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Serotonin and Colonic Motility

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Abstract

The role of serotonin (5-HT) in gastrointestinal motility has been studied for over 50 years. Most of the 5-HT in the body resides in the gut wall, where it is located in subsets of mucosal cells (enterochromaffin cells) and neurons (descending interneurons). Many studies suggest that 5-HT is important to normal and dysfunctional gut motility and drugs affecting 5-HT receptors, especially 5-HT_3 and 5-HT_4 receptors, have been used clinically to treat motility disorders. However, cardiovascular side effects have limited the use of these drugs. Recently studies have questioned the importance and necessity of 5-HT in general and mucosal 5-HT in particular for colonic motility. A paper published in this issue of *Neurogastroenterology and Motility* examines the importance of 5-HT_3 and 5-HT_4 receptors to initiation and generation of one of the key colonic motility patterns, the colonic migrating motor complex (CMMC), in rat. The findings suggest that 5-HT_3 and 5-HT_4 receptors are differentially involved in two different types of rat CMMCs: the long distance contraction (LDC) and the rhythmic propulsive motor complex (RPMC). The understanding of the role of serotonin in colonic motility has been influenced by the specific motility pattern studied, the stimulus used to initiate the motility (spontaneous vs. induced), and the route of administration of drugs. All of these considerations contribute to the understanding as well as the controversy that continues to surround the role of serotonin in the gut.

Keywords

5-hydroxytryptamine; 5-HT receptors; colonic migrating motor complex; motility reflexes; rat colon

INTRODUCTION

Serotonin (5-Hydroxytryptamine or 5-HT) has long been postulated to play a major role in gut function, since its initial isolation and localization to enteroendocrine cells by Erspamer in 1937.[1] Its association with gut motility arose out of pioneering studies from the lab of Edith Bülbring which appeared in a series of papers in 1958 and 1959. These studies demonstrated that 5-HT is released in response to increased intraluminal pressure and that 5-HT is able to initiate the peristaltic reflex and propulsive motility.[2–4] In the last 55-plus

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DISCLOSURE

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years, the history of serotonin has been one of ups and downs ranging from intense favor, to bland acceptance, to disfavor. It has been touted as a primary agent to treat dysmotility, while being discarded from pharmacological usefulness because of its cardiovascular side effects. What has not been lacking is consistent controversy and interest in defining the precise role of serotonin and its receptors in initiating and/or maintaining gut motility. To wit, there have been, on average, 105 articles/year published on serotonin and the GI tract since the original publications of Bülbring, including many recent comprehensive reviews.[5–9]

Among the controversies that surround the role of serotonin in gut motility, are the questions of whether mucosal or neuronal 5-HT is necessary for the initiation or propagation of propulsive contractions, and which receptors are involved. This in part derives from the multiple sources of and receptors for serotonin, the experimental approaches, the definition of motility patterns, and the site of origin of the motility pattern. Considering the wealth of studies and approaches, there are two main viewpoints of the initiation of propulsive motility: 1) patterns that arise as a result of a luminal stimulus such as increase in pressure, mucosal mechanical stimulation, or the presence of a nutrient or toxic substance and 2) patterns that arise spontaneously as the result of activity in enteric neurons and/or networks of the Interstitial Cells of Cajal (ICC).

SEROTONIN LOCALIZATION AND SEROTONIN RECEPTORS IN THE GUT

The characteristics of the serotonin system have been extensively discussed in the review articles noted above, but the key points bear highlighting. Serotonin is present in the gut in two main sources: the enterochromaffin (EC) cells of the mucosa, which contain the vast majority of serotonin, and myenteric neurons that project in descending pathways. These two sources of serotonin can be differentiated not only by their cellular location but by their different synthetic pathways. 5-HT synthesis from L-tryptophan in EC cells of the mucosa is mediated by the rate-limiting enzyme tryptophan hydroxylase 1 (TPH1); whereas, neuronal 5-HT synthesis is mediated by the rate-limiting enzyme tryptophan hydroxylase 2 (TPH2). This difference has been exploited in recent studies of the differing role(s) of mucosal and neuronal serotonin in motility.[10–13] Serotonin-containing neurons, although small in number (about 2% of all myenteric neurons) have broad, diverse projections which suggest a role in initiating and/or modulating gut motility.[14] Among the myriad projections the most potentially significant to gut motility are projections to other serotoninergic neurons forming a descending network of serotoninergic neurons, to nitric oxide synthase (NOS)-containing neurons which are the main inhibitory neurons of the myenteric plexus, and to ICC networks.

