

CHAPTER SIX

Introduction PART II

PART II of this thesis focuses on the endocrine response of the gastrointestinal tract upon food intake. Understanding of this response may improve perioperative strategies in order to diminish malnutrition in the surgical patient.

In the clinical setting, often problems are encountered with feeding patient in the most optimal way before and after surgery. Patients are unnecessarily retained from food intake up to 12 hours before surgery, turning them into a catabolic state and consequently into a bad shape for surgery with worse post-operative outcome. In fact surgical patients should be compared with athletes; in top sports, athletes prepare for a peak performance by a balanced diet, including carbohydrate loading. Accordingly, surgical patients should be optimally fed before and after surgery to endure surgery and recover from their peak performance. This chapter focuses on the endocrine response and how this can be influenced to optimise patient's conditions around surgery, to tolerate food intake as early as possible, and to improve gastric emptying.

GASTRIC EMPTYING AND ADMINISTRATION OF ENTERAL NUTRITION

The main drive for mechanic transport of the content from the stomach into the duodenum is thought to be primarily regulated by a pressure gradient between the stomach and the duodenum. In the fasting state the stomach is relatively small; however, upon food intake the fundal area relaxes and expands to enable accommodation of volumes up to four liters. The distended stomach rhythmically passes the contents towards the antrum and pylorus, where food particles of approximately 2 mm are eventually pushed into the duodenum. In healthy people, nutrient delivery from the stomach to the small intestine is tightly regulated at 2–3

kcal/min by small intestinal feedback (1). This process of gastric emptying is coordinated and achieved by a delicate interplay between the autonomous nervous system (mainly via the vagal nerve), the enteric nervous system, and the activity of gastrointestinal and pancreatic hormones. Any of these factors interfering with this process will therefore disrupt gastric emptying (2).

A number of different factors influence the physiological rate of gastric emptying including the size and composition of a meal, caloric content, viscosity and particle size. For example non-caloric liquids empty most rapidly and isocaloric liquids empty more rapidly than solids. Moreover, carbohydrates, proteins and fats empty unequally depending on their caloric content, viscosity and osmolarity. Furthermore, body composition and body position affect gastric emptying. Ikeda *et al.* showed that gastric emptying following a liquid meal was significantly delayed in the lying position compared to the sitting position (3).

CHAPTER 7 focusses on how gastrointestinal hormones affect gastric emptying. Delayed gastric emptying is a major problem in patients after surgery and critically ill patients, since it interferes with effective delivery of enteral nutrition. Patients are withheld from nutrition for several days because of gastroparesis or delayed gastric emptying. Enteral feeding is considered to be the most optimal method of administering nutrition to critically ill patients. Nevertheless, when fed nasogastrically, patients receive only about half of their required nutrients. An alternative can be the use of parenteral nutrition, which is a safe way of feeding but also has disadvantages. Enteral feeding is preferred over parenteral nutrition, because it preserves the intestinal integrity and prevents mucosal atrophy with associated bacterial translocation (4). Furthermore, early enteral feeding improves gastrointestinal motility, decreases infectious complication, length of hospital stay, and intensive care unit mortality (5). Therefore, improving gastric emptying is a major goal for intensive care specialists to allow early enteral feeding.

There are several different methods of administering enteral nutrition, of which gastric tube feeding is the most commonly applied route of access. In some patients, delivery of enteral nutrition via the gastric route may be problematic, because a significant percentage of critically ill patients suffer from bowel motility disorders leading to high gastric residual volumes and malnutrition. Furthermore, there is a concern that gastric feeding may lead to pulmonary aspiration (6). This problem can be overcome by inserting a jejunal feeding tube. However, bypassing the stomach and the duodenum obviates important endocrine and exocrine functions of these organs. Both are influenced by the site of enteral nutrition delivery, and consequently influence digestion and absorption. Considering the function of gastrointestinal hormones, an alteration may influence several mechanisms, interfering with nutrient digestion and absorption. Knowledge of the effect of the site of enteral nutrition delivery on gastrointestinal hormones is crucial, especially for critically ill patients, because of their already altered hormone response and delayed gastric emptying (7). This effect is investigated and discussed in CHAPTER 8.

