

Regulatory Peptide Nesfatin-1 and its Relationship with Metabolic Syndrome

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ABSTRACT

Metabolic syndrome is associated with a group of conditions abdominal obesity, high triglyceride levels, reduction in low-density lipoprotein, increased blood pressure, and increased fasting blood glucose. Hence, it poses a risk for type 2 diabetes and cardiovascular diseases. The prevalence of metabolic syndrome increases with age. Nesfatin-1, which affects different systems, has recently been discovered as a regulatory peptide molecule. With the discovery of nesfatin-1, it has been reported to inhibit the intake of nutrients and have significant regulatory effects on energy metabolism. As nesfatin-1 is present in both central and peripheral tissues, it is thought to have many functions. In addition to its suppressive effect on food intake, nesfatin-1 has also been reported to have an effect on the blood glucose level for regulating cardiac functions and affecting obesity by providing weight loss. Considering the effects of nesfatin-1, it may be associated with metabolic syndrome.

Keywords: Metabolic syndrome, Nesfatin-1, obesity, peptide

Introduction

Today, obesity has become a public health problem affecting more than one billion people worldwide. It poses an increased risk of insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia, hypertension, atherosclerosis and cardiovascular diseases. The presence of these abnormalities along with obesity is called insulin resistance syndrome or metabolic syndrome [1]. Metabolic syndrome increases the risk of type 2 diabetes and cardiovascular disease [2]. Almost one-third of the adult population in the world and in our country has metabolic syndrome. The rise in the prevalence of metabolic syndrome with age increases morbidity and mortality, and therefore metabolic syndrome has become a growing social health problem [3]. The mechanism of the development of metabolic syndrome is not fully understood; however, it has recently been shown that some new regulatory adipokines may play a key role in the pathogenesis of metabolic syndrome. Adipokines are secreted in the adipose tissue and have significant endocrine functions. Among these adipokines, nesfatin-1, retinol-binding protein 4, omentin-1, vaspin, and progranulin are secreted in the adipose tissues through a broad secretion network and participate in the pathologies directly related to metabolic syndrome [1, 4].

Nesfatin-1 is secreted by the neurons (hypothalamic paraventricular nucleus, supraoptic nucleus, arcuate nucleus, lateral hypothalamic area, and spinal cord) and peripheral tissues (pancreas, liver, subcutaneous and visceral fat tissues, brown adipose tissue, and skeletal muscles) [5]. As the secretion is distributed in the body, nesfatin-1 is thought to affect many functions. Previous studies have reported that nesfatin-1 has regulatory effects on energy metabolism through suppression of food intake. In addition, it has been reported that nesfatin-1 regulates cardiac functions, decreases blood glucose levels, acts as a neuroendocrine regulator, and causes weight loss along with reduction in energy intake [6]. The present study analyzed the relation of nesfatin-1 with metabolic syndrome and its components.

Definition of Metabolic Syndrome and its Components

Metabolic syndrome is defined as an abnormality accompanied by a decrease in high-density lipoprotein, hypertension along with the increase in triglyceride (TG), insulin resistance, hyperglycemia, and abdominal obesity [7]. The prevalence of metabolic syndrome gradually

