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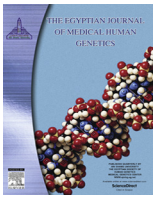

Review

NUCB2/Nesfatin-1: A Potent Meal Regulatory Hormone and its Role in Diabetes

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ABSTRACT

Background: Nesfatin-1, a newly discovered calcium and DNA binding peptide, originate from nucleobindin 2 (NUCB2) precursors and expressed by central and peripheral nervous system, and peripheral tissues such as digestive organs and adipose tissues. It has the astonishingly large number of chemical messengers for full appetite and introduced as a potential anorectic factor with ability to modulate body weight and probably, energy homeostasis.
Nesfatin-1/NUCB2 level in the circulation is elevated after meal intake and decreased during a fast. Its food intake suppression effect is independent from the leptin pathway, and act via the melanocortin signaling. On the other hand, Nesfatin-1 colocalizes with insulin in pancreatic beta islet cells and has been shown to increase insulin secretion.
Methodology: PubMed databases were searched for "NUCB2 or nesfatin-1 or nucleobindin" with the combination of "diabetes mellitus". Included papers were further searched manually for additional studies. The databases were searched up to 2015. Fifty one articles were selected for full text review.
Result: Centrally controlled Nesfatin-1 was stated to raise peripheral and hepatic insulin sensitivity by reducing gluconeogenesis and stimulating peripheral glucose uptake in vivo.
Conclusion: Nesfatin-1 has gain attention as a new target to generate, drug for treatment of endocrine nutritional and metabolic disorders like obesity and type 2 diabetes mellitus.

Contents

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1. Introduction

The endocrine system generates and discharges hormones that regulate the essential body functions. The hypothalamus, vital integrator of glands in the brain, plays main roles in controlling food intake and is a rich source of satiety regulatory peptides which participate in the long-term energy balance [1]. One of such peptides which are recognized recently is Nesfatin-1. Beside secretion of Nucb2 from hypothalamus, this peptide also is released from endocrine cells in the pancreatic beta-cells, intestinal and gastric mucosa and found in peripheral places such as the muscle and adipose tissues.

NUCB2 was first recognized in numerous regions of the hypothalamus and pancreatic beta-cells, showing the possible contribution of NUCB2 in the regulation of insulin secretion, hunger and fat storage [2]. Nesfatin-1 has rapidly proven as a novel manager of appetite, energy and glucose homeostasis and insulin secretion, with significant values to the etiology of metabolic diseases including diabetes and obesity [3–5]. Nesfatin-1 is also involved in the regulation of some other physiological procedures including anxiety and drinking [6–10].

2. Nucleobindins

In the early 1990s, a protein was recognized in mouse [11] and human cell lines [12] and named nucleobindin or DNA binding/EF-hand/acidic amino acid rich region (NEFA). This peptide includes various efficient domains as well as an N-terminal side, a leucine/isoleucine rich domain, a DNA binding domain and an assumed nuclear targeting peptide, while the C-terminal region has two Ca^{2+}-EF-hand motifs and a leucine zipper motif [13].

So far, two nucleobindins have been recognized, that is nucleobindin 1 (NUCB1 or CALNUC, rat: NM 053463.1) [14] and nucleobindin 2 (NUCB2 or NEFA, rat: NM 021663.2) [15].

Nucleobindin-1 and Nucleobindin-2 have Ca^{2+} binding multidomain that take 62% amino acid identity while two distinct and unlinked genes encode them [16]. NUCB2 and NUCB1 are identified to secrete proteins (Miuraet al. 1992), however their roles remained mainly unidentified [17]. They are homologous gene family and probably derived from one EF-hand progenitor with four domains [18]. NUCB2 is 40 residues smaller than NUCB1and is about a 50-kDa protein [19].

2.1. Nucleobindin 1 and its functions

In 1992, Nucleobindin1 was first found in a culture supernatant of a B lymphocyte cell line from mice disposed to an autoimmune disorder, systemic lupus erythematosus. Such discovery displayed its role in autoimmunity and apoptosis [15]. Nucleobindin-1 is encoded by NUCB1 gene containing 13 exons which is located on the 19q13.33 (accession no: NM_006184.5).

Researchers found that NUCB1 is widely expressed in many tissues. The cellular localization of Nucleobindin-1 has been inconsistently recommended to be a secreted nuclear protein [20,15], a resident endoplasmic reticulum protein.

