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Psychiatry Research

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Assessment of tryptophan metabolism and signs of depression in individuals with carbohydrate malabsorption

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ARTICLE INFO

Keywords:

Depression
Carbohydrates
Metabolism
Tryptophan

ABSTRACT

This prospective cross-sectional study aimed to investigate the potential association between primary-adult lactose malabsorption, fructose malabsorption, tryptophan (TRP) metabolism and the presence of depressive signs. Overall 251 patients, who were referred for lactase gene C/T.₁₃₉₁₀ polymorphism genotyping and fructose hydrogen/methane breath testing, were included. All participants filled out the Beck Depression Inventory (BDI II). Serum concentrations of tryptophan (TRP), kynurenine (KYN), kynuric acid (KYNA), and TRP competing amino acids (leucine, isoleucine, valine, phenylalanine, tyrosine) were measured by high-pressure liquid-chromatography. Logistic regression analysis was performed with lactose malabsorption, fructose malabsorption and all potential biomarkers of TRP metabolism to assess the effect on signs of depression, defined as a BDI II score > 13. Primary-adult lactose malabsorption and fructose malabsorption was detected in 65 (25.90%) and 65 (25.90%) patients, respectively. Fructose malabsorption was significantly associated with BDI II score, whereas no such relationship was found for lactose malabsorption. Serum levels of TRP and TRP metabolites were no predictors of depression. The authors suggest to conduct further prospective longitudinal studies in order to get further insight of associations between carbohydrate malabsorption, biomarkers and mood disorders.

1. Introduction

Carbohydrate malabsorption is a frequent and widespread gastrointestinal condition (Born, 2007). The disaccharide lactose and the monosaccharide fructose are important carbohydrates, which are included in the daily human diet all over the world (Born, 2007; Ladas et al., 2000).

Primary adult-type lactose malabsorption is an inherited autosomal recessive condition with declined lactase activity in the small intestine (Usai-Satta et al., 2012). The incomplete hydrolysis of the non-absorbable disaccharide lactose into the monosaccharides glucose and galactose is associated with a single nucleotide polymorphism (C/T.

₁₃₉₁₀) 14-kb upstream of the lactase gene (*LCT*) locus (Enattah et al., 2002).

As fructose is a monosaccharide, there is no enzymatic breakdown needed for its intestinal absorption. The GLUT-5 protein is a specific fructose transporter in the small bowel, which is limited in its transport capacity (Barrett and Gibson, 2012; Jones et al., 2011). Since there is no genetic approach to fructose malabsorption testing, this gastrointestinal condition can only be detected using a functional hydrogen (H₂)/methane (CH₄) breath test (Gasbarrini et al., 2009). In individuals with fructose malabsorption and lactose malabsorption the non-absorbed carbohydrates reach the large intestine, where colonic bacteria generate degradation products such as short-chain fatty acids, carbon

Abbreviations: *LCT*, lactase gene; H₂, hydrogen; CH₄, methane; CO₂, carbon dioxide; TRP, tryptophan; KYN, kynurenine; IDO, indoleamine 2,3-dioxygenase; KYNA, kynuric acid; BDI II, Beck Depression Inventory; BMI, body mass index; HPLC, high-performance liquid chromatography; CV, coefficient of variation; eGFR, estimated glomerular filtration rate

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<http://dx.doi.org/10.1016/j.psychres.2017.09.049>

Received 25 May 2017; Received in revised form 17 September 2017; Accepted 21 September 2017

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dioxide (CO₂), H₂, and CH₄ (Eisenmann et al., 2008). Furthermore, lactose and fructose molecules are also considered to interact with the tryptophan (TRP) availability by building non-absorbable carbohydrate-TRP complexes in the gastrointestinal tract (Ledochowski et al., 1998a, 1998b; Varea et al., 2005).

TRP is metabolized via the kynurenine (KYN) pathway. The cytochrome-induced enzyme indoleamine 2,3-dioxygenase (IDO) converts TRP into KYN, which is metabolized into the neuroprotective kynuric acid (KYNA) and several neurotoxins (Gabbay et al., 2010). The tryptophan break down index (= KYN/TRP) represents the activity of IDO (Myint et al., 2007a, 2007b), which is induced in the blood and in the brain by the increased production of cytokines in individuals with depression (Maes et al., 2011). The tryptophan index (= 100 × TRP/sum of TRP competing amino acids: valine, leucine, isoleucine, tyrosine, phenylalanine) indicates the TRP availability in the brain and the ratio between KYNA and KYN is calculated to assess the neuroprotective ratio (Myint et al., 2012).

A previous study comprising fifty adults reported that fructose malabsorption is associated with lower TRP serum concentrations, which may play an essential role in the development of depressive disorders (Ledochowski et al., 2001). Nevertheless, study designs investigating the serum levels of TRP and TRP metabolites in large cohorts of patients with carbohydrate malabsorption are still lacking.

The aim of the present study was to investigate the association between primary-adult lactose malabsorption, fructose malabsorption, TRP metabolism and the signs of depression in a large cohort of adult patients who were referred to our outpatient clinic for carbohydrate malabsorption testing.

