Does acute tryptophan depletion affect peripheral serotonin metabolism in the intestine?1–3

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ABSTRACT
Background: Serotonin (5-hydroxytryptamine; 5-HT), a tryptophan metabolite, plays an important regulatory role in the human central nervous system and in the gastrointestinal tract. Acute tryptophan depletion (ATD) is currently the most widely established method to investigate 5-HT metabolism.

Objective: The aim of this study was to assess the effect of an acute decrease in the systemic availability of tryptophan on intestinal 5-HT metabolism and permeability.

Design: Thirty-three healthy volunteers (17 with ATD, 3 of whom dropped out; 16 placebo) participated in this randomized placebo-controlled study. Plasma and duodenal mucosal concentrations of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), and kynurenic acid (KA) were measured by HPLC–mass spectrometry. Intestinal barrier function was assessed with a multisugar plasma test, and analysis of tight junction transcription was performed in duodenal biopsy samples obtained by gastroduodenoscopy.

Results: Mucosal 5-HT, 5-HIAA, and KA concentrations remained unaltered by ATD. In contrast, ATD significantly decreased plasma 5-HT (P < 0.05) and 5-HIAA (P < 0.0001) concentrations. After endoscopy, a significant increase in plasma 5-HT concentrations was observed in the placebo group (P = 0.029) compared with the ATD group. Moreover, a significant increase in plasma KA concentrations over time was found in the placebo group (P < 0.05). No changes in intestinal barrier function were observed.

Conclusions: An acute decrease in precursor availability does not affect mucosal concentrations of serotonergic metabolites, in contrast with systemic concentrations. ATD alters biochemical responses to acute stress from the endoscopic examination reflected by lower 5-HT concentrations. Changes in 5-HT concentrations were paralleled by alterations in KA concentrations, which suggest competition between the 2 metabolic pathways for the mutual precursor. This trial was registered at clinicaltrials.gov as NCT00731003. Am J Clin Nutr 2012;95:603–8.

INTRODUCTION
The amino acid tryptophan is the precursor of a wide array of metabolites involved in a variety of aspects of human nutrition and metabolism. Studies in the past decades have primarily focused on the metabolite serotonin (5-HT)—a signaling molecule that has been shown to play an important role in the human body, not only in the CNS, but also in the gut (1, 2). Approximately 95% of the total 5-HT content of the human body is found in the gut, of which 90% in the intestinal ECs. These cells possess the machinery to produce and store 5-HT (2, 3). Besides its large mucosal source, 5-HT is also produced by neurons of the enteric nervous system. In the gut, 5-HT plays an important role in mediating gastrointestinal secretion, motility, and perception, whereas in the CNS it modulates an extensive range of physiologic and behavioral functions, including, mood, cognition, and sleep. Besides incorporation into protein, only 1% of ingested tryptophan is converted into 5-HT, whereas the majority of tryptophan is subject to degradation via the kynurenine pathway—the primary route of tryptophan metabolism in the human body (4). Apart from 5-HT, metabolites of the kynurenine pathway have received increasing attention, because they are believed to have a regulatory role in the CNS and the gastrointestinal tract (4, 5).

The biology of the serotonergic system is often studied by using protocols that deplete the precursor tryptophan. ATD is a well-established dietary technique used to temporarily reduce 5-HT synthesis by decreasing the availability of tryptophan (6, 7). ATD involves the ingestion of a pure amino acid mixture devoid of tryptophan, which results in a 70–90% decrease of plasma tryptophan that is paralleled by lowering central 5-HT synthesis between 4 and 7 h of administration (6). Little is known of the consequences of tryptophan depletion on serotonergic functions outside the CNS. In this study, we aimed to investigate intestinal mucosal serotonin metabolism and to assess its role in maintaining intestinal barrier function in healthy volunteers. The

