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Citation for published version (APA):

Document status and date:
Published: 01/01/2004

DOI:
10.1136/gut.2004.041657

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:

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IRRITABLE BOWEL SYNDROME

Acute tryptophan depletion affects brain-gut responses in irritative bowel syndrome patients and controls

T O C Kilkens, A Honig, M A van Nieuwenhoven, W J Riedel, R-J M Brummer


Background: Serotonin, a key denominator of the brain-gut axis, is involved in the regulation of gastrointestinal motility, secretion, and perception as well as cognition and mood.

Aim: To assess the effects of an acutely lowered serotonin synthesis, using the acute tryptophan depletion (ATD) method, on visceral perception, affective memory performance, and mood in diarrhoea predominant irritable bowel syndrome patients (d-IBS) and controls.

Methods: In a randomised, double blind, crossover design, 14 d-IBS patients and fourteen matched controls were studied under ATD and placebo conditions, respectively. Perception of urge and pain was scored during rectal distensions. Affective memory performance, mood, and biochemical parameters of serotonergic metabolism were simultaneously assessed.

Results: ATD significantly decreased plasma tryptophan (67.0 (2.0) v 24.9 (2.0) μmol/l) and 5-hydroxyindole acetic acid concentrations (29.9 (1.0) v 15.8 (0.6) nmol/l). ATD was associated with significantly increased urge scores specifically in the lower pressure range and overall increased pain scores. ATD significantly lowered the perceptual threshold for first perception compared with placebo (patients 10.6 (1.2) v 13.6 (0.8) mm Hg, controls 12.6 (1.3) v 15.7 (1.2) mm Hg) but not for maximal tolerable discomfort (patients 50.5 (3.6) v 51.6 (3.3) mm Hg, controls 50.9 (3.3) v 48.8 (2.9) mm Hg). ATD induced a significant shift in affective memory bias towards preferential loss of positive material but no significant changes in mood. ATD did not differentially affect the patient or control group.

Conclusions: We have provided evidence that serotonergic modulation by ATD affects both visceral perception as well as cognition in d-IBS and controls. Simultaneous measurement of brain and gut function and the application of ATD contribute to the elucidation of the complex pathophysiology of IBS.

The pathophysiology of irritable bowel syndrome (IBS) is not fully understood. A multicomponent conceptual model of IBS has been postulated, involving physiological, affective, cognitive, and behavioural factors. The “brain-gut axis” is a theoretical model describing the bidirectional neural pathways linking cognitive and emotional centres in the brain to neuroendocrine centres, the enteric nervous system, and the immune system, and plays a major role in the concept of IBS. IBS is associated with visceral hypersensitivity and with a high co-occurrence of psychiatric symptoms, in particular affective dysregulation.

Serotonin (5-hydroxytryptamine (5-HT)) is a biogenic amine that functions as a neurotransmitter and is located predominantly in the gastrointestinal tract (80% of body 5-HT). Approximately 5% is located in the brain and cerebrospinal fluid (CSF). 5-HT is peripherally involved in the regulation of gastrointestinal secretion, motility, and perception whereas in the central nervous system (CNS) it plays a role in the regulation of mood and cognition. Manipulation of serotonergic activity by application of 5-HT modulators has been used in the treatment of both affective disorders and IBS. Hence 5-HT is a key denominator of the “brain-gut axis”.

Disturbed serotonergic metabolism seems especially prevalent in the diarrhoea predominant type of IBS (d-IBS). Increased postprandial plasma 5-HT levels in d-IBS patients and increased numbers of 5-HT containing enterochromaffin (EC) cells in postinfectious IBS (PI-IBS) have been observed. In contrast with the known effects of 5-HT on gastrointestinal motility and secretion, the role of 5-HT in visceral perception to volume based distensions has been less well established.

An acute decrease in 5-HT synthesis can be achieved by means of the acute tryptophan depletion (ATD) method. ATD selectively lowers 5-HT synthesis, between four and seven hours after oral administration of an amino acid mixture devoid of the 5-HT precursor tryptophan. In human subjects, substantial reductions in brain 5-HT synthesis and decreased levels of CSF 5-hydroxyindole acetic acid (5-HIAA), the major metabolite of 5-HT, have been demonstrated. Peripherally, the ATD method leads to a 60–70% decrease in plasma tryptophan levels.

