Pathomechanisms of the development of obesity in some endocrinopathies — an overview

Patomechanizm rozwoju otyłości w wybranych endokrynopatiach — przegląd

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Abstract

Obesity is a disease in which the excess of accumulated body fat has an adverse effect on health and consequently leads to a reduced life expectancy. It is a typical 'disease of civilisation', and is a serious public health problem because of a significant increase in its prevalance. It is also a common symptom in a variety of endocrine disorders, but the factors responsible for the development of obesity in endocrinopathies have not been clearly identified. It is not known whether a common factor responsible for the development of obesity occurs in a number of endocrine diseases. On the other hand, adipose tissue is an important endocrine organ producing biologically active substances with local or systemic action that can lead to severe disorders of the endocrine system. This study presents data on the mechanisms of the development of obesity in the thyroid diseases, polycystic ovary syndrome, hypercortisolism and pituitary insufficiency. **(Endokrynol Pol 2013; 64 (2): 150–155)**

Key words: *obesity, adipokines, endocrinopathies*

Streszczenie

Otyłość jest chorobą, w której nadmiar zgromadzonej tkanki tłuszczowej ma niekorzystny wpływ na zdrowie i w konsekwencji prowadzi do zmniejszenia długości życia. Jest typową chorobą „cywilizacyjną", która stanowi poważny problem zdrowia publicznego z powodu znacznego wzrostu częstości jej występowania. Jest także częstym objawem w różnych schorzeniach endokrynologicznych, ale czynniki odpowiedzialne za rozwój otyłości w endokrynopatiach nie zostały zidentyfikowane. Nie wiadomo czy istnieje wspólny czynnik odpowiedzialny za rozwój otyłości w wielu chorobach endokrynologicznych. Z drugiej strony tkanka tłuszczowa jest ważnym organem hormonalnego wytwarzania biologicznie aktywnych substancji o działaniu lokalnym i układowym, które mogą prowadzić do poważnych zaburzeń układu hormonalnego. W niniejszej pracy przedstawiono dane na temat mechanizmów rozwoju otyłości w chorobach tarczycy, zespole policystycznych jajników, hiperkortyzolemii i niedoczynności przysadki. **(Endokrynol Pol 2013; 64 (2): 150–155)**

Słowa kluczowe: *otyłość, adipokiny, endokrynopatie*

Introduction

According to the WHO, obesity is a medical condition in which excess body fat has accumulated to the extent that it has an adverse effect on health, leading to reduced life expectancy and/or increased health problems [1]. By definition, overweight (pre-obese) people have a body-mass index (BMI) between $25-30$ kg/m^2, while obese people have a BMI greater than 30 kg/m^2. Obesity is a typical 'disease of civilisation' and constitutes a major public health problem. In the world, in 2008, 1.5 billion people aged 20 and older were overweight. The number of overweight people is currently estimated to be 2.6 billion, while the number of obese individuals is likely to increase from 400 to 700 million within 10 years

[1]. Obesity is believed to result from a combination of environmental, genetic, psychological, metabolic and endocrine factors. An interesting association has been observed between excessive body weight and hormonal disorders of unknown origins and mechanisms. The cellular and molecular bases and the underlying biochemical mechanisms of obesity remain unknown. On the one hand, in simple obesity a number of problems have been noted in the secretion of biologically active substances; while on the other hand, obesity is a syndrome of multiple, co-occurring disorders of the endocrine glands.

White adipose tissue is not merely a fuel storage organ, but also an important endocrine organ that produces biologically active substances with local,

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peripheral, and systemic actions and influences metabolic homoeostatic mechanisms [2–5]. Hormones, adipokines, and other biologically active agents released from fat cells affect many physiological and pathological processes. The presence of visceral fat, localised within the abdominal cavity and mediastinum, correlates with an increased risk of insulin resistance and cardiovascular diseases. On the other hand, an increase of subcutaneous fat in the hypodermis is known to be associated with favourable plasma lipid profiles. Visceral adipocytes show higher lipogenic and lipolytic activities and produce more pro-inflammatory cytokines, while subcutaneous adipocytes are the main source of leptin and adiponectin.

