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Review article

The role of adipokines and gut hormones in the pathogenesis of obesity, and recent findings for the future treatment of obesity

B. ilkovska[a,*], B. Kotevska[b], D. Labudovic[c]
[a]*PHO Clinical hospital d-r Trifun Panovski Bitola R.Macedonia.*
[b]*Tokuda hospital Sofia R.Bulgaria.*
[c]*Department of Medical and Experimental Biochemistry, University School of Medicine, Skopje, Macedonia.*

[,]*Corresponding author; PHO Clinical hospital d-r Trifun Panovski Bitola R.Macedonia.

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ABSTRACT

Obesity has become one of the leading public health concern. Over one billion people are overweight or obese and the prevalence of these conditions is growing constantly. This review presents an overview of the endocrine functions of adipose tissue, the role of gut hormones and their associated neuronal networks (the gut-brain axis) in appetite control. Recent studies have improved our understanding of energy homeostasis by identifying sophisticated neurohumoral networks that transmit signals between the brain and gut to control food intake. Key adipokines, such as, leptin, adiponectin, interleukin-6, plasminogen activator inhibitor-1, resistin, tumor necrosis factor-α, adipsin and acylation stimulating protein, macrophages and monocyte chemoattractant protein-1, plasma renin, plasma angiotensin - converting enzyme and angiotensinogen linked with pituitary neuropeptide system began to clarify. Gut hormones, such as, cholecystokinin, ghrelin, peptide YY, pancreatic polypeptide, glucagon-like peptide-1, oxyntomodulin, ghrelin, insulin, glucagon, obestatin, amylin are modulated by acute food ingestion. This article highlights some of the recent findings and their implications for the future treatment of obesity, but there

are currently no effective pharmacological interventions for obesity.

1. Introduction

At the moment one of the greatest global problems is obesity. It represents a condition of increased fat tissue, or excessive accumulation of triglycerides in the fatty tissues, as a consequence of the increased food intake than the actual energy consumption and the lowered physical activity from the mostly sitting life-style (Paracchini et al., 2005). In 1985 the World Health Organization (WHO) defined obesity as a condition with body mass index (BMI) larger than 30.0 for men and larger than 28.6 for women (World Health Organisation, 1985). The Body Mass Index is calculated according to the standard formula – mass in kg divided with the square of height in m. Although, women have less bone and muscular tissue, they usually have a little more subcutaneous fatty tissue, but these subtleties are usually ignored during the standardized approach. Similarly, the muscle and bone weight are lowered with age, but these characteristics are not taken into account when defining the term. It should be emphasized that the waist – hips ratio (normally under 0.95 for men and under 0.85 for women) is generally a better prognostic indicator of the disease than the Body Mass Index (Paracchini et al., 2005). Never before in history has there been such an abundance of energy-rich, highly processed foods, as it has today (Sunye et al., 2002). The epidemic of obesity is a consequence of the economic, social and technological progress achieved during the previous few decades (Guyton et al, 2003). This so called nutritional transition combined with the more inactive life style promotes an environment which creates obesity (Sunye et al., 2002). More at risk of increased body mass and obesity are women, older people, members of minority groups and people with low socioeconomic status (Guyton et al, 2003). Obesity is not only an esthetical problem, but health problem also because it represents a risk factor for occurrence and development of diabetes mellitus type 2, vascular diseases, osteoarthritis, sleep apnoea and malignity (Silva et al., 2012). Obesity can be obtained as a result of a specific hormonal imbalance (Cushing's disease), and usual reasons are the mutations of specific genes. It can be monogenic or polygenic, but it is concluded that the polygenic forms are more common (Srivastava et al., 2007). For some genetic syndromes as Prader – Willi syndrome, Angelman syndrome and Wilson – Turner syndrome, obesity is only one symptom of many manifestations that are within the relating syndromes. Obesity might even be psychogenic. Testing of obese patients has shown that the vast percentage of obesity is consequence of psychological factors, and the reasons are stressful situations, and it is considered that food intake usually lowers tension. Obesities pathogenesis is complex and has interactions between, sex, age, race, socio-economic status, living environment, behaviour, ethnicity, genetic factors and others (Guyton et al, 2003). According to World Health Organization there are around one billion overweight people (Body Mass Index over 25 kg/m2), and 300 million of them are considered clinically obese (World Health Organization., 2000). It is supposed that 40% of adults might be obese by 2025 nationwide (Silva et al., 2012). Overweight and obesity are fifth leading risk factor for global mortality. At least 2,8 million people die each year as a result of overweight and obesity. Around 44% of diabetics, 23% of patients with ischemic heart disease and between 7% - 41% of cancer patients are obese.

In the thesis we will summarize our understandings of the pathophysiology of obesity, we will provide integrated perspective of how the metabolic signals which are synthesized in the

gastrointestinal tract, fatty tissue and other peripheral organs affect the brain and feeding centre, energy consumption and body weight.

