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# Brain peptides and the modulation of postoperative gastric ileus

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## Abstract

Postoperative ileus (POI) develops after abdominal surgery irrespective of the site of surgery. When prolonged, POI can lead to longer hospitalization times and higher healthcare costs. Moreover, it is associated with complaints for the patient. In order to develop new strategies to treat this condition, a deeper understanding of the pathophysiology of the POI is necessary. This review will focus on brain peptides (ghrelin, nesfatin-1, somatostatin, corticotropin-releasing factor, thyrotropin-releasing hormone and calcitonin gene-related peptide) involved in the mediation of POI and the possible modulation of these pathways to shorten the time of POI. Lastly, the role of vagal signaling and the possibility of reducing ambient temperature or chewing gum as potential treatment strategies of alleviating symptoms of POI is discussed.

### List of compounds discussed in the article

α-CGRP; astressin; calcitonin gene-related peptide; corticotropin-releasing factor; ghrelin; NUCB2/nesfatin-1; RX-77368; S-406-028; somatostatin; thyrotropin-releasing hormone; ulimorelin

## INTRODUCTION

Postoperative ileus regularly develops after abdominal surgery and is characterized by a delay in gastric emptying and a prolongation of intestinal transit [1]. Two decades ago



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There are no conflicts of interest.

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postoperative ileus was defined as uncomplicated delayed transit that occurred after surgery and resolved spontaneously within two to three days [2]. It is clinically characterized by symptoms such as absence of bowel movements, flatus and defecation, abdominal bloating and pain. When this conditions persists over a longer period of time (> three days after surgery), it is often referred to as paralytic postoperative ileus (or prolonged or pathological ileus) [2]. Another – more recently suggested – definition of postoperative ileus describes the ileus as time from the surgery until passage of flatus or stool together with the time to adequate oral nutrient intake [3]. This type of postoperative ileus has to be clearly distinguished from the secondary postoperative ileus aggravated by complications such as leakage, peritonitis or abscess [3, 4]. In the recovery period, the functions of stomach and small intestine are restored more quickly (within 24 to 48 h) than those of the large bowel function (up to 72 h) [5]. Besides suffering for the patient, prolonged postoperative ileus also leads to higher healthcare costs mainly due to longer hospitalization times [6, 7].

In light of these data a deeper understanding of the pathophysiological mechanisms leading to postoperative ileus is necessary in order to develop effective pharmacological treatment strategies to shorten the time of postoperative ileus. At the cellular level, the pathophysiology of postoperative ileus can be separated in an early neural and humoral [8] as well as a delayed immunological phase [9]. The present review will focus on the early phase with brain peptides involved in the mediation of postoperative ileus and also on the role of vagal signaling in the modulation of postoperative ileus and associated treatment strategies such as chewing gum or reducing ambient temperature, whereas the inflammatory mediators involved and the possible mediation of this phase to alleviate symptoms of postoperative ileus are reviewed elsewhere [10].

## MODULATION OF POSTOPERATIVE ILEUS BY BRAIN PEPTIDES AND NEURONAL ACTIVATION

### Ghrelin – expression and regulation

Ghrelin was discovered in 1999 as the endogenous ligand of the growth hormone secretagogue receptor 1a (GHS-R1a) [11] which was later renamed ghrelin (GRLN) receptor due to its main ligand [12]. Ghrelin is a 28 amino acid peptide that bears a unique fatty acid residue on the third amino acid essential for the binding to its receptor [11]. The enzyme catalyzing this acylation was long unknown and identified few years ago as a member of the superfamily of membrane-bound O-acyltransferases (MBOATs) and termed ghrelin-*O*-acyltransferase (GOAT) [13, 14]. The by far major source of ghrelin is the stomach [15] with smaller quantities produced in the intestinal tract [16], pancreas [17] and other peripheral organs including liver, kidney, adipose tissue, heart and skin [18]. Lastly, ghrelin is also produced – although in smaller quantities – directly in the brain in neurons adjacent to the third ventricle [19] and in the arcuate nucleus of the hypothalamus (Arc) [20].

