Chapter 13
Enterohormones and the Response to Critical Illness

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Abstract The secretion of a number of enterohormones is disordered in the critically ill which may mediate abnormalities in motility and glycaemia. However, these mediators can also potentially serve a protective role, dampening inflammation and modulating the enteral immune response. There are over 30 recognised enterohormones, and therapeutic manipulation of specific enterohormones or their receptors is a burgeoning area of critical care research with promising preclinical data and an increasing number of small clinical trials. Further characterisation of the effect of critical illness on the endocrine gut and how it can be manipulated to improve outcomes in critical illness warrants evaluation.

13.1 Introduction

The enteroendocrine cells constitute less than 1 % of the total epithelial cell population of the gastrointestinal tract yet together form the largest endocrine system in the body [1]. These cells are responsible for the production of over 30 peptides which in health modulate gastrointestinal motility, secretory, absorptive and immune functions and mucosal growth and repair [2]. The physiological stress of critical illness and the

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Table 13.1 Function of enterohormones and impact of critical illness

Enterohormone	Site of secretion	Dominant effects	Effect of critical illness
Ghrelin	Parietal cells	↑ Growth hormone	↑ Total concentration ? ↓ Active concentration
	Gastric fundus	↑ Appetite	
		↑ Gastric emptying	
		Energy homeostasis	
Motilin	M cells	↑ Fasting intestinal motility	Unknown
	Proximal duodenum	↑ Gastric emptying (supraphysiological)	
CCK	I cells	↑ Gallbladder contraction	↑ Concentration
	Duodenum and jejunum	↓ Gastric emptying	
		↑ Pancreatic enzyme secretion	
		↓ Appetite	
GLP-1	L cells	↑ Insulin (glucose dependent)	↑ Concentration
	Distal ileum and colon	↓ Glucagon (glucose dependent)	
		↓ Gastric emptying	
		↓ Appetite	
GIP	K cells	↑ Insulin (glucose dependent)	No effect
	Duodenum and jejunum	↑ Glucagon (glucose dependent)	
GLP-2	L cells	↑ Intestinal mucosal growth	Unknown
	Distal ileum and colon	↑ Intestinal absorptive capacity	
		↓ Intestinal permeability	
		↑ Intestinal mucosal blood flow	
Peptide YY	L cells	↓ Gastric emptying	↑ Concentration
	Distal ileum, colon and rectum	↓ Gallbladder contraction	
		↓ Gastric acid secretion	
		↓ Pancreatic exocrine secretion	

treatments administered are associated with substantially disordered gastrointestinal and metabolic functions [3], many of which have been shown to be associated with adverse outcomes [4]. While it is not a clinical practice to measure plasma enterohormone levels, which may contribute to the current paucity of data, it is increasingly evident that a number of enterohormones mediate, or have the potential to mediate, many of the functional gastrointestinal and metabolic abnormalities that occur during critical illness. This chapter will review the enterohormones most likely to be of clinical significance: ghrelin, motilin, cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide 2 (GLP-2) and polypeptide YY (PYY). A summary for each hormone is provided with a focus on location of the secretory cell and receptor for hormone function, stimulus for secretion, and if there are sufficient data, the effect of critical illness on plasma concentrations and action is outlined (Table 13.1). In addition, studies relating to enterohormone receptor pharmacological agonism or antagonism and therapeutic potential in critical illness are presented where relevant.

13.2 Ghrelin

13.2.1 Ghrelin in Health

Ghrelin is primarily secreted during fasting from parietal cells of the gastric fundus in the inactive (nonacylated) form [5]. Its secretion is suppressed in the postprandial phase as a result of the interaction of nutrient with the small intestine [5]. Ghrelin is a prohormone and requires posttranslational acylation for the majority of its biological activity [6]. Acylated ghrelin is the endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a) on the anterior pituitary, and therefore it is a natural secretagogue for growth hormone [7]. The GHS-R1a is expressed widely beyond the anterior pituitary including on pancreatic islets, B and T lymphocytes, neutrophils, myocardium, thyroid tissue and at multiple sites throughout the central nervous system, which explains the diverse physiological actions of this hormone [8]. As well as regulating growth hormone secretion, ghrelin plays important roles in stimulating appetite and modulating glucose homeostasis, decreasing insulin secretion and increasing insulin sensitivity [8]. It also modulates stress, anxiety and sleep, protects against muscle atrophy, modulates taste sensation and has vasodilatory effects [8]. Studies using exogenous ghrelin at supraphysiological concentrations indicate that ghrelin accelerates gastric emptying in humans and in animal models of sepsis-induced gastroparesis [9, 10]. In ambulant patients with diabetic gastroparesis, a ghrelin agonist has been shown to stimulate gastrokinesis [11].

13.2.2 Ghrelin in Critical Illness

In the largest study to date of endogenous ghrelin concentrations in critical illness, Koch et al. analysed plasma ghrelin in 170 critically ill patients and 60 healthy persons as a control group [12]. While they demonstrated that total ghrelin concentrations are increased during critical illness, they did not differentiate between the active (acylated) and inactive form [12]. This is important as the majority of circulating ghrelin is in the inactive form and is renally cleared, unlike the active form which undergoes organ-independent enzyme metabolism with a short half-life of 10 min [13]. Inactive ghrelin accumulates in renal failure [11], and Koch et al. demonstrated an inverse association between renal function and ghrelin concentration in non-septic critically ill patients [12]. In the only study to date to measure both active and inactive ghrelin in critical illness, Crona and MacLaren demonstrated that compared to patients tolerating enteral nutrition, patients with feed intolerance had higher concentrations of total ghrelin but lower concentrations of active ghrelin [6]. These data suggest that while total ghrelin concentrations may be elevated during critical illness, active ghrelin levels may be decreased and contribute to slow gastric emptying. Studies into the effect of exogenous ghrelin, or its agonists, to manage feed intolerance in this population are warranted.

