ORIGINAL ARTICLE

Fructose Malabsorption is Associated with Decreased Plasma Tryptophan

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Background: Fructose malabsorption is characterized by the inability to absorb fructose efficiently. As a consequence fructose reaches the colon where it is broken down by bacteria to short fatty acids, CO_2, H_2, CH_4 and lactic acid. Bloating, cramps, osmotic diarrhea and other symptoms of irritable bowel syndrome are the consequence and can be seen in about 50% of fructose malabsorbers. Recently it was found that fructose malabsorption was associated with early signs of depressive disorders. Therefore, it was investigated whether fructose malabsorption is associated with abnormal tryptophan metabolism. **Methods:** Fifty adults (16 men, 34 women) with gastrointestinal discomfort were analyzed by measuring breath hydrogen concentrations after an oral dose of 50 g fructose after an overnight fast. They were classified as normals or fructose malabsorbers according to their breath H_2 concentrations. All patients filled out a Beck depression inventory questionnaire. Blood samples were taken for plasma tryptophan and kynurenine measurements. **Results:** Fructose malabsorption (breath ΔH_2 production >20 ppm) was detected in 35 of 50 individuals (70%). Subjects with fructose malabsorption showed significantly lower plasma tryptophan concentrations and significantly higher scores in the Beck depression inventory compared to those with normal fructose absorption. **Conclusions:** Fructose malabsorption is associated with lower tryptophan levels that may play a role in the development of depressive disorders. High intestinal fructose concentration seems to interfere with L-tryptophan metabolism, and it may reduce availability of tryptophan for the biosynthesis of serotonin (5-hydroxytryptamine). Fructose malabsorption should be considered in patients with symptoms of depression and disturbances of tryptophan metabolism.

Key words: Fructose loading test; fructose malabsorption; H_2 exhalation; tryptophan

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Fructose malabsorption syndrome was first described some years ago (1–3). Patients with fructose malabsorption are unable to absorb the ingested monosaccharide in a sufficient way so that large quantities of fructose reach the colon, where it is broken down by colon bacteria into short fatty acids, CO_2, CH_4, lactic acid and H_2 which can be measured in the expired air. Bloating, abdominal discomfort and sometimes osmotic diarrhea are the consequences induced by the degradation products built by the colonic bacteria. It is believed that up to 36% of the European population have fructose malabsorption in a more or less severe form, and about half of them are symptomatic (4). Recently we have observed that fructose malabsorption was associated with early signs of depressive disorders (5), and that these signs were ameliorated upon a fructose-and sorbitol-reduced diet (6). The data available so far suggest that abnormalities of tryptophan availability could be involved in the development of fructose malabsorption associated depression. It was therefore of interest to investigate tryptophan concentrations in relation to fructose malabsorption.

Material and Methods

Patients

All adult outpatients who visited the physician's office between November 1997 and March 1998 for a medical health check and admitted gastrointestinal discomfort were studied. Subjects were included in the study if any of the following symptoms were present: stool irregularities, bloating, abdominal cramps, diarrhea, constipation or nausea. The 50 patients (16 men, 34 women) were aged from 16 to 72 years (mean, 43.3 years) and otherwise healthy. Physical examination and routine laboratory assessment did not reveal abnormalities. None of the patients showed signs of inflammatory bowel disease, any other chronic disease or infectious diseases and were—except for oral contraceptives in some cases—under no medication. Body weight and height were

measured, and blood samples for plasma tryptophan and kynurenine measurements were taken after an overnight fast before breath hydrogen testing was performed.

Hydrogen (H_2) breath tests

Breath (H_2) was measured using a Bedfont gastrolizer (Bedfont Ltd, Kent, UK) which has been validated by several authors (7–9). After a 12 h overnight fast a baseline H_2 breath test was performed. An oral dose of 50 g fructose was given in 250 ml of tap water and H_2 exhalation was monitored in 30 min intervals for at least 2 h. All tests were started between 0800 h and 0830 h. Maximum H_2 exhalation (H_2-max) after fructose load was monitored and the differences to baseline levels (ΔH_2) were calculated. Patients with fasting breath hydrogen concentrations of >10 ppm were excluded from the study. Between the monitoring of breath H_2 all patients filled out a Beck depression inventory questionnaire (10).

