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

An Editorial Focus

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Enteric neurons have a hard life. Unlike their counterparts in the CNS, 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 (7, 10), which avaricious enteric glia aid and abet (2). 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 signal, a hormone, and a neurotransmitter (3); however, it is also a neuronal growth factor during development (9) and, by stimulating submucosal cholinergic neurons, a major promoter of the growth of the mucosal epithelium (6). Interestingly, serotonin can even stimulate neurogenesis in the mature enteric nervous system (ENS) and, in adults, serotonin promotes neurogenesis and neuroprotection through the activation of 5-HT4 receptors (11). Curiously, serotonin is not straightforwardly a benign neuroprotective agent for enteric neurons. Mucosal serotonin is anything but that. Mucosal serotonin is strongly pro-inflammatory (1, 5) and, in this capacity, it is a threat to neuronal survival. Serotonin has thus been called a “sword and a shield” of the bowel (4). Mucosal serotonin is the pro-inflammatory sword, and neuronal serotonin is the anti-inflammatory shield.

The neurogenerative/neuroprotective actions of the 5-HT4 receptor appear to be vital to maintenance of a normal ENS. Mice that lack 5-HT4 receptors have the same number of enteric neurons as their wild-type littermates but the normal accretion of neurons that occurs through the first 4 months of life in wild-type animals does not occur in those that lack 5-HT4 receptors (11). In the adult bowel, neurons express 5-HT4 receptors, which are abundant on nerve terminals as well as some cell bodies, but they are also expressed on colonic epithelial cells, where they can be accessed from the luminal surface to exert prokinetic and anti-nociceptive effects (8).
In the current issue, Bianco et al report an outstanding study that clearly demonstrates the ability of the 5-HT4 agonist, prucalopride, to protect enteric neuron against oxidative (H2O2-induced) stress. This demonstration is important because the destruction of enteric neurons during inflammation depends strongly on forces of oxidative stress that inflammation unleashes (2, 7). These forces appear in vivo to involve the participation of P2X7 receptor-activated pannexin-1 channels in the neurons, which releases purines (ATP) that stimulate 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), neurospheres, 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 in 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 manuscript suggests that such testing should soon begin.

References


