The potential role of the novel hypothalamic neuropeptides nesfatin-1, phoenixin, spexin and kisspeptin in the pathogenesis of anxiety and anorexia nervosa.

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Abstract

Due to the dynamic development of molecular neurobiology and bioinformatic methods several novel brain neuropeptides have been identified and characterized in recent years. Contemporary techniques of selective molecular detection e.g. in situ Real-Time PCR, microdiffusion and some bioinformatics strategies that base on searching for single structural features common to diverse neuropeptides such as hidden Markov model (HMM) have been successfully introduced. A convincing majority of neuropeptides have unique properties as well as a broad spectrum of physiological activity in numerous neuronal pathways including the hypothalamus and limbic system. The newly discovered but uncharacterized regulatory factors nesfatin-1, phoenixin, spexin and kisspeptin have the potential to be unique modulators of stress responses and eating behaviour. Accumulating basic studies revelaed an intriguing role of these neuropeptides in the brain pathways involved in the pathogenesis of anxiety behaviour. Nesfatin-1, phoenixin, spexin and kisspeptin may also distinctly affect the energy homeostasis and modulate food intake not only at the level of hypothalamic centres. Moreover, in patients suffered from anxiety and anorexia nervosa a significant, sex-related changes in the plasma neuropeptide levels occurred. It should be therefore taken into account that the targeted pharmacomodulation of central peptidergic signaling may be potentially helpful in the future treatment of certain neuropsychiatric and metabolic disorders. This article reviews recent evidence dealing with the hypothetical role of these new factors in the anxiety-related circuits and pathophysiology of anorexia nervosa.

Key words; nesfatin-1, phoenixin, spexin, kisspeptin, anxiety, anorexia nervosa

Contents

1. Introduction

Anxiety and eating disorders are commonplace, persistent severe psychiatric impairments with poor prognosis. It is generally accepted that anxiety disorders are at present the most prevalent of psychiatric conditions (Stein et al. 2017). Importantly, a high comorbidity between anxiety and broadly defined depression disorders occurs throghout the population (Thibaut 2017). Anorexia nervosa (AN) is a relatively common disorder that affects mainly adolescent and young adult women, the male/female ratio in AN is one to five (female 83.5% vs male 16.5%), and is characterized by restriction of food intake relative to energy needs, anxious behaviour coupled with seriously distorted body image. Many patients with AN unfortunately deny the seriousness of their life-threatening conditions and standarized mortality ratio may reach 18%. (Klump et al. 2009).

Currently, there are numerous presumptions that postulate the existence of a relationship between anxiety/AN pathogenesis and disturbances in brain peptidergic circuits (Cuesto et al. 2017, Gorwood et al. 2016, Yoshimura et al. 2015). Despite the accumulating number of neurochemical studies, there is still insufficient evidence dealing with the influence of central peptidergic signaling on the course of anxiety and eating disorders. Furthermore, there is no coherent model clarifying the origin of these disturbances at the level of hypothalamic and extrahypothalamic regulatory factors and their receptors. Moreover, a fully translational experimental animal paradigm of AN is currently lacking. Recently significant progress has been made in the mechanisms and purpose of the hypothalamic regulation of food intake and energy balance. The functional description of intercellular interactions within the hypothalamic nuclei has recently been defined, with novel neuronal populations characterized and new multifunctional brain neuropeptides discovered (Stengel and Tache 2010, Yosten at. al. 2013, Porzionato et al. 2010, Fu et al. 2010). Nonetheless, the number of papers concerning the newly discovered brain regulatory factors nesfatin-1, phoenixin, spexin and kisspeptin in the context of anxiety and AN pathogenesis remains scarce. This review is focused on providing a comprehensive coverage of all available literature concerning both animal and human models to fill this void.

2. Neuropeptides in the pathogenesis of anxiety

Neuropeptides have long been implicated in the regulation of anxiety. The corticotropin-releasing factor (CRF) family, comprised of CRF and urocortins (Ucn)1, 2, and 3, is a key component of the hypothalamo-pituitary-adrenal (HPA) axis, a system critical for stress responsivity (Kormos and Gaszner 2013). CRF acts at the anterior pituitary to stimulate the release of adrenocorticotropic releasing hormone (ACTH), which ultimately induces glucocorticoid synthesis and release from the adrenal glands (Rivier et al. 1982).To date, Ucn's effects on the HPA axis are not well defined. However, UcnI may augment HPA axis activity by stimulating CRF synthesis (Bagosi et al. 2014), while UcnII and III appear to dose-dependently either stimulate or inhibit CRF (Bagosi et al. 2013).The CRF family binds to two known receptors, CRFR1 and CRFR2. While CRF has a much higher affinity for CRFR1, UcnI appears equally selective for both receptors, and UcnII and III act almost exclusively through CRFR2 (Brar et al. 2004). Interstingly, anxiety-like behavior is decreased in mice lacking CRFR1 (Smith et al. 1998), suggesting an anxiogenic role for this receptor subtype. This anxiogenic-like effect of CRFR1 has been reported by a number of groups (Bale et al. 2004), although this effect may be dependent on brain region (Sztainberg et al. 2011). In contrast, CRFR2 deficient mice show an elevation in anxiety-like behavior and an increase in stress sensitivity (Bale et al. 2000, Chotiwat et al. 2010). However, the nature of CRFR2's effects on anxiety is region-dependent, as this receptor serves an anxiogenic-like role in the medial amygdala (Alves et al. 2016) and lateral septum (Anthony et al. 2014), but appears to have an anxiolytic-like function in the ventromedial hypothalamus (Silva et al. 2017) . Thus, although CRFR1 and CRFR2 may function in opposition to one another, the effects of these receptors on anxiety are likely to be region-specific. Two additional neuropeptides, oxytocin (OT) and arginine vasopressin (AVP), are well known regulators of anxiety and stress responsivity, acting both on the HPA axis and through independent mechanisms. AVP acts synergistically with CRF to enhance ACTH release from the pituitary (Knepel et al.1984). OT's effects on HPA axis activation appear largely site-dependent, as OT inhibits CRF synthesis within the paraventricular nucleus (Jurek et al. 2015), yet augments ACTH release in response to CRF at the level of the pituitary (Gibbs et al. 1984). The AVP-deficient Brattleboro rat exhibits mildly decreased anxiety-like behavior (Fodor et al. 2016) supporting a potentially anxiogenic effect of this hormone. Similarly, mice lacking the AVP receptor V1a (Bielsky et al. 2004) and rats treated with a V1a antagonist (Bleickardt et al. 2009) show reduced anxiety-like behavior, while intracerebroventricular injection of AVP increases anxiety-like behavior in the rat (Bhattacharya et al. 1998). Despite substantial genetic homology between OT and AVP, OT largely shows a very different effect on anxiety. Female OT knockout mice have a more anxiety-like behavioral profile than controls (Mantella et al. 2003), and OT generally has an anxiolytic-like effect when administered either centrally (Sabihi et al. 2017) or peripherally (Ayers et al. 2011). While AVP and OT have a clear influence on anxiety, through HPA axis activation and inhibition respectively, these neuropeptides also mediate anxiety-like behavior through projections from the paraventricular nucleus to distal regions such as the central nucleus of the amygdala. Perhaps unsurprisingly, activation of OT receptors in this region decreases anxiety-like behavior (Knobloch et al. 2012), while V1a receptor activation has an anxiogenic-like effect (Hernandez et al. 2016), providing further support for oppositional roles for these hormones. Neuropeptide S (NPS), a brainstem multifunctional regulatory factor, seems to be another important player in the mechanism of anxiety (Slattery et al. 2015, Wegener et. al. 2012). Behavioural studies show that NPS administration has a strong dopamine-related anxiolytic effect in rats. (Lukas et al. 2012). Moreover after NPS injection into the mouse amygdala a decrease of conditioned fear occurs (Jungling et al. 2008). Some clinical trials also suggest, that NPSR gene variations could be connected with stress reaction and increased HPA axis stimulation (Kumsta et al. 2013). Orexins (hypocretins) may also play an important role in the pathogenesis of anxiety (Flores et al. 2015). Orexins A and B have a strong and preservedstructural homology in many species of incretin family neuropeptides. Orexin A is built of 33 amino acids with 2 disulphide bonds and has a higher stability in the cerebrospinal liquid and serum than orexin B. Orexin B is in turn a linear molecule composed of 28 amino acids but its concentration in the brain is 2-5 times higher in comparison to orexin A (Peyron and Kilduff 2017, Sakurai et al., 1998). Orexins are the ligands of two metabotropic receptors OX1R and OX2R with diverse affinity to orexin isoforms; OX1R has higher affinity to orexin A, whereas OX2R is equally sensitive to both molecules (Kukkonen 2013). The anatomical distribution of orexin neurons in both the human and animal brain are limited almost exclusively to the lateral hypothalamus (Sakurai et al., 1998). Patients suffering from panic attacks showed elevated level of OXs in cerebrospinal fluid in comparison with healthy controls (Johnson et al. 2010). A new finding indicates that extended stress may increase the number of orexin A expressing neurons in the male mouse hypothalamus (Jalewa et al. 2014). In rats exposed to particular volatile stressors, such as predator odour, the inhibition of orexin receptor OX1R via selective antagonist SB-334867, resulted in decreased c-Fos expression in the hypothalamus (Vanderhaven et al. 2015).