As well as influencing gut motility, there is mechanistic plausibility that ghrelin may be protective in sepsis; in multiple animal models, exogenous ghrelin has been found to downregulate proinflammatory cytokines [14], protect against endotoxaemia-induced acute kidney injury [15], ameliorate gut mucosal barrier function [16], attenuate sepsis-induced acute lung injury [17] and improve tissue perfusion [18]. Exogenous ghrelin has not been evaluated as a therapy in the critically ill but has been shown to reduce cachexia, increase appetite and improve exercise tolerance in patients with cancer, heart failure, end-stage renal disease and chronic obstructive pulmonary disease [19]. This is likely due to both anabolic growth hormone dependent and independent effects, for example, improved appetite [4].

While growth hormone is suppressed in critical illness, trials with suprapharmacological doses of growth hormone have reported adverse outcomes [20]. Despite this adverse effect of growth hormone administration, careful evaluation of ghrelin therapy in the critically ill appears warranted to establish the effects on gastric emptying, appetite and anabolism.

13.3 Motilin

13.3.1 Motilin in Health

Motilin is synthesised by M cells in the proximal duodenum and regulates the fasting pattern of motility of the gut by binding to the motilin-specific G-protein-coupled receptor [21]. Motilin is predominantly secreted in the interdigestive state, and the peak plasma motilin concentration coincides with the onset of the antegrade contractions during the fasting phase III-migrating motor complex [22]. Pharmacological concentrations of exogenously administered motilin accelerate gastric emptying in healthy individuals and in patients with gastroparesis [23]. The macrolide antibiotic erythromycin is a motilin receptor agonist and potently stimulates gastric emptying which has led to its additional use as a gastric prokinetic agent for the treatment of gastroparesis of multiple aetiologies [24].

13.3.2 Motilin in Critical Illness

Erythromycin potently stimulates gastric emptying in critically ill patients with feed intolerance and large gastric residual volumes [25–27]. Tachyphylaxis to stimulation of the motilin receptor develops quickly with erythromycin, and the effects are diminished in 60 % of critically ill patients within 1 week of regular administration [25]. While a more effective gastrokinetic drug than metoclopramide, observational data indicate that erythromycin is administered less frequently [28], perhaps because of concerns regarding adverse effects, such as the potential to exacerbate bacterial resistance, interaction with other medications metabolised by the cytochrome P450 3A4 system and prolongation of the QT

interval [29]. For these reasons there is increasing effort to identify a selective motilin receptor agonist without macrolide antibiotic properties for clinical use. There are preliminary data from a small phase 2 study that a non-macrolide selective motilin receptor agonist accelerates gastric emptying in the critically ill compared to placebo, and larger randomised controlled trials are keenly awaited [30].

13.4 Cholecystokinin

13.4.1 Cholecystokinin in Health

Cholecystokinin (CCK) is a peptide hormone secreted by I cells in the mucosa of the duodenum and jejunum in response to dietary fat, protein and, to a lesser extent, carbohydrates [31]. It binds to its specific G-protein-coupled receptor on the gastric, gallbladder and small intestinal mucosa, vagal afferents and centrally in the hypothalamus and hindbrain where it acts as a neuropeptide [32]. Endogenous CCK is the principal regulator of gallbladder contraction and has been shown to slow gastric emptying, relax the sphincter of Oddi and stimulate pancreatic enzyme secretion [33, 34]. Interaction of CCK with central satiation receptors in the hypothalamus reduces hunger and energy intake [35].

13.4.2 Cholecystokinin in Critical Illness

Our group has previously demonstrated elevated fasting and nutrient-stimulated plasma CCK levels in critical illness compared to healthy subjects [36]. Furthermore, fasting plasma CCK concentrations were higher in critically ill patients with delayed gastric emptying compared to those with normal emptying, suggesting a role for CCK in the pathogenesis of delayed gastric emptying [37]. However, our experience from studies performed in healthy participants with normal rates of gastric emptying is that the magnitude of acceleration that occurs when antagonising endogenous hormones is much less than during administration of pharmacological concentrations [38, 39]. Given that gastric emptying is slow in many patients and can be due to many causes, our opinion is that CCK antagonists would have only a modest effect on gastric emptying and feed intolerance in the critically ill.

There are preclinical data to suggest that endogenous cholecystokinin mediates the beneficial immune and antiinflammatory effects attributable to enteral nutrition in critical illness [40, 41]. In a rat model of haemorrhagic shock, CCK released in response to an enteral lipid load activates immunomodulatory receptors via vagal pathways, dampening the systemic inflammatory response and attenuating gastric epithelial permeability and bacterial translocation [40, 41]. Further studies are required to characterise the effect of critical illness on plasma CCK, the associations between plasma CCK and gastric emptying and the potential immunomodulatory role of CCK.

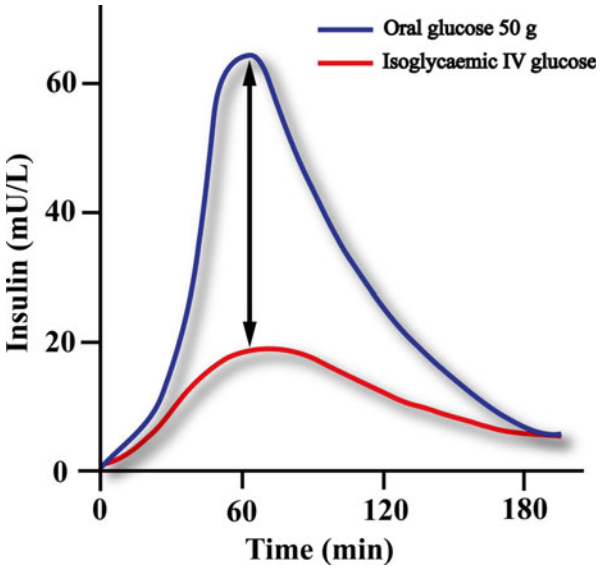

Fig. 13.1 The incretin effect (Adapted from Nauck et al. [45]). There is a substantially greater release of insulin in response to oral glucose as compared to an isoglycaemic intravenous infusion of glucose. The difference between the plasma insulin, as demonstrated by the *arrow*, is the incretin effect and is mediated by the enterohormones glucagon-like peptide 1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)

