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Intrahippocampal administration of anandamide increases REM sleep

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ABSTRACT

A nascent literature has postulated endocannabinoids (eCBs) as strong sleep-inducing lipids, particularly rapid-eye-movement sleep (REMs), nevertheless the exact mechanisms behind this effect remain to be determined. Anandamide and 2-arachidonyl glycerol, two of the most important eCBS, are synthesized in the hippocampus. This structure also expresses a high concentration of cannabinoid receptor 1 (CB1). Recent extensive literature supports eCBs as important regulators of hippocampal activity. It has also been shown that these molecules vary their expression on the hippocampus depending on the light–dark cycle. In this context we decided to analyze the effect of intrahippocampal administration of the eCB anandamide (ANA) on the sleep–waking cycle at two points of the light–dark cycle. Our data indicate that the administration of ANA directly into the hippocampus increases REMs in a dose dependent manner during the dark but not during the light phase of the cycle. The increase of REMs was blocked by the CB1 antagonist AM251. This effect was specific for the hippocampus since ANA administrations in the surrounding cortex did not elicit any change in REMs. These results support the idea of a direct relationship between hippocampal activity and sleep mechanisms by means of eCBs. The data presented here show, for the first time that eCBs administered into the hippocampus trigger REMs and support previous studies where chemical stimulation of limbic areas triggered sleep.

Classic experiments have shown that electrical or chemical stimulation of diverse areas of the brain elicits sleep within a short latency. For example, the electrical stimulation of the region lateral to the massa intermedia [1] or the intralaminar nuclei [16] of the thalamus promptly induces sleep. Likewise, the cholinergic stimulation of diverse areas of the limbic system, in particular the pyriform cortex of the temporal lobe, readily generates sleep [13,14].

It has also been observed that the administration of marijuana or its principal component Δ9-tetrahydrocannabinol (THC) induces sleep in humans [12] and rats [4]. The effects of THC, as well as marijuana, have been shown to be primarily mediated by cannabinoid-1 (CB1) [9] and -2 (CB2) receptors [25]. Together with the endocannabinoids (eCBs), the CB1 and CB2 are part of the cannabinergic system. The CB1 and CB2 receptors are mainly found in the CNS [11,29,37] and in the immune system [25], respectively. One of the most studied eCBs is the arachidonylethanolamide, anandamide (ANA) [10]. Experimental evidence suggests that eCBs are involved in diverse physiological processes, such as control of movement [2], sexual behavior [22], food intake [22,36], learning and memory [32,33], and are particularly important for sleep regulation [15]. For example, the administration of the CB1 antagonist, SR141716A, increases wakefulness at the expense of slow wave sleep (SWs) and rapid-eye-movement sleep (REMs) [34]. In addition, i.c.v. administration of ANA induces an increase of both SWs and REMs in rats [26]. Finally, mice lacking the fatty acid amide hydrolase (FAAH), the enzyme predominantly responsible for the degradation of ANA, exhibit higher amounts of sleep [17]. Despite this evidence, the mechanisms and brain structures involved in ANA's sleep-promoting effect are not yet clear.

The hippocampus is one of the structures with high concentrations of CB1 [11,29,37], and eCBs modulation seems to be crucial for its activity [30,11]. Furthermore, there is substantial evidence of hippocampal activity during sleep (for review, see [3]). The main sign of this activity is the theta rhythm. In addition, this evidence indicates that a processing of information (memory traces) is happening during sleep. For example, the activation of neural assemblies produced during active waking is reactivated during SWs and REMs [18,19,38]. On the other hand, complex intrahippocampal interactions are happening during different phases of REMs [24]. This background suggests a relationship between hippocampal activity and sleep; nevertheless, the conditions and mechanisms for this interaction remain to be determined. In this context, we decided to administrate ANA directly into the hip-