Early on, ghrelin plasma levels were shown to vary in relation to feeding status with an increase in the fasting state and before a meal and a decline thereafter [21] giving rise to a physiological role of ghrelin in the modulation of feeding. Indeed, the food-intake stimulating action of ghrelin has been well documented in humans [22]. In addition, ghrelin

is also regulated by long term changes in body weight with a decrease of ghrelin levels under conditions of obesity [23]. Interestingly, the variation of circulating ghrelin levels also shows a close association with the appearance of gastric migrating motor complexes [24]. Subsequent studies established a physiological role of endogenous ghrelin in the stimulation of gastric motility in rodents. This assumption is supported by the finding that peripheral administration of ghrelin stimulates antral motility in rodents [25] and humans [26] contributing to the acceleration of gastric emptying [27]. However, it is important to note that only pharmacological/supraphysiological doses exert gastroprokinetic effects under conditions of gastroparesis [28].

## Ghrelin – involvement in postoperative ileus

Animal studies showed that ghrelin levels are reduced following abdominal surgery with a rapid decline of acyl ghrelin occurring within the first 30 min post surgery followed by a sustained inhibition of these levels over a period of 5 h with a restoration within 24 h [29]. The decline in plasma ghrelin levels was associated with a reduction of gastric and plasma GOAT protein concentrations [29] likely contributing to the decrease in plasma ghrelin due to reduced acylation. Moreover, a stimulated de-acylation of ghrelin may contribute to the lower levels observed as recently reported following the injection of lipopolysaccharide [30]. In line with the assumption of a causal role of ghrelin for the observed changes after surgery, the intravenous injection of ghrelin or GRLN agonists reversed the surgery-induced delay of gastric emptying in rodents [31, 32] and humans [33] and accelerated the time to the first bowel movement in humans [33] resulting in a shorter hospitalization period [34] (Table 1). However, a recent randomized, placebo-controlled phase 3 trial investigating the effect of intravenously injected ulimorelin, a GRLN agonist, did not detect differences in the time to the first bowel movement after surgery compared to placebo [35]. Whether this is related to the dose or pharmacokinetic of the compound will have to be further established. Taken together, the stimulation of ghrelin signaling by GRLN mimetics or activation of GOAT may be a useful strategy to promote gastrointestinal motility after abdominal surgery.

## Nesfatin-1 – expression and regulation

Nesfatin-1 was discovered in 2006 in the rat hypothalamus and introduced as a potential cleavage product of nucleobindin2 (NUCB2) [36]. Following the description of nesfatin-1 in food intake-regulatory nuclei in the hypothalamus and brainstem [36], several studies showed the expression of NUCB2/nesfatin-1 in other distinct nuclei throughout the rodent brain [37, 38] pointing towards a pleiotropic action of this peptide. The expression of NUCB2/nesfatin-1 has also been detected in the human Edinger-Westphal nucleus [39] likely contributing to the mature nesfatin-1 detected in the cerebrospinal fluid [40]. As observed before for several other peptides once thought to be restricted to the brain, NUCB2/nesfatin-1 was also detected in peripheral organs such as stomach [41], adipose tissue [42], and pancreas [43] of humans likely contributing to the circulating peptide levels of nesfatin-1 [44]. Interestingly, ghrelin and NUCB2/nesfatin-1 were detected in the same gastric cell, the X/Alike endocrine cell, in stomachs of obese human subjects [41] highlighting this cell type as a possible dual regulator of food intake with a stimulation or inhibition of feeding depending on the peptide product released.

The brain expression of NUCB2/nesfatin-1 was shown to be decreased under conditions of fasting [36] which was in line with a reduction of plasma NUCB2/nesfatin-1 levels that were restored after re-feeding in rats [45] indicative of a role in the regulation of food intake. Nesfatin-1 is likely also involved in the regulation of long term body weight as body weight modulation affects circulating NUCB2/nesfatin-1 levels with higher levels under conditions of obesity reflected in a positive correlation with body mass index [46].

