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Molecular Characteristics and Functions of Nesfatin-1 and Nutritional Regulation of Its Gene Expression (Postprint)

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Abstract

Nesfatin-1 is a peptide derived from nucleobindin-2 (NUCB2), an anorexigenic signaling peptide expressed in the hypothalamus and peripheral tissues that inhibits animal feeding by inducing satiety. Researchers have found that, in addition to regulating body homeostasis and energy reserves through the inhibition of feeding, Nesfatin-1 also participates in various physiological processes such as puberty initiation and insulin resistance, thereby exhibiting multiple biological functions. This article reviews the molecular biological characteristics, functions, and nutritional regulation of gene expression of Nesfatin-1/NUCB2.

Full Text

Nesfatin-1: Molecular Biological Characteristics, Functions, and Nutritional Regulation of Gene Expression

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Abstract: Nesfatin-1 is a peptide fragment derived from nucleobindin 2 (NUCB2), an anorexigenic signal peptide expressed in both hypothalamic and peripheral tissues that inhibits animal feeding by inducing satiety. Research has revealed that beyond regulating whole-body homeostasis and energy storage through feed intake suppression, Nesfatin-1 participates in diverse physiological processes such as puberty onset and insulin resistance, demonstrating multiple biological functions. This review summarizes the molecular biological characteristics, functions, and nutritional regulation of gene expression of Nesfatin-1/NUCB2.

Keywords: Nesfatin-1; molecular biological characteristics; feed intake inhibition; puberty onset; gene expression; nutritional regulation

Classification Code: S852.2

Nesfatin-1 was first identified as an anorexigenic signal peptide by Oh-I et al. [1], a peptide fragment derived from nucleobindin 2 (NUCB2) that significantly reduced nocturnal feed intake and daily weight gain upon intracerebroventricular administration. Subsequent studies have demonstrated widespread expression of Nesfatin-1 in the central nervous system and peripheral tissues across multiple animal species, revealing diverse biological functions. This article provides a brief review of the molecular biological characteristics, functions, and nutritional regulation of Nesfatin-1 gene expression.

1 Molecular Biological Characteristics of Nesfatin-1/NUCB2

Nesfatin-1 originates from post-translational cleavage of NUCB2 by prohormone convertases at the N-terminus. NUCB2 contains binding sites for both DNA and calcium ions (Ca^{2}). The resulting peptides are designated as follows: amino acids 1–82 constitute Nesfatin-1, amino acids 85–163 form Nesfatin-2, and amino acids 166–396 comprise Nesfatin-3 [1]. Following lateral ventricle injection in rats, only Nesfatin-1 produced a dose-dependent reduction in food intake lasting 6 hours, while Nesfatin-2 and Nesfatin-3 showed no significant effects [2].

Lents et al. [3] employed a porcine Nesfatin-1 sequence to generate specific site probes for determining the protein amino acid sequences across humans, pigs, and rats (Figure 1 [Figure 1: see original paper]). Their analysis revealed multiple conserved sequences with high homology among the three species, with shaded regions in Figure 1 highlighting these conserved Nesfatin-1 sequences.

Nesfatin-1 expression has been confirmed in humans, pigs, fish, rodents, canines, and other species [4–6]. Central expression predominantly localizes to the hypothalamic paraventricular nucleus (PVN), arcuate nucleus (ARC), supraoptic nucleus (SON), lateral hypothalamic area (LHA), and nucleus tractus solitarius (NTS) [1,7]. Within the PVN, 24% of Nesfatin-1-secreting neurons co-localize with oxytocin-secreting neurons, 13% with corticotropin-releasing hormone-secreting neurons, and 12% with thyrotropin-releasing hormone-secreting neurons. In the SON, 35% of Nesfatin-1-secreting neurons co-localize with oxytocin-secreting neurons, indicating frequent co-expression of hormones such as oxytocin with Nesfatin-1 [7]. The hypothalamus serves as a critical regulatory center for feeding, body weight, and reproductive function. The extensive distribution of Nesfatin-1-secreting neurons across multiple hypothalamic regions and their co-expression with other functional neurons implicate Nesfatin-1 in regulatory processes beyond feeding control [8].