Tryptophan measurement

Tryptophan was measured simultaneously with kynurenine, a metabolite of the tryptophan catabolism, by high performance liquid chromatography (HPLC) according to a recently established method (11). In brief, 100 µl serum was diluted with 100 µl buffer solution (pH = 6.4) containing 10 µM 3-nitro-L-tyrosine as internal standard. Protein was then precipitated with 25 µl trichloroacetic acid (2 M). The specimens were centrifuged, and 100 µl of the supernatant was injected in the HPLC column. A Lichrochart RP-18 reversed phase column (grain size, 5 µm; Merck, Darmstadt, Germany) was applied. The elution buffer was a 15 mM phosphate buffer (pH = 6.4). The pump and the data system were from Varian (Palo Alto, CA, USA). Tryptophan was detected by its natural fluorescence (excitation, 285 nm; emission, 365 nm) with a HP 1046A fluorescence detector (Hewlett Packard, Vienna, Austria). Kynurenine and nitrotyrosine were detected by UV absorption at 360 nm with a UV detector (UV 975, Jasco, Tokyo, Japan). External calibration was done by an albumin-based standard, containing 10 µM kynurenine, 50 µM tryptophan and 10 µM nitrotyrosine. All chemicals used (Merck) were of high analytical grade.

Data analysis

The cut-off points for the diagnosis of fructose malabsorption were breath H_2 concentrations greater than 20 ppm over baseline (12). Subjects with an increase of breath H_2 concentration equal or less than 20 ppm over baseline were considered to be normal fructose absorbers. For comparison of groups the Mann–Whitney U test was employed using a standard PC statistical program (STATISTICA for Windows) (13), for correlation analyses Spearman rank correlation coefficients were calculated. Frequencies were compared by the Fisher exact test.

Table I. Comparison of fructose malabsorbers and normals

	Fructose malabsorbers $n = 35$	Normals $n = 15$
Age (years)	45.4 (24–72)	38.4 (16–57)
ΔH_2 concentration (ppm)	43.8 (21–111)	0.95 (−12 to −6)
Maximum H_2 concentration (ppm)	46.8 (22–112)	7.79 (0–51)
Beck depression score	9.47 (0–38)	7.01 (0–17)
Tryptophan (µM)	64.1 (39.0–97.2)	75.2 (53.9–110)*
Kynurenine (µM)	1.91 (0.95–3.25)	1.97 (0.97–3.39)
Kyn/Try (mM/M)	30 (18–49)	27 (18–50)

Characteristics (mean and range in parentheses) of individuals, H_2 concentrations (after fructose load, see Materials and Methods) and depression score, serum tryptophan and kynurenine concentrations and kynurenine per tryptophan ratios (Kyn/Try) split into two groups according to maximum H_2 concentrations after fructose load ≤20 ppm (normals) and >20 ppm (fructose malabsorbers); * $P = 0.02$.

Results

The main results are summarized in Table I. In 35 patients breath H_2 concentrations increased more than 20 ppm over basal fasting values. They were classified as fructose malabsorbers. The remaining 15 subjects with lower H_2 exhalation were classified as normal fructose absorbers. The two groups of individuals showed no difference in age. There was only a trend to higher Beck inventory depression scores in fructose malabsorbers (9.47 ± 7.35) than in normal fructose absorbers (7.07 ± 4.62; see Table I) but no significant difference was observed between the two groups of individuals. When subjects were split into two groups by sex, the Beck inventory depression scores were higher in female fructose malabsorbers (12.30 ± 7.16) than in females with normal fructose absorption (6.66 ± 5.50; $P = 0.02$). No such difference was observed in males.

Mean plasma tryptophan concentrations were significantly lower in fructose malabsorbers than in normal fructose absorbers ($P = 0.02$; Table I). Plasma kynurenine concentrations and tryptophan per kynurenine quotients were within the normal range of healthy controls in most individuals (4/50 had kynurenine concentrations >3 µM, 4/50 individuals presented with a kynurenine per tryptophan quotient >40) and they did not significantly differ between the two groups.