## Nesfatin-1 – involvement in postoperative ileus

Recent studies indicate that intracerebroventricular injection of nesfatin-1 delays gastric emptying in rats [45] and reduces gastroduodenal motility in mice [47]. In addition, there is evidence that abdominal surgery activates several NUCB2/nesfatin-1 positive brain nuclei in rats [48] suggesting that activated NUCB2/nesfatin-1 signaling under conditions of abdominal surgery contributes to the observed decrease of food intake and gastrointestinal transit (Table 1). This hypothesis warrants further investigation and the modulation of NUCB2/nesfatin-1 signaling by nesfatin-1 antagonists should be tested after abdominal surgery in humans. However, these studies are hampered so far by the lack of identification of the NUCB2/nesfatin-1 receptor which will be a great leap forward and allow for the generation of specific NUCB2/nesfatin-1 antagonists.

## Somatostatin – expression and regulation

Somatostatin was discovered in 1973 as a growth hormone-inhibitory factor isolated from ovine hypothalami [49] and by now known to exert its effects *via* the interaction with five somatostatin (sst) receptor subtypes ($sst_{1–5}$) [50]. Subsequent studies showed the widespread distribution of somatostatin in the whole rodent brain except the cerebellum [51] and the human brain [52] in line with the multiple central actions described including the stimulation of food intake, involvement in thermoregulation and a modulation of behavior and autonomic nervous system activity in addition of the well-established endocrine growth hormone suppression [53]. Support for a physiological role of brain somatostatin in the regulation of food intake comes from the observation that hypothalamic somatostatin expression shows a circadian variation with a peak at the beginning of the dark phase when rats as nocturnal eaters show their maximal food consumption and lowest levels in the early light phase [54]. Besides its expression in the brain, somatostatin is also widely expressed in the gastrointestinal tract [55] where it is known to act as an inhibitory modulator of several gastrointestinal peptides and functions [56].

## Somatostatin – involvement in postoperative ileus

Since the stomach is a major expression site of somatostatin [57] as well as the somatostatin receptor 2 ($sst_2$) [58], several studies also investigated the role of somatostatin-$sst_2$ signaling under conditions of abdominal surgery. The intravenous injection of the selective peptide $sst_2$ antagonist, S-406-028 prevented the surgery-induced reduction of circulating ghrelin [29]. This somatostatin-$sst_2$-ghrelin signaling pathway may represent a paracrine mode of action as somatostatin-producing D cells are located in close proximity to the $sst_2$-bearing ghrelin-producing X/A-like cells of the stomach [29]. However, the blockade of $sst_2$ signaling under conditions of abdominal surgery did not modulate the surgery-induced

gastric ileus [29]. This observation is in line with a study showing that brain activation of $sst_2$ signaling does not alter the surgery-induced delay of gastric emptying, whereas the inhibition of food intake was restored [59]. This was associated with a restoration of circulating ghrelin levels to physiological concentrations observed under conditions of fasting [59] giving rise to a dissociation of ghrelin's orexigenic and prokinetic actions under conditions of abdominal surgery when modulated by $sst_2$ signaling (Table 1). In summary, the blockade of $sst_2$ signaling may be a useful strategy to promote appetite following abdominal surgery.

## Corticotropin-releasing factor – expression and regulation

The stimulatory action of corticotropin-releasing factor (CRF) to release pituitary adrenocorticotropic hormone (ACTH) in response to various stressors was described in 1950 [60]. This factor was purified five years later [61], however, it took until 1981 until CRF was identified and characterized as a 41 amino acid peptide [62]. Besides the key involvement in the endocrine response to stress, CRF showed to have pleiotropic actions in the modulation of stress-related alterations of autonomic, visceral, immune and behavioral functions [63]. The peptide is expressed in specific brain nuclei with major localization sites in the paraventricular nucleus (PVN) of the hypothalamus, cerebral cortex, amygdala-hippocampal complex and the pontine Barrington's nucleus. CRF is also peripherally expressed in the gastrointestinal tract, enteric nervous system, adipose tissue, heart, lung and testis [64]. It is well established that acute stressors and brain or peripheral injection of CRF reduces upper gastrointestinal motility, while colonic motility and secretion are enhanced [65].

