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Endocrine implications of obesity and bariatric surgery

Michał Dyaczyński[1], Colin Guy Scanes[2], Helena Koziec[3], Krystyna Pierzchała-Koziec[4]

[1]*Siemianowice Śląskie Municipal Hospital, Department of General Surgery, Siemianowice Śląskie, Poland*
[2]*Centre in Excellence in Poultry Science, University of Arkansas, Fayetteville, Fayetteville, Arkansas, USA*
[3]*Josef Babinski Clinical Hospital in Krakow, Poland*
[4]*Department of Animal Physiology and Endocrinology, University of Agriculture in Krakow, Poland*

Abstract

Obesity is a highly prevalent disease in the world associated with the disorders of endocrine system. Recently, it may be concluded that the only effective treatment of obesity remains bariatric surgery.

The aim of the review was to compare the concepts of appetite hormonal regulation, reasons of obesity development and bariatric procedures published over the last decade.

The reviewed publications had been chosen on the base on: 1. reasons and endocrine consequences of obesity; 2. development of surgery methods from the first bariatric to present and future less aggressive procedures; 3. impact of surgery on the endocrine status of patient.

The most serious endocrine disturbances during obesity are dysfunctions of hypothalamic circuits responsible for appetite regulation, insulin resistance, changes in hormones activity and abnormal activity of adipocytes hormones. The currently recommended bariatric surgeries are Roux-en-Y gastric bypass, sleeve gastrectomy and adjustable gastric banding. Bariatric surgical procedures, particularly combination of restrictive and malabsorptive, decrease the body weight and eliminate several but not all components of metabolic syndrome.

Conclusions:

1. Hunger and satiety are mediated by an interplay of nervous and endocrine signals.
2. Healthy adipose tissue secretion of adipokines is coordinated in an anti-inflammatory, insulin-sensitizing and cardioprotective pattern. However, with increasing fat mass this secretion pattern is changed into a proinflammatory, insulin resistant, atherogenic and fatal systemic environment .
3. Bariatric surgery is not a solution of the obesity problem for everyone.
4. Long term postsurgical observations of the hormonal profile changes are necessary and should be obligatory. **(Endokrynol Pol 2018; 69 (5): 574–586)**

Key words: *obesity, endocrine dysfunctions, bariatric surgery, gastrointestinal hormones*

Introduction

Obesity is a highly prevalent disease in the world, and it is caused by an excess of nutrients, genetic background, lack of physical exercise, or a disorder of the hypothalamo-gastrointestinal axis activity. Adiposity excessive signals such as leptin and insulin as well as gastrointestinal hormones affect the metabolism of fat, carbohydrates and destroy the balance between energy spending and consumption [1, 2].

Hunger and satiety are mediated by an interplay of nervous and endocrine signals. Neural signalling takes place between the hypothalamus and other parts of the central nervous system to regulate food intake according to caloric need [3].

Morbid obesity was considered as a disease from the second half of the 20th century. In highly developed countries morbid obesity shows an extremely fast-growing tendency; it was found that since 1980 its rate doubled. For this reason World Health Organisation (WHO) officially declared obesity as a global epidemic in 1997 [4–6].

The causative treatment of obesity is still fragmentary because of the large inter-individual variability and absence of pre-treatment data, making interpretation of the results difficult. For this reason, treatment with conservative symptomatic methods, e.g. dietetic, pharmacological, or behavioural, are usually doomed to failure and never achieve the required results [7]. The efficacy of these methods in long-term weight loss without a yo-yo effect is estimated to be as little as 5% [8]. Some of the other methods (e.g. jaw-wiring), although effectively promoting weight loss, for humanitarian reasons cannot be used [9]. Recently, it may be concluded that the only effective treatment of obesity remains surgery. However, it must be pointed out that bariatric surgery, in spite of food intake suppression, has a strong effect on the metabolism, particularly carbohydrate and lipid turnover, as well as on the hormonal system [10].

Krystyna Pierzchała-Koziec, Katedra Fizjologii i Endokrynologii Zwierząt, Uniwersytet Rolniczy w Krakowie, Al. Mickiewicza 24/28, 30–059 Kraków; tel.: 698 630 422, faks:12 633 33 07, e-mail: rzkoziec@cyf-kr.edu.pl

