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Nesfatin-1 in the neurochemistry of eating disorders

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Summary

The vast majority of new neuropeptides feature unique biochemical properties as well as a wide spectrum of physiological activity applied in numerous neuronal pathways, including hypothalamus and the limbic system. Special interest should be paid to nesfatin-1 – the relatively recently discovered and still intensively studied regulatory factor and a potential modulator of eating behaviors. New information about it now allows to consider this neuropeptide as a potentially important factor involved in the pathogenesis of many different mental disorders. The considered pharmacomodulation of nesfatinergic signaling may be potentially helpful in the future treatment of some neuropsychiatric and metabolic disorders including anorexia nervosa. Although the results of some basic and clinical tests seem to be promising, all possible applications of the aforementioned neuropeptides, together with their agonists and antagonists still remain in the area of speculation. The intensive search of selective modulators of their known receptors may facilitate the opening of a promising chapter in the eating disorders therapy. This paper provides a review of recent scientific reports regarding the hypothetical role of nesfatin-1 in the neuronal pathways related to pathophysiology of anorexia nervosa.

Key words: nesfatin-1, anorexia nervosa, hypothalamus, neuropeptides

Introduction

Anorexia nervosa (AN) is a relatively frequent disorder which is especially common in female teenagers as well as young, adult women and which is characterized

by restricted food intake as compared to energetic requirements, anxiety and usually distorted perception of body image. Unfortunately, many AN patients deny their serious condition, which is life-threatening as its standardized mortality rate may reach up to 18% [1]. The most frequent comorbid mental issues in AN females are mood disorders, while among male patients anxiety and psychosis prevail. Borderline personality can be observed mainly in females, while narcissistic, or even sociopathic traits seem to be correlated with the male sex [2]. As far as AN is concerned, the male to female ratio equals one to five (males 16.5% vs. 83.5%).

Recovering from AN is often a slow process and AN is usually linked with an increased risk of development of other psychiatric conditions, including bulimic symptoms which are frequent in the first two years of AN onset [3]. At present, there are numerous premises which postulate that there are at least indirect connections between anxiety and AN pathogenesis, and abnormalities in the brain peptidergic circuits [4–6]. Despite a growing number of neurochemical studies, there is not enough information on the effect of central peptidergic signaling on the course of anxiety and eating disorders. Moreover, there is not a single coherent model explaining the origin of these disorders at the level of hypothalamic and extrahypothalamic regulatory factors and their receptors. Furthermore, there is no fully satisfactory animal experimental AN model. Recently a considerable progress can be observed in explaining the significance of hypothalamic mechanisms engaged in regulation of food intake and energetic balance. The functional description of intracellular reactions within the hypothalamic nuclei has lately been improved; new neuron populations have been characterized and new, multifunctional neuropeptides have been discovered in the brain [7–10]. Nevertheless, relatively few scientific papers are devoted to the newly discovered brain regulation factors, such as nesfatin-1, phoenixin, spexin and kisspeptin in the context of AN pathogenesis.

Classic neuropeptides in the mechanisms of anorexia nervosa

At present, there are a few molecular and functional models of AN pathogenesis. One of them assumes that AN is a form of a selective, central resistance to circulating ghrelin [11] and in some cases administration of ghrelin could be an alternative and promising strategy of AN treatment [12]. Another theory defines AN as a result of disturbances of the peptidergic pathways associated with the immune system dysfunction [13]. Finally, some assumptions refer to the supposed role of various intestinal bacteria in the AN etiology [14]. As compared to the aforementioned models, a hypothesis stating that anorexia nervosa is the result of a prolonged stimulation of the reward circuitry by orexigenic hypothalamic neuropeptides seems to be best documented and commonly accepted [5, 15]. In AN patients, expressions of ghrelin, orexin and 26RFa are generally increased, which reflects the homeostatic mechanism aimed at stimulation of eating behaviors and minimization of severe undernutrition. However, in AN

this regulatory pathway may be severely damaged and insufficient, which makes the brains of patients resistant to a series of orexigenic factors.

There is also an alternative viewpoint which speculates that a prolonged increase of the activity of neurons revealing orexin expression, the melanin concentrating hormone (MCH) and 26RFa in the lateral hypothalamus strengthens food aversion throughout stimulation of dopamine-dependent anxiety in the reward circuitries of the brain. What is interesting, in patients who recovered from AN the response to eating stimuli in the reward circuitries remains increased [16], which supports the thesis that AN is a result of the abnormally increased process of reward for pathologically restricted food intake.