## Corticotropin-releasing factor – involvement in postoperative gastric ileus

Key nuclei that mediate autonomic outflow to the stomach such as the PVN and the dorsal vagal complex in the brainstem are activated under conditions of abdominal surgery [66] responsible for the mediation of the CRF-induced inhibition of gastric motility [65]. This action can be blocked by peripheral (intravenous) as well as brain injection of a non-selective CRF antagonist, astressin [67]. It is important to note that the central gastroparetic action of CRF is independent of a stimulation of the hypothalamic-pituitary-adrenal axis based on the observation that the gastric-inhibitory response to CRF is still visible in hypophysectomized or adrenalectomized rats [68]. Since CRF is known to reduce vagal efferent activity [69] and acetylcholine stimulates ghrelin release from the stomach [70], the postoperative CRF-induced delay of gastric emptying may be mediated by a reduction of vagal efferent activity. These actions are likely to be $CRF_1$ mediated as in mice lacking the $CRF_1$ no postoperative gastric ileus following midline celiotomy, cecal exteriorization and palpation was observed [71] (Table 1).

## Calcitonin gene-related peptide - expression and regulation

Alpha-calcitonin gene-related peptide (α-CGRP) is a 37 amino acid peptide and part of the calcitonin family of peptides that acts in the brain to exert its biological actions [72]. CGRP is – besides its expression in the periphery including the gastrointestinal tract – expressed in the nucleus of the solitary tract of the brainstem and immunoreactive fibers make close contact to gastric efferent motor neurons [73]. This finding is in line with the identification

of the CGRP receptor on neurons of the dorsal motor nucleus of the vagus nerve [74], providing the neuroanatomical basis for the decrease of vagal efferent activity observed after intracisternal injection of α-CGRP [75].

### Calcitonin gene-related peptide - involvement in postoperative ileus

The α-CGRP-induced decrease of efferent vagal activity is likely to be involved in the mediation of postoperative gastric ileus as shown by experimental evidence that peripheral injection of the CGRP receptor antagonist, $CGRP_{8–37}$ reversed the abdominal surgery-induced delay of gastric emptying in dogs [76]. Similarly, immunoneutralization of CGRP using an anti-CGRP antibody reversed the inhibition of gastric emptying [77] and also of colonic transit, the reduction of fecal pellet output and also the anorexigenic response following abdominal surgery in rats [78] indicating a major involvement of CGRP signaling in the mediation of alterations of gastrointestinal functions under conditions of abdominal surgery (Table 1).

### Vagal signaling - involvement in postoperative ileus

Since the vagus nerve is a major driving source of gastrointestinal motility [79], the modulation of vagal activity is an interesting target in order to influence symptoms of abdominal surgery-induced postoperative ileus. It is well known that a reduction in ambient temperature activates the thyrotropin-releasing hormone (TRH) signaling system [80] expressed in the raphe pallidus, raphe obscurus and parapyramidal regions projecting to the dorsal vagal complex of the brainstem [81] resulting in a vagal dependent cholinergic stimulation of gastric motility and secretion through activation of gastric myenteric cholinergic neurons [80]. In line with these findings, brainstem (intracisternal) injection of the stable TRH agonist, RX-77368 or endogenous TRH induced by cold ambient temperature (4–6 °C) prevents the abdominal surgery-induced delay of gastric emptying [82] (Table 1). Interestingly, this was associated with a complete restoration of circulating ghrelin levels reduced by abdominal surgery [82] indicating the advantage of stimulating vagal activity following abdominal surgery.