Serotonin, regardless of its source, interacts with a variety of receptors present in the gut. Although there are 7 subtypes of serotonin receptors and multiple variants of each subtype, 5-HT_3 and 5-HT_4 receptors have been most widely studied with regard to gut motility leading to their potential use clinically.[15,16] Recently, 5-HT_7 receptors have also been implicated in the regulation of colonic motility; however, much less is known about their specific physiological role and therapeutic usefulness.[17] 5-HT_3 receptors are ligand-gated ion channels; whereas, 5-HT_4 receptors are G-protein coupled receptors. Both are present on

various classes of neurons within the myenteric and submucosal plexuses, intrinsic and extrinsic sensory neurons, and EC cells. This widespread presence of 5-HT receptors, including additionally their presence on smooth muscle cells and ICCs, and localization of serotonin on key components (both mucosal and neuronal) of motor circuits has contributed to the continued interest in serotonin as an initiator and/or modulator of motility. It has also led to the continued development of pharmacological agents to exploit this notion. Antagonists of the $5\text{-}HT_3$ receptor have been used to treat diarrhea and abdominal pain, presumably through actions at $5\text{-}HT_3$ receptors on intrinsic neurons that stimulate propulsive motility and extrinsic sensory neurons that signal pain and discomfort.[18,19] Conversely $5\text{-}HT_4$ receptor agonists have been used to treat constipation, presumably by increasing release of 5-HT itself from mucosal EC cells and by stimulation of both peristaltic reflex pathways and secretion.[19–21] Although each has been used effectively, these pharmacological agents have been limited in their current use because of deleterious side effects resulting from secondary actions and effects on other systems. This has spurned the continued development of newer, more selective agonists and antagonists and maintained interest in understanding the precise mechanism of action of serotonin and the elucidation of receptor subtype involvement in specific 5-HT actions.

THE PERISTALTIC REFLEX, PERISTALSIS, AND MUCOSAL SEROTONIN

As noted above, the earliest studies of Bülbring raised the notion that luminal stimuli released from mucosal enterochromaffin (EC) cells initiated the peristaltic reflex; however, failure to completely eliminate mucosal 5-HT stores with the tools available left open the possibility that 5-HT was not an absolute requirement. Subsequent studies by a variety of labs over the last half-century have essentially come to the same conclusion. The evidence in favor of the primary role of mucosal serotonin can be summarized as follows: (i) serotonin is release by mucosal mechanical and chemical (nutrient) stimuli,[22–24] (ii) agonists of the $5\text{-}HT_3$ and/or $5HT_4$ receptor applied to the mucosa or perfused intraluminally induce or augment peristalsis and propulsion; whereas, (iii) antagonists of $5\text{-}HT_3$ and/or $5HT_4$ receptors inhibit the generation of the peristaltic reflex induced by mucosal stimuli.[25–27] It seems reasonable to conclude that 5-HT released from EC cells is capable of inducing the mucosal peristaltic reflex and hence propulsive peristalsis. This is especially true in the case of nutrient-induced propulsion where nutrient presumably does not have rapid access to submucosal sensory neurons. In the case of nutrient-induced motility, 5-HT has been implicated in the peristaltic and segmental response to short and medium chain fatty acids.[24,28,29] It is noteworthy that while nutrient receptors are evident on cells they are also expressed by a variety of enteroendocrine cells which release a multitude of neurohumoral agents depending on the region of the gut.[30,31] It is likely therefore that even in terms of mucosal stimulation, there will be different mediators released in response to different luminal nutrients and that 5-HT will not be released by all luminal stimuli.[24] Thus, determining the agent released by the activation of a specific nutrient receptor and motility pattern caused by these events are important details which need to be determined moving forward.

While there has been a general acceptance that 5-HT is important to colonic motility, especially mucosally initiated motility, the debate over the relative importance of mucosal to