Orexins A and B belong to the group of neuropeptides derived from a well-preserved among species family of incretins. Orexin-A is composed of 33 amino acids and is more stable in the cerebrospinal fluid and serum than orexin-B. On the other hand, orexin-B is a linear 28-amino acid molecule, but its concentration in the brain is 2–5 times higher as compared to orexin-A [17]. Orexins are ligands of the metabotropic OX1R and OX2R receptors with diverse affinity to lisoforms of orexins; OX1R reveals a higher affinity to orexin-A, while OX2R reveals an approximately equal affinity to both molecules [18]. Anatomic distribution of orexinergic neurons both in the human and animal brain is limited almost entirely to the lateral hypothalamus [19]. In the animal model, fasting leads to the increase of the pro-orexin mRNA level – preproorexin (PPOX), while in obese mice there is a decreased expression of the PPOX gene [19]. On the other hand, insufficient orexinergic signaling in mice strongly inhibits food intake [20]. There are two independent parallel studies regarding changes in orexin concentrations in plasma of AN patients. The first study conducted by Janas-Kozik et al. [21] revealed a decreased level of orexin-A (OxA) in untreated AN females, while the second study showed an increase in the level of this neuropeptide in the same clinical conditions [22]. Despite this discrepancy, both authors observed a drop in OxA level in the course of refeeding, which may suggest an increase in orexinergic signaling in AN.

Interestingly, while refeeding the AN patients it seemed that ghrelin changes in the same manner as orexin [23]. It should be stressed that the plasma concentration of the neuropeptide is not a simple reflection of secretory changes which take place in the hypothalamus. On the other hand, contrary results may in a certain way support the hypothesis of the mixed signal in AN [24]. Orexinergic neurons seem to play a key role in the aspects of eating behavior associated with reward, their activation is closely linked with an reward as a response to food or drugs [25]. A central orexin infusion increases sugar intake in rats [26], and its directed injection into the ventral tegmental area (VTA) stimulates synaptic ends towards dopamine secretion to nucleus accumbens (NAc), which increases consumption [27]. The OX1R antagonist suppressed these effects in satiated rats [5].

Another well-known and strongly orexigenic neuropeptide is MCH with a high expression in the lateral hypothalamus [28]. Intraventricular administration of MCH leads to a considerable increase of food intake in rats throughout stimulation of two

metabotropic receptors MCHR1 [29]. Importantly, it is believed that MCH is engaged in orexigenic signaling at the level of reward loops, especially in the NAc. Upon a directed injection of MCH antagonists into the rat NAc there is a clear decrease of food intake [30]. This may suggest a potential, however not studied yet, role of MCH in a molecular event underlying AN.

Both the lateral and ventromedial hypothalamus include the group of recently described neurons which show the 26RFa expression [31]. 26RFa (QRFP) is a different orexigenic neuropeptide, a ligand of the metabotropic receptor GPR103 (QRFPR) [32]. Cells revealing the GPR103 expression are also located outside the hypothalamus, in the structures which created the reward system, such as the VTA, amygdala and NAc [33]. Intraventricular injection of 26RFa strongly promotes eating behavior in rats [34]. The 26RFa gene expression may be regulated by disturbances of energy expenditure, e.g., in the hypothalamus of obese ob/ob mice the level of 26RFa is increased [32]. An interesting chronobiologic study carried out by Galusca et al. [35] shows that females with restrictive AN had an increased daily level of 26RFa in plasma as compared to the control group. Oxytocin is also a strong anorexic factor which inhibits food intake, probably throughout blocking the reward signaling pathways [36, 37]. It should be noted that in AN females the severity of anxiety, depression and food restrictions is positively correlated with the oxytocin level in plasma measured after a meal [38]. On the other hand, it has also been suggested recently that damage to the oxytocin pathways may facilitate maintaining anxiety and depressive symptoms after a partial weight recovery in the course of AN [39].

Nesfatin-1 in the mechanisms of energetic homeostasis control

Nesfatin-1, an 82-amino acid molecule, is composed of 3 domains: N-teminal (N23), middle (M30) and C-terminal (C-29). The M30 domain seems to play a key role in inducing physiological, mainly anorectic effects of this neuropeptide [40]. Nesfatin-1 is secreted after the post-translational cleavage from the NEFA precursor/nucleobindin-2 (NUCB2) by means of the activity of specific convertases PC2 and PC3/1 [9]. In the course of proteolytic processing of NUCB2, the following inactive derivatives also emerge: nesfatin-2 and 3 [40]. NUCB2, the prohormone consisting of 396 amino acids, proceeded by a 24-amino acid signal peptide, undergoes expression both in the cell membrane and in cytoplasm [9].

The nesfatin-1 receptor has not been identified yet, which renders a directed pharmacomodulation of signaling of this neuropeptide impossible. The autoradiographic test revealed a high signal for nesfatin-1 in the periventricular nucleus, paraventricular nucleus (PVN), neocortex, cerebellum, and the brainstem [41]. In the brain, neurons revealing nesfatin-1 expression are situated mainly in the arcuate nucleus (ARC), PVN and in the supraoptic nucleus (SON), and also in the dorsomedial hypothalamus (DMH) and lateral hypothalamus (LH) [42]. Release of nesfatin-1 from the proopi-

omelanocortin/cocaine and amphetamine-regulated transcript (POMC/CART) results directly in inhibition of the orexigenic cells of neuropeptide Y/Agouti-related protein (NPY/AgRP), leading to their hyperpolarization [43]. Suppression of the orexigenic ARC neurons may play a key role in nesfatin-1-induced anorexia nervosa [44]. Most probably, unacylated ghrelin may also inhibit the ghrelin-sensitive NPY/AgRP neurons, acting through the nesfatin-1-releasing cells [45].