2. Selection of studies

Electronic data base MEDLINE and PubMed were searched (research, 01. November 2013). Research strategy was conducted for all results of interest. The researched terms were, "obesity", "fatty tissue", "adipocytes", "intestine hormones", "appetite", "Body Mass Index". Mesh titles were used, where it was possible. The research was limited on articles published in English language. The research was limited on people, date of publish was limited to 10 years. We limited the review on healthy individuals and overweight children. The extracted references are verified by the title and abstracts for inclusion and exclusion, according to the following criteria. Inclusion criteria, fatty tissue, adipocytes, red hormones, appetite, body mass index, obesity, hips size, waist – hips ratio, every ethnic group and each population of people.

Exclusion criteria, studies that do not meet inclusion criteria; studies that included research of animal models. All inclusion studies were extracted as a complete text and were evaluated again for inclusion and exclusion. The process of inclusion and exclusion was carried according to predetermined criteria by two independent reviewers and trough discussion a consensus was achieved. Total of 175 340 theses were found during the research in the electronic data bases. Forty nine studies met the criteria for inclusion and exclusion and were available as documents with a complete text. Twenty seven of them were included in the preparation of this revial thesis.

3. Central nervous system and appetite regulation

Appetite means desire for a specific type of food and helps in the choice of quality food. If the desire for food is satisfied, feeling of satiation appears (Guyton et al, 2003). The gastrointestinal tract – brain axis controls appetite through neural and hormonal signals. With the entry of the nutrients, the small intestine releases peptides that act as negative feedback for lowering the size of the meal and feeding discontinuation (Figure 1).

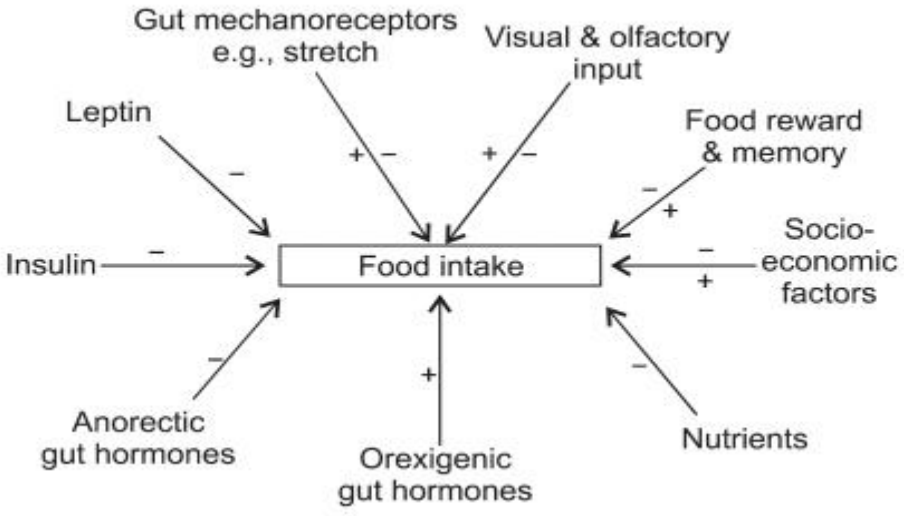

Fig. 1. The major determinants of appetite control (Silva et al., 2012).

Hormones and cytokines excreted from the peripheral organs have long-lasting effects upon the energy balance with control upon the reception of food and energy consumption. Neurons that are included in the regulation of homeostasis of nutrition are mainly located in the hypothalamus and the brainstem. The nucleus which is arc shaped located in the hypothalamus receives signals from the periphery. These signals act on two different neuronal population coding. First population that expresses agouti-related peptide (AgRP) and neuropeptide Y (NPY), stimulates the food intake; and the second neuron population, that contains pro-opiomelanocortin (POMC), cocaine – amphetamine regulated transcript (CART), inhibits the appetite (Figure 2).