Obesity is characterised by adipocyte hypertrophy and accumulation of macrophages in adipose tissue. Currently, adipokines are believed to play a major role in the development of obesity. Both adipocytes and macrophages secrete a number of pro-inflammatory molecules, which are thought to lead to insulin resistance, systemic inflammation, and cardiovascular disease. Adipocytes produce chemotactic factors to recruit monocytes and extracellular matrix molecules to increase the adhesion of macrophages. Hypertrophic adipocytes activate cytokines and chemotactic factors that attract cytotoxic T cells and inflammatory macrophages. The binding of pro-inflammatory factors to their receptors located on adipocytes causes the secretion of cytokines from macrophages and leads to a local, as well as generalised, inflammatory response [6]. Tumour necrosis factor (TNF), an active pro-inflammatory interleukin secreted by adipocytes, plays an important role in stimulating the inflammatory response and insulin resistance. TNF is responsible for tissue and systemic insulin resistance via binding to the insulin receptor subunit and its subsequent modification. Insulin resistance in adipocytes results in enhanced lipolysis, leading to increases in circulating free fatty acid concentrations that induce peripheral insulin resistance. High concentrations of free fatty acids, inflammatory chemotactic factors, and adipokines contribute to the development of systemic insulin resistance associated with obesity [7]. Insulin resistance results in hyperinsulinaemia, common in obese people, and affects weight gain because insulin is one of the hormones that affect appetite control [6].

Review

Central nervous system

Hormonal regulation of energy homeostasis takes place on three levels: in the hypothalamic nuclei, gut and adipose tissue [8]. Food intake stimulants in the central nervous system are orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP). They are produced in several hypothalamic nuclei, but the main place of their synthesis is the arcuate nucleus [9]. It has binding sites for ghrelin, leptin, insulin, and an incomplete blood-brain barrier so that the hormones and nutrients may exert their effects. Peripheral signals that are increased during positive energy balance such as insulin and leptin inhibit hypothalamic NPY expression, whereas ghrelin, growth hormone and glucocorticoids stimulate it [10]. NPY, inducing robust hyperphagia, as well as hormonal and metabolic changes that increase food efficiency, favours fat accretion [11] and energy storage. An increase in hypothalamic NPY-ergic tone decreases energy expenditure in association with decreased body temperature and suppressed thermogenic capacity of brown adipose tissue, stimulates such changes as insulin resistance in skeletal muscle, insulin hyper-responsiveness and increased *de novo* lipogenesis in white adipose tissue, activation of the hypothalamic-pituitary-adrenal axis (HPA), and decreased activity of the hypothalamic-pituitary-thyrotropic, -somatotropic, and -gonadotropic axes. These effects ultimately lead to excessive fat and weight gain [10]. Hypersensitivity of the HPA has been demonstrated in simple obesity resulting in functional hypercortisolaemia and testosterone excess in women, and testosterone deficiency in men. These disorders contribute to increased insulin resistance, and are responsible for the impaired fertility frequently observed in obese individuals. Growth hormone deficiency and hyperprolactinaemia are other changes in endocrine function observed in people who suffer from obesity.

Gut

Ghrelin is a gut hormone that strongly stimulates food intake, and is often called 'the hunger hormone'. Peak secretion has been observed before a meal and its concentration decreases post-prandially. The main site or location of its synthesis is cells in the gastric mucosa [12]. It is also produced in the duodenum, small intestine and caecum, and in small quantities also in the pancreas, pituitary, thyroid, kidneys, testes, and placenta [12–14]. Ghrelin stimulates the synthesis of NPY and AgPR by arcuate nucleus neurons and, through them, increases appetite and food intake [8]. It stimulates gastric motility, enhances adipogenesis and inhibits glucose-stimulated insulin secretion, which may lead to carbohydrate metabolism disorders [12]. Its role in the development of obesity seems to be questionable because a negative correlation has been found between ghrelin and BMI, insulin resistance and weight loss. In addition, mutations in ghrelin, proghrelin and ghrelin receptor molecules have been shown to be poorly correlated with obesity [12, 14].