An initial study revealed that leptin did not modulate the NUCB2 and nesfatin-1 expression in rat hypothalamus and inhibition of the nesfatinergic pathways did not affect the anorexigenic signaling of leptin [40]. However, recent evidence suggests that nesfatin-1 activity and mRNA expression for NUCB2 in the PVN neurons is directly increased by leptin. Two hours upon leptin injection into this PVN nucleus there is a considerable growth of the mRNA expression for NUCB2 [46]. Peripherally administered bombesin and cholecystokinine-8S (CCK-8S) may also activate nesfatin neurons [47]. And inversely, the POMC-originating α-melanotropin (α-MSH) increased calcium level in nesfatin cells in the PVN [48].

Nesfatin-1 is a factor which considerably stimulates oxytocin secretion throughout the magno – and parvocellular neurons (in the PVN) in rats. However, this did not lead to an oxytocin increase in serum [49]. Satiety, caused by a central nesfatin-1 infusion, is mitigated by the administration of the antagonist of corticotropin-releasing factor2 (CRF2) – astressin 2-B [49]. The melanocortin MC4 receptor in the PVN plays an important role in regulation of eating process, therefore it may be speculated that nesfatin neurons – by revealing the co-expression of oxytocin, vasopressin, MCH, and the corticotropin-releasing factor (CRF) — are the effectors in the melanocortin signaling pathway [50]. It was also observed that the α-MSH injection into a rat cerebral ventricles increases mRNA expression for NUCB2 in the PVN neurons. This suggests that the cells which synthesize this peptide act through melanocortin receptors [51]. Although the mechanisms of this activity have not been fully understood yet, the accuracy of the proposed hypothesis is confirmed by the fact that a change of NUCB2 expression level after a previous administration of SHU9119 – a selective antagonist of melanocortin MC3 and MC4 receptors – was not observed [43].

There are also suggestions that neurons showing nesfatin-1 expression may be sensitive to the circulating oxytocin in rats. The count of nesfatin cells in the ARC and PVN increased upon an oxytocin intraperitoneal injection, and on the other hand, a central administration of the antisense nesfatin-1 reduced the oxytocin inhibitory effect on food intake [52]. Recent studies have reported that the intraperitoneal injection of cisplatin stimulated nesfatin neurons in the hypothalamus and inhibited food intake in rats [53], which seems to be interesting from the oncological point of view. A direct nesfatin-1 injection into the lateral ventricle of the rat brain caused a dose-dependent inhibition of consumption behavior. A prolonged infusion to the third ventricle results in a considerable reduction of body weight and a reduction of white

adipose tissue amount. Intraperitoneal nesfatin-1 injection in mice induces a three-hour inhibition of food intake, and its subcutaneous administration causes a similar effect, however, the anorexigenic effect persisted for 14 hours. Repeated intraperitoneal injections significantly inhibited body weight growth in a six-day period. A prolonged subcutaneous nesfatin-1 infusion also caused a considerable drop in food intake in rats [54]. It should be stressed that the peripheral nesfatin-1 doses required to reduce food intake are approximately one thousand-times higher than those having an effect in the central nervous system. The serum nesfatin-1 level is significantly reduced in the fasting mode, and refeeding leads to its normalization.

Nesfatin-1 crosses the blood-brain barrier, which potentially may result in its therapeutic application. It seems that after reaching the hypothalamic centers, nesfatin-1 will inhibit appetite and food intake. It has recently been observed that in humans the ratio of nesfatin-1 in cerebrospinal fluid (CSF) vs. nesfatin-1 in plasma is considerably negatively correlated with the body mass index (BMI) and body weight, which may suggest that nesfatin-1 is a protein-bound neuropeptide. A hypothesis was also put forward that body weight-dependent changes in effectiveness of nesfatin-1 uptake by CSF may be caused by saturation of its transporters. It was also suggested that the hypothalamic NUCB2/nesfatin-1 are engaged in the hepatic, insulin-dependent glucose homeostasis throughout activation of the mTOR-STAT3 signaling pathways [55]. Nesfatin-1 levels in plasma were also measured in AN patients with high and low anxiety scores assessed in line with the GAD-7 protocol. In patients with high anxiety levels, an increased level of nesfatin-1 was observed, which suggested a positive correlation between the GAD-7 score and the level of this neuropeptide. The perceived stress questionnaire (PSQ-20), patient health questionnaire (PHQ-9) and the eating disorder inventory (EDI-2) were not linked with nesfatin-1, yet, its level was increased in patients with high level of anxiety [56].