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4 Abbreviations used: ATD, acute tryptophan depletion; CNS, central nervous system; EC, enterochromaffin cell; Ham-D17, 17-item Hamilton Depression Rating Scale; HPLC-MS, HPLC–mass spectrometry; KA, kynurenic acid; MUMC, Maastricht University Medical Centre+; SCL-90, Dutch version of the symptom checklist; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine.
5 Received October 25, 2011. Accepted for publication December 20, 2011. First published online February 1, 2012; doi: 10.3945/ajcn.111.028589.
intestinal barrier plays a paramount role in regulating intestinal physiology and has been reported to be affected by 5-HT (8). To influence serotonergic metabolism, we used ATD. We aimed to test the general a priori hypotheses that 1) an acute decrease in the systemic availability of the precursor induces changes in serotonergic metabolism in the intestine and 2) these changes in serotonergic conditions affect the intestinal barrier function. Furthermore, because the effects of precursor depletion on the kynurenine pathway have not been investigated previously, we aimed to assess the effects of ATD on the systemic and intestinal mucosal concentrations of KA as an indicator of changes in the kynurenine pathway.

SUBJECTS AND METHODS

Approval for the study was obtained from the Medical Ethics Committee of MUMC in full accordance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, Somerset West, and Edinburgh; a note of clarification was added in Washington and Tokyo). All volunteers gave their written informed consent before participation.

Subjects

Participants eligible for inclusion were aged between 18 and 65 y. All subjects were screened by means of a standardized general physical examination. General psychological state was assessed by using HAM-D17 and the SCL-90. Exclusion criteria included a history of gastrointestinal or psychiatric disorders, including the use of psychoactive medication or psychological symptoms, defined as a diagnosis on the global severity index score on the SCL-90 of ≥150 for females and of ≥131 for males; HAM-D17 scores ≥8; first-degree family members with psychiatric disorders; use of medication, including vitamin supplementation, except oral contraceptives, within 14 d before testing; administration of investigational drugs in the 180 d before the study; major abdominal surgery interfering with gastrointestinal function; premenstrual syndrome; dieting with gastrointestinal function; premenstrual syndrome; dieting; excessive alcohol consumption (≥20 alcoholic consumptions/wk); and smoking.

Acute tryptophan depletion

The amino acid mixtures were obtained from Tiofarma BV and were blinded by the Department of Pharmacy of the MUMC, Maastricht, Netherlands. The depleting drink contained 15 amino acids, including 5 large neutral amino acids, according to the formula of Young et al (9). The control mixture contained the same amino acids enriched with 2.3 g tryptophan to maintain normal tryptophan concentrations.

Study design

The study was conducted following a randomized, placebo-controlled, double-blind, parallel design and consisted of one test day. All women were tested in the follicular phase of the menstrual cycle or while taking oral contraception. All subjects were tested within 3 mo to avoid potential seasonal variation. Participants were requested to abstain from heavy physical exercise and consumption of tryptophan-rich food (coffee, tea, energy drinks, kiwi, avocado, fish, seafood, walnuts, banana, and tomato) on the day before their visit. After 2200, no eating or drinking (except water) was allowed.

An overview of the experimental procedures on the test day is given in Figure 1. Participants were requested to arrive at the MUMC at 0800, after which they received an intravenous cannula in the antecubital vein. After blood samples were collected, the amino acid mixtures were dissolved in 300 mL tap water, and the subjects were instructed to ingest the mixture as quickly as possible using a nose clap to avoid the unpleasant smell of the mixtures. Four hours later, a venous blood sample was taken, and the participants received an oral multisugar drink to assess intestinal permeability. The multisugar drink consisted of 1 g lactulose (Centrafarm Services), 0.5 g L-rhamnose (Danisco Sweeteners), 1 g erythritol (Cargill Nederland BV), and 1 g sucralose (Tate and Lyle Sucralose Inc). An additional blood sample was taken 5 h after ingestion of the amino acid drink. Subsequently, participants underwent a gastroduodenoscopy, and mucosal tissue samples of ~5 mg were obtained from the second segment of the duodenum by using a standard forceps (diameter: 2.8 mm) and were immediately frozen in liquid nitrogen. At the end of the test day, a blood sample was drawn at 330 min after ingestion of the amino acid drink.