Adipose tissue

Leptin is the hormone produced primarily by adipocytes and to a lesser extent by other tissues. The level of leptin is proportional to total body fat and is higher in women than in men [15–18]. It is one of the regulators of appetite and weight gain, and acts on the satiety centre through its specific obesity receptors (Ob-R). Leptin is responsible for the inhibition of food intake and increase of energy expenditure and regulates energy homeostasis by informing the central nervous system of body fat reserves [15,19-21]. Unlike ghrelin, mutations in the leptin molecule or its receptor are positively correlated with weight gain. It seems that leptin, a hormone responsible for satiety, may play a key role in the development of obesity. Therefore, later in this article we present current beliefs about the pathogenesis of obesity in various endocrine diseases, with particular emphasis on the role of leptin.

Obesity and thyroid disorders

Thyroid disorders are closely linked to changes in thermoregulation, energy expenditure of non-exercise related activity and weight gain. Some authors have suggested that abnormal thyroid function can contribute to weight gain even when levels of thyroid stimulating hormone (TSH) are normal [22, 23]. Others believe that increased weight is the primary reason for the hormonal disorders observed in thyroid diseases [23–26]. Studies have shown that even slight disturbances in thyroid functioning can lead to the development of obesity. Subclinical and overt hypothyroidism associated with decreased thermogenesis and metabolism often lead to weight gain [27–30]. More than half (54%) of patients report hypothyroidism as the first symptom of weight gain. Often the disease develops slowly — only an insidious onset with a slight increase in weight is observed. From a clinical point of view, it is known that there is a link between obesity and thyroid disease [31]. A routine procedure in an obese person is to assess TSH level to exclude the presence of hypothyroidism. Therefore it seems reasonable to evaluate antithyroid antibodies in obese patients to exclude the presence of autoimmune thyroid disease [23]. Obesity increases susceptibility to infections [32, 33], and thus the number of inflammatory processes, with the participation of adipocytokines, IL-6 and leptin [26]. Increased leptin levels observed in obese people may cause increased susceptibility to autoimmune thyroid injury because it stimulates response lymphocytes Th1 [23, 26]. Helper lymphocytes Th-1 are involved in the cellular immune response. They participate in identifying MHC class II antigens. Unfortunately, there are no studies that assess whether obesity con-
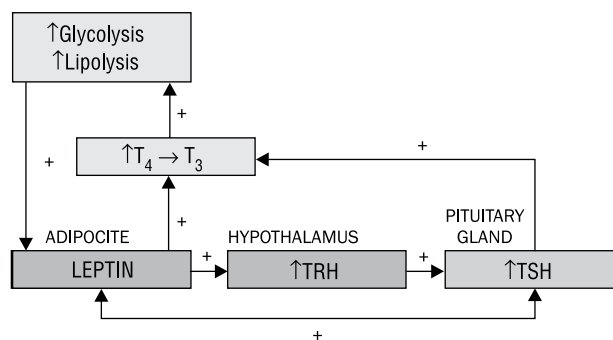

Figure 1. *Feedback mechanisms between leptin and hypothalamic-pituitary-thyroid axis. TRH — thyrotropin releasing hormone; TSH — thyroid-stimulating hormone; T₄ — thyroxin (3,5,3′5′ tetraiodothyronine); T₃ — triiodothyronine (3,5,3′ triiodothyronine)*

Rycina 1. *Mechanizm sprzężenia zwrotnego między leptyną a osią podwzgórzowo-przysadkowo-tarczycową. TRH — tyreoliberyna; TSH — tyreotropina; T4 — tyroksyna (3,5,3′5′ tetrajodotyronina); T3 — trójjodotyronina (3,5,3′ trójjodotyronina)*

tributes significantly to the increasing incidence of thyroid autoimmune diseases.

On the other hand, the secretion of both thyroxin (T_4 — 3,5,3′5′ tetraiodothyronine) and leptin is regulated by negative feedback mechanisms (Fig. 1) [34,35]. Leptin causes an increase of TSH concentrations in serum by stimulating the production of thyrotropin releasing hormone (TRH). It is an important neuroendocrinological regulator of the HPA axis that regulates TRH gene expression [30]. TSH further stimulates the secretion of leptin by fat cells [29, 30, 36–38]. A positive correlation between levels of TSH and BMI was observed, and leptin seems to be a mediator in these relationships. In patients with morbid obesity (BMI > 40 kg/m²), there have been observed increased levels of TSH and leptin, which is probably due to the mechanism described above [23]. Moreover, the progressive accumulation of fat is associated with an increase of T_3 regardless of insulin sensitivity and metabolic parameters cause leptin affects also the thyroid deiodinase activity and stimulates the conversion of T_4 to T_3 in adipocytes [25, 29]. Besides, under the influence of T_3, increases in the processes of glycolysis and lipolysis stimulate leptin synthesis (Fig. 1). It should be noted that higher concentrations of TSH, especially in patients with morbid obesity, may not always result in thyroid dysfunction, but can be an expression of the above-described mechanisms.