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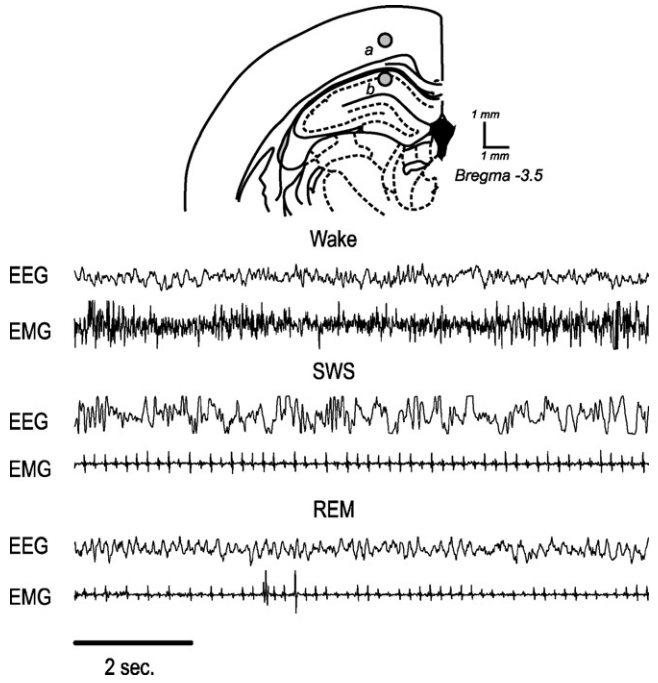

Fig. 1. Schematic representation of the injection sites (top panel, bregma = −3.5) in the hippocampus (a) and the cortex (somatosensory cortex) (b). Representative 10-s epochs of the electroencephalogram (EEG) and electromyogram (EMG) during waking, slow wave sleep (SWs), and rapid-eye-movement sleep (REMs).

pocampus of freely moving rats and analyze the patterns of sleep during 2 h following ANA's administration. Since we have shown that CB1 expression in the hippocampus varies depending on the light–dark cycle [33], we decided to perform the experiments during both phases of the cycle.

Subjects. Male Wistar rats (280–320 g) were used in this study. Animals were maintained under a controlled dark–light cycle (12:12; lights on: 08:00 AM), a constant environmental temperature (23 ± 1 °C), and with free access to food and water.

Surgery. A set of electrodes for sleep recordings was implanted in all rats under anesthesia (cocktail: 66 mg/kg ketamine + 0.26 mg/kg xylazine + 1.3 mg/kg acepromazine). This set included two stainless-steel screw-electrodes, one placed into the frontal bone ($A = 7.0$, $L = 2.0$) to ground the animal and one into the parietal bone ($A = 7.0$, $L = 2.0$) to record the electroencephalogram (EEG). Additionally, a bipolar stainless-steel wire electrode was implanted into the hippocampus ($P = 3.5$, $L = 2.5$, $V = 2.4$) to record EEG theta waves. Two additional stainless-steel wire electrodes were implanted into the muscles of the rats' neck to record the electromyogram (EMG). All the electrodes were affixed to the skull with dental acrylic. Additionally, two guide cannulae (23 gauge) were aimed at the hippocampus ($P = 3.5$, $L = 2.5$, $V = 2.2$, Fig. 1a). To ensure that the effects are specific for the hippocampus, an additional group of rats was implanted with two guide cannulae aimed at the cortex immediately above the hippocampus ($P = 3.5$, $L = 2.5$, $V = 1.2$, Fig. 1a) The injector for administrations protruded 1 mm from the tip of the guide cannula. Two additional supporting stainless-steel screws were implanted into the skull. Animals were allowed to recover from surgery for at least 10 days before starting the experiment. After ending the study, the brains were prepared for histological analysis with cresyl violet staining to verify the correct placement of the injector (Fig. 1). Stereotaxic coordinates were selected with reference to Paxinos and Watson's [28] atlas. 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.

