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Serotonin in the gut: what does it do?

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A commentary on

Essential roles of enteric neuronal serotonin in gastrointestinal motility and the development/survival of enteric dopaminergic neurons
by Li, Z., Chalazonitis, A., Huang, Y.-Y., Mann, J. J., Margolis, K. G., Yang, Q. M., Kim, D. O., Côté, F., Mallet, J., and Gershon, M. D. (2011). J. Neurosci. 31, 8998–9009

For decades, it has been widely believed that serotonin has a major role in regulating gastrointestinal (GI) function for review see Gershon and Tack (2007). This belief is based on a huge number of different findings. These include the well known observation that most of the body's serotonin is synthesized and stored in the intestine, the presence of many different serotonin receptors within the intestinal wall and a plethora of observations of altered intestinal behavior following treatment with exogenous agonists and antagonists. However, despite a mountain of evidence, the actual roles of serotonin in the GI tract have been maddeningly difficult to identify.

Reasons for this failure include that there are both neural and mucosal sources of serotonin within the gut and the widespread and overlapping distribution of specific serotonin receptor subtypes. As an example, the Dogiel type II neurons that are probably intrinsic sensory neurons (or intrinsic primary afferent neurons Furness et al., 2004) express 5-HT_3 receptors, 5-HT_{1A} receptors, 5-HT_4 receptors, and 5-HT_7 receptors (Neal and Bornstein, 2006). Other myenteric neurons express 5-HT_3 and 5-HT_4 receptors and there is strong evidence that 5-HT_3 receptors mediate fast excitatory synaptic potentials in some enteric neurons (Zhou and Galligan, 1999; Monro et al., 2004). 5-HT_3 receptors are expressed by the mucosal terminals of the intrinsic sensory neurons (Bertrand et al., 2000; Bertrand and Bornstein, 2002) and mucosal application of serotonin activates local reflex pathways via 5-HT_3 receptors (Gwynne and Bornstein, 2007) and enhances peristalsis via the same receptors (Tuladhar et al., 1997). Thus, any antagonist used to study the role of serotonin during complex behaviors will act at several different sites in the enteric circuitry.

Several attempts to answer this question have focused on mucosal serotonin in the mouse colon. The approach has been surgical removal of colonic mucosa prior to analysis of a stereotyped motor pattern, the colonic migrating motor complex (CMMC), which is diminished by blocking 5-HT_3 receptors. The idea is simple: remove mucosal serotonin and if CMMCs persist then they cannot depend on release of serotonin from mucosal stores. If CMMCs are eliminated then mucosal serotonin may have a role. Clearly this depends on the dissection. Complete removal is essential, but if the neural circuit mediating CMMCs is damaged, then loss of CMMCs might not result from loss of mucosal serotonin. Given these technical issues, it is unsurprising that two groups recently published completely opposite results from essentially the same experimental protocol. Keating and Spencer (2010) reported that CMMCs persist after complete removal of the mucosa and confirmed that the surgery had been effective using amperometry to detect residual serotonin release. Importantly, the CMMCs were sensitive to 5-HT_3 receptor blockade, presumably at synapses within the enteric neural circuitry. Heredia et al. (2009) reported that removal of colonic mucosa abolished spontaneous CMMCs, but could still trigger CMMCs mechanically confirming that the neural circuitry was intact. The latter observation has since been confirmed by Zagorodnyuk and Spencer (2011). We were thus left with considering minor technical details or trying to decide whose dissection was best.

The picture changed dramatically with a very recent paper by Li et al. (2011) in the Journal of Neuroscience. They used knockouts of tryptophan hydroxylase 1 (TPH1), the rate limiting enzyme for mucosal synthesis of serotonin, and TPH2 (the neural form) to selectively delete serotonin from the two possible sources. Crosses eliminated all serotonin, in contrast to all previous studies [e.g., Yadav et al. (2008)]; surprisingly, even these were viable. The TPH1 knockouts did not differ from the wild type in any function measured, including gastric emptying, total intestinal transit, and colonic motility (expulsion of a glass bead). By contrast, TPH2 knockouts had major changes in each function; the double knockouts were indistinguishable from TPH2 knockout mice. Another mediator may substitute for serotonin in TPH1 knockouts. However, without a likely candidate for a compensatory mediator, the conclusion is inescapable that mucosal serotonin has a very minor role in regulation of GI motility in the mouse, while neural serotonin may have a much more substantial role than previously believed.

The results of Li et al. (2011) leave the function of serotonin in limbo, with several of the more popular roles excluded, at least in the mouse. While it seems highly likely that release of serotonin acts to transduce chemical and mechanical stimuli acting at the level of the mucosa (for recent review Bertrand (2009)), the results of Li et al. (2011) indicate that this is not needed for normal function. Perhaps mucosal serotonin only plays a significant role after some kind of pathophysiological insult, like inflammation. On the other hand, neuronal serotonin is clearly required for normal function, although part of this might be an indirect effect on development of the enteric neural circuitry. This is because Li et al. (2011) also showed that enteric neural development was disturbed in the TPH2 knockout mice. Further, expression of a low activity form of TPH2 in Balb/cJ mice is associated with synaptic connections that differ subtly from those in the C57/Bl6 strain, which has a high activity form of TPH2 (Neal et al., 2009).

Clearly, the role of mucosal serotonin remains enigmatic and requires further study, especially as this is the source

for all circulating serotonin. Frontiers in Autonomic Neuroscience would like to issue a broad challenge for scientific discussion in a Research Topic on the role of serotonin in the periphery, both in the GI tract and the rest of the autonomic nervous system. A call for preliminary submissions will appear soon.

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