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Neuropeptide S reduces propofol- or ketamine-induced slow wave states through activation of cognate receptors in the rat

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ABSTRACT

Intracerebroventricular injection of NPS reduces the duration of the ketamine- or thiopental-induced loss of the righting reflex in rats. But the specific EEG activities are unknown. We therefore sought to examine the effects of the NPS-NPSR system on anesthetic-induced characteristics of EEG power spectra and sleep-wake profiles. NPS alone or together with an NPSR antagonist was injected intracerebroventricularly, whereas the propofol (50 mg/kg) or ketamine (100 mg/kg) was administrated intraperitoneally. NPS (1 or 2 nmol) significantly reduced the amount of propofol-induced EEG delta activity and slow wave states (SWS). NPS (1 or 5 nmol) significantly reduced the amount of ketamine-induced SWS and EEG delta activity. Cortical EEG power spectral analysis showed that, in saline-pretreated rats, propofol induced a marked increase in delta (0.5–4 Hz) activity, decrease in theta (4.5–8.5 Hz) activity, and decrease in high frequency activity (14.5–60 Hz), while, in rats pretreated with 1 nmol of NPS, the duration of delta activity was reduced, while its spectral pattern was not changed. Whereas injection of ketamine into saline-pretreated rats induced a marked increase in delta (0.5–4 Hz) activity, a moderate increase in theta (4.5–8.5 Hz) activity, and a marked decrease in high frequency (14.5–60 Hz) activity. However, delta activity was reduced while theta activity increased under pretreatment with 1 nmol of NPS. The inhibitory effect of NPS on anesthetic-induced SWS was characterized by a reduced SWS episode duration with no significant change in either episode number or latency to SWS. [D-Val^5]NPS, an NPSR antagonist (20 nmol), significantly attenuated the arousal-promoting effect of 1 nmol of NPS, but had no effect on SWS when injected alone. We speculate that NPS significantly reduces anesthetic-induced SWS and EEG slow activity by selective activation of the NPSR, which, in turn, would trigger subsequent arousal pathways.

1. Introduction

Several studies have reported that general anesthesia and natural sleep share some similarities. Both general anesthesia and sleep reduce arousal, responsiveness and body temperature suggesting common neuronal pathways are involved in the two processes (Franks, 2008). Brain imaging studies have shown obvious parallels between the anaesthetized brain and the brain during slow wave states (SWS) (Braun et al., 1997; Kajimura et al., 1999; Maquet, 2000). More strikingly, most anesthetics produce electroencephalogram (EEG) patterns with both spindle and delta waves, the respective EEG landmarks of falling asleep and deep, dreamless SWS (Franks, 2008). In addition, sleep deprivation facilitates sleep onset, causes sleep rebound and prolongs anesthesia time, further supporting the idea that these states share some common neural circuits (Tung et al., 2002).

Several brain areas have been recognized as important loci for initiation of sleep and anesthesia. The preoptic and anterior hypothalamus, notably its ventrolateral part (VLPO) contains a high density of sleep-promoting neurons that are more active during sleep (Sherin et al., 1996). Activation of VLPO neurons has been suggested as a common property of both natural sleep and many forms of drug-induced sedation (Mendelson, 1996; Tung et al., 2001). VLPO neurons send inhibitory γ-aminobutyric acid (GABA) fibers into the arousal histaminergic tuberomammillary nucleus (TMN) of the posterior hypothalamus which plays a key role in the maintenance of arousal and wakefulness and which prevents narcoleptic attacks by orexin neurons also present in perifornical nucleus (PeF) and lateral hypothalamic area (LH) (Lee

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et al., 2005; Saper et al., 2005; Takahashi et al., 2006). In addition, intracerebroventricular (i.c.v.) injection of orexin A reduces the duration of barbiturate- or ketamine-induced anesthesia (Kushikata et al., 2003).

