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Research paper

Microinjection of the dopamine D2-receptor antagonist Raclopride into the medial preoptic area reduces REM sleep in lactating rats

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ABSTRACT

The medial preoptic area (mPOA) is a brain structure classically related to both non-REM (NREM) sleep and maternal behavior. Although the dopaminergic system is known to play a role in the control of the states of sleep and wakefulness, its effects within the mPOA on sleep are still not clear. Microinjection of the dopamine D2 receptor antagonist Raclopride into the mPOA has been shown to promote nursing postures in lactating dams with no effects on active maternal behavior. We hypothesized that the facilitation of nursing postures may be also associated with the promotion of NREM sleep. In order to test the hypothesis, Raclopride was microinjected into the mPOA and maternal behavior and sleep were assessed in lactating rats. The changes observed included a reduction of the latency to start nursing and an increase of the time to reunite the entire litter. Contrary to our hypothesis, NREM sleep was not affected by Raclopride. On the other hand, REM sleep and its transitional stage from NREM sleep, were significantly reduced by this pharmacological agent. These data suggest that dopamine D2 receptors within the mPOA are involved in the transition from NREM to REM sleep.

1. Introduction

Since Von Economo's studies on lethargic encephalitis in 1930, the preoptic area (POA) has been proposed as a sleep promoting center [37]. Diverse kind of substances including glutamate [13] and adenosine [17] are known to promote NREM sleep within the medial POA (mPOA). However, the role of dopamine (DA), a critical neurotransmitter involved in the regulation of the states of vigilance, within the mPOA is still unclear [14,20,29].

From Fisher et al. onwards, the mPOA has been also postulated as the key component in the coordination of maternal behavior [11]. Several studies have revealed that different substances including neuropeptides and hormones promote maternal behavior within this area [27,34]. Although there is an agreement about the role of mPOA in the regulation of the active components of maternal behavior, there are some discrepancies in the literature about its role in quiescent nursing behavior [23,33]. Specifically, Miller et al. [18] have shown that microinjection of the DA D2 receptor antagonist, Raclopride, increases nursing postures without interfering with active maternal behavior. These authors considered the possibility that processes controlled by the mPOA other than maternal behavior, such as the vigilance level, could lead indirectly to an increase in nursing postures.

In particular, the mPOA receives DAergic afferents diverse regions including: the ventral tegmental area (VTA), the periventricular area of the hypothalamus, the ventrocaudal posterior hypothalamus and adjacent medial supramammillary nucleus and also from the mPOA itself [19,31]. In addition, mPOA expresses DA D2 receptor in female rats [2]. It is known at least one cell phenotype (oxytocinergic cells) that co-localized with DA D2 receptors within the mPOA [3]. However, although there are different neuronal phenotypes within the mPOA, most of them are GABAergic [22,36].

Recently, we showed that mother rats spend a considerable amount of time in NREM sleep during nursing postures [4]. Because Raclopride promotes nursing without altering active maternal behaviors [18], it is plausible that NREM sleep is also facilitated. Hence, we hypothesized that the promotion of nursing postures after Raclopride treatment is associated with increases in NREM sleep duration and/or depth. In order to test this hypothesis, we aimed to determine the effects of microinjections of Raclopride into the mPOA both on nursing and sleep in lactating rats.