The gastrointestinal hormones: ghrelin, motilin, cholecystokinin (CCK), gastrin, peptide YY (PYY), pancreatic polypeptide (PP), oxyntomodulin (OXM), glucagon like polypeptide 1 (GLP-1), glucagon like polypeptide (GLP-2), glucose dependent insulinotropic polypeptide

(GIP), secretin, and somatostatin, can influence gastric emptying directly and indirectly by affecting the food intake and/or glucose metabolism. Some of the gastrointestinal hormones have stimulating, or orexigenic effects, and some have inhibiting, or anorexigenic effects on food intake. Consequently, the gastrointestinal hormones can stimulate and inhibit glucose metabolism, while some of the gastrointestinal hormones influence gastric emptying directly.

GASTROINTESTINAL HORMONES

The gastrointestinal hormones, or gut hormones, constitute a group of hormones secreted by enteroendocrine cells in the stomach, pancreas, small and large intestine that control various functions of the digestive organs. Over the last few decades, studies have allowed us to begin to understand the role of gastrointestinal hormones in the regulation and integration of the human digestive function. A hormone is a peptide which is released into the bloodstream under natural circumstances and achieves sufficient concentrations to induce an action on peripheral tissues (8). Its hormonal role can thus be most easily analyzed by mimicking physiological plasma levels by means of an exogenous infusion of the natural substance. For most of the peptides this sort of experiment has been performed, but unfortunately, we are still a long way from fully understanding their actions. The problem is that the action of a gut hormone, like that of other hormones, cannot be understood in isolation. Inter-relationships between hormones released at the same time, the sensitivity of the target tissue, but also the rate of change of the hormone itself are all important variables. The direct interaction between gastrointestinal hormones and endocrine organs is illustrated in Figure 1 (9).

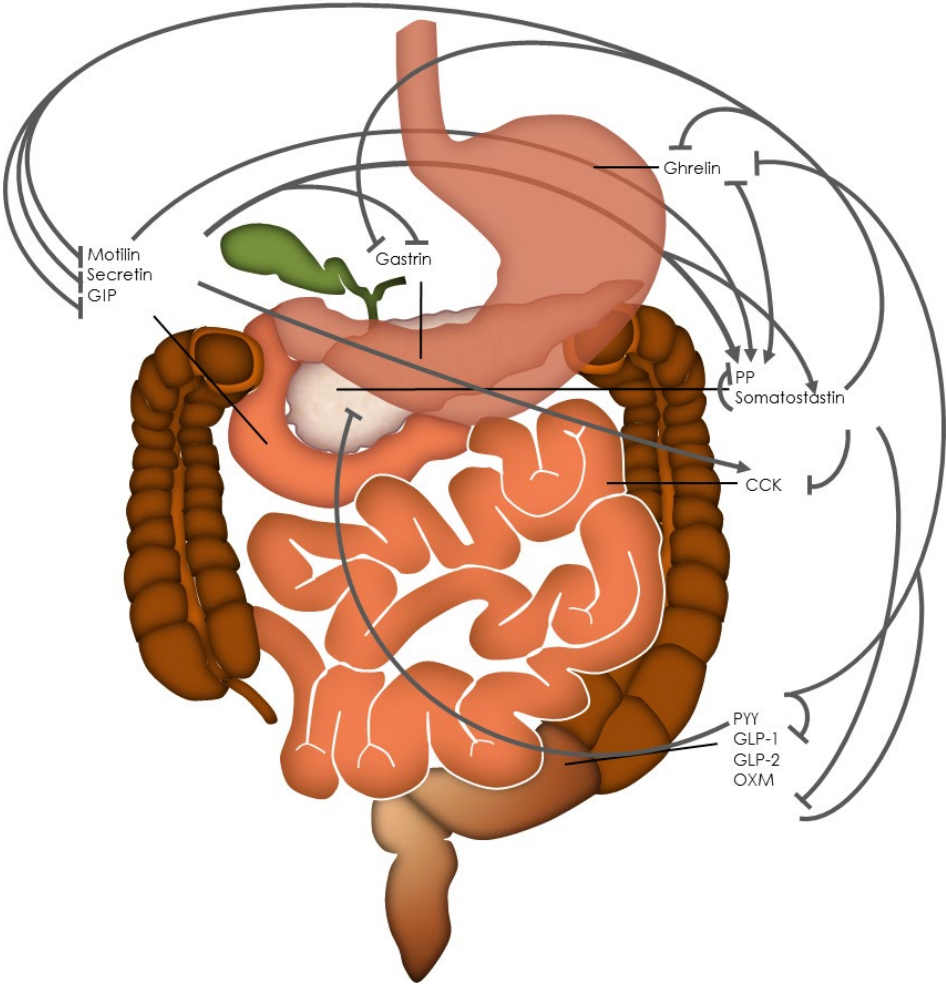
Gastrin and ghrelin are primarily gastric hormones, while CCK, motiline, secretin, GIP, PP, and somatostatin are mainly upper small intestine hormones, whereas PYY, OXM, GLP-1, and GLP-2 are lower intestine hormones. The major regulator for secretion of most gastrointestinal hormones is the composition of intestinal chyme. This is made more difficult by a different gastric emptying rate of liquids and solids, a different gastric emptying rate nutrients, the non-uniformity of bowel transit, and the different nutrient absorption rates. All of these result in a constantly changing physiological milieu in the bowel, where the composition of chyme at any level of the bowel is changing at every point in time and will be reflected by the gastrointestinal hormone profile.

