Asprosin and Effects on Glucose Metabolism

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INTRODUCTION

Asprosin is an orexigenic, glycogenic, protein-structured adipokine discovered by Romere et al. in 2016 (1). It is secreted by white adipose tissue in the fasting state and circulates at nanomolar levels. Asprosin is formed as a result of the C-terminal division of profibrils. In Greek, white is translated as aspro, and this is why this new adipokine is called asprosin. Asprosin is encoded by two exons of the gene FBN1 (1). Asprosin activates the cAMP signaling pathway through the unknown G protein-coupled receptor (GPCR) and stimulates appetite in the hypothalamus by providing glucose synthesis and/or release in the liver (2,3). OLFR734, which is the odor receptor, acts as a receptor for asprosin and is thought to increase hepatic glucose production. There is a decrease in gluconeogenesis and an increase in insulin sensitivity in Olfr734 deficiency (2). The purpose of this study is to examine the relationship between asprosin and some public health problems such as obesity and type 2 diabetes.

Effects of Hormones on Appetite Regulation

The brain plays an important role in the regulation of eating behaviors involving hedonic and homeostatic cycles from different aspects (4). Members of the appetite mechanism such as hunger, satiety are regulated by a complex system located in the arcuate nucleus of the hypothalamus. Many peptides are produced from the gastrointestinal tract in

ABSTRACT

Adipokines secreted from adipose tissue, are bioactive substances and have kinds of functions on appetite, energy, lipid, carbohydrate metabolism, regulation of blood pressure, inflammation, etc. One of the adipokines is asprosin discovered in 2016, is secreted by white adipose tissue. This is released during fasting and found in circulating nanomolar levels. Asprosin is encoded by two exons of the gene FBN1 and is known for its effects on many metabolic processes, especially glucose metabolism, and is still under investigation. This study was aimed to investigate the relationship between asprosin and some public health problems such as obesity and type 2 diabetes.

Keywords: Asprosin, Diabetes, Obesity, Glucose metabolism

ÖZ


Anahtar Sözcüklər: Asprosin, Diyabet, Obezite, Glikoz metabolizması

INTRODUCTION

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Effects of Hormones on Appetite Regulation

The brain plays an important role in the regulation of eating behaviors involving hedonic and homeostatic cycles from different aspects (4). Members of the appetite mechanism such as hunger, satiety are regulated by a complex system located in the arcuate nucleus of the hypothalamus. Many peptides are produced from the gastrointestinal tract in

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response to starvation and nutrition, and these peptides directly affect the hypothalamus (5). Peripheral peptides such as cholecystokinin, peptide YY, pancreatic polypeptide, glucagon-like peptide-1, and oxyntomodulin transmit saturation signals to the brain, and ghrelin transmits fasting signals (6). While it is thought that leptin was originally synthesized only from white adipose tissue, some studies suggest that it was synthesized from many tissues such as brown adipose tissue, hypothalamus, pituitary gland, gastric epithelium, and skeletal muscle (7). It is a 167-amino acid peptide, and leptin levels that affect the appetite mechanism are positively proportional to the body fat percentage. The level of leptin changes at different times of the day. It reaches at the highest level between midnight and morning and gradually decreases in the afternoon (8,9). Leptin has been shown to cause low inflammatory mediator concentrations in some studies and stimulate cell growth in damaged brain areas of both obese and underweight individuals. Thus, it is suggested that it can accelerate cancer and some malignancies (10).

Ghrelin is an one of the orexigenic hormone effecting on blood glucose level (11). It was detected in the stomachs of rats and humans in 1999 by Kojima et al. (12). However, its target in the brain is growth hormone-releasing hormone (GHRH). Although ghrelin is mostly secreted in the fundus or upper part of the stomach, it is also secreted from tissues such as small intestine, pineal gland, hypothalamus, lung, immune cells, ovary, and testicle. The level of ghrelin in the blood increases just before eating and when fasting, and it decreases after food intake (11). The active form of ghrelin has 28 amino acids. But, it needs a 117-amino acid precursor named preproghrelin to activate (12).

