Postoperative Ileus: Pathophysiology, Current Therapeutic Approaches

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Abstract

Postoperative ileus, which develops after each abdominal surgical procedure, is an iatrogenic disorder characterized by a transient inhibition of gastrointestinal motility. Its pathophysiology is complex involving pharmacological (opioids, anesthetics), neural, and immune-mediated mechanisms. The early neural phase, triggered by activation of afferent nerves during the surgical procedure, is short

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lasting compared to the later inflammatory phase. The latter starts after 3–6 h and lasts several days, making it a more interesting target for treatment. Insight into the triggers and immune cells involved is of great importance for the development of new therapeutic strategies. In this chapter, the pathogenesis and the current therapeutic approaches to treat postoperative ileus are discussed.

Keywords
Field effect • Gastrointestinal motility • Inflammatory phase • Macrophages • Mast cells • Neural phase • Pathophysiology • Postoperative ileus

1 Introduction

Each patient undergoing an abdominal surgical procedure, even if minimal invasive techniques are applied, will develop a transient episode of impaired gastrointestinal (GI) motility or postoperative ileus (POI). Although some argue that uncomplicated POI should be considered as a "normal" or "physiological" response of the intestine to a traumatic event and thus should be disregarded, POI clearly has a significant impact on patient morbidity with symptoms such as pain, nausea and vomiting, abdominal distension, absence of defecation, and intolerance to oral feeding (Livingston and Passaro 1990). In clinical practice, a distinction is made between this so-called physiological POI and prolonged POI. The latter is however ill defined and is considered when recovery of bowel function is delayed, ranging from more than 3 to more than 7 days after surgery (Wolthuis et al. 2016). Depending on the definition used, the incidence of prolonged POI after colorectal surgery for example is approximately 10%. Of note, POI is the most common cause of prolonged hospital stay following abdominal surgery with an annual cost estimated as much as $1.5 billion in the USA.

2 Pathophysiology

Transient inhibition of GI motility following abdominal surgery involves the entire GI tract. However not all segments are equally affected. Small intestinal motility is on average disturbed for approximately 24 h and gastric motility between 24 and 48 h, whereas colonic motility is impaired between 48 and 72 h. Before discussing the mechanisms involved in POI, it is important to emphasize that our current insight is based on murine models consisting of standardized manipulation of the small intestine. To date however, no resection of intestine or construction of anastomoses is included in these models. Therefore, these models will most likely study "physiological" POI rather than "prolonged" POI, which may be relevant with respect to translation of preclinical data to clinical practice/therapeutic studies.

The pathophysiology of POI is complex involving pharmacological (opioids, anesthetics), neural, and immune-mediated mechanisms. In the immediate postoperative

period, anesthesia and opioids contribute to POI. Opioids, often used as analgesics following various types of surgery, indeed have a major impact on GI motility by activation of μ-opioid receptors on the myenteric fibers. This leads to inhibition of acetylcholine release from myenteric neurons and reduced GI transit (Holte and Kehlet 2002). Interference with this mechanism by peripheral selective opioid antagonists such as alvimopan has indeed accelerated postoperative recovery of GI motility, but only to a minor extent (Vaughan-Shaw et al. 2012). The latter is mostly explained by the knowledge that other mechanisms play a more important role in the pathogenesis of POI. Indeed, the main cause of POI rather relates to the surgical procedure itself. Two different phases, each with its own dynamics and underlying pathophysiological mechanism (Fig. 1), are now proposed to underlie POI. The first or early phase is neurally mediated and involves neural reflexes activated during and immediately following surgery. In the late 1990s, however, the concept was introduced that manipulation of the intestine triggers the influx of leukocytes in manipulated intestinal segments impairing the contractile properties of the inflamed intestine (Kalff et al. 1998, 1999a, b). This second phase starts 3–4 h after surgery and is responsible for the sustained and thus clinically more relevant inhibition of GI motility. From a clinical perspective, interference with or prevention of this second phase is clearly expected to be most relevant and most effective in the treatment of POI.

2.1 The Neurogenic Phase of POI

Incision of the skin and opening of the peritoneal cavity briefly inhibit GI motility via adrenergic reflexes involving a spinal loop with afferent splanchnic nerves synapsing in the spinal cord activating efferents travelling back to the gut. When intestinal loops are however displaced and manipulated, the nociceptive stimuli become more intense activating additional neural pathways and leading to more prolonged inhibition of motility. The high-threshold supraspinal pathways involved relay to the hypothalamic and pontine-medullary nuclei such as the nucleus tractus solitarius and the paraventricular and supraoptic nucleus of the hypothalamus, and are also adrenergic in nature (Boeckxstaens and de Jonge 2009). In addition, more intense intestinal stimulation activates an inhibitory non-adrenergic vagally mediated pathway contributing to the neural phase of POI (Boeckxstaens et al. 1999). Activation of these pathways, at least by mechanical stimuli, will however cease once the abdomen is closed and thus other factors such as mediators released by tissue damage or subsequent inflammation therefore must come into play explaining the more prolonged nature of POI.