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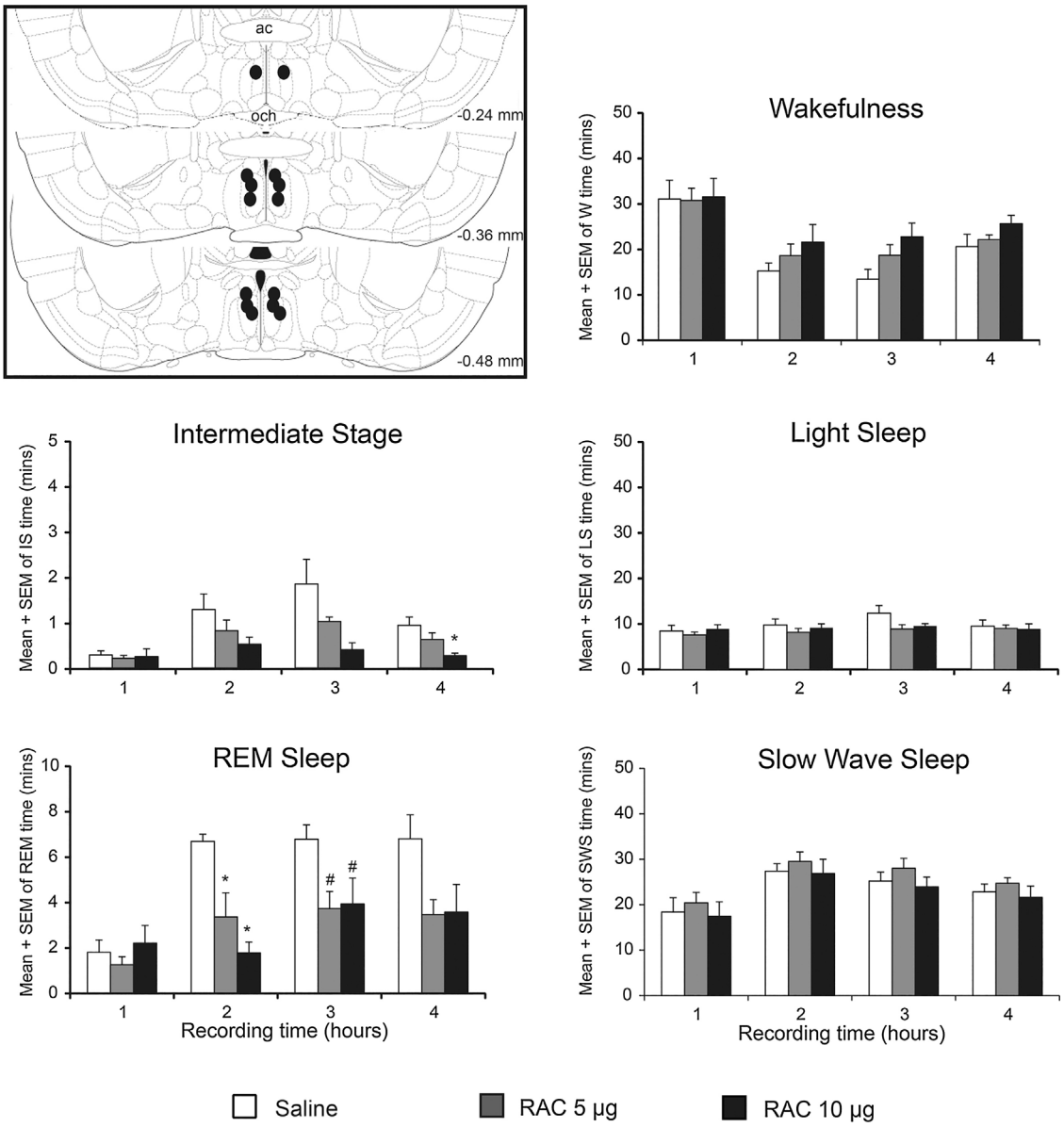

Fig. 1. Microinjections sites of Raclopride (RAC) into the mPOA and its effects on sleep and wakefulness. The inset shows schematic representations of coronal sections at the level of mPOA. Black full circles indicate the microinjection sites (n = 7); bottom numbers indicate distance from Bregma. Plates were taken from the atlas of Paxinos and Watson [26]. ac, anterior; och, optic chiasm. Graphic charts show the mean time spent in wakefulness, light sleep, slow wave sleep, intermediate stage and REM sleep after local administration of saline, $RAC_{5\ \mu g}$ and $RAC_{10\ \mu g}$ during each hour of the total recording time. Group differences were determined by one-way repeated measures ANOVA followed by Tukey as *post hoc*; Asterisk (*) indicates significant differences compared to control values while numeral (#) indicates tendency ($p \leq 0.06$) compared to control values. W, wakefulness; LS, light sleep; SWS, slow wave sleep; IS, intermediate stage; REM, REM sleep.

2. Methods

2.1. Animals and housing

Nine primiparous Wistar female rats (275–315 g) and their pups were used in this study. All animal use and experimental procedures were in strict accordance with the "Guide to the care and use of laboratory animals" (8th edition, National Academy Press, Washington D.C., 2011) and approved by the Institutional Animal Care Committee. All efforts were made to minimize the number of animals used and their suffering.

Two days before giving birth, pregnant females were housed individually in transparent cages (40 × 30 × 20 cm) containing shredded paper towels as nest-building material. The animals were placed in a temperature-controlled (22 ± 1 °C), sound-proof and electromagnetically shielded recording chamber fitted with slip rings and cable connectors for bioelectrical recordings, under a 12-h light/dark cycle (lights on at 6:00 a.m.), with *ad libitum* access to food and water. On postpartum day 1 (PPD1, birth = day 0), litters were culled to four female and four male pups per mother.

