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LINACLOTIDE AND ABDOMINAL PAIN

Linaclotide inhibits colonic nociceptors *in vitro,* and *in vivo* intracolonic administration of linaclotide reduces signalling of noxious colorectal distention to the spinal cord, according to the results of a study published in *Gastroenterology.*

Linaclotide induces fluid secretion and accelerates colonic transit, and has been approved for the treatment of moderate-to-severe IBS with constipation (IBS-C) and for chronic idiopathic constipation. Linaclotide also has an effect on the abdominal pain that is a key clinical feature of IBS-C. However, little is understood about the mechanisms of how this drug reduces abdominal pain.

"We hypothesized that linaclotide and its downstream effector, intestinal epithelial-cell derived cyclic guanosine-3',5'-monophosphate (cGMP), might be responsible for the inhibition of colonic nociceptors," explains Stuart Brierley. To that end, the researchers examined the effects of linaclotide by performing *in vitro* colonic afferent recordings from healthy mice and mice with chronic visceral hypersensitivity. They then assessed pain transmission by measuring activation of dorsal horn neurons in the spinal cord in response to noxious colorectal distention in these mice.

Linaclotide was found to inhibit colonic nociceptors *in vitro* and to reduce signalling of noxious colorectal distention to the spinal cord *in vivo*. These effects were increased in mice with chronic visceral hypersensitivity. The researchers found that the antinociceptive effects of linaclotide are mediated by the production and release of cGMP into the submucosal layer, upon activation of guanylate cyclase C expressed on intestinal epithelial cells. "Finally, we complemented these pre-clinical findings with a *post hoc* efficacy analysis of a phase III, double-blind, parallel-group, placebo-controlled trial that randomly allocated 805 patients with IBS-C to placebo or 290 μg of oral linaclotide once daily for 26 weeks," says Brierley. A greater percentage of patients who received linaclotide had ≥30% reduction in abdominal pain compared with those who received placebo.

The team will continue to investigate how linaclotide reduces nociception and abdominal pain.

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Original article Castro, J. *et al.* Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic GMP. *Gastroenterology* doi:10.1053/j.gastro.2013.08.017