Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways

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Received 23 August 1999; received in revised form 25 February 2000; accepted 2 March 2000

Abstract

Substance P (SP), a putative nociceptive transmitter, is increased in the CSF of patients with fibromyalgia syndrome (FMS). Because excitatory amino acids (EAs) also appear to transmit pain, we hypothesized that CSF EAs may be similarly involved in this syndrome. We found that the mean concentrations of most amino acids in the CSF did not differ amongst groups of subjects with primary FMS (PFMS), fibromyalgia associated with other conditions (SFMS), other painful conditions not exhibiting fibromyalgia (OTHER) or age-matched, healthy normal controls (HNC). However, in SFMS patients, individual measures of pain intensity, determined using an examination-based measure of pain intensity, the tender point index (TPI), covaried with their respective concentrations of glutamine and asparagine, metabolites of glutamate and aspartate, respectively. This suggests that re-uptake and biotransformation mask pain-related increases in EAs. Individual concentrations of glycine and taurine also correlated with their respective TPI values in patients with PFMS. While taurine is affected by a variety of excitatory manipulations, glycine is an inhibitory transmitter as well as a positive modulator of the N-methyl-D-aspartate (NMDA) receptor. In both PFMS and SFMS patients, TPI co-varied with arginine, the precursor to nitric oxide (NO), whose concentrations, in turn, correlated with those of citrulline, a byproduct of NO synthesis. These events predict involvement of NO, a potent signaling molecule thought to be involved in pain processing. Together these metabolic changes that covary with the intensity of pain in patients with FMS may reflect increased EAA release and a positive modulation of NMDA receptors by glycine, perhaps resulting in enhanced synthesis of NO. © 2000 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

Keywords: Fibromyalgia syndrome; Alldynia; Cerebrospinal fluid; Amino acids; Pain; Nitric oxide
Altered amino acid homeostasis in subjects affected by fibromyalgia

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Received 7 January 2009; received in revised form 27 February 2009; accepted 28 February 2009
Available online 10 March 2009

Abstract

Objectives: To evaluate plasma amino acid (AA) concentrations in patients affected by fibromyalgia (FM) and to study the relationships between their levels and FM clinical parameters.

Design and methods: 20 AAs were assessed in 34 FM patients and in 18 healthy volunteers by means of a modified version of the Waters picotag method.

Results: Significant lower plasma taurine, alanine, tyrosine (Tyr), valine, methionine, phenylalanine and threonine concentrations, and the sum of essential AAs were observed in FM patients vs healthy controls (P<0.05). Tyr CAA’ ratio and the sum of AAs competing with tryptophan for brain uptake were significantly reduced in FM (P<0.05). A significant correlation was found between FM clinical parameters and certain AAs.

Conclusions: Our results suggest probable defects of gut malabsorption of certain AAs in FM patients. Moreover, given the reduced Tyr CAA’ ratio in FM patients, a possible impairment of the catecholaminergic system in the FM syndrome may be suggested.

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Keywords: Fibromyalgia; Fatigue; Branched amino acids; Essential amino acids; Tyrosine; Taurine; Muscle energy
Serotonergic markers and lowered plasma branched-chain-amino acid concentrations in fibromyalgia

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Received 8 March 2000; received in revised form 27 June 2000; accepted 1 August 2000

Abstract

The aims of the present study were to examine serotonergic markers, i.e. \textsuperscript{3}Hparoxetine binding characteristics and the availability of plasma tryptophan, the precursor of serotonin (5-HT), and the plasma concentrations of the branched chain amino acids (BCAAs), valine, leucine and isoleucine, in fibromyalgia. The \textsuperscript{3}Hparoxetine binding characteristics, $B_{\text{max}}$ and $K_{\text{d}}$ values, and tryptophan and the competing amino acids (CAA), known to compete for the same cerebral uptake mechanism (i.e. valine, leucine, isoleucine, phenylalanine and tyrosine), were determined in fibromyalgia patients and normal controls. There were no significant differences in the \textsuperscript{3}Hparoxetine binding characteristics ($B_{\text{max}}$ and $K_{\text{d}}$) between fibromyalgia and control subjects. There were no significant differences in plasma tryptophan or the tryptophan/CAA ratio between fibromyalgia patients and normal controls. In the fibromyalgia patients, there were no significant correlations between \textsuperscript{3}Hparoxetine binding characteristics or the availability of tryptophan and myalgic or depressive symptoms. Patients with fibromyalgia had significantly lower plasma concentrations of the three BCAAs (valine, leucine and isoleucine) and phenylalanine than normal controls. It is hypothesized that the relative deficiency in the BCAAs may play a role in the pathophysiology of fibromyalgia, since the BCAAs supply energy to the muscle and regulate protein synthesis in the muscles. A supplemental trial with BCAAs in fibromyalgia appears to be justified. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Fibromyalgia; Serotonin; Tryptophan; Paroxetine binding; Branched chain amino acids; Leucine
Evidence for an Altered Tryptophan Metabolism in Fibromyalgia


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Received October 11, 2001; revised September 27, 2002; accepted for publication October 11, 2002

Fibromyalgia (FM) is a prevalent syndrome with chronic pain and a hypothesized underlying disturbance of the tryptophan (TRP) metabolism. We performed a tryptophan depletion (TD) test in 17 FM patients and 17 controls. TRP, 5-hydroxyindoleacetic acid (5-HIAA), kynurenine (KYN), and interleukin-6 (IL-6) were measured. Additionally, pain perception was monitored in the FM patients. FM patients and controls exhibited a decrease of TRP and KYN during TD. 5-HIAA levels also decreased in all controls and in 11 FM patients, but showed a marked increase in 6 FM patients. IL-6 significantly increased during TD in the patients, but not in the controls. Pain perception was not affected in the FM patients. These data demonstrate an altered TRP metabolism in a subgroup of FM patients, where the TD seems to activate 5-HT metabolism. Our findings may have diagnostic as well as therapeutic implications in the field of fibromyalgia.
Relationship of substance P, 5-hydroxyindole acetic acid and tryptophan in serum of fibromyalgia patients

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Received 12 October 1998; received in revised form 17 November 1998; accepted 17 November 1998

Abstract

The serotonergic system has repeatedly been discussed to be involved in the pathophysiology of fibromyalgia (FM), which is a syndrome of widespread pain and sleep disturbance. Elevated levels of substance P (SP), a mediator of nociception, have been described in FM. In this study the possible relationship between SP and serotonin (5-HT) together with its precursor tryptophan (TRP) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) was evaluated in 51 serum samples of fibromyalgia patients. These parameters were compared with clinical data such as pain intensity or sleep quality. A strong negative correlation between SP and 5-HIAA ($P = .000$) as well as between SP and TRP ($P = .009$) could be demonstrated. High serum concentrations of 5-HIAA and TRP showed a significant relation to low pain scores (5-HIAA: $P = .030$; TRP: $P = .014$). Moreover, 5-HIAA was strongly related to good quality of sleep ($P = .000$), while SP was related to sleep disturbance ($P = .005$). These data are valid to support the hypothesis of a systemic involvement of 5-HT and SP in fibromyalgia. © 1999 Elsevier Science Ireland Ltd. All rights reserved

Keywords: Fibromyalgia; Serotonin; 5-Hydroxytryptamine; Tryptophan; 5-Hydroxyindoleacetic acid; Substance P; Pain; Sleep