Drugs. ANA was obtained from Sigma–Aldrich and was administered in three different doses, 0.5 μg, 1.0 μg, or 4 μg. The CB1 antagonist AM251 (3.2 μg) was obtained from Tocris and was administered in combination with ANA (1 μg). Dimethyl sulfoxide (30%, DMSO), in phosphate-buffer saline (PBS), was used as vehicle (final volume 1 μl in all cases).

Sleep recordings. All rats were recorded in two sessions, one during the light phase and another during the dark phase, a period of 10 days elapsed between recordings. Each session consisted of two recordings, a first baseline recording (BL, 2 h sleep recording), in which all animals in all groups received the vehicle. A second recording (2 h sleep recording), under ANA (0.5 μg, 1.0 μg, or 4.0 μg; three independent groups, each $n = 5$), ANA with AM251 ($n = 5$), or vehicle administration ($n = 5$), was performed immediately after the control recording. A total of 4 h of recording was accumulated. We have previously shown that CB1 receptor expression fluctuates along the 24 h. The CB1 receptor expression peaks around 1:00 PM; whereas the lowest CB1 receptor expression is around 1:00 AM [33]. Hence, we decided to evaluate the effect of these eCBs on sleep generation, only at 4 h around this highest and lowest expression.

All animals were habituated to recording conditions for 4 h prior to the experiments. All recording sessions were performed between 11:45 and 16:15 during the light and between 23:45 and 04:15 during the dark phase of the cycle. Sleep recordings were obtained by using a commercially available software, ICELUS, in a sound-attenuated chamber where food and water were provided *ad libitum*. The recordings were visually inspected using 10-s-length epochs and three states were evaluated, wakefulness (W), SWs, and REMs (Fig. 1). Data were analyzed and expressed as the mean value of the total time of sleep and percentage of change with respect to the control recording. Duration, frequency, and latency to REMs were also determined. One- and two-way analyses of variance (ANOVA) and Bonferroni and Sheffe post hoc test were used to detect statistical significance (SigmaStat).

During the light phase of the cycle, rats spent significantly more time in both SWs ($p = 0.002$, $F_{(1,35)} = 11.76$) and REMs ($F_{(1,35)} = 18.841$, $p < 0.001$) than in waking ($F_{(1,35)} = 18.841$, $p < 0.001$), reflecting the circadian component of sleep (one-way ANOVA, Bonferroni post hoc test). During the light phase of the cycle, administration of any of the anandamide doses into the hippocampus resulted in no change in sleep patterns (Fig. 2a and b). In contrast, administration of the anandamide doses used during the dark phase of the cycle resulted in a significant increase of the total time of REMs (second 2 h of recording: one-way ANOVA $F_{(3,17)} = 3.388$, $p = 0.048$; Bonferroni post hoc test with 0.5 μg ANA, $p = 0.041$; 1.0 μg ANA, $p = 0.010$; 4.0 μg ANA, $p = 0.048$) (Fig. 3a). No significant differences were detected in SWs or waking. These differences remained consistent when data were expressed as percentage of change with respect to the first 2 h of recording, i.e., control recordings, free of drug (vs. 1.0 μg ANA, $p = 0.033$; vs. 4.0 μg ANA, $p = 0.011$; except for the 0.5 μg dose) (Fig. 3b). REMs increase was blocked when ANA (1 μg) was co-administered with AM251 (3.2 μg) indicating that the effects were due to CB1 activation (Fig. 3a and b). In addition, the administration of ANA in the cortex did not elicit REMs increases indicating that this effect was specific to the hippocampus (Fig. 3a and b). Further analysis of the data reveals that the increase in REMs is due to an increase in the frequency (Fig. 4a; two-way ANOVA $F_{(1,33)} = 18.955$, $p < 0.001$; Bonferroni post hoc test), whereas the mean duration of REMs remained unchanged (Fig. 4b). Latency to SWs and REMs remained

