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Nesfatin-1, a potent anorexic agent, decreases exploration and induces anxiety-like behavior in rats without altering learning or memory

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ABSTRACT

The anorectic neuropeptide nesfatin-1 has recently been characterized as a potential mood regulator, but the accurate effect of nesfatin-1 on anxiety and learning and memory behavior and the possible mechanisms remains unknown. In the present study, to test the hypothesis that nesfatin-1 might affect the anxiety-like and learning and memory behaviors in rats via ERK/CREB/BDNF pathway, nesfatin-1 was administered intraperitoneally to rats with the doses (10, 20, 40 μg/kg), and the behavioral performance was tested using the open field task, the Morris water maze (MWM), and the Y maze. Moreover, the protein expression of brain-derived neurotrophic factor (BDNF), total and phosphorylated-ERK in the hippocampus and the prefrontal cortex (PFC) were evaluated. The results showed that chronic administration of nesfatin-1 could decrease the moving distance, the duration in the center, and the frequencies of rearing and grooming in the open field task, decrease the moving distance, frequency, and the preference index of new arm in the Y maze, although there was no significant difference of the performance in the MWM task among groups. Furthermore, 3 weeks' consecutive administration of nesfatin-1 resulted in the decrease of protein expression of BDNF and phosphorylated-ERK in the hippocampus and the PFC. These results provided evidence that exogenous nesfatin-1 could decrease exploration and induce anxiety-like behavior in rats, the mechanism of which might be related to the reduced protein expression of BDNF and phosphorylated-ERK in the hippocampus and the PFC.

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1. Introduction

Nesfatin-1 is an 82 amino acid neuropeptide cleaved from its precursor nucleobindin 2 (NUCB2). Expressed in several discrete nuclei of the hypothalamus including the paraventricular (PVN) and the arcuate nucleus (Arc) (Oh et al., 2006), nesfatin-1 is a potent satiety factor that strongly inhibits food and water intake after acute central or peripheral administration (Oh et al., 2006; Stengel et al., 2009). Apart from the hypothalamus, nesfatin-1 is also expressed in numerous extra-hypothalamic neuronal populations, including hippocampus, cortex, amygdala and many other center and peripheral region (Stengel and Tache, 2013; Yoshida et al., 2010), and could cross the blood-brain barrier without saturation (Pan et al., 2007; Price et al., 2007). The widespread distribution of nesfatin-1 suggests that it might play broader and related biological actions beyond the well established feeding controls.

Indeed, increasing evidence has shown that nesfatin-1 could induce a wide spectrum of central activities, especially stress and its associated emotional responses (Okere et al., 2010). Human study has shown that the plasma nesfatin-1 level is associated with elevated scores of anxiety and depression (Hofmann et al., 2013; Ari et al., 2011), and the expression of nesfatin-1/NUCB2 in the midbrain of drug-free depressed suicide victims were changed with sex-specific differences (Bloem et al., 2012). Results of animal research demonstrated that restraint stress could activate nesfatin-1-immunoreactive neurons in hypothalamic nuclei, pontine and medullary nuclei (Goebel et al., 2009), and intracerebroventricular (ICV) injection of nesfatin-1 could dose-dependently increase anxiety- and fear-related behaviors in the elevated plus maze and a conditioned emotional response test (Merali et al., 2008). However, influences of peripherally administered nesfatin-1 have not been examined, and little is known about its effect on learning and memory (Zhu et al., 2013), although nesfatin-1 is widely expressed in the brain regions involved in the memory processes including the hippocampus and the prefrontal cortex (PFC) (Goebel-Stengel et al., 2011; Palasz et al., 2012).