NUCB1 has ability to bind Ca^{2+} and DNA [19]. Its Ca^{2+}-binding region is available at the central part of the protein having two EF hand motifs with the acidic domain (residues 253–316) [20]. Leucine amino acid in NUCB1 is known to be contributed in dimerization as well. The leucine zipper domain is ended by a C-terminal region that is assumed to be essentially unstructured. The composition of NUCB1 proposes various intracellular roles for this protein [19].

NUCB1 has been shown to take part significantly in Ca^{2+} Homeostasis [21]. It is related with other proteins, including G proteins [21] and cyclooxygenases [22]. NUCB1 is attached to Ca^{2+} as determined by Ca^{2+} edges, which proposes that NUCB1 might show an essential role as an agonist-releasable Ca^{2+} store in the luminal Golgi [21]. NUCB1in neutrophils are localized in the ER and Golgi system, together with cyclooxygenase-2 (COX-2) and act in the production of prostanoid. NUCB1 interacts with COX-2 with high affinity resulting in an enhance of PGE2 generation [9].

2.2. Nucleobindin2

The nucleobindin-2 (NUCB2) [23], with extremely protected sequence across mammalian and non-mammalian vertebrates, includes 420 amino acids [16], including a polypeptide formed of 396 amino acids, followed by a 24 amino acid signal peptide is placed both on the plasma membrane and in the neuroplasm [24].

This gene is located on the 11q151, and its amino acid sequence is greatly conserved in rats (95% homology) and mice (87.4% homology)[25], and consists of 14 exons covering 54785 nucleotides (accession No. NC_000011.9), the mRNA of 1612 nucleotides, which just nucleotides 246–1508 are translated (accession No. NM_005013.2) [26].

NUCB2 has also been identified by additional names which include AI607786, CALNUC, DNA-binding protein NEFA and NEFA [27]. It was newly recognized as one of 600 genes that is stimulated by the diabetic medicine, troglitazone, in SQ-5 cells, a human lung cancer-cell line [13].

Differential posttranslational proteolytic handling of NUCB2 by prohormone convertase makes three active cleavage peptides, namely 1–82 AA (Amino Acid) Nesfatin-1, 85–163 AANesfatin-2, and 166–396 AA Nesfatin-3 [24]. The structure of the 82-amino acid molecule nesfatin-1 is the effect of posttranslational cleavage by the precise convertases PC3/1 and PC2 Nesfatin-1 has an extensive homology among humans and mammals, above 85%, also in the lower vertebrates [28]. Nesfatin-1 amino acids are coded by nucleotides between Exon-3 and 5 of the NUCB2 gene.

Until now, several biological actions have been recognized for nesfatin-1 [29], while none have been explained for nesfatin-2 and nesfatin-3 [13]. On the other hand, it is important to mention that nesfatin-2 and nesfatin-3 have obtained fewer attention until now and more work are needed to found or regulate out if these cleavage yields have biological action [30].

The nesfatin-1 molecule is composed of several domains: signal peptide in N-terminal, Leu/Ile rich domain, DNA-binding domain, signal for nuclear directing, two motifs for Ca2+-EF-hand and leucine zipper domain [28].

The construction of nesfatin-1 is as well tripartite, the section beginning from the N-terminal end up to 23 amino acids is named N23, the central fragment from 23 to 53 is called M30, and the part from the 53rd to 82 near the carboxyl terminus is named C29 [31].

The M30 active core has been shown to play the key function in the stimulation of physiological consequences of this peptide, especially in anorectic reactions [32].

There are numerous arginines and lysines inside the nesfatin-1, telling additional treating of this protein processing enzymes [28].

Still the physiological act of Nucleobindin-2 is incompletely defined. It has been stated that Nesfatin-1 but not Nucleobindin-2 has anorexigenic effect as Nesfatin-1 limited food intake while a Nucleobindin-2 mutant that could not be treated into Nesfatin-1 hasnot this effect. Lately Broberger et al. stated that Nucleobindin-2 co-localizes with insulin in rat and human pancreatic β cells [24].