neuronal 5-HT has been re-ignited through studies that either manually remove the mucosal and submucosal layers of the colonic wall or through mice in which mucosal 5-HT synthesis has been selectively blocked pharmacologically or genetically.[11–13,32–35] The latter is possible since as noted above 5-HT synthesis in EC cells of the mucosa is mediated by TPH1; whereas, neuronal 5-HT synthesis is via TPH2. In these preparations with compromised mucosal 5-HT, pellet propulsion and GI transit were not abolished suggesting that mucosal 5-HT is not necessary for propulsion and that there are other mechanisms that can maintain propulsion in the absence of mucosal 5-HT. In these studies, mucosal reflexes themselves were either not possible to examine (mucosal removal) or not examined (peripheral TPH1 inhibitors, TPH2$^{-/-}$ mice). The initiation of propulsive motility in these cases could have been by two mechanisms: peristaltic reflexes initiated by distension or muscle stretch, or spontaneous propulsive contractions generated within the neural network. The former is in agreement with earlier studies demonstrating that the muscle stretch-induced peristaltic reflex is initiated in mucosa free preparations, is not accompanied by 5-HT release and is not blocked by 5-HT receptor antagonists.[22,36,37] It is likely that these stretch-induced responses are mediated by stretch-sensitive myenteric interneurons and/or extrinsic afferent neurons with collaterals projecting to myenteric motor circuits.[36,38] It is interesting that in a recent study, fecal pellets from TPH1$^{-/-}$ knockout mice were larger in size than normal pellets and that thinner artificial pellets were not propelled.[12] This suggests that in the absence of mucosal serotonin, greater stretch/distension is required for pellet propulsion. The other mechanism for initiation of propulsive motility, which can exist in the absence of mucosal 5-HT, is a spontaneous propulsive motility originating in the proximal colon which is known as the Colonic Migrating Motility Complex (CMMC). This motility pattern has also been a topic of intense investigation by several laboratories and the subject of a recent comprehensive review.[9] In the current issue of *Neurogastroenterology and Motility*, the paper by Yu et al [39] examines the generation and propagation of spontaneous propulsive contractions in the rat colon with regard to the role of 5-HT and its receptors. This study provides insight into the differential regulation of spontaneous propagating waves that progress through the entire colon as opposed to those that arise midway through the colon and propagate shorter distances.

COLONIC MIGRATING MOTOR COMPLEXES AND SEROTONIN

The colonic migrating motor complex is a rhythmic contraction that is propulsive and which moves through the colon. It can be generated in response to intraluminal mucosal stimuli but can also be generated in the absence of luminal stimuli[9,22] It is however dependent on the enteric nervous system since hexamethonium abolishes the CMMC.[23,40] Serotonin is also intimately involved in the CMMC; however, the nature of the dependence on mucosal versus neuronal serotonin and the role of specific serotonin receptors remains a point of debate. It is important to note that while CMMCs have been described in many mammalian species and often go by different names, they have been most extensively studied in the mouse.[9,17,23,32–34,42–44] CMMCs are also present in the rat, although much less studied than in the mouse.[41] Chen and colleagues previously described two different types of CMMCs in the rat large intestine, namely long-distance contractions (LDCs) and rhythmic propulsive motor complexes (RPMCs). In the rat, both are neurally-mediated and dependent on the

intrinsic pacemaker Interstitial Cells of Cajal (ICC). Both patterns are rhythmic in nature but LDCs are pan-colonic in distance of propagation; whereas, RPMCs tend to propagate across only the mid- to distal colon. The relationship between these specific patterns of motility in different species remains unclear as does their relation to motility seen in human preparations. It is currently unclear which type of rat CMMC is equivalent to the mouse CMMC, if equivalent at all. Mouse CMMCs do not seem to require any form of luminal distension, although they become more regular with luminal distension.[23] Whether the rat CMMCs require some intraluminal pressure/distension to be initiated has not been directly examined although studies to date in rat colon have all been performed in the presence of some level of luminal distension.[39,41] The paper by *Yu et al* in the current issue of *Neurogastroenterology and Motility* expands the previous work of Chen et al by investigating the differences in generation of LDCs and RPMCs in the rat colon through the use of 5-HT receptor agonists and antagonists.[39]

Yu and colleagues studied the importance of 5-HT to both LDCs and RPMCs through the use of bath application of a variety of 5-HT_3R and 5-HT_4R agonists and antagonists to intact rat colonic preparations. Through the use of spatiotemporal mapping, changes in the frequency, duration, propagation velocity, and starting point of propagating motility patterns were visualized and quantified. LDC frequency was reduced by 5-HT itself, a 5-HT_3 receptor agonist (m-CPBG), and 5-HT_3 antagonists (ondansetron, granisetron). LDC frequency and propagation length were reduced by 5-HT_4 receptor agonists (mosapride, prucalopride); whereas, the 5-HT_4 antagonist, GR125487, reduced LDCs and converted them to tandem or interrupted patterns. The LDCs most closely resemble the CMMCs in the mouse in that they originate in the proximal colon and propagate the entire length of the colon. In the present study, the authors also studied the role of serotonin receptors in the related motility pattern, the RPMC. The relationship of this pattern to motility seen in other species is not as clear. Both 5-HT_3 agonists and antagonists reduced RPMC frequency, but 5-HT itself had no effect. Spontaneous RPMC frequency and propagation length were increased by 5-HT_4 agonists; however, the 5-HT_4 antagonist had a variable but non-significant effect on spontaneous RPMCs. These studies suggest that 5-HT_3 and 5-HT_4 receptors are involved in either the initiation or maintenance of spontaneous LDCs. In contrast, spontaneous RPMCs require only 5-HT_3 receptor activation.

