Inhibition of gastrointestinal (GI) NHE3 normalizes GI transit in models of opioid-induced constipation, multiple sclerosis, and cystic fibrosis

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Background

- Sodium/glucose exchange 3 (NHE3) plays a prominent role in luminal sodium and water absorption from the gastrointestinal (GI) tract.
- Decreases in GI transit are accompanied by impaired small intestinal absorption, small-molecule inhibitors of NHE3, inhibit absorption of GI sodium and phosphate.
- In patients with constipation-predominant irritable bowel syndrome, tenapanor increases colonic transit.
- RDX011-1 is a potent, gastrointestinally restricted inhibitor of NHE3 that effectively and sustainably reduces intestinal sodium and phosphate absorption in rodents.
- RDX011-1 is a potential pharmacological tool with therapeutic potential in diverse diseases that are accompanied by impaired GI motility, including MS, OIC and CF.

Methods

In vitro characterization of RDX011-1

- The potency of RDX011-1 was assessed in OIC mice (CF) and in WT mice (Figure 1).

In vivo characterization of RDX011-1

- Male Sprague-Dawley (SD) rats were given a single oral dose of RDX011-1 0.017, 0.06 or 0.17 mg/kg for 3 days.
- Urinary sodium excretion was assessed 30 min after loperamide administration.

Results

- We observed in rodent models of multiple sclerosis (MS), opioid-induced constipation (OIC), and cystic fibrosis (CF), as characterized by impaired GI transit.

RDX011-1 dose-dependently reduced small-intestinal transit compared with vehicle (Figure 2).

In patients with constipation-predominant irritable bowel syndrome, tenapanor increases colonic transit.

Small-intestinal transit was monitored after oral administration of Evans Blue dye to measure transit time.

RDX011-1 dose-dependently reduced small-intestinal transit compared with vehicle (Figure 3).

- In vitro pharmacodynamics of RDX011-1 in rats

- Continuous, quantitative parameters were analyzed using one-way analysis of variance, and individual comparisons of treatment versus vehicle performed using Dunnett's test.

- Pharmacodynamics of RDX011-1 in rats

- In vitro pharmacodynamics of RDX011-1 in rats

- RDX011-1 dose-dependently reduced small-intestinal transit compared with vehicle (Figure 4).

Conclusions

- RDX011-1 is a potent, gastrointestinally restricted inhibitor of NHE3 that effectively and sustainably reduces intestinal sodium and phosphate absorption in rats.

- RDX011-1 is a potential pharmacological tool with therapeutic potential in diverse diseases that are accompanied by impaired GI motility, including MS, OIC and CF.

References


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