



Nesfatin-1 As a Novel Appetite-Controlling Peptide: Will Obesity Be History?

İştah Kontrolünde Yeni Bir Peptid Olarak Nesfatin-1: Obezite Tarih mi Olacak?

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Abstract

In this study, we aimed to determine the role of a novel peptide – nesfatin 1- in appetite control and define its anorectic mechanism in order to reveal whether it can be used in fight against obesity. We reviewed the articles in the literature investigating the structure, mechanism of effect and experimental usefulness of nesfatin-1. We entered the word "nesfatin" to medical databases and reviewed the literature. Administration of nesfatin-1 maintains a significant reduce in food intake. Its effectiveness in rats is proven. More and more, new researches are in progress to determine its exact mechanism of effect. Nesfatin-1 is a satiety agent. However, use of nesfatin-1 as an anti-obesity agent in humans remains an unclarified field and needs further investigations. *Türk Jem 2015; 19: 60-64*

Key words: Nesfatin-1, obesity, endocrine effects, sympathetic activity

Conflicts of Interest: The authors reported no conflict of interest related to this article.

Özet

Biz bu çalışmada yeni bir peptid olan nesfatin-1'in iştah kontrolündeki rolünü belirlemeyi ve obezite ile mücadelede kullanılabilirliğini ortaya koymak üzere anorektik mekanizmasını tanımlamayı hedefledik. Literatürde nesfatin-1'in yapısını, etki mekanizmasını ve deneysel yararlılığını araştıran makaleleri derledik. "Nesfatin" kelimesini tıbbi veritabanlarına girerek literatürü gözden geçirdik. Nesfatin-1 uygulaması yiyecek alımında belirgin bir düşüşe neden olmaktadır. Sıçanlardaki etkinliği ispatlanmıştır. Etki mekanizmasının tam olarak ortaya konulması için yeni çalışmalar artarak devam etmektedir. Nesfatin-1 doygunluk verici bir ajandır. Ne var ki, nesfatin-1'in anti-obezite ajanı olarak insanlarda kullanımı halen belirsiz bir alandır ve ileri çalışmalar gerekmektedir. *Türk Jem 2015; 19: 60-64*

Anahtar kelimeler: Nesfatin-1, obezite, endokrin etkiler, sempatik aktivite

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemiştir.

Introduction

Obesity occurs as a result of an imbalance between energy intake and expenditure (1). According to the reports of the World Health Organisation (WHO), obesity is the leading cause of mortality and morbidity worldwide (2). Obesity increases among children and adults in many countries all over the world. In a study performed in the United States, it was reported that, during the six years period from 1999 to 2004, prevalence of overweight among children and adolescents and obesity among men have increased significantly. The prevalence of extreme obesity was found to be 4.8% (3). Similarly, in Great Britain, the prevalence of obesity among adults almost tripled between 1980 and 2002 (4). In China, for example, the prevalence of obesity among preschool children living in cities increased from 1.5% to 12.6% between

1989 and 1997 (5). Obesity may effect the expression of adipose-tissue derived proteins. Obesity and dysmetabolic states are associated with altered levels of circulating cytokines, insulin, and corticosteroids, which regulate production of certain adipokines (1). Nesfatin-1 is a recently discovered peptide that may act as a satiety agent (6). It was first described by Oh et al. in 2006 as a protein corresponding to NEFA/nucleobindin 2 (NUCB2) (7). It is known to be expressed in the appetite-control hypothalamic nuclei in rats. Hypothalamic ventricular nuclei (HVN) are known to function as a center to combine various neuronal activities for feeding behavior regulation (8). Intracerebroventricular (ICV) injection of nesfatin-1 to rats reduces body weight in a dose-dependent action (7). However, the neural pathway of nesfatin-1 as an anorectic is not clear (8). In this review, we aimed to

summarize and analyze researches about nesfatin-1 and reveal its clinical availability in anti-obesity treatment in the future.