2.2 The Inflammatory Phase of POI

Already in 1978, Bueno et al. described an initial complete but short-lasting inhibition of electrical spiking activity after muscular and peritoneal incision in sheep and dogs, corresponding with the neural phase described above (Bueno et al.

1978). Of major interest was the observation that electrical activity recovered during 3–6 h, but was then inhibited for a second time for a period ranging from 6 to 72 h. These findings were later confirmed in isolated muscle strips from mice revealing two phases of inhibition of muscle contractility separated by a period of recovery (Farro et al. 2016; Kalff et al. 1999a, b). By now, it is generally accepted that this second wave of inhibition results from an immune-mediated cascade of events, also referred to as the inflammatory phase of POI.

Twenty years after the first description of the biphasic nature of POI, Kalff et al. described the temporal association between inflammation of the intestinal *muscularis* externa and the second prolonged phase of POI (Kalff et al. 1999a, b). These investigators elegantly demonstrated that 3–4 h after manipulation of the intestine, mainly neutrophils and monocytes infiltrated the muscular layer, a finding that was associated with impairment of spontaneous and stimulated contractile activity of muscle strips obtained from the inflamed intestine. Most interestingly, animals pretreated with antibodies or antisense oligonucleotides against the intercellular adhesion molecule-1 (ICAM-1) not only prevented the influx of leukocytes, but also preserved normal neuromuscular function of muscle strips providing the proof of concept that inflammation induced by manipulation indeed largely contributes to POI (de Jonge et al. 2005; Kalff et al. 1999a, b; The et al. 2005). Recently, we demonstrated that a first wave of impaired smooth muscle contractility of the manipulated intestine was maximal after 1.5 h, even before the influx of inflammatory cells, which coincided with increased expression of innate pro-inflammatory cytokines and chemokines such as TNFα, IL-1β, and IL-6 (Farro et al. 2016). A second wave of inhibition was paralleled by influx of monocytes and neutrophils entering the *muscularis* from 6 h onwards to peak at 24 h, associated with increased levels of IL-1β and CCL2. Infiltrating inflammatory cells may affect smooth muscle function by releasing pro-inflammatory cytokines and chemokines, nitric oxide (NO), prostaglandins, and other pro-inflammatory components. Cytokine levels and smooth muscle contractility both returned to baseline at day 3, indirectly suggesting that this second wave of impaired smooth muscle function may be mediated by incoming leukocytes. Interestingly however, responses evoked by electrical field stimulation, thus mediated by enteric neurons, remained abnormal until day 10 (Farro et al. 2016). Enteric neurons indeed revealed reduced expression and impaired activity of ChAT and nNOS, both playing a crucial role in intestinal peristalsis. These observations most likely explain why intestinal transit was only fully recovered by day 5, even when smooth muscle function was already normalized 2 days earlier. So based on these data, in addition to the early neural phase, three more phases can be distinguished: an early (until 6 h) and a late phase (starting at 6 h) of smooth muscle inhibition and a long-lasting (up to 10 days) phase of enteric neuron dysfunction (Fig. 1).

2.3 Mechanisms Triggering the Inflammatory Phase

To date, it is generally accepted that the resident population of *muscular* macrophages residing around the myenteric plexus play a central role in POI.