2.2. Stereotaxic surgery

The surgical procedures were similar as previous studies of our group [5,30]. On the morning of PPD1, females were anesthetized with a mixture of ketamine/xylazine/acepromazine maleate (80/2.8/2.0 mg/kg, i.p.). Using a stereotaxic device, female rats were bilaterally implanted with 22-gauge stainless steel guide cannulae with a dummy cannula (Plastic One, Roanoke, VA) aimed 2 mm dorsal to the mPOA: AP −0.5 mm (from Bregma); ML ± 0.5 mm; DV −6.5 mm (from skull surface). In addition, cortical electroencephalogram (EEG) electrodes and dorsal neck muscle electromyogram (EMG) electrodes were

Table 1
Effects of bilateral microinjections of Raclopride (RAC) into the medial preoptic area on maternal behavior parameters during 4-h-recording sessions.

Maternal parameters	Saline	$RAC_{5\ \mu g}$	$RAC_{10\ \mu g}$	ANOVA		Tuckey (p)
				F (2,12)	p	
Litter weight gain (%)	6.3 ± 0.2	6.5 ± 0.8	4.5 ± 0.4	2.25	0.147	n/a
Latency to reunion litter (min)	1.9 ± 0.41	2.6 ± 0.8	4.6 ± 0.4*	6.27	0.014	0.013
Nursing latency from (min):						
Place litter into maternal cage	9.2 ± 1.2	5.3 ± 1.2 #	6.6 ± 0.5	5.09	0.024	0.022
Reunion of the litter	6.9 ± 0.8	2.3 ± 1.2#	1.6 ± 0.7*	16.65	0.000	*0.001 #0.002
Nursing duration (min):						
Total recording time	189.2 ± 5.7	180.1 ± 3.1	189.0 ± 24.0	0.56	0.582	n/a
First Half hour	17.9 ± 0.7	14.6 ± 1.7	16.2 ± 1.8	1.21	0.331	n/a
First hour	39.5 ± 2.6	39.6 ± 2.5	42.7 ± 2.2	0.57	0.579	n/a
Second hour	51.3 ± 2.3	50.0 ± 2.2	48.8 ± 4.9	0.57	0.905	n/a
Third hour	51.0 ± 3.4	45.0 ± 3.1	49.7 ± 3.2	0.10	0.347	n/a
Fourth hour	47.3 ± 3.7	45.5 ± 1.6	47.8 ± 2.7	0.12	0.879	n/a
N° nursing episodes	21.1 ± 3.3	22.0 ± 2.3	21.0 ± 3.6	0.05	0.947	n/a
Nursing Episodes duration (min)	10.4 ± 1.4	8.9 ± 1.0	14.4 ± 5.2	0.82	0.461	n/a

Data is presented as mean ± standard error of seven rats. * and # symbols denote significant difference ($p < 0.05$) compared to control values, using one-way repeated measures ANOVA followed by Tuckey test. n/a means not applicable.

Table 2
Effects of bilateral microinjections of Raclopride (RAC) into the medial preoptic area on sleep and waking parameters during total recording time.