13.5 Glucagon-Like Peptide 1 (GLP-1)

13.5.1 GLP-1 in Health and Diabetes

GLP-1 is an incretin hormone stored in enteric L cells located predominantly in the distal small intestine and colon and is secreted in response to luminal fat, carbohydrate, protein and bile acids [42, 43]. Incretins are gut hormones that potentiate insulin secretion after a meal in a glucose-dependent manner [44]. Together with glucose-dependent insulinotropic polypeptide (GIP), GLP-1 accounts for the two to threefold greater insulinotropic response to an oral glucose load compared to the equivalent intravenous glucose load (Fig. 13.1) [46]. The primary physiological role of endogenous GLP-1 is to lower blood glucose [47] via direct effects on pancreatic islet cell G-protein-coupled receptors to propagate secondary messenger signals that stimulate insulin and suppress glucagon release and indirect effects on the gut to slow gastric emptying and small intestinal motility [38, 47, 48]. The insulinotropic and glucagonostatic effect on the pancreatic α and β cells are strictly glucose dependent such that below a blood glucose of ~6 mmol/L, even pharmacological doses of GLP-1 (and its agonists) have little or no impact on blood glucose [49]. In contrast, the ability of exogenously administered GLP-1 to slow gastric emptying persists during hypoglycaemia [39]. GLP-1 receptors are expressed

widely beyond the pancreas and gut including in the lung, kidney, skin, heart and brain [50]. A detailed review of the extrapancreatic effects of endogenous GLP-1 is beyond the scope of this chapter; however, GLP-1 is thought to play a role in regulating appetite, learning and memory, preventing cardiac cell apoptosis, increasing bone formation and decreasing dermal cytokine expression [51].

The glucose-dependent insulinotropic effect of GLP-1 is preserved in patients with type 2 diabetes [52], making the GLP-1 receptor an attractive therapeutic target in this group [53]. Native GLP-1 is rapidly metabolised by dipeptidyl peptidase-4 (DPP-4) predominantly on capillary endothelia, imparting the enterohormone with a short half-life of 1–2 min [54, 55] which makes therapeutic delivery of native GLP-1 impractical. This has led to the development of subcutaneously administered GLP-1 receptor agonists that are resistant to DPP-4 degradation such as exenatide and lixisenatide, as well as oral DPP-4 inhibitors such as sitagliptin, linagliptin and vildagliptin that have now been incorporated into standard algorithms for the management of type 2 diabetes [56].

13.5.2 GLP-1 in Critical Illness

In the critically ill, endogenous GLP-1 concentrations are increased [57–59] when compared to nutrient-stimulated physiological levels in healthy persons [60]. There appear to be associations between plasma concentration and biomarkers of inflammation, illness severity [58] and feed intolerance [59]. Murine studies have demonstrated inducible GLP-1 secretion by a range of inflammatory stimuli including endotoxin, IL-1 and IL-6 [58, 61]. Interestingly, when systemic inflammation is induced in healthy volunteers by a TNF-α infusion, there is no demonstrable change in the incretin effect [62].

13.5.3 Therapeutic Potential of GLP-1-Based Therapy in the Critically Ill

The rapid, organ-independent metabolism of a therapy that causes controlled, glucose-dependent glucagon suppression and insulin release makes GLP-1 a promising agent for the management of stress hyperglycaemia [43, 63]. To date, the use of GLP-1 in the critically ill is limited to small studies to establish proof of principle, albeit with promising results [64]. With pharmacological concentrations of intravenous GLP-1, marked glucose lowering has been observed in patients with type 2 diabetes postcardiac surgery [65, 66]. In a heterogeneous cohort of mechanically ventilated patients, exogenous GLP-1 has been observed to reduce the glycaemic response to small intestinal nutrient delivery in patients with type 2 diabetes [67] and to intragastric and intestinal nutrient delivery in patients without pre-existing diabetes [68, 69]. In a small ($n = 18$) randomised, double-blind, placebo-controlled

crossover study in critically ill surgical patients, GLP-1 in combination with intensive insulin therapy was also shown to reduce glycaemic variability when compared to intensive insulin therapy alone [70].

Administration of the commercially available GLP-1 agonist exenatide is also being explored. In an open-label, nonrandomised pilot study, Abuannadi and colleagues administered intravenous exenatide to 40 patients following major cardiac surgery [71]. Intravenous exenatide was associated with significantly reduced glycaemic variability compared to conventional intravenous insulin therapy and achieved equipotent blood glucose lowering with no episodes of severe hypoglycaemia [71]. Exenatide has also been administered subcutaneously in an open-label study in paediatric burn patients where it was shown to reduce exogenous insulin requirements [72].

While GLP-1 and its agonists have an inherently low risk of hypoglycaemia, there is a dose-dependent relationship between GLP-1 and the slowing of gastric emptying, and this has raised concerns that pharmacologically induced slower emptying may predispose to aspiration in mechanically ventilated critically ill patients [63]. Somewhat reassuringly, in a population of nondiabetic critically ill patients, our group has demonstrated that acute infusion of GLP-1 at pharmacological concentration slows gastric emptying when gastromotor function is normal at baseline but has no effect when gastric emptying is already delayed [68].

There have been no human studies into the therapeutic potential of DPP-4 inhibitors in the critically ill which may be due to their oral route of administration and resultant variable pharmacokinetics.

Whether GLP-1, its agonists or the DPP-4 inhibitors could be used as standalone therapy or in combination with insulin for the management of stress hyperglycaemia warrants further investigation.