On the other hand a recent elegant study utilizing DREADDs technique, suggests that OX2R may be involved in the generation of acute stress responses in male rats and it may depress the habituation to repeated stress under high level of orexins (Grafe et al. 2017).

3. Neuropeptides in the mechanisms of anorexia nervosa

A hypothesis that anorexia nervosa is a result of extended stimulation of reward circuits by hypothalamic orexigenic neuropeptides seems to be best documented and widely accepted (Gorwood et al. 2016, Aston-Jones et al. 2010). In patients with AN ghrelin, orexins and 26RFa expressions are generally upregulated reflecting a homeostatic mechanism to stimulate eating behaviour and to minimize severe malnutrition. Nevertheless in AN this regulatory pathway may be strongly impaired and insufficient allowing patients' brains to resist numerous orexigenic factors. There is also an alternative point of view speculating that extended increases of orexin, MCH and 26RFa neuronal activity in the lateral hypothalamus reinforce food aversion by stimulation of dopamine-dependent anxiety in brain reward circuits. Interestingly patients in remission from AN maintain an elevated response to food stimuli in the reward centres (Cowdrey et al. 2011), that supports the postulate that AN is a result of an incorrectly augmented reward process for pathologically restricted food intake. In the animal model, fasting causes up-regulation of orexin prohormone prepro-orexin (PPOX) at the transcriptional level whereas in obese mice a decreased PPOX gene expression occurs (Sakurai et al. 1998). Conversely, insufficient orexin signaling in mice strongly suppresses food intake (Hara et al. 2001). There are two parallel studies dealing with the changes in the orexin concentration in the plasma of patients suffering from AN. The first finding preformed by Janas-Kozik *et al*. (2011) revealed a decreased level of OxA in untreated females with AN, the second showed in turn an increase of the neuropeptide level under the same clinical condition (Bronsky et al. 2011). Despite this discrepancy, both the authors reported a decrease in the OxA level during refeeding that may indicate up-regulation of orexinergic signaling in AN. Interestingly, during realimentation of the AN patients, ghrelin seemed to have the same mode of changes as orexin (Janas-Kozik et al. 2007). It should be underlined that plasma neuropeptide concentration does not a direct reflection of secretory changes that take place in the hypothalamus. On the other hand, the conflicting results may in some way support the mixed-signal hypothesis of AN (Inui et al. 2001). Orexin neurons seem to play a distinct role in the reward-related aspects of feeding behaviour, their activation being strictly connected with food or drug reward (Harris et al. 2005). Central infusion of orexin increases sugar uptake in rats (Cason et al. 2010), but its targeted injection to the ventral tegmental area (VTA) stimulates the synaptic endings of the local neurons to release dopamine to the nucleus accumbens that reinforce consumatory activity (Zheng et al. 2007). An OX1R antagonist abolished these effects in satiated rats (Gorwood et al. 2016). Melanin concentrating hormone (MCH) is the next well known strongly orexigenic neuropeptide with an abundant expression in the lateral hypothalamus (Della-Zuana et al. 2012). Intracerebroventricular MCH administration causes significant increase of food intake in rats by stimulation of two metabotropic receptor MCHR1 (Forray et al. 2003). Importantly, MCH is considered to be involved in orexigenic signaling at the level of reward circuits, especially in the nucleus accumbens (NAc). After targeted injections of MCH antagonists into the rat NAc a distinct decrease in food consumption occurs (Georgescu et al. 2005). It may suggest a potential not yet investigated role of MCH in the molecular event underlying AN. Both lateral and vetromedial hypothalamus house recently described group of 26RFa-expressing neurons (Chartrel et al. 2016). The 26RFa (QRFP) is another orexigenic neuropeptide, a ligand of the metabotropic GPR103(QRFPR) receptor

(Takayasu et al. 2006). The GBP103 expressing cells are also located outside the hypothalamus, in the structures that form reward systems such as VTA, amygdala and NAc (Bruzzone et al. 2007). Intracerebrovenricular injection of 26RFa strongly promotes eating behaviour in rats (Moriya et al. 2006). Expression of the 26RFa gene may be regulated by the disturbances of energy expenditure, for instance in the hypothalamus obese ob/ob mice 26RFa levels are up-regulated (Takayasu et al. 2006). An interesting chronobiological study by Galusca et al. (2012) show that females with restrictive AN had increased plasma 26RFa levels over the day in comparison with controls. Oxytocin is also a potent anorexigenic factor that suppresses food intake probably through inhibition of reward signaling pathways (Blevins et al. 2015, Herisson et al. 2014). Noteworthy, in females with AN the intensity of anxiety, depression and eating restrictions is positively correlated with serum oxytocin levels measured after meals (Lawson et al. 2013). On the other hand it was also recently suggested that impairment of oxytocin pathways may contribute to persistent anxiety and depressive symptoms after partial weight recovery from AN (Afinogenova et al. 2016)

4. Nesfatin-1 in anxiety and eating disorders

4.1. Overview

Nesfatin-1, an 82-amino acid molecule is composed of 3 domains: N-terminal (N23), middle (M30) and C-terminal (C29). The M30 domain appears to play a crucial role in induction of physiological mainly anorexigenic effects of this neuropeptide (Atsuchi et al. 2010, Oh-I et al. 2006, Fig.1.). Nesfatin-1 is secreted after post-translational cleavage from the precursor NEFA/nucleobindin-2 (NUCB2), due to specific convertase PC2 and PC3/1 activity (Stengel and Tache 2010). During proteolytic processing of NUCB2 two inactive derivatives: nesfatin 2 and 3 are also created (Oh-I et al. 2006). Interestingly, its sister protein nucleobindin-1 (NUCB1) is a precursor of another very weakly studied neuropeptide called nesfatin-1-like peptide (NLP) that also has anorexigenic properties in animals (Gawli et al. 2017). Nesfatin-1 has a highly conserved molecular structure which is characterized by a distinct sequence homology between mammals including human, and the lower vertebrate species (Gonzales et al. 2010). As the nesfatin-1 receptor is as yet unidentified it is impossible to target the neuropeptide signaling via pharmacomodulation. An autoradiographic receptor study has detected high ^{125}I-nesfatin-1 signal in the paraventricular nucleus, neocortex, cerebellum and brainstem (Prinz et al. 2016). In the brain nesfatin-1 expressing neurons are localized mainly in the arcuate (ARC), paraventricular (PVN) and supraoptic (SON) nuclei as well as in the dorsomedial (DMH) and lateral hypothalamus (LHA) (Goebel et al. 2009). Embryological studies proved that they derived from a progenitor cell population with Developing Brain Homeobox 1 (Dbx-1) gene expression (Sokolowski et al. 2016). Nesfatin-1 is an anorexigenic factor, inducing satiety, and inhibiting food and water intake, it is assumed that the anorexigenic action of this peptide is performed mostly in the first three key regulatory hypothalamic centres.

4.2. Animal studies

Several recently conducted studies suggest that acute restrain stress is one of the factors activating nesfatin PVN, SON, NTS and Edinger-Westphal nucleus (EW) neurons (Stengel et al., 2010a). Total adrenalectomy leads to increased mRNA NUCB2 expression in PVN, but i.v. nesfatin-1 injection causes an elevation of stress hormones: ACTH and corticosterone levels in serum (Konczol et al., 2010). Nesfatin-1 seems also to contribute to generalized signs of stress; administration of this peptide into lateral ventricles of the rat brain causes elevation of blood pressure (Yosten and Samson 2010). It has been suggested that the pressor effects of centrally administered nesfatin-1 are also the result of stimulation of renal sympathetic nerves, mediated via melanocortin hypothalamic pathways (Tanida and Mori 2011). Furthermore, the expression of nesfatin-1 in raphe nuclei, locus coeruleus (LC) and EW neurons, in rats exposed to different stressors such as wrap restraint stress, abdominal surgery and lipopolysaccharide administration was increased. Nesfatin-1 activates stress-sensitive serotoninergic neurons of raphe nuclei, and noradrenergic LC neurons, that in turn stimulate CRF neurons in PVN, and finally activate the HPA axis. It has been known that the raphe nuclei and LC are also the key centres of serotoninergic and noradrenergic brain signaling systems, and their dysfunctions are closely correlated with pathogenesis of depression and anxiety disorders. At the present time, it seems probable that nesfatin-1 can play a hypothetical and nonspecific role in these mechanisms. Some authors suggest that nesfatin-1 induces anxiety or fear reactions and perhaps depressive reactions, via activation of melanocortin pathways, causing inhibition of GABA-ergic neurons or alternatively, through hyperpolarization of NPY neurons in the ARC (Bali et al. 2014, Emmerzaal and Kozicz 2013).

