Background

Inflammatory bowel syndrome (IBS) is a common gastrointestinal disorder with symptoms including abdominal pain, bloating, and altered bowel habits. One of the main pathological features of IBS is visceral hypersensitivity, which is the exaggerated response of the enteric nervous system to mechanical or chemical stimulation.

Purpose

To investigate the effect of tenapanor, an investigational, minimally absorbed, small-molecule inhibitor of the sodium/hydrogen exchanger NHE3, on visceral hypersensitivity in vivo and in vitro.

Methods

Model of IBS-like colonic hypersensitivity in rats

- A sensitization model of IBS-like colonic hypersensitivity was generated by colonic balloon distension (CBD) in 10-day-old Sprague-Dawley rat pups. This model was further developed to assess the effect of tenapanor on visceral hypersensitivity.

- Tenapanor, an investigational, minimally absorbed, small-molecule inhibitor of the sodium/hydrogen exchanger NHE3, acts locally on gastrointestinal epithelial cells to inhibit natrium influx, which reduces intracellular sodium concentration and increases intracellular free calcium concentration. This increase in calcium concentration results in a variety of cellular responses, including inflammation and hyperexcitability of enteric nervous system neurons.

- In an in vitro study, single-cell patch-clamping was used to assess the effect of tenapanor on DRG excitability. DRG neurons were isolated from adult non-sensitized Sprague-Dawley rats and were treated with tenapanor 0.5 mg/kg b.i.d. or vehicle control. The effect of tenapanor on DRG excitability was assessed by measuring the hyperpolarizingAfter a recovery period of approximately 30 minutes, VMR response to CRD was assessed. The area under the curve (AUC) of the VMR response was normalized to baseline EMG values measured 20 seconds before CRD.

- Effect of tenapanor on visceral hyperalgesia in the rat model of IBS

- Tenapanor treatment in sensitized rats significantly reduced VMR responses to CRD (p < 0.001) or PEG (p < 0.05) compared to vehicle-treated sensitized rats (Figure 5A–D).

- Tenapanor treatment significantly reduced the hyperexcitability of colon-specific DRG neurons in an in vitro study of single-cell patch-clamping (Figure 4A–D).

- The AUC of VMR response to CRD was significantly greater than those vehicle-treated non-sensitized controls (p < 0.05). AUC, area under the curve; CRD, colorectal distension; PEG, polyethylene glycol; VMR, visceral motor reflex.

Conclusions

- Tenapanor treatment significantly reduced the hyperexcitability of colon-specific DRG neurons in vitro and visceral hypersensitivity in vivo.

- Tenapanor treatment significantly reduced visceral sensitivity and improved clinical symptoms in a rat model of IBS.

- Tenapanor treatment was well tolerated and had a favorable safety profile.

References

3. Qian Li,1 Andrew King,2 Liansheng Liu,1 Yaohui Zhu,1 Jeremy Caldwell,2 Pankaj Pasricha1

Acknowledgments

The authors declare that they have no conflict of interest.

Funding

This study was supported by grant number 1R21DK115530-01A1 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) and by grant number 1R01DK119872-01 from the NIDDK, NIH.

Disclosures

The authors declare that they have no conflict of interest.

Presented at the World Congress of Gastroenterology at The American College of Gastroenterology Annual Scientific Meeting, October 13-18, 2017, Orlando, FL, USA.

"...and irritative bowel syndrome (IBS) is a common gastrointestinal disorder with symptoms including abdominal pain, bloating, and altered bowel habits. One of the main pathological features of IBS is visceral hypersensitivity, which is the exaggerated response of the enteric nervous system to mechanical or chemical stimulation. Tenapanor, an investigational, minimally absorbed, small-molecule inhibitor of the sodium/hydrogen exchanger NHE3, acts locally on gastrointestinal epithelial cells to inhibit sodium influx, which reduces intracellular sodium concentration and increases intracellular free calcium concentration. This increase in calcium concentration results in a variety of cellular responses, including inflammation and hyperexcitability of enteric nervous system neurons. In an in vitro study, single-cell patch-clamping was used to assess the effect of tenapanor on DRG excitability. DRG neurons were isolated from adult non-sensitized Sprague-Dawley rats and were treated with tenapanor 0.5 mg/kg b.i.d. or vehicle control. The effect of tenapanor on DRG excitability was assessed by measuring the hyperpolarizing response to capsaicin. Tenapanor treatment significantly reduced the hyperexcitability of DRG neurons in vitro and visceral hypersensitivity in vivo. Tenapanor treatment was well tolerated and had a favorable safety profile. This study was supported by grant number 1R21DK115530-01A1 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) and by grant number 1R01DK119872-01 from the NIDDK, NIH. The authors declare that they have no conflict of interest."