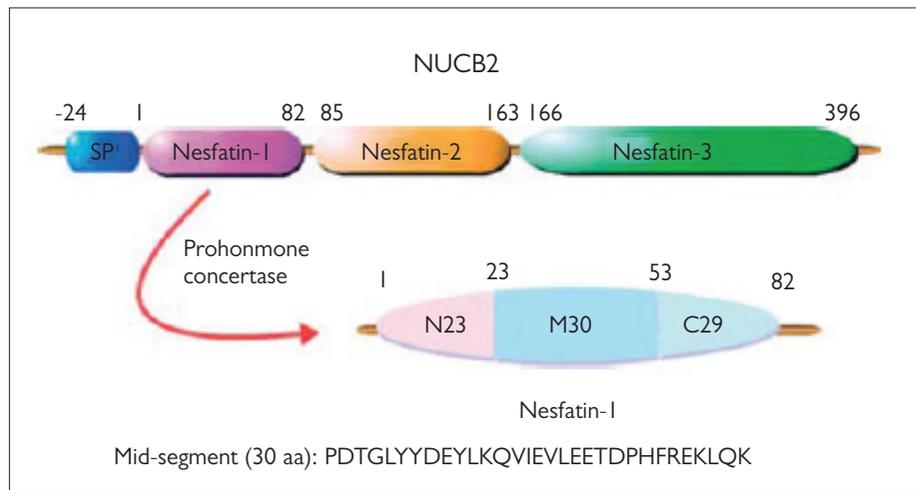


Figure 1. Structure of NUCB2 protein and Nesfatin-1 formation

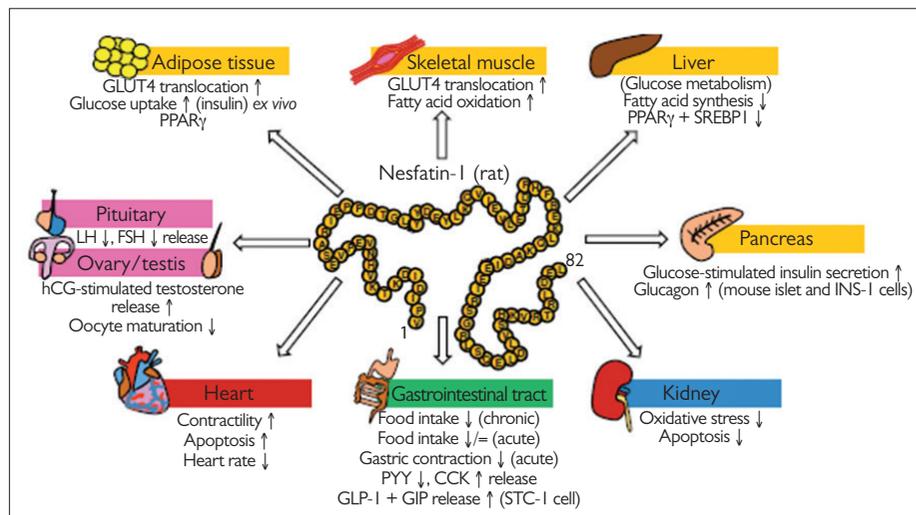


Figure 2. Nesfatin-1 and its effects

CCK: cholecystokinin; FSH: follicle stimulating hormone; GLP-1: glucagon-like peptide 1; GLUT4: glucose transporter 4; hCG: human chorionadotropin; LH: luteinizing hormone; PPAR γ : peroxisome proliferator-activated receptor gamma; PYY: peptide YY; SREBP1: sterol-regulatory element-binding protein

increases with the increase in the consumption of foods containing high fat and sugar levels, inadequate physical activity, and increased prevalence of central obesity [8]. Metabolic syndrome is a metabolic disease caused by a group of diseases adding to each other [9]. Abdominal obesity, atherogenic dyslipidemia, high blood pressure, and insulin-resistant glucose intolerance are the components of metabolic syndrome [10].

Discovery and Structure of Nesfatin-1

In 2006, Oh-I et al. [11] first described nesfatin-1 as a peptide consisting of 82 amino acids. In this study, the protein nucleobindin 2 (NUCB2) secreted in the hypothalamic nuclei of mice was analyzed. This protein consists of 396 amino acids. The NUCB2 prohormone is divided into three components as a result of proteolytic processes. The N-terminal frag-

ment constitutes nesfatin-1 (1-82), and the C-terminal fragment constitutes nesfatin-2 (85-163) and nesfatin-3 (166-396). Among the three peptides of NUCB2 prohormone, only nesfatin-1 was found to have an effect on food intake and appetite control [11, 12]. However, the functions of nesfatin-2 and nesfatin-3 are not yet known [13].

The structure of nesfatin-1 consists of three parts. The first part begins from the N-terminal end and continues to the 23rd amino acid and is called N23. The second part includes amino acids between 23 and 53 and is defined as M30. The third part includes amino acids between 53 and 82 toward the carboxy terminal and is called C29. M30 is reported to be effective in the food intake and appetite control [13]. Figure 1 shows the structure of NUCB2 protein and the formation of nesfatin-1 [14].