To summarize, nesfatin-1 levels in plasma positively correlate with perceived anxiety, and may also change in the course of eating disorder. The aforementioned clinical results may be compared with a recent study conducted by Lu et al. [57] in which they observed a sex-dependent changes in orexin-A and OX2R levels in the brain of patients suffering from depression. Immunoreactivity of orexin-A in the *post mortem* tested hypothalami was considerably increased in females suffering from depression (but not in males) as compared to healthy controls. Furthermore, in the anterior part of the cingulated cortex of men who had committed suicide a considerable increase in OX2R was observed [57]. Due to highly anorexigenic properties of nesfatin-1, it seems justified to carry out further research to analyze its potential role in pathogenesis of psychogenic eating disorders. It has recently been observed that plasma nesfatin-1 levels in patients suffering from restricting-type anorexia nervosa (AN-R) were significantly lower as compared to healthy individuals. This may point to a negative correlation with ghrelin and unacylated ghrelin levels. However, a positive

correlation was shown between nesfatin-1 levels and BMI [58]. A reverse phenomenon was demonstrated in healthy males with a normal BMI, in whom the nesfatin-1 concentration on empty stomach negatively correlated with their BMI [59]. This observation was similar to the one documented in rats [60]. Nevertheless, there is still no convincing evidence to support the thesis that an increased nesfatin-1 level lies at the basis of anxiety disorders, which frequently accompany AN-R. On the other hand, it cannot be ruled out that in the periods of extreme fasting, even a lower nesfatin-1 level does not affect the level of anxiety, which usually remains high in patients with AN, and does not stimulate food intake.

A hypothetical mechanism of nesfatin-1 action in pathogenesis of anorexia nervosa

The mechanism of food intake adaptation to energetic expenditure, as well as a proper balance in both the orexi – and anorexigenic hypothalamic neuropeptides are severely damaged in AN patients. In this case, the activity of anorexigenic POMC/CART, CRF, CCK-8S and oxytocinergic neurons in the ARC/PVN may be pathologically overstimulated by nesfatin-1 and probably spexin. On the other hand, the promoting food intake AgRP/NPY, MCH, 26RFa, and orexigenic neurons may be blocked by the same regulatory neuropeptides [44], yet the receptor mechanisms of their action have not been understood so far. Since the brain-derived neurotrophic factor (BDNF) is a strong anorexigenic factor engaged in AN pathogenesis [61], a potential effect of nesfatin-1 on its signaling pathway may be another possible strategy in restricting food intake in the course of this disorder. Similarly to nesfatin-1, the BDNF level is strictly linked both with energetic balance and the reproductive phase. Nesfatin-1 administration reduced the BDNF expression in the rat brain [62], however, the nature of the dependency between these two neuropeptides in the context of eating habits in humans has not been explained yet. It was observed that BDNF levels in serum of patients with active AN-R were lower than in healthy individuals of the control group [63]. Some previous genetic studies also suggested that the BDNF gene may be engaged in the AN development [64].

BDNF levels in plasma were increased in the bulimic-type AN patients as compared to those with the restricting-type (AN-R) [65]. Another discovery revealed that bulimic females with normal body weight had higher BDNF levels in serum as compared to AN patients [66]. BDNF concentrations in plasma in AN patients undergo fluctuations in the course of the disorder. For instance, BDNF levels in serum in women who recovered from AN were higher as compared to AN patients with severe underweight and showed a tendency to increase together with body weight gain. It should be stressed that in AN – but not in healthy control females – BDNF levels were inversely correlated with psychomotor activation [67]. It may be postulated that nesfatinergic projections from the ARC to VMH and/or local nesfatin neurons in the VMH may stimulate the BDNF synthesis and exocytosis, which leads to a prolonged

inhibition of food intake in AN, despite the fact that the receptor mechanism of this effect remains unknown.

Interestingly, the BDNF expression regulation in the rat VMH seems to be dependent on the sex. It was reported that fasting male rats – but not females – revealed a reduced BDNF level in the VMH as compared to normally fed specimens upon a 24-hour reduction of food. In obese rats on a high-fat diet (HFD) and in normal-weight rats (HFD-PF), a lower BDNF expression was observed as compared to the low-fat diet rats (LFD), which suggests that inhibition of the BDNF signaling was related to taking a diet rich in fat and not with an increased obesity. It is worth mentioning that a decreased BDNF expression during the HFD may strengthen eating behaviors and promote obesity in males. And inversely, the hypothalamic level of BDNF in female rats remains stable even in the conditions of severe energetic imbalance [68]. Despite the above-mentioned results, the latest evidence has not recommended BDNF as a reliable biomarker in women who recovered from AN, since an inverse significant correlation between the BDNF in plasma and anxiety was present only in healthy controls [69].

Eating behavior is strictly controlled by complex cerebral mechanisms of rewarding with food, regardless of the fact whether these signaling circuitries act in a normal or a disturbed mode. It has not been explained so far whether the limited pattern of food intake in AN is caused by structurally visible damages to the cerebral reward circuitries, including nesfatin neurons. A possible pharmacological treatment of these deformed pathways with medications affecting the reward-related neuronal complexes in the VTA or NAc still remains a hypothetical strategy. Moreover, it has not been proved so far in an unanimous way whether any causes of AN significantly depend on the cerebral reward system and how the cerebral food-rewarding substrates are related to eating disorders. However, it should be taken into consideration that mesolimbic dopamine and opioid systems which create hedonic inflammatory "wanting and liking" points in the brain, may be engaged in the pathogenesis of AN and other eating disorders [70]. These mechanisms may facilitate generating anxiety behaviors, e.g., a continuous and compulsive focus on being extremely thin [71].

