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Neuromedin U_2 receptor signaling mediates alteration of sleep–wake architecture in rats

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ABSTRACT

Growing evidence indicates that neuromedin U (NmU) neuropeptide system plays an integral role in mediating the stress response through the corticotrophin-releasing factor (CRF) pathways. Stress is often associated with alteration in sleep–wake architecture both in human and laboratory animals. Here, we investigated whether activation of the NmU_2 receptor, a major high affinity receptor for NmU predominantly expressed in the brain, affects sleep behavior in rats. Effects of single (acute) intracebroventricular (icv) infusion of 2.5 nmol of the full agonists porcine NmU8 and rat NmU23 were assessed on sleep–wake architecture in freely moving rats, which were chronically implanted with EEG and EMG electrodes. In addition, repeated once daily administration of NmU8 at 2.5 nmol during 8 consecutive days (sub-chronic) was studied.

Acute icv infusion of NmU23 elicited a robust alteration in sleep–wake architecture, namely enhanced wakefulness and suppressed sleep during the first 4 h after administration. Acute infusion NmU8 had no effect on spontaneous sleep–wake architecture. However, sub-chronic icv infusion of NmU8 increased the amount of rapid eye movement (REM) sleep and intermediate stage (IS), while decreased light sleep. Additionally, NmU8 increased transitions from sleep states towards wakefulness suggesting a disruption in sleep continuity.

The present results show that central-activation of NmU_2 receptor markedly reduced sleep duration and disrupted the mechanisms underlying NREM–REM sleep transitions. Given that sleep–wakefulness cycle is strongly influenced by stress and the role of NmU/NmU_2 receptor signaling in stress response, the disruption in sleep pattern associated with peptides species may support at least some signs of stress.

1. Introduction

Neuromedin U (NmU), which was originally identified in the porcine spinal cord as a potent peptide that contract uterine smooth-muscle has been isolated from various mammalian species including mouse, rat, rabbit, chicken, pig, dog and human (Brighton et al., 2004). Along with other neuropeptides, NmU a highly conserved neuropeptide is widely distributed in peripheral and several brain region including the hypothalamus, hippocampus, pituitary, suprachiasmatic nucleus and brain stem (Domin et al., 1987; Ballesta et al., 1988; Honzawa et al., 1987; O'Harte et al., 1991; Augood et al., 1988; Austin et al., 1995). This widespread distribution is consistent with several reported physiological actions of the peptide. NmU has been found not only to regulate smooth muscle contraction (Minamino et al., 1985), but also blood pressure (Chu et al., 2002), ion transport in the gut (Brown and Quito, 1988), sympathetic nervous system (Tanida et al., 2009), blood pressure and heart rate (Chu et al., 2002) and inhibits gastric acid (Mondal et al., 2003) the secretion of luteinizing hormone (Quan et al., 2003).

In addition to its peripheral roles, NmU is also found in discrete structure of the brain such as spinal cord and trigeminal sensory neurons associated with sensory processing (Honzawa et al., 1987), in the arcuate nuclei of the hypothalamus involved in neuroendocrine functions such as feeding behavior and energy balance (Vettor et al., 2002), in the neuronal pathways that control circadian rhythms as the suprachiasmatic nucleus (Schulz and Steimer, 2009), in the nuclei accumbens and substantia nigra involved in motor behavior and reward seeking-stimuli (Hikosaka et al., 2006; Horvitz, 2002; Mogenson et al., 1980; Nicola, 2007), the amygdala, hippocampus limbic system as well as pituitary and adrenals gland indicating a role of the peptide in affective spectrum disorders.

At the functional level, the neuropeptide NmU mediates the above-described functions via two receptors named NmU_1 and NmU_2. While NmU_1 is most prominent in peripheral tissues, including immune cells and the gut, receptor is almost absent in the brain. Conversely, NmU_2 is highly expressed in the CNS,

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including the arcuate and the ventromedial nucleus of the hypothalamic formation as well as in amygdala (Gartlon et al., 2004).

Several observations have suggested that NmU system is linked to the HPA axis and the central effects of neuromedin are believed to be mediated via the corticotropin-releasing factor (CRF) pathways. Central administration of neuromedin U in rats produced cardinal symptoms of stress response such as decrease body weight, increase body temperature, heat production (Nakazato et al., 2000) locomotor and face washing (Hanada et al., 2001).

Recent expression analysis study has revealed that the expression of NmU and NmU_2 mRNA exhibit a strong circadian rhythm with different phase angle with NmU mRNA peaking in the suprachiasmatic nucleus at CT4–8 while the expression of NmU_2 being high at CT16–20 (Nakahara et al., 2004). Because the hypothalamic–pituitary–adrenal (HPA) axis plays central roles in the circadian dependence alertness and modulation of sleep (see, for review, Buckley and Schatzberg, 2005, dysregulation of the hypothalamic–pituitary–adrenal (HPA)-axis axis may result in a primary or have a secondary causative role in affective spectrum disorders including sleep disorders, depression and anxiety (Arborelius et al., 1999; Healey et al., 1981; Vgontzas et al., 1998; Rodenbeck et al., 2002). In human as well as animal, stress and sleep are often related (see, for review, Buckley and Schatzberg, 2005. Disturbance of sleep architecture often follows stressful events and stressed subjects show difficulties falling asleep or maintain their sleep for long period, which may lead to emotional and behavioral dysfunction. Recently, increasing evidences indicate that neuromedin U peptide (NmU) may contribute to the mediation of stress responses by stimulating the CRF system in the hypothalamic paraventricular nuclei (PVN) Hanada et al., 2003 and therefore is likely to be a valuable target for the treatment of affective spectrum disorders, especially anorexia, stress disorders, anxiety and depression.