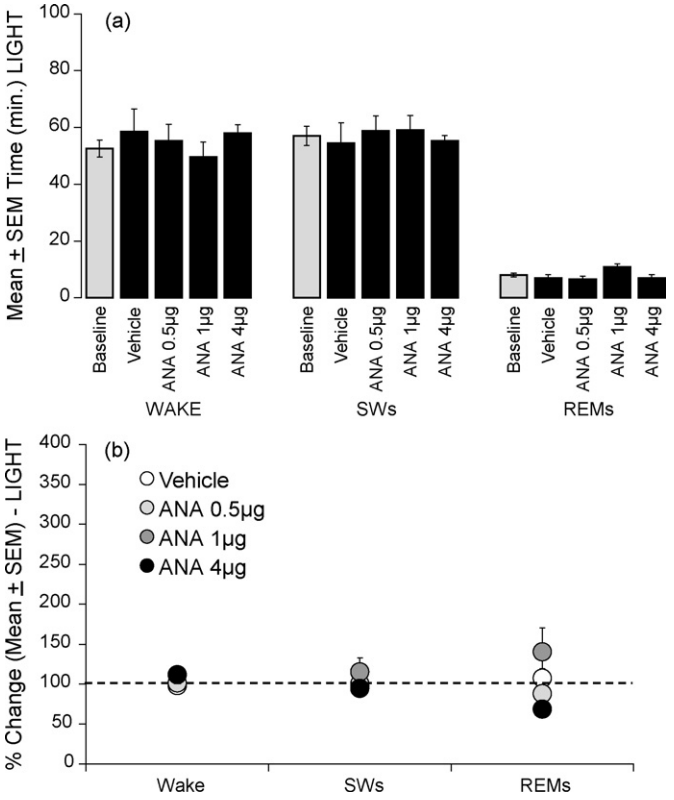

Fig. 2. (a) Total time of waking, SWs, and REMs during the light phase of the cycle. Grey column (1st control) represents the mean of the control recording under administration of vehicle for all groups, the rest of the columns represent the 2nd recording obtained under the administration of the vehicle and the different doses of anandamide. (b) Percentage of change with respect to the first 2 h of recording (drug-free control recording). Note that no significant changes were observed with any treatment during this phase of the cycle.

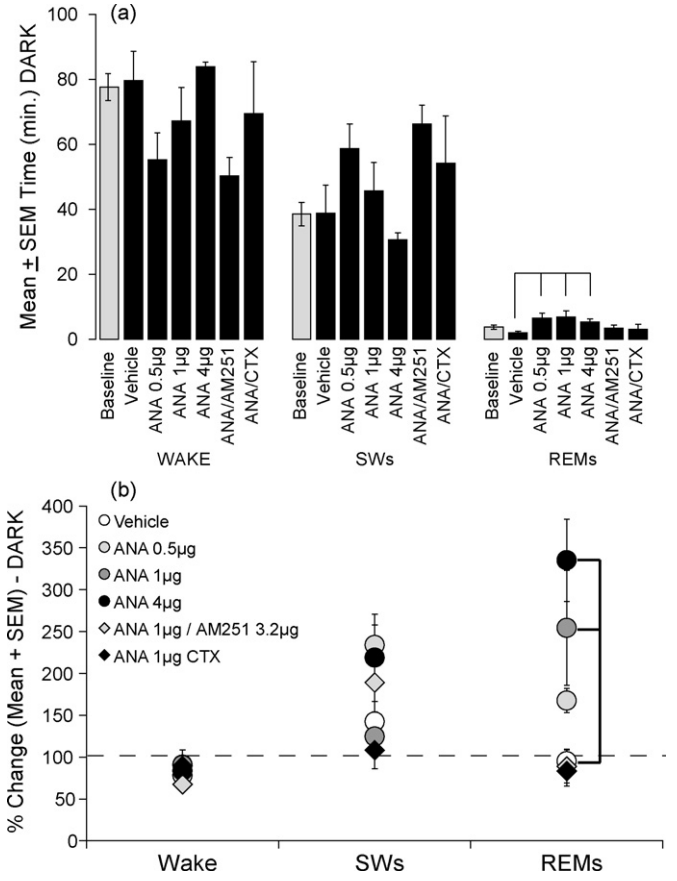

Fig. 3. Recordings during the dark phase of the cycle, explanation of plots a and b as in Fig. 1. Note that all doses of anandamide increase REMs in regard to both, total time of sleep and percentage of change ($p < 0.05$). The co-administration of ANA with AM251 in the hippocampus, as well as the injection of ANA, into the surrounding cortex did not significantly change the amount of REMs. Significant differences are marked by lines connecting against the vehicle.