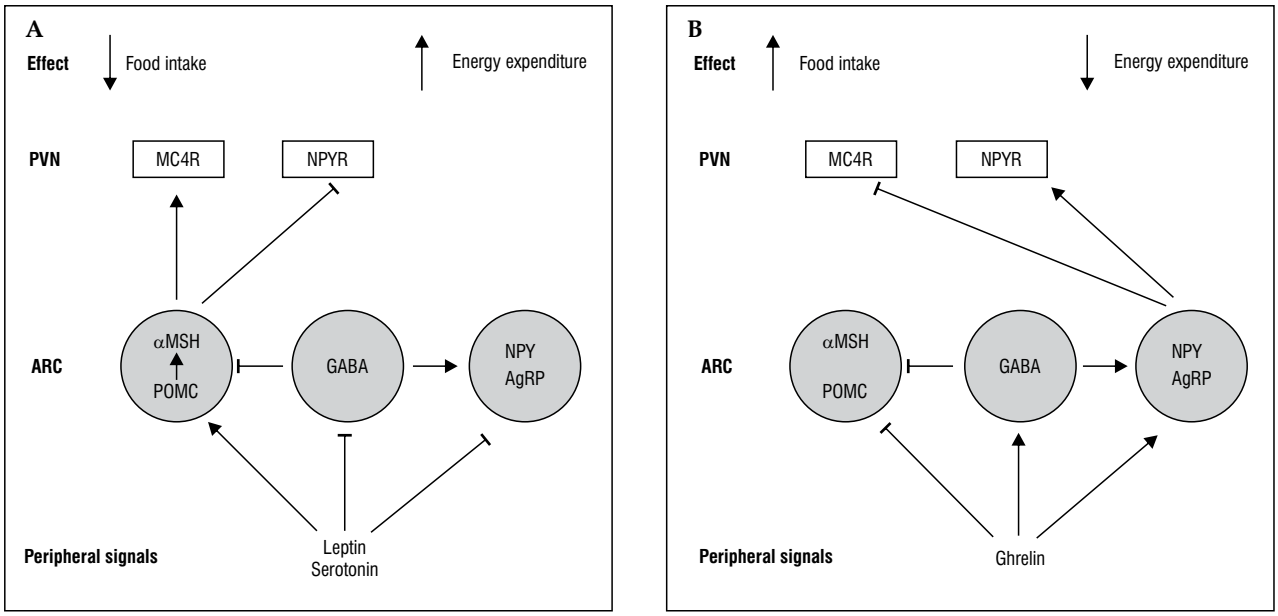

Figure 1. *Hypothalamic circuits of appetite and satiety.* **A.** *Anorexigenic pathway.* **B.** *Orexigenic pathway*
AgRP — agouti-related peptide; ARC — arcuate hypothalamic nucleus; GABA — gamma-aminobutyric acid; αMSH — α-melanocyte-stimulating hormone; MC4R — α-melanocyte-stimulating receptor; NPY — peptide Y; NPYR — receptor of NPY; POMC — proopiomelanocortin; PVN — paraventricular nucleus

Thus, based on different opinions on the efficaciousness of morbid obesity treatments, the aim of the present review was to compare the most important changes in the concepts of food intake regulation, obesity development, and bariatric procedures (methods, acceptance, popularity, and side effects) in recent years.

The reviewed publications were chosen based on:

1. reasons and consequences of obesity, particularly hormonal changes;
2. development of surgery methods from the first bariatric to present and future less aggressive; and
3. the ability to assess the effects of bariatric surgery on the endocrine status of the patient.

Regulation of food intake by hypothalamo-gastrointestinal axis

Historically, it was established that the anorexigenic centre (appetite suppressing) is located in the ventromedial hypothalamus [11]. The orexigenic (appetite stimulating) centre is in the area of the lateral hypothalamus. The hypothalamus receives the signals from the periphery derived by nervous route — predominantly the vagus nerve, and endocrine route — mainly by ghrelin, leptin, and insulin secreted into the blood. The reaction of the hypothalamus to these signals is characterised by changing activity of two opposite circuits — stimulation or inhibition of food intake. The hypothalamic circuits of hunger/appetite and satiety create two pathways — anorexigenic and orexigenic — which are responsible for food intake and energy expenditure (Figure 1) [12].

Orexigenic pathway

Neuropeptide Y and agouti-related peptide (NPY/AgRP) neurons have axon terminals that release gamma aminobutyric acid (GABA, an inhibitory neurotransmitter) to suppress the proopiomelanocortin (POMC) neurons and oxytocin neurons in the paraventricular nucleus of the hypothalamus (PVN). On the other hand, PVN neurons expressing pituitary adenylate cyclase-activating polypeptide (PACAP) have axon terminals that release glutamate (an excitatory neurotransmitter) to activate NPY/AgRP neurons [13].

The anorexigenic pathway is stimulated by peripheral leptin receptors in the arcuate nucleus of the hypothalamus (ARC). As an effect of that activity, secreted POMC stimulates melanocortin receptors in the PVN (inhibition of food intake) and IML (intermediolateral region of the spinal cord), responsible for increasing energy expenditure [14–16].

Recently, a hypothesis has been proposed stating that feeding is regulated by special neurons inside specific hypothalamic nuclei, and not by centres in the brain. According to many publications, there are three main ways of signalling from the periphery responsible for information about hunger or satiety:

1. short-term effects on food intake from gastrointestinal hormones (orexigenic or anorexigenic) [16];
2. direct mechanical stimulation of the gastrointestinal tract, mainly stomach and duodenum [17];
3. Long-term effects on food intake provided by adipose tissue hormones [18].

Development of different methods — genetic, optogenetic, and molecular — together with established methodologies allow us to have a refined understanding of neural circuits that regulate feeding behaviour.

Gastrointestinal hormones

Gastrointestinal (GI) hormones are predominantly polypeptides produced in and secreted from specialised gut endocrine cells. These peptides are involved in GI motility, secretion, absorption, growth, and development. Many of the peptides in the GI tract are also found in the enteric nervous system and the central nervous system. Gastrointestinal (GI) peptides are classified into families based on their primary structure, and conservation of amino acid sequences among different GI peptides suggests a common biosynthetic origin [18].

More than 40 enterohormones with a modifying influence on food intake have been identified so far, but the majority of them have elicited an inhibitory effect (Table I).

All chosen hormones can be divided into five groups:

1. Hormones responsible for digestion regulation and motility control (cholecystokinin, secretin, gastrin, motilin, galanin, GLP-2);
2. hormones involved into glycaemia regulation/ /incretins (GLP-1, GIP);
3. hormones regulating satiation (oxyntomodulin, PYY-3–36, obestatin, leptin);
4. those responsible for hunger control (ghrelin, opioids); and
5. peptide inhibiting the activity of most gastrointestinal hormones, such as somatostatin.

Peripheral hormones released from the pancreas (insulin, glucagon, amylin, and pancreatic polypeptide [PP]) are closely related to the gastrointestinal hormones, not only in the glucose metabolism control.