Obesity and polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder affecting approximately 6–10% of women of reproductive age [16, 34, 39–41]. It includes
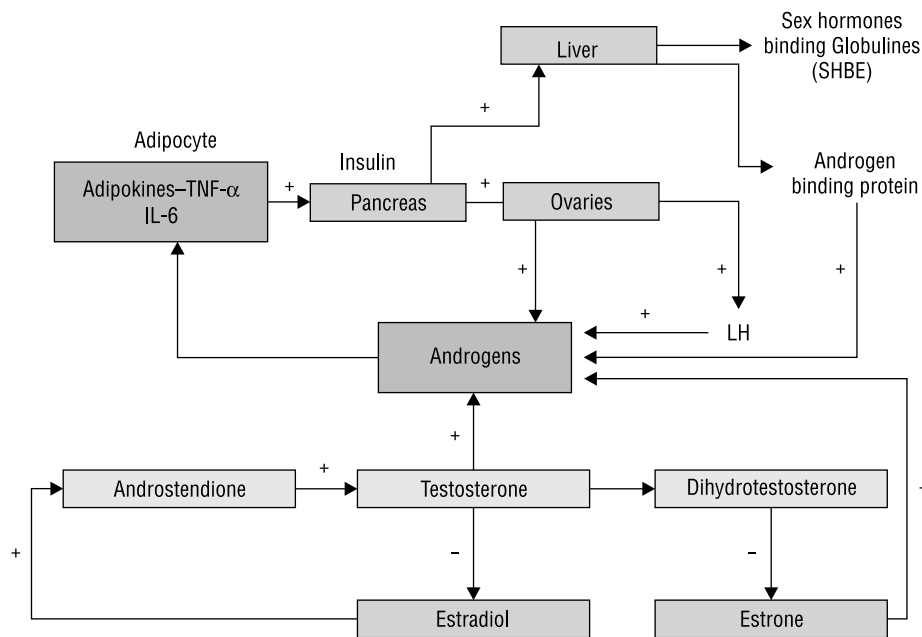
Figure 2. *Role of adipocytes in the development of polycystic ovary syndrome. TNF-α — tumour necrosis factor α; IL-6 — interleukin 6; LH — luteinising hormone*

Rycina 2. *Rola adipocytów w rozwoju zespołu policystycznych jajników. TNF-α — czynnik martwicy guza α; IL-6 — interleukina 6; LH — hormon lutenizujący*

numerous endocrine metabolic disorders, the most characteristic of which is ovarian dysfunction. The principal features of PCOS are menstrual disorders, infertility, hyperandrogenism and obesity. Approximately 60–70% of women with PCOS are obese [34, 42, 43]. Obesity coexists with hyperandrogenism and insulin resistance [43], which occurs in PCOS independent of BMI [16]. A greater than average central fat distribution is also observed in lean women with PCOS [42]. The causes of obesity in PCOS are not clearly defined [34, 41, 44]. Leptin levels correlate positively with the amount of adipose tissue in both women with PCOS and healthy women, so it seems unlikely that leptin plays a significant role in its pathogenesis [16]. It is still unclear whether obesity is a cause or a consequence of PCOS [45]. Insulin resistance and accompanying hyperinsulinaemia that characterise PCOS are important risk factors for metabolic syndrome and the occurrence of cardiovascular complications. Insulin resistance and luteinising hormone increase ovarian hyperandrogenism, reduce the hepatic production of sex hormone binding globulin (SHBG), and decrease insulin-like growth factor 1 (IGF-1) [16, 45, 46]. In addition, obesity increases the genetic predisposition to anovulatory cycles in women with PCOS [16].

