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Role of nesfatin-1 in anxiety, depression and the response to stress

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ABSTRACT

Nesfatin-1 has been discovered a decade ago and since then drawn a lot of attention. The initially proposed anorexigenic effect was followed by the description of several other involvements such as a role in gastrointestinal motility, glucose homeostasis, cardiovascular functions and thermoregulation giving rise to a pleiotropic action of this peptide. The recent years witnessed mounting evidence on the involvement of nesfatin-1 in emotional processes as well. The present review will describe the peptide's relations to anxiety, depressiveness and stress in animal models and humans and also discuss existing gaps in knowledge in order to stimulate further research.

1. Introduction

Over the past years, nesfatin-1 received a lot of attention associated with the growing evidence for its role in various physiological processes. Discovered in 2006 in the rat hypothalamus (Oh-I et al., 2006), the 82-amino acid peptide is cleaved from its precursor protein nucleobindin 2 (NUCB2) before exerting pleiotropic effects. This is supported by the fact that apart from the hypothalamus, NUCB2 mRNA expression has been detected in various central and peripheral tissues including the hippocampus, prefrontal cortex, amygdala, brain stem, gastrointestinal tract, pancreatic islets or adipose tissue (Goebel-Stengel and Wang, 2013; Prinz and Stengel, 2016).

The first effect described for nesfatin-1 was its anorexigenic property. In animal studies, it was shown to suppress food intake after central and, much less robustly, after peripheral administration and subsequently also to reduce body weight (for review see: (Stengel et al., 2013b; Weibert and Stengel, 2017)). Furthermore, intracerebroventricular (icv) injection of nesfatin-1 resulted in a delay of gastric emptying (Stengel et al., 2009a) and a reduction of gastrointestinal motility (Atsuchi et al., 2010; Xu et al., 2015a), effects likely contributing to the reduction of appetite. Moreover, nesfatin-1 has been implicated in glucose homeostasis enhancing glucose-stimulated insulin secretion and sensitivity (Gonzalez et al., 2011; Li et al., 2013) as well as in lipid metabolism where nesfatin-1 administration decreased blood lipid concentrations and suppressed lipogenesis (Yin et al., 2015) contributing to the improvement of the metabolic profile. Other important effects described for nesfatin-1 include the increase of blood pressure (Mori et al., 2017; Osaki and Shimizu, 2014), stimulation of thermogenesis (Könczöl et al., 2012; Wernecke et al., 2014) and initiation of puberty (Garcia-Galiano et al., 2010), thus influencing reproductive functions as well.

The receptor mediating these pleiotropic effects has not been characterized yet. Nevertheless, converging evidence points towards a G protein-coupled receptor (Brailoiu et al., 2007), likely expressed in central (*e.g.* cortex, paraventricular nucleus (PVN) of the hypothalamus, dorsal motor nucleus of the vagus nerve) and peripheral tissues (*e.g.* pancreas, pituitary, stomach, small intestine, heart, skeletal muscle, visceral adipose tissue) as recently shown using autoradiography in rats (Prinz et al., 2016) corroborating the suspected broad range of nesfatin-1's effects.

However, subsequent studies showed that nesfatin-1 is not only restricted to metabolic functions. Over the years, the involvement of nesfatin-1 in the regulation of psychopathological conditions like depression and anxiety has been suggested (Emmerzaal and Kozicz, 2013). Differential findings have been described for women and men leading to the hypothesis of a sex-specific regulation of this peptide.

In this review we will outline the current knowledge on the role of NUCB2/nesfatin-1 in the regulation of emotional processes with an emphasis on the functional implications in depression, anxiety and the mediation of stress. In addition, we will acknowledge the sex-specific aspects in the modulation of these processes and discuss possible gaps in knowledge in order to stimulate future investigations. Since most

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commercially available antibodies targeting nesfatin-1 also recognize full length NUCB2 (Stengel et al., 2013b), we refer to these analytes as NUCB2/nesfatin-1.