Cholecystokinin (CCK) is synthesised in the duodenum (I cells) and released in the presence of amino acids and fatty acids. CCK promotes the release of digestive enzymes from the pancreas and bile from the gallbladder, and slows gastric emptying. It is associated with satiety and glycaemia control [19, 20].

Secretin is synthetised in the duodenum (S cells) in response to a low intraluminal pH. Secretin increases production of pancreatic bicarbonate and promotes insulin release. Secretin reduces gastric acid synthesis and gastrin release, and slows gastric and duodenal motility [21].

Table I. *Gastrointestinal hormones and pancreatic hormones involved in appetite regulation*

Gastrointestinal hormones		
	Place of synthesis	**Effects**
Cholecystokinin	Duodenum	Pancreatic exocrine secretion Gastrointestinal motility
Secretin	Intestine	Pancreatic exocrine secretion
Motilin	Intestine	Gastrointestinal motility
Gastrin	Stomach	Acid secretion
Peptide P	Small intestine	Gastrointestinal motility
Galanin	Small intestine	Gastrointestinal motility Insulin inhibitor Taste
GLP-2	Small intestine	Gastrointestinal motility Growth
Oxyntomodulin	Small intestine	Satiation
$PYY_{3–36}$	Small intestine	Satiation
Obestatin	Stomach	Satiation
Leptin	Stomach	Satiation
Ghrelin	Stomach	GH release Hunger
Opioids	Intestine	Gastric motility, hunger Endocrine/exocrine secretion
GLP-1	Small intestine	Incretin activity Satiation
GIP	Small intestine	Incretin activity
Somatostatin	Intestine	Inhibition of: hormones, exocrine secretion, gastrointestinal motility
Pancreatic hormones		
	Place of synthesis	**Effects**
Insulin	Beta cells	Glucose homeostasis
Glucagon	Alpha cells	Glucose homeostasis
Amylin	Beta cells	Glucose homeostasis, gastric motility
Pancreatic polypeptide	PP cells	Gastric motility Satiation

Gastrin is a family of several peptides of varying length with different degrees of biological activity. It is released from gastric antrum and duodenum (G cells) in response to direct contact with food and stomach distension. Physiologically, gastrin is responsible for increasing the secretion of hydrochloric acid, and stomach and pancreatic enzymes, and inhibiting/reducing the appetite [22].

Motilin initiates phase III of gastric migrating myoelectric complexes (MMC). Motilin has been regarded as the initiator of the interdigestive peristaltic reflex. Motilin also inhibits nausea and improves appetite. Similarly to ghrelin, but in contrast to many other intestinal hormones, motilin is not secreted postprandially. Obesity caused a switch in the origin of phase III from antrum to duodenum. Obese patients had significantly higher motilin levels compared with controls during the MMC, but it lowers prior to phase III, which is necessary to trigger hunger [23].

Galanin is a 29 (in most species) amino acid, C-terminally amidated peptide. In humans, galanin exists as a 30 amino acid molecule with no amidation at the C-terminus. Galanin is involved in the regulation of many physiological conditions, from central nervous system functions like cognition and memory, sensation of pain, feeding behaviour, and sexual behaviour, to endocrine functions such as influencing the release of hormones, as well as acting on gastrointestinal motility and secretion. Recent publications reported significantly elevated plasma galanin levels in patients with obesity and diabetes [24].

Glucagon-like peptide-2 (GLP-2) is a 33 amino acid peptide, released from intestinal L-cells located in the distal small intestine and colon after food intake. GLP-2 increases the absorptive surface area by stimulating cellular proliferation and inhibiting apoptosis of the ileal and bowel mucosa. GLP-2 stimulates insulin secretion, inhibits glucagon, and influences gastrointestinal secretions and motility [25].

Glucose-dependent insulinotropic peptide (GIP), also known as incretin hormone, is synthesised by K cells located in the small intestine. GIP is a 42 amino acid peptide stimulating insulin release after glucose ingestion. It is a part of the intestine-pancreas axis [26]. Receptors of GIP are located in the beta islets of the pancreas, adipose tissue, central nervous system, heart, and adrenal cortex [26].

Glucagon-like peptide-1 (GLP-1) is an incretin hormone and decreases blood glucose levels by enhancing the secretion of insulin. The action of GLP-1 is preserved in patients with type 2 diabetes. Endogenous GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), neutral endopeptidase 24.11 (NEP 24.11), and renal clearance, resulting in a short half-life of less than two minutes. GLP-1-based treatment has been associated with weight loss and a lower risk of hypoglycaemia in patients with type 2 diabetes [27, 28].

Obestatin is a 23 amino acid metabolic hormone discovered in rat stomach, which is able to inhibit food intake, decrease intestinal motility, and restrain body weight gain, probably through the G-protein-coupled receptor (GPR39). Obestatin was thought to be an opponent of ghrelin because both peptides are produced from post-translational modification of the same preproghrelin peptide encoded from the ghrelin gene. It was found that obestatin might act centrally and peripherally to modulate food intake. Plasma obestatin levels are disturbed in diabetic and obese patients.

The effects of obestatin are controversial but provide convincing evidence that peptide may be acting to meliorate diet-induced impairments in lipid metabolism, and it may influence metabolism of steroid, bile acid, platelet-activating factor (PAF), and glutathione [29].

Peptide $YY_{3–36}$ (PYY_{3-36}), secreted by mucosal L-cells in the small and large intestine, inhibits gastric, pancreatic, and intestinal secretions. The effects on gastrointestinal motility and food intake, although often reported, are controversial [30].

Oxyntomodulin (OXM) is an anorexigenic peptide co-secreted with $PYY_{3–36}$ and GLP-1 from intestinal L-cells. The administration of OXM reduces hunger, food intake and ghrelin levels as well as decreases gastric acid secretion and duodenal motility [31].

