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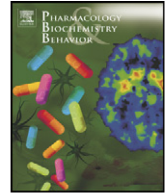

Acute and subchronic administration of anandamide or oleamide increases REM sleep in rats

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ABSTRACT

Anandamide and oleamide, induce sleep when administered acutely, via the CB1 receptor. Their subchronic administration must be tested to demonstrate the absence of tolerance to this effect, and that the sudden withdrawal of these endocannabinoids (eCBs) does not affect sleep negatively. The sleep–waking cycle of rats was evaluated for 24 h, under the effect of an acute or subchronic administration of eCBs, and during sudden eCBs withdrawal. AM251, a CB1 receptor antagonist (CB1Ra) was utilized to block eCBs effects. Our results indicated that both acute and subchronic administration of eCBs increase REMS. During eCBs withdrawal, rats lack the expression of an abstinence-like syndrome. AM251 was efficacious to prevent REMS increase caused by both acute and subchronic administration of these eCBs, suggesting that this effect is mediated by the CB1 receptor. Our data further support a role of the eCBs in REMS regulation.

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1. Introduction

Anandamide (ANA) and oleamide (OLE) are two endogenous molecules with cannabinoid activity that bind to the cannabinoid receptor 1 (CB1) (Axelrod and Felder 1998; Leggett et al., 2004) and are degraded by the fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996). Recently it has been proposed that these lipids are involved in the regulation of several physiological functions and behaviors. For example, core temperature, pain perception, locomotor activity, memory regulation, food intake, sexual behavior, and sleep (Crawley et al., 1993; Basile et al., 1999; Maione et al., 2006; Martínez-González et al., 2004; Rueda-Orozco et al., 2008a, b; Huitrón-Reséndiz et al., 2001).

Regarding anandamide, its acute intracerebroventricular (icv) administration increases non-rapid-eye movement sleep (NREM) and rapid eye movement sleep (REMS) at the expense of waking in rats (Murillo-Rodríguez et al., 1998). Likewise, anandamide administered directly into the peduncle pontine tegmental nucleus (PPTg) causes a similar although stronger effect (Murillo-Rodríguez et al., 2001). This effect was blocked with the CB1 receptor antagonist, SR141716A, indicating that the effect on sleep results from the CB1 receptor activation.

Oleamide was isolated for the first time from the cerebrospinal fluid (CSF) of sleep-deprived cats (Cravatt et al., 1995). We have observed that its systemic administration induces sleep in rats, with shortened sleep latency (Cravatt et al., 1995). In addition, 6 h of sleep deprivation increases 3- to 4-fold the oleamide concentration in rats' CSF. SR141716A, as with anandamide, prevents oleamide's sleep-inducing effects (Mendelson and Basile, 1999). Moreover, SR141716A reduces both NREM and REMS while increasing waking after its systemic administration at a 3 mg/kg dose (Santucci et al., 1996).

Furthermore, mice lacking fatty acid amide hydrolase FAAH (−/−), an enzyme that degrades anandamide and oleamide, exhibit a higher SWS expression and a higher delta power than wild-type mice (Huitrón-Reséndiz et al., 2004), further supporting the notion that eCBs modulate sleep. SR141716A prevents the REMS rebound observed in rats after a 24-h period of selective REMS deprivation (REMSD). During the rebound, consecutive to REMSD, the CB1 receptor increases in the pons of rats (Navarro et al., 2003).

This experimental evidence suggests that anandamide and oleamide improve sleep after their acute administration and this effect is a consequence of mainly, although not entirely, the activation of the CB1 receptor. In this context, we decided to evaluate the effect on sleep of the subchronic administration of these eCBs, during eCBs withdrawal, and after AM251-blocking of the CB1 receptor.

2. Materials and methods

2.1. Subjects

Adult male Wistar rats, weighing 250–280 g, were used. All animals were housed individually in Plexiglas cages. They were maintained at an ambient temperature of 22 ± 1 °C and a controlled

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12:12-h light–dark cycle (08:00 AM–08.00 PM) throughout the study. Food and water were available ad libitum.

2.2. Surgery

Rats ($n = 102$) were stereotaxically implanted under anesthesia (cocktail: 66 mg/kg ketamine, 0.26 mg/kg xylazine, and 1.3 mg/kg acepromazine) with a stainless-steel guide cannula (23 gauge) aimed at the lateral ventricle ($P = 0.8$, $L = 1.5$, $V = 3.8$) for icv administration of drugs. Two electrodes were inserted into the hippocampus ($P = 4.0$, $L = 2.5$, $V = 2.5$) according to the Paxinos and Watson atlas (1986) for recording the electroencephalographic (EEG) equivalent from this structure. Although fully develop slow waves are not obtained from this structure, we still have a signal indicative of NREM sleep. In addition, the theta rhythm is easily recorded from the hippocampus, helping us to easily differentiate between waking and REMS. Two additional screw electrodes were implanted into the frontal bones for grounding the animal. Two twisted wire electrodes were placed into the neck musculature for electromyographic (EMG) recordings. Animals were treated according to the Norma Oficial Mexicana (NOM-062-ZOO-199), the Guide for Care and Use of Laboratory Animals established by the National Institutes of Health, and the European Community Council Directive 86/609/ EEC. Additionally, our protocol was approved by the Research and Ethics Committee of the Facultad de Medicina, Universidad Nacional Autónoma de México (UNAM). Every effort was made to minimize the number of animals used and their potential suffering.

2.3. Sleep recording

After surgery, animals were monitored and allowed to recover for 10 days. Upon the completion of this period, rats were habituated to the recording conditions for 24 h. Once the habituation period was completed, rats were divided into different experimental groups. They received a daily icv administration of either vehicle or anandamide or oleamide at 8:00 AM (at the beginning of the light period). Immediately after the administration, the sleep–waking cycle was recorded for 24 h.