These results lead to some interesting questions on the role of 5-HT in rat CMMCs related to both generation and modulation. The fact that an agonist and antagonist can both induce the same effect on LDCs is on the surface surprising, but illustrates the difficulty in interpreting results in intact organs in which multiple serotonin pathways and receptor exist. In the case of this study, the authors suggest that the action of the 5-HT receptor antagonists on LDCs is the result of inhibition of endogenous neural 5-HT released during LDC generation. This 5-HT is thought to interact with the ICC network and reflects actions of 5-HT on 5-HT_3 and 5-HT_4 receptors in an excitatory pathway. In contrast, the ability of exogenous 5-HT, 5-HT_3 agonist and 5-HT_4 agonists to also inhibit LDCs reflects stimulation of 5-HT_3 and 5-HT_4 receptors in inhibitory pathways. These inhibitory pathways presumably contain inhibitory nitrergic neurons that normally restrain or regulate the frequency of CMMCs, although the exact role of nitrergic neurons in the CMMC remains uncertain.[43,44] The addition of agonist

could also partly result from desensitization of serotonin receptors, which is well known to interfere with peristalsis.[45] This also illustrates how exogenous agonist application induces simultaneous activation of multiple pathways and may not accurately reproduce the sequential and specific sites of activation occurring *in vivo*.

Most of what we know about 5-HT involvement in CMMCs comes from studies in the mouse. Heredia and colleagues found a reduced frequency of CMMCs and a dysregulation of CMMC directionality in TPH1$^{-/-}$ mice, suggesting that mucosal 5-HT is involved in generation and modulation of mouse CMMCs[12]. Application of the 5-HT$_3$ receptor antagonist, ondansetron, inhibited spontaneous CMMC generation in the normal mouse, which the authors suggest is an effect on mucosal processes of intrinsic primary afferent neurons (IPANs) or serotonergic interneurons.[12] Ondansetron, however, had no effect on the amplitude of spontaneous CMMCs in the TPH1$^{-/-}$ mouse. In light of the lack of effect of ondansetron in the TPH1$^{-/-}$ mouse, these results suggest the effects of ondansetron in the normal mouse are related to mucosal 5-HT. CMMCs induced by balloon distension (involving both mucosal stimulation and circumferential stretch) were reduced by ondansetron application or reduction in mucosal 5-HT in TPH1$^{-/-}$ mice. CMMCs could not be initiated by mucosal stimulation alone in TPH1$^{-/-}$ mice.[12] Thus, even specifically in relation to CMMCs the relative importance of 5-HT, especially from the mucosa, varies with the stimulus. Studies of CMMCs have not been performed in TPH2-KO mice, although these would be important in directly resolving the question regarding the role of neuronal 5-HT in mediating the CMMC. The current paper by Yu et al. provides the only in-depth studies on the importance of 5-HT to rat CMMCs.[39] The results suggest that 5-HT, and 5-HT$_3$ and 5-HT$_4$ receptors are also important in rat CMMCs, but the experiments do not distinguish between mucosal and neuronal 5-HT. Even though the agonist and antagonists were delivered by bath application, presumably affecting primarily 5-HT receptors in the myenteric plexus (i.e., neuronal and/or ICC), the use of luminal distension to initiate colonic motility likely also affected 5-HT release from EC cells due to mucosal deformation. Thus, the importance of mucosal 5-HT in rat CMMCs is still unknown. It is interesting to note that rat CMMCs seem to require at least an initial luminal distension of the preparation to be initiated in the isolated rat colon. It is possible that this distension releases mucosal 5-HT important to CMMC generation, which would be in agreement with the work on mouse CMMCs.

CONCLUSIONS AND UNANSWERED QUESTIONS

While the current study certainly suggests that 5-HT$_3$ and 5-HT$_4$ receptors are involved in the generation of CMMCs in rat colon, it also raises more questions about the role of 5-HT. The answers to the many critical questions are likely to require the combined efforts of multiple groups using a variety of experimental techniques. For instance, the relative importance of mucosal versus neuronal 5-HT remains to be clarified. The answer to this is likely dependent on the type and location of the stimulus, or in the case of spontaneous motility, the lack of a stimulus. Similarly, studies in mice and rat as well as other species clearly implicate 5-HT$_3$ and 5-HT$_4$ receptors in CMMCs; however, the exact location of these receptors and their relative roles in the process (e.g., initiation versus propagation) remains to be determined with certainty. While the debate on the relative importance and

exact role of 5-HT will probably continue for many years it is clear that the path to determining the importance of 5-HT has been both long and interesting.

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KEY MESSAGES

- The role of serotonin in colonic motility depends on the type and location of the stimulus.
- Serotonin promotes colonic motility via activation of multiple receptor subtypes.
- The relative roles of mucosal and neuronal serotonin in different motility patterns and in different species remains controversial.