Behavioural studies on male rats showed that intracerebroventricular injection of nesfatin-1 dose dependently shortened the time spent on the open arms of the EPM that is a reflection of its anxiogenic activity, increased the time spent freezing but decreased the food intake under an unfamiliar, potentially worrying environmental condition. Noteworthy, nesfatin-1 did not change any kinds of locomotor activity (Merali et al. 2008). Furthermore, an extended intraperitoneal nesfatin-1 administration also promoted the anxiety-like behaviour in male rats and decreased the brain derived neurotrophic factor (BDNF) and phosphorylated ERK in the prefrontal cortex and hippocampus (Ge et al. 2015). The aforementioned findings suggest a putative role of nesfatin-1 in the origin of anxiety and fear-related responses in animals. Another study reports that rats exposed to acute but not chronic stress showed increased NUCB2/nesfatin-1 and CRH mRNA expression in the hypothalamus. Plasma nesfatin-1 and corticosterone levels were also elevated (Xu et al. 2015).Important recent evidence shows that the CRHR1 receptor may be involved in the ERK1/2-dependent mechanism of nesfatin-1 effect on synapsin action. Human neuroblastoma SH-SY5Y cells treated in culture with nesfatin-1 upregulated both mRNA and protein expressions of CRH and also increased the protein levels of p-ERK1/2 and synapsin I. These effects were abolished by CP376395, a selective antagonist of CRH type 1 receptor (CRHR1). Furthermore, the specific blocker of p-ERK1/2, PD98059 selectively reversed the nesfatin-1 induced elevation of synapsin I expression (Chen et al. 2017).

Nesfatin-1 release from the hypothalamic ARC neurons including POMC/CART cells inhibits the orexigenic NPY/AgRP cells directly (Fig.3.), causing their hyperpolarization through the ATP-dependent potassium channels Kir6.2. Glibenclamide, an antagonist of Kir6.2, relieves this effect that may support this mechanism of nesfatin-1 action. A suppression of orexigenic ARC neurons can play a key role in nesfatin-1 induced anorexia (Price and Samson, 2008). Noteworthy, the blockage of NPY/AgRP neurons can be reversed by pertussis toxin, suggesting that nesfatin-1 is also a ligand of a so far unidentified G-coupled receptor. The activation of this putative receptor leads to opening of the L and P/Q-type calcium channels, since the use of their selective inhibitors verapamil and ω-conotoxin results in removal of the nesfatin-1 dependent influx of Ca^{2+} ions (Brailoiu et al., 2007). Deacylated ghrelin can inhibit the ghrelin sensitive NPY/AgRP neurons by acting through nesfatin-1 releasing cells (Inhoff et al. 2008). Primary studies revealed that leptin did not modulate the NUCB2 and nesfatin-1 expression in the rat hypothalamus and in turn inhibition of nesfatinergic pathways did not affect leptin anorexigenic signaling (Oh et al. 2006). However, more recent evidence suggests that nesfatin-1 activity and NUCB2 mRNA expression in PVN neurons is directly upregulated by leptin. Two hours after injection of leptin to this hypothalamic nucleus significant increase of NUCB2 mRNA occurs (Darambazar et al. 2015). Noteworthy, the elevation of nesfatin-1 gene expression was connected with the light phase in normal individuals, while in Zucker-fatty rats with knock out leptin receptor this circadian pattern of changes is disturbed (Sedbazar et al. 2013). Peripherally administered bombesin and cholecystokinin (CCK-8S) can also activate nesfatin-1 neurons (Engster et al. 2016, Noetzel et al. 2009). Conversely, POMC-derived-a-MSH increased calcium concentration in the PVN nesfatin-1 (Sedbazar et al. 2014). Nesfatin-1 is a factor that significantly stimulates oxytocin secretion by magno- and parvocellular neurons (PVN) in rats. However, it has not been found that it causes the elevation of oxytocin concentration in serum (Yosten and Samson, 2010). Satiety, caused by central infusion of nesfatin-1 is relieved by administration of the CRF2 receptor antagonist – astressin2-B (Yosten and Samson 2010). The melanocortin MC4 receptor in PVN plays a crucial role in the regulation of the eating process, and therefore, one may speculate that the nesfatin-1 neurons, displaying coexpression of oxytocin, vasopressin, MCH and CRF are the effectors in melanocortin signalization pathway (Kohno et al. 2008, Fort et al. 2008, Yosten and Samson, 2009). It has also been noted that the injection of a-MSH to the rat cerebral ventricles increases the expression of NUCB2 mRNA in the PVN neurons. This suggests that the cells which synthesize this peptide, act through the melanocortin receptors (Maejima et al., 2009). Although the mechanisms of these actions are still unknown, the relevance of the proposed hypothesis is supported by the fact that changes in NUCB2 expression levels had not been reported after prior use of SHU9119, a selective antagonist of melanocortin MC3 and MC4 receptors (Brailoiu et al., 2007). There are also suggestions that nesfatin-1-expressing neurons may be sensitive to circulating oxytocin in rats. A number of nesfatin-1 cells in the ARC and PVN increased after intraperitoneal injection of oxytocin, while on the other hand central administration of antisense nesfatin-1 decreased the inhibitory effect of oxytocin on food intake (Saito et al. 2017). A recent study reported that intraperitoneal injection of cisplatin stimulated nesfatin-1 neurons in the hypothalamus and suppressed food intake in rats (Akiyama et al. 2017) which seems to be interesting from the oncological viewpoint. Direct injection of nesfatin-1 to the lateral ventricle of the rat brain caused a dose dependent suppression of consumatory behaviour. Extended infusion to the III-rd ventricle results in a significant reduction of body mass, and decrease in the amount of white adipose tissue. An intraperitoneal injection of nesfatin-1 induces in mice a 3- hour suppression of food intake, a subcutaneous administration induces the identical effect, and this anorexigenic action is maintained for 14 hours. Repeated intraperitoneal doses have substantially inhibited the increase of body mass, over a 6-day period. Extended subcutaneous infusion of nesfatin-1 also caused a significant decrease of food intake in rats (Mortazavi et al. 2015). It should be underlined that the peripheral nesfatin-1 doses required to depress food intake are approx. 1000-fold higher than those effective in the CNS. A serum level of nesfatin-1 is substantially decreased in state of starvation, and refeeding leads to its normalization. Nesfatin-1 penetrates the blood-brain barrier which potentially creates a possibility for its therapeutic use. It appears that after reaching the hypothalamic centres, nesfatin-1 will inhibit appetite and food intake. It has recently been noted that in humans the CSF/plasma nesfatin-1 ratio is significantly, negatively correlated with BMI (body mass index) and body mass that can suggest that nesfatin-1 is a protein-bound neuropeptide. A hypothesis was also proposed that dependent on body mass changes,efficiency of nesfatin-1 uptake by the CSF can be caused by saturation of its transporters (Pan et al. 2007). It also suggested that hypothalamic NUCB2/nesfatin-1 is involved in the hepatic insulin-dependent glucose homeostasis through activation of the mTOR-STAT3 signaling system (Wu et al. 2014). The activation of nesfatin-1 neurons in several rat brain nuclei under conditions of long-term activity-based anorexia (ABA) was recently studied with use of immunohistochemical methods (Scharner et al. 2017). The female individuals were divided into the following experimental goups: ABA, restricted feeding (RF), activity (AC) and ad libitum fed (AL). Interestingly, the number of nesfatin-1 immunopositive neurons in the PVN, ARC, DMH, locus coeruleus and in the rostral part of the nucleus of the solitary tract was increased in ABA group compared to AL and AC groups but not to RF rats. Furhermore, significantly more c-Fos and nesfatin-1 ir double-labeled cells were found in ABA animals compared to RF, AL and AC in the supraoptic nucleus and compared to AL and AC in the PVN, ARC, DMH, dorsal raphe nucleus and the rostral raphe pallidus. It should not be exluded that the observed changes of central nesfatin-1 immunoreactivity might play a potential role also in female patients suffered from AN.