The EEG and EMG signals were amplified with a Grass Model 7 polygraph, Amplifier Model 7P511, in a frequency range of 1 to 30 and 30 to 100 Hz, respectively. Signals were acquired and analyzed with the ICELUS® software.

Animals were killed at the end of the experiment with an i.p. overdose of sodium pentobarbital to verify the position of the cannula, Ponceau red stain (5 µl) was injected into the ventricle through the cannula, aimed at dyeing the cerebral ventricle system. Brains were removed and dissected to verify that all the ventricles were stained.

2.4. Chemicals

Arachidonylethanolamide (anandamide, ANA) and oleamide (OLE) were obtained from Sigma Aldrich, and the CB1 antagonist, AM251, was obtained from Cayman Chemical. We decided to use AM251 over SR141716a for two reasons: 1, it is more specific for CB1 receptors and 2, it is commercially available. ANA or OLE was dissolved in a mixture of 5% ethanol in saline, and AM251 was dissolved in 1 µl of dimethyl sulfoxide (DMSO). Doses of drugs and volumes will be specified later in the description of each experiment.

2.5. Experimental protocol

2.5.1. Anandamide and oleamide dose–response curve

To determine the dose at which anandamide or oleamide produce a more reliable effect on sleep, seven groups of animals ($n = 6$ for each group) received an acute icv administration. The CONTROL group received 5 µl vehicle (saline with 5% ethanol), ANA1 group (1 µg/5 µl of vehicle), ANA2 (2 µg/5 µl of vehicle), ANA4 (4 µg/5 µl of vehicle), OLE6 (6 µg/5 µl of vehicle), OLE12 (12 µg/5 µl of vehicle) and OLE25 (25 µg/5 µl of vehicle). All experimental drugs were administered at 8:00 AM and sleep was recorded immediately thereafter for 24 h.

2.5.2. Subchronic administration and drug withdrawal

Three subchronic administration groups were used ($n = 6$ for each group). The same animals used in groups CONTROL, ANA2 (2 µg/5 µl of vehicle), and OLE25 (25 µg/5 µl of vehicle) for the acute administration were treated daily with identical doses at 8:00 AM for 15 days. These doses were the most efficient in increasing REMS after the acute administration. Rats were not sleep-recorded until day 15 of administration. On this day, immediately after the drug or vehicle administration, animals were sleep-recorded for 24 h. On day 16, all groups received 5 µl vehicle at the same hour and were recorded for 24 h, to detect early withdrawal signs on sleep. In addition, to further document that the sleep-inducing effect of anandamide and oleamide was mediated by the CB1 receptor, an antagonist of this receptor, AM251, was used.

2.5.3. AM251 dose–response curve

We performed an AM251 dose–response curve to determine the effect by blocking the CB1 receptor and, thereby, potentially preventing the activity of the endogenous eCBs. The dose–response curve was started with a dose that was equimolar to 2 µg of anandamide, the very dose producing the most significant effects on sleep by increasing REMS. Four groups were acutely icv administered ($n = 6$ for each group), the CONTROL group received 1 µl vehicle (DMSO), AM251-3.2 group (3.2 µg/1 µl of vehicle), AM251-6.4 (6.4 µg/1 µl of vehicle), AM251-12.8 (12.8 µg/1 µl of vehicle). Rats were injected at 8:00 AM and sleep was recorded immediately for 24 h.

2.5.4. Blockade of acute and subchronic administration of anandamide or oleamide

To block the effects of the acute administration of anandamide or oleamide, 3 groups were used ($n = 6$ for each group): CONTROL (1 µl of DMSO, 15 min before receiving 4 µl saline with 5% ethanol), AM251/ANA (3.2 µg AM251/1 µl of DMSO, 15 min before receiving 2 µg ANA/4 µl saline with 5% ethanol), and AM251/OLE (3.2 µg AM251/1 µl of DMSO, 15 min before receiving 25 µg OLE/4 µl saline with 5% ethanol). Rats were injected at 8:00 AM and sleep was recorded immediately thereafter for 24 h.

To document the AM251 blocking effect on the subchronic eCBs administration, three additional groups of rats received either the vehicle, anandamide or oleamide during 15 days ($n = 6$ for each group) exactly as described for the subchronic administration experiment. On day 15, AM251 was administered as follows: CONTROL (1 µl of DMSO 15 min before administering 4 µl saline with 5% ethanol), AM251/ANA (3.2 µg AM251/1 µl of DMSO, 15 min before administering 2 µg ANA/4 µl saline with 5% ethanol), and AM251/OLE (3.2 µg AM251/1 µl of DMSO, 15 min before administering 25 µg OLE/4 µl saline with 5% ethanol). Rats were injected at 8:00 AM and sleep was recorded immediately thereafter for 24 h.

2.6. Data analysis

Polygraphic recordings were analyzed every 12 s and classified according to the following vigilance stages: wakefulness (W), non-rapid-eye movement (NREM), and rapid eye movement (REMS) sleep. Electrophysiological criteria were used to define these stages of vigilance as follows: W was characterized by the EEG expressing mixed low fast voltage and theta activity, as well as high muscle activity. In NREM, rats showed an EEG with delta waves and EMG with decreased amplitude. Finally, in REMS rats showed an EEG with theta activity and an EMG absent activity (postural atonia). The time spent in W, NREM, and REMS per hour was calculated during two periods of 12 h (total 24 h). Latency of NREM and REM sleep was also calculated by measuring the time

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