Altered amino acid homeostasis in subjects affected by fibromyalgia

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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 cathecolaminergic 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

Introduction

Fibromyalgia (FM), as defined in the 1990 American College of Rheumatology (ACR) criteria [1] is a chronic, generalized pain condition with characteristic tender points on physical examination, often accompanied by a number of associated symptoms such as fatigue, sleep disturbance, headache, irritable bowel syndrome and mood disorders.

Pathophysiological hypotheses of FM include impairment in the functioning of the hypothalamic–pituitary axis and alterations in neuromodulators and neurotransmitters such as substance P (SP), nerve growth factor (NGF), N-methyl-D-aspartate, norepinephrine (NE) and serotonin (5-HT) [2–4]. Substance P and nerve growth factor resulted in an increase in the cerebrospinal fluid (CSF) of patients with primary fibromyalgia but not in fibromyalgia patients with associated painful inflammatory conditions (secondary fibromyalgia) [5–7]. Substance P is a putative modulator of nociception and NGF is the neurotrophic factor that regulates SP synthesis in primary afferent C-fibres, structure thought to transmit pain stimuli. 5-HT and tryptophan concentrations were found to be decreased in serum and CSF of patients with FM [8]. 5-HT is theorized to have a function in stage 4 sleep and pain threshold [9], besides its implication in psychiatric disorders such as depression, anxiety, and obsessive compulsive disorder is often present in fibromyalgic patients.

Considering that tryptophan is the amino acid (AA) precursor of serotonin synthesis and that plasma tryptophan may reflect the status of tryptophan and serotonin in the brain, several authors measured free plasma tryptophan in patients with FM. Moldofsky and Warsh [10] found that free plasma tryptophan is inversely related to morning pain in 8 fibromyalgic patients. Russell et al. [11] reported that the concentrations of serum tryptophan and 9 other amino acids (alanine, histidine, lysine, proline, threonine, serine, taurine and phosphoserine)
were significantly lower among 20 patients with fibrositis/ fibromyalgia syndrome, compared to 20 matched controls. Yunus et al. [12] measuring plasma tryptophan and its transport ratio, together with other twenty-one amino acids, in patients with fibromyalgia found that the transport ratio of tryptophan was significantly decreased in FM patients compared to the control group and the plasma tryptophan level was lower in FM patients than in healthy controls showing a trend towards significance. Also plasma histidine and serine levels were found to be significantly lower in patients with FM than in controls.

Yunus et al. [12] suggested that because tryptophan crosses the blood/brain barrier via a transport mechanism that is shared with other branched chain large neutral amino acids, the transport ratio of these amino acids provides a more meaningful index of their entry into the brain than the plasma concentrations of any one of them alone.

Some authors suggested that a malfunction of energy metabolism may be present in some of the muscle fibres of fibromyalgia patients [13,14]. It is hypothesized that muscle energy depletion could by itself evoke many of the symptoms of fibromyalgia [13,15]. A factor that could contribute to muscle energy depletion is reduced plasma concentrations of the branched chain amino acids (BCAAs), leucine, valine and isoleucine [14]. There is evidence that BCAA supplementation decreases muscle catabolism and has ergogenic values, their infusion displays several CNS-mediated effects including antinociceptive action in healthy subjects but not in FM patients [16].

Recent advances support the involvement of peripheral and central sensitization disturbances of pain-related processes involving the increased transmission of the excitatory amino acid glutamate. Few studies support the implication of this amino acid in chronic migraine and primary fibromyalgia and demonstrated increased levels of glutamate in the cerebrospinal fluid of affected patients [17]. Larson et al. [8] did not show any variation in the levels of excitatory amino acids (EEAs) in the CSF of FM patients compared to controls, while they found significant differences in the levels of excitatory amino acids (EEAs) in the CSF of FM patients and to study the relationships between their levels and age, FM clinical and diagnostic parameters. Because amino acid plasma levels have been found altered in psychiatric disorders [18,19], the presence of psychiatric comorbidity in fibromyalgic patients might represent a confounding factor during the elaboration of results. For this reason we have recruited a population of FM patients with a negative history of psychiatric disorders.

