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REVIEW

Current overview of opioids in progression of inflammatory bowel disease; pharmacological and clinical considerations

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Abstract

Inflammatory bowel diseases (IBD) belong to a subgroup of persistent, long-term, progressive, and relapsing inflammatory conditions. IBD may spontaneously develop in the colon, resulting in tumor lesions in inflamed regions of the intestine, such as invasive carcinoma. The benefit of opioids for IBD treatment is still questionable, thereby we investigated databases to provide an overview in this context. This review demonstrates the controversial role of opioids in IBD therapy, their physiological and pharmacological functions in attenuating the IBD symptoms, and in improving inflammatory, oxidative stress, and the quality of life factors in IBD subjects. Data were extracted from clinical, in vitro, and in vivo studies in English, between 1995 and 2019, from PubMed, Google Scholar, Scopus, and Cochrane library. Based on recent reports, there are promising opportunities to target the opioid system and control the IBD symptoms. This study suggests a novel approach for future treatment of functional and inflammatory disorders such as IBD.

Keywords Inflammatory bowel diseases · Opioids · Opioid receptors · Inflammation

Introduction

Inflammatory bowel diseases (IBD) consist of Crohn's Disease (CD) and Ulcerative Colitis (UC). These chronic diseases of the gastrointestinal (GI) tract are marked by periods of relapses and remissions. The most common symptoms in CD are fatigue and abdominal pain, while in UC, bloody stools, urgent bowel movement, and diarrhea are more prevalent [1]. Clinical, in vivo, and in vitro evidence confirmed the multi-factorial nature of IBD. First reports of IBD stem from traditionally high-incidence areas, such as North America, as well as Northern and Western Europe. During the last two decades, statistics revealed that the incidence rate of IBD is increasing in Eastern European and Asian countries, while the incidence rate in Western countries is decreasing [2]. Advances in single-cell analysis of samples from extensive IBD cohort studies, and IBD animal models, illustrated that many cytokines and

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cellular pathways contribute to the intestinal inflammation [3]. Cytokines seem to play key roles in driving the intestinal inflammation and local complications in IBD patients. Therefore, modulation of these cytokines may be applicable as a novel therapeutic pathway for IBD. As a result, tumor necrosis factor-alpha (TNF-α) and pro-inflammatory cytokines [i.e., a number of interleukins (ILs)] are the main targets for IBD treatment. Optimized delivery systems, personalized medicine, and approaching novel targets for cytokines, may improve clinical strategies in IBD patients [4, 5]. Current treatments are mainly based on immunomodulatory therapies. The efficacy and safety of antidepressants for treating the anxiety and depression in IBD were also evaluated, although the outcomes showed no firm conclusions. Recent evidence suggests the potential anti-inflammatory effect of cannabis [6].

Opioids are analgesic agents that are commonly used to alleviate pain, either associated with malignant or non-malignant diseases. Opioids may appear profitable in the alleviation of the main hallmarks of IBD, for instance, inflammation, oxidative stress, abdominal pain, diarrhea, and reduced the quality of life (QOL). On the other hand, chronic use of opioids may be accompanied by multiple side effects including constipation, respiratory depression, and cognitive dysfunction [7]. Opioid misuse, addiction, and overdoses are serious crisis worldwide, particularly over the past 30 years. Considering their analgesic properties, opioids are overprescribed by physicians to control pain, which may lead to their misuses. Thereby, restrictive laws were enacted and have to be revised regularly. Ultimately, reimbursement became tied to patients' perception of pain control. As a result, using more extensive amount of opioids was led to dependence and patients sought more in use. Uncontrolled usage of opioids is an important factor in the increasing death rate from opioid overdoses. In addition, identification of social, genetic, behavioral, and individual factors that are root causes of opioid misuse is a duty to health care providers, hospitals, the pharmaceutical industry, and government agencies to advocate social change and to control such a crisis [8].

This review intended to summarize the beneficial effects of opioids in IBD patients; the significant impact of opioid receptors in inflammation reduction, the remarkable decrease of inflammatory cytokines in the intestinal mucosa, improvement of wound healing and decline of the endoplasmic reticulum oxidative stress in inflamed mucosa and other effects of narcotic use in IBD subjects.

Search strategy

An electronic search in PubMed, Google Scholar, Scopus, and Cochrane library was performed and relevant clinical, in vivo and in vitro articles from 1995 to 2020 were collected. Search terms included "Inflammatory bowel disease" OR "IBD" OR "Opioids" OR "Opioid receptors" AND "Inflammation". From a total of 16,100 results, 9933 were excluded because of duplication, 12 reports were omitted for being reviews, and 6601 studies were deleted for being irrelevant to the subject of this study. Among 442 retrieved papers, finally, 175 articles including 19 in vitro or/and in vivo studies, as well as 10 human studies were used in this review. In this study, language restriction was applied and non-English articles were not considered.

Opioid receptors and their ligands

Opioid receptors are G protein-coupled receptors that are expressed by different body parts such as the central and peripheral neurons, immune cells, ectodermal cells, and the GI track. Opioid receptors are classified into three main types: the mu, delta, and kappa receptors (μ, K, δ). Mu opioid receptors (MORs) are located in the cerebral cortex, thalamus, and periaqueductal gray [9]. Binding of an agonist {i.e., DAMGO ([D-Ala, N-MePhe, Gly-ol]-enkephalin), Morphine, Fentanyl, Endomorphins (EMs), and β-endorphin} to its receptor can cause analgesia, euphoria, physical dependence, constipation and respiratory depression [9]. Naloxone (a non-selective opioid receptor antagonist) was shown to antagonize these effects. MORs have crucial responsibilities in goal-directed behavior, social attachment, and anhedonia. Long-term abuse of opioid agonists may increase the corticotropin-releasing factor (CRF) signaling [10]. In the GI, MORs are localized at the myenteric and submucosal neurons, and on the immune cells of the lamina propria. Activation of MORs blocks neural pathways through the enteric nervous system (ENS) that adjusts motility. Inhibition of this pathway increases the GI muscle activity, the resting muscle tone, spasm, and non-propulsive motility patterns, resulting in delayed gastric emptying [11]. Activation of submucosa inhibits the secretion of water and electrolyte into the gut lumen and elevates the fluid absorption from the intestine and blood flow in the intestinal wall [12].

Delta opioid receptors (DORs) are mainly located at basal ganglia. Binding of an agonist (i.e., Enkephalins, Deltorphin, β-endorphin) to its receptor leads to analgesia, convulsions and anxiolysis. These effects are antagonized with Naltrindole and Naloxone. Activation

of DORs can reduce the levels of anxiety and depressive symptoms [9]. Eventually, a decrease in DORs activities is associated with increased ethanol-drinking behavior. In the GI, DORs are located at both plexuses, where it is predominantly in varicose fibers in the plexuses, muscle, and mucosa [11].

Kappa opioid receptors (KORs) are located at the hypothalamus and periaqueductal gray. Binding of an agonist (i.e., Bremazocine, Dynorphin) to its receptors causes analgesia, diuresis, and dysphoria. These effects are antagonized with Norbinaltorphimine and Naloxone [9]. In the GI, KORs appear to be confined to the myenteric plexus and bundles of muscle fibers. Stimulation of Dynorphin/KOR and CRF was shown to contribute to dysphoria formation [10]. Peripheral MORs and DORs induce constipation and reduce inflammation [9]. Recently, a different category of opioid receptors has been found, named as opioid receptor like receptor 1 (ORL1), also called as LC132, XOR1, kappa 3, ROR-C, and C3. It was shown that high concentration of Etorphine (opiate agonist) activates, and high concentration of Naloxone inhibits the ORL1. The ligands that bind to these receptors are in fact neuropathies called Nociceptin (N) and Orphanin FQ (OFQ). ORL1 includes several conserved amino acids and motifs. ORL1 is majorly consisted of two parts; the intracellular loop (responsible for the activation and interaction with the G proteins contributed in conformational changes through receptor activation (microswitches)), and the extracellular loop. The ligand-binding pocket is restricted by the transmembrane helices, with residues from TM3, TM5, TM6, and TM7 that interact with ligand in the binding pocket [13]. Molecular techniques exhibited that in peptide agonist N/OFQ, the N-terminal sequence F-G-G-F binds to the transmembrane binding pocket, where the N-terminal amino group of N/OFQ interacts with agonists [14]. In IBD condition, MOR and KOR antagonists possess anti-inflammatory effects, decrease the macroscopic and ulcer scores, colonic wall thickness, myeloperoxidase (MPO) activity, body weight loss and the pro-inflammatory cytokines expression [15].

