



## Controlling postoperative ileus by vagal activation

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intervention to activate this neuroimmune pathway is enteral administration of lipid-rich nutrition. Perioperative administration of lipid-rich nutrition reduced manipulation-induced local inflammation of the intestine and accelerated recovery of bowel movement. The application of safe and easy to use antiinflammatory interventions, together with the current multimodal approach, could reduce postoperative ileus to an absolute minimum and shorten hospital stay.

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**Key words:** Postoperative ileus; Inflammation; Vagus; Nutritional antiinflammatory pathway

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### Abstract

Postoperative ileus is a frequently occurring surgical complication, leading to increased morbidity and hospital stay. Abdominal surgical interventions are known to result in a protracted cessation of bowel movement. Activation of inhibitory neural pathways by nociceptive stimuli leads to an inhibition of propulsive activity, which resolves shortly after closure of the abdomen. The subsequent formation of an inflammatory infiltrate in the muscular layers of the intestine results in a more prolonged phase of ileus. Over the last decade, clinical strategies focusing on reduction of surgical stress and promoting postoperative recovery have improved the course of postoperative ileus. Additionally, recent experimental evidence implicated antiinflammatory interventions, such as vagal stimulation, as potential targets to treat postoperative ileus and reduce the period of intestinal hypomotility. Activation of nicotinic receptors on inflammatory cells by vagal input attenuates inflammation and promotes gastrointestinal motility in experimental models of ileus. A novel physiological

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### INTRODUCTION

Postoperative ileus is a common pathological condition in the surgical ward and presents as an inability to tolerate enteral nutrition, nausea, abdominal distension, and lack of flatus and defecation. Although all surgical patients are at risk of developing postoperative ileus, the condition is mostly observed after abdominal surgery with manipulation of the gastrointestinal tract<sup>[1]</sup>. Cessation of bowel movement and delayed gastric emptying, which can be up to 5 d after colorectal surgery, results in increased morbidity and a prolonged hospital stay<sup>[2-4]</sup>. The duration of postoperative ileus has a major financial impact, adding an average of 6.300 US\$ to hospital costs

per patient who develops ileus<sup>[5]</sup>. The additional health care costs in the US have been estimated to be 1.5 billion US\$ annually<sup>[6]</sup>. Increased insight into the pathophysiology and discovery of novel treatment options could diminish the length of postoperative ileus, decrease patient morbidity, and reduce hospital costs.

## PATHOPHYSIOLOGY OF POSTOPERATIVE ILEUS

The pathophysiology underlying postoperative ileus is complex and multifactorial, consisting of endogenous and pharmacological characteristics. Recent experimental studies have demonstrated that the pathogenesis of the endogenous component of postoperative ileus can be grossly divided in two distinct phases<sup>[1]</sup>. The first phase, or neural phase, results from activation of mechanoreceptors and nociceptors by stimuli, such as incision of the skin and, more importantly, by direct manipulation of the intestine<sup>[7]</sup>. Activation of these receptors initiates a neural reflex, which is dependent on release of mediators, such as  $\alpha$ -calcitonin gene-related peptide and substance P, which inhibit gastrointestinal motility and result in generalized intestinal hypomotility<sup>[8-10]</sup>. The neural phase of postoperative ileus lasts minutes to hours and resolves after closure of the wound when the noxious stimuli have ceased<sup>[9,11,12]</sup>. The motility of the colon in particular depends heavily on input from the autonomic nervous system, which might explain colonic susceptibility to isolated and prolonged ileus<sup>[13]</sup>.

The second, more protracted, inflammatory phase is caused by formation of an inflammatory infiltrate in the muscular layers of the intestine<sup>[7,14,15]</sup>. Manipulation of the intestine initiates an inflammatory cascade starting with activation and degranulation of mast cells<sup>[16-18]</sup>. Subsequently, resident macrophages are activated either *via* mast cell-derived mediators or by luminal antigens<sup>[17,19,20]</sup>. These activated macrophages produce cytokines and chemokines, which attract neutrophils to the muscular layer of the intestine. Invaded neutrophils directly impair intestinal smooth muscle cell contractility *via* release of nitric oxide and prostaglandins<sup>[21,22]</sup>. The formation of an inflammatory infiltrate not only impairs motility in the manipulated areas, but also leads to generalized hypomotility of the gastrointestinal tract *via* activation of inhibitory adrenergic neural pathways. There is emerging evidence that inflammation also plays a vital role in postoperative ileus in humans, therefore a major focus of current research has been directed at the development of antiinflammatory treatments<sup>[18,23,24]</sup>. In experimental models of intestinal manipulation, it was demonstrated that administration of antiinflammatory agents, such as mast cell stabilizers<sup>[17]</sup>, non-steroidal antiinflammatory drugs<sup>[25,26]</sup>, and interleukin (IL)-10<sup>[27]</sup>, prevent development of postoperative ileus. In addition, it was recently shown in patients undergoing major abdominal surgery that an intervention with the mast cell stabilizer, Ketotifen, reduced gastroparesis<sup>[24]</sup>.

