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Title: Exploring enteric neurogenesis in post-embryonic development and regeneration

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Abstract: Background & Aims: The enteric nervous system (ENS) is essential for normal gastrointestinal motility, and defects in its function define several difficult to treat conditions. While the developmental origin of the ENS from neural crest cells is well understood, there is conflicting evidence regarding postnatal enteric neurogenesis and neuronal homeostasis. Using zebrafish as a model due to its simplified ENS which is amenable to live-imaging, we sought to explore the origin of enteric neurons that arise in post-embryonic life in both normal development and upon injury, and tested effects of the 5-HT4 receptor agonist, prucalopride, in this process. Methods: To assess enteric neurogenesis, we photoconverted enteric neurons within the intestines of a Phox2b-kaede line such that all resident neurons turned from green to red. We then performed live time-lapse imaging to look for the emergence of new, green-only, neurons. In other experiments, resident enteric neurons were removed using two-photon laser ablation. To follow the potential contribution of neural crest-derived cells to the gut, lineage tracing was performed with neural tube injections of a lipophilic dye as well as with an inducible Sox10-Cre transgenic line. Lastly, post-embryonic zebrafish were exposed to prucalopride to test this drug's effect on enteric neurogenesis both during normal development and after injury. Results: Our results suggest that the post-embryonic zebrafish intestine lacks resident neurogenic precursors, and indeed appears to have no enteric glia. Despite this, enteric neurogenesis persists post-embryonically both during normal development and after injury. Our data suggest that new enteric neurons arise from trunk neural crest-derived Schwann cell precursors that migrate along nerves to the intestine. Prucalopride increases enteric neurogenesis in normal development as well as after injury if exposure occurs prior to injury. Conclusions: Enteric neurogenesis persists in the post-embryonic period in both normal development and injury, appears to arise from gut-extrinsic Schwann cell precursors, and is promoted by prucalopride treatment.