As the most widely distributed and the most versatile neurotrophic factor in human CNS, brain-derived neurotrophic factor (BDNF) is a key component in the maintenance of synaptic plasticity and synaptogenesis in the hippocampus and PFC (Lu et al., 2013; Song et al., 2014). The alteration of BDNF level and expression, or a breakdown of BDNF signal pathway, could induce poorly differentiated neurons, synapse loss, anxiety as well as hyperactive response to stressors (Heldt et al., 2007; Rios et al., 2001). Although the entire brain is involved, the hippocampus and the PFC appear to be most important areas in memory and mood regulating specifically (Lee et al., 2015; Hock et al., 2000). It has been reported that BDNF expression was decreased in the frontal cortex and hippocampus of Alzheimer's disease (AD) patients (Hock et al., 2000; Peng et al., 2005). Cholinesterase inhibitor and nature chemistries have been demonstrated their neuroprotective effects in AD by enhancing BDNF levels, the mechanism of which might be involved with the inhibition of cholinesterase activity and improvement of ERK/CREB/BDNF pathway (Lilja et al., 2013; Lee et al., 2013). These findings suggest that BDNF is implicated in the regulation of anxiety- and cognition-related behavior. Furthermore, subsequent research has unequivocally demonstrated the role of BDNF in the linkage between the feeding behavior or feeding peptides and cognitive functions (Beck and Pourie, 2013). It has been reported that low-calorie diet during adolescence could improve the learning-memory function via increasing the hippocampal and prefrontal BDNF levels (Kaptan et al., 2015), while intraperitoneal injection of neuropeptide Y (NPY) could produce antidepressant-like effect through decreasing the hippocampal BDNF level in rat (Gelfo et al., 2012), and BDNF could induce persistent NPY production in an ERK1/2-dependent manner (Barnea and Roberts, 2001; Barnea et al., 2004). Given the interactive effect between NPY and nesfatin-1 (Palasz et al., 2012; Price et al., 2008; Sedbazar et al., 2014), it is rational to hypothesize that chronic administration of nesfatin-1 should affect the activity of the ERK/CREB/BDNF pathway in the hippocampus and the PFC, which might play a role in the effect of nesfatin-1 on anxiety and learning and memory function.

To gain further insights into the effect of nesfatin-1 on neuropsychiatric behavior including anxiety and learning and memory, nesfatin-1 was administrated to rats chronically in the present study, and a series of behavioral tasks including the open field task, the Morris water maze, and the Y maze were conducted. Moreover, the protein expressions of BDNF and total and phosphorylated-ERK in the hippocampus and the PFC were also evaluated using western blot.

2. Results

2.1. *Chronic administration of nesfatin-1 did not affect the bodyweight of rats*

Before the treatment, the bodyweight of rats in the nesfatin-1 treated group was similar to that in the control group (control: (194.50±6.18) g; nesfatin-1 (40 μg/kg) group: (190.91±4.66) g; nesfatin-1 (20 μg/kg) group: (190.40±4.45) g, nesfatin-1 (10 μg/kg) group: (186.10±5.06) g). Results of the repeated measure ANOVA (4 groups × 4 weeks with repeated measures on weeks) showed that the weeks (F (3, 36)=210.197, $P<0.001$), but not the exposure of nesfatin-1 (F (3, 36)=0.040, $P=0.989$) affected the body weight (interactive effect: F (9, 108)=0.975, $P=0.465$). The gain of bodyweight (the last bodyweight – the bodyweight before nesfatin-1 treatment) was not significantly correlated to the dose of nesfatin-1 ($r=-0.017$, $P=0.918$).

2.2. *Chronic administration of nesfatin-1 decreased the exploratory behavior and induced anxiety-like behavior of rats in the open field task*

The performance of rats in the open field task is shown in Fig. 1. Compared to the control group, the moving distance [F (3, 36)=6.078, $P=0.002$; LSD: nesfatin-1 (10 μg/kg) vs control: $P=0.006$; nesfatin-1 (20 μg/kg) vs control: $P=0.003$; nesfatin-1 (40 μg/kg) vs control: $P<0.001$], the duration in the center [F (3, 36)=3.646, $P=0.022$; LSD: nesfatin-1 (10 μg/kg) vs control: $P=0.007$; nesfatin-1 (20 μg/kg) vs control: $P=0.010$; nesfatin-1 (40 μg/kg) vs control: $P=0.012$], and the frequencies of rearing [F (3, 36)=8.713, $P<0.001$; LSD: nesfatin-1 (10 μg/kg) vs control: $P<0.001$; nesfatin-1 (20 μg/kg) vs control: $P<0.001$; nesfatin-1 (40 μg/kg) vs