IBSRELA® (tenapanor) – Mechanism of Action

Key Information

- Tenapanor is a locally acting inhibitor of the sodium/hydrogen exchanger 3 (NHE3), an antiporter expressed on the apical surface of the small intestine and colon primarily responsible for the absorption of dietary sodium. *In vitro* and animal studies indicate its major metabolite, M1, is not active against NHE3.[1]
- By inhibiting NHE3 on the apical surface of the enterocytes, tenapanor reduces absorption of sodium from the small intestine and colon, resulting in an increase in water secretion into the intestinal lumen, which accelerates intestinal transit time and results in a softer stool consistency.[1,2]
- Tenapanor has also been shown to reduce abdominal pain by decreasing visceral hypersensitivity and by decreasing intestinal permeability in animal models. In a rat model of colonic hypersensitivity, tenapanor reduced visceral hyperalgesia and normalized colonic sensory neuronal excitability.[1]
- Data suggest that there is a gradient of NHE3 expression in the gastrointestinal tract and the highest expression is in the small intestine and proximal colon.[3-7]

IBSRELA in Irritable Bowel Syndrome with Constipation (IBS-C)

Pathophysiology of NHE3 Inhibition

- The human gastrointestinal (GI) tract normally processes about 9 liters of water and about 800 mEq of Na+ each day. The majority (about 7.5 liters of water and about 600 mEq of Na+) is ingested or secreted via the stomach, biliary tree, pancreas, and small intestine as part of the digestive process. A principal function of the small intestine and colon is to maintain water/Na+ homeostasis by absorbing virtually all water and Na+ to which the GI tract is exposed.[2,8]
- The Na+/H+ antiporter NHE3 has a major role in this Na+ re-uptake process. Eight isoforms of NHEs have been identified, of which only NHE2 and NHE3 are expressed on the apical side of the enterocyte, with a much larger contribution from NHE3. NHE3 is expressed primarily in the small intestine.[2]
- Na+/H+ exchange occurs in both surface and crypt epithelium and is tightly coupled to chloride ion/bicarbonate ion (Cl-/HCO3-) exchange. The net result is the uptake of luminal sodium chloride (NaCl) into the enterocyte. The basolateral Na+/K+ adenosine triphosphatase (ATPase) generates the driving force for Na+ re-uptake by lowering intracellular Na+ concentration and extruding Na+ into the systemic circulation.[2]

Proposed Site of NHE3 Expression

- *In vitro* studies indicate that tenapanor has an effect in the human small intestines[3] and in the human colon[4] where NHE3 is expressed.
- NHE3 is expressed on the apical surface of the small intestines and proximal colon. NHE3 messenger ribonucleic acid (mRNA) expression with chronic tenapanor use was the lowest in the distal colon of normal/healthy rats, see **Figure 1.**[5]