Nesfatin-1 Expression

The mRNA and protein expression of NUCB2 have been detected in rats in the lateral hypothalamic area as well as in the arcuate nucleus, para ventricular nucleus, and supraoptic nucleus of the brain located in the region responsible for nutrition. The expression patterns have been confirmed by further studies, and NUCB2/nesfatin-1 expression is found to be present in the insular cortex, central amygdaloid nucleus, periventricular nucleus, tubular hypothalamic area, dorsomedial hypothalamic nucleus, Edinger-Westphal nucleus, and ventrolateral medulla. In the first study describing nesfatin-1, it was reported to be located in the cerebrospinal fluid and hypothalamic nuclei. However, in subsequent studies, it was also found in different peripheral tissues of rats, such as the anterior pituitary gland, adipose tissue, heart, pancreas, gastric mucosa, and testis. In addition, NUCB2 mRNA expression in the stomach was found to be ten-fold higher compared to the brain. In the pancreas, NUCB2/nesfatin-1 is found in the cells of the islets of Langerhans together with insulin. When the widespread peripheral distribution of NUCB2/nesfatin-1 was examined, it indicated homeostatic functions in addition to modulation of food intake [15].

Effect Mechanism of Nesfatin-1

Nesfatin-1 shows anorexigenic activity upon an intracerebroventricular application in the hypothalamus. Intracerebroventricular injection of nesfatin-1 significantly stimulates food intake. The central anorexigenic function induced by nesfatin-1 is achieved with the help of a mechanism dependent on the melanocortin $\frac{3}{4}$ receptor, independent of the release of leptin in the hypothalamus [16, 17]. The immunoreactivity of nesfatin-1 is localized in the forebrain and posterior brain nuclei along with various neurotransmitters regulating pituitary hormone and stress. Thus, nesfatin-1 has a variety of potentially extended biological effects, including nutritional intake, as well as neuroendocrine regulation, pain, stress, and autonomic control of internal organs [18].

In addition, studies have shown some other central effects of nesfatin-1 (Figure 2) [19]. Along with the anorexigenic effects of nesfatin-1 injection into the brain, it reduces gastric emptying and gastric motility. When nesfatin-1 was injected into the third cerebral ventricle, it was observed to improve peripheral glucose intake and insulin sensitivity in rats. Furthermore, there is evidence that it stimulates body temperature by activating sympathetic nerve activity and plays a role in the regulation of cardiovascular function [20].

Relationship between Nesfatin-I and Metabolic Syndrome

Nesfatin-I has been reported to have effects on obesity through food intake, glucose metabolism, cardiac functions, and weight loss [6]. These effects of nesfatin-I were investigated in the studies by associating it with metabolic syndrome and its components. In a study by Algül et al. [21], serum nesfatin-I level was shown to be 0.885 ± 0.01 ng/mL in individuals with metabolic syndrome and 1.094 ± 0.07 ng/mL in the control group. In another study on rats with metabolic syndrome as a result of fructose exposure, serum nesfatin-I levels in both male and female rats with metabolic syndrome were found to be higher compared to the control group [22]. In a study by Aksu et al. [23], patients with obstructive sleep apnea syndrome (OSAS) were divided into two groups as those with and without metabolic syndrome. Serum nesfatin-I levels were found to be lower in individuals with metabolic syndrome (3.97 ± 1.42 pg/mL) than in those without metabolic syndrome (4.98 ± 1.84 pg/mL). The data obtained from the studies suggest that nesfatin-I plays a role in the pathogenesis of metabolic syndrome.

Relationship Between Nesfatin-I and Metabolic Syndrome Components

Relationship Between Nesfatin-I and Obesity

As nesfatin-I has potential effects on nutrient intake and energy metabolism, several studies have been conducted to investigate the relationship between NUCB2/nesfatin-I and obesity for identifying its potential effects on the regulation of body weight [17]. In a study investigating the relationship of the nucleotide polymorphism of the NUCB2 gene with obesity, 1049 obese and 315 normal individuals were included. Nucleotide polymorphism of the NUCB2 gene was found to be related to body mass index (BMI), body weight, and lean body tissue. It was concluded that obesity and NUCB2 gene polymorphisms may play an important role in the protection of obesity in males and may have an effect on energy metabolism [24]. In another study conducted on obesity, seven variants of the NUCB2 gene were observed in a population of 471 obese children and adolescents. In such a situation, NUCB2/nesfatin-I can cause obesity to develop by bringing about possible changes in the brain physiology [25]. In an animal study on obesity, it was thought that the decrease in NUCB2 mRNA and protein levels in the hypothalamus contributed to hyperphagia seen in obese diabetic mice [26]. Considering these results, NUCB2/nesfatin-I expression may increase the risk of developing obesity in case of genetic mutations [15].

