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Opioid receptors in the GI tract: targets for treatment of both diarrhea and constipation in functional bowel disorders?

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Opioids have been used for centuries, mostly as a sedative and to treat pain. Currently, they are used on a global scale for the treatment of acute and chronic pain in diseases as osteoarthritis, fibromyalgia, and low back pain. Binding of opioids on opioid receptors can cause a range of different effects such as changes in stress response, analgesia, motor activity and autonomic functions. This review provide a synthetic summary of the most recent literature on the use of drugs acting on mu-receptors to treat two prevalent functional bowel disorders, presenting with opposite bowel habit. Eluxadoline and naloxegol, methylnaltrexone and naldemedine are recently FDA and/or EMA approved drugs demonstrated to be effective and safe for treatment respectively of irritable bowel syndrome subtype diarrhea and opioid induced constipation.

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Introduction

Irritable bowel syndrome (IBS) and opioid-induced constipation (OIC) are functional bowel disorders, identified through symptom-based characteristics defined by the Rome IV criteria. IBS is characterized by recurrent abdominal pain that is associated with defecation and a change in bowel habits. According to their predominant bowel habits, patients are divided into subgroups. These subgroups include IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and IBS with a mixed stool pattern (IBS-M). OIC has only been classified as a functional bowel disorder since the last Rome update, and is recognized through a specific etiology with similar symptoms as seen in functional constipation [1].

IBS affects 11.2% (95% CI, 9.8–12.8%) of the population world-wide [2], in which IBS-D accounts for about 40% of the total IBS population [3]. The prevalence of OIC in patients taking opioids for chronic non-cancer pain is 41%, based on a systematic review that included 15 randomized placebo-controlled trials [4].

Although both disorders do not directly lead to an increase in mortality, they lead to a reduction in quality of life (QOL). Gralnek et al. reported IBS patients suffer from a reduction in energy/fatigue, role limitations caused by physical health, and bodily pain, concluding QOL is significantly lower than the U.S. general population [5].

In clinical practice, IBS-D has been normally treated with antispasmodic drugs, including peppermint oil and the mu-receptor agonist loperamide. More recently, rifaximin has been approved by FDA for these patients but evidence on long-term benefit are still lacking [6]. Ondansetron has been proposed as an additional treatment [6] and a large multicenter study is ongoing to confirm the efficacy and safety of this 5-HT3 antagonist for IBS-D. OIC is normally managed with treatments similar to those applied in functional constipation, including fibers, stimulant and osmotic laxatives, lubiprostone, linaclotide and prucalopride [6,7]. However, surveys have shown that only 46% of patients with OIC achieve desired treatment results >50% of the time [8]. Finally, these treatments do not target the underlying mechanism of OIC [9].

Due to conventional treatments not always resolving patients' symptoms, developments in pharmacological treatment have been focusing on new targets including gastrointestinal (GI) tract opioid receptors. This review revise the data concerning use of medications targeting μ-opioids receptors to treat two conditions characterized by opposite bowel habits, IBS-D and OIC.

Opioid receptors in the gastrointestinal tract

Opioids have been used for centuries, mostly as a sedative and to treat pain. Currently, they are used on a global scale for the treatment of acute and chronic pain in diseases as osteoarthritis, fibromyalgia, and low back pain.

Binding of opioids on opioid receptors can cause a range of different effects such as changes in stress response, analgesia, motor activity and autonomic functions [10]. Four different receptors, all G-protein coupled receptors, are present in the central nervous system (CNS): μ, κ, δ and opioid receptor-like-1 (ORL-1). These opioid receptors can bind opioids from different origins such as plants, endogenous opioid peptides, and amphibian skin opioids [11]. Other than binding to receptors in the CNS, opioids can bind to opioid-receptors in the GI tract, where the μ, κ, and δ receptor have been identified [12].

Enteric neurons synthesize and release opioid peptides as neurotransmitters next to other neurotransmitters as acetylcholine, substance P, and vasoactive intestinal peptide [13]. Amongst these are met-enkephalin, leu-enkephalin, β-endorphin and dynorphin, all endogenous opioids. These play a major regulatory role in GI signaling, causing changes in motility, secretion and transport of fluids and electrolytes [10]. After opioid binding, recruitment of G-protein receptor kinases, phosphorylation, binding of β-arrestin proteins, endocytosis through inactivation of ADP-ribosylation factor, and recycling at varying rates takes place [14].