In a study conducted on dextran sulfate sodium (DSS)-induced colitis wild type mice and nociception receptor (NOR)-deficient mice, upon Noc/OFQ treatment, the body weight reduced in wild-type mice but not in NOR-deficient animals. Subsequent to treatment, the Noc/OFQ was up-regulated and the MAdCAM-1 expression level increased in both groups. Following the administration of DSS in wild-type mice, the Nociceptin expression and the number of β7-integrin-positive cells enhanced. In non-treated wild-type or NOR-deficient mice, the vascular cell adhesion molecule 1 gene was not expressed, although the intercellular adhesion molecule 1 gene was expressed [13].

Endogenous opioids

The central nervous system (CNS) and peripheral tissues such as adrenal glands, are the main manufactures of endogenous low-molecular opioid peptides. Under stress conditions like inflammation or cancer, these natural ligands bind to opioid receptors. There are three types of opioid peptides, including endorphins, enkephalins, and Dynorphins, with a similar structure to enkephalin at the N-terminus and dissimilar sequences at the C-terminus. These opioid peptides are synthesized via cleavage of 3 precursor proteins: Proopiomelanocortin (POMC), Prodynorphin (PDYN), and Proenkephalin (PENK). POMC is the precursor of a- and b-endorphin, and some non-opioid peptides such as Dynorphin A and B, as well as neoendorphin a and b. PENK is a precursor for several types of enkephalins, including Leu-enkephalin, Met-enkephalin, etc. b-endorphin showed comparable affinity towards MORs and DORs, Dynorphins belong to KORs agonist, whereas enkephalins have been associated with DORs [16].

In the GI tract, endogenous opioid peptides are found to control the intestinal motility and secretion. In the GI tract, these peptides are located at the neural networks and endocrine cells, particularly the ENS. PENKs are mainly placed at myenteric neurons and submucosal plexus, while PDYNs are confined to submucosal and myenteric neurons, as well as fibers of the celiac ganglion. In ENS, enkephalins and Dynorphins are co-localized with major neural transmitters such as acetylcholine (ACh) or peptides like substance P (SP), though, endorphin peptides are more likely limited to endocrine cells. Enkephalins are short length peptides, mainly produced in the GI tract, as well as the gastric, and intestinal endocrine cells [17]. [Leu5] enkephalin and [Met5] enkephalin are two types of enkephalins that participate in molecular signaling through opioid receptors. Both peptides have high agonist affinity for DORs and to a lesser extent for MORs. Physiologically, enkephalins are antinociceptive peptides, able to mediate the analgesia and pain signals in the CNS and periphery, especially the GI tract, to inhibit and exacerbate nociception and may be involved in inflammatory pathways. Initially, N/OFQ was identified as the endogenous ligand. Next studies disclosed that N/OFQ and its receptor (N/OFQergic system) are widely distributed in the central and peripheral nervous systems (PNS) as well as the GI tract of humans and animals. N/OFQ is involved in a broad spectrum of biological functions such as pain perception, intestinal motility and secretion, immune modulation, and stress [18]. None of the molecules that target the N/OFQergic system have succeeded in going through clinical trials, specifically due to the intestinal pathologies, indicating that further studies are requisite. A significant reduction in the messenger RNA (mRNA) expression of the nociceptin opioid peptide receptor (NOP) receptor in colonic biopsies

of male and female CD patients has been reported, but not in UC patients. In another study, the beneficial effect of a NOP-specific agonist in a mouse model of trinitrobenzenesufonic acid (TNBS)-induced intestinal colitis was proven. Together, these data suggest a protective role of the endogenous N/OFQergic system in IBD. Despite being controversial, all experimental studies indicated that there is a correlation between the N/OFQergic system and the intestinal inflammatory conditions (peptide, receptor or both), signifying an implication of this system in IBD [19].

Alkaloids and diterpenes

Morphine is an analgesic alkaloid that mainly is used to reduce the acute and chronic pain. The compound acts as a potent agonist of MORs, while it has weak affinity toward KORs. Morphine can pass through the blood brain barrier and affects the CNS. Prolonged and frequent administration of Morphine may cause tolerance, nausea, or sedation [20]. There are controversies about the effect of Morphine on the GI transit time, either through MORs, or the CNS and the periphery, or both. Advances in cellular and molecular techniques helped to characterize Morphine tolerance; however, it is not clear in case of the GI function [20].

Animal and clinical studies demonstrated that there is a regional difference between the acute and chronic administration of Morphine throughout the GI, mainly mediated by MORs and β-arrestin 2. Repeated administration of Morphine enhances tolerance to the Morphine analgesic effects in the upper GI, particularly in the circular muscle of the ileum but not in the colon. This leads to the suppression of β-arrestin 2 and reduces tolerance to Morphine, constipation and opioid bowel dysfunction (OBD). OBD defines as several GI side effects that are associated with opioid consumption such as constipation, nausea, vomiting, dry mouth, incomplete evacuation, gastric reflux, abdominal cramping, spasms, and bloating. Of note, opioid-induced constipation has been reported to be the most important and common GI complication related to OBD. OBD negatively affects the QOL in patients, mainly those receiving treatment for pain in cancer and in palliative care [21]. It was proposed that the transporter glycoprotein P may participate in opioid tolerance. In healthy adult horses, intravenous administration of Morphine (0.5 mg/kg), every 12 h for six days, reduced propulsive motility, and moisture content in the GI lumen [22]. Morphine and other alkaloids stimulate the immune response regulated by the opioid receptors in the GI tract. In mice fragment cultures of ileal segments, Peyer's Patches (PPs), and mesenteric lymph nodes; administration of a Morphine slow-release pellet led to specific inhibition of Ag-specific immunoglobulin (Ig)-A response in gut-associated lymphoid tissue through inhibiting the transforming growth factor (TGF). Morphine significantly inhibited the cholera toxin-specific IgA and IgG production levels in fragment culture supernatants and serum, which was modulated by opioid receptors.

In another study, Morphine suppressed the TGF-mRNA expression in PPs and ileal segments [23]. Administration of slow-release Morphine pellet (75 mg) accelerated oral infection with *Salmonella typhimurium* in mice, leading to typhoid fever in a murine model and caused gastroenteritis in humans. Morphine implementation via mini pumps could not alter the sensitivity to the *Salmonella* infection and heavily suppressed the GI transit in comparison with Morphine pellets [24]. These experiments suggest that Morphine may also be involved in bacterial infections.