Most general anesthetics, the $GABA_A$ type, such as propofol, barbiturates, benzodiazepines, and volatile agents, produce anesthesia by increasing the activity of inhibitory $GABA_A$ receptors, and their use is associated with a slow–wave EEG pattern (Sloan, 1998), while others, the NMDA type, most strikingly ketamine, potently inhibit excitatory *N*-methyl-D-aspartate (NMDA) receptors and, at high dose, produce a prolonged anesthetic level of sedation with a predominantly delta rhythm EEG (Kushikata et al., 2011; Lu et al., 2008).

The neuropeptide S (NPS) and cognate receptor (NPSR) system is a newly identified sleep-waking regulation system (Adamantidis et al., 2010; Guerrini et al., 2010; Murillo-Rodriguez et al., 2012). Our previous study showed that i.c.v. injection of NPS promotes wakefulness at the expense of SWS and paradoxical sleep (PS) and enhances c-Fos expression in histaminergic and orexinergic neurons in the posterior hypothalamus (Zhao et al., 2012). In this area, a high expression of NPSR mRNA was identified (Xu et al., 2007, 2004; Yao et al., 2009), suggesting that NPS actives histaminergic and orexinergic neurons to promote wakefulness. Previous studies suggested that, i.c.v. injection of NPS reduces the duration of the ketamine- or thiopental-induced loss of the righting reflex in rats (Kushikata et al., 2011). However, detailed characteristics of EEG power spectra and subsequent sleep-wake profiles were not clarified.

Therefore, the present study was designed to examine the effects of the NPS-NPSR system on $GABA_A$- and NMDA-type anesthetic-induced characteristics of EEG power spectra and sleep-wake profiles and hypothesized that NPS, by causing selective NPSR activation on wake-promoting pathways, could also counteract general anesthesia produced by different anesthetics.

2. Materials and methods

2.1. Animals and surgical implantation

Adult male Sprague-Dawley rats, weighing 250–300 g (8- to 10-week-old), purchased from the Experimental Animal Center of Lanzhou University (Lanzhou, China), were housed at an ambient temperature (22 ± 1 °C) and 50% relative humidity on an automatically controlled 12:12-h light dark cycle (lights on 8:00–20:00 h, illumination intensity ≈ 100 lx), with food and water available *ad libitum*. The experimental protocol was approved by the Ethics Committee of Lanzhou University (permit number: SCXK Gan 2009–0004).

Under chloral hydrate anesthesia (350 mg/kg, i.p.), four stainless steel screws (1 mm diameter), used as EEG electrodes, were screwed into the skull, and three silver wires, used as electromyogram (EMG) electrodes, were inserted into the dorsal cervical neck muscles for polysomnographic recordings. The cortical electrodes were inserted into the dura through two pairs of holes located, respectively, in the frontal (2 mm lateral and anterior to the bregma) or parietal (2 mm lateral to the lambda) cortex. A guide cannula (23 gauge) was stereotaxically implanted into the right lateral ventricle (AP −0.92, ML +1.5, DV −3.3, according to the atlases of Paxinos and Waston (Paxinos and Watson, 1998)) for i.c.v. injections. The free ends of the electrode leads were soldered into a pedestal socket. This electrode leads and the cannula were chronically fixed to the skull with dental cement.

2.2. Pharmacological treatments

Mouse and rat NPS are equally effective in altering sleep-waking states in rats in our previous study (Zhao et al., 2012). In the present study, we used mouse NPS (Shanghai Mocell Biotech Co., Ltd.). In order to examine the effects of the NPS-NPSR system on anesthesia-induced sleep, we used the NPSR antagonist [D-Val^5]NPS (Shanghai Mocell Biotech Co., Ltd.) at a dose of 20 nmol (Guerrini et al., 2009; Peng et al., 2010; Shao et al., 2013). In pilot experiments, we found that propofol (Xi'an Libang Pharmaceuticals Co. Ltd.) 50 mg/kg i.p. or ketamine sodium (Fujian Gutian Pharmaceuticals Co. Ltd.) 100 mg/kg i.p. produced 30–40 min of sleep in Sprague-Dawley rats and therefore these doses were chosen in the present study.