Ghrelin

Ghrelin is a 28 amino acid, Ser3-acylated peptide, which acts through growth hormone secretagogue receptor (GHS-R) [32]. The main source of ghrelin was established by Kojima et al. in 1999 in X/A type endocrine cells located in the gastric fundus [33]. Ghrelin is also synthesized in each part of intestines, pituitary, kidney, lung, and pancreas. Ghrelin stimulates appetite, secretion of growth hormone, and gastrointestinal hypermotility and is involved in regulation of the cardiovascular, immune, and nervous systems.

Ghrelin is a key regulator of nutrient sensing, meal initiation, and appetite. Apart from its orexigenic effect, ghrelin signalling has increasingly been recognized as an important regulator of obesity, insulin resistance, and diabetes. Interestingly, many of these functions appear to be independent of ghrelin's effect on food intake [34, 35]. Ghrelin regulates glucose homeostasis through inhibition of insulin secretion and regulation of hepatic glucose output. Ghrelin regulates energy homeostasis by decreasing thermogenesis to reduce energy expenditure. Ghrelin also has cardioprotective effects in the myocardium and anti-atrophic effects in muscle. Ghrelin enhances the orexigenic effect, protein anabolism, anti-inflammatory actions, and cardiovascular protection in haemodialysis patients [36].

Opioids

Endogenous opioid peptides belong to three main families: proopiomelanocortin (POMC), proenkephalin (PENK), and prodynorphin (PDYN). Representatives

of POMC, endorphins, act through mu (μ) receptors, pentapeptides Met- and Le-enkephalin, enzymatically cleaved from PENK, are ligands for delta (δ) receptors, dynorphins released from PDYN bind to kappa (κ) receptors [37].

Paradoxically, proopiomelanocortin (POMC), the anorexigenic hypothalamic regulator of food uptake, is the precursor of some endogenous opioid peptides stimulating food intake. Endorphins and enkephalins are expressed in the central nervous system, as well as in peripheral tissues, including the gastrointestinal tract, adrenals, blood vessels, and pancreas.

The presence of opioids in certain structures of the digestive tract and in the areas of the hypothalamus responsible for regulation of feeding behaviour (arcuate nucleus and nucleus ventricularis) provide additional evidence of the involvement of these peptides in the regulation of nutrition [38].

Opioid receptors and endogenous opioid peptides are the main "players" in the functioning of reward and pleasure systems as well as regulators of energy balance. Recent data provided convincing evidence on participation of opioidergic neurotransmission in feeding behaviour, and it was found that the density of opioid receptors in corpus striatum and thalamus and body mass index (BMI) are inversely related [38].

Obesity is closely related to aberrations in opioidergic neurotransmission at the central and peripheral levels. In overweight patients, plasma β-endorphin levels were elevated, which might correlate with the changes in activity of opioid receptors in the brain. Presumably, the failure of opioid receptors is the main reason for overeating as an attempt to compensate for the lack of positive emotions. Moreover, opiate receptor antagonists prevented development of obesity in genetically obese experimental animals [39].

An orexigenic effect of opioids (endorphins and enkephalins) has been proposed by some investigators, which suggests that endogenous opioid peptides and specific receptors could be considered as effective targets for counteracting obesity [39].

Somatostatin

Somatostatin (STS) is a tetradecapeptide isolated in the early 1970s from sheep hypothalamus [40]. It has been found in every organ of the body, and it is particularly abundant in the gastrointestinal tract.

Somatostatin exerts an inhibitory action on numerous physiological functions, acting as a hormone, a local (paracrine) regulator, or a neurotransmitter. Somatostatin actions are mediated through five distinct receptor subtypes (sts1–5). The main mediators of the gastrointestinal effects of the peptide are sts2 and sts5 [41]. Biologically active somatostatin exits in two molecular forms: somatostatin-14 and somatostatin-28. Both are the products of post-translational processing of preprohormone precursor encoded by the somatostatin 1 gene (*STS*). STS-14 is the predominant form in the brain, while STS-28 is mainly produced by intestinal enteroendocrine cells [41].

Somatostatin is distributed throughout the central nervous tissue and the heart, thyroid, skin, eye, and thymus. Somatostatin is abundant in the gastrointestinal tract and pancreas, where it is synthesized by paracrine and endocrine-like D cells and by enteric nerves. Originally discovered as an inhibitor of growth hormone release, it is now known to inhibit a variety of gastrointestinal processes including gastric acid secretion, gastric emptying, intestinal motility, and release of all gastrointestinal hormones [42].

Moreover, STS inhibits the release of GH and thyroid-stimulating hormone, and has various neuromodulatory roles in learning, cognitive functions, locomotor activity, anxiety, and depression [41]. Recently, development of selective somatostatin agonists and antagonists have become critical in understanding the physiological and pathophysiological functions of somatostatin within the gastrointestinal tract [43].

Hormonal activity of adipose tissues

As well as adipocytes, white adipose tissue contains white blood cells, fibroblasts, adipocyte progenitor cells, and endothelial cells, which secrete a variety of proteins involved in many processes. Perception of the adipose tissues has changed recently from passive lipid storage tissue to active endocrine organ regulating and modulating whole-body energy homeostasis, metabolism, and inflammatory and immune responses by secreting a multitude of bioactive molecules: adipokines, enzymes, hormones, and growth factors [44]. They are involved in the regulation of reproduction, apoptosis, inflammation, blood pressure, atherogenesis, and fibrinolysis through impact on the proliferation and hyperplasic changes, particularly in the presence of obesity. Adipose cells express receptors for these factors and are able to respond to metabolic changes, mainly energy and glucose homeostasis [45–47].