Opioid receptors genes

Opioid receptors are encoded by OPRM1, OPRK1, OPRD1, and OPRL1 genes; induced by endogenous opioid peptides: beta-endorphin, prodynorphin, enkephalin, and nociceptin/orphanin. OPRM1, OPRD, and OPRK1 genes are responsible for inducing MORs, DORs, and KORs, respectively. OPRM1, OPRK1, and OPRD1 genes are located at cytogenetic band 6q25.2, on chromosome 8q11.2 and chromosome 1p36, respectively [25]. Opioid receptor genes are tightly preserved in their homologous coding exons, the 7-transmembrane domain, located at the center of each gene. In addition to the common 7-transmembrane domain, their DNA, amino acid sequences, and exon-intron boundaries (splicing junctions) are also homologous. However, these genes vary in their amino and carboxyl termini that results in diverse ligand binding and intracellular signaling patterns. All three genes are mediated through 2 main networks; (1) common pathways involving the member of Sp, AP1, Ik, NF-κB, and the Signal Transducer and Activator of Transcription (STAT) family; and (2) variant transcription factors specific to each gene. Of note, the importance of epigenetic regulation is undeniable. Beyond their similar gene regulatory mechanisms, each gene follows a particular route of expression, leading to the production of different mRNA isoforms. It has been suggested that each receptor gene is derived from alternative splicing, alternative promoters, alternative polyadenylation sites, or from the inclusion of non-coding exons, which results in distinct function and protein production [26]. OPRM1 gene includes 23 transcription variants, of which the primary subtype consists of four exons, and MOR-1O is the most abundant type. DORs contain three exons, and the main transcription variant of KORs has four exons (50 is non-coding) [27].

Exon 1 encodes the N-terminus and transmembrane domain I (TMI) of all opioid receptors, exon 2 encodes the distal TM domains (TMV–VII), and exon three induces TMII–IV and the intracellular C-terminus [28]. The most crucial polymorphism

in OPRM1 is A118G, a single nucleotide polymorphism (SNP), that encods an amino acid substitution (Asn40Asp). A118G participates in receptor binding or alters the expression ability of the gene. It was shown that SNP A/G (rs569356) upregulates the OPRD1 promoter activity by increasing the binding affinity of transcription factors. Evidence is pointing to the association and/or functionality of several SNPs in the opioid system genes, suggesting the involvement of these SNPs for future therapeutic approaches [26].

Opioid receptors in the gastrointestinal tract

The gut has the highest number of all neurons outside the brain, known as the ENS. Thus, this system actively expresses, synthesizes, and releases the transmitters, neuropeptides, and neuropeptide receptors like opioid peptides as their transmitters [16].

In the CNS, opioid receptors are located at the cerebral cortex, striatum, and hippocampus of the brain, whereas in the GI tract, opioid receptors are mainly sited at neurons of the ENS (the myenteric and submucosal plexus), smooth muscle cells, the terminals of sympathetic peripheral neurons, and endocrine cells of the intestinal mucosa. These receptors control the motility and secretion of the system and vary among different species [29]. For example, in rats, MORs have been detected in neurons of the submucosal and myenteric plexus, and in neurons innervating the GI smooth muscle, vasculature, and mucosa, as well as in the myenteric and deep muscular plexus. In the guinea pig, MORs are distributed in myenteric plexus neurons with higher density in the small intestine, mainly the ileum and smooth muscle layer of muscular plexus [29].

In the human GI system, DORs are found in the myenteric plexus of the ENS. DORs are implicated in enhancement of the SP and choline acetyltransferase production, which leads to the suppression of interneurons and the motoneurons that express nic oxide synthase (NOS). DORs are also distributed in nitrergic myenteric neurons in the mouse colon [30]. KORs are localized at the CNS and ENS, and are frequently expressed in the dermal fibroblasts and epidermal keratinocytes, in nerve terminals of muscles, joints, viscera, as well as in dorsal and trigeminal root ganglia. In the GI tract, KORs are localized at myenteric and submucosal neurons, blood vessels, mucosa, and muscle fibers. Absolute quantitative real-time technique confirmed the distribution of KOR in the liver. The presence of opioid receptors on the surface of lymphocytes and macrophages was also reported [30].

The function of opioid receptors in the gastrointestinal tract

Several physiological components are contributing to the proper operation of the GI tract; mainly consisted of ENS, the intestinal mucosa, the GI smooth muscle cells as well as blood vessels. Submucosal plexus manages local absorption and the secretion activities of the GI. Opioid receptors are constantly upregulated in the myenteric and the submucosal plexus, thereby actively assist in maintaining the GI homeostasis, mainly through adjusting the GI transit and mucosal transport of fluids and electrolytes. In a different way, opioid receptor antagonists may act as prokinetics, by reducing the gastrointestinal hypo-motility, preliminary due to the excessive activity of the enteric opioid [12]. The outcomes of three different studies offered a significant interaction between the opioid and glutamate receptors in the guinea pig ileum [31].

It has been proposed that stimulation of the nitrergic pathway may trigger the opioid-receptor expression. It is worth mentioning that the opioid receptor agonists reduce the tonic/segmental contractions and alleviate the impairment of peristalsis, through the attenuation of the release of ACh and SP. In addition, the opioid receptor agonists decrease the GI secretion by alleviating the ACh and vasoactive intestinal peptide (VIP) activities [32].

Dietary nutrients, water, and electrolytes are predominantly absorbed by the intestinal mucosa. The active absorption of Na^+ and secretion of Cl^- throughout the intestinal mucosa is pivotal for digestive processes, adjustment of the balance of water-electrolyte ratio, and for protection against bacterial infections [33]. It was evidenced that opioids decrease the epithelial secretion and increase water-electrolyte absorption, principally through stimulation of DORs and MORs. Opioid receptors also regulate the stimulation of cyclic nucleotide concentration, induce the Cl^- secretion, and inhibit the Na^+/Cl^- absorption [34]. Overall, opioids decline the number of transient lower esophageal sphincter relaxations; delay gastric emptying and small bowel transit; impair bile duct flow; induce common post-operative symptoms; and induce narcotic bowel syndrome. In contrast, opioids improve the absorption of fluids from the intestinal contents. Concerning the high density of opioid receptors in the GI, aberrant activities of these receptors have been implicated in several adverse effects such as constipation, nausea, dysphagia, abdominal discomfort or pain, bloating, vomiting, and delayed transit time [34].

Furthermore, the opioid receptor agonists may control the gastric activity through altering the neuronal excitability. For instance, stimulation of MORs downregulated both tonic and phasic Gamma-Aminobutyric Acid-A (GABA-A) receptor signalings in the medial sub-nucleus of the tractus

solitarius (mNTS), resulting in reduced intragastric pressure and phasic contractions, as well as gastric motility [35]. These functions of the MOR agonists are accompanied by local GABA inhibition, in which, it was shown to lessen the gastric tone and motility [36]. In another study, microinjection of low doses of the MOR agonists (30–300 fmol) through the mNTS area altered the gastric motility through reducing the intragastric pressure and phonic contractions. Pretreatment with a selective MOR antagonist or vagotomy can fade the inhibitory effect of the MOR agonists in the mNTS area [37].

Beneficial effect of opioids on the gastrointestinal track

Opioid therapy in various medical fields has grown and attracted much attention. However, opioids are widely used to attenuate severe acute and chronic pains, yet the consequences of their long-term consumption are questionable. Opioids are mainly classified based on their analgesic potentials and the types of receptors that they may stimulate. Low potent opioid analgesics include Codeine, Meperidine, Propoxyphene, and Pentazocine, while Hydrocodone, Methadone, Oxycodone, Morphine, Hydromorphine, and Fentanyl have shown high analgesic potency. According to the receptor subtypes, opioids are divided into the agonists (Codeine, Dihydrocodeine, Dextropropoxyphene, Tramadol, Morphine, Methadone and Oxycodone), partial agonists (Buprenorphine); and mixed agonists/antagonists (Pentazocine) types. G-protein, μ, K, and δ receptors are frequently distributed in the CNS and PNS, predominantly in myenteric and submucosal neurons of the gut [38]. Studies suggest that the opioid agonists possibly decrease the input of pain transition through the CNS, but have no effects on source of pain.