Individuals diagnosed with anorexia nervosa and who had chronic nutritional intake restrictions were found to have significantly lower plasma nesfatin-I levels compared to healthy controls [27]. Plasma nesfatin-I levels have been shown to be associated with BMI, insulin resistance, fasting blood glucose and fasting insulin levels, and body weight and fat mass [28, 29]. The data indicate that nesfatin-I derived especially from fat is crucial for the metabolism and nutrient intake [30]. In a study conducted by Başar et al. [31], a negative correlation was found between serum nesfatin-I levels and fasting blood glucose and BMI. Serum nesfatin-I concentrations in obese individuals were found to be significantly lower compared to non-obese individuals. Similar results were obtained in another study investigating the relationship between obesity and nesfatin-I [32]. Obese individuals were found to have lower fasting nesfatin-I levels than non-obese individuals. BMI, body fat percentage, body fat weight, and blood glucose levels showed a negative correlation with nesfatin-I levels [32].

In several studies, it was revealed that NUCB2/nesfatin-I plasma levels positively correlated with BMI, and an increase was observed in the number of gastric NUCB2/nesfatin-I-expressing cells in obese patients with increased BMI [33, 34]. It is assumed that there is a connection between body weight and NUCB2/nesfatin-I, but the results obtained from the studies vary [20].

Obesity is a risk factor for many diseases and importantly for OSAS [35]. Obesity is observed in 60%-70% of patients with OSAS [36]. Plasma nesfatin-I levels were investigated in obesity-related diseases after the relationship between obstructive obesity and nesfatin-I was suggested. In a study, plasma nesfatin-I levels were found to be significantly lower in OSAS patients than in healthy controls. Moreover, there was a negative correlation between apnea hypopnea index and nesfatin-I levels, and a negative correlation was found between neck circumference and nesfatin-I levels in OSAS patients [37]. Similar results were obtained in another study, and serum nesfatin-I levels were found to be significantly lower in patients with OSAS [38]. In this study, the nesfatin-I levels in individuals with severe OSAS were lower than those with mild and moderate OSAS. A negative correlation was found between serum nesfatin-I levels and BMI, waist-hip ratio, Homeostatic Model Assessment for Insulin Resistance score, and apnea hypopnea index. Contrasting results were obtained in another study; no significant relationship was found between the nesfatin-I levels of individuals with mild, moderate, and severe OSAS and that of healthy controls

[23]. It is observed that there is a relationship between low nesfatin-I level and OSAS. In the light of future research, the relationship between nesfatin-I, obesity, and OSAS will be clearly understood.

Relationship between Nesfatin-I and Glucose Metabolism

In addition to regulating nutrient intake, NUCB2/nesfatin-I plays a role in the regulation of glucose metabolism, which is justified by the presence of NUCB2/nesfatin-I and insulin together in the human and rodent pancreas. Following glucose release, NUCB2/nesfatin-I has been shown to be released from the pancreatic cells. In vitro studies have shown that nesfatin-I increases the expression of pre-proinsulin mRNA and also increases glucose-induced insulin secretion by stimulating calcium flow involving the L-type channels [15].

In a study investigating the effect of nesfatin-I on glucose metabolism, the antihyperglycemic effect of nesfatin-I has been demonstrated. Intravenous administration of nesfatin-I significantly reduced blood glucose levels in hyperglycemic db/db mice (mimics of the type 2 diabetes model). In the same study, intracerebroventricular administration of nesfatin-I to db/db mice prevented food intake, but the high blood glucose levels were not affected. The results revealed that the anti-hyperglycemic effect of nesfatin-I was dependent on peripheral administration, time, dose, and insulin [39].

