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The involvement of the μ-opioid receptor in gastrointestinal pathophysiology: Therapeutic opportunities for antagonism at this receptor

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Abstract

The localization of opioid receptors and their endogenous peptide ligands within the gastrointestinal (GI) tract and their role in the coordination of propulsion and secretion underscores the importance of opioid receptors in the maintenance of GI homeostasis. The peripherally acting μ-opioid receptor antagonists alvimopan and methylnaltrexone (MNTX) are currently under investigation as therapeutic agents to treat the deleterious GI side effects associated with opioid administration. These compounds have demonstrated efficacy in numerous animal models of GI function, and clinical studies have revealed their efficacy in the treatment of postoperative ileus (POI) and opioid-induced bowel dysfunction. Preservation of opioid-mediated analgesia has been demonstrated for these compounds in both the preclinical and clinical settings. Future studies exploring the benefits of selective antagonism of the peripheral μ-opioid receptor in the treatment of other GI conditions may open new therapeutic opportunities for alvimopan and MNTX.

Keywords: Alvimopan; Constipation; Ileus; Gastrointestinal; Methylnaltrexone; Opioid-induced bowel dysfunction

Abbreviations: ALV, alvimopan; APAP, acetaminophen; BM, bowel movement; BW373U86, (±)-4-((α-*R**)-α-((2*S**, 5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*,*N*-diethyl-benzamide; CNS, central nervous system; CRT, colorectal transit; DADLE, D-Ala^2, *N*-MePhe^4, Gly^5-ol-enkephalin; DAMGO, D-Ala^2, MePhe^4-enkephalin; DPDPE, [D-Pen^2, D-Pen^5]enkephalin, where D-Pen is D-penicillamine; GI, gastrointestinal; GTPγS, guanosine-5′-*O*-(3-thio)triphosphate; IBS, irritable bowel syndrome; IHC, immunohistochemistry; IR, immunoreactivity; MNTX, methylnaltrexone; NAL, naloxone; OBD, opioid-induced bowel dysfunction; PCA, patient-controlled analgesia; PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; POI, postoperative ileus; RT-PCR, reverse transcription polymerase chain reaction; TNBS, trinitrobenzenesulfonic acid; U-50,488H, *trans*-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]benzeneacetamide methanesulfonate; U-69,593, (5α,7α,8β)-(+)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxaspiro[4, 5]dec-8-yl)benzeneacetamide; VAS, visual analog scale.

Contents

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1. Introduction

Over the past 20 years, it has been demonstrated that opioid receptors present in peripheral tissues (Hedner & Cassuto, 1987; Kromer, 1988; Sternini, 2001; DeHaven-Hudkins, 2003; Sternini et al., 2004) can be selectively targeted to produce specific pharmacological actions (Brown & Goldberg, 1985; Hargreaves & Joris, 1993; Stein et al., 2003; DeHaven-Hudkins & Dolle, 2004). The ability to dissociate the central and peripheral effects of opioid agonists in the gut was the basis for the development of gastrointestinal (GI)-selective opioid agents in the 1970s, such as the peripherally acting agonists loperamide and diphenoxylate (Heel et al., 1978; Niemegeers et al., 1981; Awouters et al., 1983, 1993), for the treatment of diarrhea. Research in the area of peripheral analgesia led to the discovery that direct administration of opioid receptor agonists to the site of an injury produced a locally mediated antinociceptive response that could be dissociated from centrally mediated antinociception (Stein et al., 1989). This observation, coupled with the knowledge that opioid agonists could be peripheralized, was paralleled by the development of peripherally selective opioid receptor antagonists in order to investigate the role of central vs. peripheral opiate receptors in a variety of agonist-mediated responses (Bianchi et al., 1982; Brown & Goldberg, 1985; Zimmerman et al., 1994a, 1994b).

As was the case for peripheralized opioid agonists, therapeutic opportunities also exist for the use of peripheral opioid antagonists to minimize or alleviate the GI side effects associated with opioid administration and to selectively treat GI tissue where dysregulation of endogenous opioid tone is the underlying pathology. This review will provide a brief overview of μ-opioid receptor distribution and function in the GI tract, as well as a comprehensive presentation of the preclinical pharmacology and clinical data for the 2 best-characterized peripherally selective opioid receptor antagonists, alvimopan and methylnaltrexone (MNTX).

2. Anatomical distribution and function of μ-opioid receptors in the gastrointestinal tract

Descriptions of the anatomical localization and distribution of endogenous opioid peptides (Kromer, 1988), as well as μ, δ and κ opioid receptors (Kromer, 1988; Sternini et al., 2004) in GI tissue has given a better understanding of the precise function of these receptors within the enteric nervous system (ENS). The distribution of μ-opioid receptors in the ENS has been elegantly reviewed by Sternini (2001, 2004). Expression of μ-opioid receptors has been described in the submucosal plexus, myenteric plexus, and longitudinal muscle of ilea from various species (Table 1). Although species differences in μ receptor distribution do exist, common elements include localization in submucosal and myenteric plexi, localization to Dogiel type I myenteric neurons comprised of motor neurons and interneurons, and proximity to cells of Cajal, the pacemaker cells for GI motility. The localization of opioid receptors to interneurons and secretomotor neurons within the GI tract serves to maintain gut homeostasis within the ENS by coordination of the propulsive and secretory functions of the GI tract.

Early studies attempted to use receptor autoradiography techniques to identify binding sites for opioid receptors in GI tissue, generally using subtype-selective compounds either to label receptors or to define nonspecific binding. In general, resolution was suboptimal due to the low concentration of receptors in GI tissues. Specific binding for [^{3}H]naloxone or [^{3}H]dihydromorphine was detected in villi and crypts of rat small intestine (Dashwood et al., 1985) and [^{3}H]loperamide binding was observed in ileum of rat and human (Dashwood et al., 1990). Species differences between rat and guinea pig were observed for the distribution of μ-opioid receptors labeled by [^{3}H]dihydromorphine or [^{3}H]naloxone (Nishimura et al., 1986), where ileal mucosa of rat exhibited specific labeling, whereas receptors in guinea pig were confined to submucosal plexus, myenteric plexus, and muscle layers. Binding patterns for [^{3}H]DAMGO in porcine jejunum (Quito et al., 1991) were similar to those reported for rat ileum (Dashwood et al., 1985; Nishimura et al., 1986).

Historically the guinea pig ileum has been used as a functional assay to evaluate the activities of opioid receptor agonists and antagonists (Kosterlitz et al., 1972). Work by Sternini's group (Ho et al., 2003) has shown colocalization of μ-opioid receptors with transmitters and peptides controlling excitatory and inhibitory responses in the GI tract of guinea pig. This association of μ-opioid receptors with diverse types of myenteric neurons would serve an integrative role for the regulation of GI effects by μ-opioid receptors. The immunoreactivity was localized to Dogiel type I myenteric neurons and