The results published by Chen et al. [72] shed new and intriguing light on the hypothesis about the role of nesfatin-1 in the AN genesis, suggesting its direct action on dopaminergic reward circuitries. Directed nesfatin-1 injection into the VTA strongly reduced both food intake and dopamine release in the NAc. The effect of nesfatin-1 on the VTA seems to be analogous to the activity of leptin, but different than that of ghrelin [73, 74]. Therefore, it is possible that the nesfatin neurons in the lateral amygdala send their inhibitory efferent branches to the VTA neurons, which results in the anorexigenic effect. The mode of action of nesfatin-1 in the reward circuitries may remind the activity of oxytocin in the NAc, while its injection to this structure caused a considerable drop in food intake in rats [75]. It should not be excluded that the nesfatin-1 activity which

restricts food intake in AN may be initiated by the release of endogenic anorexigenic factor GLP-1 (glucagon-like peptide 1) to the hypothalamus. The GLP-1 neurons in rat's NTS send their long, stimulating projections to the CRF and nesfatin cells in the PVN. GLP-1 administered *in vitro* initiates a cascade of calcium signaling in nesfatin neurons isolated from the PVN. Interestingly, a precise injection of the GLP-1 receptor antagonist –exendin (9–39) to the PVN increased food intake [76].

Recapitulation

The recently identified neuropeptide nesfatin-1 is characterized by the wide spectrum of its sex-dependent regulatory activity in the brain. There is a growing body of evidence to accept it as a new, potentially significant factor which is engaged in the pathogenesis of a few mental conditions. Therefore, it should not be excluded that the considered pharmacomodulation of signaling of this neuropeptide may be potentially helpful in the future treatment of some neuropsychiatric and metabolic disorders, such as anorexia nervosa. Undoubtedly, more advanced studies in this field are of a special interest. Although the results of some basic and clinical tests seem to be promising, all possible applications of the aforementioned neuropeptides, together with their agonists and antagonists still remain in the area of speculation. Nevertheless, the intensive search of selective modulators of their known receptors may facilitate the opening of a promising chapter in the eating disorders therapy.

References

1. Klump KL, Bulik CM, Kaye WH, Treasure J, Tyson E. *Academy for eating disorders position paper: Eating disorders are serious mental illnesses*. Int. J. Eat. Disord. 2009; 42(2): 97–103.
2. Valente S, Di Girolamo G, Forlani M, Biondini A, Scudellari P, De Ronchi D et al. *Sex-specific issues in eating disorders: A clinical and psychopathological investigation*. Eat. Weight Disord. 2017; 22(4): 707–715.
3. Jagielska G, Kacperska I. *Outcome, comorbidity and prognosis in anorexia nervosa*. Psychiatr. Pol. 2017; 51(2): 205–218.
4. Cuesto G, Everaerts C, Leon LG, Acebes A. *Molecular bases of anorexia nervosa, bulimia nervosa and binge eating disorder: Shedding light on the darkness*. J. Neurogenet. 2017; 31(4): 266–287.
5. Gorwood P, Blanchet-Collet C, Chartrel N, Duclos J, Dechelotte P, Hanachi M et al. *New insights in anorexia nervosa*. Front. Neurosci. 2016; 10: 256.
6. Yoshimura M, UezonoY, Ueta Y. *Anorexia in human and experimental animal models: Physiological aspects related to neuropeptides*. J. Physiol. Sci. 2015; 65(5): 385–395.
7. Fu LY, Pol van den AN. *Kisspeptin directly excites anorexigenic proopiomelanocortin neurons but inhibits orexigenic neuropeptide Y cells by an indirect synaptic mechanism*. J. Neurosci. 2010; 30(30): 10205–10219.