4.3. Human studies.

Given the generally proven regularity that AN is often accompanied by anxiety and depressive-like behaviour (Lulé at al. 2014, Gauthier et al. 2014, Thornton et al. 2011) we decided to discuss a putative involvement of nesfatin-1 in the origin of these disorders jointly. This novel food intake inhibiting factor might be involved in the modulation of anxiety and in the central regulation of eating beaviour in AN (Hofmann et al. 2015a).

In patients sufferring from major depressive disorder (MDD), a higher serum nesfatin-1 level has been revealed, compared to levels reported in a control population (Ari et al. 2011). This may be a proof of bidirectional permeability of the blood-brain barrier for nesfatin-1. The mechanism of this phenomenon is unknown due to a lack of information indicating which nesfatin-1 expressing cell populations of the brain are responsible for the increased neuropeptide secretion in patients with MDD. Moreover, it also cannot be excluded that the additional source of circulating nesfatin-1 may be secondarily activated by some cells, located outside of the CNS. A study performed by Bloem et al. (2011) has revealed that nesfatin-1/NUCB2 mRNA expression in the human Westphal-Edinger nucleus (EW) was significantly elevated in suicidal cases among males, whereas among females, this content was lower, compared to controls. Midbrain CART mRNA levels were in turn elevated in both male and female victims. Noteworthy, the deceased individuals did not have diagnostically confirmed psychiatric disorders. This intriguing finding is the first to show sex-related changes in the neuropeptides levels in the brainstem of suicide victims. The colocalization of nesfatin-1/NUCB2 and CART in the EW was also found, suggesting the existence of potential interplay between both neuropeptides in the brain. Thus, the possible role of nesfatin-1 signaling in the pathogenesis of depressive-like and anxiety behaviour should be taken into consideration.

Despite the accumulating studies on novel neuropeptides the relationships between anxiety and nesfatin-1 action are understudied in humans.The clinical experiment carried out by Gunay et al. (2012) showed that male patients with generalize anxiety disorder had a decreased plasma level of nesfatin-1 than control groups. Another study aimed to find the potential sex-related correlations between serum nesfatin-1 levels and anxiety in obese patients and their changes during the treatment. In women, at the beginning and during of therapy the nesfatin-1 level was positively correlated with anxiety scores. Conversely a distinct negative correlation occurred in men during the treatment. Interestingly, neither female nor male patients with improved anxiety scores showed significant fluctuations in plasma nesfatin-1 levels. This finding suggests that women and men display an inverse relation between NUCB2/nesfatin-1 and anxiety. Females show positive but males negative correlation but this association was not statistically significant in men at the initial phase of treatment (Hofmann et al. 2015b). Noteworthy, no correlation was found between serum nesfatin-1 concentrations and BMI (Hofmann et al. 2015a). The same research team previously reported a positive correlation between plasma nesfatin-1 levels and depression scores in obese females (Hofmann et al. 2013) that is in line with the evidence showing elevated neuropeptide concentrations in normal weight patients with depression (Ari et al. 2011).

The plasma nesfatin-1 levels were also measured in AN patients with low and high anxiety scores evaluated according to the GAD-7 protocol. In patients with high anxiety scores the elevated nesfatin-1 level was found suggesting a positive correlation between the GAD-7 value and neuropeptide concentration. Both depressiveness (PSQ-20) perceived stress (PHQ-9) and disordered eating (EDI-2) scales were not associated with nesfatin-1 but were increased in the high anxiety patients. Taken together, plasma nesfatin-1 levels correlate positively with perceived anxiety without any asssociations with the symptoms of eating disturbances (Hofmann et al. 2015a). The aforementioned clinical results may be compared with a recent study by Lu *et al*. (2017) revealed sex-related changes of orexin A and OX2R levels in the brain of depression patients. The orexin A immunoreactivity in the *post mortem* examined hypothalamus was significantly increased in depressive females but not in males in comparison to healthy controls. Moreover in the anterior cingulate cortex of males who had committed suicide a significant increase of OX2R was found (Lu et al. 2017). Due to highly anorexigenic properties of nesfatin-1, it seems justified to conduct further research studies analyzing its potential role in pathogenesis of psychogenic eating disorders. Recently, it has been noted that plasma nesfatin-1 levels in patients suffering from restricting-type anorexia nervosa (AN-R) were significantly lower, compared with healthy controls. This may indicate a negative correlation with ghrelin and des-acyl ghrelin levels. In contrast, a positive correlation between nesfatin-1 levels and BMI was demonstrated (Ogiso et al., 2011). An opposite phenomenon was displayed in healthy men, with normal body mass index, in whom the fasting nesfatin-1 concentration negatively correlated with their BMI (Tsuchiya et al., 2010). This observation was similar to the one reported in rats (Stengel et al., 2009). However, there is still no convincing evidence that this low nesfatin-1 level underlies anxiety disorders, often accompanying AN-R. On the other hand, it cannot be excluded that during periods of extreme starvation, even the decreased nesfatin-1 level may reduce anxiety or fear, and stimulate food-intake.

5. Phoenixin in autonomic and mental functions

Phoenixin (PNX) a newly identified, endogenous regulatory neuropeptide of the brain (Yosten et al. 2013) exists in two different, active molecular forms PNX-14 and PNX-20 (Fig.1). Both of them are extremely conserved across vertebrate species, products of prohormone SMIM20 postranslational cleavage. The phoenixin was identified using a novel bioinformatic algorithm created by the Human Genome project that allows to predict previously unknown neuropeptides such as neuronostatin (Samson et al. 2008). According to this method some potential receptor molecules with a transmembrane domain are eliminated (SMART database) but putative proteins that contain signal peptides are included (SignalP database). In the next step, all sequences encoding known molecules were excluded. Finally, peptides with dibasic cleavage domains flanking a core region were taken into account using BioRegEx database and their highly conserved sequences were identified with NCBI BLAST. PNX may affect the pituitary gonadotropin release by modulation of GnRH-R receptor expression. Preliminary studies also suggested, that phoenixin sensitizes hypophysis to releasing factors rather than directly stimulates hormone exocytosis from pituitary cells (Yosten et al. 2013). The presence of PNX was identified in the limited neural populations in the lateral hypothalamus, VMH, SON, PVN, ARC, anterior horns of spinal cord, spinal trigeminal and solitary tracts and sensory ganglia (Lyu et al. 2013). Surprisingly, a distinct assembly of phoenixin-expressing cells was recently found in the rat central amygdala (Prinz et al. 2017). The arcuate nucleus contains a population of kisspeptin neurons with PNX expression that send their efferents to the GnRH cells in the medial preoptic area (Gottsch et al. 2014). PNX may be therefore a novel hypothalamic regulatory factor that stimulates the action of pituitary gonadotopes. Hypothetically, PNX may also activate kisspeptin neurons through an autocrine manner and/or via connections with other PNX-expressing cells (Treen et al 2016). Noteworthy, a distinct majority of nesfatin neurons in the rat hypothalamic nuclei exhibits phoenixin expression, that may suggest an existence of potential so far unknown functional correlations between these neuropeptides in the brain (Pałasz et al. 2015). PNX is a ligand of metabotropic GPR173 receptor significantly expressed in both kisspeptin and GnRH neurons (Treen et al. 2016). GPR173 alternatively known as SREB3 belongs to the superconserved receptor expressed in the brain (SREB) family, that has been found in the brain and ovaries and may play an important role in the regulation of the HPG axis (Matsumoto et al. 2005) Recent evidences suggest that GPR173 receptor in the hypothalamic neurons acts via cAMP/protein kinase A pathway through CREB, and probably C/EBP-β and/or Oct-1 to stimulate the kisspeptin-1 and GnRH expression. (Treen et al. 2016). Previous findings hypothesized, that PNX does acivate MAPK/ERK signaling pathway (personal communication). The selective modulators of GPR173 are yet to be unraveled that substantialy limits the range of pharmacological investigations dealing with PNX neurophysiology. It was also reported that PNX may prefentially inhibit visceral but not thermal pain. Recent evidence revealed that intracerebroventricular but not intraperitoneal infusion of PNX-14 during the subjective day increased food intake in rats. This change was not connected with any significant alterations in motor function or grooming activity. The PNX administration during the dark phase did not affect eating behaviour (Schalla et al. 2017). It may be therefore suggested that PNX is a new hypothalamic orexigenic neuropeptide being controlled by circadian rhythms. Moreover, these valuable results enable us to make the hypothesis that peripherally secreted PNX does not cross the blood barrier or does it to a minimal degree. One can therefore finally conclude that only brain-derived PNX can play a significant role in the central control of food intake. Noteworthy, an elevated plasma PNX-14 level in women with polycystic ovary syndrome (PCOS) suggests a potential involvement of PNX in the pathogenesis of this hormonally-related disease (Ullah et al. 2017). A valuable study by Jiang *et al*. (2015a) proved that PNX-14 acts as a potent anxiolytic factor in male mice when administered centrally. An infusion of PNX-14 into the lateral ventricle or anterior hypothalamic area (AHA) but not into the amygdala evoked anxiolytic-like behaviour in the open field and elevated plus maze test in adult animals. Importantly, treatment with a selective GnRH receptor antagonist (cetrorelix) abolished the anxiolitic action of PNX-14. In turn, a blockage of oxytocin/vasopressin receptors by atosiban did not change this effect. It should be therefore accepted that PNX-14 generates its oxytocin-independent anxiolytic activity via the stimulation of GnRH signaling system in the anterior hypothalamus. A recent clinical investigation by Hofmann et al. (2017b) examined for the first time a relationship between peripheral phoenixin levels and anxiety in a large group (68) of obese psychometrically diagnosed (GAD-7) male in-patients. The levels of depression and perceived stress were also measured using PHQ-9 and PSQ-20 scales respectively. The plasma phoenixin concentration was negatively correlated with anxiety scores, while any associations with other parameters were not detected. Since GnRH system may play a role in the regulation of learning and memory processes a possible effect of PNX-14 in these phenomena was examined using object recognition (NOR) and object location recognition (OLR) tasks. Intriguingly, an intracerebroventricular injection of PNX-14 immediately after testing significantly facilitated memory formation in rats. Furthermore, the memory retention was also extended under this experimental condition. The same changes occurred after direct infusion of PNX-14 into the hippocampus but they were inhibited by a selective GnRH antagonist (cetrorelix). It was also reported that central PNX-14 injection may decrease the memory impairment induced by the amyloid-β1-42 peptide and scopolamine suggesting that PNX-14 may be effective as a potential therapeutic in the treatment of Alzheimer′s disease (Jiang et al. 2015b). A new study by Yuruyen *et al*. (2017) concerned with the aforementioned problem and examined for the first time the relationships between plasma PNX level and subjective memory complaints in geriatric patients with mild cognitive impairment (MCI). Interestingly, the mean serum