2. Potential role in anxiety

Anxiety disorders, including generalized anxiety disorder, social anxiety disorder, specific phobias and panic disorder with or without agoraphobia are the most common psychiatric disorders worldwide (Kessler et al., 1994; Stein et al., 2017; Wittchen and Jacobi, 2005). In large epidemiological community surveys, the reported annual prevalence of anxiety disorders is up to 21% and the lifetime prevalence even up to 34% with women suffering approximately twice as likely than men (Bandelow and Michaelis, 2015). A recent systematic review and meta-regression indicated a global prevalence of 7% for anxiety disorders (Baxter et al., 2013). Due to these high prevalence rates, the associated reduction in quality of life of those affected as well as the high health care costs (Bandelow and Michaelis, 2015; Wittchen and Jacobi, 2005) it is necessary to characterize the pathomechanisms: psychosocial factors that maintain the symptoms but also possible biological contributors such as peptide hormones potentially involved in the development of these mental disorders.

Early after the identification of nesfatin-1, its implication in the modulation of different emotional states like anxiety has been examined. In particular, changes in behavior have been observed in animal studies after icv or peripheral injection of nesfatin-1 using standardized tests. Initially, innate and conditioned anxiety responses of rats were assessed in different behavioral tests after icv injection of 5 or 25 pmol of nesfatin-1 (Merali et al., 2008). In the elevated plus maze, a method to measure innate anxiety-like behavior (Rodgers and Dalvi, 1997), the higher dose resulted in a significant reduction of time spent in the open arms, the number of open arm entries and the number of unprotected head dips in comparison to the vehicle group reflective of a decreased explorative behavior (Merali et al., 2008). Moreover, both doses of nesfatin-1 resulted in a significantly prolonged latency to eat and a reduced consumption of palatable snacks when moved into a novel cage (Merali et al., 2008) as part of the novelty-induced hypophagia test (Merali et al., 2003). Although centrally injected nesfatin-1 was initially demonstrated to inhibit food intake (Oh-I et al., 2006), icv injected nesfatin-1 had no effect on snack consumption in the home cage (Merali et al., 2008), possibly pointing towards an indirect effect on food intake subsequent to the stimulation of anxiety. In order to assess conditioned fear responses the fear-potentiated startle test (Davis, 1990) was conducted, where noises (conditioned stimulus) and foot shocks (unconditioned stimulus) were combined and the startle amplitude after nesfatin-1 injection measured. Rats that received nesfatin-1 icv at a dose of 25 pmol displayed a significantly greater startle potentiation than controls (Merali et al., 2008). Lastly, rats treated with this dose showed a significantly elevated time engaged in freezing (Merali et al., 2008), a behavior displayed in response to conditioned fear (Davis, 1990). Based on this pioneer study, nesfatin-1 was implicated in the central mediation of anxiety-related behavior.

In line with these findings, a subsequent study demonstrated a stimulated anxiety-like behavior in rats after repeated intraperitoneal (ip) injections of nesfatin-1 over a period of three weeks (Ge et al., 2015a). In the open field test, rats treated with nesfatin-1 spent significantly less time in the center representing the vulnerable zone of the test, and displayed significantly decreased frequencies of grooming and rearing as well as reduced moving distances than the control group (Ge et al., 2015a). Furthermore, a significantly reduced frequency of entering all three arms of the Y maze, an overall reduced moving distance and a decreased preference index of the unexplored arm were observed after nesfatin-1 administration (Ge et al., 2015a), supporting the findings of the open field test and the assumption of an exploration-suppressive action by peripherally administered nesfatin-1 and therefore, an anxiety-enhancing effect when faced with a novel environment.