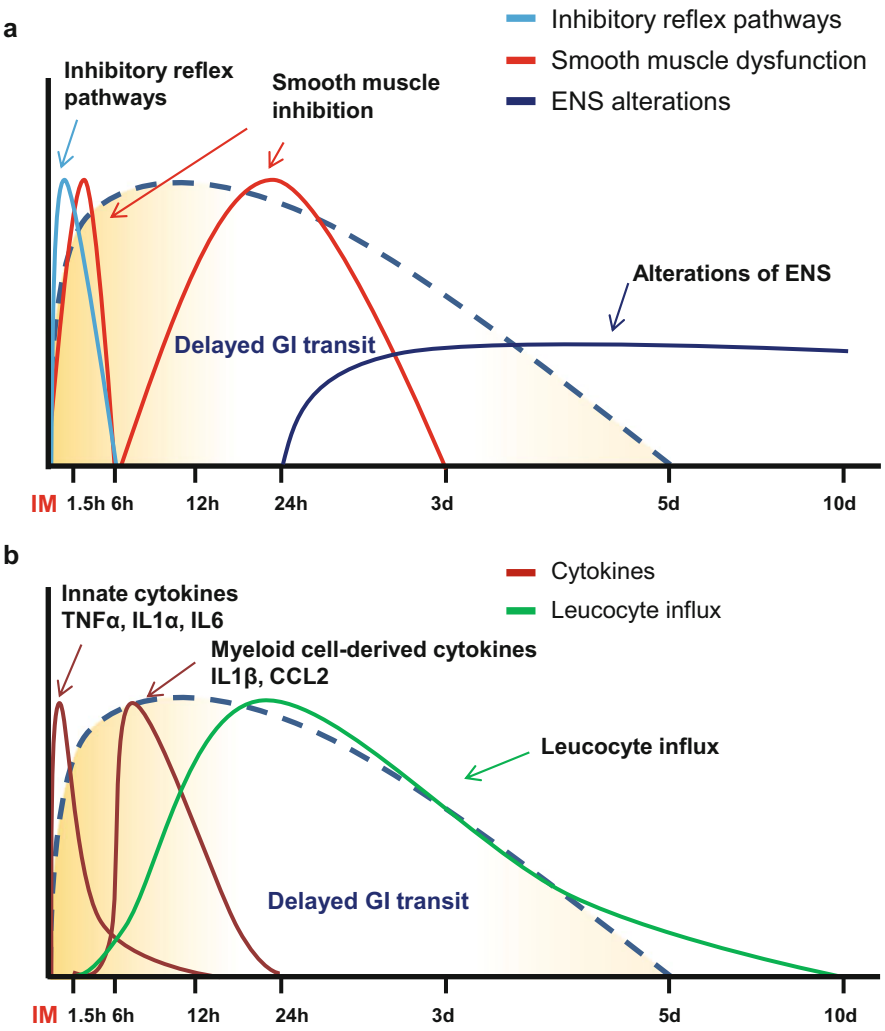

Fig. 1 Schematic representation of the hypothesis proposed regarding the different mechanisms and phases underlying postoperative ileus (POI). Reprinted with permission from Farro et al. (2016)

These macrophages are tolerogenic in nature and are quiescent under normal physiological conditions. Their importance in POI was first demonstrated by Kalff et al. who showed activation of these macrophages by surgical manipulation (Kalff et al. 1999a, b), resulting in activation of transcription factors such as nuclear factor kB (NF-kB), signal transducer and activator of transcription 3 (STAT3) (Wehner et al. 2005), early growth response protein 1 (EGR-1) (Schmidt et al. 2008), and production of pro-inflammatory cytokines and chemokines, integrins, and cell adhesion molecules. As a result, inflammatory cells from the circulation,

mainly neutrophils followed by monocytes, subsequently enter the *muscularis*, further contributing to POI by releasing factors such as NO (Kalff et al. 2000; Turler et al. 2006) and prostaglandins (Kreiss et al. 2003). Conversely, pharmacological or genetic depletion resulted in a decrease of inflammatory mediators and a reduction in the recruitment of leukocytes into the *muscularis* (Bauer and Boeckxstaens 2004; Boeckxstaens and de Jonge 2009).

The mechanisms leading to the activation of the resident macrophages remain however unclear. One potential mechanism may be through activation of damage-associated molecular pattern (DAMP) receptors by molecules released by damaged cells. DAMPs are molecules with no inflammatory capacity per se. They only become pro-inflammatory when released by damaged, stressed, and dying cells into intracellular space (Chen and Nunez 2010). Besides intracellular molecules, also extracellular matrix (ECM) components are danger signals. In fact, degradation of ECM has indeed been demonstrated to contribute to *muscularis* inflammation in POI (Moore et al. 2011). Manipulation of the intestine or even exposure to air leading to dehydration and drop in temperature during surgery may lead to tissue damage and thus release mediators such as ATP, HMGB1, or IL-1α, known to be potent activators of macrophages. IL-1α for example is upregulated maximally 1.5 h after surgery (Farro et al. 2016), while mice pretreated with antibodies against IL-1α and IL-1R$^{-/-}$ mice are protected against POI and show a reduced influx of inflammatory cells (Stoffels et al. 2014), clearly showing that IL-1α and tissue damage may play a crucial role. Although IL-1R is known to be universally expressed (Dinarello 2009), this receptor was shown to be mainly expressed by enteric glia cells, suggesting that enteric glia may be an important source of cytokine production in the very early phase of POI. The degree of tissue damage will clearly depend on the intensity of intestinal manipulation and/or the duration of surgery, and will thus be an important determinant of POI severity (van Bree et al. 2013).

