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THE ROLE OF NESFATIN-1 IN METABOLISM REGULATION: AN OVERVIEW*

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Abstract

The hypothalamus synthesizes molecules involved in the regulation of feeding behaviour. Nesfatin-1 is a recently discovered substance expressed in both the brain and peripheral tissues and exerts a strong anorectic action. Nesfatin-1-immunoreactive cell bodies are distributed in arcuate (ARC), paraventricular (PVN) and supraoptic (SON) nuclei, where the peptide has been found to be co-expressed with pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), oxytocin (OX) and vasopressin (VP). More detailed studies have shown a wide distribution of nesfatin-1-positive neurons in several brain areas, such as the forebrain, hindbrain, brainstem and spinal cord. Moreover, nesfatin-1 has been also expressed in peripheral tissues, co-localizing with ghrelin in the gastric mucosa and insulin in β-cells of the endocrine pancreas and adipose tissue. Functional studies have revealed that exogenous nesfatin-1 administered into the brain ventricles, subcutaneously or intraperitoneally, was able to decrease both food intake in the dark phase as well as body weight gain in a dose-dependent manner. In addition, recent findings suggest the involvement of nesfatin-1 in the control of insulin secretion as well as immune and stress-related responses. However, since there is still a deficiency of data concerning the nesfatin-1 receptor, the possible implementation of nesfatin-1 analogs during human metabolic disorders requires further study.

Key words: nesfatin-1, feeding behaviour, hypothalamus, metabolism, anorexia

The regulation of food intake in mammals is performed by an intricate network of neurons located in the central nervous system (Morton et al., 2006). The main region of the brain involved in these processes is the hypothalamus, which is continuously informed about the nutritional, energetic and environmental status of the body (Simpson et al., 2009). The hypothalamic nuclei integrate signals from the periphery of the body, mainly from the gastrointestinal tract and adipose tissue as well as from the brain stem. The arcuate nucleus (ARC) is the chief hypothalamic area involved in the control of food intake (Simpson et al., 2009). This nucleus contains two distinct

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subsets of neurons. One of them acts as a feeding stimulator and releases neuropeptide Y (NPY) and agouti-related peptide (AGRP). The second population of neurons acts as an anorexigenic and down regulates food intake. These neurons synthesize pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) (Druce et al., 2004). Neurons of the ARC project connect to the paraventricular nucleus (PVN), the dorsomedial nucleus (DMV), the lateral hypothalamic area (LHA) as well as the perifornical area (PFA) (Shioda et al., 2008). After a meal, satiety signals are generated in the gastrointestinal tract. Following the arrival of food into the stomach and intestinal lumen, enteroendocrine cells liberate several peptides that activate vagal ascending pathways to the nucleus of the solitary tract (NTS). NTS integrates the peripheral satiety signals and sends this information to the hypothalamus (Dockray, 2009). Peptides produced peripherally can both inhibit and stimulate the digestion. The most potent anorexigenic peptides are cholecystokinin, glucagon, glucagon-like peptide-1, leptin and peptide YY. In contrast, ghrelin shows the opposite effect and is considered to be the main orexigenic peripheral peptide. Adequate receptors, which bind the above-mentioned substances, are also expressed within hypothalamic neurons (Arora and Anubhuti, 2006). Thus, these molecules can reach the hypothalamus via the bloodstream and interact with their receptors and modulate feeding behaviour. Due to the potential therapeutic effects of these peptides, they have been deeply investigated. To date, the list of substances involved in the regulation of feeding behaviour has been updated with a newly-discovered molecule, NUCB2/nesfatin-1. In this review, we report on the current knowledge of the structure, function and physiological action of nesfatin-1.