ATD has been used over the past decade in the psychiatric setting to investigate the role of the central-5-HT system in patients with affective disorders (depression and anxiety) and their first degree relatives. It serves as a biological model for inducing symptoms of depression such as impaired mood and affective memory performance (loss of words with a positive connotation). In addition, recent findings at our department showed that ATD also affects gastrointestinal physiology by delaying gastric emptying in healthy females.

The above findings indicate that the ATD method offers a potential technique to study the contribution of 5-HT to regulation of the “brain-gut axis”. This paper describes the effects of serotonergic modulation, using the ATD method, at...
the level of both the brain and gut, in patients with d-IBS and healthy controls. We applied this novel model to investigate whether: (1) ATD influences visceral perception during rectal distensions and (2) whether ATD simultaneously influences affective memory performance and mood. Based on the known effects of ATD on the CNS and given the lines of evidence that (1) IBS is associated with enhanced visceral perception\(^2\) and lowered mood\(^10\) and (2) lowered mood is associated with decreased serotonergic activity,\(^3\) we hypothesised that decreased serotonergic synthesis would be associated with enhanced visceral perception and impaired affective memory performance and mood.

### MATERIALS AND METHODS

#### Subjects (Table 1)

All subjects were screened which involved a standardised psychiatric examination using the mini international neuropsychiatric interview (MINI)\(^26\) to determine the present psychiatric state. General psychological state was assessed using the 17 item Hamilton depression rating scale (HAM-D17),\(^27\) the Dutch version of the symptom checklist (SCL-90),\(^28\) and the hospital anxiety and depression rating scale (HADS).\(^29\) Physical health was assessed by means of a standardised physical examination using the mini international neuropsychiatric interview; HAM-D17, 17 item Hamilton depression rating scale; SCL-90, symptom checklist; GSI, global severity index; HADS, hospital anxiety and depression rating scale.

*Significant difference between groups.
†Independent samples t-tests comparing d-IBS patients versus control subjects.
‡Four subjects had a psychiatric diagnosis: depression, agoraphobia, social phobia, and anxiety disorder, respectively.

<table>
<thead>
<tr>
<th>Subject characteristics (mean (SEM))</th>
<th>d-IBS patients</th>
<th>Controls</th>
<th>Patients v controls (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M) (n)</td>
<td>8/6</td>
<td>8/6</td>
<td>–</td>
</tr>
<tr>
<td>Oral contraceptives (n)</td>
<td>6/8</td>
<td>6/8</td>
<td>–</td>
</tr>
<tr>
<td>Age</td>
<td>34.1 (3.0)</td>
<td>33.9 (3.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Intelligence quotient</td>
<td>106 (3.6)</td>
<td>110 (3.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.3 (1.0)</td>
<td>22.9 (0.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Alcohol units/day</td>
<td>0.61 (0.2)</td>
<td>0.52 (0.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>2.71 (1.2)</td>
<td>1.43 (0.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diagnosis on MINI</td>
<td>41</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>HAM-D17</td>
<td>3.64 (1.1)</td>
<td>0.86 (0.3)</td>
<td>0.03*</td>
</tr>
<tr>
<td>SCL-90 (GSI)</td>
<td>114 (6.3)</td>
<td>97.4 (2.3)</td>
<td>0.02*</td>
</tr>
<tr>
<td>HADS (total)</td>
<td>5.14 (0.9)</td>
<td>3.93 (0.9)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

| d-IBS, diarrhoea-predominant IBS; MINI, mini international neuropsychiatric interview; HAM-D17, 17 item Hamilton depression rating scale; SCL-90, symptom checklist; GSI, global severity index; HADS, hospital anxiety and depression rating scale. |

#### Study design (fig 1)

The study was conducted following a randomised, placebo controlled, double blind, crossover design. The two test days were separated by a minimum of seven days. All women were tested in the follicular phase of the menstrual cycle or while taking oral contraception.\(^32\) All subjects were tested within three months to avoid possible seasonal variation.\(^32\) They were asked to abstain from heavy physical exercise and consumption of alcoholic beverages the day prior to their visit. All subjects attended the laboratory twice after an overnight fast (after 10:00 pm no eating, drinking, or smoking was allowed) at 8:00 am. At t = 8:30 the amino acid drink (ATD or placebo mixture) was administered. Blood samples were taken at t = 8:00 and t = 15:00. Affective memory performance and visceral perception were assessed at t = 12:30 and t = 14:00, respectively. Mood was assessed six times during each test day at t = 8:00, 10:30, 12:30, 14:00, 14:30, and t = 15:00.