When patients were divided into two groups by sex, serum tryptophan concentrations were lower in individuals with fructose malabsorption compared to normals only in females (fructose malabsorbers: 61.3 ± 14.0 µM, normals: 74.7 ± 16.5 µM, $P = 0.03$; Fig. 1) but not in males (fructose malabsorbers: 70.3 ± 10.4 µM, normals: 76.4 ± 12.5 µM, P = not significant). Kynurenine concentrations (females, fructose malabsorbers: 1.81 ± 0.58 µM, normals: 1.98 ± 0.64 µM; males, fructose malabsorbers: 2.12 ± 0.46 µM, normals: 1.93 ± 0.30 µM) and kynurenine per tryptophan ratios (females, fructose malabsorbers: 30 ± 9 mM/M, normals:

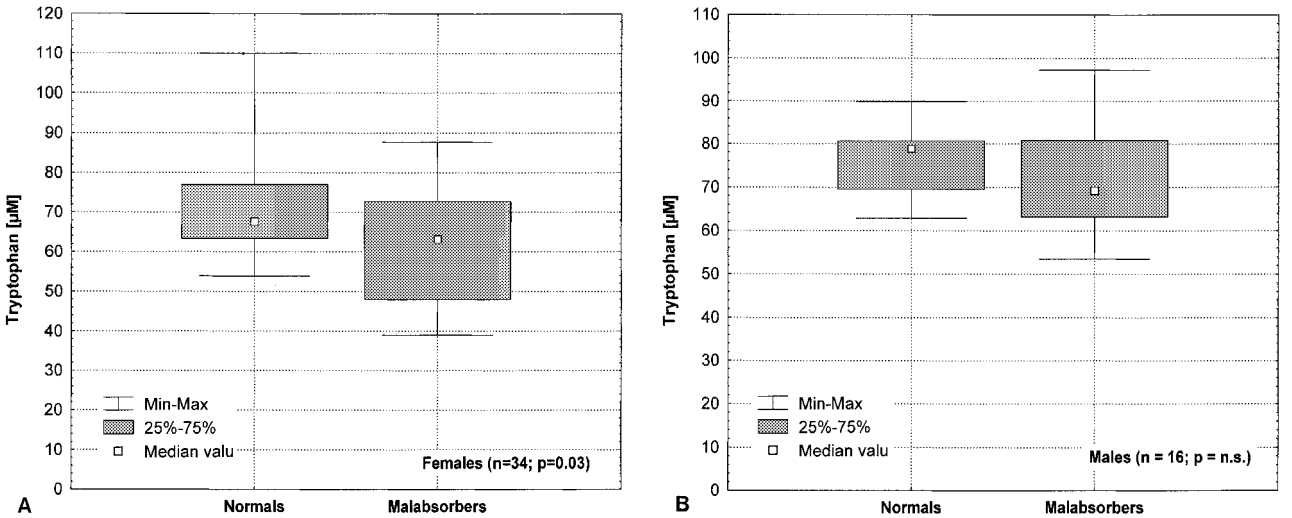

Fig. 1. Serum tryptophan concentrations in females and males with fructose malabsorption and healthy controls with normal fructose absorption (plots show medians = horizontal lines, 25th–75th percentiles = dotted box, and 5th–9th percentiles = bars); the difference is significant for females only ($P = 0.03$).

27 ± 10 mM/M; males, fructose malabsorbers: 31 ± 8 mM/M, normals: 26 ± 3 mM/M) did not differ between the groups.