Alternatively, the initial neural phase may be the trigger for the later inflammatory phase. Indeed, intense activation of afferent nerve fibers may trigger neurogenic inflammation via the local release of pro-inflammatory neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP) (Bueno et al. 1997). A role for CGRP released from afferent nerves in response to surgery has been reported already in the early 1990s. In rats, pretreatment of celiac ganglia with capsaicin (eliminating afferent nerves) and a CGRP antagonist (but not an SP antagonist) indeed prevented delayed gastric emptying assessed immediately following surgery (Plourde et al. 1993; Zittel et al. 1994). Of note, activation of IL-1R was proposed to induce the release of CGRP from visceral afferents (Coimbra and Plourde 1996), creating a link between tissue damage (see above) and neurogenic inflammation. Recently, evidence was provided that both intestinal manipulation and capsaicin depleted CGRP from muscular nerve fibers, confirming CGRP release from visceral afferents by intestinal manipulation (Glowka et al. 2015). Of note, both capsaicin and the CGRP antagonist BIBN4096BS reduced *il1β* and *il6* mRNA expression in the *muscularis* externa at 3 h after surgery (Glowka et al. 2015), while CGRP stimulated *il1β* and *il6* mRNA expression in peritoneal macrophages, shown to

express the receptor for CGRP. Taken together, these data indicate that afferent nerves may indeed be involved in the activation of resident *muscular* macrophages and the triggering of the inflammatory cascade. Of interest, the same investigators demonstrated that mast cells were not activated by CGRP. This is somewhat surprising as mast cells have been repeatedly proposed to be a main player in neurogenic inflammation (Bueno et al. 1997) and to be involved in POI both in preclinical models (de Jonge et al. 2004; Snoek et al. 2012) and in humans (Berdun et al. 2015; The et al. 2008, 2009). A recent study, using a specific mast cell-deficient mouse model (Cpa3-Cre), however showed that mast cells, at least in mice, are not involved in POI (Gomez-Pinilla et al. 2014a, b).

Finally, macrophages are potently activated by bacterial cell wall molecules interacting with Toll-like receptors (TLR). Especially as intestinal permeability is transiently increased following intestinal manipulation, bacterial translocation may represent another potential mechanism by which resident macrophages may be stimulated (Schwarz et al. 2002; Snoek et al. 2012). However, as TLR2 and TLR4 knockout mice are not protected against POI, this possibility seems rather unlikely (Stoffels et al. 2014).

2.4 Recovery Phase of POI

Resolution of inflammation is a somewhat neglected phase of the inflammatory process. Mainly a switch of a pro-inflammatory M1 to a tolerogenic M2 microenvironment triggers the resolution phase, a phenomenon mainly mediated by resolvins, a class of polyunsaturated fatty acid-derived proresolving lipid mediators (Serhan 2014). The enzyme involved in the synthesis of resolvins, 12/15-lipoxygenase, is strongly expressed by monocytes infiltrating the postoperative intestinal *muscularis* externa and mediates the production of mainly protectin DX and resolving D2 by these leukocytes. Of interest, pretreatment with protectin DX reduced postoperative influx of neutrophils and improved GI motility. Along the same line, IL-10, mainly expressed by incoming $F4/80^{+}$ monocytes/macrophages, has been proposed to play an important role in the recovery from POI (Stoffels et al. 2009). Mice deficient in IL-10, a cytokine known to possess potent anti-inflammatory properties, had increased expression of numerous pro-inflammatory mRNAs and proteins associated with an increased release of NO and prostanoids. Most importantly, postoperative motility never recovered in these mice, while treatment with recombinant mouse IL-10 reduced neutrophil recruitment and improved POI (Stoffels et al. 2009). We recently showed that also mice lacking monocytes ($CCR2^{-/-}$) recover much slower from POI, indicating that incoming monocytes indeed play an important role in restoring homeostasis and normalizing neuromuscular function (Farro et al. in revision).