	Saline	$RAC_{5\ \mu g}$	$RAC_{10\ \mu g}$	ANOVA		Tukey (p)
				F (2,12)	p	
Wakefulness						
Total duration (min)	80.0 ± 6.3	89.8 ± 6.2	101.1 ± 10.4	1.89	0.194	n/a
Number of episodes	126.0 ± 9.4	126.2 ± 21.4	125.1 ± 21.7	1.87	0.197	n/a
Episodes duration (min)	0.7 ± 0.0	5.0 ± 4.0	7.1 ± 5.9	0.24	0.793	n/a
Light Sleep (LS)						
Total duration (min)	40.4 ± 4.9	33.9 ± 2.4	36.8 ± 2.1	1.10	0.364	n/a
Number of episodes	201.9 ± 12.1	91.0 ± 15.8	211.3 ± 13.9	0.17	0.847	n/a
Episodes duration (min)	0.2 ± 0.0	0.16 ± 0.0	0.2 ± 0.0	1.69	0.225	n/a
Latency (min)	11.2 ± 0.5	8.2 ± 1.5	9.9 ± 2.8	0.90	0.43	n/a
Slow Wave Sleep (SWS)						
Total duration (min)	93.8 ± 6.4	102.6 ± 6.0	89.9 ± 9.5	1.30	0.308	n/a
Number of episodes	182.0 ± 16.4	169.4 ± 13.2	167.7 ± 11.7	0.33	0.724	n/a
Episodes duration (min)	0.6 ± 0.1	0.6 ± 0.1	0.2 ± 0.0	0.97	0.405	n/a
Latency	18.5 ± 4.0	13.9 ± 3.5	15.2 ± 3.5	1.89	0.19	n/a
Intermediate stage (IS)						
Total duration (min)	4.4 ± 0.8	2.7 ± 0.4	1.6 ± 0.3*	5.79	0.017	0.013
Number of episodes	18.8 ± 3.8	15.3 ± 1.9	8.7 ± 1.7*	4.01	0.463	0.040
Episodes duration (min)	0.19 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.56	0.591	n/a
REM Sleep						
Total duration (min)	21.5 ± 0.9	10.9 ± 2.4 #	10.8 ± 2.3*	13.98	0.001	#0.002 *0.002
Number of episodes	21.9 ± 4.1	14.1 ± 2.1	8.5 ± 1.7*	4.17	0.042	0.034
Episodes duration (min)	0.8 ± 0.1	0.8 ± 0.1	1.2 ± 0.2	1.94	0.186	n/a
Latency (min)	48.9 ± 3.4	68.7 ± 14.8	84.4 ± 25.4	1.14	0.35	n/a

Data is presented as mean ± standard error of seven rats. * and # symbols denote significant difference ($p < 0.05$) compared to control values using one-way repeated measures ANOVA followed by Tuckey test. n/a means not applicable.

implanted for the assessment of sleep and wakefulness (W) states. Recording electrodes for EEG were placed in the frontal cortex (AP = + 4.0; ML = 2.0), parietal cortex (AP = −4.0, ML = 2.0), occipital cortex (AP = −7.0, ML = 3.0), and over the cerebellum as a reference electrode (AP = −11.0, ML = 0.0) [26]. Two additional stainless-steel screws were implanted into the skull as anchors. All electrodes were soldered to a six-pin connector. The connector and the guide cannulae were cemented to the skull using dental acrylic.

2.3. Experimental design

All experiments were performed between PPD4-8 during the light phase. Before experiments began, a baseline recording session was performed to corroborate that all sleep parameters and maternal behaviors were adequate. Each animal received a total of three microinjections (0, 5 and 10 µg of Raclopride), each one on different days (PPD4, PPD6 or PPD8) in a counterbalanced design. The following day after the microinjections, no experiments were performed.

2.4. Drug

Raclopride (S(−)-Raclopride (+)-tartrate salt; Sigma–Aldrich, St Louis, MO, USA) was diluted in sterile saline to obtain a final concentration of 25 and 50 µg/µl. Aliquots for these doses were prepared in

advance, frozen at −20 °C, and thawed immediately before use.

2.5. Microinjection procedure

Females were bilaterally microinjected into the mPOA with either Raclopride (5 [$RAC_{5\ \mu g}$] or 10 μg [$RAC_{10\ \mu g}$] in 0.2 μl of saline) or the same volume of saline over a period of 2 min, with the injection cannulae (28 gauge) extending 2 mm beyond the tip of guide cannulae using a constant-rate infusion pump (Harvard apparatus, USA). The administration cannulae were left in place for an additional minute to allow for the diffusion of the drug. Raclopride doses were chosen based on its effects on maternal and sexual behavior; administration of these doses into the mPOA does not affect general motor activity [18,21].

2.6. Experimental sessions

During each experimental day, pups were removed from the maternal cage and placed under a heat lamp at 9 a.m. for three hours. Fifteen minutes before the completion of maternal separation, microinjection procedure was performed and immediately after the female was returned to her home cage and connected to the recording system in order to initiate the polysomnographic recording. Thereafter, the entire litter was weighed, and, 10 min after the microinjection procedure, the pups were scattered in the mothers' home cage opposite to the nest. After a 4-h-recodring session where polysomnographic and maternal behavior data were collected, the mother rat was disconnected from the recording device and the entire litter was weighed again (Adapted from [18]).

2.7. Maternal behavior

The latency to retrieve the entire litter was annotated. If the entire litter re-union did not occur within 5 min after reunion, any unretrieved pup was placed in the nest by the researcher and was given a latency of 5 min.