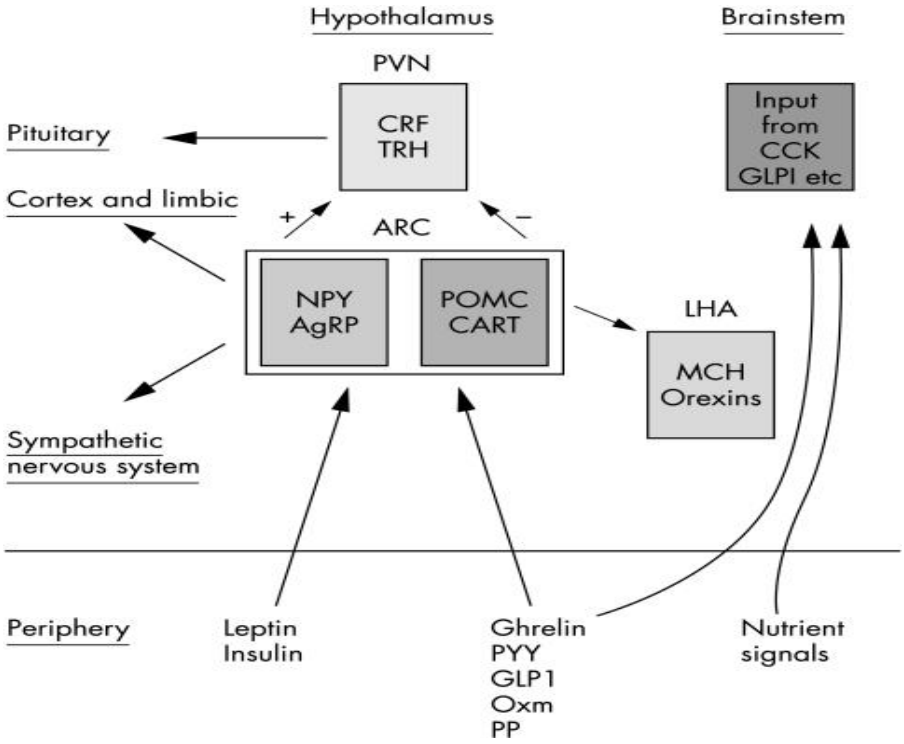

Fig. 2. Schematic representation of appetite control—actions of gut hormones and long term adiposity signals on neuronal populations in the arcuate nucleus and the integrated response of anorexigenic and orexigenic populations of neurones in the hypothalamus. ARC, arcuate nucleus; PVN, paraventricular nucleus; LHA, lateral hypothalamic area; CRF, corticotroph releasing factor; TRH, thyrotropin releasing factor (form part of integration with energy expenditure); NPY, neuropeptide Y; AgRP, agouti related peptide; POMC, proopiomelanocortin; CART, cocaine and amphetamine regulated transcript; MCH, melanin concentrating hormone; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY; Oxm, oxyntomodulin; PP, pancreatic polypeptide (Druce et al., 2006).

Pro-opiomelanocortin is a precursor of alfa-melanocyte-stimulating hormone (α-MSH) that influences upon the receptor of melanocortin (MC4R), which decreases food consumption (Schwartz et al., 2000).

4. Adipose tissue, active endocrine organ and obesity

Adipose tissue is highly active metabolic and endocrine organ, which is essential for regulation of body weight (Kershaw et al., 2004). It is composed of cells filled with triglycerides (adipocytes), preadipocytes – adipocytes precursor, stromal cells, immune cells, collagen

network, fibroblasts, macrophages and blood vessels. These components work together as one integrated unit (Frayn et al., 2003). Except for the basic function of storage and release of energy, fatty tissue contains a metabolic apparatus that enables communication with further organs including CNS. Through this interactive network, fatty tissue is integral included in coordinating with different biological processes, including energy metabolism, neuroendocrine function and functions of the immunological system (Tartaglia et al., 1995). The endocrine function of the fatty tissues is particularly emphasized in unwanted metabolic consequence – excessive fatty tissue or obesity. Excessive fatty tissue, particularly in the visceral parts is associated with insulin resistance, hyperglycaemia, dyslipidemia, elevated blood pressure and with prothrombotic and proinflammatory state (Grundy et al., 2004). Fatty tissue secretes great number of different peptides, also known as adipokines which operate on local (autocrine / paracrine) and systemic (endocrine) level and have a wide biological activity. They control feeding, energy balance, neuroendocrine and other functions (Table 1).

Table 1
Examples of adipocyte-derived proteins with endocrine functions (Kershaw et al., 2004).

Cytokines and cytokine-related proteins	**Leptin**
	TNFα
	IL-6
Other immune-related proteins	MCP-1
Proteins involved in the fibrinolytic system	PAI-1
	Tissue factor
Complement and complement-related proteins	Adipsin (complement factor D)
	Complement factor B
	ASP
	Adiponectin
Lipids and proteins for lipid metabolism or transport	Lipoprotein lipase (LPL)
	Cholesterol ester transfer protein (CETP)
	Apolipoprotein E
	NEFAs
Enzymes involved in steroid metabolism	Cytochrome P450-dependent aromatase
	17βHSD
	11βHSD1
Proteins of the RAS	AGT
Other proteins	Resistin

Protein and cytokine molecules which are created in the fatty tissue are, leptin, adiponectin, angiotensine, atrial natriuretic peptide, cholesteryl ester transferase, estrogen, fatty-acid-binding-proteins ap2 FFA / Glicerol, IGF – binding proteins 3 (IGFBP – 3), insulin as growth factor – 1 (IGF – 1) interleukin – 1 beta, interleukin – 6 (IL – 6), interleukin – 8 (IL – 8), lipoprotein lipase – Monobutyrin, PAI – 1, resistin, retinol binding protein – 4, sterol regulatory elements, TNF-α, visfatin and others (Kershaw et al., 2004).

