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Mini-review

## Opioids and opioid receptors in the enteric nervous system: from a problem in opioid analgesia to a possible new prokinetic therapy in humans<sup>☆</sup>

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### Abstract

The gut is a neurological organ, which implies that many neuroactive drugs such as opioid analgesics can seriously disturb gastrointestinal function, because many of the transmitters and transmitter receptors present in the brain are also found in the enteric nervous system. One of the most common manifestations of opioid-induced bowel dysfunction is constipation which results from blockade of peristalsis and intestinal fluid secretion. The discovery of opioid receptor antagonists with a peripherally restricted site of action, such as N-methylnaltrexone and alvimopan, makes it possible to normalize bowel function in opiate-treated patients without compromising central opioid analgesia. There is emerging evidence that opioid receptor antagonists may also have prokinetic actions, reversing pathological states of gastrointestinal hypomotility that are due to overactivity of the enteric opioid system.

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*Prologue.* Although hardly containing any opiates, poppy seeds represent a delicacy of the Hungarian, Bohemian and Austrian cuisine, to name a few. It is not totally inappropriate, therefore, that endogenous opioid peptides were identified with a gastrointestinal (GI) bioassay in which opioid receptor agonists are quantified by their ability to inhibit electrically evoked contractions of the guinea-pig ileum. The explosion of neuropeptide research that followed the discovery of opioid peptides led Manfred Zimmermann to initiate the foundation of the European Neuropeptide Club and to be elected as its inaugural president. At the Second Meeting of the Club in 1992, Manfred Zimmermann gave a dinner speech in the Villa Le Molina near Pisa, in which he deliberated on the bidirectional brain-gut connection. He mentioned that motivations determining brain thought and action are likely to have a strong input from the gut, mediated by a wealth of neuropeptides and their receptors, and that the gut therefore may even have had political impact in history. This issue had previously been contemplated about by the French philosopher Voltaire who once remarked: “The fate of a nation has often depended on the good and bad digestion of its Prime Minister.” Manfred Zimmermann went on to hypothesize

that, along the same neuronal network, the gastronomic richness we are enjoying now in a free Europe may facilitate progress in the unity of Europe.

*The gut as a neurological organ.* The function of the GI tract is not only to ensure the metabolic survival of the body but also to sort the ingested food in terms of its nutritive, toxic and pathogenic properties. These tasks are under multiple control systems among which neurons are particularly important. Since the alimentary canal is equipped with the largest collection of neurons outside the central nervous system (CNS), the gut can rightly be considered as a neurological organ [16]. The communication network of the enteric nervous system (ENS) involves acetylcholine, tachykinins (substance P, neurokinin A), nitric oxide, adenosine triphosphate, vasoactive intestinal polypeptide, opioid peptides, neuropeptide Y and 5-hydroxytryptamine as major transmitters. Enteric neurons supply all layers of the alimentary canal and thus are in a position to regulate virtually each aspect of digestion [16].

The ENS is arranged in polarized circuits that typically are composed of intrinsic primary afferent neurons, a variable number of interneurons and excitatory or inhibitory output neurons to the effector tissues (motor, secretomotor and vasodilator neurons). As the intrinsic primary afferent neurons supply the information that is required to regulate digestion according to need, the ENS issues its own programmes to

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govern the activity of the GI effectors independently of the CNS [16]. A typical ENS programme is the motor pattern of intestinal peristalsis which involves a temporally and spatially coordinated interaction of several polarized pathways of the ENS with the muscular layers of the intestine and thereby propels the intestinal contents in an aboral direction. GI ion and fluid secretion, circulation, endocrine and immune activity are also regulated by the ENS [16].

*The gastrointestinal tract as a victim of neuroactive drugs.* The significant role which neurons play in GI function has implications that extend beyond gastroenterology. On the one hand, various diseases and disorders of the GI tract are now thought to be related to neuropathies of enteric, sensory or autonomic neurons, alterations in gut-brain communication or changes in the brain-gut axis [16]. On the other hand, neuroactive drugs such as those used in neurology, psychiatry, anaesthesiology and intensive care medicine can disturb ENS function, because many of the transmitters and transmitter receptors present in the brain have also been localized to the ENS. This is particularly true for opioid receptors and adrenoceptors whose activation by opiates and catecholamines, respectively, interferes with ENS pathways involved in motility and secretion [6,7].