### Tryptophan depletion

The Department of Pharmacy of the University Hospital prepared the amino acid mixtures. The tryptophan deficient amino acid (ATD) mixture consisted of 15 amino acids, including five large neutral amino acids (LNAA).\(^21\) The placebo mixture contained the same amino acids plus 3 g of tryptophan in order to prevent a decrease in tryptophan levels.\(^3\) The mixture was dissolved in 200 ml of tap water and

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**Figure 1** Schematic representation of a test day (flow chart).
subjects were instructed to ingest the mixture as quickly as possible.

**Visceral perception**

Bowel preparation consisted of a tap water enema administered one hour before the barostat procedure. The rectal probe was lubricated and placed into the rectum so that the attached end of the bag was 3 cm from the anal sphincter. The probe consisted of a 700 ml polyethylene bag secured on a rectal catheter (external diameter = 18 French). The catheter was connected to the electronic distension device (Electronic Barostat, Distender Series II; G&J Electronics Inc., Toronto, Ontario, Canada) using the Protocol Plus Deluxe Software (G&J Electronics Inc.). The barostat inflation rate was 50 ml/s to a constant pressure plateau. Subjects were not given any auditory or visual clues that they were to receive a stimulus and were not told the exact nature of the distension protocol. To reduce the influence of adipose tissue mass and abdominal wall tone, subjects were all placed in the left lateral decubitus position.

In order to unfold the rectal probe, a five minute 10 mm Hg distension followed by a one minute 20 mm Hg distension was administered. Subsequently, the barostat protocol consisted of intermittent semi-random staircase distensions of 60 seconds duration (15, 10, 25, 20 mm Hg, etc.) separated by an interval of 30 seconds of baseline pressure. The end point to stop the series of distensions was the perceptual threshold for maximal tolerable discomfort or if the safety value of the maximal volume of 600 ml was exceeded. During each distension (after 13 seconds of distension) subjects were asked to report their perception of urge and pain. Urge was scored on a panel (Deluxe Perception Panel; G&J Electronics Inc., Toronto, Ontario, Canada) using the Protocol Plus Deluxe Software (G&J Electronics Inc.). The perceptual threshold for urge was scored on a panel (Deluxe Perception Panel; G&J Electronics Inc., Toronto, Ontario, Canada) using the Protocol Plus Deluxe Software (G&J Electronics Inc.). The barostat inflation rate was 50 ml/s to a constant pressure plateau. Subjects were not given any auditory or visual clues that they were to receive a stimulus and were not told the exact nature of the distension protocol. To reduce the influence of adipose tissue mass and abdominal wall tone, subjects were all placed in the left lateral decubitus position.

In order to unfold the rectal probe, a five minute 10 mm Hg distension followed by a one minute 20 mm Hg distension was administered. Subsequently, the barostat protocol consisted of intermittent semi-random staircase distensions of 60 seconds duration (15, 10, 25, 20 mm Hg, etc.) separated by an interval of 30 seconds of baseline pressure. The end point to stop the series of distensions was the perceptual threshold for maximal tolerable discomfort or if the safety value of the maximal volume of 600 ml was exceeded. During each distension (after 13 seconds of distension) subjects were asked to report their perception of urge and pain. Urge was scored on a panel (Deluxe Perception Panel; G&J Electronics Inc.) with six buttons labelled: 1, not perceptible; 2, first perception; 3, minor urge to defecate; 4, normal urge to defecate; 5, strong urge to defecate; and 6, maximal tolerable urge. Pain was scored using a 100 mm visual analogue scale (no pain–maximal tolerable pain). Rectal volumes were measured at the end of each distension (after 60 seconds of distension). Volume was corrected for air compressibility. Rectal compliance (ΔV/ΔP; P = 10–45 mm Hg) was estimated for each subject.