PNX concentration was negatively correlated with logical memory. Decreased plasma PNX levels should be potentially taken into account in the initial stages of MCI as a putative predictive biological marker. Unexpectedly, PNX levels did not correlate with cognitive functions in patients with AD. To date, extremely little is known about PNX role in the higher mental functions, so the mechanism of its action should be investigated in future studies.

6. Spexin as a potent anorexigenic factor

Spexin (SPX) is a recently described neuropeptide, a transcript of the *Ch12orf39* gene which was discovered with bioinformatics tools (Mirabeau et al. 2007). SPX was identified using a hidden Markov model (HMM) based algorithm that integrates several neuropeptide sequence properties for the detection of new signaling molecules. Noteworthy, HMMs may applied to both gene prediction and protein domain analysis (Birney et al. 2004, Krogh et al. 1994). An HMM facilitates to find unknown protein sequence motifs, and it can also be used to determine whether a protein contains a specific domain. SPX has no structural similarities to known neuropeptides but it is phylogenetically highly conserved among the vertebrate species, rodent SPX differs from primate molecules by only one amino acid at the C-terminal domain (Porzionato et al. 2010, Fig.1.). In the rat brain, many SPX-expressing neural populations have been detected with the highest reaction in the hypothalamic paraventricular and supraoptic nuclei. SPX immunoreactivity has been also found in the hippocampus, amygdala, cerebellum and brainstem (Porzionato et al. 2010). A recent study suggested that SPX is an alternative endogenous ligand for the GALR2/3 receptors, that exhibits even higher affinity toward GALR3 than galanin (Kim et al. 2014). The galanin receptors are considered as modulators of fear responses (Bailey et al. 2007, Lu et al. 2008). This anxiety behaviour was observed in GALR1 and GALR2 knock-out mice (Holmes et al. 2003), the GALR2-mediated effect is in turn distinctly different than GALR3 action, as selective GALR3 antagonists decrease anxiety and promote depression-like behavior in rats (Swanson et al. 2005) SPX acting as GALR2/3 ligand should be theoretically evoked anxiolytic effects. Indeed, the SPX-like GALR2-specific agonist causes an acute anxiolytic profile in the elevated plus-maze (Reyes-Alcaraz et al. 2016).

SPX has multiple physiological functions with studies in goldfish revealing the involvement of SPX in reproduction and food-intake regulation. Treatment of animals with SPX decreased the secretion of luteinizing hormone and also suppressed appetite. Brain injection of goldfish with SPX inhibited both basal and NPY- or orexin-dependent consumatory behaviour and food intake (Wong et al. 2013). Recent findings also demonstrate a role for SPX in the control of cardiovascular/renal function and nociception (Porzionato et al. 2012), for instance SPX infusion to the rat brain ventricles decreased the heart rate without effecting blood pressure, but with an increase of renal filtration rate (Toll et al. 2012). It also reported that SPX stimulated basal aldosterone secretion by adrenal endocrine cells *in vitro*. After long-term exposure of this culture to SPX a moderate increase in corticosterone secretion but a significant decrease of cell proliferation occured (Ruciński et al. 2010). Intriguing recent results published by Walewski *et al*. (2014) showed that SPX may be a potent anorexigenic factor involved in weight regulation, with a possible application for obesity therapy. Peripheral SPX injections caused a strong depression of food intake and significant reduction of body weight in both DIO mice and rats. No taste-aversive effects of SPX administration were reported. Interestingly, a negative relation between leptin and SPX levels in the plasma of obese and normal weight patients was also revealed suggesting that both neuropeptides may play antagonistic roles in the regulation of eating behaviour and energy expenditure. SPX may also be a fat-expressed satiety factor and its gene was the most down-regulated in microarray assessment of human adipocytes (Walewski et al. 2010). A valuable piece of information about spexin physiology stems also from studies on a fish model. In goldfish an elevated plasma SPX level after eating was detected with simultaneous increase of SPX mRNA expression in the liver. The same effect on SPX mRNA concentration was also found in the liver and hypothalamus after intraperitoneal injection of glucose and insulin, respectively. Interstingly an insulin release triggered by glucose may stimulate SPX gene expression in the brain. Probably both central and peripheral effects of insulin on SPX gene expression in goldfish were mediated by insulin receptor and to a lesser degree by IGF-1 receptor coupled to mitogen-activated protein kinases 3/6/p38, phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin but not 1/2/extracellular signal-regulated kinase 1/2 pathways. Insulin can therefore act as the postprandial signal linking food intake with SPX signaling system in lower vertebrates (Ma et al. 2017). A recent result corroborates a role of SPX as a metabolic biomarker of glucose control in humans. Clinical study by Hodges *et al*. (2017) examined the effect of obesity, type 2 diabetes and glucose administration on serum SPX concentrations in adolescents of both sexes. Unexpectedly, the median fasting SPX levels were unchanged between the groups. Moreover, they were also not correlated with biochemical parameters and body composition. Judging by the potent anorexigenic properties of SPX it should not be excluded that a putative excess in the hypothalamic SPX signaling may be associated with the origin of AN. This interesting possibility certainly requires further basic and clinical studies.