2.3. Polygraphic recordings and analysis

After surgery, the animals were housed singly in transparent barrels (30 cm diameter, 40 cm height) where they were monitored by an infrared video camera during both the light and dark phases and allowed to recover for 1 week.

To easily observe the hypnotic effect of drugs, we performed the experiments during the dark period in which rats spend most of the time in wakefulness, so most sleep observed was likely to be due to the anesthetic. The rats were acclimatized to the recording cable for 2 days, then

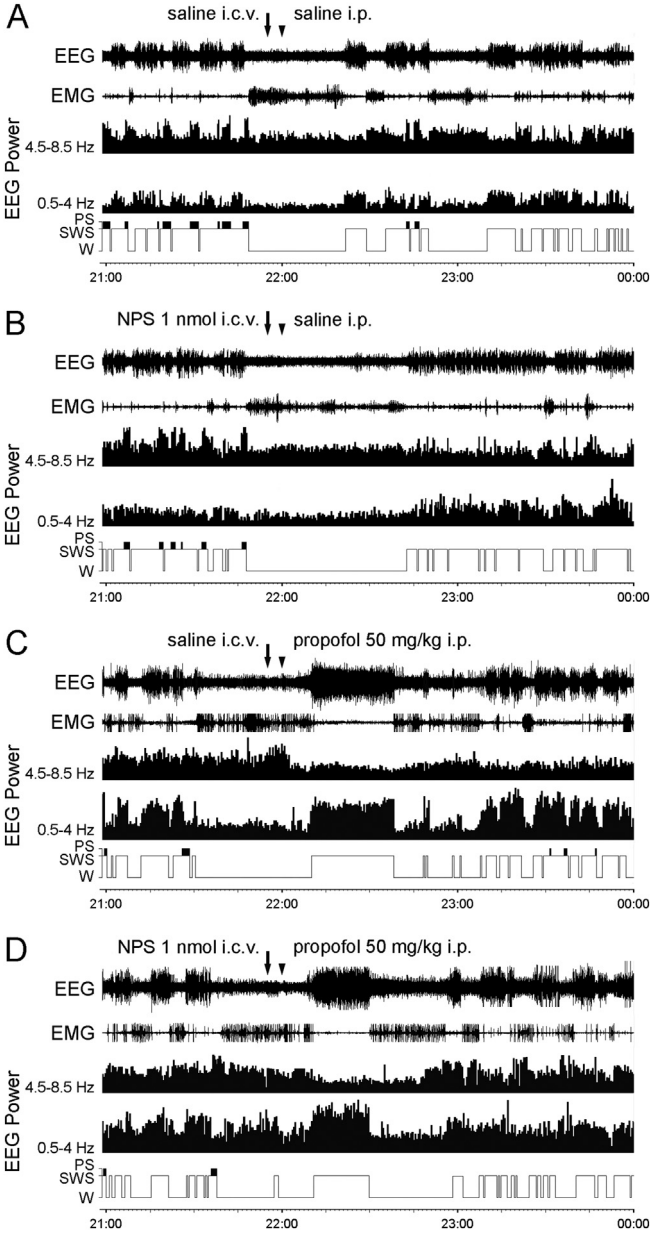

Fig. 1. Effects of i.c.v. injection of saline and NPS 1 nmol on the EEG and sleep-wake states in saline-treated (ST) and propofol-treated (PT) rats. (A–D) Representative 3-h (21:00–0:00 h) EEG, EMG, hypnograms, and cortical spectra at 0.5–4 and 4.5–8.5 Hz in ST rats pretreated with saline (A) or 1 nmol of NPS (B) and in PT rats pretreated with saline (C) or 1 nmol of NPS (D).

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