2. Materials and methods

2.1. Study design and patients

The data of this prospective study were collected from August 25, 2015 to May 31, 2016. A total of 251 adult patients, who were referred by general practitioners and specialists for primary-adult lactose malabsorption and fructose malabsorption testing to our outpatient clinic, were included. All participants provided their written informed consent. They underwent genotyping for the lactase *LCT* C/T₁₃₉₁₀ polymorphism, 25 g fructose H₂/CH₄ breath test, and blood sampling after an overnight fasting state (12 h) in the morning between 08:00 and 10:00 a.m. During the fructose H₂/CH₄ breath test all subjects were asked to fill out the Beck Depression Inventory (BDI II) questionnaire (Steer et al., 1999). Additionally, height (cm) and weight (kg) were determined with a wall-mounted metric tape measure and a calibrated personal scale in order to calculate the body mass index (BMI) (kg/m²). Data about medical comorbidities and medication were collected with clinical anamnesis and the examination of case histories.

The inclusion criteria for this study were patients for lactose malabsorption and fructose malabsorption testing, aged between 18 and 70 years, and an obligatory overnight fasting state and non-smoking period of > 12 h.

Patients with colonoscopy or antibiotic-based therapy at least 4 weeks before the H₂/CH₄ breath test, patients with active or chronic inflammatory bowel disease, and individuals with neuropsychiatric comorbidities were excluded from the study.

This study was approved by the Ethical Committee of the Johannes Kepler University Linz (Linz, Austria) (trial registration number: C-95-15) and carried out in accordance with the current version of the Declaration of Helsinki.

2.2. *LCT* C/T₁₃₉₁₀ genotyping and fructose H₂/CH₄ breath test

Genomic DNA was purified from 200 μL EDTA blood using the MagNA Pure Compact Nucleic Acid Isolation Kit I and the MagNA Pure Compact Instrument (Roche Diagnostics, Rotkreuz, Switzerland)

according to the manufacturer's instructions. To detect the *LCT* C/T₁₃₉₁₀ polymorphism real-time PCR based on fluorescence-labeled hybridisation probes, followed by melting curve analysis (*LCT* T-13910C ToolSet™; Roche Diagnostics, Rotkreuz, Switzerland), was performed on the LightCycler® 2.0 Instrument (Roche Diagnostics) (Enko et al., 2015).

A fructose HMBT protocol was established to detect individuals with fructose malabsorption. Gaschromatography was employed using a QuinTron Model DP Plus MicroLyzer™ (QuinTron, Milwaukee, WI, USA). After determining baseline breath H₂/CH₄ concentrations, fructose was given in a dose of 25 g dissolved in 200 mL of water. The end-expiratory breath H₂/CH₄ concentrations were measured at 15, 30, 45, 60, 75, 90, and 120 min. According to the literature (Eisenmann et al., 2008; Enko et al., 2014), patients were classified as malabsorbers, if a H₂/CH₄ increase > 20 ppm above baseline concentrations was observed.

2.3. BDI II score

The BDI II was used to measure the existence and severity of self-reported depressive symptoms. Each of the 21 items (scale: 0–3) corresponding to a symptom of depression was summed to give a single score for the BDI II (Steer et al., 1999). According to the literature (Beck et al., 1996; Smarr and Keefer, 2011; Wang and Gorenstein, 2013), patients with a BDI II score threshold > 13 were classified as individuals with the presence of depressive symptoms.

2.4. TRP, KYN, KYNA and amino acids measurements

TRP, KYN and KYNA were measured in serum samples by high-performance liquid chromatography (HPLC) with a simultaneous ultraviolet and fluorimetric detection system (Hervé et al., 1996). In brief, 100 μL plasma sample was deproteinized by adding 100 μL of 5% (v/v) perchloric acid. After vortexing and 5 min centrifugation at 11,000 g, 20 μL of the clear supernatant was injected in the chromatographic system. Separations were achieved on a Chromolith RP18e column (100 × 4.6 mm, 5 μm, Merck Darmstadt, Germany) at 30 °C by isocratic elution with a mobile phase (pH 4.9) consisted of 50 mmol/L ammonium acetate, 250 mol/L zinc acetate and 3% (v/v) acetonitrile, at a flow-rate of 0.8 mL/min. KYN and TRP were detected on an Agilent 1200 VWD detector (Agilent, Palo Alto, CA, U.S.A.) at 235 nm, KYNA was detected fluorometrically at the emission wavelength 344 nm and emission wavelength 404 on an Agilent 1260 FLD detector. Acquisition and processing of the chromatograms were performed using an Agilent 1200 system equipped with a Chemstation software (Agilent, Palo Alto, CA, U.S.A.). The concentrations were determined as the peak-height measurement against external standards. All reagents were p.A. grade from Merck (Darmstadt, Germany). Intra-assay coefficients of variation (CVs) for different concentrations were in the range of 0.7–2.9% for TRP, 1.7–4.3% for KYN, and 2.6–4.5% for KYNA. The inter-assay CVs were 6.3–9.3%, 2.0–5.4% and 8.4–11.6%, respectively.

Serum concentrations of the amino acids leucine, isoleucine, valine, phenylalanine and tyrosine were determined by previously described chromatographic methods (Mangge et al., 2016; Schwarz et al., 2005). Briefly, after precipitation of EDTA plasma with perchloric acid following neutralization of the supernatant with sodium carbonate, the extracted amino acids were derivatized with o-phthalaldehyde and separated on a reversed phase column with gradient elution. Quantification was performed with ratios of fluorescence signals of the interesting amino acids to the internal standard norvaline in comparison to the appropriated calibration curves. Intra- and inter-assay CVs were all below 10%. The TRP break down index (= KYN/TRP), the neuroprotective ratio (= KYNA/KYN), and the TRP index (= 100 × TRP/competing amino acids) were calculated according to the literature (Myint et al., 2007a, 2007b).

Creatinine was measured with an enzymatic method applied to an

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