In this introduction background information is provided on the physiology of the gastrointestinal hormones, whereas in CHAPTER 7 the focus is on their role and future role in gastric emptying.

Ghrelin

Ghrelin was first identified in 1999 as an endogenous ligand for the growth hormone secretagogue receptor type 1a (GHSR-1a) (10). In both humans and rodents intravenous injected ghrelin stimulates growth hormone release (11, 12). GHSR-1a is at this moment the only identified ghrelin receptor. Two types of ghrelin circulate in the blood: acylated ghrelin and unacylated ghrelin. Acylated ghrelin, which accounts for 10% of the total amount of ghrelin, has a fatty-acid modification which is necessary for binding and activating the GHSR-1a. The remaining circulating ghrelin is unacylated (10, 13). Since gastrectomy in rodents and humans is followed by approximately two-third reduction of plasma the ghrelin levels, we

FIGURE 1. Main distribution and interaction between gastrointestinal hormones.



know that ghrelin is mainly secreted in the stomach (14). The remainder is produced in the small intestine (15). Expression of ghrelin is not restricted to the gastrointestinal tract, but is also present, although in relatively low amounts, in the hypophysis, hypothalamus, heart, kidney, immune cells, placenta, pancreas, lymphocytes, lung, testis, and ovary (15, 16). Gastric ghrelin is released from the X/A-like endocrine cells located in the mucosal layer of the gastric fundus just before a meal (17). In adult humans, plasma ghrelin levels rise twofold before a meal and decline to normal levels within 1 hour after eating. Main functions of ghrelin are to stimulate food intake, to gain weight, to increase the secretion of growth hormone and gastric acid, and to encourage gastric motility (10, 11, 17, 18). Furthermore, ghrelin induces a positive inotropic effect on the heart and causes vasodilatation (13, 19).

Motilin

Motilin and ghrelin are structurally related peptides. Motilin is secreted by M-cells in the upper part of the duodenum (20). Motilin levels cyclically peak every 100 minutes in the fasted state and fall postprandially. Generally, motilin is active in the fasted state whereas it does not act in the fed stomach. The main role of motilin is to control the interdigestive contractions. Effects on stomach motility concern mainly phase III contractions (21). Interestingly, intraperitoneal injection of motilin at doses of 5 and 10 $\mu\text{g kg}^{-1}$ stimulates food intake in fasted rats; however feeding is inhibited by injection of 100 $\mu\text{g kg}^{-1}$. This is possibly a secondary effect to the primary actions of motilin on gut motility (22). Furthermore, motilin stimulates gallbladder contraction and enzyme secretion from the stomach and pancreas; among which pepsin from the stomach and trypsin from the pancreas (21). Intravenous injection of motilin stimulates Pancreatic Polypeptide (PP) release although the exact mechanism of this interplay remains unclear (21, 23).