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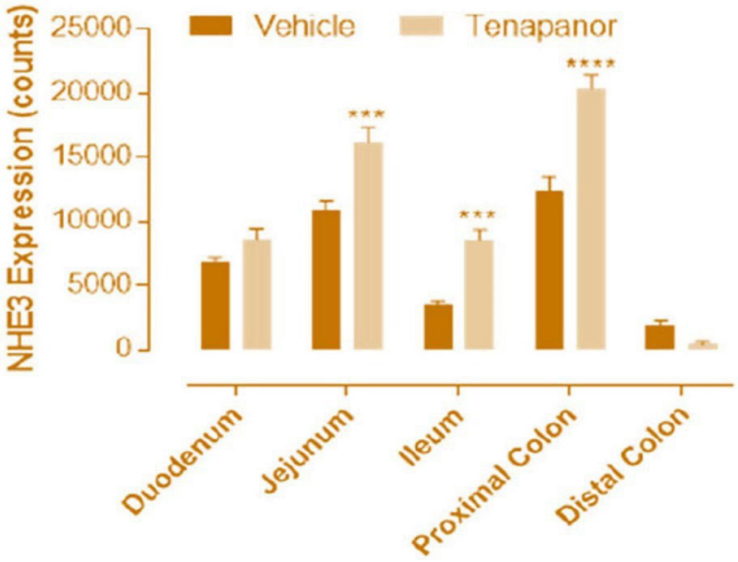
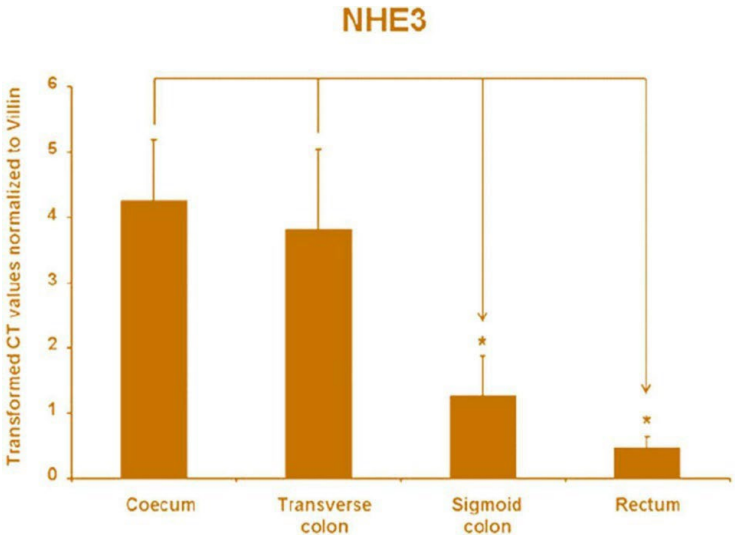
Figure 1. Changes in Intestinal Transporter NHE3 Expression in Response to Chronic *In Vivo* Tenapanor Treatment in Healthy Rats[5]



***P<0.001, ****P<0.0001 vs vehicle
Mean ± SEM; two-way ANOVA, with post hoc testing in each segment with Bonferroni's correction.
Abbreviations: ANOVA=analysis of variance; NHE3=Na/H exchanger-3; SEM=standard error of mean.

- In a different rat study, immunofluorescence staining of NHE3 in the colon indicated that the proximal colon (first ~50%) expresses NHE3 protein whereas the distal colon is nearly devoid of NHE3.[6]
- In biopsy samples from healthy humans, NHE3 expression was also significantly lower in the distal colon as shown by mRNA levels in the sigmoid colon and rectum, see **Figure 2**.[7]

Figure 2. mRNA Expression of NHE3 in the Noninflamed Human Biopsies Collected from Cecum to Rectum[7]



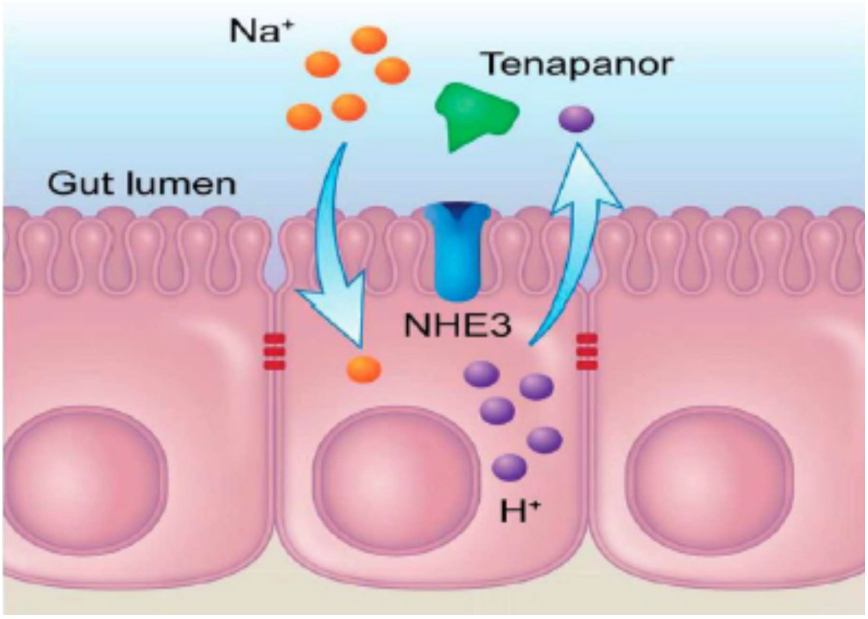
*Significant difference (P<0.05) between the different parts of the colon.
RNA was isolated from human biopsies and real-time PCRs were conducted. For each region, RNA was isolated from several biopsies of 3-5 controls. Data are presented as means ± SEM.
Abbreviations: CT=the cycle number at the threshold level of log-based fluorescence; mRNA=messenger ribonucleic acid; NHE3=Na/H exchanger-3; PCR=polymerase chain reaction; SEM=standard error of mean.