13.6 Glucose-Dependent Insulinotropic Polypeptide (GIP)

13.6.1 GIP in Health and Type 2 Diabetes

Glucose-dependent insulinotropic polypeptide, previously known as gastric inhibitory polypeptide, is secreted from duodenal and jejunal K cells in response to luminal fat and carbohydrate [44]. GIP exerts its incretin effect through distinct G-protein-coupled receptors that are highly expressed in islet β-cells, and like GLP-1, the insulinotropic action of GIP is strictly glucose dependent [44]. GIP also has glucose-dependent effects on the α-cell, dose dependently stimulating glucagon secretion during hypo- and euglycaemia with no effect during hyperglycaemia [73]. GIP has no direct enterogastrone effect on either gastric acid secretion or gastric emptying but may slightly accelerate gastric emptying via indirect mechanisms through lowering systemic glycaemia [32]. GIP receptors are expressed widely and have been identified in the fat, bone, brain and cardiac tissue with in vitro and murine studies, suggesting potential roles for GIP in triglyceride metabolism, bone formation and neuroprotection [44]. GIP is also metabolised by DPP-4 with a resultantly short half-life of ~4 min [74].

Unlike GLP-1, the insulinotropic effect of GIP is profoundly reduced in patients with type 2 diabetes and long-standing chronic hyperglycaemia [45]. This is likely due, at least in part, to the direct toxic effects of chronic hyperglycaemia downregulating GIP receptor expression on the β-cell [75], an effect which may be reversible with Hϕjberg et al. reporting that the insulinotropic property of GIP increased severalfold following 4 weeks of near-normal glycaemia in patients with type 2 diabetes [76].

13.6.2 GIP in Critical Illness

It does not appear that critical illness alters fasting or nutrient-stimulated GIP levels [57, 77]. There is a persuasive rationale for a potential therapeutic role for exogenous GIP in the management of stress hyperglycaemia, specifically its inherent safety profile; it stimulates glucagon release during hypoglycaemia and insulin release during hyperglycaemia and does not slow gastric emptying [78, 79].

In the only studies in the critically ill to date, our group has investigated GIP both as a solo agent and in combination with GLP-1 for the management of stress hyperglycaemia [78, 80]. Consistent with the lack of effect in patients with type 2 diabetes, we have shown that GIP has a negligible effect on glycaemia, gastric emptying, glucose absorption, insulin or glucagon secretion during critical illness [80] and provides no additional glucose lowering or insulinotropic effect when administered in conjunction with GLP-1 [78]. Together, these data suggest that future studies should focus on GLP-1 or its agonists, rather than GIP for the management of stress hyperglycaemia.

13.7 Glucagon-Like Peptide-2

13.7.1 GLP-2 in Health

GLP-2 is co-secreted with GLP-1 in response to luminal nutrient from L cells that are located primarily in the distal ileum and colon [81]. GLP-2 is a pleiotropic hormone influencing multiple facets of intestinal physiology, the foremost of which is stimulation of intestinal mucosal growth in the small and, to a lesser extent, the large bowel [82]. GLP-2 acts through G-protein-coupled receptors primarily located in the small intestine [82]. While the receptor has been demonstrated on gastrointestinal endocrine cells, enteric neurons and myofibroblasts, its absence on both crypt epithelial cells and enterocytes suggests an indirect mechanism of its primary intestinotrophic action [81]. Like GLP-1 and GIP, GLP-2 is rapidly inactivated by the ubiquitous enzyme DPP-4, conferring a short half-life of ~7 min [83].

The majority of the gastrointestinal effects of GLP-2 have been elucidated following exogenous administration of GLP-2 or degradation-resistant GLP-2 analogues such as teduglutide. The intestinotrophic effects of GLP-2 are mediated via an increase in intestinal crypt cell proliferation, a reduction in villous cell

apoptosis and improved mesenteric blood flow, collectively increasing mucosal mass and surface area with an accompanied increase in intestinal digestive and absorptive capacity [81, 83]. GLP-2 administration also decreases gastric acid secretion and is glucagonotropic, but unlike GLP-1 has no effect on insulin secretion, gastric emptying or postprandial glycaemia [4].

13.7.2 Therapeutic Role of GLP-2 in Gastrointestinal Disease

Exogenously administered GLP-2 and GLP-2 analogues significantly improve morbidity and increase gastrointestinal absorptive capacity in a diverse range of preclinical intestinal injury models, including small bowel resection [84], enteritis [85], necrotizing pancreatitis [86] and ischaemic-reperfusion injury [87]. Furthermore, GLP-2 enhances epithelial barrier capacity, decreasing transcellular and paracellular permeability and reducing bacterial translocation [81, 86, 88]. These promising preclinical results encouraged human trials of the GLP-2 analogue, teduglutide, which has since gained FDA approval for the management of short bowel syndrome after demonstrating increased gastrointestinal absorptive capacity and a reduction in faecal weight, energy expenditure and total parenteral nutrition (TPN) requirement [89].

13.7.3 Therapeutic Potential of GLP-2 in Critical Illness Implicate

Critically ill patients fasted for >4 days, demonstrating significant duodenal mucosal atrophy and increased gut permeability [90], and bacterial translocation has been implicated to play a role in the development of sepsis and multi-organ failure [91]. The physiological concentrations and potential effects of pharmacological concentrations of GLP-2 are yet to be studied in the critically ill. It is plausible that during critical illness the administration of GLP-2 may attenuate mucosal atrophy, improve nutrient absorption and reduce secondary infections.

13.8 Peptide YY

13.8.1 Peptide YY in Health

Peptide YY (PYY) also known as peptide tyrosine-tyrosine is secreted by L cells located throughout the gastrointestinal tract but with the highest density in the colon [92]. PYY is released in response to enteral nutrient with fat being the most potent stimulus [93]. As PYY levels increase within 15 min of meal ingestion, an indirect mechanism mediated via CCK-dependent pathways has been proposed to initiate the initial secretory response which is later maintained via direct enteral stimulation

of the lower gastrointestinal tract [93]. PYY exerts predominantly inhibitory functions in health, slowing gastric and gallbladder emptying and inhibiting gastric acid and pancreatic exocrine secretion [32]. PYY receptors are also located centrally, and exogenous PYY has been shown to be anorectic, inhibiting appetite and energy intake in overweight humans [94].