Glucose-dependent insulin releasing polypeptide

GIP was originally found to inhibit gastric acid secretion; this action is representative for its former name: gastric inhibitory polypeptide (24, 25). Subsequent studies on GIP observed that GIP also exerts glucose induced insulin release from pancreatic β -cells. This incretin function gives GIP its present name: glucose-dependant insulin releasing polypeptide (26). GIP is secreted by endocrine K-cells, the majority of which are located in the duodenum and proximal jejunum, but with smaller numbers also occurring throughout the entire small intestine. GIP is released upon food intake, especially after absorption of glucose or fat. Where fat is the most potent stimulator of GIP secretion in humans. GIP receptors are expressed in the pancreas, gut, adipose tissue, heart, pituitary, adrenal cortex, and in several regions of the brain (26). GIP is, similar to GLP-1, and GLP-2, rapidly degraded into inactive metabolites by the enzyme dipeptidyl-peptidase-IV (DPP-IV) (26, 27).

Glucagon-like peptide-1

GLP-1 is formed after preproglucagon cleavage within the intestine. GLP-1, similar to PYY, CCK, and oxyntomodulin, is eventually released from the L-cells located in the distal intestine (28, 29). GLP-1 secretion by L-cells is dependent on the presence of nutrients, such as carbohydrates, proteins, and lipids in the lumen of the small intestine. Once in the circulation, GLP-1 has a very short half-life of less than 2 minutes, due to rapid degradation by the enzyme DPP-IV (30). Circulating GLP-1 exists in a number of forms, namely GLP11-37 and GLP11-36. Neither of them is significantly biologically active. Further N-terminal truncation is required for biological activity (31). For instance, GLP11-36 promotes insulin release from isolated pancreatic cells but only at supraphysiological levels (32). GLP17-36 is the truncated form that is a very potent insulin release stimulator; it mediates glucose-dependant insulinotropic effects (33-35).

GLP-1 is released into the circulation upon food intake proportionally to caloric content and acts both centrally and peripherally as a strong insulin stimulator. Both intracerebroventricular and paraventricular nuclei administration of GLP-1 potentially reduce food intake in humans.

Flint *et al* reported a 21% reduction in food intake as well as an increase in satiety and fullness during GLP-1 administration in healthy human subjects (36). GLP-1 has a powerful inhibitory effect on gastric emptying of liquids and solids (37, 38). It relaxes the proximal stomach, inhibits antral action and stimulates pyloric motility (39, 40). The effects of GLP-1 are partly mediated by cholinergic pathways (41). Furthermore, GLP-1 inhibits gastric acid secretion and pancreatic enzyme output (29, 37). In addition, GLP-1 seems to act on more distal parts of the gut, as it also inhibits small bowel motility. Release of PYY (co localized with GLP-1 in the L-cells of the intestinal mucosa) is inhibited by GLP-1, suggesting a negative feedback mechanism (29, 38).

Glucagon-like peptide-2

GLP-2 is, similar to GLP-1, formed by a cleavage of proglucagon in the intestine (L-cells) and in the central nervous system (42). GLP-2 receptors have been detected in the gastrointestinal tract and in the hypothalamus, brainstem, and lung (43). Like GLP-1, GLP-2 is released into the circulation upon food intake; fat and carbohydrates are potent stimulators of GLP-2 release. GLP-2 does not influence appetite in humans. GLP-2 exerts, similar to GLP-1, different effects when administered centrally or peripherally. Whereas an intracerebroventricular injection of GLP-2 in rats shows an inhibitory effect on food intake, peripherally administered GLP-2 did not appear to affect food intake in rodents or humans (44-48). In animal and human studies GLP-2 decreases gastric acid secretion, inhibits antral gastric emptying, and improves intestinal blood flow (49-51). Peripherally administered GLP-2 is involved in stimulating gastrointestinal motility, absorption, and growth (47). Considering gastrointestinal motility, both GLP-1 and GLP-2 inhibit antral emptying in man, although GLP-1 is a more potent inhibitor (52).