- Altogether, these data suggest that there is a gradient of NHE3 expression in the gastrointestinal tract and the highest expression is in the small intestine and proximal colon.[3-7]

IBSRELA Mechanism of Action

- IBSRELA is a first-in-class small-molecule inhibitor of the NHE3, designed for minimal systemic bioavailability[9] due to high molecular weight and total polar surface area.[10] NHE3 is expressed on the luminal surface throughout the small intestine and proximal colon (**Figure 3**).[9]
- NHE3 is a sodium hydrogen exchanger that is primarily responsible for the absorption of dietary sodium. Apical NHE3 inhibition with IBSRELA reduces the absorption of sodium from the small intestine and colon, resulting in an increase in water content in the intestinal lumen, which accelerates intestinal transit and results in softer stool consistency, improving GI motility.[1,10,11]

Figure 3. Mechanism of Action of IBSRELA[9]



Abbreviations: NHE3=Na/H exchanger-3.

IBSRELA on Intestinal Permeability and Hypersensitivity

- Various lines of evidence point toward an interplay between increased intestinal permeability, low levels of inflammation, and visceral hypersensitivity in IBS, in both human studies and animal models. Disruption of the mucosal barrier and increased intestinal permeability in IBS may result in enhanced bacterial translocation from the GI lumen and low-grade inflammation with an abnormal immune response to luminal microbes resulting in the influx of mast cells and other immune cells. These cells release soluble mediators to activate intrinsic submucosal enteric nerves and dorsal root ganglia nociceptive nerves, resulting in abdominal pain.[4,12,13]
- By impacting the tight junction structure of the paracellular pathway through NHE3 inhibition, IBSRELA restores the gut barrier function by attenuating increased intestinal permeability in animal models.[1,3]
    - *In vitro* studies show that treatment of colonic cells with IBSRELA attenuates the increase in permeability of colonic cells to macromolecules, induced by cytokines or human fecal supernatants.[4]

- By blocking the NHE3 transporter, IBSRELA causes a decrease in the intracellular pH of enterocytes (reduced proton [H^+] extrusion). Decreased intracellular pH is associated with changes in the tight junctions to reduce paracellular permeability.[2]
- This reduction in permeability of luminal macromolecules, and the significant increase in transepithelial electrical resistance [TEER]), may reduce the hyperexcitability of sensory neurons (intrinsic submucosal enteric nerves and dorsal root ganglia nociceptive nerves) responsible for the abdominal pain.[2,4,12]

- Based on animal data, IBSRELA reduces visceral hypersensitivity to colorectal distension and normalizes colonic sensory neuronal excitability, likely through inhibition of transient receptor potential vanilloid subfamily, member 1 (TRPV1) cation channel, a central receptor involved in the nociceptive pathway.[14,15]
  - TRPV1, commonly referred to as the capsaicin receptor highly expressed in sensory neurons is recognized as a molecular integrator of inflammatory mediators and plays a central role in the transduction of pain.[15]
  - In an established rat model of IBS-like colonic hypersensitivity, treatment with IBSRELA resulted in significantly reduced visceral motor responses to colorectal distension, and normalized colonic sensory neuronal excitability and TRPV1 currents.[1,14]

References

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