

Serotonin in gastrointestinal disorders

Citation for published version (APA):

Keszthelyi, D. (2023). Serotonin in gastrointestinal disorders: Delineating Peripheral vs Central Effects. *Gastroenterology*, 164(6), 1027-1028. <https://doi.org/10.1053/j.gastro.2022.10.026>

Document status and date:

Published: 01/05/2023

DOI:

[10.1053/j.gastro.2022.10.026](https://doi.org/10.1053/j.gastro.2022.10.026)

Document Version:

Version created as part of publication process; publisher's layout

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

CORRESPONDENCE

Readers may submit letters to the editor concerning articles that appeared in *Gastroenterology* within one month of publication. Detailed guidelines regarding the content are included in the Instructions to Authors.

Serotonin in Gastrointestinal Disorders: Delineating Peripheral vs Central Effects

Dear Editors:

I read with interest the article by Truyens et al¹ reporting on the results of a trial of 5-hydroxytryptophan (5-HTP), the direct precursor of serotonin, aimed at reducing fatigue in IBD patients in remission. The authors hypothesized that 5-HTP, which can readily cross the blood-brain barrier, in contrast to serotonin, would boost serotonergic signaling in the brain and thereby decrease symptoms of fatigue.

This is a much-welcome study, allowing more insight into the biologic roles of serotonin in gastrointestinal disorders. The study, however, did not provide evidence for an added effect of 5-HTP above placebo as far as fatigue is concerned. Some important aspects, however, in terms of interpreting the results were not addressed in the article¹ or the accompanying editorial.²

The study regrettably did not determine the effects of the intervention in the gastrointestinal mucosa. This would have necessitated retrieval of mucosal biopsy samples. Most serotonin biosynthesis (90%) can be attributed to the gastrointestinal tract. The 5-HTP administered undergoes metabolism in the intestinal mucosa by action of the aromatic amino acid decarboxylase, abundantly present in intestinal epithelial cells.³ Even bacteria possess this enzyme that can accept 5-HTP as a substrate.⁴ An increase in intestinal serotonin can therefore be assumed, and this will spill over to the systemic compartment. This is reflected by the increased serum levels of serotonin after 5-HTP administration, as described by the authors. Furthermore, most of the serotonin circulating in the systemic compartment is stored in platelets, because they also express the serotonin transporter SERT. For this reason, “free” serotonin levels are generally measured using platelet-poor plasma, which can be produced by centrifuging blood samples at lower gravitational forces, leaving platelets intact.⁵

It may very well be the case that the increase in mucosal serotonin has opposite effects compared with 5-HTP crossing the blood-brain barrier to yield serotonin in the brain. Indeed, the authors were cautious in not raising the 5-HTP dose too high because this could result in visceral hypersensitivity.⁶ Therefore, the peripheral and central effects could in fact have “canceled” each other out.

Theoretically, one can inhibit the amino acid decarboxylase enzyme whereby conversion of 5-HTP to serotonin in the mucosa is limited. This way, higher concentrations of 5-HTP can reach the brain as it escapes conversion in the periphery. The same principle is applied in the treatment of Parkinson’s disease when levodopa, the precursor of dopamine, is co-administered with a peripheral decarboxylase

inhibitor, such as benserazide or carbidopa, to increase dopamine availability in the brain. These inhibitors cannot cross the blood-brain barrier and therefore have no effect on the enzymatic conversion in the brain.

An earlier study in healthy volunteers showed that single-dose administration of 100 mg 5-HTP with carbidopa resulted in a 15-fold higher serum concentration of 5-HTP than 100 mg without carbidopa and 7-fold higher than 200 mg without carbidopa.⁷ It would therefore be interesting to assess the effects of 5-HTP administered in combination with such an enzyme inhibitor to tease out peripheral and central effects of increased serotonin production.

Another important readout from the current trial is that fatigue improved regardless of the intervention (5-HTP or placebo) given. It would therefore be worthwhile examining what the differences were between the “care” provided within the constraints of the trial vs “care as usual” that would have been given in a regular outpatient setting. The authors did not specify how often trial participants were contacted either in person, by phone, or digitally during the study period. Is the improvement merely attributable to the placebo response of taking a pill or should we invest in examining the type of support that can have the greatest impact on patients’ well-being, more specifically fatigue? This appears particularly relevant, because the context in which a treatment is given probably outweighs the benefits of mere pharmacologic effects.

DANIEL KESZTHELYI

Department of Internal Medicine
Division of Gastroenterology-Hepatology
Maastricht University Medical Center
Maastricht, the Netherlands

References

1. Truyens M, et al. *Gastroenterology* 2022.
2. Pekow J. *Gastroenterology* 2022.
3. Fernandez-Reina A, et al. *Foods* 2018;7.
4. Sugiyama Y, et al. *Gut Microbes* 2022;14.
5. Brand T, et al. *Clin Chem* 2011;57:1376–1386.
6. Keszthelyi D, et al. *Neurogastroenterol Motil* 2015; 27:1127–1137.
7. Gijsman HJ, et al. *J Clin Psychopharmacol* 2002; 22:183–189.

Conflicts of Interest

The author discloses the following: Daniel Keszthelyi received research funding from Allergan, Will Pharma, Grunenthal, MLDS, UEG, Horizon 2020, Rome Foundation, and ZonMw and speaker’s fee from Dr Falk (paid to institution).

<https://doi.org/10.1053/j.gastro.2022.10.026>