**Cognition and mood**

The affective memory test consisted of a list of 30 emotionally loaded stimulus words (12 positive, 12 negative, and six neutral). All 30 words on the list were consecutively presented three times on a computer screen. Each presentation of the list ended with a free recall of the words. Recall scores were summed to comprise the total immediate recall score. After the third presentation, subjects performed a 30 minute distraction task and subsequently subjects were requested to recall all of the previously learned words as possible (delayed recall). Outcome measures were the percentages of positive, negative, and neutral words recalled of the total immediate recall and delayed recall score. Mood was assessed with visual analogue scales adapted from the profile of mood states (POMS). It consisted of 32 items describing bipolar mood adjectives (for example, happy–sad). Items were grouped to form measures of five mood dimensions: depression, tension, vigour, anger, and fatigue, respectively.

**Biochemical parameters**

Total plasma tryptophan concentrations and the tryptophan/ΣLNAAs ratios (sum of tyrosine, valine, leucine, isoleucine, and phenylalanine concentrations) were determined. This ratio provides an estimate of tryptophan uptake into the brain and consequently central 5-HT synthesis. In addition, concentrations of platelet 5-HT, platelet poor plasma (ppp) 5-HT, its major metabolite 5-HIAA, and 5-HT turnover (5-HIAA:5-HT) were determined as markers of peripheral 5-HT metabolism. Blood was sampled in EDTA Vacutainer tubes. Samples for tryptophan and LNAAs were immediately placed on ice and centrifuged within 30 minutes (10 minutes, 900 g, 4°C). For platelet 5-HT measurement, whole blood was used. In addition, an aliquot of blood kept at room temperature was used for whole blood platelet counting. Samples for ppp 5-HT and 5-HIAA were kept at room temperature and centrifuged (20 minutes, 2600 g, 20°C). As a control of the ppp preparation procedure, platelets were also counted in the ppp using a Coulter Counter (Coulter MD Series, Coulter Corporation, Hialeah, Florida, USA). All samples were stored at −80°C until analysis. Plasma tryptophan, LNAAs, 5-HT, and 5-HIAA samples were analysed using high performance liquid chromatography, as previously described.

![Figure 2](image1.png)

**Figure 2** Pressure-urge scores (mean (SEM)) during intermittent pressure distension of the rectum in diarrhoea predominant irritable bowel syndrome (d-IBS) patients and control subjects, during acute tryptophan depletion (ATD) and placebo. Overall, ATD did not significantly affect urge scores compared with placebo. However, post hoc analysis indicated that in the lower pressure range, ATD was significantly associated with increased urge scores compared with placebo (p < 0.0001) (10–15 mm Hg).

![Figure 3](image2.png)

**Figure 3** Pressure-pain scores (mean (SEM)) during intermittent pressure distension of the rectum in diarrhoea predominant irritable bowel syndrome (d-IBS) patients and control subjects, during acute tryptophan depletion (ATD) and placebo. Overall, patients showed significantly increased pain scores compared with controls (p = 0.02). ATD was significantly associated with increased pain scores (p = 0.04).
Acute tryptophan depletion and the brain-gut axis

**RESULTS**

**Visceral perception**

**Urge and pain (figs 2, 3)**

Urge and pain scores increased significantly with increasing pressure (F(7, 13) = 199.0, p < 0.0001; F(7, 12) = 7.1, p < 0.01, respectively). For urge scores, there was a strong significant pressure × diagnosis of d-IBS interaction (F(7, 133) = 3.2, p < 0.005), indicating that patients had relatively higher urge scores in the lower pressure range and relatively lower urge scores in the higher pressure range compared with controls (fig 2). Post hoc analysis indicated that in the lower pressure range (10–15 mm Hg), patients had significantly higher urge scores compared with controls (F(1, 26) = 4.6, p < 0.05).

Patients experienced overall significantly more pain compared with controls (F(1, 17) = 4.7, p < 0.05) and their pain scores increased significantly more with increasing pressure compared with controls (pressure × diagnosis of d-IBS interaction) (F(9, 119) = 7.1, p < 0.0001), which confirms the presence of hypersensitivity in our d-IBS population.