**Methods**

**Subjects**

34 patients affected by fibromyalgia (29 F, 5 M), aged 49.56 ± 13.82 years (mean age ± S.D.) were enrolled. Patients were recruited and clinically classified at the Division of Rheumatology, University of Pisa (St. Chiara Hospital) according to the 1990 American College of Rheumatology criteria (ACR criteria) [1], which include: pain for more than 3 months from all of the four body quadrants, axial skeletal pain and pain upon digital palpation of at least 11 out of 18 specific bilateral points. Healthy volunteers (17 F, 1 M, 39.35 ± 12.76 years) were recruited from the Transfusion Centre of the St. Chiara Hospital (Pisa) and they were all routinely monitored blood donors. Exclusionary criteria for normal volunteers were: any of the above ACR criteria for fibromyalgia; use of any medication. Exclusionary criterion for patients was: the presence of a major clinical condition other than fibromyalgia. The patients and controls with recent or past history of psychiatric disorders and pregnant females were excluded from the study. All patients maintained their usual diet or physical activity and they had a drug wash out period of at least 2 weeks before blood sampling.

Written consent was obtained from all subjects after a full explanation of the study.

**Evaluation of clinical parameters**

Tenderness at tender points was evaluated in each subject using the Fischer dolorimeter [20]. A rheumatologist applied the instrument at a rate of 1 kg/s and the patient was instructed to say when this procedure became painful. The pain threshold was calculated for 18 points, and the tender point (TP) count was determined by the number of tender points that had a threshold of ≤ 4 kg/cm². The total fibromyalgic tender point score (right + left) was used in the statistical analysis.

To estimate the impact of fibromyalgia on the quality of life, all the patients received a “Fibromyalgia Impact Questionnaire” consisting of 10 items. The resulting score (FIQ total score), which indicates the impact of the disease on life, ranged from 0 (no impact) to 100 (maximum impact). For each patient an evaluation was also made of fatigue by means of a visual analogic scale (VAS, 0–10). Each patient was asked if they had frequently suffered from restless sleep (frequent and/or early awakening as well as inability to fall asleep) [21]. Also the duration of disease (years) was taken into consideration for FM patients.

**Blood collection, plasma separation and deproteinization, plasma amino acid identification**

Blood sodium–EDTA treated samples were collected and immediately centrifuged at 2600 × g for 15 min. Plasma aliquots were diluted 1:1 with HCl 0.1 N, containing 100 μM internal standard (Iss: beta-alanine, alpha-aminobutyric acid, norleucine). After mixing this plasma dilution, acetonitrile (2.8 vol.) was immediately added to precipitate plasma proteins. Samples were maintained on ice for 15–20 min and centrifuged for 15 min at 12,000 × g, 10 °C. The amino acids were determined by means of a modified version of the Waters picotag method (Waters S.p.a.) using phenylisothiocianate as the derivatizing agent (our unpublished data).
Twenty amino acids were assessed: glutamate, OH-proline, serine, glycine, glutamine, taurine, alanine, arginine, proline, tyrosine, valine, methionine, isoleucine, leucine, phenylalanine, lysine, histidine, threonine, tryptophan and ornithine.

Transport ratio for tryptophan was calculated as follows [22,12]: tryptophan transport ratio = micromolar concentration of plasma tryptophan/sum of micromolar concentrations of other plasma large neutral amino acids. The same formula was used for the determination of the transport ratio of tyrosine.

For the statistical analysis of the data, Mann–Whitney test and Spearman correlation were used, setting the significance level at $P<0.05$.

### Results

The demographic data and clinical characteristics of the FM patients are shown in Table 1.