2.5 The "Gastrointestinal Field Effect"

POI involves the entire GI tract, and not only the part manipulated during surgery, a phenomenon referred to as the "GI field effect." Two main theories have been proposed to explain this observation: the first includes activation of neural inhibitory pathways by the inflammatory process in the manipulated region (Bauer and Boeckxstaens 2004; Boeckxstaens and de Jonge 2009; de Jonge et al. 2003). Manipulation of the small intestine indeed resulted in inflammation of the manipulated region, not of the stomach or colon, and was associated with c-fos expression (marker of neural activation) in the lumbar spinal cord. Moreover, postoperative neural blockade with hexamethonium and guanethidine normalized gastric emptying without affecting small intestinal transit (de Jonge et al. 2003). This was further corroborated by increased c-fos expression in the spinal cord and brain stem and increased nerve activity of spinal afferent nerves triggered by the intestinal infiltrate (Kreiss et al. 2003; Mueller et al. 2008; van Bree et al. 2013). The second hypothesis proposes the migration of Th1 memory T cells from the inflamed area to the rest of the intestine (Engel et al. 2010; Schwarz et al. 2004). These T cells, under the influence of IL-12 released by dendritic cells, are believed to migrate from surgically manipulated sites through the bloodstream to unmanipulated intestinal areas to induce inflammation and ileus by releasing interferon-γ. Peripheral blood samples indeed reveal increased memory T cells following intestinal manipulation, while prevention of T cell migration with the immunosuppressive agent FTY720 prevented POI (Engel et al. 2010). More recent studies however could not confirm increased levels of IL-12 in the manipulated intestine (Snoek et al. 2012) and could not detect dissemination of inflammation to the large intestine and stomach (van Bree et al. 2013).

3 Current Therapeutic Approaches

Mainly as colonic motility recovers last, first defecation and flatus are often used as primary outcome parameters in clinical trials. These parameters are however nonspecific, mainly as passage of flatus strongly depends on patient reporting, while passage of stool may simply reflect rectal emptying. Using scintigraphic assessment of intestinal transit, we recently showed that the combination of the time to tolerance of solid food and having had defecation best indicates recovery of colonic transit (van Bree et al. 2014), and should preferentially be considered as primary outcome measure in clinical trials evaluating new compounds as treatment of POI.

3.1 Non-pharmacological Strategies

3.1.1 Multimodal Enhanced Recovery After Surgery Programs (Fast-Track Care)

Enhanced recovery after surgery (ERAS) protocols or fast-track programs aim to shorten POI and reduce the rate of perioperative morbidity by a series of general

measures, such as perioperative fluid management, early ambulation and feeding, and optimal analgesia (Kehlet 2011). The LAFA study, a large randomized controlled study evaluating the impact of fast-track care in patients undergoing either laparoscopic or open colectomy, revealed that patients receiving fast-track care already tolerated solid food after 1 day, while those receiving standard care only tolerated solid food at day 3 (laparoscopic) or 4 (open) after surgery (Vlug et al. 2011). Of interest, this clinical improvement was associated with a faster GI transit recovery for fast-track versus standard care (van Bree et al. 2011). Despite the apparent effectiveness of the fast-track approaches, this approach has unfortunately not been fully implemented in the majority of surgical wards. Clearly, programs to enhance its wide implementation should therefore be encouraged.

3.1.2 Laparoscopic Surgery

Minimal invasive surgery using laparoscopy has many potential advantages over conventional open surgery, such as smaller incisions, less pain and inflammation, earlier GI recovery, and shorter hospital stay. Overall, abundant evidence (Basse et al. 2003; Lacy et al. 2002; Milsom et al. 1998), including a recent meta-analysis comprising 4,614 patients with colon cancer (Ohtani et al. 2011), underscores that laparoscopic surgery significantly reduces time until recovery of bowel function (on average 1 day) and duration of hospital stay compared with open colonic resection. In mice, laparoscopic surgery even failed to induce intestinal inflammation and POI compared to standard intestinal manipulation (Gomez-Pinilla et al. 2014a, b).

3.2 Pharmacological Strategies

3.2.1 Prokinetics

Prokinetics are routinely used in clinical practice in the postoperative period to provide symptomatic relief. A recent Cochrane review indicates however that routine administration of these older prokinetics (metoclopramide, cisapride, erythromycin, cholecystokinin, and dopamine antagonists) is not recommended for the prevention of POI (Traut et al. 2008). Clinical studies with metoclopramide for example, a dopamine D_2 receptor antagonist with mixed 5-HT_3 receptor antagonist and 5-HT_4 receptor agonistic properties, are underpowered and reveal controversial results ranging from a reduction in time until first bowel movement and resumption of oral soft diet to no effects (Chan et al. 2005; Seta and Kale-Pradhan 2001).