Concurrently, Nesfatin-1/NUCB2 is widely distributed in peripheral tissues, including gastric mucosal cells, cardiomyocytes, subcutaneous adipose tissue, pan-

creatic islet cells, duodenal mucosa, and testes of male animals [9–12]. The Nesfatin-1 protein can freely cross the blood-brain barrier via an unsaturated bidirectional mechanism, potentially influencing its distribution between central and peripheral compartments [13].

2.1 Inhibition of Food Intake

While researchers have established that Nesfatin-1 suppresses animal food intake, the precise mechanisms remain incompletely understood. Intracerebroventricular injection of Nesfatin-1/NUCB2 mRNA in rats produced a dose-dependent decrease in food intake within 6 hours, an effect reversed by subsequent administration of Nesfatin-1 antibody Ab24 [2]. Intracerebroventricular (i.c.v.) injection of -melanocyte-stimulating hormone (-MSH) elevated NUCB2 mRNA expression in the PVN, thereby inhibiting rat food intake. This anorexigenic effect was blocked by subsequent injection of -MSH antisense receptor, suggesting that Nesfatin-1 may influence appetite through the -MSH pathway [2]. Additional studies indicate that Nesfatin-1 can modulate feeding by inhibiting neuropeptide Y (NPY) activity in the arcuate nucleus, potentially involving the insulin pathway [14–15].

Varricchio et al. [16] hypothesized that Nesfatin-1 participates in gastric distention regulation within the porcine enteric nervous system, though the specific physiological mechanisms remain unclear. Using in vitro single-cell culture techniques, researchers demonstrated that Nesfatin-1 in the LHA regulates gastric distention by inhibiting most gastric distention-excitatory neurons (GD-E) in the PVN while activating nearly half of the gastric distention-inhibitory neurons (GD-I) [17]. The oxytocin receptor inhibitor H4928 can inhibit GD-I activity and simultaneously block Nesfatin-1' s effects on gastric distention. Nesfatin-1 can feedback onto gastric distention-sensitive neurons and modulate glucose-sensing neurons in the dorsal motor nucleus of the vagus (DMNX) in rats, representing a potential component of its food intake suppression mechanism [18].

2.2 Regulation of Puberty Onset in Female Animals

Energy reserves are closely linked to appetite-regulating factors, while puberty onset and gonadal axis development are highly sensitive to energy status. As an anorexigenic signal peptide, Nesfatin-1 can influence puberty onset [3]. Nesfatin-1 may participate in regulating female puberty onset through both central nervous system and whole-body energy balance mechanisms [3,19], though the specific pathways remain to be fully elucidated. Researchers have demonstrated that Nesfatin-1 can affect luteinizing hormone (LH) in multiple hypothalamic regions, thereby regulating puberty onset in female animals.

2.2.1 Distribution and Expression in the Prepubertal Stage

Nesfatin-1/NUCB2 mRNA is significantly expressed in the LHA, PVN, SON, and zona incerta (ZI) of the hypothalamus in prepubertal female rats (35 days

old), with faint expression observed in the dorsomedial nucleus (DMN) and ARC [20].

Quantification of NUCB2-expressing cells and Nesfatin-1/NUCB2 mRNA expression in the LHA, PVN, and SON during the prepubertal period (20–35 days old) revealed significantly higher expression at 35 days compared to 20 days. Total NUCB2 mRNA expression increased approximately threefold at 35 days relative to 20 days [20]. These findings indicate that during the prepubertal transition, the organism upregulates Nesfatin-1 mRNA expression in an increasing trend, suggesting that Nesfatin-1 expression may be an essential preparatory step for female puberty onset.

Rapid feed restriction of prepubertal rats created negative energy balance feedback to the central nervous system, significantly reducing hypothalamic NUCB2 mRNA expression and thereby disrupting the puberty onset process [21]. Intracerebroventricular (i.c.v.) injection of NUCB2 antisense-morpholino oligonucleotides (MON) in prepubertal female rats decreased LH expression and delayed puberty onset [20]. These results demonstrate that Nesfatin-1 not only participates in regulating food intake and energy homeostasis but also plays a crucial role in metabolic regulation within the gonadotropin axis. Deficiency of Nesfatin-1 during prepuberty disrupts the normal progression of puberty onset.

2.2.2 Regulation of Reproductive Hormones in the Prepubertal Stage

Lents et al. [3] administered Nesfatin-1 and saline to the lateral ventricles of prepubertal gilts in experimental and control groups, respectively, and monitored LH expression over time. Intracerebroventricular injection of Nesfatin-1 in prepubertal gilts significantly increased LH expression, peaking at approximately 30 minutes post-injection at about twice the control group value, demonstrating that Nesfatin-1 can promote pituitary LH expression via the hypothalamus.