When comparing tryptophan concentrations with the Beck depression inventory scores, there was no significant relationship in the whole group of individuals ($n = 50$; $r_s = -0.182$, not significant). There was also no significant relationship when groups were separated by sex. However, individuals with tryptophan concentrations lower than the median (= 67.0 µM) more often presented with a Beck depression inventory score above the median value of six ($P = 0.036$; Fisher exact test). When analyses were restricted to fructose malabsorbers, a significant inverse relationship between tryptophan concentration and Beck score were found for the whole group of individuals ($n = 35$; $r_s = -0.348$, $P = 0.043$) and for females ($n = 24$; $r_s = -0.503$, $P = 0.014$; Fig. 2). There was no such association between the Beck score and serum tryptophan levels in male fructose malabsorbers ($n = 11$; $r_s = 0.205$, $P =$ not significant).

Discussion

A pathogenic link between fructose malabsorption and functional bowel disease—a typical psychosomatic disorder—was discussed by several authors (14–17). However, this association could not be found by other investigators (18, 19). In a previous study (5) we described an association between fructose malabsorption and early signs of depressive disorders as reflected by the Beck depression inventory score especially in females. The data in the present study confirm and extend this observation. Moreover, the association between fructose malabsorption and decreased serum tryptophan concentrations found in our study supports the view that abnormal tryptophan availability could be involved in the higher risk for developing signs of mental depression in female patients with fructose malabsorption. Earlier studies imply that disturbances of L-tryptophan metabolism are involved in inducing depression (20–22) and pre-menstrual syndrome (23), since low tryptophan levels may limit the biosynthesis of serotonin (5-hydroxytryptamine).

The finding of decreased serum tryptophan concentrations in patients with fructose malabsorption supports the view that fructose malabsorption interferes with tryptophan metabolism. On the one hand, fructose malabsorption may reduce transit time in the gut and thus reduce the absorption of the essential amino acid similar as with folic acid (24). However, reduced transit time obviously does not contribute largely to decreased serum tryptophan concentrations as we could not

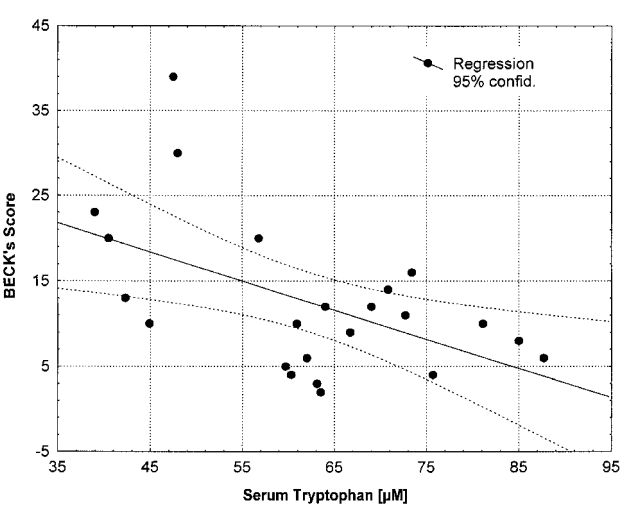

Fig. 2. Association between serum tryptophan and the Beck depression scores in female patients with fructose malabsorption ($r_s = -0.503$, $P = 0.014$).

find such lower serum tryptophan concentrations in subjects with lactose maldigestion (data not included).

On the other hand, fructose, as other saccharides, reacts with proteins and amino acids such as L-tryptophan (25), thereby a fructose–L-tryptophan complex can be formed which results in a decrease in protein quality due to the loss of amino acid residues and decreased protein digestibility. This chemical interaction according to the so-called Maillard reaction (26) could provide an explanation for the possible association between fructose malabsorption and disturbed tryptophan metabolism. Maillard products can also inhibit the uptake and metabolism of other free amino acids such as L-tryptophan and of other nutrients such as zinc (26).

In our study, two-thirds of subjects were classified as fructose malabsorbers, and there were no non-H_2-producers. We are aware that a large dose of 50 g of fructose may be insufficiently absorbed by many individuals and increase the percentage of fructose malabsorption in the study population. In this study, using 50 g of fructose the highest ΔH_2 value in normal fructose absorbers was 8 ppm and the lowest ΔH_2 value of fructose malabsorbers was 20 ppm, so that a cut-off value of 10 does not change the overall message. However, in a few patients 50 and 25 g were administered on two distinct days. As expected the overall H_2 exhalation was lower when subjects received 25 g of fructose and some of these subjects had ΔH_2 values between 10 and 20 ppm. However, also when we stratified the data of H_2 breath tests with administration of 25 g fructose there was practically no difference in the relationship to tryptophan and Beck depression scores.

