the dorsal horn neuron to relay a nociceptive message to the brain. Substance P caused an increase in the size or number of mechanosensitive receptive fields involving nociceptive neurons, and it induced a lowering of the threshold for postsynaptic potentials. All of these effects support hypothetical models in which substance P is viewed as a facilitator of nociception.

Serotonin in FMS

For more than 20 years, a relative serotonin deficiency has been suspected in FMS (7, 18). In support of that hypothesis, our group found low concentrations of TRP in the serum (24) and in the CSF of FMS patients (27). Our finding of a low serum serotonin in FMS (23) was supported by European investigators (11). A population study (34) documented that serum serotonin was lower than normal in FMS and correlated with the numbers of tender points only among individuals who met clinical criteria for FMS. The low serum serotonin in FMS is due to lower than normal levels of serotonin in their peripheral platelets (12). A total body reduction of serotonin metabolism among FMS is suggested by the finding of significantly lower than normal 24 h total urinary excretion of serotonin's main metabolic product, 5-hydroxyindole acetic acid (5HIAA) (14). Aerobic exercise increases blood serotonin (Geel, Russell, and Vipraio, unpublished).

Measurement of CSF components suggests that the peripheral blood findings may parallel similar changes in the CNS of FMS patients (26, 27). The results include borderline low levels of TRP, significantly low levels of 5-HTRP, and borderline low levels of 5HIAA in FMS.

Substance P in FMS

Normal substance P levels have been found in the serum (21) (Russell, unpublished) and in the urine (Russell and Clauw, unpublished) of people with FMS. Vaeroy et al., (31) were the first to recognize that the concentration of substance P was elevated (about 3-fold) in the CSF of FMS patients compared with normal controls. Those findings have now been confirmed in three other clinical studies (4, 25, 33) with the average CSF substance P level in FMS being two- to three-fold higher than normal.

In our original study, over 87% of FMS patients exhibited CSF substance P concentrations greater than the highest normal control value (25). Age and gender had no influence on the measured CSF substance P levels but minor differences related to ethnicity (25). There appears to be no cranial to caudal gradient of CSF substance P concentration and induction of noxious pressure on the lower body tender points did not increase the CSF substance P level. A study of serial CSF sample collection has documented a significant, direct relationship between a progressive increase in CSF substance P and a progressive increase in pain/tenderness among 30 FMS patients over the span of 12 months (Russell, et al., 1997, unpublished).

Clinical relevance of elevated CSF substance P in FMS

From the observed influence of intrathecally administered substance P in animals, it is logical to predict that the elevated levels of CSF substance P in FMS patients are similarly related to the painful symptoms, but a cause-to-effect relationship has yet not been proven. The fact that serotonin levels also appear to be low (both peripherally and centrally) in FMS provides additional evidence for a systemic process of altered regulation of nociception.

An important question, which must be settled, is whether the elevated CSF substance P is unique to FMS. Substance P levels were normal or low in a variety of chronic painful conditions including low back pain (8, 29). They were lower than normal in idiopathic pain diseases (1), and in chronic neurogenic pain syndromes such as diabetic neuropathy (30). By contrast, CSF substance P was mildly elevated in patients with severely painful osteoarthritis of the hip and it normalized after total hip arthroplasty (20).

A curious finding (4) was that the elevated CSF substance P levels in FMS correlated with a decrease in the regional cerebral blood flow (rCBF) found in their caudate nucleus and thalamus. The reasons for this relationship are not yet clear because substance P is a potent vasodilator rather than a vasoconstrictor of cerebral vessels (34). One could hypothesize that the excess substance P was produced in response to tissue hypoxia, as an attempt to restore more normal blood flow (16). That explanation seems unlikely, because major brain hypoxic injury, caused in neonatal rats by ligation of an internal carotid artery, resulted in a substantial decrease in brain tissue levels of substance P (13). Notice, however, that the CSF substance P levels were not actually measured.

Ongoing and future studies must to focus on both the causes of the elevated substance P in FMS and on its consequences. It may be of value to prepare a variety of specific biological inhibitors of nociception to determine their effects on the chronic symptoms of FMS. It may be that such search will identify new treatments of clinical value.

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