unaffected in all groups, yet a slight tendency to decrease REMs latency can be observed in all groups treated with ANA (Fig. 4c). No significant differences were observed in these parameters with any of the treatments during the light phase of the cycle (data not shown).

Our data indicate that, unlike the light phase, anandamide administration during the dark phase of the cycle induces REMs. Many studies on the functions of sleep have been conducted to elucidate the effects of sleep on the hippocampus and memory formation (for review, see [21]). For example, it has been shown that REMs deprivation impairs hippocampal long-term potentiation [5,8], as well as hippocampal dependent memory tasks [23]. Previous studies were mainly focused on one direction, the effects of sleep on hippocampal activity; here we report, for the first time, that the administration of eCBs directly into the hippocampus affects the patterns of sleep. This evidence suggests that the activity of the hippocampus is implicated in REMs modulation, and that the relationship "hippocampus-sleep mechanisms" is bidirectional, i.e., not only sleep modulates hippocampal activity but also the hippocampus participates in the modulation of REMs. This notion is further supported by the fact that our treatments affect principally the frequency but not the duration of REMs, and that the hippocampus projects to nuclei involved in the sleep/waking cycle such as the tuberomamillary nuclei and the preoptic area [6,20,35].

Another interesting point is that ANA's administrations were effective only during the dark phase of the cycle, a moment in which rats naturally have less probability to fall into REMs. What is intriguing is that, in a previous study, we showed that the expression of the CB1 receptor in the hippocampus varies depending on the light–dark cycle, and the highest concentrations correspond to the light phase [33], the moment at which rats express more REMs. However, we have also observed that selective REMs deprivation followed by 2 h of sleep rebound is associated with an increase in both REMs itself and a higher expression of the CB1 receptor. In this context, our data suggest that the mechanisms responsible for the expression of REMs are, at least in part, mediated by the CB1 receptor in the hippocampus. Actually, blockade of the CB1 receptor by SR141716A prevents REMs rebound [27]. Moreover, in currently undergoing studies in our laboratory, we have observed that ANA is unable of increasing REMs in rats that are REMs selectively deprived for 24 h and are in the period of REMs rebound. In this context, since the CB1 receptor expression is already high during the light phase and potentially participating in the spontaneous generation of REMs, the addition of more eCBs produces a negligible increase of REMs. In contrast, during the dark phase when REMs and CB1 are naturally low, the exogenous administration of a CB1 agonist results in an important REMs increase. These findings could be of particular interest in the therapeutic area, since cannabinoids are able to induce REMs in a naturally unfavorable context, they could also induce sleep during insomnia; nevertheless, specific experiments should be performed to address this point.

Our study agrees with several other studies showing that the electrical or chemical stimulation of several regions of the brain may readily induce sleep. For example, Hernández-Peón [13,14] mapped almost the entire central nervous system with microcrystals of acetylcholine or atropine eliciting in this way the appearance