Assessment of serotonergic metabolism

To assess systemic concentrations of 5-HT metabolites, blood samples were collected into prechilled K2EDTA tubes. One milliliter of 1.4% ascorbic acid (Sigma Aldrich) was added to all tubes for 5-HT analysis to prevent oxidative breakdown. Plasma collection tubes were centrifuged at 2000 × g at 4°C for 10 min to obtain platelet-poor plasma. Supernatant fluid was collected and stored at −80°C until analyzed. Concentrations of 5-HT, 5-HIAA, the main metabolite of 5-HT, and KA (a metabolic product of the kynurenine pathway) were determined by HPLC-MS as described by Danaceau et al (10). Mucosal concentrations of 5-HT, 5-HIAA, and KA were measured by using the same method after measurement of the wet weight of tissue samples. Furthermore, gene expressions of the proteins serotonin transporter (responsible for mucosal clearance of 5-HT released from ECs) and tryptophan hydroxylase 1 (the rate-limiting step in 5-HT synthesis in ECs) were investigated in mucosal biopsy specimens by quantitative real-time polymerase chain reaction (see “Supplemental data” in the online issue).

Assessment of intestinal barrier function

Intestinal barrier function was assessed by using the sugar recovery test. Measuring the plasma concentrations of orally ingested sugar is a generally accepted method to investigate intestinal permeability (11). The ratio of a monosaccharide and a disaccharide is indicative of intestinal mucosal permeability, because these probes...
differ in the manner of transport, ie, paracellular or transcellular. In the healthy small bowel, the permeability for larger sugars such as lactulose or sucralose is much lower than for smaller sugars such as erythritol or rhamnose. Lactulose and other larger molecules pass through the intercellular spaces, which are regulated by intercellular tight junctions (11). Plasma sugar concentrations were measured as described by van Wijck et al (12).

Furthermore, gene transcription of tight junction proteins (occludin, claudin-3, claudin-4, and zonuline occludens-1) and myosin light-chain kinase (involved in regulating tight junction function) in biopsy specimens was determined by quantitative real-time polymerase chain reaction. Glyceraldehyde 3-phosphate dehydrogenase and 18S rRNA were used as reference genes.

Assessment of the stress response to the endoscopic examination

To assess the magnitude of the stress response to the endoscopic examination, serum was collected before and after the endoscopy to measure cortisol concentrations. Serum collection tubes were stored at room temperature for 1 h and centrifuged at 3000 x g at 4°C for 10 min. Serum cortisol concentrations were analyzed by ELISA at Medische Laboratoria Dr. Stein & Colleges (Maastricht, Netherlands).

Statistical analyses

Statistical analyses were performed by using SPSS 17.0 for Windows (SPSS Inc). Data were tested for normality by using the Kolmogorov-Smirnoff test. Normally distributed data were analyzed by using Student’s t test. ATD, acute tryptophan depletion; KA, kynurenine; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine.

TABLE 1
Concentrations of 5-HT, 5-HIAA, and KA in duodenal mucosal samples

<table>
<thead>
<tr>
<th></th>
<th>ATD (n = 14)</th>
<th>Placebo (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT (pmol/mg)</td>
<td>45.6 ± 7.3</td>
<td>42.5 ± 6.7</td>
<td>0.76</td>
</tr>
<tr>
<td>5-HIAA (pmol/mg)</td>
<td>1.57 ± 0.3</td>
<td>1.97 ± 0.3</td>
<td>0.36</td>
</tr>
<tr>
<td>KA (pmol/mg)</td>
<td>2.07 ± 1.3</td>
<td>2.29 ± 1.3</td>
<td>0.91</td>
</tr>
</tbody>
</table>

All values are means ± SEMs. The data were analyzed by using Student’s t test. ATD, acute tryptophan depletion; KA, kynurenine; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine.

