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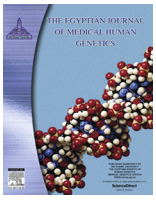

Review

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