Cholecystokinin

CCK was first reported over 30 years ago. CCK has a dual role as neurotransmitter in the enteric and the central nervous system (53). The family of CCK peptides exists in several bioactive molecular forms. CCK-8 and CCK-33 are the active forms released after food intake (54, 55). CCK-8 is mainly found in nervous tissue whereas CCK-33 is mainly found in the gut (56). There are two types of CCK-receptors that have been classified as CCK-1 and CCK-2, previously known as CCK-A and CCK-B/gastrin (57-59). Both receptor types are found throughout the CNS and gut, although CCK-1 is mainly found in the alimentary tract and CCK-2 in the brain (59). CCK is secreted by L-cells in the upper small intestine in response to the presence of products of fat and protein digestion (60-62). The main actions of CCK include contraction of the gallbladder, relaxation of the sphincter of Oddi, stimulation of somatostatin release and stimulation of pancreatic growth and enzyme release via the CCK-1 receptor (59). CCK is the first described gut hormone that inhibits food intake (61). CCK binds to receptors on vagal afferents, and mucosal receptors, in the stomach and small intestine, to potentiate gastric relaxation, stimulate mechanoreceptors sensitive to gastric stretch, and slow gastric emptying (63). Interaction with receptors in satiation centers in the hypothalamus and hindbrain also reduces appetite (64). Cholecystokinin, therefore, acts synergistically with mechanical gastric distension to induce feelings of fullness in response to food (65). In critically ill patients plasma CCK levels are elevated by approximately two-fold, compared with healthy subject. Within the

ICU population, patients who have food intolerance, the plasma levels of CCK are substantially higher than in those without intolerance (66).

Gastrin

Gastrin is structurally related to CCK and is released by the antroduodenal G-cells. Gastrin stimulates secretion of gastric acid during meal ingestion by parietal cells and enterochromaffin-like cells (ECL; one of the enteroendocrine cells) of the stomach, and supports gastric motility (67, 68). The acid secretory effect of gastrin is thought to be mediated primarily via release of histamine from ECL cells (68, 69). Its actions on gastric mucosa are mediated via the CCK-2 receptor, that also binds gastrin with high affinity (70). Furthermore, gastrin has the ability to enhance growth, inhibit apoptosis, increase angiogenesis, and enhance cell migration and proliferation (68, 69, 71).

Peptide YY

In 1982 PYY was first isolated from porcine intestine (72). PYY is present throughout the GI tract: in low concentrations in the small intestine, in higher concentrations in the colon, up to a maximum in the rectum. PYY is released from L-cells of the distal gut (73). Additionally PYY is present in the central nervous system (74). PYY3-36 is more bioactive than PYY1-36 (75-77). PYY3-36 (34 amino acids) is created from PYY1-36 (proPYY) by cleavage of its N-terminus Tyr-Pro residues by DPP-IV (78). PYY is known as a pluripotent hormone. Amongst others, actions involve the regulation of food intake, gastric emptying, and glucose metabolism. Furthermore, PYY administration increases postprandial absorption of fluids and electrolytes from the ileum, reduces cardiac output, causes vasoconstriction, and reduces glomerular filtration rate, plasma rennin, and aldosterone activity (79-81).

PYY is released upon food intake. Fat intake induces higher PYY levels compared to proteins and carbohydrates (73). PYY levels are low when fasted and rise immediately upon food intake which indicates that PYY is involved in short-term feeding control (82, 83). PYY reaches its plateau level after 1-2 hours (73). Interestingly, PYY is released before food has reached the distal intestinal tract. This implies that PYY release is regulated by a neural reflex; possibly by the vagal pathway system (82). Most effects of PYY are inhibitory, such as the inhibition of gastric, pancreatic, and intestinal secretion or reduction of GI motility, gallbladder emptying, and GE (84, 85).