Molecular Structure of Nesfatin-1

The central nervous system (CNS) contains various neuroactive molecules play roles in energy homeostasis regulation. Deteriorated homeostasis may result in obesity due to increase in appetite and decrease in energy consumption (9). Nesfatin/NUCB2 is expressed in the appetite-control hypothalamic nuclei such as paraventricular nucleus (PVN), arcuate nucleus (ARC), supraoptic nucleus (SON) of hypothalamus, lateral hypothalamic area (LHA), and zona incerta in rats. In addition to the hypothalamus, nesfatin-1 immunoreactivity may be observed in neurons of the nucleus of solitary tract (NTS) (7). In the PVN and SON, nesfatin-1 immunoreactive neurons are colocalized with oxytocin and vasopressin (10). Therefore, the regulation of feeding and metabolism is maintained by the possible interaction between the neurons containing these neuropeptides and nesfatin-1 neurons in the PVN and SON (11). It was shown that central nesfatin-1 injection decreases food intake and results in loss of body weight, consequently. Adversely, immunoneutralization of endogenous nesfatin-1 stimulated appetite (7). It has also been reported that centrally administered nesfatin-1 and feeding activate nesfatin-1 and oxytocin neurons located in the PVN. When nesfatin-1 neurons are activated, they stimulate oxytocin neurons in the PVN. These processes drive oxytocinergic signaling to anorectic NTS pro-opiomelanocortin (POMC) neuron, at least one of the targets, thereby cause melanocortin-dependent anorexia (8). Nesfatin-1 (named as acronym for NEFA/nucleobindin2-encoded satiety- and fat-influencing protein) is an 82-amino-acid polypeptide, with a molecular mass of 9.7 kDa, which was first described by Oh et al. in 2006 (7). It was identified as the amino-terminal fragment of NUCB2. NUCB2 is a protein that is found in humans, mice, and rats in high concentrations. The protein comprises a 24-amino-acid N-terminal signal peptide sequence. It is followed by a 396-amino-acid sequence that is proteolytically processed by a pro-hormone convertase to at least three peptides, nesfatin-1, nesfatin-2, and nesfatin-3. When administered into the rat cerebral ventricle, only nesfatin-1 suppresses nocturnal food intake and body weight gain in rats (12,13). As a result of structural analyses, three different fragments of nesfatin-1 were identified. These are N-terminal fragment (residues 1-23), mid-terminal fragment (residues 24-53) and C-terminal fragment (residues 54-82). They were all tested for food intake suppression in rats. Results of these analyses revealed that only the mid-fragment was responsible for inducing anorectic responses, thus, unveiling the active core of nesfatin-1 molecule in terms of feeding control (9,14).

Anorectic Mechanism of Nesfatin-1

Feeding, as a basic need of all animals, is a complex behavior organized by a multitude of signaling molecules released from central and peripheral neurons and cells. Signaling molecules, including ghrelin, orexins, adiponectin, agouti-related peptide, and cocaine- and amphetamine-regulated transcript peptide that

prompt or suppress feedings, have recently been identified (10). Wide distribution of NUCB2/nesfatin-1, with major expression not only in hypothalamic nuclei but also in various brainstem areas and autonomic centers can be taken as an index of its possible function as an integral regulator of energy homeostasis (14). In addition to the anatomical evidence, functional analyses on the metabolic regulation of NUCB2/nesfatin expression in the hypothalamus have further unveiled its role in the central control of food intake and energy balance. NUCB2 mRNA levels and nesfatin-1 content decreased, selectively at the PVN, following a 24 hour fasting in rats (7). Conversely, re-feeding potentially activates nesfatin-1 neurons at the PVN and SON, as measured by c-Fos immunoreactivity (11). These responses emphasize role of nesfatin-1 as an anorectic molecule. Noteworthy, the mechanism whereby nesfatin-1 conducts such feeding-suppressive actions seems not to be dependent to leptin signaling, as nesfatin-1 was capable of inhibiting food intake in rodents bearing inactivating mutations of leptin receptor (7,9). Hypothalamic leptin signaling pathway does not exist at the downstream of the pathway by which nesfatin-1 causes anorexia (15). The first site of food contact is stomach and oxyntic mucosa contains a variety of endocrine cells (16,17). These cells are particularly located in the basal region of the epithelium (18). Gastrin-producing cells (G cells) and somatostatin cells (D cells) are the main endocrine cell types in the antrum. The oxyntic mucosa establishes a variety of physiologically important transmitters involved both in the regulation of acid secretion and in energy homeostasis of the body. In a study, Stengel et al. have reported a significant down-regulation of NUCB2 mRNA supporting the assumption of NUCB2/nesfatin-1 playing a role in energy homeostasis not only in the brain but also in the stomach (12).

Literature Review

In 2006, Oh et al. presented nesfatin-1 as a protein expressed in the appetite-controlling hypothalamic nuclei in rats (7). They have reported that ICV injection of nesfatin-1 decreased food intake dependent to dose. They also maintained appetite stimulation by injection of an antibody neutralizing nesfatin-1. While body weight reduced by chronic injection of nesfatin-1, after chronic ICV injection of antisense morpholino oligonucleotide against the gene encoding NUCB2, rats gained weight. They have also reported that nesfatin-1 induced anorexia occurred in rats with a leptin receptor mutation. They have also reported that anorectic effect of nesfatin-1 was impeded by SHU9119, a melanocortin antagonist. Bralioiu et al. revealed nesfatin-1 immunoreactive cells in Edinger-Westphal (EW) nucleus, dorsal motor nucleus of the vagus, and caudal raphe nuclei, in addition to recently reported presence in hypothalamus and NTS. Nesfatin-1 released from the vagus nerve may modify the activity of the gastrointestinal tract and may indicate the regulatory role of nesfatin-1 in ingestive behaviors. However, the authors could not clarify the functional significance of nesfatin-1 neurons in the EW nucleus. They also suggested that nesfatin-1 via sympathetic bulbospinal pathways, such as nucleus raphe obscurus and raphe pallidus, might play a role in the thermogenesis and related energy homeostasis. They also found