In a recent rat study, the influence of sequentially applied stress early in life on anxiety-like behavior in adulthood was investigated (Jing et al., 2017). Young animals underwent maternal separation (postnatal day 2-21) and were periodically treated with acute gastric irritation (day 10-16) followed by daily 90-min restraint stress over a period of seven days (Jing et al., 2017). Since NUCB2 mRNA expression in the gastric oxyntic mucosa was reported to be 10-fold higher than in the brain (Stengel et al., 2009b), alterations of NUCB2/nesfatin-1 were assessed – besides in hippocampus and plasma – also in the gastric fundus. Following the sequential stress, rats displayed increased anxiety-like behavior as indicated by less time spent in and fewer entries into the open arms of the elevated plus maze (Jing et al., 2017). Similarly, animals showed significantly less attendance to stay in the central area as well as significantly lower moving distance and slower movement in the open field test compared to non-stressed controls (Jing et al., 2017). Since this was accompanied by higher NUCB2/nesfatin-1 peptide levels in hippocampus, plasma and stomach (Jing et al., 2017), endogenous nesfatin-1 upregulated under conditions of stress may play a role in the development of anxiety.

Subsequently, the potential association of nesfatin-1 and anxiety was also examined in human studies. A study in male normal-weight patients diagnosed with generalized anxiety disorder (GAD) reported 45% lower NUCB2/nesfatin-1 plasma levels in these patients compared to age- and sex-matched healthy controls (Gunay et al., 2012). Another study reported an increase of NUCB2/nesfatin-1 plasma levels in a mixed-sex, normal weight population with panic disorder compared to a healthy control group (Bez et al., 2010). Furthermore, a positive correlation between NUCB2/nesfatin-1 and the severity of the panic disorder ($r = 0.467$, $p = 0.011$) was found (Bez et al., 2010). Also in male and female patients with an obsessive compulsive disorder significantly higher NUCB2/nesfatin-1 plasma levels were found compared to healthy controls (Bez et al., 2012). However, no association was observed between NUCB2/nesfatin-1 and the severity of obsessions and compulsions (Bez et al., 2012). It is important to note that these studies did not assess possible sex differences in the regulation of NUCB2/nesfatin-1 that may contribute to the partly discrepant findings described above.

Psychiatric diseases like anxiety and depression are often comorbid disorders in obesity. In particular, obesity is reported to be associated with anxiety (Gariepy et al., 2010). Moreover, NUCB2/nesfatin-1 was reported to be positively associated with body mass index and fat mass in humans (Ramanjaneya et al., 2010; Tan et al., 2011). Therefore, our group primarily investigated the association between nesfatin-1 and anxiety in female obese patients (Hofmann et al., 2013) in order to shed more light on nesfatin-1 as a potential link between food intake/nutrition and the emotional state. Plasma NUCB2/nesfatin-1 concentrations were assessed along with the severity of anxiety symptoms using the generalized anxiety disorder scale (GAD-7, 7-item scale, scores range from 0 to 21), a self-report questionnaire for the diagnosis of generalized anxiety disorder but also a sensitive screening tool for social anxiety, panic and posttraumatic stress disorders (Spitzer et al., 2006). According to the GAD-7 scores, the study population was divided in females with low anxiety (mean ± SD, 5.0 ± 2.7) and high anxiety (14.2 ± 3.3, $p < 0.001$) (Hofmann et al., 2013). We observed that women with high anxiety scores had significantly higher NUCB2/nesfatin-1 plasma levels (+33%) compared to females with low anxiety (Hofmann et al., 2013). Moreover, we detected a positive correlation between NUCB2/nesfatin-1 levels and GAD-7 scores ($r = 0.680$, $p < 0.001$) (Hofmann et al., 2013) suggesting a role for nesfatin-1 in the mediation of anxiety in humans as well. This finding was corroborated in patients with anorexia nervosa, a disease also frequently associated with anxiety (Kaye et al., 2004), with 65% higher NUCB2/nesfatin-1 plasma levels in patients reporting high anxiety (GAD-7 score: 16.0 ± 3.0) compared to those with lower anxiety levels (7.5 ± 3.3, $p < 0.001$) resulting in a positive association between anxiety scores and NUCB2/nesfatin-1 ($r = 0.32$, $p = 0.04$) (Hofmann