Identification and structure of nesfatin-1

In 2006, Sinsuke Oh-I et al. for the first time reported the discovery of nesfatin-1, a new peptide exhibiting an anorexigenic effect (Oh-I et al., 2006). While studying the fact that troglitazone (a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist) might modify satiety as well as express some peptides in both the hypothalamus and peripheral adipose tissue, the brain medulloblastoma (HTB185) and 3T3-L1 cell lines were used. It was noted that expression of one gene was considerably stimulated by troglitazone and it was subsequently shown that this gene encodes nucleobindin 2 (NUCB2), also termed NEFA protein (for DNA binding/EF-hand/acid protein). NUCB2 has been found to be composed of a signal 24 amino acid and a protein structure containing 396 amino acids. NUCB2, together with NUCB1, are secreted proteins, but their functions have remained largely unknown (Karabinos et al., 1996). These two proteins have a very high amino acid homology in various species such as rats, mice and humans (Barnikol-Watanabe et al., 1994). NUCB2 has the presence of several conserved cleavage sites recognized by pro-hormone convertases (PC3/1 and PC2). As a result of the proteolytic activity of PC3/1, the molecule NUCB2 is cleaved into several active peptides (Duckert et al., 2004). The major fragments of such processing were named nesfatin-1 (residue 1–82), nesfatin-2 (residue 85–163) and nesfatin-3 (residue 166–396) (Fig. 1). Only nesfatin-1 suppresses nocturnal food intake and body weight gain (Oh-I et al., 2006).

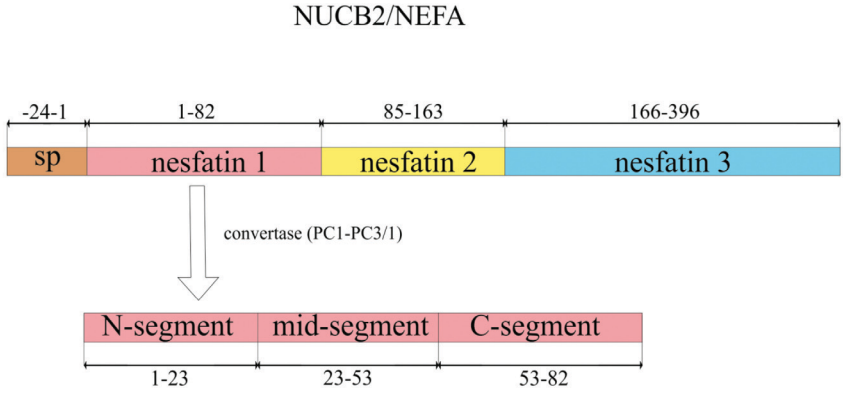

Figure 1. The primary structure of nesfatin-1 and its prohormone NUCB2. SP, signal peptide. Nesfatine-1 is cleaved to three active fragments. Below amino acid sequence of three distinct fragments of nesfatin-1

Distribution in the central nervous system

The application of immunohistochemical methods, as well as *in situ* hybridization, have shown that nesfatin-1 is abundantly expressed in several regions of the hypothalamus which play essential roles in food intake control (Foo et al., 2008; Goebel-Stengel et al., 2011). Cell bodies immunoreactive to nesfatin-1 have been detected in the supra-optic nucleus (SON), PVN, ARC and LHA. Moreover, nesfatin-1 perikarya were disclosed outside of the hypothalamus. Nesfatin-1-like immunoreactive neuronal somata were encountered in the Edinger-Westphal nucleus (EW), nucleus of the solitary tract (NTS), dorsal motor nucleus of vagus (DMV) and intermediolateral cell columns of the spinal cord. Additionally, this peptide was mapped in the forebrain, central amygdaloid nucleus, hindbrain nuclei as well as in preganglionic sympathetic and parasympathetic neurons of the thoracic, lumbar and sacral segments of the spinal cord (Brailoiu et al., 2007; Foo et al., 2008). It is noteworthy that nesfatin-1 immunoreactivity was expressed only in the cytoplasm of cell bodies and primary dendrites, but not in varicosities or axon terminals. This fact suggests that nesfatin-1 is mainly an intracellular modulator. However, the existing data are insufficient to exclude its role as an extracellular regulatory peptide (Foo et al., 2008). To date, the distribution of nesfatin-1 has only been described in rodents, especially in rats and mice (Foo et al., 2008; Goebel-Stengel et al., 2011). Double immunohistochemical staining has shown that nesfatin-1-positive neurons also exhibit the presence of other peptides which are involved in the regulation of feeding behaviour. The type of substances which co-localize with nesfatin-1 depends on the part of the nervous system studied. Within the SON and PVN, nesfatin-1 was observed in the majority of oxytocinergic and vasopressinergic neurons (Brailoiu et al., 2007; Foo et al., 2008; Shimizu et al., 2009 a). Likewise, a large subpopulation of thyrotropin-releasing hormone (TRH)- and corticotropin-releasing hormone