P < 0.05; Figure 2A). The 2-factor ANOVA showed a significant interaction between treatment and time (P < 0.01). Also, the concentrations of the principal metabolite 5-HIAA were significantly decreased after ATD (11.7 ± 1.2 nmol/L) compared with after placebo (22.7 ± 1.8 nmol/L) (P < 0.0001; Figure 2B). Two-factor ANOVA showed significant interaction between treatment and time (P < 0.001). KA concentrations remained unaltered in the ATD group, whereas a significant increase over time was observed in the placebo group (6.5 ± 1.4 compared with 14.2 ± 3.3 nmol/L, respectively; t = 0 compared with t = 240 min; P < 0.05; Figure 2C). Two-factor ANOVA showed a significant interaction between treatment and treatment (P = 0.03).

Effect of ATD on intestinal permeability

ATD did not affect the plasma concentrations of the sugars lactulose, rhamnose, sucralose, and erythritol. Therefore, no significant differences were found in the lactulose:rhamnose or sucralose:erythritol ratios (Table 3). Furthermore, ATD did not lead to any changes in the transcription of the tight junction proteins claudin-3, claudin-4, zonula occludens-1, and occludin or in myosin light-chain kinase (Table 2).

Effect of acute stress response on 5-HT and kynurenine metabolites

Serum cortisol concentrations increased significantly after endoscopic examination, from 11.9 ± 1.6 to 15.8 ± 1.3 μg/dL after endoscopy (P = 0.001). The increase in cortisol

TABLE 2
Gene transcription of genes associated with serotonergic metabolism and intestinal barrier function

<table>
<thead>
<tr>
<th></th>
<th>ATD (n = 14)</th>
<th>Placebo (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPH1</td>
<td>0.0006 ± 0.0002</td>
<td>0.0004 ± 0.0001</td>
<td>0.399</td>
</tr>
<tr>
<td>SERT</td>
<td>0.99 ± 0.35</td>
<td>0.57 ± 0.20</td>
<td>0.413</td>
</tr>
<tr>
<td>Claudin-3</td>
<td>1.64 ± 0.49</td>
<td>1.42 ± 0.50</td>
<td>0.764</td>
</tr>
<tr>
<td>Claudin-4</td>
<td>2.02 ± 0.65</td>
<td>1.75 ± 0.49</td>
<td>0.741</td>
</tr>
<tr>
<td>ZO-1</td>
<td>0.58 ± 0.19</td>
<td>0.79 ± 0.18</td>
<td>0.446</td>
</tr>
<tr>
<td>Occludin</td>
<td>1.04 ± 0.35</td>
<td>0.76 ± 0.20</td>
<td>0.496</td>
</tr>
<tr>
<td>MLCK</td>
<td>1.52 ± 0.34</td>
<td>1.01 ± 0.25</td>
<td>0.237</td>
</tr>
</tbody>
</table>

All values are normalized expression ratios ± SEMs. The data were analyzed by using Student’s t test. ATD, acute tryptophan depletion; MLCK, myosin light-chain kinase; SERT, serotonin transporter; TPH1, tryptophan hydroxylase 1; ZO-1, zonula occludens-1.
with placebo; compared with placebo. 

Student’s t test. Plasma sugar concentrations were corrected for their initial value measured before ingestion of the sugar drink. 

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>ATD (n = 14)</th>
<th>Placebo (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose:rhamnose ratio</td>
<td>0.0017 ± 0.001</td>
<td>0.0021 ± 0.001</td>
<td>0.434</td>
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<tr>
<td>Sucrose:erythritol ratio</td>
<td>0.0044 ± 0.001</td>
<td>0.0042 ± 0.001</td>
<td>0.540</td>
</tr>
</tbody>
</table>

1 All values are means ± SEMs. The data were analyzed by using Student’s t test. Plasma sugar concentrations were corrected for their initial value measured before ingestion of the sugar drink.

2 ATD, acute tryptophan depletion.

postendoscopy concentrations correlated significantly with the increase in serum cortisol concentrations observed over the same period of time (r = 0.879, P = 0.02). The observed 5-HT increase after endoscopy remained absent in the ATD group (Figure 2A). At the same time, KA concentrations decreased to their initial concentrations after the endoscopy in the placebo group, whereas no significant alterations in KA concentrations were seen in the ATD group.