*Adverse effects of opiates on gut function: opioid-induced bowel dysfunction.* Morphine and related opioid analgesics are the mainstay of therapy in many patients with moderate to severe pain. A delay in GI transit and constipation are the most common and often disabling side effects of opiates, which result from blockade of propulsive peristalsis, inhibition of intestinal ion and fluid secretion and an increase in intestinal fluid absorption [6]. Importantly, though, constipation is just one symptom of an often under-recognized condition known as opioid-induced bowel dysfunction (OBD), whose manifestations also include incomplete evacuation, abdominal distension, bloating, abdominal discomfort and increased gastro-oesophageal reflux and which may lead to secondary complications such as pseudo-obstruction of the bowel, nausea, vomiting as well as interference with oral drug administration and absorption [10,20]. Although centrally mediated effects of opiates to slow GI transit have also been implicated in the pathophysiology of OBD, opiate-induced blockade of gut motility correlates better with opiate concentrations in the ENS than with opiate concentrations in the CNS [10]. It is, therefore, widely assumed that the adverse effects of opiates on GI function result primarily from interaction with opioid receptors in the gut [20].

*Opioids and opioid receptors in the gastrointestinal tract.* The adverse effect of opioid analgesics on GI function is consistent with the expression of opioid peptides [5,11] and opioid receptors [9,27] by distinct enteric neurons and intestinal muscle cells. When released from these neurons, opioid peptides are likely to play a transmitter role in the enteric regulation of propulsive motility and secretory processes [6,15,26]. The inhibitory effect of opioid receptor agonists on peristalsis is thought to arise primarily from interruption of transmission within enteric nerve pathways

governing muscle contraction [30]. Transmission is blocked via a presynaptic site of action, whereby the release of acetylcholine and other excitatory transmitters is attenuated, although postsynaptic effects have also been described [6]. However, the action of opiates on GI motility is subject to species differences. Thus, besides inhibiting peristalsis, opiates may block propulsive motility also by evoking tonic spasms in the intestine of humans and other species. The effect of opiates to contract intestinal muscle may involve depression of nitric oxide release from inhibitory enteric neurons [2,21] or direct activation of muscle cells that express opioid receptors [14,23]. Induction of stationary segmentations combines with inhibition of peristalsis and depression of secretory activity to bring about constipation.

The actions of opioids on the GI tract are mediated by multiple opioid receptors. Studies with isolated tissues from the human intestine suggest that delta-, kappa- and mu-opioid (OP<sub>1</sub>, OP<sub>2</sub> and OP<sub>3</sub>) receptors contribute to opiate-induced inhibition of muscle activity [1,3]. Peristalsis in the rat intestine is blocked by delta- and mu-opioid, but not kappa-opioid, receptor agonists [6], whereas peristalsis in the guinea-pig intestine is suppressed by activation of kappa- and mu-opioid, but not delta-opioid, receptors [26]. Opiate-induced inhibition of cholinergic transmission in the guinea-pig gut is likewise mediated by mu- and kappa-opioid receptors [18].

*Management of opioid-induced bowel dysfunction by opioid receptor antagonists with a peripherally restricted site of action.* The symptoms of OBD are predominantly mediated by peripheral mu-opioid receptors [10,20], given that mu-opioid receptors take a prominent position in mediating opiate actions in the gut of humans and other species and the most effective opioid analgesics are mu-opioid receptor-selective agonists. In view of the additional presence of delta- and kappa-opioid receptors in the human GI tract it appears unlikely that the GI adverse effect profile of opioid analgesics could be overcome by the use of delta- or kappa-opioid receptor-selective agonists. An alternative approach that has therefore been chosen is to selectively target peripheral opioid receptors with orally administered opioid receptor antagonists that have limited systemic absorption [10,20]. As a number of studies has shown, this approach is successful in preventing OBD while saving the analgesic action of opiates which is preferentially mediated by central mu-opioid receptors. The search for gut-selective opioid receptor antagonists has been spurred by the discovery of the mu-opioid receptor-selective agonist loperamide which is used as an antidiarrhoeal drug without having an analgesic action.

The first attempt to selectively target opioid receptors in the periphery was made with the pan-opioid receptor antagonist naloxone and related tertiary opioid receptor antagonists such as nalmefene [10,17]. Since the systemic bioavailability of oral naloxone is as low as 2% because of extensive first-pass metabolism, this compound has been found to improve OBD without alleviating opiate-induced analgesia. However, the therapeutic index of naloxone turned out to be very narrow and

its utility limited because of the need to titrate peripherally versus centrally active doses [28].

A break-through advance was the development of quarternary opioid receptor antagonists such as N-methylnaltrexone whose absorption following oral administration is very low (oral bioavailability < 1%) and which does not cross the blood–brain barrier [10]. When this compound is given together with a centrally active opioid receptor agonist, the analgesic action of the opiate is maintained whereas the peripheral adverse effects on GI function are prevented in non-rodent animals and humans [10]. The species-dependence of the peripheral selectivity of N-methylnaltrexone is related to demethylation of the compound to naltrexone in rodents but not humans, naltrexone in turn being able to reach the CNS. Apart from its therapeutic potential, the action of N-methylnaltrexone to decrease the GI side effects of acute and chronic opiate treatment while preserving analgesia reinforces the concept that OBD is primarily brought about by activation of opioid receptors in the gut. Furthermore, the separation of the central wanted from the peripheral unwanted effects of opiates with N-methylnaltrexone allows for a more aggressive use of opioid analgesics with better pain relief but fewer side effects [10].

