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CROSSTALK

Rebuttal from Terence K. Smith and Michael D. Gershon

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The question at hand is whether 5-HT is necessary for peristalsis. Smith & Gershon (2015) have marshalled experimental evidence that makes a compelling case for the necessity of 5-HT. Spencer *et al.* (2015) rebut none of that evidence but advance an argument that refutes a straw man of assertions that no one has made. 5-HT receptors are arbitrarily assigned constitutive activity so that antagonists can be called inverse agonists with no supporting data. Spencer *el al.* also use an *ad hominem* attack to denigrate contrary observations which are dismissed as the result of an inadequate number of experiments that have been performed incorrectly. In fact, the mucosa was removed from over 80 preparations without ever observing a spontaneous colonic migrating motor complex (CMMC), yet ongoing neural activity of the myenteric plexus was preserved (Heredia *et al.* 2009; Bayguinov *et al.* 2010; Dickson *et al.* 2010).

Moreover, it is not new that mucosal removal, or mucosal asphyxiation or anaesthetization, abolishes peristaltic reflexes in guinea pigs, rabbits and cats (Bülbring *et al.* 1958) and verified (Frigo & Lecchini, 1970). Bülbring proposed that enterochromaffin (EC) cells secrete 5-HT, which stimulates sensory (primary afferent) neurons to initiate peristaltic reflexes, and predicted that prevention of mucosal 5-HT biosynthesis would impair peristaltic reflexes. In fact, despite the incorrect contrary assertion of Spencer *et al.* (2015), it does (Heredia *et al.* 2013). Brushing of the mucosal surface elicits CMMCs in isolated wild-type colon but not in that of mice lacking tryptophan hydroxylase 1 (TPH1KO mice) and thus mucosal 5-HT. To evoke CMMCs in the absence of mucosal 5-HT, it is necessary to dilate/stretch the gut, which short circuits the mucosa and activates mechanosensitive neurons (Smith *et al.* 2010). In the TPH1KO colon small pellets, which fail to dilate the gut, are not propelled. Although fecal pellets form *in situ* in the TPH1KO colon they are oversized and the colon is elongated and dilated, illustrating the pathophysiological toll exacted by the absence of mucosal 5-HT. Equally important, motility is a direct function of luminal bacteria that regulate 5-HT biosynthesis in EC cells (Yano *et al.* 2015). Altering mucosal 5-HT biosynthesis (Brown *et al.* 2011) or actions (Chey *et al.* 2015) has, furthermore, proven to be effective therapeutically in treating intestinal motility disorders. Mucosal 5-HT might not be the only driver of peristalsis since 5-HT neurons are still present, but it is a necessary one that provides insights into GI physiology, pathophysiology and therapy.

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Additional information

Competing interests

None declared.

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