**DISCUSSION**

Decreasing tryptophan availability by ATD has been shown to decrease brain 5-HT synthesis throughout much of the cerebral cortex in healthy volunteers (15). Because tryptophan hydroxylase, the rate-limiting synthesis of 5-HT, is half saturated under normal physiologic conditions (16), 5-HT synthesis in the brain is highly dependent on the availability of tryptophan in plasma, which is largely influenced by the competitive uptake of tryptophan and other large neutral amino acids across the blood-brain barrier through the large neutral amino acid transporter 1 (17). Next to the CNS, the gut is a principle organ of 5-HT synthesis and metabolism. A similar competitive uptake is theoretically also possible for the carrier responsible for the intestinal absorption of tryptophan and all other neutral amino acids, B0AT1, which has a relatively low affinity for tryptophan (4). This could provide a basis for a decreased uptake of tryptophan through the intestinal epithelium after ATD, which could affect intestinal 5-HT metabolism. Here we investigated whether an acute decrease in tryptophan availability can affect intestinal mucosal 5-HT metabolism, in particularly in the ECs—the primary site of 5-HT synthesis in humans.

This study suggests that the machinery responsible for maintaining serotonergic homeostasis in the intestinal mucosa has the capacity to compensate for an acute decrease in the precursor availability, thereby leaving intestinal 5-HT concentrations unaffected. In support of this finding, we found no alterations in the duodenal mucosal concentrations of serotonergic metabolites during ATD. In addition, no changes in the mucosal expression of genes related to intestinal serotonergic metabolism were observed. Also, the intestinal barrier function was investigated. In a recent study we showed that oral administration of the precursor of 5-HT, 5-hydroxytryptophan, reinforces small intestinal barrier function by lowering intestinal sugar permeability, inducing the expression of the tight junction protein zonula occludens-1 and causing alterations in the intracellular distribution of tight junction proteins. This suggests that changes in serotonergic conditions can influence intestinal barrier function (18). However, in the current study, which used ATD, neither the expression
of genes related to intestinal barrier function nor plasma concentrations of orally ingested sugars indicative of altered intestinal permeability were affected. Furthermore, the current findings are supported by a recent study suggesting that an acute decrease in precursor availability is unlikely to interfere with serotonergic metabolism in ECs of the mucosa (19). These observations are in line with the fact that maintenance of steady state mucosal 5-HT concentrations is essential for the orchestration of intestinal function.

The fact that a decrease in precursor availability was indeed achieved by ATD in our study was reflected by profound alterations observed in systemic concentrations of 5-HT metabolites induced by ATD: plasma concentrations of 5-HT and 5-HIAA, the main metabolic product of 5-HT, had decreased significantly 5 h after ATD in comparison with the placebo drink. Earlier studies showed that ATD induces a significant decrease in both plasma and cerebrospinal fluid concentrations of 5-HIAA (19–22). Cerebrospinal fluid 5-HIAA is thought to reflect central 5-HT turnover and is presumed to correlate with brain 5-HIAA in humans (23), which supports the hypothesis that ATD affects serotonergic conditions in the CNS. Given the lack of effect on mucosal serotonergic metabolism, it is tempting to assume that alterations seen in systemic concentrations of 5-HT metabolites originate from changes induced in other than mucosal sources of 5-HT. Because 5-HT synthesis in the CNS is highly dependent on plasma tryptophan availability, we postulate that alterations observed in systemic 5-HT concentrations after precursor depletion originate from changes in the CNS.