8. Porzionato A, Rucinski M, Macchi V, Stecco C, Malendowicz LK, De Caro R. *Spexin expression in normal rat tissues*. J. Histochem. Cytochem. 2010; 58(9): 825–837.
9. Stengel A, Tache Y. *Nesfatin-1 – Role as possible new potent regulator of food intake*. Regul. Pept. 2010; 163(1–3): 18–23.
10. Yosten GL, Lyu RM, Hsueh AJ, Avsian-Kretchmer O, Chang JK, Tullock CW et al. *A novel reproductive peptide, phoenixin*. J. Neuroendocrinol. 2013; 25(2): 206–215.
11. Ueno H, Shiiya T, Nakazato M. *Translational research of ghrelin*. Ann. N. Y. Acad. Sci. 2010; 1200: 120–127.
12. Hotta M, Ohwada R, Akamizu T, Shibasaki T, Kangawa K. *Therapeutic potential of ghrelin in restricting-type anorexia nervosa*. Methods Enzymol. 2012; 514: 381–398.
13. Fetissov SO, Hallman J, Oreland L, Af Klinteberg B, Grenbäck E, Hulting AL et al. *Autoantibodies against alpha-MSH, ACTH, and LHRH in anorexia and bulimia nervosa patients*. Proc. Natl. Acad. Sci. USA. 2002; 99(26): 17155–17160.
14. Borgo F, Riva A, Benetti A, Casiraghi MC, Bertelli S, Garbossa S et al. *Microbiota in anorexia nervosa: The triangle between bacterial species, metabolites and psychological tests*. PLoS One 2017; 12(6): e0179739.
15. Aston-Jones G, Smith RJ, Sartor GC, Moorman DE, Massi L, Tahsili-Fahadan P et al. *Lateral hypothalamic orexin/hypocretin neurons: A role in reward-seeking and addiction*. Brain Res. 2010; 1314C: 74–90.
16. Cowdrey FA, Park RJ, Harmer CJ, McCabe C. *Increased neural processing of rewarding and aversive food stimuli in recovered anorexia nervosa*. Biol. Psychiatry 2011; 70(8): 736–743.
17. Peyron C, Kilduff TS. *Mapping the hypocretin/orexin neuronal system: An unexpectedly productive journey*. J. Neurosci. 2017; 37(9): 2268–2272.
18. Kukkonen JP. *Physiology of the orexinergic/hypocretinergic system: A revisit in 2012*. Am. J. Physiol. Cell Physiol. 2013; 304(1): C2–32.
19. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H et al. *Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior*. Cell. 1998; 92(4): 573–585.
20. Hara J, Beuckmann CT, Nambu T, Willie JT, Chemelli RM, Sinton CM et al. *Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity*. Neuron 2001; 30(2): 345–354.
21. Janas-Kozik M, Stachowicz M, Krupka-Matuszczyk I, Szymszal J, Krysta K, Janas A et al. *Plasma levels of leptin and orexin A in the restrictive type of anorexia nervosa*. Regul. Pept. 2011; 168(1–3): 5–9.
22. Bronsky J, Nedvidkova J, Krasnicanova H, Vesela M, Schmidtova J, Koutek J et al. *Changes of orexin A plasma levels in girls with anorexia nervosa during eight weeks of realimentation*. Int. J. Eat. Disord. 2011; 44(6): 547–552.
23. Janas-Kozik M, Krupka-Matuszczyk I, Malinowska-Kolodziej I, Lewin-Kowalik J. *Total ghrelin plasma level in patients with the restrictive type of anorexia nervosa*. Regul. Pept. 2007; 140(1–2): 43–46.
24. Inui A. *Eating behavior in anorexia nervosa – An excess of both orexigenic and anorexigenic signalling?* Mol. Psychiatry 2001; 6(6): 620–624.

25. Harris GC, Wimmer M, Aston-Jones G. *A role for lateral hypothalamic orexin neurons in reward seeking*. Nature 2005; 437(7058): 556–559.

26. Cason AM, Smith RJ, Tahsili-Fahadan P, Moorman DE, Sartor GC, Aston-Jones G. *Role of orexin/hypocretin in reward-seeking and addiction: Implications for obesity*. Physiol. Behav. 2010; 100(5): 419–428.

27. Zheng H, Patterson LM, Berthoud HR. *Orexin signaling in the ventral tegmental area is required for high-fat appetite induced by opioid stimulation of the nucleus accumbens*. J. Neurosci. 2007; 27(41): 11075–11082.

28. Della-Zuana O, Audinot V, Levenez V, Ktorza A, Presse F, Nahon JL et al. *Peripheral injections of melanin-concentrating hormone receptor 1 antagonist S38151 decrease food intake and body weight in rodent obesity models*. Front. Endocrinol. (Lausanne) 2012; 3: 160.

29. Forray C. *The MCH receptor family: Feeding brain disorders?* Curr. Opin. Pharmacol. 2003; 3(1): 85–89.

30. Georgescu D, Sears RM, Hommel JD, Barrot M, Bolanos CA, Marsh DJ et al. *The hypothalamic neuropeptide melanin-concentrating hormone acts in the nucleus accumbens to modulate feeding behavior and forced-swim performance*. J. Neurosci. 2005; 25(11): 2933–2940.

31. Chartrel N, Picot M, El Medhi M, Arabo A, Berrahmoune H, Alexandre D et al. *The neuropeptide 26RFa (QRFP) and its role in the regulation of energy homeostasis: A mini-review*. Front. Neurosci. 2016; 10: 549.

32. Takayasu S, Sakurai T, Iwasaki S, Teranishi H, Yamanaka A, Williams SC et al. *A neuropeptide ligand of the G protein-coupled receptor GPR103 regulates feeding, behavioral arousal, and blood pressure in mice*. Proc. Natl. Acad. Sci. USA 2006; 103(19): 7438–7443.

33. Bruzzone F, Lectez B, Alexandre D, Jegou S, Mounien L, Tollemer H et al. *Distribution of 26RFa binding sites and GPR103 mRNA in the central nervous system of the rat*. J. Comp. Neurol. 2007; 503(4): 573–591.

34. Moriya R, Sano H, Umeda T, Ito M, Takahashi Y, Matsuda M et al. *RFamide peptide QRFP43 causes obesity with hyperphagia and reduced thermogenesis in mice*. Endocrinology 2006; 147(6): 2916–2922.

35. Galusca B, Jeandel L, Germain N, Alexandre D, Leprince J, Anouar Y et al. *Orexigenic neuropeptide 26RFa: New evidence for an adaptive profile of appetite regulation in anorexia nervosa*. J. Clin. Endocrinol. Metab. 2012; 97(6): 2012–2018.

36. Blevins JE, Graham JL, Morton GJ, Bales KL, Schwartz MW, Baskin DG et al. *Chronic oxytocin administration inhibits food intake, increases energy expenditure, and produces weight loss in fructose-fed obese rhesus monkeys*. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2015; 308(5): R431–438.