Opioids are able to affect the GI tract in several ways, mainly due to the abundance of their receptors in myenteric plexus. Primarily, opioids decrease the GI secretion and motility, which results in less abdominal spasm and pain. Thereby, opioids may be promising therapeutic options for patients with irritable bowel syndrome (IBS), particularly for IBS with diarrhea (IBS-D) patients [38]. In 2008, a clinical trial was designed to investigate the effect of Asimadoline (kappa-opioid receptor agonist) on IBS-D patients. Asimadoline significantly enhanced the relief time and improved IBS symptoms, i.e., abdominal pain, urgency, and stool frequency. Canadian Association of Gastroenterology Clinical Practice Guideline (published in 2019) suggested that Eluxadoline [mu & kappa-opioid receptor agonists and delta-opioid receptor antagonists] could attenuate the symptoms in IBS-D patients. The Eluxadoline efficacy was proved by three randomized controlled trials (n = 3235) [39, 40]. Markedly, Eluxadoline did not reduce the abdominal pain significantly, but could improve the stool consistency [39]. In recent years, it was evidenced that the Endogenous Opioid System (EOS) has positive anti-nociceptive and anti-secretion activities, which might be beneficial for management of some GI disorders, i.e., IBS. Of note, EOS peptides have a short life span, since they are quickly inactivated by peptidase enzymes. This makes the enkephalinase inhibitors more crucial. In contrast to exogenous opioid agents, the EOS interacts with natural signaling pathways through the body; thereby, the enkephaline inhibitors do not have any side effects. For instance, it was shown that the enkephalinase inhibitors alter the intestinal habits in IBS patients and can be proper candidates to manage chronic abdominal pain [41]. Racecadotril, another enkephalinase inhibitor, is known as a potent and safe anti-diarrheal compound for both the adults and children. Additionally, it was evidenced that Naloxone reversed the anti-diarrheal effect of Racecadotril in vitro, which was attributed to its anti-secretory but not anti-motility action. The efficacy of Racecadotril was significantly higher than Loperamide, without causing constipation [42]. In another study, Marta Zielinska et al. demonstrated that methyl-orvinol (a mu opioid receptor agonist and a kappa opioid receptor antagonist) is a valuable medical choice to cure the GI disorders related to the peristalsis and pain, mainly due to its anti-motility and anti-nociceptive properties [43].

Opioids can effect on the GI track through modulating inflammation. Inflammation is known to be the main etiology of IBD. Data suggest that opioids such as Morphine and Methadone have potential anti-inflammatory properties. Morphine was shown to suppress the inflammation associated cytokines such as TGF-β1 and IL-10 [44], whereas Methadone downregulates the TNF-α, and IL-1B activities [45]. Therefore, opioid agents are worth consideration in IBD therapeutic approaches. In acute DSS-induced colitis mice, Anselmi et al. demonstrated that mu opioid receptor agonists significantly decreased diarrhea, the blood in the stool and the weight loss, mainly through suppression of the nuclear factor Kappa-light-chain-enhancer of activated B cells (NF-κB) expression. This study suggested that opioids are beneficial for maintenance therapy [46]. In another study, Oxymatrine (opioid agonist) and Mesalazine ameliorated the congestion and erosion in luminal mucosa and improved the IBD symptoms induced by inflammation [47].

Along the advantages of opioids for some conditions in digestive system, several adverse effects including constipation, nausea, dizziness or vertigo, somnolence, vomiting and pruritus were also reported by patients using drugs containing opioids (i.e., Fentanyl, Tramadol, Codeine, Methadone, Oxycodone, Loperamide, and etc.). Accordingly, the majority of studies suggested individualization for chronic opioid therapy [48].

Opioids in IBD

IBD may also induce neuropeptide expression, i.e., SP, VIP, and CRH neural damage [49]. Therapeutic approaches in IBD patients should focus on controlling inflammation and improving the QOL. Abdominal pain is a well-known symptom of IBD, which increases the cramping sensation and intensity [50]. Increase of viscera, obstruction, and inflammation can induce abdominal pain and hypersensitivity in the GI tract. Recently, it was elucidated that prolonged use of opioids leads to enhancement of pain. In bimodal opioid regulation system, activation of excitatory pathways over time may lead to opiate tolerance and pain intensification through releasing of anti-opioid neuromodulators such as Dynorphin and Cholecystokinin [51]. It has been verified that primary afferent neurons are sensitive to variations in intrinsic sensory neurons and nociceptive specific proteins genes. This process induces the production of pro-inflammatory mediators by neurogenic inflammation, of which may cause swelling, edema, and vasodilation [52].

Opioids also modulate the inflammatory process through MOR ligands, highlighting their crucial immunomodulatory roles. It has been demonstrated that inflammation results in overexpression of POMC mRNA by immune cells, which eventually leads to endorphin production and antinociceptive action. In mice, administration of MOR agonists, DALDA and DAMGO, improved colitis, where MOR−/− mice showed higher vulnerability to inflammation compared with wild type animals. It has been shown that opioids modulate the pro-inflammatory cytokines (i.e., IL-12, IL-6, TNF-α) production in peritoneal macrophages in mice. It has also been proposed that the anti-inflammatory effect of MOR is associated with the regulation of T cell proliferation and the cytokines secretion. Philippe et al. exhbited that MOR is upregulated during IBD, resulting in accelerating the intestinal transit and reducing the pathological intestinal inflammation [19].

Administration of (MOR)-specific agonist [D-Arg2,Lys4] dermorphin-(1,4)-amide (DALDA) improved the DSS-induced bowel injury in mice through suppression of the Signal Transducer and Activator of Transcription 3 (STAT3), cytoprotective genes (Reg3b, Ccnd1, Cox2, myc), and the enterocyte expression, which attenuates the disease symptoms. DALDA has also been shown to improve the intestinal barrier damage through IBD. It has been demonstrated that inhibition of MOR can also reduce inflammation. Thereby, MOR antagonists are favorable for IBD therapy through downregulating the expression of pro-inflammatory cytokines such as IL-6 and IL-12. Smith and colleagues reported that co-administration of Morphine and Naloxone enhances the anti-inflammatory effect of Naloxone. In RAW264.7 macrophages, Naloxone suppressed the endotoxin-induced activation of intracellular NF-κB pathway in a way that was more dependent on L-type calcium channels than opioid receptors. Clinical evidence displayed that Naltrexone (4.5 mg) significantly improved the GI mucosal inflammation. The side effects were rare and include insomnia, diarrhea, and abdominal pain [53].

Aminosalicylates and corticosteroids are the main classes of medication for IBD management, however, the immunosuppressive and anti-TNF-α agents are the latest alternative drugs. Although, conventional medications for IBD modulate inflammation, but their efficacies are fading each year, thus, invasive intervention (i.e., surgery) or corticosteroid dependency are the next steps [54, 55]. Altogether, there is still a demand for novel therapeutic approaches. There are strong evidence supporting the idea that the impairment of opioid receptors is a considerable factor for IBD development [56]. It was demonstrated that DORs play key roles in analgesia and reduction of colonic motility and contraction. The MOR agonists possess fewer side effects like constipation, respiratory depression, and addiction in comparison with other opioid agents. KORs were also shown to reduce inflammation and nociceptive visceral pain by modifying visceral sensation [57].