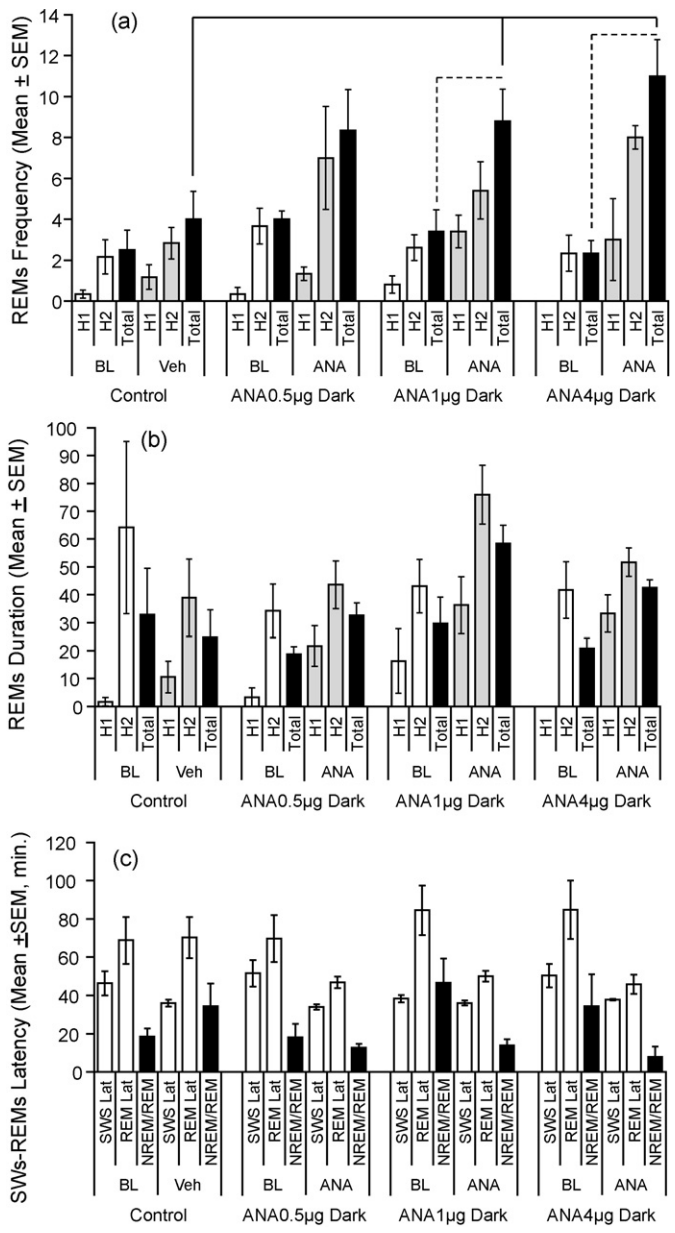

Fig. 4. REMs frequency (a) and REMs duration (b) during control recordings (1st) and experimental recordings (2nd). (c) SWs and REMs latency. Data correspond to dark phase recordings where treatments were effective. Plot display means during baseline (BL) and experimental (2nd) recordings (2 h divided in H1 and H2). Note that anandamide increases REMs frequency (veh vs. 1 μg ANA, $p = 0.019$; veh vs. 4 μg ANA, $p = 0.004$; 1 μg ANA-BL vs. 1 μg ANA-2nd, $p = 0.012$; 4 μg ANA-BL vs. 4 μg ANA-2nd, $p = 0.003$) but not duration or latency. Significant differences are marked by lines connecting treatments.

of REM sleep or preventing it. In our context, one of the pertinent observations of Hernández Peón's study is that the cholinergic stimulation of the pyriform cortex of the temporal lobe also induced REMs within a latency of 27 min.

Finally, it has been shown previously that activation of the CB1 in the hippocampus decreases its excitability [2], reduces glutamatergic and GABAergic transmission (for review, see [30]), as well as the power of theta and gamma oscillations [31]. These eCBs' local actions may account for the effect we have observed; nevertheless, further experiments should be performed to elucidate the exact mechanism underlying these effects. Our present data further support the notion that the cannabinergic system is implicated in the modulation of hippocampal activity and, consequently, exerts a crucial influence upon the vigilance states. In conclusion, our study suggests a tight interaction between memory mechanisms and REMs mechanisms. Likewise, this study indicates that eCBs are mediators in this interaction.

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