7. A hypothetical nesfatin-1 and phoenixin mode of action in the mechanism of anxiety and anorexia nervosa.

In spite of the ongoing research on nesfatin-1 physiology its role in the mechanism of anxiety is as yet not explained. Taking into account that hypothalamus, a structure especially rich in peptidergic neurons is the main area of nesfatin-1 action several hypotheses can be formulated. The first one suggests a direct effect of nesfatin-1 on the CRF synthesis and release that may control the HPA axis activation (Merali et al. 2008). The crucial position of CRF in the central circuits regulating anxiety, fear reactions and stress responses is generally accepted (Borrow et al. 2016, Bale and Vale 2004). Patients suffering from AN show both extremely reduced food intake and increased physical activity. According to anxiety-related model of this disorder, these patients have highly elevated CRH and glucocorticoid release during eating that reflects the activation of hypothalamic-pituitary-adrenal (HPA) axis (Connan et al. 2007). Moreover, food intake stimulates CCK secretion, generating satiety and simultaneously activating CRH release that causes an elevated anxiety responses and inhibited consumatory behaviour. Given both high CRF-nesfatin-1 coexpression and numerous paracrine interconnections between nesfatin-1 and CRF cells this possibility seems to be especially reliable (Fig.2.). Molecular studies also prove that PVN neurons release nesfatin-1 from secretory vesicles (Maejima et al. 2009). CRF-expressing cells may be sensitive to nesfatin-1, however its receptor is still unknown therefore the precise mechanism of nesfatin-1 action is not clear. It should be taken into account that CRF neurons in the PVN differ both in their response to paracrine neuropeptide release and their influence on target neuronal populations. (Dabrowska et al. 2013). The potential anxiogenic effect of nesfatin-1 may be a result of putative G-coupled receptor stimulation and activation of intracellular signaling cascades that enable the CRF release into the median eminence. The increased level of calcium in the CRF neurons isolated from rat PVN after exposure to nesfatin-1 supports this hypothesis. Moreover, central injection of nesfatin-1 without additional stressogenic stimuli causes elevation of circulating ACTH and cortiosterone levels (Yoshida et al. 2010). Interestingly, nesfatin-1 sensitive noradrenergic and serotoninergic neurons in the respectively locus coeruleus and dorsal raphe send their projections to CRF neurons in PVN that may stimulate HPA axis in an alternative way (Cunningham and Sawchenko 1988). Taken together, only centrally expressed nesfatin-1 is involved in the anxiety generation and nesfatinergic neurons both in the hypothalamus and brainstem may evoke early phase fear responses through the stimulation of CRF and aminergic neurons. Regardless of direct or indirect stimulation of CRF neurons by nesfatin-1, the final physiological outcome of neuropeptide action depends on the type of CRF receptor which will be activated. It should not be therefore excluded that nesfatin-1 may also affect the synthesis and release of urocortins at the level of hypothalamic circuits. On the other hand, it should be suggested that nesfatin-1 may be an alternative ligand of CRF receptors. Additionally, nesfatin-1 signalling may also play a role in the mechanism of visceral hypersensitivity by modulation of CRF/CRF1 system (Jia et al. 2013). The influence of nesfatin-1 on CRF signaling may also take place outside thehypothalamus, especially in the amygdala, where distinct NUCB2 expression occurs (Goebel et al. 2009). There is a hypothesis suggesting that stress-related anxiety can be regulated by different groups of CRF neurons in the amygdaloid complex and BNST (Walker 2009). It should not be excluded that nesfatin-1 coexpressing CRF neurons belong to one of these cellular populations. A study by Regev *et al*. (2011) revealed that CRF ovexpression in the central nucleus of amygdala (CeA) caused decreased stress-dependent anxiety symptoms in rats. Conversely, another report showed elevated level of anxiety in rats with excess CRF expression in CeA and increased in the PVN (Shepard and Myers 2008). Nesfatin-1 released in the CeA may probably affect the anxiety responses through modulation of the CRF exocytosis from local neurons. A recent advanced study with use of retrograde tracing showed that the nesfatin-1 neurons in the CA1 region of hippocampus send their stimulatory projections to the ventromedial hypothalamus. Furthermore, an electrical stimulation of these cells evoked excitation of the VMH neurons. Nesfatin-1 injection to VMH decreases the activity of gastric distension responsive neurons through the modulation of CRF signaling circuit (Feng et al. 2017). One can therefore hypothesize that nesfatin-1 signalling may connect the hypothalamic and limbic structures responsible for both anxiety responses and consumatory behaviour.

The BDNF pathway may also be a potential target for nesfatin-1 action in the central mechanisms of anxiety. As previously mentioned long-term intraperitoneal injection of nesfatin-1 decreased BNDF protein expression in the rat hippocampus and prefrontal cortex and exerted anxiety-like behaviour (Ge et al. 2015). It may support the reports suggesting an involvement of BDNF in the pathogenesis of anxiety and depression (Janke et al. 2015, Suliman et al. 2013).

As previously mentioned the nesfatin-1 neurons, may act through the melanocortin receptors (Maejima et al., 2009). It suggests that the melanocortin signaling, both hypothalamic and limbic, may also be an alternative target for nesfatin-1 action in the brain mechanisms of anxiety. The melanocortin receptors, especially MC4R, which is highly expressed in brain, may play crucial roles in the regulation of stress and anxiety reactions (Chaki and Okubo 2007). A recent study proved that the anxiogenic action of another central neuropeptide PACAP was dependent on MC4R stimulation in the rat CeA (Iemolo et al. 2016). Moreover, activating MC4R in the medial amygdala (MeA) exerted anxiogenic and anorexigenic effects with a stimulation of the HPA axis in rats. Blocking MC4R in the MeA abolished such restraint stress-induced phenomena (Liu et al. 2013).

The mechanism of adaptating food intake to energy expenditure as well as appropriate balance of both orexi- and anorexigenic hypothalamic neuropeptides are strongly altered in patients with AN. In this case the activity of anorexigenic POMC/CART, CRF, CCK-8S and oxytocin neurons in ARC/PVN may be pathologically overstimulated by nesfatin-1 and probably spexin (Fig.3.). Phoenixin seems to be in turn an orexigenic factor (Schalla et al. 2017). Food intake promoting AgRP/NPY, MCH, 26RFa and orexin neurons can be in turn blocked by the same regulatory neuropeptides (Price et al. 2008) but the receptor mechanisms of their actions are so far unknown. Since the brain derived neurotrophic factor (BDNF) is a potent anorexigenic factor involved in the pathogenesis of AN (Monteleone and Maj 2013, Rios 2013), a potential influence of nesfatin-1 on its signaling pathway may be another possible strategy in the food intake depression in the course of this disorder. As well as nesfatin-1, the BDNF level as well as nesfatin-1 is strictly related to both energy equilibrium and reproductive phase. Nesfatin-1 administration decreased the BNDF expression in the rat brain (Ge et al. 2015) however, the nature of the relationships between these two neuropepetides in the context of eating behaviors in humans is not yet clarified. It was found that patients with active restricting AN had lower serum BDNF levels than healthy controls (Brandys et al. 2011). Some previous genetic studies do also suggest that the BDNF gene may be involved in the development of AN (Ribases et al. 2005). The plasma BDNF levels were increased in patients with binge-eating/purging type AN when compared to restricting type AN individuals (Eddy et al.2015). Another finding reported that normal-weight women with bulimia nervosa had increased serum BDNF levels compared with AN patients (Saito et al. 2009). The plasma BDNF levels in patients with AN undergo changes in the course of disorder. For instance, serum BDNF levels in women recovered from AN was higher in comparison to acutely underweight AN patients and had a tendency to increase with weight gain. Noteworthy, in AN but not healthy female controls, BDNF concentrations were inversely correlated with psychomotor activation (Zwipp et al. 2014). One can postulate, that nesfatinergic projections from ARC to VMH or/and local nesfatin-1 neurons in VMH may stimulate the BDNF synthesis and exocytosis that causes extended inhibition of food intake during AN, although the receptor mechanism of this effect remains unknown. Interestingly, the regulation of BNDF expression in the rat VMH seems to be sex-dependent. It was reported that fasted males but not females showed decreased BDNF level in the VMH in comparison to the control fed individuals following 24-hour food restriction. In male high fat diet (HFD) obese and HFD-PF normal weight rats a lower BDNF expression compared with low fat diet (LFD) males occurred, suggesting that suppressed BDNF signaling was associated with a fat-rich diet consumption instead of increased adiposity. Noteworthy, decreased BDNF expression during HFD may reinforce the eating behaviour and promotes the obesity in male animals. Conversely, hypothalamic BDNF level in females remains stable even in condition of the severe energy imbalance. (Liu et al. 2014). Despite of the aforementioned findings a recent evidence does not recommend BDNF as a reliable biomarker in women with recovery from AN because an inverse significant correlation between plasma BDNF and anxiety occured only in healthy controls (Kawada 2017).