In vivo and in vitro interventions

It was evidenced that biphasic effects of Heroin and Morphine increase the level of inflammatory cytokines, such as IL-1β, IL-2, TNF-α, and IFN-γ in the acute phase and decreased the levels of anti-inflammatory cytokines such as TGF-β1 and IL-10 [44] (Table 1, Fig. 1). Endogenous Morphine, secreted from neutrophils, was shown to contribute to the inflammatory response through lipopolysaccharide and IL-8 induction in the presence of $Ca+^{2}$ [72]. In mice, oral administration of some MOR agonists called soymorphins, particularly soymorphin-5, -6, and -7, reduced food intake and the small intestinal transit in a Naloxone-dependent manner via μ1-opioid receptor by mediating a number of downstream μ1-opioid receptor such as 5-HT1A (WAY100135), D2 (raclopride), and GABA-B (saclofen) receptors [73]. Zhou et al. compared the efficacy of Oxymatrine (opioid agonist) and Mezalazine with their control groups, of which both agents significantly attenuated congestion and erosion in the luminal mucosa and the wall thickening by activating DORs. Their efficacies were comparable [47] (Table 1). In an in vitro study in 2014, intraperitoneal and oral administration of P317, an opioid receptor agonist, increased the MOR and DOR mRNA levels in TNBS- and DSS-induced colitis mice, while alleviated mucosal lesions, the colon wall thickness, the colon weight and length, and decreased the MPO activity (as an index of tissue neutrophil infiltration). Real-time Polymerase chain reaction analysis

Table 1 In vivo animal evidence of opioid in IBD therapy

Ref.	Type of animal	Model of IBD	Intervention		Rout of administration	Duration of treatment	Numbers of animals	Outcomes	Adverse effects
			Case	Control					
[58]	Male CD1 mice	TNBS & DSS	Salvinorin A	Vehicle	IP (3 mg/kg twice daily) and orally (10 mg/kg twice daily)	3 days after the infusion of TNBS & 7 days after DSS	24–32 (4 groups of 6–8 mice)	Anti-inflammatory activity	–
[59]	Female C57BL/6 mice	DSS	Specific NOP receptor antagonist SB612111 (30 mg/kg)	Vehicle	IP	12 days	–	Fecal bleeding ↓; IFN-γ, IL-1β, IL-6 & TNF-α ↓	–
[60]	Mice C57BL/6	Intestinal ischemia I/R-induced injury	DALDA (50 μg/kg)	Vehicle	SC	–	Groups of 5–6 mice	p13k signaling pathway↓; caspase-3↓	–
[61]	Male balb/Cmice	TNBS	BU08070 (1 mg/kg twice daily)	Vehicle	IP	4 days	Groups of 6–8 mice	Severity of the intestinal inflammation ↓; MPO activity level ↓; TNF-α & abdominal pain ↓	–
[45]	Male Sprague-Dawley rats (8–12 weeks)	TNBS	Propranolol + phentolamine (50 μg)	SC saline & ICV saline	Injection	7 days	24 (4 groups of 6 rats)	TNF-α & IL-1β↓; BDNF protein expression ↑	
[62]	Male Wistar rats (6–7 weeks)	Acetic acid	1. Methadon (5 & 10 mg/kg, IP) 2. Methadon (50 & 300 ng/rat, ICV) 3. MNTX (5 mg/kg, IP) 4. NTX (5 mg/kg, IP) & (10 ng/rat, ICV) 5. NTX (10 ng/rat, ICV) + methadone (10 mg/kg, SC) 6. Saline (ICV) + methadone (10 mg/kg, SC)	SC ICV	IP ICV	72 h	162 (18 groups of 7–9 rats)	Severity of the intestinal inflammation ↓	–
[63]	Rat	CD	1. NTX (7.5 mg/kg for 24 h) 2. Salfasalazine, naltrexone & their combination	Water	PO	12 days	–	Severity of the intestinal inflammation & TNF-α ↓	–

Table 1 (continued)

Ref.	Type of animal	Model of IBD	Intervention		Rout of administration	Duration of treatment	Numbers of animals	Outcomes	Adverse effects
			Case	Control					
[64]	Mice were on a mixed genetic background (50% C57BL6/J—50% SV129P)	DSS	Healthy mice	DSS	–	–	8–10	MOR endogenous tone would protect against inflammatory regulations; TNF-α ↓	–
[65]	Mice	UC	NTX	–	–	6–8 weeks	24 mice	Weight loss ↓; constipation ↓	–
[66]	Male Wistar rats (6–7 weeks old)	Acetic acid	1. Two groups received L-NAME (10 mg/kg, IP) or NTX (5 mg/kg, IP) 30 min before administration of olive extract (750 mg/kg) for two successive days 2. Two groups were administered either NTX (5 mg/kg) or L-NAME (10 mg/kg)	Acetic acid (IR) 1 h after administration of saline (IP)	1. Olive extract (PO) 2. L-NAME, NTX & dexamethasone, (IP) 3. Acetic acid (IR)	3 days	10 groups (6 rats)	Inflammation ↓; TNF-α & IL-12 ↓	–
[15]	Naive male C57B1/6 mice (6–8 weeks)	TNBS & DSS	EMDB-1 & NLX	Vehicle DSMO	IR & IP	1. In TNBS colitis mice; for acute (3 days); for semichronic (6 days) & for chronic (13 days) 2. In DSS colitis mice (6 days)	6–10	MPO activity ↓; expression of TNF-α & IL-1β ↓; weight loss ↓	–

Table 1 (continued)

Ref.	Type of animal	Model of IBD	Intervention		Rout of administration	Duration of treatment	Numbers of animals	Outcomes	Adverse effects
			Case	Control					
[67]	Male CD-1 mice (9 to 10 weeks), RAG2−/− mice, male C57B1/6	Mustard oil	–	No colitis	IR	3 days	1. Colitis (n = 11) 2. No colitis (n = 9)	Neural receptors (delta-opioid receptors) & soluble mediators (prodynorphin, proenkephalin1, NK1, prokineticin-1) ↑; immunodeficient C57Bl/6 RAG2 mice exhibited OM colitis of equal severity as seen in wt C57Bl/6 & CD-1 mice; upregulation of delta-opioid receptor; mOPR was not detected; mRNA for a number of peptides colon tissues from mice undergoing OM colitis↑; (mOPR) mRNA were not detected before or after colitis induction	–
[68]	Adult male CD1 mice or BALB/c mice	TNBS & DSS	Buprenorphine (0.05 mg/kg, every 8–12 h) Tramadol (20 mg/kg, every 24 h)	Analgesic or saline alone	SC	2 h	Groups of 6–7 mice	Inflammation ↓; MPO activity ↓; weight loss ↓; CSMC hyperplasia ↓	Water intake ↓
[15]	Male balb/c mice (6–8 weeks)	TNBS & DSS	Sialorphin (1 mg/kg twice daily)	Vehicle	Sialorphine (IP) Mesalazine (PO)	14 days	Groups of 6–10 mice	MPO activity↓; TNF-α & IL-1β ↓; weight loss ↓	–

Table 1 (continued)

Ref.	Type of animal	Model of IBD	Intervention		Rout of administration	Duration of treatment	Numbers of animals	Outcomes	Adverse effects
			Case	Control					
[46]	Adult C57BL/6J mice	DSS (in 2 forms of acute & delayed)	1. Acute form: DAMGO (0.01,0.02,0.04,0.08 mg/kg, SC in a day); DAMGO + μOR antagonist (0.2, 2, 4 mg/kg CTAP + DAMGO 0.02 mg/kg) 2. Delayed form: DSS+DAMGO (0.02 mg/kg)	Water	Water (PO) DAMGO (SC)	1. Acute (3 days) 2. Delayed (15 days at least)	1. Acute colitis (n = 56 total) 2. Delayed (n = 14)	Improvement in IBD symptoms ↑; DAI ↓; MPO activity ↓; Weight loss ↓; Bcl-xL, NF-κB expression ↓	–
[69]	Male Sprague-Dawley rats	TNBS	Acupuncture at behind anus	Not acupuncture	Acupuncture	20 min/day for 7 days	–	Scores of adhesion & macroscopic damages ↓; MPO activity ↓; colonic motility ↓	–
[70]	Male C5BL/6j	DSS	An opioid receptor antagonist JTC-801 (1 mg/kg day)	Visible light	Irradiation on eye locally	5 days	1. Control group 2. Case group with different doses of UV/B irradiation	μ-opioid receptor expression ↓; TNF-α, histamine, ACTH, IL18, IL-6, CRH, substance P & urocortin 2↑	–

Table 1 (continued)