Recent studies point towards the benefit of chewing sugarless gum as an applicable mean to stimulate vagal activity which has proven effective to shorten the time to the first flatus and bowel movement and to reduce the period of hospitalization as indicated in a meta-analysis reviewing the data of nine studies with a combined population of more than 400 patients that underwent abdominal surgery [83]. The treatment appears to be safe as no difference in complication rates was observed for chewing gum *versus* placebo [84] (Table 1). These data are corroborated by a recent randomized clinical trial investigating women after cesarean section that showed a shortened time to the first bowel movement, first passage of flatus, first defecation and first hunger sensation in the gum *versus* control group [85].

## SUMMARY

Postoperative ileus is a frequent condition occurring after abdominal surgery that may lead to suffering for the individual patient and increased health care costs for the society. Although our understanding of the pathophysiology underlying postoperative ileus increased

during the past years, this did not lead to widely accepted and generally recommended treatment strategies for this medical condition. Promising pharmacological targets encompass the promotion of prokinetic pathways inhibited by surgery namely vagal activation, ghrelin, and to block receptors activated by abdominal surgery namely CRF, CGRP and $sst_2$ and inhibit gastric motor function. Clinical studies providing evidence that chewing gum reduces the duration of postoperative ileus corroborate the role of activating central vagal mechanisms as an important approach consistent with experimental studies.

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**KEY POINTS**

- Postoperative ileus is a frequent condition after abdominal surgery causing suffering for the patient and significant costs for the healthcare system.
- Several brain peptides are involved in the development of postoperative ileus.
- Chewing gum as a mean to stimulate vagal signaling may be an applicable method to alleviate symptoms of postoperative ileus.

## Highlights

- Postoperative ileus (POI) is a frequent condition after abdominal surgery
- POI causes suffering for patients and significant costs for the healthcare system
- Several brain peptides are involved in the development of POI
- Chewing gum may be an applicable method to alleviate symptoms of POI

## Table 1

Modulation of postoperative ileus by centrally acting peptides.

| Peptide | Proposed physiological function | Modulation of postoperative ileus | Reference |
|---|---|---|---|
| Ghrelin | stimulation of food intake and gastrointestinal motility | reversal of surgery-induced delay of gastric emptying; acceleration of time to first bowel movement; earlier hospital discharge | [33, 34] |
| Nesfatin-1 | inhibition of food intake and gastrointestinal motility | no data available so far under conditions of postoperative ileus; NUCB2/nesfatin-1 brain nuclei are activated by abdominal surgery | [48] |
| Somatostatin | peripheral: inhibition of food intake and gastrointestinal motility; central: stimulation of food intake | peripheral: $sst_2$ blockade restores ghrelin levels but does not alter the surgery-induced gastric ileus; central: $sst_2$ activation does not alter the surgery-induced delay of gastric emptying but restores circulating ghrelin levels and stimulates food intake | [29, 59] |
| CRF | key hormone in the response to stress, reduction of upper gastrointestinal and stimulation of colonic motility and secretion | $CRF_1$ mediates delay of gastric emptying in mice | [71] |
| CGRP | decrease of vagal efferent activity | immunoneutralization of CGRP reverses postoperative inhibition of gastric empting, delay of colonic transit, reduction of fecal pellet output and the anorexigenic response | [77, 78] |
| TRH | stimulation of gastrointestinal motility and secretion | cold-induced TRH-mediated vagal activation restores gastric emptying and ghrelin levels post surgery; chewing gum shortens time to first flatus and bowel movement after surgery and reduces time of hospitalization | [82, 83] |

Abbreviations: CGRP, calcitonin gene-related peptide; CRF, corticotropin-releasing factor; $CRF_1$, corticotropin-releasing factor receptor subtype 1; $sst_2$, somatostatin receptor subtype 2; TRH, thyrotropin-releasing hormone