Table 1 shows the results of amino acid measurements: patients with fibromyalgia had significantly lower plasma taurine, alanine, tyrosine, valine, methionine, isoleucine, leucine, phenylalanine, lysine, histidine, threonine, tryptophan and ornithine.

Transport ratio for tryptophan was calculated as follows [22,12]: tryptophan transport ratio = micromolar concentration of plasma tryptophan/sum of micromolar concentrations of other plasma large neutral amino acids. The same formula was used for the determination of the transport ratio of tyrosine.

For the statistical analysis of the data, Mann–Whitney test and Spearman correlation were used, setting the significance level at $P<0.05$.

### Results

The demographic data and clinical characteristics of the FM patients are shown in Table 1.

Tables 2a–d show the results of amino acid measurements: patients with fibromyalgia had significantly lower plasma taurine, alanine, tyrosine, valine, methionine, phenylalanine and threonine concentrations than healthy controls. Histidine levels were also lower without reaching the statistical significance ($P=0.06$) (Table 2a). Moreover, the sum of essential AAs was significantly lower in fibromyalgia than in normal controls.

<table>
<thead>
<tr>
<th>Essential AA</th>
<th>FM patients</th>
<th>Normal controls</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valine (**)</td>
<td>191.50±34.48</td>
<td>245.60±63.01</td>
<td>0.0032</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>69.53±16.79</td>
<td>65.64±18.02</td>
<td>N.S.</td>
</tr>
<tr>
<td>Leucine</td>
<td>123.40±23.39</td>
<td>124.70±28.83</td>
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</tr>
<tr>
<td>Phenylalanine (**)</td>
<td>62.69±15.19</td>
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</tr>
<tr>
<td>Lysine</td>
<td>162.8±46.21</td>
<td>155.80±52.47</td>
<td>N.S.</td>
</tr>
<tr>
<td>Histidine (°)</td>
<td>75.14±26.77</td>
<td>86.39±25.38</td>
<td>0.06</td>
</tr>
<tr>
<td>Threonine (**)</td>
<td>67.77±30.53</td>
<td>147±77.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>82.61±42.36</td>
<td>79.03±27.32</td>
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</tr>
<tr>
<td>Methionine (**)</td>
<td>31.61±7.36</td>
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<td>Sum essential AAs (**)</td>
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<td>BCAAs (°)</td>
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<td>431±98.8</td>
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</table>

BCAAs: the sum of branched amino acids valine, leucine and isoleucine.

(⁎) Statistically significant differences; (°) differences near statistical significance.

Results are shown as mean±S.D. Amino acid levels are expressed in μmol/L (μM).

There was a trend toward significantly lowered plasma BCAA’ concentration in fibromyalgia patients ($P=0.05$). The tryptophan CAA’ ratio was not different between patients and controls, instead the Tyr CAA’ ratio and the sum of AAs competing with Trp for brain uptake (CAA Trp) were significantly reduced in FM (Table 2c).

In FM patients, age correlated positively with tryptophan ($r=0.48$, $P=0.023$), glutamine ($r=0.367$, $P=0.036$) and taurine ($r=0.342$, $P=0.05$), while with alanine ($P=0.08$), lysine ($P=0.07$) and glutamic acid ($P=0.079$) the results are near significance.

A significant and positive correlation was found between glutamate and the number of TPs in FM patients ($r=0.495$, $P=0.0139$). FIQ correlated negatively with plasma histidine ($r=-0.415$, $P=0.020$) and phenylalanine ($r=-0.375$, $P=0.038$), while a slight tendency toward significance was found for isoleucine ($r=-0.349$, $P=0.086$).

Patients have been separated according to the presence/absence of restless sleep. Patients with restless sleep ($N=22$) showed significantly elevated plasma concentrations of serine (86.86 vs 76.98, $P=0.044$ Mann–Whitney test), and taurine (35.07 vs 28.68, $P=0.039$), while glutamine (462 vs 409.4, $P=0.039$).