Interestingly the association of fructose malabsorption with signs of mental depression is more expressed in females than in males. However, the number of male patients is still small in this study for a final judgment. Since blood concentrations of L-tryptophan are already significantly lower in healthy females than in males (11, 27), disturbed absorption of L-tryptophan may have more impact to precipitate clinically relevant disturbances of serotonin metabolism in females than in males. In 7/24 female patients tryptophan concentrations below 50 μM were observed, this is almost the same range seen in patients with, e.g. endogenous depression (27). This goes along with findings of sex differences in mood responses to acute tryptophan depletion by several authors (21, 23, 28). The impact of fructose malabsorption may be more pronounced in females with symptoms of gestagen deficiency as it is the case in women with pre-menstrual syndrome and in perimenopausal women.

Reduced tryptophan concentrations in general could be due to enhanced degradation of tryptophan. Immune activation in patients, e.g. due to clinically inapparent infections or autoimmune disorders, could activate indoleamine (2, 3)-dioxygenase which degrades tryptophan to form kynurenine metabolites (11, 28). Of our patients with fructose malabsorption only 4/50 had an elevated tryptophan per kynurenine quotient. When these subjects were excluded from the statistical evaluation, the association between fructose malabsorption and lower tryptophan concentrations remained significant ($n = 46$: $P = 0.035$ versus $n = 50$: $P = 0.022$). Thus, enhanced degradation of tryptophan is unlikely the reason of decreased tryptophan in patients with fructose malabsorption.

We conclude that fructose malabsorption is associated with lower tryptophan levels. High intestinal fructose concentrations seem to interfere with L-tryptophan metabolism and hence reduce the availability of serotonin (5-hydroxytryptamine). Low tryptophan concentrations may play a role in the development of symptoms of mental depression. Although the correlations found do not necessarily confirm a causal relationship, this observation suggests that fructose malabsorption may be implicated in the pathogenesis of mood disturbances and depressive disorders.

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References

1. Rumessen JJ, Gudmand-Hoyer E. Malabsorption of fructose–sorbitol mixtures. Interactions causing abdominal distress. Scand J Gastroenterol 1987;22:431–6.
2. Gotza H, Mahdi A. Fructose malabsorption and dysfunctional gastrointestinal manifestations [see comments]. Monatsschr Kinderheilkd 1992;140:814–7.
3. Rumessen JJ. Fructose and related food carbohydrates. Sources, intake, absorption, and clinical implications. Scand J Gastroenterol 1992;27:819–28.
4. Born P, Zech J, Lehn H, Classen M, Lorenz R. Colonic bacterial activity determines the symptoms in people with fructose-malabsorption. Hepatogastroenterology 1995;42:778–85.
5. Ledochowski M, Sperner-Unterweger B, Widner B, Fuchs D. Fructose malabsorption is associated with early signs of mental depression. Eur J Med Res 1998;3:295–8.
6. Ledochowski M, Widner B, Bair H, Propst T, Fuchs D. Fructose-and sorbitol-reduced diet improves mood and gastrointestinal disturbances in fructose malabsorbers. Scand J Gastroenterol 2000. In press.
7. Braden B, Braden CP, Klutz M, Lembcke B. [Analysis of breath hydrogen (H_2) in diagnosis of gastrointestinal function: validation of a pocket breath H_2 test analyzer]. Z Gastroenterol 1993;31:242–5.
8. Fleming SC. Evaluation of a hand-held hydrogen monitor in the diagnosis of intestinal lactase deficiency. Ann Clin Biochem 1990;27:499–500.
9. Duan LP, Braden B, Clement T, Caspary WF, Lembcke B. Clinical evaluation of a miniaturized desktop breath hydrogen analyzer. Z Gastroenterol 1994;32:575–8.
10. Hautzinger M, Bailer M, Worall H, Keller F. Beck Depression Inventory—German version/author. 1994, Beck Depressions Inventar (BDI) 1994; Huber.
11. Widner B, Werner ER, Schennach H, Wachter H, Fuchs D. Simultaneous measurement of serum tryptophan and kynurenine by HPLC. Clin Chem 1997;43:2424–6.
12. Veligati LN, Treem WR, Sullivan B, Burke G, Hyams JS. Delta 10 ppm versus delta 20 ppm: a reappraisal of diagnostic criteria for breath hydrogen testing in children. Am J Gastroenterol 1994;89:758–61.
13. STATISTICA for Windows [computer program manual]. Tulsa, OK: StatSoft, Inc., 2325 East 13th Street. StatSoft I; 1995. (5.0).
14. Fernández-Banares F, Esteve-Pardo M, de Leon R, Humbert P,