Recent evidence has demonstrated that there are over 50 different adipokines secreted from adipose tissue [48–51]. The main processes regulated by adipokines may be divided into three groups:

1. lipids and glucose metabolism;
2. inflammatory processes; and
3. blood pressure and haemostasis.

The main adipokines involved in lipid and glucose metabolism and energy expenditure

Some adipokines, such as TNF-alpha, serpin E1, and HB-EGF, are not specific to adipose tissue, but contribute to its detrimental effects. Others appear to be adipose-specific: leptin, which is appetite-controlling but also proinflammatory, and adiponectin, which enhances insulin action but is downregulated in obesity.

Leptin is a 16kDa peptide whose central function is the regulation of body weight by limiting food intake and increasing energy expenditure. Above this, leptin is involved in the regulation of the neuroendocrine axis, inflammatory responses, and blood pressure. The LEP gene is located on chromosome 7q31.3 and encodes a 167 amino acid precursor protein. Leptin activates the anorexigenic axis in the ARC of the hypothalamus by several processes and reduces inhibition by local orexigenic neuropeptide Y neurons [52–54].

Resistin is a 12 kDa protein identified in mice in a screen for genes suppressed by an agonist of the peroxisome proliferator-activated receptor-γ (PPAR-γ). The name resistin is derived from the original observation that this protein induced insulin resistance in mice. Resistin belongs to a family of four proteins referred to as FIZZ proteins, which comes from "found in the inflammatory zone" and is called FIZZ3 [55].

In mice, resistin expression increases during adipocyte differentiation, and levels of resistin increase in diet-induced obesity [56]. Lower levels of resistin lead to decreased expression of gluconeogenic enzymes and consequent reduction in hepatic glucose production. Conversely, elevation of resistin levels is associated with increased hepatic glucose production and glucose intolerance. Overexpression of resistin in human hepatocytes impairs insulin-stimulated glucose uptake and glycogen synthesis. Resistin has also been shown to exert a pro-inflammatory effect on smooth muscle cells [56].

Adiponectin was independently isolated by four different laboratories, leading to different names: adiponectin; adipocyte complement-related protein of 30kDa (ACRP30); adipoQ, gelatine-binding protein 28kDa (BGP28); and adipocyte most abundant gene transcript 1 (apM1). The adiponectin gene (*ADIPOQ*) is located on chromosome 3q27.3, and the two alternatively spliced mRNAs encode the same 244 amino acid protein. The hormone exists as a trimer, hexamer, and as high-molecular-weight oligomer forms. In addition to the structure, the active form of adiponectin has to be glycosylated [57]. Unlike leptin, levels of adiponectin are reduced in obese individuals and in patients with type 2 diabetes and increased in patients with anorexia nervosa. The major biological actions of adiponectin are increased insulin sensitivity and fatty acid oxidation [58]. Adiponectin activity is inhibited by adrenergic stimulation and glucocorticoids [59, 60]. Expression and release of adiponectin is stimulated by insulin and inhibited by TNF-1α. Conversely, adiponectin exerts inflammatory modulation by reducing the production and activity of TNF-1α and IL-6. Adiponectin functions by interaction with two specific cell-surface receptors: AdipoR1 expressed at highest levels in skeletal muscle and AdipoR2 in liver [61].

Visfatin

Visfatin, also known as pre-B cell colony-enhancing factor (PBEF), is a 52-kDa protein found in all living species. It is produced by the visceral adipose tissue. The expression of visfatin is increased in individuals with abdominal obesity and type 2 diabetes. PBEF/visfatin is expressed widely, and it has been shown to be anti-apoptotic and to regulate energy metabolism during stress responses and immune activation. Visfatin lowers plasma glucose due to its ability to bind and stimulate the insulin receptor [62, 63].

Vaspin

Vaspin is an adipokine (visceral adipose tissue-derived serine protease inhibitor — SERPINA12) synthesized mainly in visceral adipose tissue but also in the cells of hypothalamus and in some parts of the stomach, liver, and pancreas [64].

Vaspin was first identified as adipokine, which is predominantly secreted from visceral adipose tissue in the Otsuka Long-Evans Tokushima Fatty (OLETF) rat model of obesity and type 2 diabetes. The expression of human vaspin is positively correlated with body mass index and insulin sensitivity, and it increases glucose tolerance *in vivo*, suggesting a compensatory role in response to diminished insulin signalling in obesity.

Recently, several lines of evidence suggest that vaspin is a promising candidate for drug development for the treatment of obesity-related insulin resistance and inflammation [65].

Healthy adipose tissue secretion of adipokines is coordinated in an anti-inflammatory, insulin-sensitising, and cardioprotective pattern. However, with increasing fat mass this secretion pattern is changed into a pro-inflammatory, insulin resistant, atherogenic, and fatal systemic environment (Figure 2).

Bariatric procedures

A bariatric surgery has been created for the treatment of extreme obesity (morbid obesity) carrying the

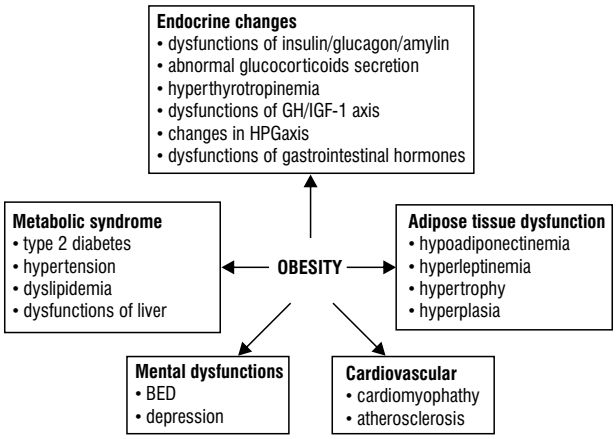

Figure 2. *Obesity-related diseases and dysfunctions*

life-threatening consequences of patients with BMI exceeding 40. The World Health Organisation definition of obesity is that BMI greater than or equal to 25 is overweight, and a BMI greater than or equal to 30 is obesity [5]. According to the guidelines of bariatric associations, BMI less than 40 justifies an attempt at conservative treatment, which includes the care of a psychologist, a nutritionist, and a fitness trainer. Unfortunately, based on numerous empirical studies, the long-term success of the above method in decreasing the body weight comes to about 5–7%. Thus, in the present state of scientific knowledge on obesity, it may be concluded that the only effective symptomatic treatment remains surgery.