Pancreatic polypeptide

PP is mainly produced in the endocrine pancreas by F-cells located in the periphery of the pancreatic islets. However, the exocrine pancreas and rectum have also been found to produce PP (86). Furthermore, PP secretion is controlled by pancreatic and GI hormones; ghrelin, motilin, and secretin stimulate PP release and somatostatin inhibits PP release (87-89). The presence of PP within the central nervous system is still a matter of debate (86, 90). Release of PP is subjected to the vagal nerve system (91). PP shows preferential binding to the Y4 and Y5 receptors (92). PP plays a role in food intake, affects gastric emptying and might influence glucose metabolism. Furthermore, PP reduces gastric ghrelin expression and

increases vagal tone.

PP also increases aerobic metabolism/oxygen consumption and stimulates sympathetic activity, leading to the suggestion that PP increases energy expenditure (93, 94). PP exerts a variety of regulatory actions, including inhibition of pancreatic exocrine secretion, contraction of the gallbladder, stimulation of glucocorticoid secretion, modulation of gastric acid secretion, and GI motility (95, 96).

Somatostatin

Somatostatin is present in many organ systems throughout the body, including the brain, intestine, stomach, and the pancreas. Somatostatin or 'somatotrophin release inhibitory factor' (SRIF) is synthesized in the D-cells of the gut and endocrine pancreas (97). Somatostatins function is mainly antisecretory, it inhibits release of gastrin, CCK, secretin, motilin, GIP, and OXM. Furthermore, it inhibits gastric acid production, reduces intestinal motility, decreases splanchnic blood flow, and prolongs gastric emptying. Furthermore, it inhibits the release of insulin, glucagon, and exocrine pancreatic secretions (97, 98).

Oxyntomodulin

OXM is, similar to GLP-1 and GLP-2, formed out of preproglucagon in the intestine and central nerve system (99-101). OXM, exerts its effect via the GLP-receptor. However, affinity of OXM for the GLP-1 receptor is lower than that of GLP-1, suggesting that OXM also acts via another receptor which is still unknown (99, 102). The GLP-1 receptor can be found in the brain, pancreas, heart, lung, kidney, and gastrointestinal tract. OXM is released upon food intake from L-cells in the intestine according to the amount of calories ingested (103, 104). OXM acts in several ways; among others it inhibits food intake, has incretin effects and is involved in decreasing weight gain. Other actions of intestinal release of OXM are inhibition of gastric acid secretion and gastric emptying in rodents and humans (99-101).

Secretin

Secretin was the first intestinal hormone to be identified. Secretin is found in various tissues throughout the body namely; the brain, stomach, pancreas, intestine, reproductive system, spleen, heart, lung, and kidney (105-107). Secretin is mainly produced in the S-cells of the duodenum in response to low duodenal pH (4-4.5) and primarily acts to regulate the pH of the duodenal contents by controlling gastric acid secretion and buffering with bicarbonate; released from the pancreas after secretin stimulus (62, 108-110). Secretin reduces acid secretion from the stomach by inhibiting release of gastrin from the G-cells. Other actions of secretin are to stimulate the release of PP and somatostatin. Furthermore, secretin enhances the effects of CCK to induce the secretion of digestive enzymes (111).