In another study, it was observed that the blood glucose levels decreased as a result of continuous subcutaneous nesfatin-I infusion into mice during an oral glucose tolerance test (OGTT). In the same study, it was also seen that infusion of intracerebroventricular nesfatin-I did not have an effect on blood glucose levels. These findings suggest that peripherally administered nesfatin-I rather than centrally administered nesfatin-I was effective in glucose metabolism [40]. In male Fischer 344 rats, the continuous subcutaneous infusion of nesfatin-I resulted in an increase in the circulating insulin level and a decrease in the glucagon level in the first 30 minutes of OGTT. These findings suggest that nesfatin-I affects insulin sensitivity [41].

In a study conducted in patients with type 2 diabetes, plasma nesfatin-I levels decreased in patients with type 2 diabetes compared to healthy controls or patients with type 1 diabetes [42]. In another study, serum nesfatin-I levels were found to be lower in pregnant women with gestational diabetes mellitus than in healthy controls [43].

Relationship between Nesfatin-I and Cardiovascular System

Nesfatin-I plays a role in the regulation of cardiovascular function. Nesfatin-I distribution at the central level shows that it may play an important role in the regulation of cardiovascular functions and mechanisms that contribute to cardiovascular homeostasis [44]. For example, intra-cerebrospinal injection of nesfatin-I increases arterial blood pressure. Nesfatin-I, which is localized with oxytocin in the paraventricular nucleus, stimulates the release of oxytocin by depolarization. It is also known that nesfatin-I activates the melanocortin pathway through oxytocin. Therefore, the hypertensive effect is thought to be related to either central oxytocin or melanocortin pathways [45].

In an animal study, nesfatin-I was administered intravenously and this was shown to cause vasoconstriction and high blood pressure, inhibiting nitric oxide production. Nesfatin-I inhibits the sodium nitroprusside-induced relaxation in rat isolated mesenteric artery. Intravenous administration of nesfatin-I produces a potentially hypertensive effect both in the central nervous and by modulating arterial resistance [46]. When 40 hypertensive patients and 40 healthy control patients were compared, the plasma nesfatin-I levels were found to be higher in the hypertensive patients [47]. In another study, it has been shown that high plasma nesfatin-I levels may be associated with increased systolic and diastolic blood pressure values and increased heart rate in polycystic ovary syndrome [48]. In an in vitro study, the mRNA of nesfatin-I and its precursor NUCB2 were detected in rat hearts. In the same study, it was revealed that nesfatin-I levels decreased in the heart tissue under an ischemia/reperfusion injury. Hence, it has been concluded that nesfatin-I causes a significant decrease in infarction size against ischemia/reperfusion injury and induces functional recovery after ischemic contraction [49].

Relationship between Nesfatin-I and Lipid Metabolism

A recent study has shown that in addition to the involvement in insulin and glucose metabolism, nesfatin-I plays a role in the regulation of peripheral lipid accumulation and hepatic lipid metabolism in mice. In the study, it was observed that chronic infusion of nesfatin-I decreased plasma TG level in mice fed with normal or a high-fat diet. Moreover, compared to the control group, the infusion of nesfatin-I reduced the diameter of lipid droplets, infiltration of inflammatory cells, and epididymal fat mass and decreased the plasma cholesterol level in mice fed with a high-fat diet. The levels of lipogenesis-related enzymes,

such as peroxisome proliferator-activated receptor gamma, in the epididymal fat mass of mice fed with a high-fat diet were significantly reduced. In vitro experiments with primary hepatocytes showed that the stimulation with nesfatin-I reduced the expression lipogenesis-related and β oxidation-induced genes. Furthermore, reduced hepatic lipid content and decreased lipid droplet size were noted [50].

Conclusion

The data obtained from the studies indicate that nesfatin-I is associated with metabolic syndrome and its components. The studies examining the relationship between obesity and nesfatin-I have revealed that plasma nesfatin-I levels are associated with BMI, body weight, and fat mass. The peripheral application of nesfatin-I has been proven to have an antihyperglycemic effect on glucose metabolism. When the effects of nesfatin-I on the cardiovascular system were examined, nesfatin-I has shown to affect blood pressure, and it plays a role in the regulation of peripheral lipid accumulation and hepatic lipid metabolism. Therefore, nesfatin-I plays several roles as a regulator in the metabolism and to has an effect on metabolic syndrome and its components. Nesfatin-I is thought to be a pioneer in the diagnosis and treatment of diseases, such as metabolic syndrome, obesity, diabetes, and cardiovascular diseases.

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