5-HT₄-mediated neuroprotection: a new therapeutic modality on the way?

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ENTERIC NEURONS HAVE A HARD LIFE. Unlike their counterparts in the central nervous system, enteric neurons lack the protection against mechanical damage that a hard skull and the cushioning of cerebrospinal fluid provide. Myenteric neurons, moreover, must also endure the shearing and pressure that accompany their location between the circular and longitudinal layers of smooth muscle. Even submucosal neurons have to survive the motion of the bowel, which waxes and wanes but rarely ceases. The lumen of the gut, furthermore, contains the enteric microbiome, which may be a net plus but is also a source of invasion, defensive immune reactions, and inflammation. Inflammation, for example, has been documented to lead to an indiscriminate loss of enteric neurons (8, 11), which avaricious enteric glia aid and abet (3). Clearly, neuroprotection is essential for long-lived cells, which neurons must necessarily be, to survive in the inhospitable environment of the intestinal wall.

Mechanisms of enteric neuroprotection are multiple; nevertheless, it is interesting that enteric neurons have evolved the means of using at least one of their own signaling molecules for this purpose. Serotonin is, in the adult bowel, a paracrine (ATP) to stimulate P2X7 receptors and execute neurons. Which opens connexin-43 hemichannels that release more purine (P2Y1 receptors on glia. The activated glia then produce NO, which opens connexin–43 hemichannels that release more purine (ATP) to stimulate P2X7 receptors and execute neurons. Bianco et al. make clear that the neuroprotective effect of prucalopride they observe is specific and depends on the ability of the drug to activate the 5-HT₄ receptor; the 5-HT₄ antagonist GR113808 inhibits prucalopride-mediated neuroprotection. Bianco et al. utilize human cells (neuroblastoma line), neurosphere, and submucosal neurons in biopsy specimens to add the novelty of human relevance to their work. Bianco et al. transcend prior work on 5-HT₄-mediated neuroprotection by showing that it applies to oxidative stress. It is also significant that the 5-HT₄ agonist they use, prucalopride, is available for therapeutic use in Europe and may soon be cleared for use in the USA. It is a bit surprising, particularly since Bianco et al. studied neurospheres, that they did not devote more attention to 5-HT₄-mediated neurogenesis. Still, the conclusion of the current report is clear and well supported by data. The utility of a neuroprotective agent in the treatment of inflammatory bowel disease and degenerative disorders of the ENS has not yet been tested. The current article suggests that such testing should soon begin.

DISCLOSURES
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REFERENCES