Ref.	Type of animal	Model of IBD	Intervention		Rout of administration	Duration of treatment	Numbers of animals	Outcomes	Adverse effects
			Case	Control					
[47]	Male Sprague-Dawley rats	TNBS	Oxymatrine (63 mg/kg day) Mesalazine (0.5 g/kg day)	Vehicle	Oxymatrine (IM) Mesalazine lavage (PO)	15 days	40 (n = 10)	Expression of DOR, β-arrestin1, Bcl-2 protein & mRNA ↑ (model group); expression of DOR, β-arrestin1, Bcl-2 protein & mRNA ↓ (mesalazine- & oxymatrine-treated groups); UC development reduced by regulating the DOR-β-arrestin1-Bcl-2 signal transduction pathway (oxymatrine group); edema, congestion, erosion in colonic mucosa & thickening of the wall ↓ (mesalazine- & OMT-treated groups)	–
[71]	Male balbC mice	TNBS	P-317 (0.1 mg/kg, twice daily)	Vehicle	I.p.	3 days	n = 4–6	Inflammation ↓; MPO activity ↓	–
[71]	Male balbC mice	DSS	P-317 (0.1 mg/kg, twice daily)	Vehicle	I.p.	7 days	n = 4–6	Inflammation ↓; total macroscopic score ↓; MPO activity ↓	–

IP, intraperitoneal; PO, per os (orally intake); IBD, inflammatory bowel diseases; CD, Crohn's Disease; UC, Ulcerative Colitis; QOL, quality of life; GI, gastrointestinal tract; KOR, Kappa Opioid Receptors; DAMGO, D-Ala2, N-MePhe4, Gly-ol; DSS, dextran sulfate sodium; mNTS, medial subnucleus of the tractussalitarius; SC, subcutaneous; TNBS, trinitrobenzene sulfonic acid; OM, Mustard oil; NK1, neurokinin1; UVA, ultra violet; NOR, nociception receptor; IL, interleukin; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor α; NF-kB, nuclear factor kB; MPO, myeloperoxidase; OMT, oxymatrine; DMSO, dimethyl sulfoxide; MOPR, mu-opioid receptor; ICV, intracerebroventricular; CRP, C reactive protein; CSMC, coronary vascular smooth muscle cell; NLX, naltrexone; MTNX, methylnaltrexone; N, Not reported; JTC-801, N-(4-amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxymethy)benzamide monohydrochloride; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor

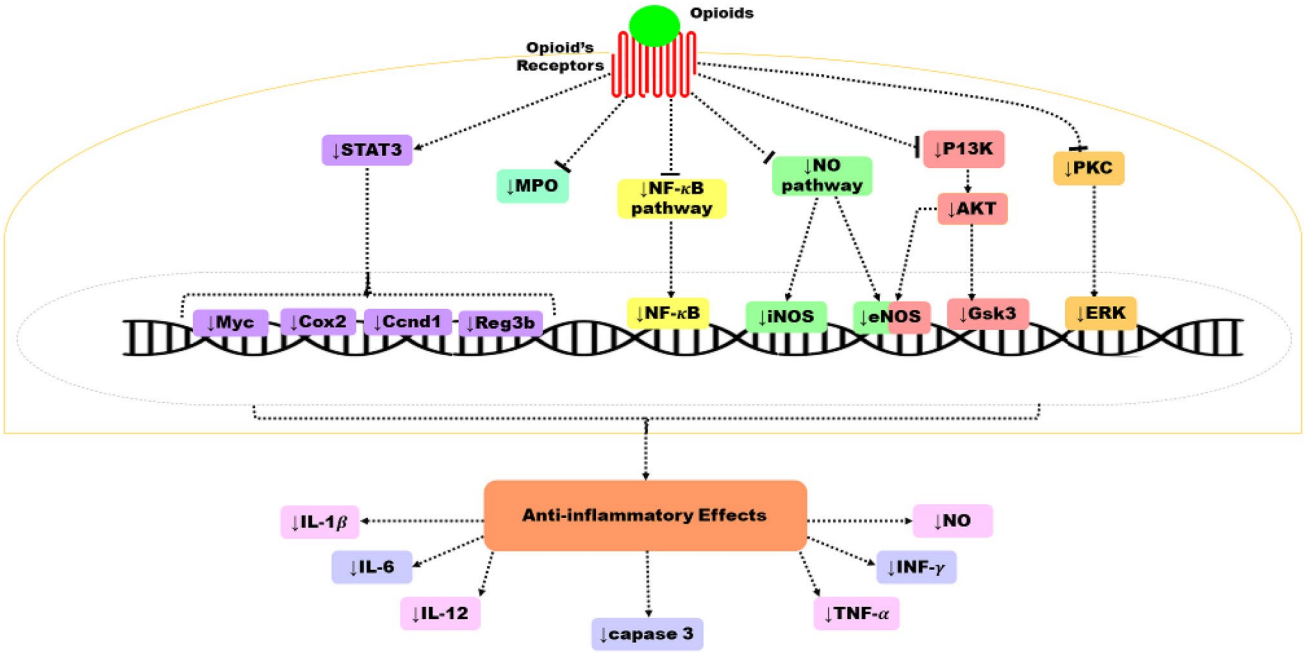

Fig. 1 Opioid-dependent anti-inflammatory molecular mechanisms. Abbreviations: IL, interleukin; GSK3, glycogen synthase kinase-3; ERK, extracellular signal-related kinase; INF-γ, interferon gamma; TNF-α, tumor necrosis factor α; STAT3, signal transducer and activator of transcription 3; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; NF-kB, nuclear factor kB; COX-2, cyclooxygenase-2; Akt, protein kinase B; iNOS, inducible nitric oxide synthase; MPO, myeloperoxidase; P13k, phosphoinositide 3-kinase; Ccnd1, cyclin D1; Reg3b, regenerating islet-derived protein 3-beta

exhibited significant decrease in IL-1 and TNF-α mRNA expression levels [71] (Fig. 1).

The serum level of [Met5] enkephalin was reduced in IBD patients, while it was elevated in colonic inflammatory lesions [74]. Recently, it was shown that a selective MOR agonist, ([D-Ala2, N-Me-Phe4, Gly5-ol]-Enkephalin), with a dose of 0.02 mg/kg ameliorated diarrhea, blood in the stool and weight loss in DSS-colitis mice. This compound affected the acute phase of the disease by reducing the TNF-α, IL-1β, IL-6, and IL-10 levels, suppressing the MPO activity, and downregulating the NF-κB expression. However, the Bcl-xL level enhanced, but not in delayed phase [46] (Table 1, Fig. 1). Therefore, the MOR agonists can be suggested for remission induction in IBD, but they are not appropriate for maintenance therapy. In DSS-induced colitis knocked out mice (MOR-floxed and DOR-floxed), the colon sensitivity has augmented in colorectal distention assay, indicating that the endogenous MOR and DOR agonists are able to reduce chronic intestinal pain [64] (Table 1).

