PERSPECTIVES

Enteric serotonergic neurones . . . finally!

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The involvement of serotonin (5-HT) in gastrointestinal (GI) physiology was recognized even before its structure had been discovered or anything was known about its role in the central nervous system. In 1937, Vittorio Erspamer extracted a factor, derived from the enterochromaffin (EC) cells of the GI epithelium, which he identified as an amine and called 'enteramine' (Erspamer, 1937). 'Enteramine' was unknown to Maurice Rapport when, in 1948, he isolated 5-HT as a serum vasoconstrictor and demonstrated its chemical structure (Rapport *et al.* 1948). 5-HT has thus been known to posterity as serotonin, not 'enteramine'.

Modern functional studies of 5-HT physiology in the GI tract began when Edith Bülbring demonstrated that increased intraluminal pressure releases 5-HT from EC cells and initiates peristaltic reflexes by activating 'sensory' neurones in the gut wall (Bülbring & Crema, 1959). This work, since corroborated (Gershon & Tack, 2007) and extended to secretory reflexes (Cooke & Christofi, 2006), was exciting and non-controversial; however, because peristaltic reflexes persist when mucosal 5-HT is depleted, 5-HT is clearly not the only agent that initiates peristaltic reflexes (Gershon & Tack, 2007). EC cells, furthermore, are not only paracrine, but endocrine, and utilize 5-HT as a hormone, which decreases bone formation and regulates bone density (Yadav *et al.* 2008).

The idea that 5-HT might be present, not only in EC cells, but also in the enteric nervous system (ENS) was highly controversial when first proposed (Gershon *et al.* 1965). At the time, the autonomic nervous system was thought to function with only two neurotransmitters, acetylcholine and noradrenaline, and many investigators were loath to accept a third. The hypothesis that 5-HT might be an ENS neurotransmitter, moreover, was originally based on the selective synthesis in the ENS, of ^{3}H-5-HT from ^{3}H-5-hydroxytryptophan (^{3}H-5-HTP) and the release of ^{3}H-5-HT. The rate-limiting enzyme in the biosynthesis of 5-HT, however, is tryptophan hydroxylase (TPH), which is bypassed by 5-HTP. The biosynthesis of ^{3}H-5-HT from ^{3}H-tryptophan was subsequently demonstrated and 5-HT ultimately fulfilled the criteria needed for neurotransmitter identification (Gershon & Tack, 2007); nevertheless, the nagging question remained of whether the putative enteric serotonergic neurones actually contain TPH.

There are two TPH isoforms, TPH1 and TPH2; TPH1 is peripheral and critical for 5-HT biosynthesis in EC cells, while TPH2 is critical for 5-HT biosynthesis in neurones (Cote *et al.* 2003; Walther *et al.* 2003). When TPH1 is ablated in transgenic mice, brain 5-HT is unaffected but peripheral 5-HT is eliminated – except for a 'residual' store in the gut, which is compatible with ENS TPH2-dependent 5-HT biosynthesis. 5-HT is also present in murine enteric neurones despite the knockout of the serotonin transporter, which prevents neuronal 5-HT uptake (Gershon & Tack, 2007). Although evidence from *in situ* hybridization and RT-PCR has suggested that enteric neurones express TPH2 (Gershon & Tack, 2007), the ENS is often ignored and many investigators call TPH2 the 'brain' form of the enzyme.

The soon-to-be classical paper in this issue of *The Journal of Physiology* by Neal *et al.* has eliminated any doubt about the role of 5-HT as an enteric neurotransmitter (Neal *et al.* 2009). It is one; enteric serotonergic neurones express TPH2 and participate in mediating propagating contractile complexes (essentially a redefinition of the peristaltic reflex). Enteric and brain TPH2, moreover, manifest the same strain-specific polymorphisms, suggesting that disorders associated with these polymorphisms may have enteric ramifications, which, but for the authors' careful work, would probably go undetected and/or unexplained. It is to be hoped that the authors' paper will finally bring the ENS into the mainstream of 5-HT research and drug discovery.

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