(CRH)-positive cell bodies also contain nesfatin-1. In the LHA, nesfatin-1 immunoreactive cell bodies co-expressed melanin-concentrating hormone (MCH) and in the ARC, nesfatin-1 was present in neurotensine (NT), melanocyte-stimulating hormone (α-MSH) as well as growth hormone-releasing hormone (GHRH) immunoreactive cell bodies. Furthermore, a large population of nesfatin-1 positive neurons co-expressed the CART peptide. The co-expression of these peptides was observed in all previously-described hypothalamic areas. Moreover, double-labelling showed the co-localization of nesfatin-1 and tyrosine hydroxylase (TH) within neurons of the NTS and co-expression of nesfatin-1 with choline acetyltransferase (ChAT) in the cells of the DMV. The co-localization of nesfatin-1 with NPY was initially not found, although close apposition of the ARC nesfatin-1-IR perikarya with NPY positive nerve fibres was reported (Brailoiu et al., 2007; Foo et al., 2008; Fort et al., 2008; Shimizu et al., 2009 a, b; Stengel and Taché, 2010). However, current papers have reported a small number of double-labelled NPY/nesfatin-1 -positive neurons within the ARC (Inhoff et al., 2010).

Distribution in peripheral tissues

Although hypothalamic peptides affect energy maintenance and expenditure, the peptidergic content of the gastrointestinal tract significantly exceeds that in the hypothalamus. Both structures communicate via an afferent pathway through the vagal nerve or the bloodstream (Berthoud and Neuhuber, 2000). This fact strongly suggests that nesfatin-1 expressed in different peripheral tissues may be involved in metabolism and body weight homeostasis. Indeed, immunohistochemical studies have provided evidence confirming this hypothesis. Among others, the presence of nesfatin-1 was detected in the endocrine cells of stomach, small intestine and the pancreas (Stengel et al., 2008; Foo et al., 2010; Zhang et al., 2010). Moreover, our preliminary investigations found nesfatin-1 positive cells in the mucosal layer of the canine descending colon (Gonkowski et al., 2012). Nesfatin-1 positive cells in the mucosa of stomach are particularly distributed in the middle and lower segments of gastric mucosal glands. Double-labelled staining of these cells reveals the co-localization of nesfatin-1 with orexigenic hormone ghrelin. High magnification showed that these peptides are located in a distinct subpopulation of vesicles (Stengel et al., 2008). Nesfatin-1-positive cells were also described in the submucosal layer of the duodenum and Brunner's glands (Zhang et al., 2010) as well as in the endocrine parts of the pancreas, while in humans and rats it was found only in β-cells (Foo et al., 2010). It should be pointed out that, as in stomach endocrine cells, the subcellular cytoplasmic localization of nesfatin-1 does not overlap insulin. Significant expression of nesfatin-1 was also confirmed in human and murine adipose tissue (Ramanjaneya et al., 2010). Despite the fact that nesfatin-1 was initially regarded to be a specific hypothalamic neuropeptide, numerous studies have confirmed that, as in the case of many other central regulatory appetite peptides, it is also expressed in different peripheral tissues. However, although the above-mentioned data indicate the possible roles of nesfatin-1 in the control of food intake and other potential physiological processes, the exact physiological function of the peptide still remains unknown.

The biological function of nesfatin-1 and its anorexigenic effects

General information

Along with the discovery of nesfatin-1 by Oh-I et al. (2006), its effect on food intake was also demonstrated. Intracerebroventricular (icv) injection of nesfatin-1 (5 pmol = 0.05 μg/rat) in male rats reduces food consumption and body weight gain, whereas injections of an antibody neutralizing nesfatin-1 stimulate food consumption. The effect was continued for 6 h after icv injection (Oh-I et al., 2006). A similar effect was achieved when nesfatin-1 was injected into the fourth ventricle and cisterna magna (Stengel et al., 2009). It is worth underlining that the action of nesfatin-1 was observed only during the dark phase, whereas nesfatin-1 administered during the light phase in overnight-fasted rats had no effect on the food intake (Stengel et al., 2009; Goebel et al., 2011). Since detailed studies have shown that other fragments processed from NUCB2 (nesfatin-2, nesfatin-3 and nesfatin 2/3) do not promote satiety, it seems that the process of enzymatic cleavage of NUCB2 molecules is required to induce an anorectic effect of nesfatin-1. In addition, nesfatin-1 has three distinct segments: an N-terminal fragment composed of 23 amino acids, a mid-segment with 30 aa and a C-terminal fragment with 29 aa. Among these three separate segments, only the injection of the mid-segment has an effect on the feeding behaviour similar to the full sequence of nesfatin-1 (Shimizu et al., 2009 b). Support for this hypothesis comes from the discovery by Pan et al. (2007) who reported that nesfatin-1 can cross the blood brain barrier without saturation.