One study investigated the effect of acupuncture on the GV01 area (an area between anus and tail of mouse) of TNBS-induced colitis rats. Colonic motility reduced, while diarrhea improved. The MPO activity was significantly lower than control or non-acupoint groups in the histologic assessment. Pretreatment by Naloxone reversed these effects, representing the involvement of the endogenous opioid pathway. Notably, acupuncture did not decrease colonic motility in control group, which may signify that opioid receptors may be more sensitive in inflamed intestinal mucosa [69] (Table 1, Fig. 1). It was shown that several endogenous agonists named EMs, EM-1 and EM-2, are active in the GI tract and have high affinity for MORs. In rat esophagus, EM-1 and EM-2 suppressed the striated and smooth muscle responses in a Naloxone reversible manner. In another study, EM-2 reduced the TNF-α, IL-10, and IL-12 productions in rat peritoneal macrophages and inhibited the macrophage chemotaxis and the superoxide anion production, indicating the immunomodulatory effect of EMs in the GI tract through modulation of the production and function of the innate immune system cytokines. It was also demonstrated that the activation of some opioid receptors, mainly μ1 (Naloxonazine-sensitive), μ2 and other subsets of μORs (β-FNA-insensitive) increased the EMs-induced mouse colonic motility. Further, EMs repressed the contractions of longitudinal muscle in distal colon, while improved the contractile function in proximal and mid colon circular muscle [75] (Table 1, Fig. 1). In a chronic constriction injury rat model, intravenous administration of an EM-1 analog, derived from lactose linkage to the N-terminus of EM with a succinamic acid spacer, caused an antinociceptive activity dose-dependently, enhanced the membrane permeability and metabolic stability, and decreased the stool

hydration compared with Morphine. Administration of DALDA showed protection against ischemic colitis caused by ischemia/reperfusion process in mice gut [60]. Indeed, DALDA did not effect on the NF-κB signaling in intestinal epithelial cells. However, DALDA inhibited the MOR competitively, and abolished the glycogen synthase kinase-3 phosphorylated (GSK3P) phosphorylation. Therefore, DALDA protected the intestinal epithelial cells from apoptosis in prolonged hypoxia through the phosphatidylinositol 3-kinase (PI3K) / protein kinase B (Akt) / glycogen Synthase Kinase-3 (GSK3) survival pathway [60]. Accordingly, opioid agents possess crucial roles in improving ischemic colitis in IBD condition (Table 1, Fig. 1). It was demonstrated that Naltrexone antagonized the inhibition of TGF-β by Morphine, which resulted in immune response in the GI tract [76]. DSS induces the T helper-2 dominant colitis similar to UC, while TNBS induces the T helper-1 dominant colitis similar to that of CD.

Neuronal signaling from the intrinsic ENS to the intestinal tract has been considered to play major role in IBD. For instance, Lidocaine inhibits the TNBS-induced colitis effect and Vanilloid receptor antagonists reverse the DSS colitis. Mustard oil, a neuronal stimulator, is a model of neurogenic colonic inflammation. Mustard oil elevates the IL6, IL-1β levels, and the macrophage and neutrophil activating chemokines such as granulocyte-macrophage colony-stimulating factor. Mustard oil also increases neuronal receptors through neurokinin1, cannabinoid receptor type 1, NO, and endogenous opioids. It was shown that opioid receptors are upregulated in colitis. In addition, Kimball et al. reported that two precursors of endogenous agonists of MORs and DORs named proenkephalin-1 and prodynorphin, are upregulated in IBD [67] (Table 1, Fig. 1).

Salvinorin A, a selective KOR agonist, extracted from *Salvia divinorum* caused anti-inflammatory effects in the GI tract. Under physiological condition, Salvinorin A inhibited cholinergic contractions in mouse and guinea pig intestine, which effected on KOR and cannabinoid receptor type 1. In mice, Salvinorin A reduced the ileal hypermotility induced by croton oil or endotoxin [77]. In the endotoxin model, the modulatory action of Salvinorin A on epithelial barrier function was mediated through the NO signaling pathway. In murine models of IBD, Salvinorin A decreased inflammation and showed nociceptive effects [77]. In another study, intraperitoneal administration of Salvinorin A (3 mg/kg, twice daily) potentially decreased the GI motility by interacting with KORs in peripheral neurons and the immune system. Salvinorin A particularly reduced the MPO activity and the macroscopic damage scores in histological evaluation in both DSS- and TNBS-induced colitis. Intracolonic and oral administration of Salvinorin A (10 mg/kg) decreased the MPO activity, but did not change the macroscopic scores. Intraperitoneal administration of Salvinorin A blocked the mustard oil-induced pain sensation, whereas, intracolonic injection did not have any effect on sensation of pain. Together, this study concluded that medications designed based on the structure of Salvinorin A are proper choices for IBD treatment [58] (Table 1, Fig. 1). Currently, it was shown that eye exposure to ultra violet A enhances the serum level of β-endorphin released from the pituitary gland system, increases the MOR expression, and decreases the TNF-α, which worsen the UC symptoms such as diarrhea, fecal bleeding, colon length, body weight, and the intestinal mucosal thickness. On the contrary, ultra violet B exposure to eyes activated urocortin 2 to deteriorate UC, while inducing the pituitary and hypothalamus glands to release more adrenocorticotropic hormone, and corticotropin-releasing hormone [70] (Table 1, Fig. 1).

Endogenous opioids in supernatant of cDSS mice, was shown to have antinociceptive action on neurons excitability, which was mediated by DORs and MORs. This effect was associated with endosomal signaling, activating the protein kinase C, and the extracellular signal-related kinase in subcellular compartments. Unexpectedly, analgesic effect of opioids was very high in acute phase, but the mechanism is not clear [78]. In UC rats, central and peripheral injection of Methadone ameliorated the macroscopic and microscopic lesions and caused a significant reduction in TNF-α and IL-1β levels of the intestinal mucosa. Effect of Methadone on IBD was mainly through the central route. This effect was completely reversed by Maltrexone and partially reversed by Methyl naltrexone [45] (Fig. 1).

In another investigation, Sialorphin, a natural inhibitor of endogenous opioid peptide-degrading enzymes neprilysin and aminopeptidase N, attenuated the macroscopic scores (i.e., ulcer scores, colonic wall thickness, colonic weight and length), and suppressed the MPO activity in TNBS-induced colitis, but not in DSS-induced colitis. These effects were reversed by the KOR and MOR antagonists [15] (Fig. 1). In TNBS-induced colitis mice, intraperitoneal injection of Biphalin, a mixed MOR and DOR agonist, caused antinociceptive but not anti-inflammatory activity. Though, its intracranioventicular administration caused antinociceptive and anti-inflammatory effects, and improved the macroscopic, histological, and ulcer scores, suggesting central interaction by MOR [79].

Another in vivo study investigated the protective effect of the hydroalcoholic extract of the olive leaf (OLE) on colitis. Oral application of OLE significantly reduced the IL-2 and TNF-α levels, which attenuated the inflammatory responses and inhibited the proceeding to fibrosis, as a complication of IBD. It was shown that OLE improved the macroscopic and microscopic scores in histopathological evaluation by interacting with nitrergic system through increasing the endothelial NOS or blockage of inducible NOS, and by upregulation

of opioidergic systems via the intestinal opioid receptors [66] (Table 1, Fig. 1).

As mentioned, GI contains numerous endogenous opioid and NORs that participate in anti-inflammatory processes. BU08070, a mixed NOR and MOR agonist, reduced the MPO activity, neutrophil infiltration and TNF-α in the colon. BU08070 ameliorated the shortening of the colon, weight loss and ulceration by inactivation of NF-κB [62] (Fig. 1). Stress hormones (i.e., epinephrine and corticosterone) directly increase the pain signaling through stimulating the dorsal root ganglion neurons and in indirect interaction with the immune system, thus, may reduce endogenous opioids in inflammatory disorders. Opioids reduce the pain sensation by suppressing the neuronal stimulation and blockade of the transient receptor potential vanilloid 1 ion channels [80]. In indomethacin-induced colitis rats, combination of low dose naltrexone (LDN) and Sulfasalazine improved disease activity index, and the histopathologic symptoms such as hyperemia, edema, and mucosal lesions. This combination reduced the inflammatory mediators like TNF-α and C reactive protein. The combination of LDN and Sulfasalazine was more potent than each compound alone [63].