13.8.2 PYY in Critical Illness

Fasting and nutrient-stimulated PYY concentrations are elevated two to threefold in critical illness which progressively normalise as critical illness resolves [95]. The PYY response is substantially greater in those critically ill patients with feed intolerance, suggesting a role for PYY in critical illness-induced delayed gastric emptying [96]. This highlights a potential role for PYY receptor antagonists in the management of feed intolerance in the critically ill; however, at present there are no PYY antagonists available for clinical use.

13.9 Conclusion

The secretion of a number of enterohormones is disordered in the critically ill which may mediate abnormalities in motility and glycaemia while also potentially serving a protective role, dampening inflammation and modulating the enteral immune response. There are over 30 recognised enterohormones, and therapeutic manipulation of specific enterohormones or their receptors is a burgeoning area of critical care research with promising preclinical data and an increasing number of small clinical trials. Further characterisation of the effect of critical illness on the endocrine gut and how it can be manipulated to improve outcomes in critical illness warrants evaluation.

References

1. Rehfeld JF (2012) Beginnings: a reflection on the history of gastrointestinal endocrinology. Regul Pept 177(Suppl):S1–S5
2. Schmidt WE (1997) The intestine, an endocrine organ. Digestion 58(Suppl 1):56–58
3. Thompson JS (1995) The intestinal response to critical illness. Am J Gastroenterol 90(2): 190–200
4. Deane A, Chapman MJ, Fraser RJ, Horowitz M (2010) Bench-to-bedside review: the gut as an endocrine organ in the critically ill. Crit Care 14(5):228
5. Parker BA, Doran S, Wishart J, Horowitz M, Chapman IM (2005) Effects of small intestinal and gastric glucose administration on the suppression of plasma ghrelin concentrations in healthy older men and women. Clin Endocrinol 62(5):539–546
6. Crona D, MacLaren R (2012) Gastrointestinal hormone concentrations associated with gastric feeding in critically ill patients. JPEN J Parenter Enteral Nutr 36(2):189–196

7. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K (1999) Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402(6762):656–660
8. Muller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD, Argente J, Batterham RL, Benoit SC, Bowers CY, Broglio F et al (2015) Ghrelin. Mol Metab 4(6):437–460
9. Tack J, Depoortere I, Bisschops R, Delporte C, Coulie B, Meulemans A, Janssens J, Peeters T (2006) Influence of ghrelin on interdigestive gastrointestinal motility in humans. Gut 55(3):327–333
10. De Winter BY, De Man JG, Seerden TC, Depoortere I, Herman AG, Peeters TL, Pelckmans PA (2004) Effect of ghrelin and growth hormone-releasing peptide 6 on septic ileus in mice. J Neurogastroenterol Motil 16(4):439–446
11. Ejskjaer N, Vestergaard ET, Hellstrom PM, Gormsen LC, Madsbad S, Madsen JL, Jensen TA, Pezzullo JC, Christiansen JS, Shaughnessy L et al (2009) Ghrelin receptor agonist (TZP-101) accelerates gastric emptying in adults with diabetes and symptomatic gastroparesis. Aliment Pharmacol Ther 29(11):1179–1187
12. Koch A, Sanson E, Helm A, Voigt S, Trautwein C, Tacke F (2010) Regulation and prognostic relevance of serum ghrelin concentrations in critical illness and sepsis. Crit Care 14(3):R94
13. Cummings DE, Overduin J (2004) Circulating Ghrelin levels in pathophysiological conditions. In: Ghigo E (ed) Ghrelin. Springer Science + Business Media, Boston, pp 213–214
14. Wu R, Dong W, Cui X, Zhou M, Simms HH, Ravikumar TS, Wang P (2007) Ghrelin down-regulates proinflammatory cytokines in sepsis through activation of the vagus nerve. Ann Surg 245(3):480–486
15. Wang W, Bansal S, Falk S, Ljubanovic D, Schrier R (2009) Ghrelin protects mice against endotoxemia-induced acute kidney injury. Am J Physiol Renal Physiol 297(4):F1032–F1037
16. Wu R, Dong W, Qiang X, Wang H, Blau SA, Ravikumar TS, Wang P (2009) Orexigenic hormone ghrelin ameliorates gut barrier dysfunction in sepsis in rats. Crit Care Med 37(8):2421–2426
17. Wu R, Dong W, Zhou M, Zhang F, Marini CP, Ravikumar TS, Wang P (2007) Ghrelin attenuates sepsis-induced acute lung injury and mortality in rats. Am J Respir Crit Care Med 176(8):805–813
18. Wu R, Dong W, Zhou M, Cui X, Hank Simms H, Wang P (2005) Ghrelin improves tissue perfusion in severe sepsis via downregulation of endothelin-1. Cardiovasc Res 68(2):318–326
19. Garin MC, Burns CM, Kaul S, Cappola AR (2013) Clinical review: the human experience with ghrelin administration. J Clin Endocrinol Metab 98(5):1826–1837
20. Doig GS, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, Dobb G (2008) Nutrition Guidelines Investigators of the ACTG: effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA 300(23):2731–2741
21. Poitras P, Peeters TL (2008) Motilin. Curr Opin Endocrinol Diabetes Obes 15(1):54–57
22. Vantrappen G, Janssens J, Peeters TL, Bloom SR, Christofides ND, Hellemans J (1979) Motilin and the interdigestive migrating motor complex in man. Dig Dis Sci 24(7):497–500
23. Peeters TL, Muls E, Janssens J, Urbain JL, Bex M, Van Cutsem E, Depoortere I, De Roo M, Vantrappen G, Bouillon R (1992) Effect of motilin on gastric emptying in patients with diabetic gastroparesis. Gastroenterology 102(1):97–101
24. Janssens J, Peeters TL, Vantrappen G, Tack J, Urbain JL, De Roo M, Muls E, Bouillon R (1990) Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. N Engl J Med 322(15):1028–1031
25. Nguyen NQ, Chapman MJ, Fraser RJ, Bryant LK, Holloway RH (2007) Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness. Crit Care Med 35(2):483–489
26. MacLaren R, Kiser TH, Fish DN, Wischmeyer PE (2008) Erythromycin vs metoclopramide for facilitating gastric emptying and tolerance to intragastric nutrition in critically ill patients. JPEN J Parenter Enteral Nutr 32(4):412–419
27. Dive A, Miesse C, Galanti L, Jamart J, Evrard P, Gonzalez M, Installe E (1995) Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients: a double-blind, randomized, placebo-controlled study. Crit Care Med 23(8):1356–1362

