

The Novel Role of Opioid μ -receptors in Gastroenterology

Hsien-Hui Chung

Hsien-Hui Chung, Institute of Basic Medical Sciences, College of Medicine, National Cheng Kung University, Tainan City 70101, Taiwan,

Correspondence to: Hsien-Hui Chung, PhD, Institute of Basic Medical Sciences, College of Medicine, National Cheng Kung University, Tainan City 70101, Taiwan. hsienhuichung@yahoo.com.tw

Telephone: +886-6-235-3535 Fax: +886-6-275-1371

Received: October 1, 2012 Revised: November 29, 2012

Accepted: December 2, 2012

Published online: June 21, 2013

ABSTRACT

Constipation and gastrointestinal dysmotility are common problems in critical care patients. The cancer patients often suffer from pain and are alleviated with opioid analgesics, which attenuate gastrointestinal (GI) motility and result in adverse outcomes. Although opioid μ -receptors have critical influence on gastroenterology, the novel role of opioid μ -receptors in opiate-induced constipation (OIC) remains obscure. Thus, some peripheral opiate agonists are applied to investigate the involvement of opioid μ -receptors in OIC and their possible mechanism(s). The activation of opioid μ -2 receptors seems associated with OIC induced by opioid analgesics. It is meaningful that a novel target is provided for handling of OIC in cancer patients receiving chronic opioid therapy.

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Key words: Constipation; Gastroenterology; Opioid receptors

Chung HH. The Novel Role of Opioid μ -receptors in Gastroenterology. *Journal of Gastroenterology and Hepatology Research* 2013; 2(6): 614-617 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/399>

INTRODUCTION

In gastrointestinal system, opiates have several effects on gastrointestinal functions^[1,2]. The opioid peptides were released to activate opioid receptors on the enteric circuitry controlling secretion and motility, including increase in sphincter tone, induction of stationary motor patterns and inhibition of gastric emptying.

Constipation results from inhibition of ion and fluid secretion, which is one of the most burdensome adverse effects of opioid analgesic treatment^[3,4]. In recent years, opiate-induced constipation (OIC) has attracted much attention because it is frequently occurred in cancer patients receiving chemotherapy^[5-7]. The handling and management of constipation continue to evolve. Although osmotic laxatives such as polyethylene glycol remain mainstay, several new agents that target different mechanisms appear promising such as chloride-channel activator (lubiprostone), 5HT₄ agonist (prucalopride), guanylate cyclase agonist (linaclotide), and peripherally acting μ -opioid receptor antagonists (alvimopan and methylnaltrexone) for OIC^[8-11]. Thus, development of a better treatment for handling of OIC in cancer patients receiving chronic opioid therapy is urgent.

Some opioid analgesics are thought to cause OIC via opioid receptors^[12,13]. In addition, the previous report showed that opioid peptides revealed the relaxant effects in the rat small intestine, which was associated with the involvement of opioid μ -receptors^[14]. Loperamide is commonly used in clinic for a variety of diarrheal syndromes, including acute and nonspecific (infectious) diarrhea^[15-17]. Loperamide has been introduced as the peripheral agonist of opioid μ -receptors with poor ability to cross the blood-brain barrier^[18,19]. In an attempt to clarify the subtype of opioid μ -receptors in regulation of intestinal tone, loperamide is used as an agonist to induce intestinal relaxation, and specific antagonists are applied to investigate the potential mechanism(s) in OIC.

On the other hand, ATP-sensitive K⁺ (KATP) channels are involved in the regulation of intestinal smooth muscle^[20]. Actually, KATP channel opening is introduced to lower intracellular Ca²⁺ concentration^[21-23]. Moreover, the KATP channel opener, diazoxide had the ability to attenuate indomethacin-induced small intestinal damage in rats^[24]. Thus, the role of KATP channel in opiate-induced gastrointestinal transit seems important.