3. NUCB2/nesfatin-1 distribution

NUCB2/nesfatin-1 was first identified in several regions of the hypothalamus, later, it was found not only in the hypothalamus

but also in peripheral tissues including adipocytes, gastric mucosa, pituitary, and cardiac autonomic nuclei in spinal cord, in human and rat pancreatic beta-cells [33]. Foo et al. 2010 has been demonstrated the detection of nesfatin-1 and insulin co-localization only in pancreatic beta-cells but not in other islet cells or in the exocrine pancreas. Expression of NUCB2/nesfatin-1 in pancreatic beta-cells indicates its possible involvement in the regulation of insulin secretion [34]. Expression of nesfatin-1 mRNA has been established to be 10-fold more in gastric mucosa compared in the brain, showing the stomach is the key basis of circulating nesfatin-1 [35]. Nesfatin-1 has been described to pass the brain-blood-barrier through a non-saturable membrane, resulting the possibility that nesfatin-1 secreted from the stomach can act centrally [36,37]. Expression of NUCB2 and nesfatin-1 has also been released in adipocytes. It is notable that this expression is chiefly obvious in the subcutaneous fat tissue cells [32].

The comprehensive supply of NUCB2/nesfatin-1 in the hypothalamus and brain stem areas is supposed to be revealing of an essential role for nesfatin-1 in the regulation of energy homeostasis.

Nucleobindin-2 (NEFA) was stated to be localized in the cytoplasm, on the plasma membrane, as well as being secreted in by both peripheral tissues and CNS [16].

4. Nesfatin-1 functions

4.1. The anorexic effects of nesfatin-1

This factor was termed nesfatin-1 (for NEFA/NUCB2-encoded satiety- and fat-influencing proteins) [34]. It has been shown that nesfatin-1 is regulated by hunger and satiety and it has demonstrated an anorexigenic activity [38]. Also, NUCB2-1 has been demonstrated to cross the blood-brain barrier bi-directionally in a non saturable way [39], the half-life of NUCB2 messenger ribonucleic acid (mRNA) was just about 6 h [31].

In the study of Oh-I et al. [2], it has been proposed that intracerebroventricular (ICV) injection of the central 30 amino acid segment of nesfatin-1 decreases food intake in a dose-dependent mode in rats. The amino acid sequence of this mid-segment is like to that of α-melanocyte-stimulating hormone (α-MSH) and Agouti-related peptides (AgRP) In contrast, ICV injection of nesfatin-2 and nesfatin-3 was without consequences [17]. In the line with this finding, ICV injection of antibodies against nesfatin-1 augmented appetite, indicating that endogenous nesfatin-1 contributes in appetite regulation [40]. This finding suggests that agonists of nesfatin-1 may be useful for obesity therapeutics in the future.

Because ICV injection of nesfatin-1 can inhibit food intake in leptin-receptor-mutant rats, it has been postulated that its food intake inhibition is independent of the leptin pathway. It suppress food intake via the melanocortin signaling [41].

To date numerous studies have completed these primary results and have recognized that injections of nesfatin-1 centrally or peripherally make an important decrease of food intake in rodents [19,41,42] supporting the act of endogenous nesfatin-1 in the monitoring of feeding. It has been revealed that fasting decreased the expression of NUCB2 mRNA in gastric system, suppresses gastric emptying, suggesting that nesfatin-1 may influence digestion and absorption. Gastric emptying suppression has also been reported following ICV injection of nesfatin-1. However in the recent study in 2016, food intake did not change in transgenic mice overexpression of nesfatine1, in normal diet and upon over feeding with high fat diet, and these mice showed increase in body weight. These results indicate that nesfatin may be involved in triglyceride accumulation and insulin resistant independent of energy intake [43].

4.2. Effects on glucose control and insulin release

4.2.1. Expression in the pancreas

Owing to the condensed expression of nesfatin-1/NUCB2 in the pancreas and the special colocalization of nesfatin-1 immunoreactivity with insulin in endocrine β-cells of rats [32,44] and human [45], a potential role of nesfatin-1 in glucose control has been suspected. Later on, in 2010, Diggs-Andrew et al. revealed that, hyperglycemia activates nesfatin-1 expressions in the hypothalamic neurons. Additionally, they showed that high level of glucose in blood improved the release of nesfatin-1 in the endocrine cells of pancreas [46]. In support of the role for nesfatin-1 in the regulation of glucose level, Su et al. [43] described that intravenous injection of nesfatin-1 decreased blood glucose in hyperglycemic db/db mice. They also reported that this anti-hyperglycemic effect is not observed in animals with normal level of blood glucose, indicating an insulinotropic action by Nesfatin1 [31,47]. Later, a few studies confirmed and extended these finding; for example, Yang et al. in 2012 [48] reported that ICV injection of nesfatin-1 in rats with diet-induced obesity, resulted in inhibition of hepatic glucose construction through regulation of hepatic gluconeogenesis [47].