Peripheral and central action of nesfatin-1

It is assumed that both peripherally-synthesized and exogenously-administered nesfatin-1 can enter the brain and inhibit food intake. These observations have been confirmed by intraperitoneal and subcutaneous injections of nesfatin-1. In both cases, a reduction in food consumption was observed. However, in the case of intraperitoneal injection, food intake was suppressed over a period of 3 h after injection, while subcutaneous administration of nesfatin-1 inhibited food intake for 14 hours (Shimizu et al., 2009 b). The dose at which the response occurred was approximately >1000-fold higher than that required when the peptide was injected intraventricularly. In these doses, nesfatin-1 and its mid-fragment do not alter the blood glucose level or induce unusual changes in behaviour (Shimizu et al., 2009 b; Stengel and Taché, 2010). Further reports have indicated more precise mechanisms of nesfatin-1 action as well as interactions with other peptides involved in food intake (Maejima et al., 2009; Gina et al., 2010). The inhibitory effect of nesfatin-1 was retained under leptin-resistant conditions (genetically obese, genetically diabetic and high-fat diet-induced obesity) in mice and Zucker fatty rats with a leptin-receptor mutation (Shimizu et al., 2009 b; Maejima et al., 2009). These data indicate a leptin-independent mechanism of nesfatin-1 action. The effect was confirmed by both injections of a full sequence of nesfatin-1 as well as its mid-segment component. Moreover, it has been shown that an intraperitoneally-injected mid-segment of nesfatin-1, significantly stimulated c-Fos protein expression in the NTS, but did not induce c-Fos synthesis in the neurons of the ARC. A similar effect was observed in changes of expression of CART and POMC – two important peptides participating in metabolism regulation. A particu-

larly significant increase of expression of these peptides after mid-segment injections of nesfatin-1 was observed only in the NTS, without changes in the ARC (Shimizu et al., 2009 b). The anorexigenic effect of the peripherally-administered nesfatin-1 mid-segment was abolished in mice by their pre-treatment with capsaicin as well as by injections of the nicotinic cholinergic blocker hexamethonium (Shimizu et al., 2009 b). On the other hand, atropine methyl nitrate (an antagonist for the muscarinic cholinoreceptor) did not affect nesfatin-1 mid-segment suppression on food intake (Shimizu et al., 2009 b). These data, along with the mapping of c-Fos positive neurons within NTS in reaction to intraperitoneal injections of nesfatin-1 or its mid-segment, suggest that the vagal nerve can play an important role in the induction of anorexia (Shimizu et al., 2009 b; Stengel and Taché, 2010). Additionally, an anorexic effect of nesfatin-1 can be achieved as a result of activating POMC and CART-positive neurons in the NTS. The lack of inhibiting effect on food intake by injections of C-terminal and N-terminal nesfatin-1 fragments, while a clear effect was exerted by the nesfatin-1 mid-segment, strongly suggests that the middle region of nesfatin-1 contains an essential site responsible for physiological effects. Moreover, the amino acid sequence of this fragment is well conserved in various species and it is likely to be rich in α-helix structures, which is probably essential for interaction with the receptor (Shimizu et al., 2009 b; Stengel and Taché, 2010).