Growth hormone (GH), one of the anabolic hormones, is found in various types of immune cells. The GH performs many functions through the release of insulin-like growth factor 1 (IGF-1). It is synthesized in the hematopoietic system and pituitary gland (13).

Neuropeptide Y (NPY) is one of the peptides, having effect on appetite mechanism. Family of NPY consists of NPY, peptide YY (PYY), pancreatic polypeptide (PP), and peptide Y (PY) polypeptides (14). NPY consists of 36 amino acids and is the most abundant polypeptide in the mammalian nervous system. (15). This peptide, which has an orexigenic feature, plays an important role in the regulation of eating behaviors and works as a leptin antagonist.

Glucagon-like peptide 1 (GLP-1) is a residual product of preproglucagon gene. It is expressed in α cells of the pancreas, L cells of the small intestine, neurons in the tail of the brain stem, and the hypothalamus (16). GLP-1 is secreted biphasically in response to the food intake. The early first response occurs postprandially in minutes and lasts up to 30 minutes, and the second response can last hours later (17). GLP-1 affects gastrointestinal motility through both peripheral and central receptors. The vagus nerve is thought to effectively mediate these effects on the circular muscles of the intestine (18,19).

Oxyntomodulin (OXM) is a 37-amino acid peptide hormone secreted in the small intestine along with GLP-1 in proportion to food intake (20). OXM is mainly produced in the endocrine L cells of gut by prohormone convertase 1/3 by the process of the proglucagon precursor (21-23). GLP-1 and OXM act on satiety signals and energy expenditure. It reduces nutrient intake, body weight, and adiposity. Its effects on energy balance are realized through the hypothalamus and brainstem (24).

Agouti-related peptide (AGRP) was discovered in 1997 and has important functions in energy metabolism. It is thought to play a role in pregnancy-related hyperphagia (25). It is one of the orexigenic peptides. Decreased food intake and low level of AGRP were associated with some diseases, such as Prader-Willi syndrome in the newborn (26). AGRP affects fatty acid synthesis, leptin expression, and blocks the melanin-concentrating hormone (MCH)-dependent effect of leptin (27-29). In addition to its effect on adipocytes, AGRP has a paracrine role in adrenal gland function by inhibiting corticosteroid production by alpha-melanocyte-stimulating hormone (α—MSH) (30,31). There are few studies on AGRP, and the results contradict each other. Some studies report that plasma AGRP levels are higher in obese patients compare to healthy individuals (32).

MCH, one of the orexigenic hypothalamic peptide hormones that stimulate growth hormone secretion, includes 19-amino acid (13). It causes an increase in food intake in mammals and contributes to the maintenance of energy, heat, reproductive functions, biological rhythm balance, and endocrine homeostasis (33). It has been suggested in studies that MCH receptor (MCHR) antagonists can play an effective role in the treatment of obesity, anxiety, and depression (34,35).

Nesfatin-1 is a peptide with an anorexigenic effect independent of leptin. It suppresses food intake by a mechanism dependent on the melanocortin 3/4 receptor (36). While nesfatin-1 works as a agonist with leptin that is found low in obese people, it does so antagonist with ghrelin (37,38). It is also found in peripheral tissues such as adipose tissue, stomach, pancreatic islets, liver, testicles, and especially, brain tissues (39,40). High levels of nesfatin-1 in patients with mental disorder such as depression suggest
the possibility of a relationship between nesfatin-1 and these diseases (41).

**Asprosin**

Asprosin is an orexigenic hormone that activates AGRP neurons and increases nutrient intake and body weight in the case of starvation (3). A genetic deficiency in asprosin causes decreased appetite and an increase in lean mass. Asprosin level is low in individuals with congenital progeroid syndrome (NPS), and this is associated with decreased subcutaneous adipose tissue and very low body mass index (BMI) (3).

**Asprosin and Obesity**

Obesity is one of the most important health problems and diagnosed with cut-off values of BMI. BMI is categorized as low body weight (weak), healthy, slightly overweight, and obese according to the limit values created by the World Health Organization (WHO). If the BMI cut-off value is <18.5 kg/m², it is defined as low body weight (weak), between 18.5 and 24.9 kg/m² healthy (normal), and between 25 and 29.9 kg/m² overweight Obesity is a risk factor for many diseases such as cardiovascular diseases, stroke, diabetes, infertility, and obstructive sleep apnea syndrome. (42).