Clinical studies

Statics reported that there is a persistent use of opioids among the IBD population. Patients with chronic obstructive pulmonary disease, mental health disorders, CD, and indeterminate colitis are more prone to persistent opioid use during experiencing a flare [81]. For instance, Loperamide, as an opioid receptor agonist in the intestinal lumen, decreased the GI motility and secretion, so it has been recommended for diarrhea and colonic pain. Nevertheless, Loperamide did not affect the CNS, nor had positive effect on addiction. Opioids or their combination with systemic steroids shortened the life expectancy in IBD patients in comparison with Mesalazine, which prolonged the life expectancy in these populations [82]. In healthy subjects, chronic administration of Morphine (0.05 mg/kg) postponed colonic transit time. Likewise, a metabolite of Naloxone named Naloxone-3-glucuronide (0.16 mg/kg), improved the Morphine efficacy [83]. Similarly, oral administration of Naloxone-3-glucuronide (0.16 mg/kg) reversed Morphine-induced delay (0.05 mg/kg) of colonic transit time in 15 male subjects. This indicates that Naloxone-3-glucuronide reduces the constipation symptoms without antagonizing the opioid-analgesic effects [83]. Naltrexone (MOR antagonist) often exists at high concentrations. Administration of LDN (4.5 mg, once daily) resulted in the upregulation of endogenous enkephalin and endorphin levels, which improved wound healing and reduced the endoplasmic reticulum stress in inflamed mucosa in IBD patients. LDN made 74.5% clinical development and remission in 25.5% of IBD patients [60, 84, 85] (Table 2). In a randomized double-blind placebo-controlled study, the efficacy and safety of Naltrexone was evaluated. Oral administration of Naltrexone (4.5 mg, once-a-day, 12 weeks) in CD adults led to a 5-point reduction from the baseline of Crohn's disease endoscopic index surgery score in 78% of CD subjects. 33% of patients that had received Naltrexone achieved remission in comparison with 8% of the placebo group. Naltrexone improved endoscopic appearance, as well as clinical and inflammatory symptoms of patients with moderate to severe CD. The only reported adverse effect was fatigue, which was dominant in placebo group [53].

According to the Pediatric Crohn's disease activity index, consumption of Naltrexone (0.1 mg/kg, orally, eight weeks) in children with moderate to severe CD was well tolerated and 67% of the subjects experienced improvement of disease activity, and 25% considered in remission. It was proposed that selective blockage of excitatory opioid responses is the main mechanism underlying the effect of LDN, however, more evaluation is warranted. QOL was assessed by the IMPACT III survey and developed, overly. Few adverse effects were reported in Naltrexone treated group. Although, similar adverse effects were observed in control group. In addition to be cost-effective, Naltrexone exhibited better compliance, especially in teenagers. It has been proposed that high polar Naloxone derivatives peripherally suppress the GI motility, signifying that peripheral receptors play a crucial role in modulating the opioids function in the GI tract [93].

Chronic use of opioids and corticosteroids increased the risk of infections in patients undergoing joint replacement surgery. However, this effect was not seen with immunosuppressant or anti-TNF drugs [94]. Additionally, long-term use of opioids was associated with more infections, revision, and repeated surgery [53, 90, 95] (Table 2). Chronic opioid users in CD population experienced a longer duration of the disease, more use of Prednisone and a higher number of admissions, and according to Harvey Bradshaw Index, even a chance of surgery associated with CD. Chronic opioid usage also reduced QOL in these subjects, even when the other severity factors of the disease were controlled [91] (Table 2). The prevalence of heavy opioid users among the IBD population is 5% during the first ten years of diagnosis, which is strongly correlated with a history of moderate opioid consumption. Concomitantly, three main reasons for being susceptible to heavy opioid use have been defined as developing a tolerance for opioid effects, their use in the treatment of Loperamide resistant diarrhea, and the reluctance of clinicians to use other analgesics such as Nonsteroidal anti-inflammatory drugs [7]. Based on Wren et al. study in 2018, nearly 18.2% of 93,668 IBD individuals met chronic opioid therapy criteria. Sustained chronic opioid use in adolescents and young adults with IBD is increasingly

Table 2 Clinical evidence of opioid in IBD therapy

Ref.	Type of study	Type of IBD	Intervention		Duration of treatment	Subjects	Outcomes	Adverse effect
			Case	Control				
[85]	Clinical trial	UC	Sufentanil bolous (0.5 mg/kg) & continuous infusion (0.3 mg/kg)	–	2.5 years	16 patients	Inflammatory process ↓	–
[86]	Clinical trial	UC	Sulphasalazine (1 g/daily); codeine phosphate BP (60–240 mg/day); prednisolone enema (daily)	–	4 weeks	7 patient	Prostaglandin synthetase ↓	–
[87]	Clinical trials	–	Ketamine (0.05–0.4 mg/kg)	–	24 h, 48 h, & on the day after discontinuation of ketamine infusion	230 patients (median age of 14 years)	Inflammatory markers: CRP, leukocytes and fibrinogen pain scores in treated patients ↓	–
[88]	Clinical trial	CD (54%), UC (44%), indeterminate colitis (2%)	Receiving a questionnaire	–	1 year	1263 completed questionnaires	Pain management ↑; QOL ↑	
[89]	Clinical trial	CD	Using opioids	Not using opioids	–	38 CD patients using opioids & 62 patients not using opioids	QOL ↑	–
[90]	Clinical trial	CD	GM-CSF (6 μg/kg/day) + 2 mg loperamide + mesalamine	–	10 days	–	Abdominal pain ↓; inflammatory markers ↓	–
[53]	Clinical trial	CD	Naltrexone (4.5 mg)	Placebo	12 weeks	40 CD patients	Improvement in the mucosa ↑; microscopic inflammatory scores ↓	–
[91]	Clinical trial	CD	Using opioids	Not using opioids	–	38 patients used opioid 62 patients did not use opioid	Opioid dependency ↑; surgeries related to CD ↑; disease activity ↑; QOL ↓	–
[92]	Clinical trial	CD or UC	Diphenoxylate HCI-atropine	–	–	–	Motility ↓	Psychological dependence
[71]	Human biopsy	UC	P-317 (0.1 mg/kg, IP) & (1 mg/kg, PO)	–	–	–	Inflammation ↓	–

IP, intraperitoneal; PO, per os (orally intake); IBD, inflammatory bowel diseases; CD, Crohn's Disease; UC, Ulcerative Colitis; QOL, quality of life; GI, gastrointestinal tract; KOR, Kappa Opioid Receptors; DAMGO, D-Ala2, N-MePhe4, Gly-ol; DSS, dextran sulfate sodium; mNTS, medial subnucleus of the tractussalitarius; SC, subcutaneous; TNBS, trinitrobenzene sulfonic acid; OM, Mustard oil; NK1, neurokinin1; UVA, ultra violet; NOR, nociception receptor; IL, interleukin; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor α; NF-kB, nuclear factor kB; MPO, myeloperoxidase; OMT, oxymatrine; DMSO, dimethyl sulfoxide; MOPR, mu-opioid receptor; ICV, intracerebroventricular; CRP, C reactive protein; CSMC, coronary vascular smooth muscle cell; NLX, naltrexone; MTNX, methylnaltrexone; N, Not reported; JTC-801, N-(4-amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxymethy)benzamide monohydrochloride; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor

common, underscoring the need for screening and intervention for this vulnerable population. Chronic opioid therapy increases the risk of comorbidities like depression, anxiety, and arthritis. Major risk factors were recorded in female sex and CD subjects [96] (Table 2).

Conclusion

Conventional treatments of IBD are majorly limited to those that control the IBD symptoms. The critical core of today's drug discovery is personalized therapy, requiring multidimensional genetic and molecular knowledge of the disease, attentive drug selection, and directing the drugs to their molecular targets within the cells. The personalized based opioid therapy would certainly target various molecular pathways that might lead to the development of tolerance or OBD. In conclusion, opioid receptors may become crucial pathways in the modulation and alleviation of an inflammatory process in IBD, mainly due to their effect on immune cells. The importance of opioid receptors and their ligands in the GI and also controversial outcomes of clinical and in vitro studies warrant further investigations on possible therapeutic actions of opioids for IBD management. Of note, many of the opioids side effects or their particular pharmacological actions in IBD subjects have not been explored enough. Therefore, programmed clinical trials are mandatory to clarify the safety and efficacy of opioids in IBD patients.

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