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News and Reviews

Nesfatin-1, a unique regulatory neuropeptide of the brain

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ABSTRACT

Nesfatin-1, a newly discovered NUCB2-derived satiety neuropeptide is expressed in several neurons of forebrain, hindbrain, brainstem and spinal cord. This novel anorexigenic substance seems to play an important role in hypothalamic pathways regulating food intake and energy homeostasis. Nesfatin-1 immunoreactive cells are detectable in arcuate (ARC), paraventricular (PVN) and supraoptic nuclei (SON), where the peptide is colocalized with POMC/CART, NPY, oxytocin and vasopressin. The nesfatin-1 molecule interacts with a G-protein coupled receptor and its cytophysiological effect depends on inhibitory hyperpolarization of NPY/AgRP neurons in ARC and melanocortin signaling in PVN. Administration of nesfatin-1 significantly inhibits consumatory behavior and decreases weight gain in experimental animals. These recent findings suggest the evidence for nesfatin-1 involvement in other important brain functions such as reproduction, sleep, cognition and anxiety- or stress-related responses. The neuroprotective and antiapoptotic properties of nesfatin-1 were also reported. From the clinical viewpoint it should be noteworthy, that the serum concentration of nesfatin-1 may be a sensitive marker of epileptic seizures. However, the details of nesfatin-1 physiology ought to be clarified, and it may be considered suitable in the future, as a potential drug in the pharmacotherapy of obesity, especially in patients treated with antipsychotics and antidepressants. On the other hand, some putative nesfatin-1 antagonists may improve eating disorders.

Contents

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1. Introduction

1.1. Overview

In recent years, thanks to a dynamic development of molecular biology, a number of new regulatory neuropeptides have been identified and described. A great majority of them have unique characteristics, a wide multidirectional spectrum of physiological activity and act at the level of many neuronal pathways. In this context, a recently discovered and still relatively unknown nesfatin-1 (NEFA/NUCB2-encoded satiety and fat-influencing protein) appears to be a particularly interesting substance. The first information regarding its existence was provided in 2006 by Oh et al., as result of studies on lung carcinoma cell lines, revealing the expression of leptin receptors following activation by the PPAR-γ ligand - troglitazone. Presently, research studies on nesfatin-1 and its neurophysiological properties are still in their initial phase.

Nesfatin-1 is a potent anorexigenic factor inducing satiety and strongly inhibiting food and water intake (Stengel and Tache, 2010; Stengel et al., 2010a; Pałasz et al., 2010; Shimizu et al., 2009). Upon direct injection to a lateral ventricle of the rat brain, it causes a dose dependent depression of consumatory behavior. Continuous infusion to the III-rd ventricle results in a significant reduction of body mass and in a decreased amount of white adipose tissue. An intraperitoneal injection of nesfatin-1 induces a 3-hour suppression of food intake in mice. Also, its subcutaneous administration induces the identical effect, and this anorexigenic action can be maintained for 14 h. Repeated intraperitoneal doses have substantially inhibited the increase of body mass, over a 6-day period (Shimizu et al., 2009). It should be underlined that the peripheral nesfatin-1 doses required to suppress food intake are approximately 1000-fold higher than those effective in the CNS (Stengel et al., 2010a).

Serum levels of nesfatin-1 are substantially decreased in the state of starvation, while refeeding leads to normalization. Nesfatin-1 penetrates the blood–brain barrier (Pan et al., 2007) that may potentially create an opportunity for its putative therapeutic use. It appears that after reaching the hypothalamic centers, nesfatin-1 may inhibit appetite and food intake. It has recently been noted that in humans, the CSF/plasma nesfatin-1 ratio is negatively correlated with body mass index (BMI) and body mass, possibly suggesting that nesfatin-1 is a protein-bound neuropeptide. A hypothesis has been proposed that, dependent on body mass changes, efficiency of nesfatin-1 uptake by the CSF can be caused by saturation of its transporters (Tan et al., 2011). Recently, studies clearly suggesting the participation of nesfatin-1 in brain actions diverse from energy balance regulation have been published. Nesfatin-1 appears to be a neuropeptide that plays a significant role in reproductive processes, stress responses, and pathology of mental and neurological disorders (Könczöl et al., 2010; Ogiso et al., 2011; Aydin et al., 2011, Stengel and Tache, 2011). These completely innovative aspects of nesfatin-1 physiology are more extensively presented in subsections of this review.