In contrast, central injections of alpha-melanocyte-stimulating hormone (α-MSH) cause an increase of nesfatin-1 gene expression in the PVN (Maejima et al., 2009). In contrast, the melanocortin 3/4 receptor antagonist SHU9119 injected into the third ventricle was able to abolish the inhibitory effect of nesfatin-1 (Shimizu et al., 2009 b). The paraventricular nucleus seems to be an important site of the central action of nesfatin-1. Nesfatin-1 injected into the third ventricle induces the expression of c-Fos in the PVN perikarya. More detailed analysis has shown that c-Fos-positive neurons in the PVN also contain oxytocin. Double immunofluorescence labelling demonstrated that 22% of nesfatin-1-immunoreactive neurons also expressed oxytocin and 49% of oxytocin-positive neurons were also nesfatin-1-immunoreactive (Maejima et al., 2009). In addition, some nesfatin-1-immunoreactive neurons are located in close proximity to oxytocin-IR and oxytocin/nesfatin-IR perikarya. These data, collectively, provide evidence that nesfatin-1 could be released by perikarya with neighbouring oxytocin-positive neurons. Examinations of the PVN slices incubated with exogenous nesfatin-1 indicated the ability to release oxytocin (Maejima et al., 2009). Moreover, it has been reported that nesfatin-1 administered under superfusion conditions increased Ca^{2+} levels in single oxytocin immunoreactive neurons of PVN. The anorexigenic effect of nesfatin-1 was reversed by pre-treatment with H4928 (an oxytocin receptor antagonist). These results indicate the possibility that oxytocin may be involved in nesfatin-1 induced anorexia and also suggest the important role of the PVN nucleus in the post-prandial regulation of feeding behaviour (Maejima et al., 2009).

It has been reported that nesfatin-1 co-localizes with POMC and CART, but not with prominent orexinergic peptides such as NPY and AgRP in neurons of the ARC. This suggests that these neuronal populations could be directly hyperpolarized by nesfatin-1, possibly released from the CART/POMC positive perikarya. In the extra-

cellular space, nesfatin-1 directly or indirectly activated the ATP-dependent potassium channels ($K_{ir6.2}$) (Price et al., 2008). The hyperpolarization of the NPY neurons may play a significant role in the mechanisms of nesfatin-1-induced anorexia.

Despite an increase in the number of studies on the biological actions of exogenously administered nesfatin-1 and the expression of endogenous nesfatin-1 in various tissues, there is still a lack of data on nesfatin-1 receptors mediating those effects. To date, only one study has reported that nesfatin-1 elevated the intracellular Ca^{2+} concentration in cultured hypothalamic neurons in rats. This response was inhibited by pre-treatment of the cells with three substances: pertussis toxin and calcium channels blocker and the protein kinase A inhibitor. These data suggest that the interaction between nesfatin-1 and a G-protein-coupled receptor leads to an increase in the Ca^{2+} flux which is linked to protein kinase A (Iwasaki et al., 2009).

Some studies have shown an increase in the number of nesfatin-1-positive cells during stress and peripheral inflammatory processes (Bonnet et al., 2009; Stengel et al., 2011). Intraperitoneal injections of bacterial lipopolysaccharide (LPS) (which is a well-known pro-inflammatory factor) cause an increase in nesfatin-1 concentration in the blood plasma with a simultaneous enhancement of gastric NUCB2 mRNA concentration. Moreover, intraperitoneal LPS administration promotes the expression of nesfatin-1 in hypothalamic neurons. In particular, it increases the number of c-Fos/nesfatin-1 positive neurons in the PVN, SON and NTS and, to a lesser extent, in the ARC (Bonnet et al., 2009; Stengel et al., 2011). Therefore these results suggest that nesfatin-1 may affect the onset of physiological changes occurring during acute inflammation and also can be involved in the modulation of feeding behaviour during endotoxemic anorexia.

The function of nesfatin-1 in metabolic disorders and diabetic disorders

In pioneering studies performed in rats, Oh-I et al. (2006) observed a reduction in dark phase food intake following the third ventricular administration of nesfatin-1. The following studies have proven the wide distribution of this peptide as well as its different functions in the regulation of food intake (Brailoiu et al., 2007; Goebel-Stengel et al., 2011). The abundant expression of nesfatin-1 in the pancreatic β islets suggests that this peptide participates in the regulation of glucose metabolism and the pathophysiology of diabetes (Su et al., 2010). The initial data have shown the ability of exogenously administered recombined nesfatin-1 to reduce the blood glucose level in streptozotocin-induced type-1 diabetic mice (Foo et al., 2010; Su et al., 2010). This anti-hyperglycemic effect depends on the dose of nesfatin-1 and the time of its administration. It is worth noting that its efficient effect was achieved only with a simultaneous co-administration of insulin. The *in vivo* research conducted on cultured MIN6 cells and pancreatic islets isolated from mice has confirmed that the effective increase in insulin secretion by nesfatin-1 occurs in the presence of an elevated glucose level in medium (Gonzalez et al., 2011). The high glucose medium concentration (16.7 mM) induced a four-fold increase of nesfatin-1 release from MIN6 cells compared to a low-glucose medium concentration (2.0 mM) (Gonzalez et al., 2011). Interestingly, streptozotocin-induced diabetes in mice resulted in a significant decrease of NUCB2 levels, as well as a reduced number of nesfatin-1 immunoreac-