28. Gungabissoon U, Hacquoil K, Bains C, Irizarry M, Dukes G, Williamson R, Deane AM, Heyland DK (2015) Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. JPEN J Parenter Enteral Nutr 39(4):441–448
29. Sanger GJ, Wang Y, Hobson A, Broad J (2013) Motilin: towards a new understanding of the gastrointestinal neuropharmacology and therapeutic use of motilin receptor agonists. Br J Pharmacol 170(7):1323–1332
30. Chapman MJ, Fraser R, Nguyen NQ, Deane AM, O'Conner SN, Duncan R, Hacquoil K, Vasist L, Barton M, Dukes G (2011) The effect of GSK962040, a selective motilin agonist, on gastric emptying in critically ill patients with enteral feed intolerance (Mot112572). Crit Care Med 39(12):195
31. Pilichiewicz AN, Chaikomin R, Brennan IM, Wishart JM, Rayner CK, Jones KL, Smout AJ, Horowitz M, Feinle-Bisset C (2007) Load-dependent effects of duodenal glucose on glycemia, gastrointestinal hormones, antropyloroduodenal motility, and energy intake in healthy men. Am J Physiol Endocrinol Metab 293(3):E743–E753
32. Luttikhold J, de Ruijter FM, van Norren K, Diamant M, Witkamp RF, van Leeuwen PA, Vermeulen MA (2013) Review article: the role of gastrointestinal hormones in the treatment of delayed gastric emptying in critically ill patients. Aliment Pharmacol Ther 38(6):573–583
33. Wank SA (1995) Cholecystokinin receptors. Am J Physiol 269(5 Pt 1):G628–G646
34. Fried M, Erlacher U, Schwizer W, Lochner C, Koerfer J, Beglinger C, Jansen JB, Lamers CB, Harder F, Bischof-Delaloye A et al (1991) Role of cholecystokinin in the regulation of gastric emptying and pancreatic enzyme secretion in humans. Studies with the cholecystokinin-receptor antagonist loxiglumide. Gastroenterology 101(2):503–511
35. Rayner CK, Park HS, Doran SM, Chapman IM, Horowitz M (2000) Effects of cholecystokinin on appetite and pyloric motility during physiological hyperglycemia. Am J Physiol Gastrointest Liver Physiol 278(1):G98–G104
36. Nguyen NQ, Fraser RJ, Chapman MJ, Bryant LK, Holloway RH, Vozzo R, Wishart J, Feinle-Bisset C, Horowitz M (2007) Feed intolerance in critical illness is associated with increased basal and nutrient-stimulated plasma cholecystokinin concentrations. Crit Care Med 35(1): 82–88
37. Nguyen NQ, Fraser RJ, Chapman M, Bryant LK, Wishart J, Holloway RH, Horowitz M (2006) Fasting and nutrient-stimulated plasma peptide-YY levels are elevated in critical illness and associated with feed intolerance: an observational, controlled study. Crit Care 10(6):R175
38. Deane AM, Nguyen NQ, Stevens JE, Fraser RJ, Holloway RH, Besanko LK, Burgstad C, Jones KL, Chapman MJ, Rayner CK et al (2010) Endogenous glucagon-like peptide-1 slows gastric emptying in healthy subjects, attenuating postprandial glycemia. J Clin Endocrinol Metab 95(1):215–221
39. Plummer MP, Jones KL, Annink CE, Cousins CE, Meier JJ, Chapman MJ, Horowitz M, Deane AM (2014) Glucagon-like peptide 1 attenuates the acceleration of gastric emptying induced by hypoglycemia in healthy subjects. Diabetes Care 37(6):1509–1515
40. Luyer MD, Greve JW, Hadfoune M, Jacobs JA, Dejong CH, Buurman WA (2005) Nutritional stimulation of cholecystokinin receptors inhibits inflammation via the vagus nerve. J Exp Med 202(8):1023–1029
41. de Haan JJ, Lubbers T, Hadfoune M, Luyer MD, Dejong CH, Buurman WA, Greve JW (2008) Postshock intervention with high-lipid enteral nutrition reduces inflammation and tissue damage. Ann Surg 248(5):842–848
42. Schirra J, Katschinski M, Weidmann C, Schafer T, Wank U, Arnold R, Goke B (1996) Gastric emptying and release of incretin hormones after glucose ingestion in humans. J Clin Invest 97(1):92–103
43. Plummer MP, Chapman MJ, Horowitz M, Deane AM (2014) Incretins and the intensivist: what are they and what does an intensivist need to know about them? Crit Care 18(1):205
44. Campbell JE, Drucker DJ (2013) Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 17(6):819–837
45. Nauck M, Stockmann F, Ebert R, Creutzfeldt W (1986) Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia 29(1):46–52