Obesity, giving rise to death 4.7 million individuals worldwide in 2017, was the fifth leading cause of death in 2017. In Turkey, obesity ranks third in the cause of death according to 2017 data (43). Studies show that asprosin can be a good indicator of obesity (44-47). In a study conducted in 2018, 20 healthy and adult male rats were divided into two groups. Two groups included the control group and the intervention group, were formed by subcutaneous injection of asprosin (30 μg daily for 10 days). The effects of asprosin on body weight, BMI, serum glucose, insulin, insulin resistance, and lipid profiles were observed and analyzed. The subcutaneous asprosin injection group was shown with significantly increased body weight and serum glucose levels compared to the control group (44).

Childhood obesity is one of the most important and serious public health problems in the 21st century. The number of overweight children under the age of 5 was found to be around 42 million worldwide in 2010. Nearly, 35 million of these children live in developing countries. The main causes of childhood obesity are physical inactivity, packaged high-calorie foods, sweetened beverage consumption, portion size, and environmental factors (45).

In a study carried out by Silistre and Hatipoğlu in 2020, 44 obese, 54 underweight, and 60 ideal weight (healthy) children were evaluated for serum asprosin levels. The study results showed a significantly higher level of serum asprosin in obese children as compared to children with normal body weight (46). Plasma asprosin levels of 40 healthy and 47 obese children were measured in another study conducted in 2019. Obese children had significantly lower asprosin levels compared to healthy children. As for obese children, it was observed that boys have lower asprosin levels than girls (47).

Another study aimed to assess the relationship between asprosin levels of obese and non-obese. Participants of the study include 117 bariatric operated patients that had BMI > 35 kg/m² and 57 non-obese ones. The asprosin levels of obese were found to be significantly higher than non-obese individuals. Asprosin levels significantly decreased 6 months after the bariatric surgery (162.2 ± 169.1 ng/mL). There was no relationship between asprosin and serum glucose levels (48). Hu et al. conducted a study that serum asprosin levels were evaluated in anorexic individuals (n: 46) and healthy control group (n=47), who did not receive medical treatment in 2020. Significantly higher asprosin levels were observed in the plasma of anorexic patients compared to control group. The increasing in asprosin levels of the anorectic participants might be attributed to the compensation of energy deficiency (49).

**Asprosin and Diabetes Mellitus**

Diabetes is the most common disease seen in all ages in different forms. According to the WHO data, in 2014, 422 million adults have diabetes all over the world, and nearly half of them are unaware of their disease (50). This figure will increase to about 642 million in 2040 (51). Diabetes is classified into four categories: type 2 diabetes, type 1 diabetes, gestational diabetes, and specific types of diabetes because of other causes. In all these types of diabetes, 90% of the cells of the pancreas have problems with insulin secretion as a result of autoimmune damage (52).

Groener et al. conducted a study using an intravenous glucose tolerance test in order to determining hyperglycemia. Afterwards, the hyperinsulinemia clamp test was done for checking hypoglycemia (53). Fifteen type 1 diabetics with and without hypoglycemia awareness were included. There was no difference between the asprosin levels of individuals with and without hypoglycemia awareness. However, those with insulin resistance, high liver stiffness, high low-density lipoprotein (LDL), and low high-density lipoprotein during hypoglycemia asprosin was not found high in them. Insulin resistance and changes in the liver have been seen in people with nonalcoholic fatty liver disease and type 1 diabetes. This resulted in increased asprosin levels and a vestigial asprosin response in hypoglycemia (53).
Insulin Resistance

The pathogenesis of type 2 diabetes mostly include insulin resistance. Disruption of insulin signaling leads to the formation of metabolic syndrome and insulin resistance (54,55). Insulin resistance is defined as a decrease in the response to insulin stimulation in various organs (56). Although β-cell dysfunction is the cause of diabetes, insulin resistance in skeletal muscle causes β-cell apoptosis because of obesity (57). Skeletal muscle performs glucose uptake under the influence of insulin in the case of postmeal hyperglycemia. Therefore, it is important to maintain skeletal muscle insulin sensitivity in the management of type 2 diabetes (58). Hepatic gluconeogenesis plays a crucial role in maintaining glucose homeostasis to meet energy demands during fasting and also contribute to developing type 2 diabetes (59,60).