Wang et al. [22] injected Nesfatin-1 into the lateral ventricles of prepubertal rats, observing that vulva opening time in the experimental group [(31.83±1.27) days] occurred approximately 10 days earlier than in the control group [(42.67±1.83) days], and ovarian weight [(36.83±7.23) mg] was about 15 mg greater than controls [(21.17±5.07) mg]. Nesfatin-1 also significantly enhanced pituitary LH and follicle-stimulating hormone (FSH) mRNA expression, with serum LH and FSH content increasing significantly 15 minutes after injection, ultimately advancing puberty onset. These findings are consistent with the results of Lents et al. [3].

Notably, while intracerebroventricular injection of Nesfatin-1 in prepubertal female rats significantly elevated serum LH and FSH content, similar administration in adult female rats produced no significant changes in serum LH and FSH [22]. This suggests that Nesfatin-1 may specifically influence gonadal development in prepubertal female animals, with this effect diminishing progressively after puberty onset.

2.3 Effects on GnRH Expression via Insulin

The relationship between Nesfatin-1 and insulin resistance may represent part of the mechanism underlying its involvement in puberty onset regulation. Hypothalamic Nesfatin-1 enhances the insulin receptor/insulin receptor substrate-1/protein kinase B (InsR/IRS-1/AKT) signaling cascade, inhibits transcription and expression of phosphoenolpyruvate carboxykinase (PEPCK), and increases insulin sensitivity in liver and peripheral tissues [23–24]. The molecular mechanism by which Nesfatin-1 inhibits hepatic gluconeogenesis, promotes muscle glycogen synthesis, and enhances insulin sensitivity involves the transducer of regulated cAMP-response element binding protein 2 (TORC2) [25].

TORC2 serves as a key factor regulating transcription of gluconeogenesis-related genes; Nesfatin-1 enhances TORC2 phosphorylation, thereby increasing insulin sensitivity [26].

Additionally, Nesfatin-1 enhances L-type calcium channel activity, facilitating Ca^{2} influx into mouse pancreatic -cells [27]. Consequently, Nesfatin-1 can increase insulin expression by potentiating glucose-induced effects.

Insulin directly promotes GnRH expression and release during animal reproduction or indirectly modulates GnRH expression through alternative pathways. Research indicates that insulin may: 1) promote GnRH expression via early growth response protein 1 (Egr-1) in an insulin-dependent manner; 2) indirectly stimulate GnRH gene expression by influencing extracellular regulated protein kinases (ERK) activity; and 3) stimulate or inhibit the GnRH pulse generator by suppressing NPY [15].

In summary, Nesfatin-1 in the hypothalamus, liver, and other peripheral tissues may regulate GnRH expression by modulating insulin sensitivity and expression, thereby influencing puberty onset (Figure 2 [Figure 2: see original paper]).

2.4 Other Biological Functions

Beyond the aforementioned functions, both in vivo and in vitro studies demonstrate that hypothalamic Nesfatin-1 can elevate arterial pressure and accelerate heart rate, mechanisms linked to stimulating depolarization/hyperpolarization of neurons in the medial nucleus tractus solitarius (mNTS) or enhancing sympathetic nerve excitability [28–29]. Furthermore, research indicates that Nesfatin-1 possesses anti-inflammatory and anti-apoptotic capabilities. Since animal energy balance is co-regulated by body temperature and food intake, Nesfatin-1 may also participate in thermoregulation [30].

3 Nutritional Factors Affecting Nesfatin-1/NUCB2 mRNA Expression

As a satiety signal peptide widely distributed across hypothalamic regions and peripheral tissues, Nesfatin-1/NUCB2 mRNA expression is regulated by dietary

nutrition, whole-body energy balance, and other factors.