According to the NIH, as well as the American College of Surgeons (ACS) and the American Society for Metabolic and Bariatric Surgery (ASMBSQ), qualifications for bariatric should include:

1. BMI ≥ 40;
2. BMI ≥ 35 with at least two obesity-related co-morbidities such as type 2 diabetes (T2DM), hypertension, sleep apnoea and other respiratory disorders, non-alcoholic fatty liver disease, osteoarthritis, lipid abnormalities, gastrointestinal disorders, or heart disease;
3. the inability to achieve a healthy weight loss sustained for a period of time with prior weight-loss efforts [66, 67].

Milestones of bariatric surgery

The literature throughout the 20th century promoted the long list of different surgical procedures (Table II), and this approach continues today, yet history would suggest that this optimism was often misplaced. At present, bariatric surgery exists as a metabolic surgery more by realisation of past and current accomplishments than by evolution [68, 69].

Table II. *Milestone of bariatric procedures*

Year	Procedure
1954–1970	Intestinal bypass
1967–1995	Gastric bypass
1978–1985	Horizontal gastric bypass
1980–1990	Vertical gastric bypass
1978–still	Biliopancreatic diversion
1990–2000	Biliopancreatic diversion-duodenal switch
1990–2000	Vertical banded gastroplasty
1990–2000	Gastric band nonadjustable
1990–present	Adjustable gastric band
1993	Laparoscopy adjustable gastric band
1995	Laparoscopy RYGB (Roux-en-Y gastric bypass)
2000–present	Sleeve gastrectomy
2002	Laparoscopy sleeve gastrectomy
2005–present	Gastric plication
2010–present	Endoscopic/transoral treatments

Nowadays, surgical procedures can be grouped into three main categories:

1. Restrictive procedures that reduce the stomach volume or limit the amount of food intake (sleeve gastrectomy-SG adjustable gastric band, experimental procedure — gastric plication-GP) [70].
2. Malabsorption procedures (biliopancreatic diversion — BPD, biliopancreatic diversion with duodenal switch — BPD-DS). Malabsorptive procedures divert digestive liquids such as bile and pancreatic enzymes and shorten the length of bowel that participates in food absorption [71].
3. A combination of both restrictive and malabsorption procedures (Roux-en-Y gastric bypass-RYGB, mini gastric bypass-MGB) [72].

Combination of restrictive and malabsorption procedures

Combined procedures have both restrictive and malabsorptive components. Gastric bypass surgery is a modified partial vertical gastrectomy called Roux-en-Y gastric bypass (RYGB).

Recent research, however, demonstrates that the essential effects of bariatric procedures, partucularly of RYGB and gastric sleeve, cannot be explained based on the restriction of food intake alone. These data suggest that bariatric procedures produce multiple effects, such as changes in gastrointestinal hormones secretion, energy expenditure, intestinal bacterial colonisation, bile acid metabolism, and epigenetic changes modifying gene expression. It appears that

Table III. *Side effects of gastric bypass and gastric banding*

Complications of surgery	Stenosis Leaking Anastomotic dehiscence Anastomotic Fistula Anastomotic stricture Internal hernia Band sliding (30%) Band migration Late postoperative band problems-reoperation (50%)
Gastrointestinal problems	Vomiting Thrombo-embolic reactions Anastomotic ulcer Anastomotic swelling Gastro-oesophageal reflux Megaoesophagus Pouch food-related bezoars Dumbing syndrome (carbohydrate, fat) Gastritis biliaris
Metabolic problems	Vitamins deficiency Hypoglycaemia Low effectiveness in sweet addicts Loss of amino acids
Endocrine problems	Hypothyroidaemia Excess of GLP-1 Complication GH/IGF axis Hyperinsulinaemia Disorders of leptin

Table IV. *Hormonal changes after bariatric procedure*

Hormone	Sleeve gastrectomy	Gastric bypass
Ghrelin	↓ ↔	↓↑
$PYY_{3–36}$	↑	↑
GLP-1	↑	↑
Leptin	↓	↓
Insulin	↔	↓
OXM	↔	↑
Adiponectin	↔	↑
Resistin	↓	↔
Amylin	↔	↓
CCK	↑	↔

↑ increase; ↓ decrease; ↔ no changes

particularly the effects of bariatric surgery on comorbid conditions, such as diabetes, are mediated by the aforementioned mechanisms [73]. All current bariatric procedures have gained several subsequent technical modifications together with laparoscopy and staple technique installation (since 1993).

Bariatric procedures are often followed by quite serious side effects, many of them are similar for restrictive and restrictive-malabsorptive methods. In spite of a relatively low complication rate (estimated by 3%) of all surgeries, they are severe in their consequences (Table III).

Most of the publications reported that the risk of death is around 1% during the early postoperative period. Personal author experience (M.D.) showed that after performing 350 bariatric procedures (open surgery or laparoscopically) during last 10 years only 5% of patients had complications such as bleeding, leakage, or stoma.