37. Sabatier N, Leng G, Menzies J. *Oxytocin, feeding, and satiety*. Front. Endocrinol. (Lausanne) 2013; 4: 35.

38. Lawson EA, Holsen LM, Santin M, DeSanti R, Meenaghan E, Eddy KT et al. *Postprandial oxytocin secretion is associated with severity of anxiety and depressive symptoms in anorexia nervosa*. J. Clin. Psychiatry 2013; 74(5): e451–457.

39. Afinogenova Y, Schmelkin C, Plessow F, Thomas JJ, Pulumo R, Micali N et al. *Low fasting oxytocin levels are associated with psychopathology in anorexia nervosa in partial recovery*. J. Clin. Psychiatry 2016; 77(11): e1483–e1490.

40. Oh IS, Shimizu H, Satoh T, Okada S, Adachi S, Inoue K et al. *Identification of nesfatin-1 as a satiety molecule in the hypothalamus*. Nature 2006; 443(7112): 709–712.

41. Prinz P, Goebel-Stengel M, Teuffel P, Rose M, Klapp BF, Stengel A. *Peripheral and central localization of the nesfatin-1 receptor using autoradiography in rats*. Biochem. Biophys. Res. Commun. 2016; 470(3): 521–527.

42. Goebel M, Stengel A, Wang L, Lambrecht NW, Tache Y. *Nesfatin-1 immunoreactivity in rat brain and spinal cord autonomic nuclei*. Neurosci. Lett. 2009; 452(3): 241–246.

43. Brailoiu GC, Dun SL, Brailoiu E, Inan S, Yang J, Chang JK et al. *Nesfatin-1: Distribution and interaction with a G protein-coupled receptor in the rat brain*. Endocrinology 2007; 148(10): 5088–5094.

44. Price CJ, Samson WK, Ferguson AV. *Nesfatin-1 inhibits NPY neurons in the arcuate nucleus*. Brain Res. 2008; 1230: 99–106.

45. Inhoff T, Monnikes H, Noetzel S, Stengel A, Goebel M, Dinh QT et al. *Desacyl ghrelin inhibits the orexigenic effect of peripherally injected ghrelin in rats*. Peptides 2008; 29(12): 2159–2168.

46. Darambazar G, Nakata M, Okada T, Wang L, Li E, Shinozaki A et al. *Paraventricular NUCB2/nesfatin-1 is directly targeted by leptin and mediates its anorexigenic effect*. Biochem. Biophys. Res. Commun. 2015; 456(4): 913–918.

47. Engster KM, Kroczek AL, Rose M, Stengel A, Kobelt P. *Peripheral injection of bombesin induces c-Fos in NUCB2/nesfatin-1 neurons*. Brain. Res. 2016; 1648(Pt A): 46–53.

48. Sedbazar U, Ayush EA, Maejima Y, Yada T. *Neuropeptide Y and alpha-melanocyte-stimulating hormone reciprocally regulate nesfatin-1 neurons in the paraventricular nucleus of the hypothalamus*. Neuroreport 2014; 25(18): 1453–1458.

49. Yosten GL, Samson WK. *The anorexigenic and hypertensive effects of nesfatin-1 are reversed by pretreatment with an oxytocin receptor antagonist*. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2010; 298(6): R1642–1647.

50. Yosten GL, Samson WK. *Nesfatin-1 exerts cardiovascular actions in brain: Possible interaction with the central melanocortin system*. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2009; 297(2): R330–336.

51. Maejima Y, Sedbazar U, Suyama S, Kohno D, Onaka T, Takano E et al. *Nesfatin-1-regulated oxytocinergic signaling in the paraventricular nucleus causes anorexia through a leptin-independent melanocortin pathway*. Cell Metab. 2009; 10(5): 355–365.

52. Saito R, Sonoda S, Ueno H, Motojima Y, Yoshimura M, Maruyama T et al. *Involvement of central nesfatin-1 neurons on oxytocin-induced feeding suppression in rats*. Neurosci. Lett. 2017; 655: 54–60.

53. Akiyama Y, Yoshimura M, Nishimura K, Nishimura H, Sonoda S, Ueno H et al. *Activation of central nesfatin-1/NucB2 after intraperitoneally administered cisplatin in rats*. Biochem. Biophys. Res. Commun. 2017; 490(3): 794–799.

54. Mortazavi S, Gonzalez R, Ceddia R, Unniappan S. *Long-term infusion of nesfatin-1 causes a sustained regulation of whole-body energy homeostasis of male Fischer 344 rats*. Front. Cell. Dev. Biol. 2015; 3: 22.

55. Wu D, Yang M, Chen Y, Jia Y, Ma ZA, Boden G et al. *Hypothalamic nesfatin-1/NUCB2 knockdown augments hepatic gluconeogenesis that is correlated with inhibition of mTOR-STAT3 signaling pathway in rats*. Diabetes 2014; 63(4): 1234–1247.

56. Hofmann T, Ahnis A, Elbelt U, Rose M, Klapp BF, Stengel A. *NUCB2/nesfatin-1 is associated with elevated levels of anxiety in anorexia nervosa*. PLoS One 2015; 10(7): e0132058.