4.1. Leptin

Discovery of leptin by Friedman and his colleagues in 1994 was an event that was groundbreaking in the research field of obesity. Leptin (Greek leptos, meaning thin) is a 16-kDa polypeptide that contains 167 amino acids and is similar to cytokines structurally (Kershaw et al., 2004). LEP gene, which encodes leptin, is localized in chromosome 7aplpha31.3 and is composed of three exons and two introns (Paracchini et al., 2005). It is manufactured primarily in adipocytes of white fatty tissue and is proportional with (to) the total amount of fat tissue, and with nutrition status (Fain et al., 2004). Leptin, in small amounts, is synthesized in other tissues of the human body, stomach, heart, epithelium in the mammary gland and the placenta. Leptin manifests its effects through receptors (OBR) which are mostly localized in the hypothalamus and cerebellum, but it can be also found in the placenta, vascular tissue, stomach and brain (El-Atat et al., 2003). Leptin crosses the blood-brain barrier, connects to the receptor localized in the hypothalamus, inhibits the hunger feeling and increases energy consumption level and thus plays a major role in the establishment of energy balance (El-Atat et al., 2003). It lowers obesity through lowering appetite and increasing thermo genesis (Schwartz et al., 2000). Leptin, acting upon its receptor in the hypothalamus, activates the neurons of pro – opiomelanocortin (POMC), cocaine – amphetamine regulated transcript (CART) and inhibits neurons on neuropeptide Y (NPY) and agouti – related protein (AgRP). These pathways are interacting with other brain centre to coordinate appetite (Bils et al., 2009). Leptin signals are transported by JAK/STAT mechanism which takes place as it follows, the leptin receptor phospohrylates under the influence of Janus kinase enzyme (JAK), bonts with STAT – proteins (Signal transducers and activators of transduction)) which further phosphorylate under the influence of the same enzyme. Phospholytatet STAT – proteins enter the nucleus bonding with specific DNA sequences thus regulating the expression of specific genes. Leptin functions upon the principle of negative feedback, causing stimulation of hunger sense upon low concentrations and its inhibition upon high concentrations (Tanaskoska et al.,2009). It is assumed that increased body weight results with reduction of leptin activity upon leptin receptors in hypothalamus otherwise known as “leptin resistance” i.e. the effect of leptin in reducing the appetite and increasing the energy consumption is obstructed. Because of these, for obese individuals, despite high concentrations of leptin, it is observant positive energetic balance accompanied with increase of body weight (Tanaskoska et al.,2009). Deficiency of leptin receptor is rare, thereby the person is born with normal birth weight but shows quick weight gain in the first few months of life, which results with overweight obesity. It is characterized with expressed hyperphagia with needs for food and aggressive behaviour when food is not given. Energy input during meal by personal choice is increased significantly for persons with leptin and leptin receptor deficiency (Bils et al., 2009). According to the newest studies, leptin is recognized as one of the most sensitive adipokines markers for prediction of accumulation of risk factors for cardiovascular diseases and metabolic syndrome on adolescents (Arslan et al., 2010). Some other endocrine functions of leptin include regulation of the function of the immune system, haematopoiesis, angiogenesis, creation of bone tissue and wound healing (Margetic et al., 2002).

4.2. Adiponectin

Adiponectin is discovered in 1995 and 1996 by four groups of scientists using different methods, hence the different names, apM1 (adipose most widespread gene transcript 1), Acrp30 (adipocytes related to proteins of 30 kDa), adipoQ and GBP28 (gelatine binding protein of 28 kDa (Maeda et al., 1996, Scherer et al., 1995, Nakano et al., 1996, Hu et al., 1996). It is one of a kind specific protein of fatty tissue, with MM 30-kDa, that has a structural homology to collagen type VIII and X complement C1q factor. Adiponectin is composed of N-terminal signal

sequence, variable domain, domain similar to the collagen and C-terminal tail domain. It circulates in the human plasma in great amounts (Diez et al., 2003). Adiponectin expression and secretion is increased by activators PPAR-γ (Stefan et al., 2002). Adiponectin has powerful anti-inflammatory and anti-atherosclerotic influence (Goldstein et al., 2004), including inhibition of expression of TNF-α that induces endothelial adhesion, transformation of macrophages to foam cells, TNF-α expression in macrophages and fat tissue and smooth muscle cell proliferation (Ouchi et al., 2003). Producing is lowered by insulin resistance, showing that hypoadiponectinemia level is more related to the level of insulin resistance and hyperinsulinemia than to the level obesity and glucose intolerance (Weyer et al., 2001). Two adiponectin receptors are identified – AdipoR1 and AdipoR2 (Yamauchi et al., 2003). A strong and consistent inverse relation is determined between adiponectin and insulin resistance and inflammatory conditions. The concentration of adiponectin is reduced during obesity and is increased during hunger. Further more several polymorphisms in the adiponectin gene are associated with obesity and insulin resistance (30). Mechanisms of influence of adiponectin (Diez et al., 2003, Chandran et al., 2003) in the liver - adiponectin improves insulin sensitivity, reduces the intake of non-esterified fatty acids, increases the oxidation of fatty acids and reduces the export of glucose from the liver. In muscles, adiponectin stimulates glucose utilization and fatty acid oxidation. In vascular walls adiponectin, inhibits monocyte adhesion by reducing the expression of adhesion molecules thus inhibiting macrophageal cells transformation into foam cells and reduced proliferation of smooth muscle cells migrating in response to growth hormone. Adiponectin increases synthesis of nitric oxides in endothelial cells and stimulates angiogenesis. These effects are mediated with increased phosphorylation of the insulin receptor, activation of AMP-activated protein kinase and modulation of core factor κB(Diez et al., 2003, Chandran et al., 2003). Considering the above effects it can be concluded that adiponectin is the only hormone secreted by adipocytes with anti-diabetes, anti-inflammatory and anti-atherogenic effects(Chandran et al., 2003) .