Overall, there was a significant pressure × treatment interaction for the perception of urge (F(7, 133) = 3.1, p < 0.01), indicating that in the lower pressure range ATD enhanced the perception of urge whereas this enhancing effect of ATD was no longer present in the higher pressure range (fig 2). Post hoc analysis showed significantly increased urge scores in the lower pressure range (10–15 mm Hg) during ATD compared with placebo (F(1, 26) = 23.6, p < 0.0001).

ATD was significantly associated with increased overall pain scores compared with placebo (F(1, 17) = 3.4, p < 0.05). For the pain scores there was, in contrast with the urge scores, no significant pressure × treatment interaction (p > 0.3), indicating that the effect of ATD was not specific for the higher or lower pressure range (fig 3). The effects of ATD compared with placebo on urge and pain scores did not differ significantly between patients and controls.

**Perceptual thresholds (table 2)**

Patients tended to have lower first perception thresholds compared with controls although this did not reach significance (F(1, 26) = 2.5, p = 0.06). Thresholds for maximal tolerable discomfort did not differ between patients and controls (F(1, 26) = 0.1, p = 0.8).

ATD significantly lowered the perceptual threshold for first perception compared with placebo (F(1, 26) = 9.03, p = 0.003). ATD did not significantly influence the perceptual threshold for maximal tolerable discomfort (F(1, 26) = 0.06, p = 0.8) (table 2). The effects of ATD compared with placebo on perceptual thresholds did not differ significantly between patients and controls (p > 0.4).

**Rectal compliance (fig 4)**

The pressure-volume curves differed significantly between patients and controls (F(1, 20) = 5.7, p < 0.05) (fig 4). There was no significant difference in pressure-volume relation or apparent rectal compliance during ATD compared with

---

**Table 2**

<table>
<thead>
<tr>
<th>Pressure threshold (mm Hg)</th>
<th>d-IBS patients</th>
<th>Controls</th>
<th>ATD vs placebo (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First perception</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATD</td>
<td>10.6 (1.2)</td>
<td>12.6 (1.3)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.6 (0.8)</td>
<td>15.7 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Maximal tolerable discomfort</td>
<td>50.5 (3.6)</td>
<td>50.9 (3.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>ATD</td>
<td>51.6 (3.3)</td>
<td>48.8 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 4**

Pressure-volume curves (mean (SEM)) during intermittent pressure distension of the rectum in diarrhoea predominant irritable bowel syndrome (d-IBS) patients and control subjects, during acute tryptophan depletion (ATD) and placebo. Patients showed significantly decreased rectal volumes compared with controls (p = 0.02). ATD did not significantly influence pressure-volume relations.
placebo (F(1, 20) = 0.09, p = 0.8; F(1, 26) = 0.03, p = 0.9, respectively).

Cognition and mood (table 3)

Immediate and delayed memory performance as well as percentages of recalled positive and negative words did not significantly differ between patients and controls (p>0.3). However, patients tended to have greater loss of delayed recalled neutral words compared with controls (F(1, 26) = 9.5, p = 0.06) (table 3).

ATD was significantly associated with impaired immediate and delayed recall performance (F(1, 26) = 3.3, p<0.05; F(1, 26) = 9.5, p<0.005, respectively) compared with placebo. Impaired delayed recall was due to impaired recall of positive words (F(1, 26) = 10.7, p<0.005). Delayed recall of negative and neutral words was not significantly affected by ATD.

ATD did not differentially affect the patient or control group (p>0.3). There were no significant differences in mood between groups or treatment conditions (p values >0.2).

Biochemical parameters (table 4)

Biochemical parameters did not differ significantly between groups or treatment conditions at baseline. There were no significant correlations between baseline biochemical values and perception scores under placebo conditions. Tryptophan/sigma neutral amino acids (LNAAs) ratios decreased significantly over time during ATD compared with placebo (F(1, 26) = 252.5, p<0.0001; F(1, 26) = 164.8, p<0.0001, respectively). ATD did not significantly influence platelet 5-HT or ppp 5-HT concentrations (table 3). 5-HIAA concentrations and ppp 5-HT turnover decreased significantly under ATD conditions compared with placebo (F(1, 26) = 338, p<0.0001; F(1, 26) = 11, p<0.01, respectively). The change in biochemical parameters induced by ATD did not significantly differ between patients and controls (p>0.5) although a trend towards a differential effect of ATD on ppp 5-HT concentrations was observed (F(1, 26) = 32, p = 0.09).