Eating behaviour is controlled intimately by complex brain mechanisms of food reward, whether those signaling circuits act in normal or disturbed modes. To date it is not clarified whether the restricted pattern of food intake in AN are caused by structurally visible injuries in brain reward centres including nesfatin-1 neurons. A possible pharmacological treatment of those distorted pathways with drugs that affect reward-related neuronal assemblies in VTA or NAc still remains a hypothetical strategy. Moreover, it is not yet definitely proven whether any causes of AN are essentially dependent on brain reward system and how brain substrates of food reward relate to eating disorders. Nonetheless, it should be taken into account that mesolimbic dopamine and opiod systems that form hedonic “wanting-liking” brain hotspots may be involved in the pathogenesis of AN and other eating disorders (Castro and Berridge 2014). Those mechanisms might contribute to generating obsessive dreads e.g. a persistent and compulsive focus on remaining extremely thin (Faure et al. 2008). The results published by Chen et al. (2015b) shed a new intriguing light on the hypothesis of nesfatin-1 role in the origin of AN suggesting its direct action on the dopaminergic reward circuits. Targeted nesfatin-1 injection to the ventral tegmental area (VTA) strongly decreased both the food consumption and dopamine release in the NAc. Nesfatin-1 effect on VTA seems to analogous to the leptin but different than ghrelin action (Hommel et al. 2006, Abizaid et al. 2006) It can be therefore possible that nesfatin-1 neurons in the lateral amygdala send their inhibitory efferents to the VTA neurons that evoke the anorexigenic effect. The nesfatin-1 mode of action in the reward circuits may resemble the effect of oxytocin at the NAc, while its injection to this structure caused a significant depression of food intake in rats (Herisson et al. 2016). It should be not excluded that the food intake restricting action of nesfatin-1 in AN may be initiated by the release of the endogenous anorexigenic factor GLP-1 into the hypothalamus. The GLP-1 neurons in the rat nucleus of solitary tract (NTS) send their long stimulatory projections to the CRF and nesfatin-1 cells in the PVN. GLP-1 administered *in vitro* evokes the calcium signaling cascade in the nesfatin-1 neurons isolated from PVN. Interestingly, precise injection of a GLP-1 receptor antagonist exendin (9-39) to the PVN increased food intake (Katsurada et al. 2014). We realize that our hypothetic model may be considered a bit preliminary or even controversial. Indeed, some of the data are purely correlational e.g. measurements of plasma neuropeptide levels, whereas other ones such as testing sufficiency or necessity of neuropeptide signaling are direct tests of involvement. Unquestionably, a comparative degree of interpretative weight to each of these types of results should be placed cautiously. It is also difficult to determine what are the actual sources of circulating neuropeptides (brain, peripheral nerves and ganglia or even endocrine cells) and what do plasma levels tell us about signaling actions within specific neural circuits in the brain. It should be taken into consideration that it is not absolutely clear whether the correlational data warrant the high level of interpretive emphasis. Despite the aforementioned limitations and doubts we are convinced that our original hypothesis may open a new chapter in the discussion of the peptidergic signaling in anxiety and anorexia nervosa.

8. Kisspeptin in anxiety responses, depression and anorexia nervosa

Kisspeptin, a C-terminally amidated neuropeptide and endogenous ligand of metabotropic Kiss1R (GPRS54) receptor plays an essential role in the hypophyseal regulation of the ovarian cycle (Constantin 2017, Navarro et al. 2015). The core molecule kisspeptin-54 is proteolytically cleaved into several smaller peptides kisspeptin-13 and 14 (Fig.1.). The majority of kisspeptin neurons are located in the hypothalamic ARC and anteroventral periventricular (AVPV) nuclei (Mikkelsen et al. 2009) Kisspeptin regulates the gonadotropin releasing hormone (GnRH) synthesis in the hypothalamic neurons via stimulation of their firing and depolarization (Quaynor et al. 2007). The Kiss-1 gene expression in the hypothalamic nuclei is strictly controlled by circulating sex steroids (Navarro et al. 2004). Recent studies showed that mice with deletion of Kiss-1 gene in the GnRH neurons manifested disturbed sexual differentiation at the level of brain structures (Clarkson et al. 2014).

Kisspeptin decreases food intake and may be therefore identified as the next hypothalamic anorexigenic factor (De Bond and Smith 2014, Stengel and Tache 2011). Importantly, kisspeptin neurons send axonal projections to key regulatory neurons in the arcuate nucleus (Hrabovszky 2014). These efferents may directly stimulate POMC/CART and indirectly inhibit NPY/AgRP cells through enforced of GABA-ergic transmission (Fu et al. 2010).

Kiss-1 mRNA expression was identified in the hippocampus, where it is about 5-100 times weaker than in the hypothalamus (Arai and Orwig 2008). It is known, that some neuropeptides e.g. NPY and somatostatin affect the plasticity and excitability of hippocampal neurons (Baratta et al. 2002). This kisspeptin mode of action seems to be unique, because this neuropeptide increases stimulatory responses of neurons via modulation of postsynaptic signaling (Arai et al. 2009). Kisspeptin facilitates hippocampal synaptic transmission by activation of MAP kinase (MAPK) pathway in the granular cells of dentate gyrus. Perhaps this regulatory system plays so far unknown role in the mechanisms of learning and also in the pathogenesis of epilepsy. Kisspeptin and Kiss1R expressing neurons were recently identified also in the rat posterodorsal subnucleus of the medial amygdala (MePD) There are justified suggestions that kisspeptin in the MePD may affect male sexual behavior. Direct bilateral infusion of kisspeptin-10 to the MePD caused multiple erections, an effect connected with Kiss1 receptor activation, because Kiss1R antagonist abolished this physiological reaction. Conversely, an intracerebroventricular injection of kisspepetin did not exert any penile stimulation in rats. Interstingly enough, the kisspeptin increased plasma LH levels to comparable value when infused into both MePD and lateral ventricle (Pineda et al. 2017, Gresham et al. 2016). Fluorescent studies using retro- and anterograde tracers, and viral transfection systems in wild-type and transgenic rodents revealed the presence of reciprocal connections between the kisspeptin neurons in the accessory olfactory bulb and amygdala. The kisspeptin neurons may inhibit the mitral cells in the accessory olfactory bulb. Noteworthy, kisspeptin neurons in the amygdala send their efferents to GnRH neurons in the hypothalamic preoptic area and they are probably innervated by vasopressinergic and dopaminergic neurons. Interestingly, peripheral kisspeptin administration significantly supressed signal intensity in the rat amygdala but increased LH secretion in rodents. Moreover, a direct kisspeptin injection into the medial amygdala (MeA) caused an elevation of LH release. Conversely, an inhibition of amygdalar kisspeptin signaling by targeted injecting of selective Kiss1 antagonist (peptide-234) generally depressed LH signaling. Taken together, this may prove that the kisspeptin regulatory system within the amygdala affects gonadotropin release and pulsatility. Furthermore, kisspeptin may be consider as the pivotal regulator of reproductive processes, connecting limbic centres with the hypothalamic GnRH neurons (Comninos et al. 2016). In the light of aforementioned information it has to be especially emphasized that Kiss-1 gene expression in both hippocampus and amygdala are dependent on the concentrations of circulating estrogens and progesterone (Cao and Patisaul 2013, Kim et al. 2011, Arai 2009). Behavioural studies revealed the anxiogenic effect of centrally injected kisspeptin-13 in rats, a neuropeptide administration caused a significant preference for the close arms in the EPM test (Csabafi et al. 2013). It suggests that kisspeptin stimulates stress-related CRF and AVP neurons both in the HPA axis in the amygdala (Pineda, et al. 2017). Kisspeptin is also considered as the novel endogenous antidepressant. Animal studies with modified forced swimming test (FST) revealing that kisspeptin-13 may reverse the immobility, climbing and swimming times in rats that may support this suggestion. Interstingly, the selective antagonists of $\alpha(2)$-adrenergic and 5-HT(2) serotonin receptors (phenoxybenzamine, yohimbine and cyproheptadine) abolished the behavioural effects of kisspeptin-13. It may prove, that antidepressant-like properties of kisspeptin-13 are mediated via interaction with the adrenergic and serotoninergic signaling pathways (Tanaka et al. 2013). Because the food intake-regulatory neuropeptides may affect physical activity Hofmann et al. (2017a) examined potential relationship between the exercises and plasma levels of several regulatory factors including kisspeptin in females with AN. Additionally, associations with psychometric parameters: (PHQ-9), anxiety (GAD-7), perceived stress (PSQ-20) and disordered eating (EDI-2) and body composition were measured. Women showed disparate forms of physical activity revealed a negative correlation with kisspeptin but positive association with ghrelin level. Interestingly no signifant correlations occured between intensive exercise and orexin-A, FGF-21 and R-spondin-1 concentrations. There was also a positive association between kisspeptin level and BMI but negative with the interpersonal distrust subscale of the EDI-2. Taken together, depression, anxiety, and perceived stress were not correlated with serum kisspeptin level in AN. Kisspeptin seems to be inversely, but ghrelin positively, associated with physical activity in AN suggesting a potential role of these neuropeptides in the regulation of motor functions in AN. (Hoffman 2017a). A recent study by Bacopoulou et al. (2017) examined the serum kisspeptin levels in adolescent females with typical and atypical AN. Atypical AN is a less severe eating disorder that does not met all diagnostic criteria for AN. Interestingly, the kisspeptin concentrations were lower in women with typical AN and higher in patients with atypical one. An increase of kisspeptin levels in the women with atypical AN whose ovarian activity weakened might have been caused by kisspeptin secretion in an effort to maintain menstruation. An excess of kisspeptin released by hypothalamic centres might have caused in a depletion of the neuropeptide reserve and thus in no further elevation in kisspeptin levels, as typical AN along with amenorrhea became physiologically determined. Since kisspeptin regulates the GnRH-dependent LH release the females with typical AN manifested lower LH plasma levels compared to healthy participants. Additionally, the plasma kisspeptin levels were negatively correlated with BMI in the patients with typical AN.