Metabolic and endocrine aspects of bariatric surgery

The last 15 years has shown that bariatric surgery has much broader possibilities and it could spread to almost global intracellular metabolism. It transpires that a combination of restrictive and malabsorptive mechanisms not only diminishes the body weight of extremely obese patients but also affects all components of metabolic syndrome (hypertension, insulin-dependent type 2 diabetes, hyperlipidaemia, cardiac overload or pre-existing heart disease, lower limb venous thrombotic syndrome, steatosis hepatitis) previously recognised as selected separate autonomous diseases.

It has been proven beyond reasonable doubt that surgical switch of the duodenum and the first part of the jejunum from the intestinal transit results (in an incretin effect mechanism) in glycaemia normalisation in type 2 diabetic patients. Recently [66], it was discovered that duodenal switch is also effective in non-obese type 2 diabetic patients, and it was revealed that the obtained incretin effect is sustained after 10-year observation. An increasing number of studies suggest that postsurgical changes within the neurohormonal system may account for a proportion of postsurgical weight loss [75]. Gastrointestinal hormone levels are often altered following bariatric procedures and may contribute to postsurgical reductions in caloric intake and body weight (Table IV).

Postsurgical reductions in ghrelin, as well as earlier and enhanced postprandial elevations of $PYY_{3–36}$ and GLP-1, may reduce hunger and promote satiety. Recent evidence also suggests that postsurgical changes in such hormones may lead to changes in brain activation in response to appetite signals [76].

Gut peptides known to cross the blood–brain barrier and induce changes in neural activation are probable candidates to account for the currently unexplained effects of bariatric surgery. Ghrelin, PYY, GLP-1, CCK, insulin, and leptin are released in the periphery and act indirectly on the vagus nerve and/or directly on target areas of the hypothalamus [77–79].

The most important hormonal changes after bariatric surgery

CCK

After bariatric surgery CCK levels were increased postprandially in response to a mixed meal, probably by stimulation of parasympathetic nerves. Presumably the high CCK levels contribute to the increased satiety and improved glucose homeostasis following RYGB [80].

Secretin

After bariatric surgery postprandial plasma secretin levels were lower than those of healthy people. The secretin release depends on the part of the intestine anastomoses. Early publications suggested that gastrointestinal anastomosis, which contains many secretin secretory cells, may help to prevent pancreatic dysfunction after gastrectomy and other surgical reconstructions [80].

Gastrin

Reduction of G cells as an effect of some bariatric procedures (RYGB) causes a decrease of gastric secretion. It may be speculated that increased levels of secretin and somatostatin as the effect of bariatric procedures also inhibit gastrin secretion. Some bariatric procedures (gastric banding, gastric sleeve) may be associated with increased gastrin levels or do not have any effect on this hormone [80].

Motilin

After RYGB surgery motilin levels decreased in parallel with hedonic hunger scores, initiating phase III of gastric migrating myoelectric complexes [23].

Anorexigenic and orexigenic gut hormones

The release of anorexigenic gut hormones such as GLP-1, PYY_{3-36}, and oxyntomodulin was enhanced after bariatric surgery.

GLP-1 levels during an oral glucose or meal stimulation have been shown to be persistently increased after RYGB. Levels of gastric inhibitory peptide were inconsistent after bariatric surgery, although an increase was reported after RYGB. Like the incretins and PYY_{3-36}, postprandial OXM is increased 1–2 months after RYGB. However, further studies are needed to understand the role of gut peptides in energy balance regulation after RYGB [80].

Ghrelin levels rise with prolonged fasting and fall after a meal; therefore, weight loss via calorie restriction increases ghrelin levels, which may contribute to the poor long-term efficacy of dietary manipulation to control obesity. The short- and long-term effects of bariatric surgery upon ghrelin levels are still unclear; different bariatric procedures appear to have variable effects upon ghrelin secretion [81]. Gastric banding appears to be associated with an increase in ghrelin levels. Studies on 33 patients for 12 months after RYGB found that those who had a good weight loss response had a higher degree of ghrelin suppression compared to poor responders. However, not all studies have been able to replicate a suppressant effect of RYGB on ghrelin in human or animal work [82, 83]. Interestingly, sleeve gastrectomy may decrease circulating acylated ghrelin concentrations, possibly due to the removal of ghrelin-producing cells in the stomach [84].

Experimental results

Surgical procedures have an impact on the neuroendocrine status of patients, which are very difficult or even impossible to compare with "control" surgery. In such cases it is necessary to judge what impact the bariatric procedure has compared to other surgical treatments.

Thus, the aim of our experiments performed on non-obese rats was to compare the impact of different abdominal surgeries on the neuroendocrine status of healthy animals.

Male rats underwent laparotomy, sleeve gastrectomy, or gastric plication. After 14 days of recovery, the blood, hypothalamus, and pituitary and adrenal glands were taken out and directed to estimation of hormones. Hypothalamic level of the neurotransmitter Met-enkephalin was significantly higher only after sleeve gastrectomy; in contrast, gastric plication decreased the concentration of endogenous opioid. Interesting results were observed in the activity of pituitary adrenal axis, where the bariatric procedures decreased the pituitary ACTH level and significantly increased concentration of corticosterone in adrenal gland and in blood (Table V). Laparotomy caused only an increase of corticosterone plasma level compare to the observed value in intact animals [85].

Recently published results of a meta-analysis underline the hypothetical positive effects of bariatric procedures on the control of glucose metabolism and improvements of normoglycaemia in diabetic patients [86–88].