The alteration of sleep architecture in animals following exposure to stress raised the hypothesis that the NmU neuropeptides and its centrally expressed receptor NmU_2 might be involved in the mechanism underlying the stress response. For this purpose, we have conducted experiments to examine the effects on sleep–wake behavior of two full agonists; the porcini's NmU8 and the rat's NmU23 administered directly in the ventricle.

2. Materials and methods

2.1. Animals, surgery and recordings

Male Sprague–Dawley rats (Charles River, France) weighing 250–300 g at the time of surgery were used in the polygraphic recording experiments. Rats were provided with a microchip for identification purposes, housed in individually ventilated cages, lo-

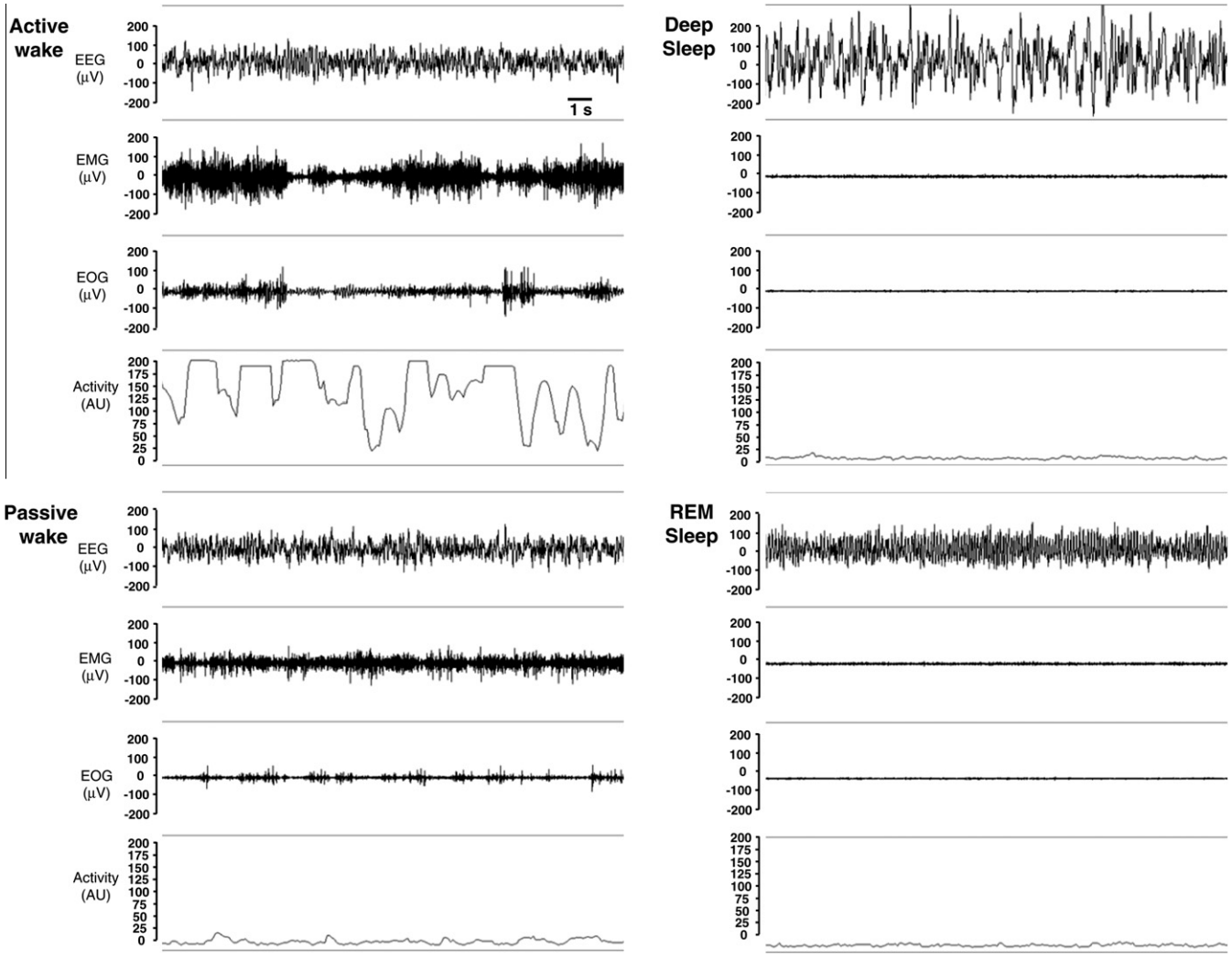

Fig. 1. Twenty seconds recordings of EEG, EMG, EOG and activity signals are displayed for active wake, passive wake, deep sleep and REM sleep, respectively. EEG, EMG, EOG are expressed in microvolt; activity is expressed in arbitrary units. Vigilance states were classified according to multiple waveform features described in Section 2.