The gut–brain interaction in opioid tolerance

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The prevailing opioid crisis has necessitated the need to understand mechanisms leading to addiction and tolerance, the major contributors to overdose and death and to develop strategies for developing drugs for pain treatment that lack abuse liability and side-effects. Opioids are commonly used for treatment of pain and symptoms of inflammatory bowel disease. The significant effect of opioids in the gut, both acute and chronic, includes persistent constipation and paradoxically may also worsen pain symptoms. Recent work has suggested a significant role of the gastrointestinal microbiome in behavioral responses to opioids, including the development of tolerance to its pain-relieving effects. In this review, we present current concepts of gut–brain interaction in analgesic tolerance to opioids and suggest that peripheral mechanisms emanating from the gut can profoundly affect central control of opioid function.

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Introduction

Opioids are the most effective and highly prescribed analgesics. The therapeutic effects of morphine and other opioids are limited by their side effects that include nausea, vomiting, abdominal pain and constipation that are collectively referred to as 'opioid induced bowel dysfunction' [1,2]. Opioid-induced constipation is the most common of these symptoms and arises largely due to inhibition of peristaltic activity, increased sphincter tone and segmental non-propulsive contractions. These effects of opioids result in dry and hard feces and chronic use paradoxically may also be associated with increased abdominal pain. The over-prescription of opioids in the recent decades, and the current crisis of increasing deaths due to opioid overdose has highlighted the need for better understanding of mechanisms of opioid function. More recently, the role of the gut–brain axis in physiological processes has been identified and novel concepts have emerged regarding mechanisms by which the effects of opioids in the gastrointestinal tract alter what was thought to be an exclusive central effect of analgesic tolerance and hyperalgesia. In this review we summarize some of these current findings and illustrate potential areas for further research to develop better therapeutics for pain treatment.

Of the three major G-protein coupled and naloxone-sensitive opioid receptors, μ, κ, and δ, the major aspects of opioid function on gastrointestinal motility occur as a result of the activation of the μ opioid receptor. The classes of opioid receptors and their functional localization within the gastrointestinal tract have been reviewed recently [3–5]. In the GI tract, opioid receptors are mainly expressed on neurons within the myenteric and submucosal plexus throughout the gastrointestinal tract at both pre- and post-synaptic membranes and on the cell bodies within the ganglia. The activation of the μ receptor in neurons within the myenteric ganglia or on nerve terminals innervating smooth muscle cells reduces motility, while activation of submucosal neurons reduces secretion. The inhibition of neuronal activity affects pain transmission in the central neurons whereas in the gastrointestinal tract, both secretory functions and muscle contractility are altered upon opioid receptor activation in enteric neurons. Reduced excitability of neurons is due to opioid modulation of ionic conductances, particularly inwardly rectifying potassium channels and inhibition of sodium and calcium channels. Several μ-opioid agonists increase potassium conductance [6] that results in membrane hyperpolarization thus preventing action potential generation. More recently, voltage clamp studies in isolated myenteric neurons have shown that morphine inhibits tetrodotoxin (TTX)-resistant sodium channels on neuronal cell bodies thus affecting the threshold for action potentials [7,8]. Sodium channels were inactivated in the presence of morphine thus rendering the neurons incapable of firing multiple action potentials resulting in an overall decreased excitability. The receptor mediated biophysical alterations of the sodium channel by opioids underlie the potential cellular basis for reduced neuronal excitability of enteric neurons. Interaction of morphine with activation of inwardly rectifying potassium channels and inhibition of calcium channels involves direct interaction of G-protein subunits in a membrane delimited pathway following receptor activation [9]. Whether similar mechanisms are involved with inhibition of TTX-resistant sodium channels in enteric neurons is not

known. The reduced excitability of motor and sensory neurons in the myenteric plexus reduces motility and sensory transmission, including the extrinsic pathway whose cell bodies lie within the dorsal root ganglia thus modulating pain transmission to central neurons emanating from the gastrointestinal tract.

In addition to coupling to ion channels, μ opioid receptor mediated analgesia is linked to several signaling pathways including inhibition of adenylate cyclase, β-arrestin recruitment, receptor phosphorylation by protein kinases C and A, and ERK 1/2, particularly in the context of tolerance development [10]. The relationship between β-arrestin2 and opioid tolerance development has been investigated recently with regard to drug development for novel pain analgesics with less side-effects, including opioid-induced constipation. Understanding tolerance development to repeated use of opioids is central to drug development for novel analgesics. It is now clear that in both animals and man the rate and extent of tolerance to most opioids develops at different rates and to different extents. For example, tolerance to analgesia and euphoria occurs faster than to respiratory depression and predisposes to the potential for death due to overdose [11]. Tolerance does not develop to the constipating effects of opioids, resulting in persistent constipation [4].