Experiments performed on pigs (non-obese) showed that during the 30 days following laparoscopic sleeve gastrectomy the adrenal and pancreas hormonal activity was significantly changed (Table VI, unpublished data). The concentration, and the *in vitro* cortisol secretion from the adrenals as well as the plasma level of glucocorticoid were significantly increased during the 30 days following the surgical procedure. Unexpectedly, the plasma and pancreas levels of insulin were lowered in experimental piglets. In contrast, *in vitro* insulin basal secretion was increased after surgery; however,

Table V. *Neuroendocrine changes after bariatric procedure in non-obese rat*

	Hypothalamic Met-enkephalin (pmol/mg w.t.)	Pituitary ACTH (pmol/mg w.t.)	Adrenal corticosterone (nmol/mg w.t.)	Blood plasma corticosterone [nmol/ml]
Control (intact)	4.1 ± 0.03	0.43 ± 0.02	0.10 ± 0.01	0.028 ± 0.002
Laparotomy	3.9 ± 0.02	0.42 ± 0.02	0.16 ± 0.01	0.042 ± 0.003*
Sleeve gastrectomy	6.5 ± 0,11*	0.27 ± 0.01*	0.23 ± 0.02*	0.200 ± 0.03*
Gastric plication	3.1 ± 0.01*	0.24 ± 0.01*	0.24 ± 0.02*	0.110 ± 0.01*

*P < 0.01compare to control value

Table VI. *The effect of laparoscopic sleeve gastrectomy on the adrenals and pancreatic activity in non-obese piglets*

	Adrenal		Pancreas	
	Control	Experimental	Control	Experimental
	Cortisol [pmol/ml]		Insulin [μIU/ml]	
Plasma level	87.35 ± 5.82	145.72 ± 9.93*	18.91 ± 0.90	15.74 ± 0.71*
	Adrenal [pmol/mg]		Pancreas [μIU/mg]	
Tissue concentration	2.57 ± 0.16	13.74 ± 0.61*	8.05 ± 0.72	5.65 ± 0.43*
Secretion *in vitro*	Adrenal (fmol/mg/20′)		Pancreas (nIU/mg/20′)	
• basal	11.86 ± 0.60	25.13 ± 0.91*	4.82 ± 0.23	6.19 ± 0.34*
• stimulated	Dexamethasone		Hyperglycaemia	
	11.37 ± 0.59	7.75 ± 0.30[a]	3.96 ± 0.12[a]	3.62 ± 0.11[a]

*P < 0.05–0.001 between control and experimental piglets, [a]P < 0.001 between basal and stimulated hormones secretion

stimulation with hyperglycaemic medium attenuated this secretion. This experiment proved the effect of bariatric procedure (at least the sleeve gastrectomy) on the activity of adrenal and pancreas in healthy animals, so it can be speculated that the mechanism of glucose control in obese individuals would be also improved [88].

It can be suggested that the suspected risks of bariatric procedures include disorders of the neuroendocrine system at the levels of brain and the peripheral organs in addition to the digestive system disorders. Previous results of animal experiments showed changes in the activity of endogenous opioid peptide, Met-enkephalin, involved in pain, appetite, ghrelin, and stress regulation [85]. Previously, it was also found that Met-enkephalin interacts with the ghrelin activity at the gastrointestinal and central nervous system levels under stressful situations [85], so we decided to include the measurements of both, Met-enkephalin and ghrelin, into the hormonal profile of patients undergoing bariatric surgery.

During routine procedure, blood was taken from patients undergoing bariatric surgery 24 hours before and 72 hours after the surgery. The bariatric procedure significantly decreased the plasma levels of Met-enkephalin in females as well as in males. In contrast, plasma level of ghrelin was significantly higher in all patients (Table VII, unpublished data). However, it should be noted that, in spite of different basal levels, the percentages of hormonal changes after surgery were very similar in males and females.

Table VII. *Plasma levels of Met-enkephalin and ghrelin in patients before and after bariatric surgery*

	Females	Males
Met-enkephalin [pmol/ml]		
A (n = 30)	1.05 ± 0.04	1.14 ± 0.05[a]
B (n = 30)	0.44 ± 0.02*	0.50 ± 0.02*[a]
Ghrelin [fmol/ml]		
A (n = 20)	22.9 ± 0.01	31.83 ± 2.56[A]
B (n = 20)	30.01 ± 2.50*	41.41 ± 2.99*[a]

A — 24 hrs before surgery, B — 72 hrs after surgery

*P < 0.01 between A and B,
[a]P < 0.05 between females and males,
[A]P < 0.01 between females and males

Bariatric procedures are safe and effective in inducing weight loss and controlling comorbid conditions among obese patients. Malabsorptive procedures have a stronger effect on weight loss, although patients undergoing them are also at a higher risk of significant malnutrition. The RYGB and gastric sleeve achieves similar results with minimal risk for malnutrition or vitamin deficiency [89].

Conclusions

Hunger and satiety are mediated by an interplay of nervous and endocrine signals. Neural and hormonal signalling takes place between the hypothalamus, other parts of central nervous system, and peripheral organs, mainly the gastrointestinal tract and adipose tissue, to regulate food intake according to caloric need.

Perception of the adipose tissues has changed from passive lipid storage tissue to active endocrine organ regulating and modulating whole-body energy homeostasis and metabolism, inflammatory and immune responses by secreting a multitude of bioactive molecules, named adipokines.

Healthy adipose tissue secretion of adipokines is coordinated in an anti-inflammatory, insulin-sensitising, and cardioprotective pattern. However, with increasing fat mass this secretion pattern is changed into a pro-inflammatory, insulin resistant, atherogenic, and fatal systemic environment.

It is very important to keep in mind that bariatric surgery is not a solution to the problem for everyone who is obese. It is recommended only in cases when all other weight-loss measures have been attempted. For generally obvious reasons, only the life-threatening, extremely advanced forms of obesity should be treated with the surgical method. Long-term postsurgical observations of the hormonal profile changes are necessary and should be obligatory.

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Conflict of interest
The authors declare no conflict of interest

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