4.3. Interleukin-6

Interleukin - 6 (IL–6) is a cytokine associated with obesity and insulin resistance in adults and children (Yeste et al., 2007). Secretion of IL-6 is two to three times higher in visceral compared to subcutaneous fat. It circulates in blood in multiple glycosylated forms, sized from 22 to 27 kDa. The receptor for IL–6 in fatty tissue is homologous to the leptin receptor (Arslan et al., 2010).

Circulating level of IL-6 positively correlates obesity and impaired glucose tolerance and insulin resistance; it has been noticed that loss of body weight decreases levels of concentration of IL-6. Moreover, plasma concentration of IL-6 predicts the development of type 2 diabetes and cardiovascular disease. IL-6 inhibits adipogenesis and reduces the secretion of adiponectin. These effects of IL-6 confirm its role in the development of obesity and insulin resistance (Fernandez-Real et al., 2003).

4.4. Tumour necrosis factor alpha, TNF – α

The 26-kDa is a transmembrane protein that manifests its effects through type I and type II TNFα receptors. It is a cytokine originally described as endotoxin induced factor that causes necrosis of tumors, and later it was proved to be identical with cachexin, secreted factor by macrophages (Ruan et al., 2003). TNFα is secreted by adipocytes and stromal vascular cells. Although, initially it was suspected to play a role in cachexia, today it is known that it correlates positively with obesity and insulin resistance and inflammatory changes in vascular tissue

resulting in endothelial disfunction and the development of atherosclerosis and elevated blood pressure (Hotamisligil, 2003, Hotamisligil, et al., 1993)

4.5. Monocyte and macrophages chemoattractant protein (MCP) – 1

Obesity is associated with increased infiltration of macrophages in adipose tissue. Activated macrophages secrete mediators of inflammation, such as IL-6 and TNFα, which contribute to insulin resistance (Wellen et al., 2003, Weisberg et al., 2003, Xu et al., 2003). Adipose tissue secretes MCP-1, chemokine that attracts monocytes to the inflamed area (Wellen et al., 2003). Moreover, it is demonstrated on cultured, in vitro, cells that MCP-1 reduces glucose intake stimulated by insulin and tyrosine phosphorylation of the insulin receptor to induce insulin. Thus MCP-1 contributes to insulin resistance in adipose tissue (Sartipy et al., 2003).

4.6. Plasminogen activator inhibitor – 1, PAI-1

Adipose tissue secretes several proteins involved in the coagulation system or fibrinolysis, including tissue factor and plasminogen activator inhibitor-1, PAI-1 (Mertens et al., 2002). Secretion of PAI-1 is greater than visceral compared to subcutaneous adipose tissue (Fain et al., 2004). PAI-1 is an inhibitory member of the family of serine proteases and is the primary physiological inhibitor of fibrinolysis by deactivating urokinase and tissue plasminogen activator in blood and is known to contribute to thrombus formation and the development of acute and chronic cardiovascular diseases. Plasma levels of PAI-1 are regulated upon genetic basis and the accumulation of visceral fat is considered as a major regulator of PAI-1. Plasma level of PAI-1 are elevated in obesity and insulin resistance and positively correlate with the occurrence of metabolic syndrome and also they are predictors of risk of diabetes type -2 and cardiovascular disease (Mertens et al., 2002, Juhan-Vague et al., 2003). It is assumed that PAI-1 may not only be increased in response to obesity and insulin resistance, but may also have a direct role in the occurrence of obesity and insulin resistance (Sikaris, 2004). It is established that TNF-α contributes to elevated PAI-1 levels in obese people and people with insulin resistance (Fain et al., 2004). PAI-1 is also involved in other biological processes, including angiogenesis and atherogenesis (Kershaw et al., 2004).

4.7. Resistin

Resistin (insulin resistance) is a 12-kDa polypeptide (Sikaris, 2004) that belongs to the only protein family that is cysteine-rich residues of C-ends (Kershaw et al., 2004). It is considered that resistin has pro-diabetogenesis ability. Although evidence exists that (that)circulating levels of resistin are proportional to the degree of obesity (Sikaris, 2004) and the distribution of fat, the levels are not in proportion to the degree of insulin resistance (Steppan et al., 2004, Courten et al., 2004, Heilbronn et al., 2004).