Asprosin can cause insulin resistance and diabetes, and indirectly leads to gluconeogenesis. The relationship between some biochemical parameters and plasma asprosin levels in healthy women with type 2 diabetes and polycystic ovary syndrome (PCOS) was examined in a study published in 2018. Plasma asprosin levels of participants with type 2 diabetes and PCOS were reported to be significantly higher than healthy participants. Plasma asprosin levels of participants with type 2 diabetes were found to be significantly higher than that of PCOS participants. A significant correlation was observed between plasma asprosin levels and fasting glucose, hemoglobin A1c (HbA1c), and homeostasis model assessment of insulin resistance (HOMA-IR) parameters in participants of both type 2 diabetic and PCOS. At the end of this study, it was assumed that serum asprosin levels can be used as a marker for some metabolic diseases in the future (61).

Zhang et al. conducted a study that including 60 type 2 diabetic and 60 non-diabetic (with normal glucose tolerance) individuals, was intended to assess serum asprosin levels of participants. Both fasting and postprandial asprosin levels were found to be higher in type 2 diabetics. Postprandial asprosin levels in individuals with normal glucose tolerance were found lower than fasting asprosin levels (62).

In another study, serum asprosin levels of diabetic individuals, including 97 newly diagnosed patients with type 2 diabetes and 97 healthy individuals, were found that asprosin levels of diabetics was higher than healthy controls. In this study tip 2 diabetes has also been associated with asprosin, insulin resistance, and the total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio (atherosclerotic risk factor of cardiovascular disease) in diabetics (63). Zhang et al. conducted a study in 2019 that included 84 diabetic and 86 healthy individuals. As a result of this study, diabetics had higher serum asprosin levels than controls. It was showed that asprosin was correlated independently with fasting glucose and triglycerides in type 2 diabetic individuals (64).

Asprosin and Heart Diseases

Ischemic heart disease (IHD) is caused by a limited blood supply to the heart muscle. The cause of IHD is coronary blood flow reduction caused by coronary artery atherosclerosis in more than 95% of patients (65). The role of asprosin is debated in IHD determination.

Serum and tissue asprosin levels in kidney, heart, stomach, testicle, and brain were determined in a study conducted in 2020. The experimental group consisted of diabetic rats with an additional dose of streptozotocin (50 mg/kg). Asprosin was detected in hepatocytes in the liver, cortical distal tubule cells in the kidney, cardiomyocytes in the heart, gastric fundus surface epithelial cells, interstitial Leydig cells in the testicles, and cortical neurons in the brain at the end of the study. While asprosin levels in the kidney, liver, heart tissues of diabetic rats were decreased, asprosin levels of stomach and testicular tissues levels were increased. Besides, asprosin levels of brain tissue was not changed in this study. (66).

It was concluded in 2017 that asprosin can be considered as a biomarker to predict the severity of unstable angina pectoris, which has not yet found a clinically useful marker (67). Zhang et al. conducted a study in 2019, where mesenchymal stromal cells were injected into heart samples with an in vivo infarction and then treated with asprosin. Cardiac function and fibrosis were evaluated at 4 weeks after myocardial infarction (MI) induction, and 1 week after induction outside of mesenchymal stromal cells. The study showed that asprosin regulates the function of mesenchymal stromal cells, enhances mesenchymal stroma therapy for IHD, and inhibit reactive oxygen species (68).

CONCLUSION

There has been a growing body of literature that examines effects of asprosin on some public health issues. It is thought that asprosin has effect on gluconeogenesis and hepatic glucose releasing. Thus, it leads to insulin resistance and diabetes.

Also, it may have protective role on cardiovascular disorder and be used as a biomarker in the future. Studies should related to the treatment of obesity, insulin resistance, diabetes and other common health disases as well as include asprosin more effectively. More informative and large-scale studies on asprosin are needed.
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