It is well documented that recruitment of β-arrestin2 following receptor activation mediates additional signaling pathways and also results in receptor internalization and forms one of the basic pathways for tolerance development [10]. Thus, antinociceptive tolerance does not occur in the β-arrestin2 knockout mice. The role of β-arrestin2 in tolerance to morphine mediated inhibition of gastrointestinal motility differs from that to antinociceptive tolerance. Chronic exposure to morphine in the mouse ileum reduces β-arrestin2 expression and induces tolerance [12]. In the colon however, β-arrestin2 remains elevated following chronic morphine and is associated with lack of tolerance development. The disparate effects of morphine tolerance between one clinical effect, i.e. constipation versus another, i.e. analgesia have been exploited to develop biased agonists that would preferentially activate G proteins but do not recruit β-arrestin2 resulting in agents with significant analgesic effects without the adverse effects of analgesic tolerance and constipation [13]. The experimental and clinical evidence for reduced gastrointestinal motility remains unclear. Oliceridine (TRV130) is a G-protein biased ligand with low levels of β-arrestin2 recruitment and was reported to produce antinociception with reduced signs of constipation [14]. However, recent studies show that with repeated administration *in vivo*, TRV130 significantly reduced gastrointestinal motility and prevented antinociceptive tolerance [15]. In a phase 2 trial in a bunionectomy model, TRV130 at 1 mg was equi-analgesic to morphine (4 mg) but induced constipation in 15% (6/38)

of patients compared to 5% (2/39) for morphine [16]. A structurally different μ opioid compound, PZM21, recently reported as a G-protein biased agonist with minimal β-arrestin2 recruitment, also reduced gastrointestinal motility. Although it was reported that PZM21 was less potent in reducing gastrointestinal motility than morphine, an equi-analgesic dose to morphine was not tested [17]. These findings highlight the complexity of the different mechanisms between opioid-induced constipation and analgesia.

Opioid-induced gut brain interaction

Clinical studies have demonstrated that narcotic use escalates the disease severity of patients with Crohn's disease (CD) and may be associated with increased recurrence from remission [18]. Data from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) Registry comprises over 6000 patients with CD, suggest that narcotic use was associated with a 1.5 fold increased risk of mortality and 3-fold increased risk of infection compared to patients not taking opioid analgesics [19,20]. The increased risk of infection can arise from bacterial translocation in the colon and lead to sepsis [21] and immune dysregulation that occurs not only in the GI tract but also systemically [22]. Recent studies show that chronic opioid use is associated with microbial dysbiosis in man [23•,24•] and mice [25,26,27•]. The disruption of gut epithelial barrier by chronic morphine in mice enhances 'leakiness' allowing for bacterial translocation in ileum [26] and in colon [27•]. Meng et al. [26] reported disruption of the gut epithelial barrier as a result of morphine mediated activation of the toll-like receptors (TLR) on the epithelial cells, allowing for bacterial products to translocate. Both Gram-positive and Gram-negative bacterial products can activate toll-like receptors (TLRs) on immune cells and enteric glia [28]. Enteric glia are key players in mediating GI functions and are importantly involved in immune modulation through their interaction with enteric neurons. Bhave et al. [29•] found that activation of the connexin-purinergic pathway in enteric glia by the bacterial product, lipopolysaccharide, was a significant source of cytokine release with chronic morphine treatment. *In-vivo* treatment with chronic morphine resulted in upregulation of P2X purinergic receptors and enhanced ATP induced currents in the enteric glia from the mouse colon. P2X receptors are cation channels allowing for calcium entry, an essential component in cytokine release. Furthermore, the bacterial product, LPS upregulated connexin43 (Cx43) expression in enteric glia cells. Cx43 are hemichannels through which ATP is released. Thus, the combination of Cx43 and P2X receptor upregulation in enteric glia with chronic morphine provides a significant amplification of an inflammatory response as purines are also a large component of the inflammatory soup [30]. Inhibition of Cx43 by carbenoxolone reversed chronic opioid-induced constipation in mice [29•].