Oral Treatment with SP-333, an Agonist of Guanylate Cyclase-C, Dramatically Ameliorates Methadone-Induced Bowel Dysfunction in Rats

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BACKGROUND

Constipation is the most common adverse effect of opiate use. Oral treatment with SP-333, an agonist of guanylate cyclase-C (GC-C), has been shown to dramatically ameliorate methadone-induced bowel dysfunction in rats.

METHODS

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RESULTS

Mechanisms of Oral Methadone Treatment with SP-333

SP-333 Promotes Daily Fecal Output in Methadone-Treated Rats

Mechanisms of Oral Methadone Treatment with SP-333

Possible Mechanism for SP-333 Mediated Reduction of Opioid-induced Delay of GI Transit

CONCLUSIONS

1. Treatment with SP-333, an agonist of guanylate cyclase-C, enhances short circuit current and opens TAC channel via activation of GC-C/PKG-CFTR signaling.
2. Pre-treatment or treatment with methadone (10 µM) or morphine (10 µM) did not affect SP-333-mediated increases in lec TAC channel.
3. Oral administration of SP-333 increases GI transit rates.
4. Methadone or morphine treatment slows GI transit by 50%. Oral treatment with SP-333 completely reverses this inhibition in GI transit rates.
5. Repeat daily dosing with methadone or morphine significantly reduces fecal output but daily treatment with SP-333 restores fecal output in rats.
7. Study opens a novel avenue for development of SP-333 as a novel orally-delivered and maximally active drug candidate for treatment of opioid-induced constipation.