With regard to the anorectic properties of nesfatin-1, the recent presumption that it can display some characteristics of neuroprotective factors seems particularly intriguing. At the present time, the only source of these suggestions is the study conducted by Özsavci et al. (2011), who examined the influence of nesfatin-1, administered intraperitoneally, on the profile of oxidative stress markers and the permeability of blood–brain barrier in rats with subarachnoid hemorrhage (SAH). The authors have noted that the levels of SAH-induced oxidative brain injury markers and plasma levels of pro-inflammatory cytokines: TNF-α, IL-1β, and IL-6 as well as proapoptotic protein caspase-3 were significantly decreased in animals exposed to the actions of nesfatin-1. Moreover, these authors have reported that nesfatin-1 reduced the, SAH-dependent, histological structural changes of basilar arteries by inhibiting neutrophil infiltration. This research allows us to deduce that nesfatin-1 can play the role of anti-inflammatory and antiapoptotic factor in the central nervous system. However, as of today, it is still too early to conclude that nesfatin-1 represents a compound which plays the key role in the neuroprotective mechanisms of the brain. There is no doubt that this remarkably interesting issue requires further experimental studies.

1.2. Molecular structure

Formation of the 82-amino acid molecule nesfatin-1 is the effect of posttranslational cleavage of prohormone NEFA/nucleobindin-2 (NUCB2), performed by the specific convertases PC3/1 and PC2 (Garcia-Galiano et al., 2010, Stengel and Tache, 2010). NUCB2, a polypeptide composed of 396 amino acids (aa), preceded by a 24-aa signal peptide is located both on the plasma membrane and in the neuroplasm. This precursor protein consists of the following domains: N-terminal signal peptide, Leu/Ile rich region, DNA-binding domain, nuclear targeting signal, two Ca^{2+}-EF-hand motifs and leucine zipper domain (Stengel et al., 2010a). Nesfatin-1 has a substantial, above 85% homology, of its sequences between humans and mammals, and even the lower vertebrates (Gonzales et al., 2010). The nesfatin-1 molecule is composed of three domains: N-terminal (N23), middle part (M30) and C-terminal (C29). The M30 active core appears to play the key role in the induction of physiological effects of this peptide, and especially in its anorectic responses (Fig1. A). Another effect of the NUCB2 proteolytic processing is a production of its inactive derivatives: nesfatin 2 and 3, spanning residues 85–163 and 166–396, respectively (Oh et al., 2006).

1.3. Distribution

In the rat hypothalamus, neurons localized in the arcuate nucleus (ARC), paraventricular nucleus (PVN), supraoptic nucleus (SON), dorsomedial (DMH), lateral hypothalamus (LHA), and zona incerta are characterized by expression of nesfatin-1 (Stengel et al., 2010a; Shimizu et al., 2009). It is assumed that the anorexigenic action of nesfatin-1 is performed mostly in the first three key regulatory hypothalamic centers. The nesfatin-1 immunopositive neurons are also present in the brain stem, including serotoninergic cells – of the raphe pallidus (RPa), raphe obscurus (ROb), and cholinergic cells – of the nucleus accessorius of oculomotor nerve (nucleus Westphal-Edinger; EW), and nucleus dorsalis of vagus nerve (Foo et al., 2008). Since some sympathetic axons originate from the raphe nuclei and terminate in brown adipose cells, it is suggested that nesfatin-1 takes part in the regulation of thermogenesis (Brailoiu et al., 2007). It is also possible that nesfatin-1, which is released from the synaptic endings' of the vagus nerve, can have an impact on secretory and motor activity of the gastrointestinal tract, and may regulate the course of digestive functions (Stengel et al., 2010a; Goebel et al., 2009). On the other hand, it has recently been demonstrated that pretreatment with capsaicin (to block autonomic C fibers) abolished the food intake reduction caused by peripheral nesfatin-1 injection. These findings indicate a putative role of vagal afferents in peripheral nesfatin-1 signaling to the brain centers (Shimizu et al., 2009). As further evidence to this, it has been demonstrated that nesfatin-1 activates cell bodies in the nodose ganglion *in vitro*. This assembly of neurons contains the perikarya of vagal nerve fibers projecting to the nucleus of the solitary tract (Iwasaki et al., 2009). The nesfatin-1 contribution to the physiological functions of the oculomotor nerve has not been clearly explained (Goebel et al., 2009). In addition, perikarya