46. Perley MJ, Kipnis DM (1967) Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. J Clin Invest 46(12):1954–1962
47. Schirra J, Nicolaus M, Roggel R, Katschinski M, Storr M, Woerle HJ, Goke B (2006) Endogenous glucagon-like peptide 1 controls endocrine pancreatic secretion and antro-pyloro-duodenal motility in humans. Gut 55(2):243–251
48. Edwards CM, Todd JF, Mahmoudi M, Wang Z, Wang RM, Ghatei MA, Bloom SR (1999) Glucagon-like peptide 1 has a physiological role in the control of postprandial glucose in humans: studies with the antagonist exendin 9–39. Diabetes 48(1):86–93
49. Nauck MA, Heimesaat MM, Behle K, Holst JJ, Nauck MS, Ritzel R, Hufner M, Schmiegel WH (2002) Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab 87(3):1239–1246
50. Pyke C, Heller RS, Kirk RK, Orskov C, Reedtz-Runge S, Kaastrup P, Hvelplund A, Bardram L, Calatayud D, Knudsen LB (2014) GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology 155(4):1280–1290
51. Muscogiuri G, Cignarelli A, Giorgino F, Prodram F, Santi D, Tirabassi G, Balercia G, Modica R, Faggiano A, Colao A (2014) GLP-1: benefits beyond pancreas. J Endocrinol Invest 37:1143–53
52. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W (1993) Preserved incretin activity of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest 91(1): 301–307
53. Nauck M (1996) Therapeutic potential of glucagon-like peptide 1 in type 2 diabetes. Diabet Med 13(9 Suppl 5):S39–S43
54. Nauck MA (2009) Unraveling the science of incretin biology. Am J Med 122(6 Suppl): S3–S10
55. Holst JJ (2007) The physiology of glucagon-like peptide 1. Physiol Rev 87(4):1409–1439
56. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR et al (2012) Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 35(6): 1364–1379
57. Deane AM, Rayner CK, Keeshan A, Cvijanovic N, Marino Z, Nguyen NQ, Chia B, Summers MJ, Sim JA, van Beek T et al (2014) The effects of critical illness on intestinal glucose sensing, transporters, and absorption. Crit Care Med 42:57–65
58. Kahles F, Meyer C, Mollmann J, Diebold S, Findeisen HM, Lebherz C, Trautwein C, Koch A, Tacke F, Marx N et al (2014) GLP-1 secretion is increased by inflammatory stimuli in an IL-6-dependent manner, leading to hyperinsulinemia and blood glucose lowering. Diabetes 63(10):3221–3229
59. Summers MJ, DI Bartolomeo AE, Zaknic AV, Chapman MJ, Nguyen NQ, Zacharakis B, Rayner CK, Horowitz M, Deane AM (2014) Endogenous amylin and glucagon-like peptide-1 concentrations are not associated with gastric emptying in critical illness. Acta Anaesthesiol Scand 58(2):235–242
60. Muscelli E, Mari A, Casolaro A, Camastra S, Seghieri G, Gastaldelli A, Holst JJ, Ferrannini E (2008) Separate impact of obesity and glucose tolerance on the incretin effect in normal subjects and type 2 diabetic patients. Diabetes 57(5):1340–1348
61. Nguyen AT, Mandard S, Dray C, Deckert V, Valet P, Besnard P, Drucker DJ, Lagrost L, Grober J (2014) Lipopolysaccharides-mediated increase in glucose-stimulated insulin secretion: involvement of the GLP-1 pathway. Diabetes 63(2):471–482
62. Nielsen ST, Lehrskov-Schmidt L, Krogh-Madsen R, Solomon TP, Lehrskov-Schmidt L, Holst JJ, Moller K (2013) Tumour necrosis factor-alpha infusion produced insulin resistance but no change in the incretin effect in healthy volunteers. Diabetes Metab Res Rev 29(8):655–663