### Results

The demographic data and clinical characteristics of the FM patients are shown in Table 1.

Table 2a shows the results of amino acid measurements: patients with fibromyalgia had significantly lower plasma taurine, alanine, tyrosine, valine, methionine, phenylalanine and threonine concentrations than healthy controls. Histidine levels were also lower without reaching the statistical significance ($P=0.06$) (Table 2a). Moreover, the sum of essential AAs was significantly lower in fibromyalgia than in normal controls.

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BCAAs: the sum of branched amino acids valine, leucine and isoleucine.

(⁎) Statistically significant differences; (°) differences near statistical significance.

Results are shown as mean±S.D. Amino acid levels are expressed in μmol/L (μM).
Table 2d
Plasma concentrations of sulfur-containing amino acids (SAAs).

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>FM patients</th>
<th>Normal controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taurine</td>
<td>31.66±8.71</td>
<td>66.33±14.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Methionine</td>
<td>31.61±7.36</td>
<td>43.17±8.20</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

(*) Statistically significant differences.

Results are shown as mean±S.D. Amino acid levels are expressed in μmol/L (μM).

P=0.093 and arginine (86.91 vs 72.28, – >P=0.05) showed a trend to higher plasma levels (Table 3).

No-significant correlations were found between plasma amino acids and VAS fatigue or disease duration. No-significant correlations were found between age and AA levels in normal controls.

Discussion

FM syndrome is characterized by an abnormal sensory processing of pain signals and is thought to arise from a combination of interactions between neurotransmitters, external stressors, behavioural constructs, hormones, and the sympathetic nervous system. The measurement of serum/plasma amino acid concentrations has been helpful in understanding the pathogenesis of several clinical disorders characterized by low levels of selected amino acids in the blood due to inadequate gastrointestinal absorption or to faulty conservation of the kidney or to a combination of both defects [23–25]. We studied the plasma amino acid concentrations to investigate the amino acid homeostasis in fibromyalgic patients.

Our results showed significant lowered concentrations of plasma taurine, alanine, tyrosine, valine, methionine, phenylalanine and threonine in FM patients with respect to normal controls. Also concentrations of histidine were lower in FM patients with a trend toward significance.

In literature, a general trend of lowered plasma or serum concentrations in FM patients with respect to healthy controls has been shown. Yunus et al. [12] found significant lowered concentrations of the following plasma amino acids: serine and histidine and a trend to lower concentrations of arginine, methionine, threonine and tryptophan. Russell et al. [11] found significant lower serum concentrations of: alanine, histidine, lysine, proline, serine, thaurine, threonine and tryptophan. Maes et al. [14] found lower concentrations of the following plasma amino acids: phenylalanine, valine, leucine, isoleucine and a trend for tryptophan.

We showed that the sum of essential AAs was significantly lower in FM patients than in normal controls, and also plasma mean concentrations of BCAAs were lower in patients. Also Maes et al. [14] found significantly lower plasma concentrations of BCAAs, which may be supportive of the muscle energy depletion hypothesis of fibromyalgia. Moreover there are many studies which showed that BCAA supplementation may decrease muscle catabolism and has ergogenic values [26,27]. In fact provision of BCAAs may also decrease central fatigue, through increased competition for the cerebral uptake mechanism of tryptophan [28]. We have also supported the muscle energy depletion hypothesis in a previous research [29] showing significant lower ATP levels and higher calcium and magnesium concentrations inside platelets of FM patients.

The tryptophan (Trp)CAA’ ratio is an indicator for the availability of Trp to the brain and hence for the 5-HTT synthesis in the brain; we did not find any differences of plasma Trp concentration or Trp ratio, according to Maes et al. [14] but in contrast with Yunus et al. [12] and Russell et al. [11]. Instead, we found for the first time in FM patients significant lowered concentrations of: plasma tyrosine, the sum of AA competing with Trp for brain uptake, and Tyr CAA ratio.