Following the proof of concept with N-methylnaltrexone (which is a non-selective, though mu-opioid receptor-preferring antagonist), a mu-opioid receptor-selective antagonist with a peripherally restricted site of action was developed. This compound, alvimopan (ADL 8-2698, formerly known as LY246736), has both low systemic absorption (oral bioavailability of 0.03% in dogs) and a limited ability to enter the CNS [25]. This spectrum of properties enables alvimopan to prevent morphine from delaying GI transit in healthy subjects without antagonizing central morphine effects such as analgesia and pupillary constriction [22]. A similar activity profile was seen in patients treated with opiates for chronic pain or opioid addiction, in which alvimopan reversed OBD without compromising opioid-induced analgesia or provoking CNS symptoms of opioid withdrawal [25]. Furthermore, alvimopan was found to improve the manage-

ment of postoperative ileus in patients who underwent abdominal surgery and received opioids for acute postoperative pain [29]. In this study, the time to achieve normal bowel function after the operation and the duration of hospitalization were shortened and the overall incidence of GI side effects including postoperative nausea and vomiting was reduced by alvimopan, whereas analgesia was not compromised [29].

*Opioid receptor antagonists with a peripherally restricted site of action as possible prokinetic drugs.* There is good reason to predict that opioid receptor antagonists with a peripherally restricted site of action may become important adjuncts of opioid analgesic therapy in order to avoid OBD [10,19,25]. I want to propose here that peripherally restricted opioid receptor antagonists may also have potential to alleviate intestinal motor stasis unrelated to opiate use. Such a prokinetic action can be envisaged from the finding that the pan-opioid receptor antagonist naloxone as well as selective mu- and kappa-opioid receptor antagonists can per se facilitate propulsive peristalsis in the guinea-pig isolated small intestine (Fig. 1) [6,15,26]. It follows that endogenous opioid peptides released in the course of propulsive motility [8] play an important role in the neural control of peristalsis as they dampen peristaltic performance via activation of mu- and kappa-opioid receptors [26]. This inference is consistent with the effect of mu- and kappa-opioid receptor antagonists to enhance the release of acetylcholine from the myenteric plexus [4] and of naloxone to increase the release of substance P during peristalsis [8]. Similarly, N-methylnaltrexone is able to enhance neurogenic contractions in the isolated human small intestine [31].

Another reason to conjure a prokinetic action of opioid receptor antagonists derives from the ability of naloxone to rescue propulsive motility from blockade by noradrenaline, atropine and hexamethonium [13,15]. It thus seems as if motor inhibition caused by activation of adrenoceptors, muscarinic and nicotinic acetylcholine receptors in the ENS involves endogenous opioids which block distinct enteric transmission processes [15]. If it can be proved that

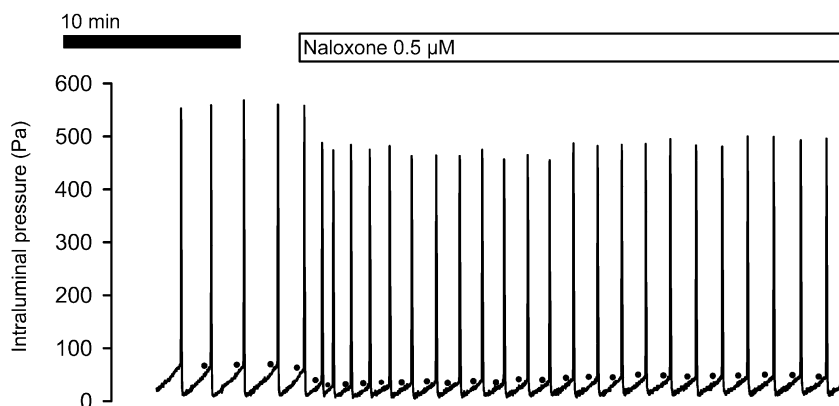


Fig. 1. Stimulant effect of naloxone (concentration as indicated) on propulsive peristalsis in an isolated segment of the guinea-pig small intestine. The stimulant effect of naloxone is evident from a decrease in the peristaltic pressure threshold at which peristaltic waves are elicited (indicated by dots) and from an increase in the frequency of peristaltic waves. For details see Shahbazian et al. [26].

upregulation and/or overactivity of the opioid system in the ENS is causally involved in pathological states of GI motor inhibition, there would be a rationale to test the prokinetic potential of peripherally restricted opioid receptor antagonists in various GI hypomotility states. There is indeed preliminary evidence that naloxone has beneficial effects in idiopathic chronic obstipation [19], intestinal pseudo-obstruction [24] and constipation-predominant irritable bowel syndrome [12].

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