4.8. Adipsine and Acylation stimulating protein

Adipsine (complement D), serine protease, is one of the complement components that are obtained in adipose tissue that is required for enzymic creation of protein that stimulates acylation (ASP). Adipsine and ASP, have an impact on the metabolism of lipids and carbohydrates (Cianflone et al., 2003). They positively correlate with obesity, insulin resistance, dyslipidemia and cardiovascular diseases (Cianflone et al., 2003)

4.9. Proteins of renin-angiotensin system (RAS)

Several proteins of the classical renin-angiotensin system are produced in adipose tissue, such as renin, angiotensinogen (AGT), angiotensin I, angiotensin II, angiotensin receptor type 1 (AT1) and type 2 (AT2), angiotensin-converting enzyme (ACE) and other proteases capable of producing angiotensin II. Plasma renin activity, plasma angiotensin-converting enzyme activity and adipose tissue angiotensinogen are positively correlated with obesity (Engeli et al., 2003, Goossens et al., 2003)

5. Role of the hormones of gastrointestinal tract in pathogenesis of obesity

Gastrointestinal tract function is not only as a conduit for food, but also is essential for digestion and absorption of nutrients. Visual, olfactory and taste signals stimulate exocrine and endocrine secretions and stomach motility even before food enters the mouth. Swallowing stimulates mechanoreceptors, resulting in a coordinated series of distension, digestion and absorption of nutrients (Ahima et al., 2008). When the stomach and duodenum are stretched during the food intake, strain causes transmitting signals through the nervus vagus, in order to block the centre for food intake and reduce the desire for food (Guyton et al, 2003).

Appetite is controlled by intestinal hormones also. The gastrointestinal tract is the largest endocrine organ in the body that secretes over 30 different regulatory peptide hormones (Table 2).

Content of imported food stimulates intestinal secretion of many of these intestinal hormones which interact with receptors located at various points in the "stomach – brain axis" and thus affects the short-term and long-term sense of hunger and satiety (Silva et al., 2012). Hormones that are secreted by the gastrointestinal tract and affect the appetite centre in the hypothalamus and satiety are the following.

Table 2
The Major Gut Hormones Involved in Appetite Regulation (Silva et al., 2012).

	Hormone	Site of secretion	Major receptors	Major actions
Anorectic	PYY	Gastrointestinal L cells	Y_2	Delays gastric emptying Vagal and CNS effects
	GLP-1	Gastrointestinal L cells	GLP-1	Glucose dependant insulin release Delays gastric emptying Vagal and CNS effects
	Oxyntomodulin	Gastrointestinal L cells	GLP-1/? other	Glucose dependant insulin release Delays gastric emptying Vagal and CNS effects
	Glucagon	Pancreatic α cells	Glucagon	Gluconeogenesis Glycogenolysis
	Cholecystokinin	Intestinal I cells	CCK 2	Gall bladder contraction Delays gastric emptying Pancreatic enzyme secretion
	Pancreatic polypeptide	Pancreatic PP cells	Y_4	Delays gastric emptying
	Amylin	Pancreatic β cells	AMY_{1-3}	Inhibits gastric secretion Delays gastric emptying Decreases blood glucose
Orexigenic	Ghrelin	Gastric fundal A cells	GHS-R	Increases gastric motility Growth hormone release

Ghrelin is the first known hormone that stimulates appetite (Tschop et al., 2000). Ghrelin is acylated 28-amino-acid peptide, which is mainly secreted by oxyntic stomach glands, circulates in the blood and activates NPY / AgRP neurons in arcuate nucleus (Inui, 2001). Gastrectomy resulted in 80% reduction in plasma levels of ghrelin, and the remaining 20% is excreted from the small intestine, pancreas, pituitary gland and colon (Hosoda et al., 2006). Ghrelin is included in short-term and long-term regulation of the appetite and the body weight. Circulating levels rise sharply before feeding and decrease after meals (Cummings et al., 2001).

In humans, ghrelin has a diurnal rhythm, which is identical with the daily rhythm of leptin, so that both hormones are elevated during the day to reach its peak at 13 pm, then their level decreases, so the minimum occurs around 21 h (Cummings et al., 2001). In adults, the level of ghrelin is inversely proportional to body mass index (Druce et al., 2006). The concentration of ghrelin is influenced by pubertal development. It causes positive energy balans, stimulates food intake and reduces energy consumption. Levels are reduced in obese individuals, with the exception of patients with Prader-Willi syndrome, and increased in anorexia nervosa (Otto et al., 2000), low-calorie food (Nakazato et al., 2001), in cachexia caused by malignant diseases (Wisse et al., 2001).