Because tyrosine is the precursor of the catecholamine norepinephrine, epinephrine and dopamine these evidences let us suppose an impairment at the level of catecholamine synthesis in FM patients, differently from those results which underline an impairment in the serotonin synthesis. In accordance with this hypothesis, recent studies support the hypothesis of a dysfunction of dopaminergic transmission in FM patients [30] indicating that it represents a relevant target for the treatment of fibromyalgia. Dopaminergic agonists of receptors D3/2 have been efficacious in decreasing the symptoms of fibromyalgia. Holman et al. [31,32] in a pilot double blinded study, reported a decrease of pain evaluated by visual analogic scale (VAS), and improvement in other parameters such as rigidity and myalgic score of TPs after the treatment with ropinirole and pramipexole. Recently, Buskila et al. [33] have reported on an association between fibromyalgia and the D4 dopamine receptor exon III repeat polymorphism and a relationship to novelty seeking personality traits. Interestingly, it was shown [34] that dopaminergic rather than serotonergic neurotransmission is altered in fibromyalgia, suggesting increased sensitivity or density of D2 dopamine receptor in fibromyalgia patients. Also the beneficial effects of the use of new and selective norepinephrine and

Table 3
Comparison between plasma amino acid concentrations (mean±S.D., μmol/L) in FM patients with or without unrest sleep.

<table>
<thead>
<tr>
<th>Amino acids</th>
<th>Unrestful sleep (N=22)</th>
<th>No unrestful sleep (N=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>29.98±11.98</td>
<td>23.04±10.95</td>
<td>N.S.</td>
</tr>
<tr>
<td>OH-proline</td>
<td>13.57±5.79</td>
<td>14.07±4.75</td>
<td>N.S.</td>
</tr>
<tr>
<td>Serine*</td>
<td>86.86±19.86</td>
<td>76.98±19.19</td>
<td>0.04</td>
</tr>
<tr>
<td>Glycine</td>
<td>212.8±80.39</td>
<td>181.1±68.15</td>
<td>N.S.</td>
</tr>
<tr>
<td>Glutamine</td>
<td>462±93.77</td>
<td>409.4±128.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Taurine</td>
<td>35.07±7.94</td>
<td>28.68±6.78</td>
<td>0.039</td>
</tr>
<tr>
<td>Alanine</td>
<td>282±47.72</td>
<td>284.1±54.64</td>
<td>N.S.</td>
</tr>
<tr>
<td>Arginine</td>
<td>86.91±22.93</td>
<td>72.28±13.29</td>
<td>0.05</td>
</tr>
<tr>
<td>Proline</td>
<td>199±66.31</td>
<td>185.1±91.09</td>
<td>N.S.</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>68.06±12.66</td>
<td>66.01±20.62</td>
<td>N.S.</td>
</tr>
<tr>
<td>Valine</td>
<td>199.4±37.37</td>
<td>186.9±35.23</td>
<td>N.S.</td>
</tr>
<tr>
<td>Methionine</td>
<td>31.24±6.23</td>
<td>34.12±9.53</td>
<td>N.S.</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>70.59±12.69</td>
<td>72.52±23.00</td>
<td>N.S.</td>
</tr>
<tr>
<td>Leucine</td>
<td>126.5±17.00</td>
<td>124.9±32.43</td>
<td>N.S.</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>64.45±14.50</td>
<td>63.92±17.80</td>
<td>N.S.</td>
</tr>
<tr>
<td>Lysine</td>
<td>178.6±49.90</td>
<td>146.2±31.44</td>
<td>N.S.</td>
</tr>
<tr>
<td>Histidine</td>
<td>73.48±22.05</td>
<td>84.60±34.44</td>
<td>N.S.</td>
</tr>
<tr>
<td>Threonine</td>
<td>73.79±35.93</td>
<td>64.72±16.49</td>
<td>N.S.</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>81.45±31.29</td>
<td>94.34±55.26</td>
<td>N.S.</td>
</tr>
<tr>
<td>Ornithine</td>
<td>37.02±18.61</td>
<td>25.45±20.18</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

(*) Statistically significant differences.
serotonin reuptake inhibitors (duloxetine, milnacipram and desvenlafaxine) in FM patients [35–37] support the hypothesis of a dysfunction of catecholaminergic system in this pathology.