63. Combes J, Borot S, Mougel F, Penfornis A (2011) The potential role of glucagon-like peptide-1 or its analogues in enhancing glycaemic control in critically ill adult patients. Diabetes Obes Metab 13(2):118–129
64. Pinelli NR, Jones MC, Monday LM, Smith Z, Rhoney DH (2012) Exogenous glucagon-like peptide-1 for hyperglycemia in critically ill patients. Ann Pharmacother 46(1):124–129
65. Meier JJ, Weyhe D, Michaely M, Senkal M, Zumtobel V, Nauck MA, Holst JJ, Schmidt WE, Gallwitz B (2004) Intravenous glucagon-like peptide 1 normalizes blood glucose after major surgery in patients with type 2 diabetes. Crit Care Med 32(3):848–851
66. Sokos GG, Bolukoglu H, German J, Hentosz T, Magovern GJ Jr, Maher TD, Dean DA, Bailey SH, Marrone G, Benckart DH et al (2007) Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular function in patients undergoing coronary artery bypass grafting. Am J Cardiol 100(5):824–829
67. Deane AM, Summers MJ, Zaknic AV, Chapman MJ, Fraser RJ, Di Bartolomeo AE, Wishart JM, Horowitz M (2011) Exogenous glucagon-like peptide-1 attenuates the glycaemic response to postpyloric nutrient infusion in critically ill patients with type-2 diabetes. Crit Care 15(1):R35
68. Deane AM, Chapman MJ, Fraser RJ, Summers MJ, Zaknic AV, Storey JP, Jones KL, Rayner CK, Horowitz M (2010) Effects of exogenous glucagon-like peptide-1 on gastric emptying and glucose absorption in the critically ill: relationship to glycemia. Crit Care Med 38(5): 1261–1269
69. Deane AM, Chapman MJ, Fraser RJ, Burgstad CM, Besanko LK, Horowitz M (2009) The effect of exogenous glucagon-like peptide-1 on the glycaemic response to small intestinal nutrient in the critically ill: a randomised double-blind placebo-controlled cross over study. Crit Care 13(3):R67
70. Galiatsatos P, Gibson BR, Rabiee A, Carlson O, Egan JM, Shannon RP, Andersen DK, Elahi D (2014) The glucoregulatory benefits of glucagon-like peptide-1 (7–36) amide infusion during intensive insulin therapy in critically ill surgical patients: a pilot study. Crit Care Med 42(3):638–645
71. Abuannadi M, Kosiborod M, Riggs L, House JA, Hamburg MS, Kennedy KF, Marso SP (2013) Management of hyperglycemia with the administration of intravenous exenatide to patients in the cardiac intensive care unit. Endocr Pract 19(1):81–90
72. Mecott GA, Herndon DN, Kulp GA, Brooks NC, Al-Mousawi AM, Kraft R, Rivero HG, Williams FN, Branski LK, Jeschke MG (2010) The use of exenatide in severely burned pediatric patients. Crit Care 14(4):R153
73. Meier JJ, Gallwitz B, Siepmann N, Holst JJ, Deacon CF, Schmidt WE, Nauck MA (2003) Gastric inhibitory polypeptide (GIP) dose-dependently stimulates glucagon secretion in healthy human subjects at euglycaemia. Diabetologia 46(6):798–801
74. Deacon CF, Ahren B (2011) Physiology of incretins in health and disease. Rev Diabet Stud 8(3):293–306
75. Zhou J, Livak MF, Bernier M, Muller DC, Carlson OD, Elahi D, Maudsley S, Egan JM (2007) Ubiquitination is involved in glucose-mediated downregulation of GIP receptors in islets. Am J Physiol Endocrinol Metab 293(2):E538–E547
76. Hojberg PV, Vilsboll T, Rabol R, Knop FK, Bache M, Krarup T, Holst JJ, Madsbad S (2009) Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. Diabetologia 52(2):199–207
77. Layon AJ, Florete OG Jr, Day AL, Kilroy RA, James PB, McGuigan JE (1991) The effect of duodenojejunal alimentation on gastric pH and hormones in intensive care unit patients. Chest 99(3):695–702
78. Lee MY, Fraser JD, Chapman MJ, Sundararajan K, Umapathysivam MM, Summers MJ, Zaknic AV, Rayner CK, Meier JJ, Horowitz M et al (2013) The effect of exogenous glucose-dependent insulinotropic polypeptide in combination with glucagon-like peptide-1 on glycemia in the critically ill. Diabetes Care 36(10):3333–3336

79. Kar P, Cousins CE, Annink CE, Jones KL, Chapman MJ, Meier JJ, Nauck MA, Horowitz M, Deane AM (2015) Effects of glucose-dependent insulinotropic polypeptide on gastric emptying, glycaemia and insulinaemia during critical illness: a prospective, double blind, randomised, crossover study. Crit Care 19(1):20
80. Kar P, Jones KL, Horowitz M, Chapman MJ, Deane AM (2015) Measurement of gastric emptying in the critically ill. Clin Nutr 34(4):557–564
81. Dube PE, Brubaker PL (2007) Frontiers in glucagon-like peptide-2: multiple actions, multiple mediators. Am J Physiol Endocrinol Metab 293(2):E460–E465
82. Wallis K, Walters JR, Forbes A (2007) Review article: glucagon-like peptide 2--current applications and future directions. Aliment Pharmacol Ther 25(4):365–372
83. Estall JL, Drucker DJ (2006) Glucagon-like Peptide-2. Annu Rev Nutr 26:391–411
84. Scott RB, Kirk D, MacNaughton WK, Meddings JB (1998) GLP-2 augments the adaptive response to massive intestinal resection in rat. Am J Physiol 275(5 Pt 1):G911–G921
85. Boushey RP, Yusta B, Drucker DJ (1999) Glucagon-like peptide 2 decreases mortality and reduces the severity of indomethacin-induced murine enteritis. Am J Physiol 277(5 Pt 1): E937–E947
86. Kouris GJ, Liu Q, Rossi H, Djuricin G, Gattuso P, Nathan C, Weinstein RA, Prinz RA (2001) The effect of glucagon-like peptide 2 on intestinal permeability and bacterial translocation in acute necrotizing pancreatitis. Am J Surg 181(6):571–575
87. Prasad R, Alavi K, Schwartz MZ (2000) Glucagonlike peptide-2 analogue enhances intestinal mucosal mass after ischemia and reperfusion. J Pediatr Surg 35(2):357–359
88. Cameron HL, Perdue MH (2005) Stress impairs murine intestinal barrier function: improvement by glucagon-like peptide-2. J Pharmacol Exp Ther 314(1):214–220
89. Wilhelm SM, Lipari M, Kulik JK, Kale-Pradhan PB (2014) Teduglutide for the treatment of short bowel syndrome. Ann Pharmacother 48(9):1209–1213
90. Hernandez G, Velasco N, Wainstein C, Castillo L, Bugedo G, Maiz A, Lopez F, Guzman S, Vargas C (1999) Gut mucosal atrophy after a short enteral fasting period in critically ill patients. J Crit Care 14(2):73–77
91. Deitch EA (1990) The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. Arch Surg 125(3):403–404
92. Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR (1985) Human distribution and release of a putative new gut hormone, peptide YY. Gastroenterology 89(5):1070–1077
93. Lin HC, Chey WY, Zhao X (2000) Release of distal gut peptide YY (PYY) by fat in proximal gut depends on CCK. Peptides 21(10):1561–1563
94. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, Bloom SR (2003) Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med 349(10):941–948
95. Nematy M, O'Flynn JE, Wandrag L, Brynes AE, Brett SJ, Patterson M, Ghatei MA, Bloom SR, Frost GS (2006) Changes in appetite related gut hormones in intensive care unit patients: a pilot cohort study. Crit Care 10(1):R10
96. Nguyen NQ, Fraser RJ, Bryant LK, Chapman MJ, Wishart J, Holloway RH, Butler R, Horowitz M (2007) The relationship between gastric emptying, plasma cholecystokinin, and peptide YY in critically ill patients. Crit Care 11(6):R132