9. Sex differences in nesfatin-1, phoenixin and kisspeptin signaling.

A number of aforementioned recently published clinical studies revealed certain sex-related differences in plasma nesfatin-1, phoenixin and kisspeptin levels in various groups of patients suffered from AN, anxiety and obesity (Fig. 4.). The nesfatin-1 concentration was decreased in females with AN but increased when the women suffered from AN with anxiety symptoms (Ogiso et al. 2011, Hofmann et al. 2015a). In male anxiety patients the serum nesfatin-1 level was lower when compared to controls (Gunay et al. 2012). Also phoenixin level was decreased in overweight men with anxiety (Hofmann et al. 2017a). Obese men showed negative but women positive correlation between nesfatin-1 levels and anxiety scores (Hofmann et al. 2015b, 2013). The serum kisspeptin level was increased in woman with atypical but decreased in patiens with typical symptoms of AN (Bacopoulou et al. 2017). Additionally, both females and males with mild cognitive impairment had depressed levels of phoenixin (Yuruyen et al. 2017). Although these results are still rather difficult to interpret some hypothetical explanations can be formulated. First of all, it has to be emphasized that women reveal in general higher plasma nesfatin-1 levels than men (Bergmann et al. 2015, Feijoo-Bandin et al. 2013). Furthermore, due to a distinct prevalence of anxiety and depression in women compared to men (Gorman et al. 2006, Kuehner 2003), a potential sex-specific modulation of nesfatinergic and/or phoenixinergic signaling in the stress and fear responses seems to be especially interesting. An unusual report revealing the sex-related associations between plasma nesfatin-1 level and incidences of suicidal behaviour can support this point of view (Bloem et al. 2012). Since nesfatin-1, phoenixin and kisspeptin are involved in reproductive processes acting as gonadotropic axis stimulators their differential regulation may be related to sex steroid activity (Garcia-Galliano and Tena-Sempere 2013). Interestingly, NUCB2/nesfatin-1 expression in the pituitary gland of female rats is regulated by the ovarian 17β-estradiol and progesterone (Chung et al. 2015). In turn, in the male mice hypophyseal but not hypothalamic NUCB2 mRNA expression was depressed after castration (Seon et al. 2017). In these animals the NUCB2 mRNA level in the adenohypopohysis was increased after testosterone administration. Conversely, the NUCB2 mRNA expression in the hypothalamus was significantly decreased after hormone treatment. The NUCB2 mRNA expression in isolated hypothalamic cell culture was also significantly decreased with testosterone. An inverse effect occured with the same treatment in pituitary cells *in vitro*. Taken together, it suggests that sex steroids may affect the NUCB2 mRNA signaling in the rat HPG axis (Seon et al. 2017). This hypothesis is also supported by a report showing that testosterone increased NUCB2/nesfatin-1 mRNA and protein expression in murine hypothalamic (GT-1-7) and pituitary (LβT2) cells *in vitro*. Interstingly, 17β-estradiol did so only in the hypohyseal cell culture. Kisspeptin and GnRH modulate central NUCB2/nesfatin-1 signalling, treatment with kisspeptin caused an elevation of NUCB2/nesfatin-1 mRNA and protein expression in hypothalamic cells. Nesfatin-1 in turn increased GnRH and Kiss1R protein expression in both studied cells (Hatef and Uniappan 2017). It should not be excluded, that some female hormonally dependent anxiety-like neuropsychiatric disturbances such as postpartum depression and premenstrual dysphoria may be related to some impairment of the nesfatin-1/kisspeptin regulatory system in the brain (Miller 2002, Noble 2005). Since brain nesfatin-1 and kisspeptin actions are CRF-related a study showing that long-term treatment of adolescent female mice with androgenic steroids enhanced anxiety via increased CRF signaling of CeA efferents seems to be especially interesting (Costine et al. 2010). There are intriguing hypothesis suggesting that gender may affect differentially the activity of the CeA and PVN in rats. Electric shock increased CRF mRNA level in the CeA in both sexes, with higher amplitude in females in proestrus than in males. Conversely, psychological stress augmented amygdalar CRF mRNA expression only in male individuals. A conclusion that hypothalamic CRF gene expression in the PVN is related to psychological stressors only in females may be a key point to explain of the neurochemical pathways underlying the sex-differential mechanism of AN (Iwasaki-Sekino et al. 2009). Both nesfatin-1 and kisspeptin neurons are considered as sensitive to circulating sex hormones thus generally anxiogenic effect of ERα as well as anxiolytic action of ERβ may be potentially associated with their influence on anxiety-related hypothalamic peptidergic systems including nesfatin-1 and kisspeptin circuits (Borrow and Handa 2017). A study suggesting an involvement of ER□ and oxytocin in the HPA-dependent generation of anxiety may support this hypothesis (Kudwa et al. 2014). Undoubtedly, a number of further studies are required to elucidate the potential sex-related associations of the newly identified neuropeptides and anxiety in the context of eating disorders.

10. Concluding remarks

Recently identified neuropeptides nesfatin-1, phoenixin, spexin and kisspeptin are characterized by a broad spectrum of sex-dependent regulatory activity in the brain. Accumulating evidence considers them as novel and potentially important factors involved in the pathogenesis of several mental disorders. It should not be therefore excluded that the putative pharmacomodulation of neuropeptide signaling may be potentially helpful in the future treatment of certain neuropsychiatric and metabolic disorders including anxiety and anorexia nervosa. Undoubtedly, more advanced investigations on this field merits special attention. Although the outcome of some basic and clinical studies seems to be encouraging, any possible applications of the aforementioned neuropeptides as well as their agonist and antagonists still remain in the area of speculation. Nonetheless, intensive searching for the selective modulators of their known receptors may contribute to opening of a promising chapter in therapy of anxiety and eating disorders.

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Figure captions;

Fig. 1. Comparative molecular structure of nesfatin-1, phoenixin, spexin and kisspeptin.

Fig. 2. An outline potential involvement of nesfatin-1 and kisspeptin in the mechanism of anxiety. Nesfatin-1 and kisspeptin neurons activate the synthesis and release of CRF both in the hypothalamus and central amygdala. The physiological outcome of neuropeptides action depends on the type of CRF receptor which will be stimulated. The CRF binding to CRF1 receptor exerts anxiogenic effects, whereas CRF2 receptor activation leads to anxiolytic effects. The melanocortin circuits, both hypothalamic and limbic, may also be a target for nesfatin-1 action in the central mechanisms of anxiety. Nesfatin-1 and kisspeptin released in the central amygdala may probably affect the anxiety responses through modulation of the CRF release from local neurons. A group of nesfatin-1 neurons in the CA1 region of hippocampus send their stimulatory projections to BDNF cells in the ventromedial hypothalamus

Fig. 3. A hypothetical model of nesfatin-1, phoenixin, spexin and kisspeptin roles in the modulation of orexigenic pathways that activate reward system in anorexia nervosa. Extremely restricted food intake in AN stimulate the neuronal populations in the lateral hypothalamus (LHA) that will release a set of orexigenic neuropeptides (orexins, MCH and 26RFa) in the ventral tegmental area (VTA). These factors increase the dopamine exocytosis in the nucleus accumbens. In the course of AN, the activation of the reward circuits causes perisistent food aversion associated with elevated anxiety that will, in turn, reinforce the fasting behaviour. An important supporting roles in the mechanism of this reinforcement may play the newly found hypothalamic neuropeptides. An excess of nesfatin-1 may strongly inhibit orexigenic NPY/AgRP neurons but stimulate anorexigenic POMC/CART and kisspeptin neurons in ARC. The nesfatinergic projections can also directly stimulate anorexigenic CRF neurons in PVN and block the aforementioned feeding promoting cells in LH. Hypothalamic spexin may additionally activate the POMC/CART and probably oxytocin cells through the galanin Gal2/3 receptors. Conversely, PNX seems to stimulate the main orexigenic NPY/AgRP cells probably via GPR173 receptor, antagonizing the nesfatin-1 and spexin effects. Kisspeptin may also activate anorexigenic POMC/CART neurons via Kiss-1 receptor.

Fig 4. Sex-related changes in the plasma nesfatin-1, phoenixin and kisspeptin levels in patients with diverse neuropsychiatric disorders. AN, anorexia nervosa; AN(A), typical AN; AN(A), atypical AN; MCI, mild cognitive impairment; Ob, obesity.