## CLINICAL STRATEGIES TO TREAT POSTOPERATIVE ILEUS

A number of strategies for preventing postoperative ileus are combined in the so-called fast-track program. The goals of fast-track surgery are reduction of perioperative surgical stress and promotion of postoperative recovery. Adequate pain relief, minimal invasive surgery and early enteral nutrition are important to achieve these goals<sup>[28]</sup>. Adequate pain relief can attenuate postoperative ileus in two important ways. First, intraoperative spinal anesthesia and postoperative epidural analgesia with local anesthetics during abdominal surgery reduce the neural phase of ileus by interruption of neural transmission. Second, local anesthetic interventions minimize the use of opioid-derivatives<sup>[29,30]</sup>. Both endogenous opioids, released in response to noxious stimuli, and exogenous opioids are notorious for their inhibitory effect on gastrointestinal motility, thereby aggravating postoperative ileus<sup>[31]</sup>. Blocking the  $\mu$ -opioid receptor with Alvimopan, a selective, peripherally active antagonist, has been demonstrated to accelerate recovery of bowel function and decrease hospital stay, without affecting the analgesic effects of opioids<sup>[32,33]</sup>. In addition, non-steroidal anti-inflammatory drugs seem promising for their opioid-sparing and antiinflammatory effects<sup>[26,34]</sup>. However, caution should be taken as the use of cyclo-oxygenase-2 inhibitors after colonic surgery has been associated with increased anastomotic leakage<sup>[35]</sup>.

Surgical trauma and direct manipulation of the intestine are major factors in the occurrence of postoperative ileus. The degree of gastrointestinal hypomotility correlates with the degree of manipulation and intestinal inflammation<sup>[19]</sup>. The introduction of minimally invasive techniques, such as laparoscopy, significantly reduced the duration of postoperative ileus and length of hospital stay<sup>[36]</sup>. This improvement is probably due to minimization of trauma, resulting in less pain and a diminished release of neurotransmitters and inflammatory mediators<sup>[18,28,37]</sup>.

Finally, enteral nutrition is found to be essential for enhanced recovery after surgery. Ingestion of nutrients elicits various reflexes and releases several neuropeptides that promote gastrointestinal motility<sup>[38,39]</sup>. Traditionally however, a nil-by-mouth regime is often enforced starting from several hours before surgery until days postoperatively. Recent studies have demonstrated that early enteral nutrition is safe and well tolerated after abdominal surgery. In addition, early enteral nutrition reduces postoperative ileus and length of hospital stay<sup>[40,41]</sup>. Unfortunately, studies investigating the effect of early enteral nutrition on postoperative ileus remain difficult to interpret, as the studies often lack essential information on the type of analgesia that was used<sup>[2]</sup>. Enteral nutrition is a promising intervention to treat ileus; however, future well-designed studies are needed to evaluate the effect of early enteral nutrition on intestinal motility. When implementing early enteral nutrition routinely,

caution should be taken, as there is a small chance that enteral nutrition could lead to intestinal ischemia in the circulatory compromised patient<sup>[42,43]</sup>.

The implementation of fast-track regimes in the surgical field has improved the course of postoperative ileus. However, despite these efforts, it still remains an important clinical challenge. Inhibition of the inflammatory phase, by targeting the cellular and molecular changes underlying postoperative ileus is another focus of treatment.

## EXPERIMENTAL STRATEGIES TO CONTROL POSTOPERATIVE ILEUS

The inflammatory phase dominates the course of postoperative ileus. Novel experimental interventions aimed at preventing the activation of inflammatory cells, such as administration carbon monoxide<sup>[44,45]</sup>, pretreatment with blocking antibodies to intracellular adhesion molecule-1 and lymphocyte function-associated antigen-1<sup>[7,46]</sup>, inactivating macrophages<sup>[47]</sup>, and preventing mast cell activation<sup>[17]</sup>, have displayed promising results in reducing gastrointestinal hypomotility. Borovikova *et al.*<sup>[48]</sup> described a novel approach for modulating the inflammatory response; electrical stimulation of the vagus nerve attenuates systemic inflammation in a murine endotoxin model. Stimulation of the vagus nerve modulates inflammation *via* release of acetylcholine that binds to nicotinic receptors on inflammatory cells, hence the term “cholinergic anti-inflammatory pathway”<sup>[49,50]</sup>. In addition, the vagus nerve has recently been identified as an important modulator of intestinal health; loss of vagal integrity aggravates intestinal inflammation and augments loss of gut barrier function<sup>[51,52]</sup>.