THE INCRETIN EFFECT

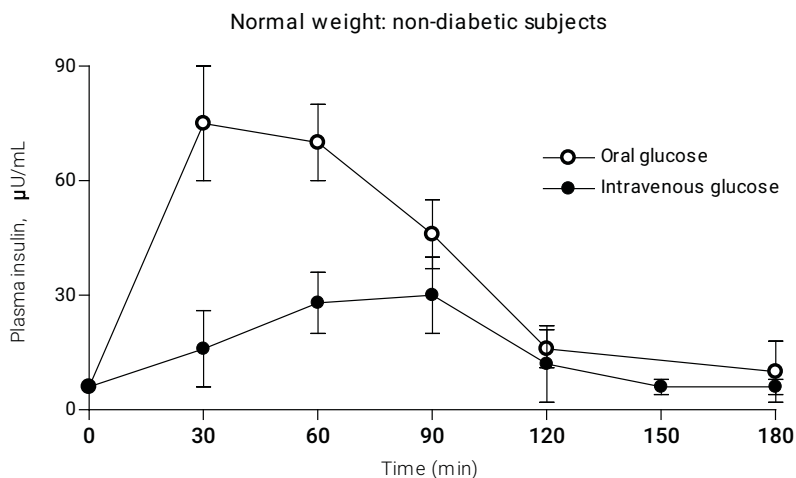
Incretins are a type of gastrointestinal hormones that cause an increase in the amount of insulin released from the β -cells of the islets of Langerhans after food intake, even before blood glucose levels become elevated. They also slow the rate of absorption of nutrients into

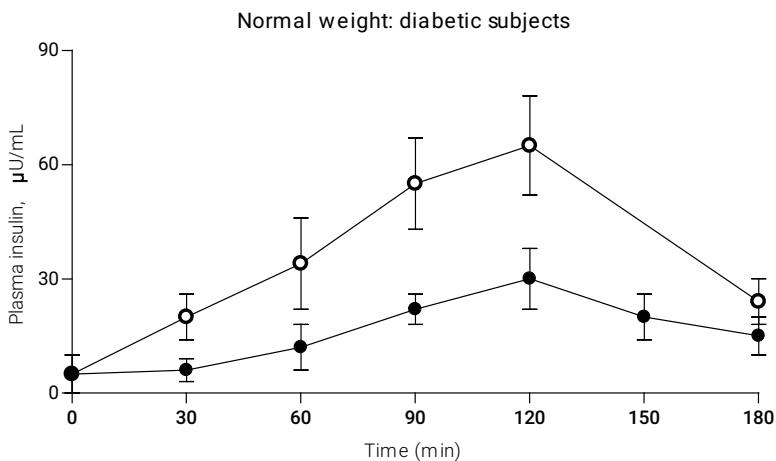
the bloodstream by reducing gastric emptying and may directly reduce food intake (112).

If glucose is intravenously injected, blood glucose immediately rises prompting pancreatic insulin release. After the same amount of oral glucose intake, however, the pancreas releases more insulin, and blood glucose rises to a lesser extent. The increased insulin rate observed in response to oral carbohydrates is known as the incretin effect, and the gastrointestinal hormones, GLP-1 and GIP, are known as the incretin hormones. GIP was identified as an incretin hormone in 1970, and GLP-1 and its truncated form GLP-1(7-36) were recognized as incretins in 1985 (113). The incretin effect is illustrated in Figure 2 (114). These figures illustrate the plasma insulin responses to the oral and intravenous administration of glucose in normal subjects and in subjects with type 2 diabetes. In both groups, the plasma insulin response to intravenous glucose was markedly less pronounced than after oral glucose ingestion. This indicates that insulin secretion is strongly influenced by alimentary factors (incretins) as well as by plasma glucose levels. The incretin effect accounts for 50% to 70% of the insulin response to oral glucose in normal subjects. In patients with type 2 diabetes, however, this meal-stimulated insulin release is markedly reduced. Type 2 diabetes is characterized by deficiencies with respect to each of the incretin hormones. The insulinotropic action of GIP is substantially blunted in the disorder, although its secretion is largely preserved. In contrast, whereas physiologic responses to GLP-1 are preserved in patients with type 2 diabetes, its secretion is markedly impaired (115). Multiple antidiabetic qualities of GLP-1(7-36) and its analogues have been demonstrated, and there is continuing interest in pharmacologically manipulating the incretin effect for therapeutic benefit.