The lower concentrations of tyrosine may also influence the synthesis of the thyroid hormones triiodothyronine (T₃) and thyroxine (T₄) which are derived from tyrosine in the colloid of the thyroid. Aside from being a proteogenic amino acid, tyrosine has a special role by virtue of the phenol functionality; it occurs in proteins that are part of signal transduction processes functioning as a receiver of phosphate groups that are transferred by way of protein kinases (so-called receptor tyrosine kinases) and phosphorylation of the hydroxyl group changes the activity of the target protein. Moreover many studies indicated the use of tyrosine in particular conditions such as stress [38], fatigue [39] and insomnia [40,41].

In accordance with Maes et al. [14] we also observed significantly lower plasma levels of the tyrosine precursor phenylalanine in FM patients. Besides its role in catecholamine synthesis, phenylalanine concentrations may affect hepatic functions and eventual cirrhosis [44]; lowers circulating levels of the sulfur-containing amino acids taurine [44,45]; promotes detoxification of xenobiotics via the sulfation pathway. Low levels of the sulfur-containing amino acids; lower concentrations of alanine in FM patients. This amino acid plays a key role in the glucose–alanine cycle between tissues and liver, carrying amino acid nitrogen from muscle to liver where its carbon skeleton is converted to glucose via gluconeogenesis. This pathway seems therefore altered in FM patients.

We found an interesting correlation between clinical index and some amino acids: glutamic acid correlated significantly with TPs, histidine and phenylalanine correlated negatively with FIQ. Moreover patients with restless sleep showed elevated plasma concentrations of serine, taurine arginine and elevated but not significant concentrations of glutamine.

The findings of significant relations between clinical index and certain amino acids may support the hypothesis of a metabolic disturbance in FM. Fibromyalgic patients might have inadequate gastrointestinal absorption or a faulty conservation of the kidney or a combination of both defects. Some authors [13] have suggested that the lowered serotonergic metabolism in FM is related to a defective absorption of the precursor amino acid tryptophan from the gut. Nevertheless irritable bowel syndrome is a documented clinical characteristic presented in high percentage in patients with fibromyalgia [4]. All these evidences support the hypothesis of an altered amino acid homeostasis in subjects affected by FM.

In summary the major findings of this article are: patients with FM have significantly lower plasma concentrations of the sum of essential amino acids, in particular lower concentrations of the sulfur-containing amino acids; lower concentrations of the sum of BCAAs, and lower tyrosine and Tyr CAA ratio than normal controls.

We did not find any significant differences in plasma Trp and the Trp CAA ratio, thus, our results are not in agreement with the hypothesis that a deficiency in serotonergic neuronal functioning may be related to the pathophysiology of fibromyalgia. Literature is controversial at this regard probably this is attributable to a different recruitment of patients, in some cases findings in FM were found when all individuals with this disorder were studied, but not when individuals free of psychiatric comorbidities were studied, suggesting that some of the findings may track more closely with psychiatric comorbidity than inherent features of FM.

Our results indicate a possible impairment of catecholaminergic system and suggest probable defects of gut malabsorption of certain important groups of amino acids: essentially, the ergogenic BCAA and the sulfur-containing amino acids in the fibromyalgic syndrome. These results are representative of a group of FM patients without recent or past history of psy-
chiatric disorders, thus, further studies are needed to investigate the amino acid homeostasis in FM patients with psychiatric comorbidities.

References