New 5-HT_4 agents such as prucalopride and mosapride seem more promising. A recent phase II randomized clinical trial, including 110 patients undergoing elective GI surgery, showed a moderate reduction in time to defecation, passage of flatus, and postoperative length of stay in those patients treated with 2 mg of prucalopride (Gong et al. 2016). It should be emphasized that treatment was however only started 24 h after surgery. This may be relevant as we recently showed in our murine model of POI that administration of prucalopride is only effective if administered prior to surgery (Fig. 2) (Gomez-Pinilla et al. 2014c). Only then, prucalopride has anti-inflammatory properties (see below) and prevents POI. Similar preclinical findings were reported with the 5-HT_4 agonist mosapride (Tsuchida et al. 2011). A small clinical study ($n = 30$) evaluated the

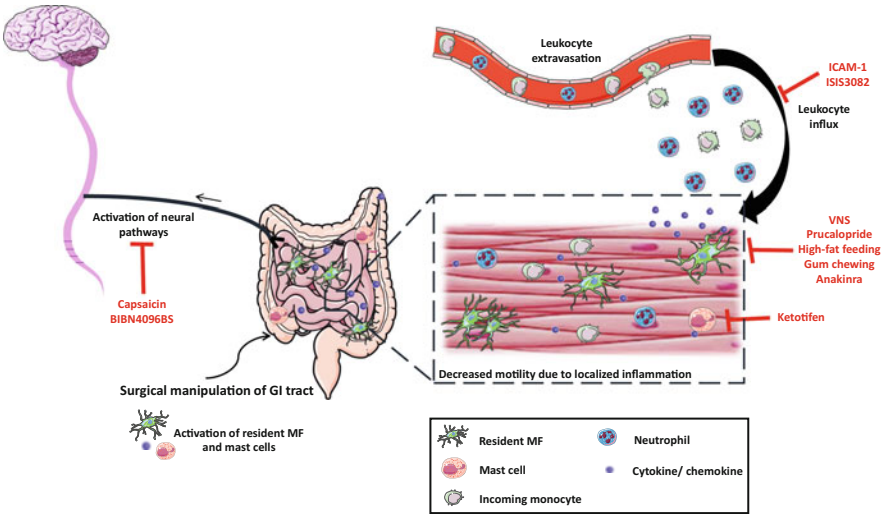

Fig. 2 Schematic representation of the possible therapeutic approaches to prevent postoperative ileus (POI). In the early neuronal phase, GI motility is inhibited via adrenergic and non-adrenergic reflexes activated by skin incision, opening of the peritoneum, and manipulation of the intestines. This neuronal activation can be prevented by capsaicin and BIBN4096BS. In addition, intestinal manipulation activates quiescent resident macrophages and possibly mast cells (at least in humans) present in the intestinal muscularis externa, thereby initiating the inflammatory phase. These activated resident immune cells release cytokines and chemokines, followed by influx of leukocytes, a process that can be inhibited by vagus nerve stimulation, prucalopride, high-fat feeding, and gum chewing, while mast cell activation can be prevented by ketotifen. The influx of leukocytes can be inhibited by ICAM-1 and ISIS3082

effect of 15 mg administered three times a day from the afternoon of postoperative day 1 to the evening of postoperative day 7 and reported a reduction in time to first flatus and defecation. These clinical parameters were associated with an improvement in gastric contractility measured on postoperative day 8 (Toyomasu et al. 2011). Although interesting, these data clearly need confirmation.

3.2.2 Opioid Antagonists

Opioid agonists are often used for postoperative analgesia, and as described above contribute to POI in the early postoperative period mainly by decreasing intestinal motility via stimulation of μ-opioid receptors in the gut. The peripherally acting μ-opioid receptor antagonist alvimopan belongs to a new class of drugs designed to reverse these opioid-induced GI side effects without affecting centrally mediated opioid analgesic effects and thus not compromising pain relief (Becker and Blum 2009). A recent meta-analysis selected five randomized, double-blind, placebo-controlled, phase III trials (Drake and Ward 2016). Administration of alvimopan prior to surgery (6–12 mg) showed beneficial and significantly reduced the time to tolerance of solid food and first defecation. Across all studies, alvimopan was well tolerated and no increased adverse events or serious adverse events were reported compared to

placebo. Methylnaltrexone, another peripherally acting μ-opioid antagonist, was recently studied in two placebo-controlled phase III trials evaluating intravenous (i.v.) administration of 12 and 24 mg. No improvement in time to first bowel movement was observed in a total of 1,048 randomized patients undergoing segmental colectomy (Yu et al. 2011). As both alvimopan and methylnaltrexone intervene with the detrimental effects of opioids administered in the early postoperative period, it remains to be awaited if these compounds will be clinically valuable given the recent strategies to reduce the perioperative use of opioids.