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FIGURE 2. *The Incretin Effect from Nauck et al. Plasma insulin responses to oral- and intravenous administration of glucose in (A) normal weight non-diabetic subjects and (B) normal weight diabetic subjects (114).*





ENDOCRINE RESPONSE TO GASTRIC BARIATRIC BYPASS SURGERY

The ever rising prevalence of obesity and its associated co morbidities, especially type 2 diabetes, is causing a major health threat and involves increasing numbers of morbidity and mortality. Additionally the existing weight-losing and -maintaining strategies are limited. However, durable weight reduction is achieved by bariatric surgery. Bariatric surgery is indicated in subjects with a BMI of more than 40 kg/m² and for those with a BMI of more than 35 kg/m² with obesity related co morbidity and no successful results with nonsurgical methods for weight reduction (116). Bariatric surgery gives the greatest chance for amelioration of obesity-associated complications (112). Dramatic improvements in glycemic control have been observed in subjects with type 2 diabetes following bariatric surgery, especially after a Roux-en-Y gastric bypass procedure (117).

Since gastric bariatric bypass surgery involves anatomical changes, physiology is hence altered. The interplay between food intake and gut function of the altered gastrointestinal system apparently results in clinical improvement. It has been postulated that this improvement in glycemic control, reduction in appetite, and subsequent weight loss following bypass surgery may be due to changes in circulating gut hormones. For better understanding of hormonal involvement in gastric bariatric bypass surgery, the physiology of gastrointestinal hormones will be discussed in CHAPTER 7 and 8 in extensive detail focusing mainly on the impact of administrating enteral nutrition either gastric or jejunal on endocrine responses in vivo in humans.

ENDOCRINE AND METABOLIC DISRUPTION AFTER PREOPERATIVE FASTING

Under normal conditions, carbohydrate intake results in a release of insulin into the circulation, which in turn activates a series of metabolic reactions. These include a reduction in endogenous glucose release, activation of glucose transporting systems in insulin-sensitive tissues, and activation of enzymes securing storage of excess glucose as glycogen. Surgery induced stress hampers the metabolic effects of insulin by the influence of catecholamines, glucocorticosteroids, glucagon, and growth hormone, all of which oppose the action of insulin.

This forms the basis for stress induced insulin resistance.

After surgery, insulin sensitivity is reduced. Recent studies show that if the patient is operated under the influence of insulin while given a fairly high load of intravenous glucose (as opposed to the overnight fasted state with no insulin governing metabolism), glucagon release is attenuated and cortisol release is completely abolished (118). In addition, preoperative carbohydrate loading, causing a release of insulin, will result in higher levels of free insulin-like growth factor-1 and increases insulin sensitivity (119). Hence, metabolism is far less catabolic in patients after surgery when given preoperative carbohydrates instead of undergoing an overnight fast.

Overnight fasting has serious consequences for patients' metabolism and endocrine response during and after surgery. It results in depletion of glycogen stores, dehydration, muscle wasting, a weakened immune response and unnecessary production of inflammatory mediators (120). Overnight fasting has been reported to induce postoperative insulin resistance, resulting in decreased cellular uptake of glucose, despite high levels of glucose and adequate levels of insulin in the blood. Insulin resistance is a transient phenomenon that can last for up to 3 weeks after elective open abdominal surgery (121). Insulin resistance is an unwanted phenomenon in modern surgical practice because it may lead to increased infectious complication and prolonged hospital stay (122).

Although European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines advocate that long periods of pre-operative fasting should be avoided, fasting before surgery is still common practice in many Western countries (123). Because the "nil per mouth principle" has been considered an undesirable and unnecessary concept, preoperative carbohydrate loading can support the patient metabolically (124). Patients receiving a carbohydrate-rich drink (Nutricia preOp or Roosvicee Original Fruitmix) prior to surgery preserved their immune system (expressed in HLA-DR expression on the monocyte) postoperatively, compared to fasted patients (125). In CHAPTER 9 we focus on carbohydrate loading given preoperatively to rats; it changes the fasted state into a fed state and counteracts the disadvantageous effects of fasting on well-being. Carbohydrate loading reduces postoperative insulin resistance, improves muscle strength, has a positive effect on well-being, and shortens length of hospital stay (126-129). In addition, it is safe, simple, and empties rapidly from the stomach to decrease the risk of gastric aspiration (130).

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