In humans, binding of opioids to the μ-opioid receptor has shown to delay colonic transit [15]. This results from binding to opioid receptors in the GI tract, causing inhibition of enteric nerve activity through suppression of enteric nerve excitability, neurotransmitter release, and pre-synaptic and post-synaptic inhibition of transmission of excitatory and inhibitory motor pathways, and secretomotor pathways [16]. In addition, mucosal signaling transduction pathways can activate submucosal neurons, which secrete acetylcholine and vasoactive intestinal peptide, projecting to the mucosa, mucosal glands and submucous arterioles [17]. Finally, secretomotor neurons can activate epithelial cell chloride channels, leading to osmosis of water to the gut lumen [18]. Opioid agonists can bind to these submucosal secretomotor neurons causing hyperpolarization, leading to dry, hard stools [19].

Treatment options through opioid receptor binding in IBS-D: the case of loperamide and eluxadoline

Loperamide

The use of loperamide, an opiate analogue of the piperidine class with low bioavailability, in acute and chronic diarrhea has been established for over three decades due to its capacity to inhibit GI peristalsis and secretion [20]. Loperamide is a substrate for the P-glycoprotein efflux transporter. These efflux transporters actively pump drugs back from the brain into the blood, preventing it from binding to central receptors [21].

In total four trials [22–25] have been performed in IBS-D or IBS-M patients. Two trials measured a general response, which was favorable for loperamide, in the IBS-D groups. Further, loperamide showed a positive response on stool consistency [22,23,25], urgency [25] and frequency [23,24]. This reduction in frequency was reflected in a delay in both small bowel and whole gut transit time for loperamide compared to placebo [25].

Some trials [22,23] were able to show a reduction in pain but recent systematic reviews [6] have rated this quality of evidence as very low and have suggested that there is insufficient evidence to support the use of loperamide in IBS_D. Common side effects of loperamide are nausea, vomiting, constipation, dry mouth, dizziness, and stomach discomfort. Finally, abuse or misuse of loperamide has been associated with cardiac adverse events (AEs) [26].

Eluxadoline

Eluxadoline is an orally administered μ-opioid receptor agonist, delta-opioid receptor antagonist, and kappa-opioid receptor agonist [27]. Eluxadoline acts mainly peripherally due to low bioavailability when administered orally [28].

The exact mechanism of eluxadoline is unknown, but the dual mechanism of μ-opioid receptor antagonist activity and delta-receptor agonist activity is thought to be a favorable finding. This dual mechanism can result in a weakened dependence liability, lead to analgesic advantages, and reduce constipation [29]. Although evidence from animal studies concerning the analgesic effect of eluxadoline was not strong [28].

Two multicenter, double-blind, placebo-controlled, phase 3 studies have been conducted, including 2428 patients with IBS-D. These studies included a 26-week double blind, placebo-controlled study, followed by a 26-week follow-up period for safety assessment and a 2-week post-treatment follow-up period in one, or a 4-week withdrawal period in the other trial. Data were evaluated according to the FDA and EMA endpoints of 12 and 26 weeks, respectively. Patients were considered to be 'responders' when they experienced a $\geq$30% reduction from their baseline score of worst abdominal pain in $\geq$50% of the days and a stool consistency score of $<$5 on the Bristol stool scale.

More patients who received twice-daily 75 mg and 100 mg eluxadoline compared to placebo met the FDA endpoint [23.9% and 25.1% respectively vs. 17.1%; $p = 0.004$, 28.9% and 28.9%, respectively, vs. 16.2%; $p < 0.001$]. However, for the EMA endpoints, only the 100 mg dose showed a statically significant result compared to placebo in both trials (29.3% vs. 19.0%; $p < 0.001$ and 32.7% vs. 20.2%; $p < 0.001$). These positive results over placebo were already observed in the first week of treatment.

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