3.2.3 Ghrelin Agonists

Ghrelin is a 28-amino acid peptide mainly produced in the fundus of the stomach and in the pancreas. In view of their powerful prokinetic properties, ghrelin and ghrelin agonists such as ipamorelin and ulimorelin (TZP-101) have been evaluated as potential therapy for POI. To date, two phase IIb studies have been reported on TZP-101 safety and efficacy in POI management. Treatment with 20–600 μg/kg ulimorelin by 30-min i.v. infusion within 1 h of surgical closure and then daily for up to 7 days accelerated the time to first bowel movement and shortened hospital stay (Popescu et al. 2010). In the other phase IIb study, the effect of ulimorelin treatment (480 μg/kg) was tested in 168 patients subjected to major surgery yielding comparable results (Bochicchio et al. 2012). Two subsequent randomized placebo-controlled phase III trials ($n = 332$ and $n = 330$ patients included) however failed to demonstrate a reduction in POI (Shaw et al. 2013). In line, no improvement was found with ipamorelin in 117 patients undergoing colonic resection (Beck et al. 2014), further dampening the enthusiasm to develop this class of compounds as treatment for POI.

3.3 Potential New Treatments

Given that inflammation of the intestine is the main mechanism responsible for POI, one might expect that strategies targeting this process are more effective than those currently available. Conversely, the knowledge that the contractility of the inflamed intestine is significantly compromised may also explain why prokinetics are not as effective as one might anticipate.

Accepting that activation of visceral afferents and the subsequent neurogenic inflammation is one of the first events triggering the inflammatory cascade, compounds interfering with this mechanism may hold promise to treat POI. As indicated earlier, the antagonist of CGRP, BIBN4096BS, is effective in reducing intestinal inflammation and shortens POI in preclinical studies (Fig. 2) (Glowka et al. 2015). BIBN4096BS has been used with success to treat acute attacks of migraine (Olesen et al. 2004). A recent trial evaluated the potential of another CGRP antagonist MK-0974 (telcagepant) for prevention of migraine. Patients received this compound twice daily for a period of 12 weeks. Although the results were promising, the trial was terminated due to hepatotoxicity, indicating that daily use cannot be supported (Ho et al. 2014). To what extent

it can be used safely in the perioperative period for only a few days remains to be investigated.

In view of the important role of IL-1 in POI, IL-1R antagonists may be interesting compounds to study as treatment for POI (Stoffels et al. 2014). Anakinra indeed potently prevented POI in mice (Fig. 2). This compound is studied in immune-mediated diseases such as arthritis (Singh et al. 2016) and sepsis (Shakoory et al. 2016). A promising alternative may be IL-1 receptor accessory protein-Ig/IL-1 receptor-type II-Ig heterodimer which more potently blocks IL-1R than anakinra (Hanawa et al. 2011).

Extravasation of leukocytes into the manipulated intestine results from the upregulation of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1). Pretreatment with the monoclonal antibodies to ICAM-1 (de Jonge et al. 2003; Kalff et al. 1999a, b) or the ICAM-1 antisense ISIS 3082 (The et al. 2005) both reduced manipulation-induced inflammation and POI, suggesting that targeting adhesion molecules may indeed be an interesting approach to prevent POI in humans (Fig. 2). However, no human studies are currently available.

Targeting the immune cells involved may be another interesting approach. Especially as resident macrophages seem to orchestrate the inflammatory process, reducing their activation may prove effective to shorten or prevent POI. Inhibition of p38 mitogen-activated protein kinase (p38 MAPK), one of the intracellular signaling pathways involved in macrophage activation, by semapimod (The et al. 2011; Wehner et al. 2009) or its orally active salt CPSI-2364 (Wehner et al. 2012) has been proven to effectively reduce inflammation and POI in mice and swine. Somewhat related, inhaled carbon monoxide (CO) and administration of CO-releasing molecules possess anti-inflammatory properties through interaction with the p38 MAPK pathway, and other intracellular signaling pathways (Gibbons et al. 2013) have proven effective in POI (De Backer et al. 2009; Moore et al. 2003). The advantage of CO-based therapies would be that it can be administered on an acute basis and potentially be delivered close to the site of action by intraperitoneal injection (Nakao et al. 2006). To date, however, no human data are available.