Altogether, these facts show that chronic changes in glucose concentrations influence the pancreatic NUCB2 expression proposing a controlling action in glucose homeostasis, particularly under situations of pathologically changed blood glucose levels. Facts up to now points towards an intracellular or auto/paracrine rather than endocrine mode of action of pancreatic nesfatin-1/NUCB2 [17].

4.3. Antihyperglycemic effects of nesfatin-1

Current observations suggest a potential action of peripheral nesfatin-1 in controlling of glucose homeostasis [6]. In the study of Su Y. et al. in 2010, intravenous injection of nesfatin-1 to hyperglycemic db/db mice decreased the blood glucose level significantly. Anti-hyperglycemic effect of nesfatin-1 is peripheral and independent of its anorexic effect. This is documented by the fact that ICV injection of nesfatin-1 did not affect high glucose level while it lowers food intake.

Nesfatin-1 resulted in elevated glucose-stimulated insulin release from pancreatic *b*-cells. Another study has revealed that nesfatin-1 increases insulin secretion by a direct increase in Ca^{2+} influx inside pancreatic *b*-cells through activation of L-type calcium channels [10]. Its effect of increasing intracellular ca2+ level is glucose dependent. However the relationship between this effect and ca2+ channel is still unclear.

5. Regulation under condition of diabetes mellitus

Type 2 diabetes mellitus (T2DM), the genetically heterogeneous syndrome, is related to insulin resistance and reduced insulin secretion. The common form of T2DM is the complex polygenic diseases [49,50] and is growing at a disturbing level worldwide even in the developing countries. Raised levels of blood glucose are reflected to be accountable for additional impediments causing morbidity and mortality [6].

Latest clinical observations presented a decrease in fasting plasma nesfatin-1/NUCB2 in type 2 diabetic people compared with normal controls which has been proposed to play a possible effect in diabetic hyperphagia [51]. Kuculer et al. in 2016 revealed that low level of nesfatin 1 in patients with gestational diabetes mellitus suggesting that it may have an effect in the pathogenesis of gestational diabetes mellitus [52]. However, Aydin et.al in 2013, demonstrated that plasma NUCB2-1 level and its transcription activity were increased in T2DM patients, which raised the

question that altering NUCB2-1 level may be a physiologic reaction or a compensatory mechanism for decreased insulin action [31].

This discrepancy in the level of nesfatin-1/NUCB2 in T2DM may be due to different study plan, such as case selection and experimental situations [34].

As mentioned above, Nesfatin-1, is a metabolic controller. Remarkably, injection of nesfatin-1 into the third ventricle may prevent hepatic glucose creation and stimulate glucose uptake meaningfully [53]. New studies revealed that the expression of NUCB2 mRNA in peripheral tissues comprising heart, spinal cord, pancreas, islets, stomach, and adipose tissue, [33,54] muscle have crucial physiological roles in body weight and they also contribute to the pathophysiology of insulin resistance and its associated metabolic problems in obesity and diabetes [4].

Li et al. established that fasting concentrations of NUCB2 are significantly lower in T2DM patients. Guo, Y and coworkers [4] found that NUCB2 mRNA and protein levels of muscle and adipose tissues were markedly elevated in T2DM patients compared with controls. The consequence of NUCB2 transcription activity and insulin resistance rests uncertain now. Additionally these results recommend that NUCB2 may have a chief role in insulin resistance or T2DM [4]. The beginning of T2DM classically follows a change in glucose metabolism symbolized by insulin resistance, atypical fasting glucose levels, and reduced glucose tolerance. Managing of glucose intolerance is often problematic, because of inadequate findings about the mechanisms by which over-nutrition harms glucose homeostasis [35].

6. Conclusion

In comparison with all other anti-hyperglycemic factors, nesfatin-1 possibly symbolizes a novel agent of insulin contributors. Composed, the anorexigenic and anti-hyperglycemic properties of nesfatin-1 prominently influence both food intake and glucose metabolism, involving its noteworthy parts in the metabolic regulator of the body. It is necessary that additional works on nesfatin-1 would be respected to the management of metabolic diseases particularly for type-2 diabetes and obesity. Nonetheless, the specific physical and pathophysiological roles of nesfatin-1 on glucose and energy mechanism now persist unidentified. Therefore, the physiological effect of elevated plasma NUCB2-1 in patients with nT2DM and IGT observed in the present study is uncertain. Different study plan, such as case selection (e.g., obese vs lean, glycemia level, and diet type) and experimental situations, may have related to the discrepancy.

Conflict of interest

There is no Conflict of Interest to declare in the paper.

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