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Analgesia from a peripherally active kappa-opioid receptor agonist in patients with chronic pancreatitis

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Abstract

Preclinical studies suggest that visceral afferents constitutively express kappa-opioid receptors (KORs) and that noxious visceral stimuli can be inhibited at a peripheral site by KOR activation. To test the relevance of these observations to humans, we infused, in a randomized, double blind manner, a peripherally selective KOR agonist (ADL 10-0101) or placebo into six patients with chronic pancreatitis and ongoing abdominal pain despite mu-opioid agonist therapy. Pain was assessed using a pain magnitude estimate, an open ended scale of each patient's choosing and compared to their rating of pain from a 1.6 cm(2) thermode applied to the skin and heated to 49 degrees C for 5s. Normalizing pain scores to this rating as 100, pain prior to study drug treatment was 4070, and was unaffected by placebo infusion in the two individuals receiving this therapy. In contrast, ADL 10-0101 infusion reduced pain score from 63+/-7.6 (mean+/-SE) prior to infusion to 23+/-15 4h after infusion ($P<0.05$ vs. baseline). One patient receiving placebo and one receiving ADL 10-0101 experienced a mild headache during the study. One patient receiving ADL 10-0101 experienced restlessness and another had assymptomatic transient dysrhythmia upon standing after the 4h study. Neither of the treatments affected blood pressure, heart rate, respiratory rate, or oxyhemoglobin saturation, and no patient experienced nausea during the study. These limited data support the hypothesis that human visceral afferents express KOR and that peripherally restricted KOR agonists produce analgesia in patients with chronic visceral pain.

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