Groundbreaking work in the field of sepsis has introduced the concept that the vagus nerve possesses anti-inflammatory properties by inhibition of macrophages, referred to as the cholinergic anti-inflammatory pathway (CAIP) (Tracey 2002). Based on the insight that activation of resident macrophages triggers the inflammatory phase of POI, the therapeutic potential of the CAIP in POI has been intensively studied. Electrical stimulation of the vagus nerve (VNS) indeed dampens the activation of intestinal resident macrophages reducing the release of pro-inflammatory cytokines, preventing the influx of leukocytes, and restoring intestinal transit (de Jonge et al. 2005; Matteoli et al. 2014; The et al. 2007). This effect is mediated by vagally mediated stimulation of cholinergic neurons releasing acetylcholine interacting with α7nAChRs on the resident macrophages (Fig. 2). As 5-HT_4 agonists such as prucalopride and mosapride increase the release of acetylcholine from enteric neurons, these agents are proposed to have anti-inflammatory properties by mimicking the effect of VNS (Gomez-Pinilla et al. 2014c; Tsuchida et al. 2011). In mice, prucalopride indeed reduced manipulation-induced intestinal inflammation and improved POI, but only when administered preoperatively

(Gomez-Pinilla et al. 2014c), explaining why clinical trials have been rather disappointing so far. Clinical studies evaluating the effect of electrical stimulation of the abdominal vagus nerve in patients undergoing abdominal surgery are ongoing (Fig. 2) (NCT02524626, NCT02425774).

Not only electrical stimulation can activate the vagus nerve, but also compounds activating motor neurons of the vagus in the brain stem could be effective, as shown for semapimod, indeed mimicking the effect of VNS (The et al. 2011). Interestingly, activation of vagal afferents by high-fat enteral feeding also stimulates the CAIP, an effect mediated by the release of CCK (Fig. 2) (Luyer et al. 2005). In rats, high-fat enteral feeding indeed reduced peritoneal levels of TNF-α and IL-6, reduced the influx of neutrophils, and significantly improved intestinal transit (Lubbers et al. 2009). Of note, also in patients undergoing major rectal surgery for rectal carcinoma, early enteral feeding hastened the time to first defecation and reduced the hospital stay from 16–7 to 13–4 days (Boelens et al. 2014). A multicenter double-blind randomized trial (NCT02175979) is currently evaluating perioperative nutrition on POI and anastomotic leakage in patients ($n = 280$) undergoing colorectal surgery. Sham feeding or gum chewing is believed to have a similar effect by stimulation of the vagus nerve. A recent meta-analysis of randomized trials identified 81 studies evaluating the effect of gum chewing on postoperative recovery of GI function including 9,072 patients (Short et al. 2015). This meta-analysis identified some evidence for the benefit of postoperative gum chewing, but the studies included were rather small and of poor quality, so clearly larger studies of better quality are required (Fig. 2).

Finally, as we know that the resident macrophages are inhibited by acetylcholine and nicotine via binding to α7nAChRs, administration of nicotine, but preferentially specific α7nAChR agonists, could be of interest. In mice, the α7nAChR agonists AR-R17779 prevented POI and reduced leukocyte influx and cytokine upregulation (The et al. 2007) comparable to the effect of VNS. Of note, administration of an equimolar dose of nicotine was not tolerated, most likely as nicotine will act on a variety of nicotine receptors. Although nicotine gum chewing has been proposed as a novel strategy to shorten POI, these data would argue against this approach (Wu et al. 2014).

Mast cells have also been implicated to play a role in POI. The evidence in mice however should be interpreted with care as the mast cell-deficient mice used in these studies also lack interstitial cells of Cajal and are immune compromised (de Jonge et al. 2004; Snoek et al. 2012). Using a cleaner mast cell-deficient mice, the role of mast cells, at least in mice, could not be confirmed (Gomez-Pinilla et al. 2014a, b). Mast cell activation has however been demonstrated in humans (Berdun et al. 2015; The et al. 2008), while a small pilot study using the mast cell stabilizer/histamine 1 receptor antagonist ketotifen improved postoperative gastric emptying (Fig. 2) (The et al. 2009). Although promising, no clinical trials are currently available to further support mast cells as important target to treat POI.

4 Conclusions

Over the past few decades, our insight into the mechanisms leading to POI has significantly increased. Especially the role of inflammation in the transient paralysis of the entire gastrointestinal tract has been appreciated. The introduction of minimal invasive surgery or laparoscopy is another major breakthrough significantly reducing the impact of the surgical procedure and the tissue damage induced, and reducing the need for postoperative opioids, all contributing to faster recovery. Similarly, earlier mobilization and feeding of patients, as in the fast-track care programs, is a significant improvement of patient care shortening hospitalization and reducing costs. Current pharmacological management is however rather disappointing, but the increased knowledge will undoubtedly lead to new and more efficient treatments.

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