Cabre E, Llovet JM, et al. Sugar malabsorption in functional bowel disease: clinical implications. Am J Gastroenterol 1993; 88:2044–50.
15. Born P, Vierling T, Barina W. Fructose malabsorption and the irritable bowel syndrome [letter; comment]. Gastroenterology 1991;101:1454.
16. Fernández-Banares F, Esteve-Pardo M, Humbert P, de Leon R, Llovet JM, Gassull MA. Role of fructose–sorbitol malabsorption in the irritable bowel syndrome [letter; comment]. Gastroenterology 1991;101:1453–4.
17. Rumessen JJ, Gudmand-Hoyer E. Functional bowel disease: the role of fructose and sorbitol [letter; comment]. Gastroenterology 1991;101:1452–3.
18. Nelis GF, Vermeeren MA, Jansen W. Role of fructose–sorbitol malabsorption in the irritable bowel syndrome [see comments]. Gastr6oenterology 1990;99:1016–20.
19. Evans PR, Piesse C, Bak YT, Kellow JE. Fructose–sorbitol malabsorption and symptom provocation in irritable bowel syndrome: relationship to enteric hypersensitivity and dysmotility. Scand J Gastroenterol 1998;33:1158–63.
20. Benkelfat C, Ellenbogen MA, Dean P, Palmour RM, Young SN. Mood-lowering effect of tryptophan depletion. Enhanced susceptibility in young men at genetic risk for major affective disorders. Arch Gen Psychiatry 1994;51:687–97.
21. Ellenbogen MA, Young SN, Dean P, Palmour RM, Benkelfat C. Mood response to acute tryptophan depletion in healthy volunteers: sex differences and temporal stability. Neuropsychopharmacology 1996;15:465–74.
22. Neumeister A, Praschak Rieder N, Besselmann B, Rao ML, Gluck J, Kasper S. Effects of tryptophan depletion on drug-free patients with seasonal affective disorder during a stable response to bright light therapy. Arch Gen Psychiatry 1997;54:133–8.
23. Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome. J Affect Disord 1994;32:37–44.
24. Ledochowski M, Überall F, Propst T, Fuchs D. Fructose malabsorption is associated with lower plasma folic acid concentration in middle aged subjects. Clin Chem 1999;45:2013–4.
25. Davis EA. Functionality of sugars: physicochemical interactions in foods. Am J Clin Nutr 1995;62:170S–7S.
26. Dills WL. Protein fructosylation: fructose and the Maillard reaction. Am J Clin Nutr 1993;58:779S–87S.
27. Gasse T, Widner B, Baier-Bittelich G, Sperner-Unterweger B, Leblhuber F, Wachter H, et al. Abnormal tryptophan metabolism, neurologic/psychiatric disturbances and its relationship to immune activation. In: Quereshi GA, editor. Neurochemical markers of degenerative nervous diseases & drug addiction. Progress in HPLC-HPCE. 7th ed. The Netherlands: VSP Press, Zeist; 1997.
28. Salomon RM, Delgado PL, Licinio J, Krystal JH, Heninger GR, Charney DS. Effects of sleep deprivation on serotonin function in depression. Biol Psychiatry 1994;36:840–6.

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