3.1 Glucose

In rat studies, the pancreas responds to glucose by expressing Nesfatin-1 concurrently with insulin [31-32]. MIN-6 cells cultured in high glucose (16.7 mmol/L) medium expressed four-fold higher Nesfatin-1 levels compared to low glucose (2.0 mmol/L) medium [33]. In type I diabetic rats induced by streptozotocin (STZ) pancreatic injection, both pancreatic NUCB2 and insulin precursor mRNA expression decreased. However, in type II diabetic rats induced by high-fat, high-sugar diets, glucose specifically induced Nesfatin-1 expression in adipose and muscle tissues. In vitro culture of rat gastric mucosal (mouse stomach ghrelinoma, MGN3-1) cells demonstrated dose-dependent increases in Nesfatin-1 mRNA expression with glucose concentration, though expression was not significantly correlated with duration in the glucose environment [34]. While the precise mechanism of glucose induction of Nesfatin-1/NUCB2 remains incompletely understood, it is evident that Nesfatin-1-secreting neurons are highly sensitive to glucose and play an important role in insulin expression and glucose homeostasis regulation [35].

3.2 L-Tryptophan

In vitro culture of rat MGN3-1 cells in L-tryptophan-containing medium revealed that cells in 10 mmol/L L-tryptophan expressed substantially higher Nesfatin-1/NUCB2 mRNA than those in 0.07 mmol/L or 1.0 mmol/L L-tryptophan medium. However, translated Nesfatin-1 protein expression was similar in 1.0 mmol/L and 10 mmol/L L-tryptophan media (both significantly higher than in 0.7 mmol/L L-tryptophan medium) [34]. These findings indicate that Nesfatin-1-secreting neurons are sensitive to L-tryptophan content, but Nesfatin-1 expression is regulated at the mRNA translation or post-translational level.

3.3 Fatty Acids

Even trace amounts (1 mol/L) of oleic acid significantly reduced Nesfatin-1/NUCB2 mRNA expression in MGN3-1 cells, while caprylic acid and linolenic acid treatments produced no significant changes [34]. The effects of other fatty acids on Nesfatin-1 expression require further investigation.

In diet-induced obese (DIO) rats fed high-sugar, high-fat diets, hypothalamic Nesfatin-1/NUCB2 mRNA expression was significantly lower than in normal mice [35], suggesting that Nesfatin-1/NUCB2-secreting neurons may be more sensitive to lipids than carbohydrates.

Wu et al. [36] subjected rats to a 6-week repetitive starvation/refeeding protocol followed by high-fat diet feeding until 12 weeks, resulting in significantly attenuated hypothalamic NUCB2 gene expression in obese rats. Prolonged single high-energy feeding also disrupts whole-body energy regulation mechanisms,

such that hypothalamic Nesfatin-1/NUCB2 mRNA expression did not increase upon returning to normal feeding.

Kohno et al. [7] performed 48-hour fasting followed by 2-hour ad libitum refeeding in 7–9-week-old female rats, then conducted neuropeptide c-Fos immunohistochemical assays. Nesfatin-1 expression in the PVN increased approximately 10-fold compared to the fasting period, while SON expression increased about 30-fold. After 48 hours of fasting, gastric mucosal Nesfatin-1/NUCB2 mRNA expression in mice showed no significant change, whereas protein expression decreased [37], again confirming that Nesfatin-1/NUCB2 regulation occurs at the translation or post-translational level.

In summary, under feeding or high-energy dietary conditions, gastric distention activates hypothalamic Nesfatin-1/NUCB2-secreting neurons. Nesfatin-1 simultaneously activates GD-I neurons, inhibits GD-E neurons, and impedes gastric distention, ultimately achieving food intake inhibition and whole-body energy balance regulation. During this process, oxytocin neurons and Nesfatin-1/NUCB2-secreting neurons exhibit significant co-expression (Figure 3 [Figure 3: see original paper]).

3.5 Other Factors

Nesfatin-1/NUCB2 expression is also influenced by additional factors, including different organs and tissues, age, and long-term or short-term feeding conditions, all of which can modulate Nesfatin-1/NUCB2 expression [38–40].

Nesfatin-1 is an anorexigenic signal peptide widely distributed throughout the central nervous system, digestive system, and peripheral tissues. To date, research has primarily focused on experimental animals and in vitro studies. Preliminary findings indicate that Nesfatin-1 not only regulates food intake but also influences critical life processes such as whole-body energy metabolism and puberty onset. Future research should employ a broader range of animal models, particularly through in vivo experiments, to elucidate the specific mechanisms underlying the various biological functions of Nesfatin-1 and the interconnections between central and peripheral tissues. Additionally, investigation of additional nutritional factors affecting Nesfatin-1/NUCB2 expression will facilitate the practical application of Nesfatin-1.

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