The total nursing time staged in 5-s epochs was calculated for the 4-h-recording session and for each hour separately from digital videos captured using a video tape recording attached to the Spike 2 software (CED, Cambridge, UK). In addition, the latency to retrieve the entire litter and the first nursing bout ≥2 min were measured. Nursing behaviors included nursing the litter in the kyphotic posture, lying supine on the dam's side with pups attached to nipples, and lying prone over the pups with little or no leg support (Adapted from [4,32]).

Also, the litter weight gain was calculated and expressed as the percentage of litter weight gain: (final weight − initial weight [grs]) × 100/initial weight [grs].

2.8. Sleep recording

Bioelectric signals were amplified (×1000), filtered (0.1–500 Hz), sampled (1024 Hz, 2^{16} bits) and stored in a PC for further analysis using the Spike 2 software. The states of light sleep (LS), slow wave sleep (SWS), REM sleep and W were determined in 5-s epochs with standard criteria [4,5]. Additionally, the intermediate stage (transition from NREM to REM sleep) was also distinguished (IS, sleep spindles combined with theta activity [12]).

Total time spent in W, LS, SWS, NREM sleep (LS + SWS), IS and REM sleep over the total recording time and each hour separately were analyzed. In addition, sleep latencies (first episodes ≥20 s from the beginning of the recordings), number, and duration of episodes of each state were calculated.

2.9. EEG analysis

In order to determine if Raclopride treatment modified NREM sleep depth [6], we further examined the absolute delta power (1–4 Hz) during SWS. For this purpose, the maximum number of non-transitional and artefact-free periods of 5 s were selected for each treatment and each hour of recording during SWS. Then, the Fast Fourier Transformation (FFT) was applied to each window obtaining the power spectrum with a 0.5 Hz resolution using the Spike 2 software. The data were expressed as mean ± standard error of the delta band power (absolute values).

2.10. Histological verification of microinjection sites

At the end of the experiment, animals were euthanized with sodium pentobarbital (60 mg/kg, i.p.), perfused with 4% paraformaldehyde, and their brains were removed for histological processing. Thereafter, the brains were cut in 100 μm coronal sections with a vibratome. The location of mPOA microinjection sites were verified according to the neuroanatomical Atlas of Paxinos and Watson [26].

2.11. Statistics

All values are presented as mean ± S.E.M. (standard error). The statistical significance of the difference among groups was evaluated utilizing one-way repeated measures (ANOVA) followed by Tukey *post hoc* test. The criterion used to discard the null hypotheses was $p < 0.05$.

3. Results

3.1. Sites of injection

As shown in Fig. 1, the microinjection sites in seven rats were located within the mPOA between −0.24 and −0.48 mm from Bregma, based on examination of cannula tracks in histological sections [26]. Two animals were excluded from the data analysis due to misplaced cannulae.

3.2. Effect of Raclopride on maternal behavior

Litter weight gain was no affected after Raclopride treatment (Table 1). The latency to group the entire litter into the nest was significantly increased after the high dose of Raclopride but was not altered with the low dose (Table 1). All mother rats reunited the entire litter after vehicle microinjection, while after $RAC_{5\ \mu g}$ treatment this did not occur within 5 min in three out of seven dams, and after $RAC_{10\ \mu g}$ in six out of seven rats.

The latency to begin nursing, calculated both from the reunion of the litter and from the introduction of the litter into the maternal cage, decreased following Raclopride treatment compared to control values (Table 1). The nursing time, either the total time or each hour independently, did not vary after Raclopride treatment compared to control sessions (Table 1). Neither the number nor duration of nursing episodes varied after Raclopride treatment.

3.3. Effect of Raclopride on sleep and waking states

The sleep and wake parameters after local delivery of Raclopride (0, 5 and 10 μg/side) into the mPOA during the 4-h-recordings are depicted in Table 2. The total time spent in REM sleep differed between groups; it was significantly reduced for $RAC_{5\ \mu g}$ and $RAC_{10\ \mu g}$ compared to vehicle value. Also, the number of REM episodes differed between groups; local delivery of $RAC_{10\ \mu g}$ significantly reduced this parameter when compared to control (Table 2). Fig. 1 shows that when analyzed each hour separately, REM sleep was significantly reduced after both doses of Raclopride during the second hour ($F(2, 12) = 11.69$, $p = 0.010$; Tukey: $RAC_{5\ \mu g}$ *vs.* saline $p = 0.010$, $RAC_{10\ \mu g}$ *vs.* saline $p = 0.002$), while there was a tendency to be reduced during the third hour ($F(2, 12) = 4.32$, $p = 0.038$; Tukey: $RAC_{5\ \mu g}$ *vs.* saline $p = 0.067$, $RAC_{10\ \mu g}$

vs. saline p = 0.057).