5.2. Peptide YY (PYY)

Peptide YY is a hormone that suppresses appetite. Peptide YY (PYY, peptide tyrosine tyrosine) belongs to the PP family that includes neuropeptide Y (NPY) and pancreatic polypeptide (PP). Peptide YY is built of 36 amino acids; it is secreted by L-cells of the gastrointestinal tract, with maximum concentrations in the terminal ileum, colon and rectum. Its name comes from its tyrosine (Y) residues in both the N and S ends. PYY is released after a meal and mediates postprandial satiety, reducing appetite and (lose) weight loss (Srivastava et al., 2007). Two endogenous forms, PYY1-36 and PYY3-36 are released postprandially into the circulation. After the meal, circulating levels of PYY3-36 are elevated within 15 minutes, the peak is around 90 minutes, and remains elevated up to 6 hours. The size of the elevated PYY3-36 is in proportion to calories (Silva et al., 2012). Obese people have lower basal levels of PYY and reduced postprandial levels but remain sensitive to the inhibitory effects on appetite after the exogene administration. Thus PYY 3-36 could represent candidate targets for therapy for obesity (Batterham et al., 2003).

5.3. Glucagon-like peptide – 1 (GLP-1)

Proglucagon is 160 amino acidic prohormone which is generated from α-cells of the pancreas and L-cells of the distal parts of the digestive tract and CNS. Selective post-translational proteolysis of proglucagon from prohormone convertase 1 and 2 results in specific tissue synthesis of many biologically active fragments. GLP-1 is released after eating, by L-cells of the stomach in proportion to the amount of food consumed and affects the pancreas to release insulin (Ghatei et al., 1983). GLP-, manifests its influence through G-protein bonded GLP-1 receptor located in the pancreatic islets where GLP-1 acts as an incretin hormone. It amplifies the postprandial excretion of insulin, inhibits glucagon secretion, and slows gastric emptying (Gutniak et al., 1992). Intravenous intake of GLP-1 inhibits food intake in healthy individuals, diabetics and obese individuals (Verdich et al., 2001). Secretion of GLP-1 is reduced in obese people and by reducing body mass, levels are normalized. Decreased secretion of GLP-1 may contribute to the pathogenesis of obesity (Verdich et al., 2001, Naslund et al., 2004)

5.4. Oxyntomodulin (Oxm)

Oxyntomodulin is a 37-amino acid peptide (Bataille et al., 1981), obtained by processing preproglucagon in the intestines and brain and is released after a meal in proportion to the amount of ingested food (Druce et al., 2006). OXM has a suppressive effect on appetite and GLP-1 but with a much weaker effect, at the same time, it inhibits gastric secretion of hydrochlorid acid and delays gastric emptying (Schjoldager et al., 1989).

5.5. Cholecystokinin (CCK)

Cholecystokinin is the first intestinal hormone that was discovered in the role of control of appetite (Gibbs et al., 1973). Plasma levels of CCK rise within 15 minutes after intaking the meal. It has a short plasma half-life - a few minutes. Its effect manifests through two subtypes of CCK receptors - CCK1 and CCK2 receptors, previously classified as CCK A and CCK B. CCK 1 and 2 receptors are widely distributed in the brain including the brain stem and hypothalamus. Appetite – suppressive effect of CCK appears to be partly mediated by CCK1 receptors on vagal nerve (Suzuki et al., 2012).

It is dominantly released in response to fats intake in duodenum and has a strong direct impact upon the centre for food intake reducing the further food intake (Guyton et al, 2003). Stimulates contractions of the gallbladder, pancreatic secretion and peristalsis of the intestines (Schjoldager et al., 1989), stimulates and delayed gastric emptying (Suzuki et al., 2012).

5.6. Pancreatic polypeptide (PP)

Pancreatic polypeptide is secreted from PP-cells in Langerhans islets as a response of food intake. It was/is built from a chain of 36 amino acids (Michel et al., 1998). PP has appetite-suppressive effect and its levels are lower in obese individuals (Adrian et al., 1976). Plasma levels of PP have diurnal variation, thus, the lowest levels are seen in the early morning and highest in the evening (Suzuki et al., 2012).Circulating PP levels are inversely proportional to obesity; higher values of PP are published for people with anorexia nervosa (Uhe et al., 1992). Some, but not all studies have shown a significant reduction in circulating levels of PP in obese individuals (Suzuki et al., 2012). Moreover, it is known that obese individuals with Rrader-Willi syndrome have a reduced release of PP in the basal and postprandial conditions (Zipf et al., 1983).

5.7. Obestatin

Obestatin is a 23 amino acid peptide hormone produced by posttranslational split of preproghrelin and is released from the stomach (Zhao et al., 2008). In rodents is found that, unlike ghrelin that stimulates appetite, obestatin suppresses the appetite by reducing food intake, delayed gastric emptying and decrease in body mass (Lacquaniti et al., 2011). However, the potential of appetite suppression remains controversial because other investigators have failed to confirm this effect (Gourcerol et al., 2007, Lacquaniti et al., 2011, Zhao et al., 2008)

5.8. Amilin

Amilin functions as a suppressive hormone of appetite. Circulating levels of amilin are higher for obese persons compared to skinny individuals (Reinehr et al., 2007, Reda et al., 2002). It lowers the food intake and lowers the body weight (Lenard et al., 2008).