ROLE OF OPIOID RECEPTOR IN OPIATE-INDUCED CONSTIPATION

Opioid receptors are a group of G protein-coupled receptors with opioids as ligands^[25,26]. In general, opioid receptors can be divided into three subtypes, including μ , κ , and δ ^[27,28]. Among the three subtypes, opioid μ -receptors can protect against colitis through anti-

inflammatory effects on the regulation of cytokine production and T cell proliferation, two important immunologic events required for patients with inflammatory bowel disease (IBD) and the development of colitis in mice^[29]. In addition, opioid receptors play an important role in the regulation of gastrointestinal transit^[30,31]. The cellular expression patterns of mu-, delta- and kappa-opioid receptors in the rat ileum have been identified using fluorescence immunohistochemistry^[32]. The previous study showed that loperamide caused a dose-dependent delay of gastrointestinal transit using charcoal meal test in mice^[33]. Also, loperamide induced relaxation in ileum strips of mice contracted with acetylcholine, which suggests the possible mechanism of OIC. The loperamide-induced constipation seems mainly related to the activation of intestinal opioid receptors because loperamide can't penetrate into central nervous system^[19].

Clinical studies have proved the concept that some peripherally acting μ -opioid receptor antagonists can prevent OIC without interfering with analgesia^[34-38]. In addition, opioid μ -receptors myenteric neurones are most numerous in the small intestine, followed by the stomach and the proximal colon, and their immunoreactive fibres are dense in the muscle layer and the deep muscular plexus, where they are in close association with interstitial cells of Cajal^[39]. Generally speaking, opioid μ -receptor has been divided into 3 subtypes, including μ -1, μ -2 and μ -3 opioid receptors^[40-42]. The analgesic action through activation of opioid μ -1 receptors has been reported to exert spinal antinociception^[43,44]. Besides, activation of opioid μ -1 receptors seems associated with smooth muscle contraction via PLC-PKC pathway^[45,46]. Moreover, opioid μ -3 receptors are mostly presented in endothelial cells associated with the production of nitric oxide to induce vasodilatation^[47,48]. Although constipation is mainly a large bowel manifestation, the intestinal motility was investigated to account for OIC in the previous study^[33]. The loperamide-induced constipation is effectively attenuated by a specific opioid μ -receptor antagonist, cyprodime, indicating an activation of opioid μ -receptors. Nevertheless, the loperamide-induced constipation was not reversed by naloxonazine which can block opioid μ -1 receptors^[33]. Thus, mediation of opioid μ -1 receptors seems not involved in the loperamide-induced constipation. Taken together, mediation of opioid μ -1 or μ -3 receptors in OIC can be ruled out. On the other hand, an activation of opioid μ -2 receptors is more reliable to participate in the action of OIC. Actually, activation of opioid μ -2 receptors has been mentioned to be correlated with the relaxation of guinea pig ileum and inhibition of gastrointestinal transit^[36,49], which demonstrates OIC is related to activation of opioid μ -2-receptors.

THE POTENTIAL MECHANISMS OF OPIATE-INDUCED CONSTIPATION

Since intestinal relaxation can delay gastrointestinal transit, slow gastrointestinal transit leads to constipation^[50,51]. Speaking of intestinal relaxation, potassium channels play an important role in the regulation of intestinal smooth muscle cells^[52,53]. Moreover, the ATP-sensitive K⁺ (KATP) channels are composed of four inwardly rectifying K⁺ channel subunits and four regulatory sulphonylurea receptors^[54]. The activation of KATP channels causes hyperpolarization of cell membrane and consequently relaxes smooth muscle. Thus, the involvement of KATP channels in intestinal relaxation is associated with OIC. Additionally, forskolin was applied as a positive reference because forskolin has been introduced as the direct activator of adenylate cyclase that can increase the intracellular cyclic AMP (cAMP) to activate cAMP-dependent

protein kinase (PKA) for opening of KATP channels^[55,56]. Forskolin-induced intestinal relaxation was attenuated by glibenclamide^[33] or abolished by H-89 at the concentration sufficient to block PKA^[55,57] and enhanced by IBMX at concentration enough to inhibit cAMP-phosphodiesterase^[58]. Some studies report that intestinal smooth muscle contains several cyclic nucleotide phosphodiesterase enzymes (PDE) isozymes and that selective inhibition of PDE isozymes can increase cyclic nucleotide content to affect intestinal motility and antagonize contractile responses^[59,61]. The potential mechanism for OIC is possibly mediated through cAMP-PKA pathway to open KATP channels. Therefore, the evidence provides a novel insight into the action mechanisms of opioid μ -receptors especially the understanding of OIC.

CONCLUSION

In conclusion, the activation of opioid μ -2 receptor to open KATP channels seems responsible for the mechanism of OIC. Therefore, the development of antagonists for peripheral opioid μ -2 receptors will be beneficial for handling of OIC in cancer patients receiving chronic opioid therapy.

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