57. Lu J, Zhao J, Balesar R, Fronczek R, Zhu QB, Wu XY et al. *Sexually dimorphic changes of hypocretin (orexin) in depression*. E. Bio. Medicine 2017; 18: 311–319.

58. Ogiso K, Asakawa A, Amitani H, Nakahara T, Ushikai M, Haruta I et al. *Plasma nesfatin-1 concentrations in restricting-type anorexia nervosa*. Peptides 2011; 32(1): 150–153.

59. Tsuchiya T, Shimizu H, Yamada M, Osaki A, Oh IS, Ariyama Y et al. *Fasting concentrations of nesfatin-1 are negatively correlated with body mass index in non-obese males*. Clin. Endocrinol. (Oxf.) 2010; 73(4): 484–490.

60. Stengel A, Goebel M, Wang L, Rivier J, Kobelt P, Monnikes H et al. *Central nesfatin-1 reduces dark-phase food intake and gastric emptying in rats: Differential role of corticotropin-releasing factor2 receptor*. Endocrinology 2009; 150(11): 4911–4919.

61. Monteleone P, Maj M. *Dysfunctions of leptin, ghrelin, BDNF and endocannabinoids in eating disorders: Beyond the homeostatic control of food intake*. Psychoneuroendocrinology 2013; 38(3): 312–330.

62. Ge JF, Walewski JL, Anglade D, Berk PD. *Regulation of hepatocellular fatty acid uptake in mouse models of fatty liver disease with and without functional leptin signaling: Roles of NfKB and SREBP-1C and the effects of spexin*. Semin. Liver Dis. 2016; 36(4): 360–372.

63. Brandys MK, Kas MJ, Elburg van AA, Campbell IC, Adan RA. *A meta-analysis of circulating BDNF concentrations in anorexia nervosa*. World J. Biol. Psychiatry 2011; 12(6): 444–454.

64. Ribases M, Gratacos M, Fernandez-Aranda F, Bellodi L, Boni C, Anderluh M et al. *Association of BDNF with restricting anorexia nervosa and minimum body mass index: A family-based association study of eight European populations*. Eur. J. Hum. Genet. 2005; 13(4): 428–434.

65. Eddy KT, Lawson EA, Meade C, Meenaghan E, Horton SE, Misra M et al. *Appetite regulatory hormones in women with anorexia nervosa: Binge-eating/purging versus restricting type*. J. Clin. Psychiatry 2015; 76(1): 19–24.

66. Saito S, Watanabe K, Hashimoto E, Saito T. *Low serum BDNF and food intake regulation: A possible new explanation of the pathophysiology of eating disorders*. Prog. Neuropsychopharmacol. Biol. Psychiatry 2009; 33(2): 312–316.

67. Zwipp J, Hass J, Schober I, Geisler D, Ritschel F, Seidel M et al. *Serum brain-derived neurotrophic factor and cognitive functioning in underweight, weight-recovered and partially weight-recovered females with anorexia nervosa*. Prog. Neuropsychopharmacol. Biol. Psychiatry 2014; 54: 163–169.

68. Liu X, Zhu Z, Kalyani M, Janik JM, Shi H. *Effects of energy status and diet on Bdnf expression in the ventromedial hypothalamus of male and female rats*. Physiol. Behav. 2014; 130: 99–107.

69. Kawada T. *Plasma BDNF levels and anxiety in women with recovery from anorexia nervosa*. Physiol. Behav. 2017; 177: 263.

70. Castro DC, Berridge KC. *Advances in the neurobiological bases for food 'liking' versus 'wanting'*. Physiol. Behav. 2014; 136: 22–30.

71. Faure A, Reynolds SM, Richard JM, Berridge KC. *Mesolimbic dopamine in desire and dread: enabling motivation to be generated by localized glutamate disruptions in nucleus accumbens*. J. Neurosci. 2008; 28(28): 7184–7192.

72. Chen X, Shu X, Cong ZK, Jiang ZY, Jiang H. *Nesfatin-1 acts on the dopaminergic reward pathway to inhibit food intake*. Neuropeptides 2015; 53: 45–50.

73. Abizaid A, Liu ZW, Andrews ZB, Shanabrough M, Borok E, Elsworth JD et al. *Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite*. J. Clin. Invest. 2006; 116(12): 3229–3239.

74. Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB et al. *Leptin receptor signaling in midbrain dopamine neurons regulates feeding*. Neuron 2006; 51(6): 801–810.

75. Herisson FM, Waas JR, Fredriksson R, Schioth HB, Levine AS, Olszewski PK. *Oxytocin acting in the nucleus accumbens core decreases food intake*. J. Neuroendocrinol. 2016; 28(4). DOI: 10.1111/jne.12381

76. Katsurada K, Maejima Y, Nakata M, Kodaira M, Suyama S, Iwasaki Y et al. *Endogenous GLP-1 acts on paraventricular nucleus to suppress feeding: Projection from nucleus tractussolitarius and activation of corticotropin-releasing hormone, nesfatin-1 and oxytocin neurons*. Biochem. Biophys. Res. Commun. 2014; 451(2): 276–281.

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