The fact that precursor availability strongly affects 5-HT synthesis in the CNS was reflected by an altered reaction to a stress response. In this study, we carried out gastroduodenoscopy to obtain biopsy specimens from the duodenal mucosa. Interestingly, we observed an unanticipated significant increase in plasma 5-HT concentrations in the placebo group after the endoscopic procedure, which was absent in the ATD group. We postulate that the increase was caused by an acute stress response related to the endoscopic examination and was not the result of normal plasma 5-HT kinetics after tryptophan administration, because an earlier study showed no significant change in plasma 5-HT up to 7 h after intake of the amino acid drink (20). Acute stress and anxiety have been associated with increased plasma concentrations of 5-HT, which have been postulated to be the result of impaired uptake of 5-HT into platelets as a result of increased adrenergic activity (24). To assess potential stress or anticipatory anxiety, we measured serum cortisol concentrations that generally increase after acute stress due to HPA-axis activation. Both groups had a significant increase in serum cortisol concentrations, which supports an acute stress response. The absence of an increase in 5-HT concentrations in the ATD group is likely to be the result of precursor depletion, which also supports the hypothesis that alterations observed in systemic serotonergic metabolite concentrations induced by ATD are driven centrally.

A possible limitation of our study was that the time window of 5.5 h might have been suboptimal with regard to detecting changes in intestinal 5-HT metabolism. Although Geeraerts et al (19) showed an absolute decrease in duodenal 5-HT content, insufficient evidence exists to determine the optimal time window in which to assess changes in intestinal 5-HT metabolism. Furthermore, Geeraerts et al (19) observed modest effects on gastric physiology 5 h after ATD, with no alterations in gastric sensitivity and compliance. Therefore, the profound alterations observed in systemic 5-HT concentrations, the relative stability of plasma 5-HIAA concentrations within the time period examined, and the modest effects on functional outcomes from both the current study and the study by Geeraerts et al all point to the fact that no profound effects can be observed in the intestine after ATD.

In this study, we also investigated the effects of a decrease in tryptophan availability on the kynurenine pathway. The vast majority (95%) of ingested tryptophan is subject to metabolism along this pathway (4). Plasma tryptophan concentrations are largely under control of the liver by clearing any excess tryptophan through tryptophan dioxygenase—the initiating enzyme of the kynurenine pathway (4). Tryptophan, which was administered in the placebo group but not in the ATD group, was, therefore subject to conversion along the kynurenine pathway, which was reflected by significantly increased plasma concentrations of KA. This is in line with findings from early studies that used tryptophan loading and showed an increase in urinary KA concentrations (25). On the other hand, the synthesis of KA was apparently independent of plasma precursor concentrations, because plasma and intestinal mucosal KA concentrations remained unaltered in the depleted group. Additionally, we observed that alterations in plasma concentrations of KA were counterbalanced by changes in plasma concentrations of 5-HT. As a result of the acute stress response, the initially increased KA concentrations observed in the placebo group decreased to baseline, whereas 5-HT concentrations increased significantly. This suggests that the 2 metabolic pathways (5-HT and kynurenine) compete for their mutual precursor, tryptophan, and lead to lower concentrations of KA on increased 5-HT synthesis. Vice versa, diversion of tryptophan to the kynurenine pathway may lead to a relative deficiency of 5-HT synthesis and hence to serotonergic dysfunction (26). This is supported by previous reports suggesting that such metabolic imbalance plays a role in the development of disorders associated with serotonergic dysfunction in both the CNS and the periphery, such as mood disorder and irritable bowel syndrome (4, 27).

In this study, we showed that serotonergic metabolism in the intestinal mucosa was not affected by an acute dietary decrease in precursor availability, whereas profound effects on systemic concentrations of serotonergic metabolites were observed. We also showed that precursor depletion alters responses to acute stress, because systemic 5-HT concentrations did not increase in the ATD group as a result of depletion of the precursor. Furthermore, changes in plasma 5-HT concentrations were paralleled by alterations in systemic concentrations of KA, which suggests competition between the 2 metabolic pathways for the mutual precursor. The findings of this study contribute to a more complete understanding of 5-HT and kynurenine metabolism and provide a further basis for the development of novel therapeutic entities for disorders associated with serotonergic dysfunction.

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The authors’ responsibilities were as follows—DK: conducted the research, analyzed the data, and wrote the manuscript; DM and JD: contributed to the study design; EvD and WB: contributed to the manuscript preparation; FT: supervised conduction of the research; and AM: had primary responsibility for the final content. All authors read and approved the final manuscript. None of the authors declared a conflict of interest.
REFERENCES