6. Hormones secreted by the pancreas

6.1. Insulin

It is synthesized in the beta cells of the pancreas, it is secreted rapidly after feeding and has hypoglycemic effect (Suzuki et al., 2012). Insulin, together with leptin acts as an appetite suppressive signal in the arc shaped core (Suzuki et al., 2012), reducing food intake (Lenard et al., 2008). It participates in long-term regulation of energy balance (Suzuki et al., 2012). Circulating levels of insulin and leptin are positively correlated with body fat mass (Suzuki et al., 2012).

6.2. Glucagon

It is produced by the alpha cells of the pancreatic islets and increases the concentration of glucose in response to hypoglycemia. Glucagon enhances the physiological response of the body during stress by increasing energy consumption. It reduces food intake and body weight, but causes hyperglycemia (Suzuki et al., 2012).

7. Obesity treatment

7.1. Physical activity

Loss of body mass in many obese persons/people may be increased with the intensification of physical activity. More exercise means better daily energy consumption and quicker decrease of obesity (Guyton et al, 2003).

7.2. Drug treatment

Different medicines to reduce hunger are used in the treatment of obesity. Some of them are, Amphetamine-that directly inhibits eating centre in the brain; Sibutramine – it is a sympathicomimetic which reduces food intake and increases energy consumption (Guyton et al, 2003), but has several side effects such as tachycardia and hypertension (Druce et al., 2006), and that is why it was recently withdrawn from the market (Silva et al., 2012). Currently the only licensed pharmacological treatment for obesity is Orlistat, an inhibitor of intestinal lipase; it works by altering the lipid metabolism reducing the intestinal digestion of fats. This causes part of the input to lose fat in the faeces and also reduces the absorption of energy. However, the loss of fat through the faeces can cause unpleasant gastrointestinal side effects as (are) loss of liposoluble vitamins through faeces(Guyton et al, 2003).

The role of intestine hormones in appetite control is studied for over 30 years, with a clear demonstration that they have a role in mediating the postprandial satiety. Appetite suppressive intestinal hormones, such as PYY and GLP-1 play an important role in reducing the food intake, but still do not have application (Schwartz et al., 2000).

7.3. Surgical treatment of obesity

Three surgical procedures are in use at the moment, gastric restriction, gastric bypass and biliopancreatic diversion (Druce et al., 2006). Bariatric surgeries are procedures that are based on malabsorption, include Jejunoileal bypass, resulting in reduced absorption of nutrients by shortening the length of the functioning large intestine and allowing nutrients to pass directly from the proximal jejunum to the terminal ileum. Roux-en-Y gastric bypass (RYGB) is a combined restrictive and malabsorption procedure that provides long-term weight loss with an acceptable level of risk. RYGB achieves its beneficial effects through BRAVE effects, change in bile flow, reducing the size of the stomach, anatomical rearrangement of the stomach, changes the flow

of nutrients, vagal manipulation and subsequent modulation of enteric gastrointestinal hormones (Suzuki et al., 2012).

7.4. Stomach microflora

The potential link between stomach microflora and pathogenesis of obesity has been recently discovered. The stomach contains 1000-1150 bacterial species called stomach microflora. In a randomized, double-blind, parallel, placebo-controlled study to evaluate the effect of probiotics on plasma levels of intestine hormones, 10 healthy subjects received either 16 g probiotics /a day or 16 g maltose dextrin /a day for 2 weeks. On the people treated with probiotics, increased gastric microflora was noticed, increased fermentation, decreased appetite, improved postprandial response to glucose and increased plasma levels of GLP-1 and PYY. Adjustment to probiotics led to certain modulations of gastric mikroflora. Studies suggest (suggest) that gastric microflora may be associated with development of obesity and probiotics are the new treatments for obesity. These observations may help to develop new pharmacological strategy for patients with overweight (Suzuki et al., 2012).

8. Conclusion

Overweight as a phenomenon has a growing trend in modern society, especially in developed countries. Body mass index, although it is not an ideal parameter, nevertheless is accepted as an indicator of obesity. The control of obesity involves large number of hormones, proteins, adipokines, cytokines and other substances suppressing the appetite, in contrast, the number of appetite stimulators is reduced to one - ghrelin. It is important to have a practical approach to the investigation and treatment of patients with obesity because they are at greater risk of morbidity and mortality. The need to treat excessively obese patients in recognized centres will increase the need to cooperate with academic centres with expertise and experience in this field, to make laboratory research more accessible to patients in need. Treatment for excessive obese patients is becoming more sophisticated and requires the development of new biochemical and molecular genetic diagnostics.

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