In a murine model of intestinal manipulation, electrical stimulation of the vagus nerve ameliorates postoperative gastrointestinal hypomotility *via* inhibition of local intestinal inflammation. Vagal stimulation activates the  $\alpha 7$  nicotinic acetylcholine receptor on intestinal macrophages and attenuates release of pro-inflammatory cytokines *via* the Jak2-Stat3 signaling pathway<sup>[53]</sup>. Furthermore, administration of the selective  $\alpha 7$  receptor agonist, AR-R17779, prevented postoperative ileus in mice<sup>[54]</sup>. Although very effective in preventing postoperative ileus in animal models, caution should be taken when implementing electric vagus stimulation and pharmacologic interventions in patients. Electrical stimulation remains an invasive procedure, while pharmacologic stimulation of nicotinic receptors might cause unwanted stimulation of different cell types and organs<sup>[55,56]</sup>.

A more physiological way to activate the vagal anti-inflammatory pathway is by administration of enteral nutrition enriched with lipids. Administration of lipid-rich nutrition prior to, or following, hemorrhagic shock attenuates systemic inflammation and preserves intestinal integrity<sup>[57,58]</sup>. These positive effects of lipid-rich nutrition on gut barrier function and systemic inflammation are specific for the amount of lipids in the nutrition, as a low-lipid control feeding did not exert these protec-

tive effects. The enteral presence of lipids activates the autonomic nervous system *via* cholecystokinin (CCK) receptors. Subsequently, inflammation is inhibited through activation of nicotinic receptors on inflammatory cells *via* the efferent vagus<sup>[59]</sup>. Enteral administration of lipid-rich nutrition was demonstrated to reduce postoperative ileus in a rodent model of intestinal manipulation<sup>[16]</sup>. Enteral nutrition enriched with lipids prevented degranulation of mast cells, inhibited release of macrophage-derived tumor necrosis factor- $\alpha$  and IL-6, and prevented influx of neutrophils into the intestinal muscularis to a greater extent than the control, low-lipid, nutrition. More importantly, the beneficial effect of lipid-rich nutrition on manipulation-induced local inflammation promoted gastrointestinal transit in a CCK-receptor-dependent manner<sup>[16]</sup>. These findings indicate that lipid-rich nutrition reduces postoperative ileus *via* activation of the nutritional antiinflammatory pathway. Luminal lipids are known to activate the autonomic nervous system *via* CCK-mediated stimulation of peripheral CCK-1 receptors on afferent vagal fibers, resulting in several regulatory digestive functions, such as satiety<sup>[60]</sup>. Therefore, the antiinflammatory potential of lipid-rich enteral nutrition could rely on activation of a nutritional CCK-dependent vagovagal reflex.

Interestingly, sham feeding is another physiological technique that activates the cephalic vagal axis by mimicking food intake, thereby stimulating bowel motility<sup>[38,39]</sup>. Furthermore, activation of the cephalic phase elicits digestive functions *via* vagovagal cholinergic reflexes<sup>[61]</sup>. Sham feeding by chewing gum has been shown to improve bowel movement and reduce time to first flatus and first defecation after open gastrointestinal surgery, and demonstrates a trend towards a reduced hospital stay<sup>[62,63]</sup>. However, the exact mode of action remains to be investigated.

## CONCLUSION

Surgical interventions, and abdominal surgery in particular, are frequently accompanied by the occurrence of postoperative ileus. Postoperative ileus is a multifactorial surgical complication that requires a multifactorial treatment approach. Minimal invasive surgery to reduce surgical stress, epidural analgesia to block inhibitory reflexes, minimizing opioid use, and attenuation of intestinal inflammation by antiinflammatory interventions should reduce postoperative ileus to a minimum. The development of safe and easy-to-use treatments to prevent intestinal inflammation will play a key role in controlling postoperative ileus and deserves further investigation. Stimulation of the vagal antiinflammatory pathway, by interventions such as enteral administration of lipids, is one of the promising interventions contributing to a further reduction of postoperative ileus.

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