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## The importance of neuronal serotonin in colonic motor patterns

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5-hydroxytryptamine (5-HT, serotonin) has two sources in the gut, descending myenteric 5-HT interneurons (~5% of all 5-HT) and enterochromaffin (EC) cells (~95% of 5-HT). 5-HT is synthesized by the rate limiting enzyme tryptophan hydroxylase (TPH); TPH1 in EC cells and TPH2 in EC cells. In the colon, these two pools of 5-HT appear to be connected by intrinsic primary afferent neurons (IPANs) that have sensory endings in the mucosa and synapse with 5-HT interneurons. The prominent inhibitory effects of 5-HT<sub>1A/2B/3/4</sub> and 7 receptor antagonists on colonic motility suggests that many of these receptors are on various cell types including glia that are largely activated by 5-HT interneurons. Major motility patterns in the colon involving 5-HT include tonic inhibition of the muscle layers interrupted by rhythmic peristaltic waves called colonic migrating motor complexes (CMMCs) and secretomotor activity and possibly blood flow. In large mammals (e.g. Dog, pig and human colon) 5-HT neurons occur in both the myenteric plexus and the extensive Henle's plexus, that synapse with secretomotor neurons in Meissner's plexus. Henle's plexus also provides a motor innervation to submucosal pacemaker cells that generate slow waves. Some 5-HT neurons also project to prevertebral ganglia suggesting they are viscerofugal neurons that they can activate postganglionic sympathetic neurons, whose terminals surround 5-HT neurons. We propose that asynchronous firing in 5-HT neurons excite inhibitory motor neurons (IMNs) to generate tonic inhibition and suppress pacemaker activity. In contrast, 5-HT released from EC cells activates IPANs that synchronizes 5-HT neurons. Synchronized firing of 5-HT neurons likely activates glial cells, which release PGE<sub>2</sub>, that switch off IMNs and remove tonic inhibition. Synchronized 5-HT neurons also likely generate a slow excitatory postsynaptic potential (sEPSP) in IPANs by activating 5-HT<sub>7</sub> receptors that generate CMMCs that in turn excite excitatory motor neurons and pacemaker cells.

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