The total time spent in IS differed between groups; this time was reduced after $RAC_{10\ \mu g}$ compared to saline microinjection. This effect was related to a significant reduction in the number of IS episodes (Table 2). The IS time decrement induced by $RAC_{10\ \mu g}$ reached significance during the fourth recording hour ($F(2, 12) = 5.51$, $p = 0.02$; Tukey: $RAC_{10\ \mu g}$ *vs.* saline $p = 0.016$) (Fig. 1).

In contrast, values corresponding to W, LS, SWS and NREM sleep parameters did not differ among groups (Table 2 and Fig. 1).

No differences were found in delta frequency band power among $RAC_{5\ \mu g}$, $RAC_{10\ \mu g}$ or control treatment in the frontal, parietal or occipital cortices (Supplementary Fig. 1).

4. Discussion

Contrary to our expectations, the microinjection of the DA D2 antagonist Raclopride did not affect NREM sleep while significantly reduced the time spent in REM sleep and IS sleep. In addition, Raclopride produced subtle effects on maternal behaviors.

We found minor changes in nursing postures after Raclopride treatment. Specifically, mother rats started to nurse earlier after Raclopride treatment. This particular result is in accordance with experimental data by Miller et al. [18]. However, we could not completely replicate Miller et al. [18] as nursing duration did not vary in our results. Minor methodological differences may account for this apparent discrepancy with Miller et al. [18], since we did not clean the pups from feces and urine before introducing the litter into the maternal cage. This fact may have affected maternal responsiveness or nursing.

We also found that mother rats took longer to reunite the entire litter only with after $RAC_{10\ \mu g}$. Although we did not measure any other active maternal behavior, our data is in line with the knowledge that the DAergic system has a role in maternal motivation [34]. Although Miller et al. [18] found no alteration on active components of maternal behavior at the $RAC_{5\ \mu g}$, no higher doses were used. Thus, it can be speculated that a larger blockade of the DA D2 receptor within the mPOA is needed to evidence an effect on active maternal behaviors.

Neither the duration nor the depth of NREM sleep were altered by the intra-mPOA administration of Raclopride. However, this DA D2 antagonist markedly altered REM sleep and its transitional state from NREM sleep. This is in accordance with Ramesh et al. [29], who found that total sleep deprivation decreases DA levels in the mPOA. Although a great number of studies relate mPOA exclusively to NREM sleep, our data is supported by experimental evidence that points to the additional involvement of mPOA in the regulation of REM sleep [1,35]. Particularly, Suntsova and Dergacheva [35] found that most mPOA recorded neurons increase their firing rate during REM sleep compared to W and NREM sleep, increasing their firing rate 20–70 s before the initiation of cortical desynchronization in half of these neurons. In addition, electrical stimulation of the mPOA during NREM sleep promotes the entrance to REM sleep [35].

Our data is in accordance with the fact that the DAergic neuronal activity is modified during REM sleep. Dahan et al. [8] put in evidence that there is a prominent burst firing increase in VTA DAergic neurons during REM sleep. Also, the release of DA both in the nucleus accumbens shell and prefrontal cortex is increased during REM sleep in comparison to NREM sleep [15]. Furthermore, DAergic receptors are regulated during sleep [24].

The fact that the antagonism of the D2-receptor in the mPOA decreases REM sleep (present results), is in accordance with Lima et al. [16] and Proenca et al. [28]. These authors proposed that the particular action of the DAergic neurotransmission in REM sleep relies on D2 activation. Dzirasa et al. [10] also demonstrated that REM sleep alterations in the DAergic transporter knockout mice could be recovered by selective activation of the D2. These results, together with the literature that states the mPOA as a NREM sleep promoting area [13,17], drove us to hypothesize that the DAergic projections toward the mPOA may facilitate the transition from NREM to REM sleep. However, administration into the mPOA of other DA agents should be done to confirm this hypothesis.

Although no data is available about the changing expression of DA receptors within the POA, it is known that the mPOA and DAergic system are heavily conditioned by maternal experience [7,9,25]. Thus, the present experiments should be replicated in non-maternal rats to determine if these results are specific of mother rats.

In summary, REM sleep, a state where DA plays a crucial role, was reduced after the administration of a DA D2 receptor antagonist into the mPOA, a sleep-promoting area. Further studies are needed to understand the physiological role of DA in the integration of different behaviors within the mPOA.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2017.08.077.

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