that nesfatin-1 operates via calcium influx stimulation in cultured hypothalamic neurons by interacting G protein coupled receptor (10). Kohno et al. confirmed the colocalization of nesfatin-1 with oxytocin, vasopressin, corticotropin-releasing hormone (CRH), and thyrotropin-releasing hormone (TRH) in the PVN as reported by Bralioiu priorly. They have reported that the specific subtype of nesfatin-1 neuron that coexpresses CRH in the PVN could be involved in the potent anorectic effect of nesfatin-1. It is known that feeding and food intake increases c-Fos expression in the SON and PVN. Kohno et al. confirmed this previous data and they found that feeding significantly stimulates c-Fos expression in nesfatin-1 immunoreactive neurons in the SON and PVN. Physiological roles of the nesfatin-1 neurons are probably related to the metabolic effects of vasopressin (11). Another study demonstrated that nesfatin-1 co-expressed in melanin concentrating hormone (MCH) neurons might play a complex role both in food intake regulation and in other essential integrative brain functions involving MCH signaling, ranging from autonomic regulation, stress, mood, cognition to sleep (19). Correspondingly, Merali et al. have reported that, besides its role as a satiety agent, nesfatin-1 might also be involved in the mediation of anxiety and fear-related responses. They assessed the ICV injection of nesfatin-1 to rats in several paradigms that are thought to reflect anxiety and/or fear. They have determined that nesfatin-1 caused anxiety in rats (6). In the same year, Gina et al. have confirmed the anorexigenic and anxiogenic properties of nesfatin-1 and demonstrated that the peptide was involved in cardiovascular regulation. After ICV administration of nesfatin, a significant increase in mean arterial pressure (MAP) was determined. They have also reported that the effect of nesfatin-1 on MAP appeared to be mediated through a leptin-independent melanocortin-3/4 receptor (MC3/4R). These findings support the data in the literature that nesfatin-1 producing cells colocalize with POMC neurons. Thus, they concluded that nesfatin-1 increased sympathetic activity (20). Kaori et al. have also shown the effects of nesfatin-1 on gut motility as well as feeding behavior. In food deprived mice, they measured food intake after ICV administration of nesfatin-1. They assessed antral and duodenal motility using a manometric method. They found that ICV administered nesfatin-1 not only decreased food intake but also inhibited gastroduodenal motility (21). Goebel et al. have reported another localization of nesfatin-1. They found nesfatin-1 immunoreactivity in both sympathetic and parasympathetic preganglionic neuronal groups. Immunohistochemical staining also revealed the presence of nesfatin-1 in the piriform and insular cortex, endopiriform nucleus, nucleus accumbens, lateral septum, bed nucleus of stria terminalis, central amygdaloid nucleus, medial preoptic area, dorsal raphe nucleus, ambiguous nucleus, ventrolateral medulla and gigantocellular reticular nucleus, and Purkinje cells of the cerebellum. These findings may be a proof that nesfatin-1 plays a role not only as an anorexigenic agent but also plays a role in autonomic regulation (22). Okere et al. revealed the relationship between nesfatin-1 and acute stress. Acute stress stimulates the secretion of non-preganglionic EW neurons and the production of nesfatin-1 (23). Another evidence that NUCB2/nesfatin plays a role