Studies looking at the correlation between levels of adipokines in patients with PCOS and the occurrence of obesity show that adiponectin levels are decreased in obese women with PCOS compared to those with normal body weight [47]. A study of 64 women with PCOS showed statistically lower levels of adiponectin compared to women with normal androgen levels [48]. Multivariate regression analysis revealed that free testosterone levels, waist-to-hip ratio (WHR) and age were all adiponectin value-dependent factors [16, 48]. Other studies have also shown lower values of adiponectin in PCOS patients compared to controls [49, 50]. Therefore, it appears that adipocytes play a key role in the development of PCOS (Fig. 2). However, the role of obesity in the pathogenesis of PCOS remains unknown.

Obesity and pituitary-adrenal axis

Cortisol acts within cells in multiple ways — by its actions on the intracellular glucocorticoid receptor, mineralocorticoid receptor, a part of the thyroid/steroid receptor and also by acting as a transcription factor. In adipose tissue, it stimulates the differentiation of pre-adipocytes into adipocytes, hypertrophy of adipocytes and increases lipogenesis [34, 51].

Inactive serum cortisone is converted in the cell into active cortisol by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1). 11β-HSD-1 is an NADPH-dependent enzyme highly expressed in key metabolic tissues including liver, adipose tissue, and the CNS. A two- to three-fold increase in the activity of this enzyme and its mRNA expression in adipose tissue

have been reported in obese people [52–55]. The rise in cortisol levels causes an increase in the number of glucocorticoid receptors in visceral adipose tissue and fatty acid serum concentrations, which drive the development of insulin resistance. Glucocorticoids also increase insulin resistance [56, 57] by stimulating the expression of TNF-α and also cause leptin resistance and increase its concentration in serum [56]. Differentiation and hypertrophy of adipocytes lead to increased production of 11β-HSD-1 and cortisol. In Cushing's syndrome, the chronic effects of glucocorticoids on adipose tissue lead to a characteristic increase in central deposition of fat. This mechanism is probably associated with increased expression of 11β-HSD-1 in visceral adipose tissue compared to subcutaneous tissue [34, 52, 58].

In a metabolic syndrome, phenotypically resembling Cushing's syndrome, elevated serum cortisol concentration was not observed [7, 59]. The explanation for this paradoxical phenomenon could be increased expression of 11β-HSD1 in visceral tissue compared to the subcutaneous tissue responsible for increased dynamics of cortisol change without an increase of its concentration in the serum [55].

Obesity and hypopituitarism

Another cause of obesity of the endocrine type is damage to the pituitary gland. Impaired action of growth hormone (GH) is often associated with an increase in body weight. The mechanisms by which obesity results due to abnormal GH secretion is not completely clear [60]. It is known that through stimulation of IGF-1, GH stimulates pancreatic beta cells to increase insulin secretion and to develop adipose tissue. Recent data clearly supports such a concept, as IGF-1 serves a role in the regulation of β-cell mass, insulin secretion and the regulation of insulin sensitivity [60, 61]. Furthermore, it has been proposed that both leptin and ghrelin play a role in the development of obesity. Ghrelin is an endogenous GH-releasing peptide predominantly produced by the stomach but also in hypothalamic centres, acting on GH-secreting receptors. Ghrelin acts not only as a stimulator of GH secretion, but also as a regulator of energy balance. High concentrations of ghrelin have been found in women with anorexia nervosa. Currently it is known that ghrelin secretion and concentration are regulated by caloric intake — its levels are reduced by a high-fat diet and increased by a low protein diet. Ghrelin has also the ability to stimulate lactotropic and corticotropic pituitary cells. Lower levels of ghrelin have been reported in obesity. However, the exact roles of leptin and ghrelin in pituitary diseases are not yet fully understood.

Conclusions

Due to its widespread prevalence in modern society, obesity is an important and growing globally relevant public health problem. In spite of many research studies being conducted to determine the causes of the emergence and development of obesity, the factors responsible have not yet been clearly identified. Adipose tissue is an important endocrine organ producing biologically active substances with local, peripheral and systemic action, leading to severe endocrine dysfunction. A significant role of adipokines, mainly leptin, has been suggested in this process. However, one can speculate whether the reason for the emergence of endocrinopathies is obesity or whether there is a common factor found in many endocrine diseases that is responsible for the development of obesity. In general, a co-occurrence of endocrine disorders and obesity should always be considered in patients with treatment-resistant obesity.

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