tive cells within the islets. In contrast, during diabetes-induced obesity in mice, an increase in both NUCB2 mRNA expression and the density of nesfatin-1 immunoreactive islets was observed (Foo et al., 2010; Su et al., 2010). These differences in expression of the nesfatin-1 during the course of experimentally-induced mellitus type I and II diabetes may result from the different pathophysiology of these diseases. The type 2 diabetes is due to insulin resistance primarily within the muscles and fat tissue and inadequate insulin production and relative insulin deficiency. While the pathophysiology in type I diabetes originates from destruction of β cells in the pancreas and a complete loss of insulin secretion. Nevertheless, these results indicate that nesfatin-1 is an insulinotropic peptide that directly affects the pancreatic islet β-cells. However, the precise mechanisms underlying the physiology of nesfatin-1 actions and the pathological processes during diabetes and obesity remain elusive and require further studies. Recent reports suggest that *in vivo* nesfatin-1 augments glucose-induced insulin secretion through the activation of L-type calcium channels in the β cells of mice (Nakata et al., 2011). Nesfatin-1 can also exert functions which are not connected with feeding behaviour (Pałasz et al., 2012).

Summary

Hypothalamic nuclei synthesize and release numerous bioactive substances regulating food intake. A recently-discovered molecule, nesfatin-1, has been found to exert a strong anorectic effect. Neuronal somata expressing nesfatin-1 have been localized mainly in the arcuate, paraventricular and supraoptic nuclei. Nesfatin-1 -synthesizing perikarya co-express POMC, CART, oxitocin and vasopressin. This peptide has also been identified in neurons of the rhombencephalon, brain stem and medulla oblongata.

Nesfatin-1 has also been found in peripheral tissues. In gastric mucosa cells, this peptide has been co-localized with ghrelin, while in pancreatic beta cells it has been co-localized with insulin. Functional examinations of the nesfatin-1 physiological properties carried out on rats and mice have revealed that its intraventricular, subcutaneous and intraperitoneal administration decreased food intake and body mass gain in a dose-dependent manner. Moreover, current reports have suggested its possible function in the control of insulin secretion and immunological response. Nevertheless, the nesfatin-1 receptor still remains unknown and the therapeutic application of nesfatin-1 analogues in patients suffering from metabolic disorders requires further study.

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Rola nesfatyny-1 w regulacji metabolizmu: artykuł przeglądowy

STRESZCZENIE

Podwzgórze syntetyzuje i uwalnia liczne substancje, które odgrywają ważną rolę w procesie pobierania pokarmu. Nesfatyna-1 jest ostatnio odkrytą molekułą wywierającą silny efekt anorektycz-

ny. Ciała komórek nerwowych, które zawierają nesfatynę-1 znajdują się przede wszystkim w jądrze łukowatym, przykomorowym i nadwzrokowym. W wyżej wymienionych strukturach nesfatyna-1 współwystępuje z proopiomelanokortyną, peptydem stymulowanym kokainą i amfetaminą, oksytocyną oraz wazopresyną. Dokładniejsze badania wykazały obecność nesfatyny-1 w innych rejonach mózgu, takich jak tyłomózgowie, pień mózgu czy rdzeń przedłużony. Dodatkowo ekspresja nesfatyny-1 została potwierdzona w tkankach obwodowych. W komórkach błony śluzowej żołądka nesfatyna-1 współwystępowała z greliną oraz insuliną w komórkach beta wysp trzustkowych. Badania nad funkcjonalnymi właściwościami nesfatyny-1 przeprowadzone na szczurach oraz myszach wykazały, że peptyd ten podany do komór mózgu, wstrzyknięty podskórnie lub do otrzewnowo znacznie obniżał pobieranie pokarmu oraz zmniejszał masę ciała w sposób zależny od dawki. Co więcej ostatnie wyniki dowodzą udział nesfatyny-1 w kontroli sekrecji insuliny oraz w odpowiedzi immunologicznej. Jednak z drugiej strony nic nie wiadomo na temat receptora dla nesfatyny-1, dlatego zastosowanie analogów tego peptydu u ludzi z chorobami metabolicznymi wymaga dalszych badań.