**DISCUSSION**

We have demonstrated for the first time that acute tryptophan depletion (ATD) affects both visceral perception and cognition in d-IBS patients and healthy controls. In addition, we have described an experimental model which can detect changes in the “brain-gut axis” due to acute alteration of serotonergic activity.

The role of specific 5-HT modulators, mainly 5-HT3 antagonists and 5-HT4 agonists, in visceral perception has been the subject of earlier studies. However, it is not feasible to compare our results with studies using receptor specific 5-HT modulators as both at the CNS as well as the gastrointestinal level 5-HT interacts with a number of different 5-HT receptor subclasses that are either stimulatory or inhibitory. It is not known how ATD specifically influences these subreceptors. Data concerning the role of the...
Acute tryptophan depletion and the brain-gut axis

In addition, animal studies have shown that an ATD lowers central 5-HT synthesis and our findings of ATD resulted in large variations in our pain data. Threshold for maximal tolerable discomfort. Hence this a pressure dependent effect for the perception of pain may rectal afferents. Apart from this biological reason, the lack of excitability can be overcome by activation of nociceptive controls. In our opinion however affective memory bias may mood status, using the POMS, in IBS patients or healthy validation and may have consequences in the clinical practice in the neurophysiology of visceral perception needs further study. Although it is of interest to know whether pharmacological and metabolic serotonergic modulation primarily acts at the CNS or peripheral level, one has to keep in mind that the brain-gut axis consists of bidirectional neurohumoral pathways and hence modulation at one level may affect various levels of the brain-gut axis. Increased postprandial ppp 5-HT levels in d-IBS patients and increased numbers of 5-HT containing EC cells in PI-IBS have been observed. This seems paradoxical to our findings of decreased 5-HT levels associated with enhanced visceral perception. Increased postprandial ppp 5-HT levels have been associated with postprandial symptomatology in d-IBS. However, we did not show increased ppp 5-HT levels in d-IBS. This can be explained by analytical and methodological differences as well as the fact that the subjects in our study were fasted of any nutrients during the five hours before the assessment of visceral perception and ppp 5-HT. Our results suggest a different, although not significant, effect of ATD on ppp 5-HT levels between patients and controls. This may support evidence concerning disturbed serotonergic metabolism in the d-IBS subgroup type of IBS. Dunlop et al showed that increased EC cells as well as depression are equally important independent predictors of developing PI-IBS. Gastrointestinal motility may be primarily peripherally determined and our study does not solve the contribution of central versus peripheral 5-HT in the role of altered motility and perception in IBS. Recently, two tryptophan hydroxylase (rate limiting enzyme of 5-HT synthesis) isoforms have been identified which differentially modulate peripheral and central 5-HT effects. This duality of the 5-HT system may open new avenues for specific investigational and therapeutic approaches exclusively affecting central or peripheral 5-HT actions.

The time window of ATD induced metabolic activity at the CNS level may differ from that at the gut level. However, our cognitive and biochemical results indicated that ATD influenced both the CNS as well as the periphery during our experiments. Our results concern the change in brain-gut interaction due to an acute decrease in serotonergic activity. Whether these findings are also valid in prolonged changes in serotonergic activity by pharmacological or nutritional means needs to be investigated. We did not find a significant effect of ATD on rectal compliance. Although our barostat protocol was primarily designed to detect changes in visceral perception, this suggests that acute changes in serotonergic activity differentially affect visceral perception and rectal compliance. The ATD model mimics characteristics of IBS in healthy controls. During ATD, healthy controls had urge scores comparable with those of patients in the placebo condition.
The fact that ATD did not increase pain scores in the control group to levels observed in the patient group suggests that pain and urge perception are different entities.

Our results support further study of the effect of serotonergic modulation on the brain-gut interaction in IBS. We have provided evidence that serotonergic modulation by ATD affects both visceral perception as well as cognition in d-IBS patients and controls. Simultaneous measurement of brain and gut function and application of ATD may contribute to elucidation of the complex pathophysiology of IBS.

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