in the control of the stress axis is the report of Konczol et al. (24). They reported that ICV injection of nesfatin-1 elevated the levels of major components of the hypothalamic-pituitary-adrenal axis, both adrenocorticotrophic hormone (ACTH) and corticosterone. Moreover, bilateral adrenalectomy increased NUCB2/nesfatin expression in PVN. In a study by Price et al., it was observed that, after nesfatin-1 exposure neuropeptide Y (NPY) neurons hyperpolarized (25). This finding suggests that nesfatin-1 induced feeding inhibition may be mediated by the inhibition of orexigenic NPY neurons in the arcuate nucleus. Maejima et al. have reported that the anorectic effect of central nesfatin-1 was blocked by an antagonist for oxytocin receptor and oxytocin-induced anorexia was antagonized by SHU991. These findings were correlated with the findings of Oh et al. They have also reported that nesfatin-1 regulated oxytocin neuron of the PVN was functionally and anatomically linked to NTS (8). In a study, the effect of peripherally administered nesfatin-1 on food intake was examined (9). When nesfatin-1 was injected peripherally, the mid-segment (one of three segments of nesfatin-1) was found to decrease food intake. Besides, it was found that it did not have any toxic or aversive effects. The mid-segment of nesfatin-1 interacts with receptors via its α -helical structure. In the same study, nesfatin-1 was found to be leptin-independent, compatible with the findings of previous studies. The peripheral signaling by nesfatin-1 activates neurons expressing anorexigenic molecules POMC and cocaine- and amphetamine-regulated transcript (CART) in the NTS to produce anorexia. A recent research revealed that NUCB2/mRNA was expressed ten times more in gastric mucosa when compared to the heart, brain and other viscera. This finding meant that the role of NUCB2/nesfatin-1 in energy homeostasis was not limited to the brain but expanded to gastric mucosa (12). Yosten et al. have reported that the effects of nesfatin-1 on food and water intake, and mean arterial pressure could be blocked by an oxytocin receptor blocker, ornithine vasotocin (OVT) (26). These observations showed the possible role of central oxytocin system as a downstream mediator of these actions of nesfatin-1. In a study with human subjects and murinae, it has been reported that NUCB2/mRNA and nesfatin-1 were significantly higher in adipose tissue compared to other tissues (1). Moreover, nesfatin-1 was introduced as a novel adipokine. Increasing expression of nesfatin-1 during the process of maturation of preadipocytes into adipocytes may suggest that nesfatin-1 plays a role in adipocyte development and differentiation. It was also found that obese animals had greater SC NUCB2/nesfatin-1 expression. In humans, correspondingly, nesfatin-1 levels were positively correlated with body mass index. Stengel et al. investigated the effect of nesfatin-1 on nocturnal feeding in rats and they observed that low dose nesfatin-1 injection into the lateral ventricle of the brain before the onset of dark period reduced the food intake by 45% (27). They have not noted any changes in blood glucose levels and behavior during the process. They have also found that nesfatin-1 reduced gastric emptying in a dose-dependent manner. However, Su et al. suggested that nesfatin-1 was anti-hyperglycemic (28). They have reported that IV injection of nesfatin-1 significantly reduced blood glucose levels in hyperglycemic mice. In another study, nesfatin-1

was administered peripherally and feeding was monitored (29). It has been reported that, when nesfatin-1 was injected peripherally, food intake did not alter. Compatible with the literature, when nesfatin-1 was given ICV, it caused a dose-dependent reduction in nocturnal food intake. However, Stengel et al. observed that both peripheral and central injection of nesfatin-1 inhibits dark-phase feeding in rodents (30). Fasting plasma nesfatin-1, insulin and glucose levels were measured and analyzed in healthy subjects and in patients with type 1 diabetes mellitus (DM) and type 2 DM. While nesfatin levels in patients with type 1 DM were slightly higher compared to healthy subjects, they were significantly lower in type 2 DM patients compared to healthy subjects and type 1 DM patients. In the same study, any differences in nesfatin-1 levels between sexes were determined (31). Xu et al. have reported that nesfatin-1 might play a role in leptin-mediated feeding control in male rats only (32). In another study with obese children by Anik et al., it has been reported that oral glucose load in obese children might not be sufficient for nesfatin-1 response and that, in short-term regulation of food intake, nesfatin-1 might be ineffective (33). However, Abaci et al. have reported significantly lower serum nesfatin-1 levels in obese subjects when compared to control subjects. They concluded that that nesfatin-1 may play an important role in regulation of food intake in obese individuals (34). Recent studies have demonstrated that nesfatin-1 also had effects on pubertal timing. It has been reported by Galiano et al. that ICV administration of nesfatin-1 induced elevations of circulating gonadotropins. Although it is known that fasting reduces levels of gonadotropins, nesfatin-1 injected pubertal female rats showed a significant increase (35).

Conclusion

NUCB2/nesfatin is a composition of 396 amino acids. It has a high degree of homology among rats, mice and humans. Since it was first described in hypothalamus, many studies have shown its presence in different sites of the brain and other tissues (14). There are considerable anatomical and functional evidences suggesting that it has an important role in energy homeostasis and, probably, autonomic regulation of visceral-endocrine functions (22). However, the mechanism of the effect of nesfatin-1 on body functions is still unclear. Use of nesfatin-1 as a pharmacological treatment against obesity may be a field of interest for the future investigators. Animal experiments have revealed that while nesfatin-1 administration reduces food intake, while immunoneutralization of endogenous nesfatin-1 increases food intake (1). Further investigations on human subjects are needed to reveal its activity in human body. In conclusion, after all its metabolic and endocrine effects are clarified, nesfatin-1 may be an anti-obesity agent in the future.

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