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Effects of biperiden on sleep at baseline and after 72 h of REM sleep deprivation in the cat

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Abstract. We examined the effects of the muscarinic M1 antagonist biperiden in cats. In the first experiment a dose-response analysis was performed with intraventricular injection (IV ventricle) of biperiden. In the second experiment after REM sleep deprivation cats were injected with either biperiden (0.1 mg/kg) or saline. Biperiden produced a reduction in REM sleep percentage and an increase in REM sleep latency with these high doses. The 0.1 mg/kg biperiden dose, which did not suppress REM sleep at baseline, did reduce the REM sleep rebound. The present study suggests a modulatory role of biperiden on REM sleep regulatory processes. The fact that an effect of biperiden is noted only at the high doses suggests that at these doses the drug is influencing non-M1 receptors. Changes in the sensitivity of these receptors as a result of REM sleep deprivation might explain why a dose of biperiden will reduce REM sleep rebound, while being ineffective in suppressing REM sleep at baseline.

Key words: Muscarinic receptors – REM sleep – Cholinergic – Biperiden – Cats – REM sleep deprivation

Cholinergic hypotheses regarding sleep function were proposed first by Hernandez-Peon et al. (1963). Specifically, studies show that rapid eye movement (REM) sleep is controlled by cholinergic mechanisms (Jouvet 1962; McCarley and Hobson 1975; Sitaram and Gillin 1980). Recent information has identified subclasses of the major two cholinergic systems (Watson 1987). The administration of cholinergic agonistic M2 drugs produce an increase in REM sleep, whereas the M1 agonist did not have the same effect (Velasquez-Moctezuma 1989). Biperiden (Akineton) is a M1 preferential antagonist drug (Eltze and Figala 1988) used clinically as an anti-parkinsonian drug, but its effects on sleep, both in humans and animals, have not been established yet.

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REM sleep deprivation seems to change cholinergic sensitivity in humans (Salin-Pascual et al. 1989), so this modification in muscarinic sensitivity may change the response to an anticholinergic drug (i.e. biperiden) at previous doses. The purposes of the present study were two-fold: first to determine the dose-related effects of biperiden on baseline sleep and second to determine if a dose which in the previous study did not produce REM sleep suppression will have a significant effect on REM sleep rebound after 72 h of REM sleep deprivation in the cat.

Materials and methods

Experiment 1. Thirty adult cats (2–2.5 kg) were surgically prepared for polygraphic recording and with intraventricular (IV ventricle) canulae by the following method. Animals were anesthetized with pentobarbital (3.5 mg/kg IP) and implanted with electrodes for recording electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG) and PGO waves. Stainless steel guide tubes (24 gauge) were stereotaxically aimed at the fourth ventricle (theta = 45 degrees). After easy extraction of cerebrospinal fluid the cannula was cemented in place with dental acrylic. Two weeks after the surgery the animals were acclimatized to the polygraphic recording chamber for 1 week. On the experimental day the cats were restrained and a stainless-steel cannula (31 gauge) was inserted into the fixed guide tube. Injections of saline or biperiden (0.01, 0.1, 0.35 and 0.5 mg/kg) were made using a 1.0 µl Hamilton syringe. All of the injections were in a volume of 50 µl. After the injections the animals were placed in their sound attenuated chambers and recorded for 11 h.

Experiment 2. Twenty-eight cats from experiment 1 were utilized in this experiment. After 2 weeks for recovery from experiment 1, they were assigned to one of four groups (seven cats per group): control + saline; control + biperiden; REM sleep deprivation + saline; REM sleep deprivation + biperiden. Biperiden, a single dose of 0.1 mg/kg, was administered intraventricularly (IV ventricle) as in the previous experiment. REM sleep deprivation (72 h) was performed by the platform method (10 cm diameter). After the deprivation the animals were injected with either saline or biperiden (0.1 mg/kg) and were placed in their recordings chambers for 11 h.

All the biperiden injections in experiments 1 and 2 were performed at 0700 hours, the polygraphic recording session started at

Table 1. Sleep variables: experiment 1 [mean (SD)]

	Dose (mg/kg)						
	0	0.01	0.1	0.35	0.5	*F*	*P*
Sleep variables[a]							
Wake time	20.9	17.7	20.9	17.8*	12.2*	3.02	0.03
(%)	(4.8)	(2.1)	(8.1)	(6.0)	(5.4)		
S–I	16.03	13.6	12.9	15.9	13.7	0.54	0.70
(%)	(7.8)	(3.8)	(3.3)	(4.5)	(1.9)		
S–II	39.5	47.1	50.62	58.2*	59.7*	5.08	0.004
(%)	(6.9)	(9.9)	(10.9)	(8.13)	(8.5)		
REM	23.4	21.7	15.3	12.9*	10.3*	4.94	0.004
(%)	(4.9)	(8.5)	(8.7)	(3.7)	(3.1)		
REM L	43.6	37.7	36.6	100.2*	92.6*	11.1	0.0001
(min)	(23.7)	(6.8)	(20.9)	(40.4)	(4.8)		

[a] One-way repeated measures ANOVA; n = six cats per group; * Students' t (Post-hoc)

Table 2. Sleep variables: experiment 2 [mean (SD)]

	Control	REMSD	ANOVA**
REM sleep time			
Saline	174.0 (33.28)	308.61* (43.01)	
Biperiden	141.5 (48.12)	216.9 (78.9)	a, b, c
REM sleep latency			
Saline	35.9 (19.0)	19.65 (10.5)	
Biperiden	38.8 (6.8)	21.7 (11.5)	b
Stage 2			
Saline	276.6 (66.1)	196.04 (68.3)	
Biperiden	314.1 (63.9)	237.5 (107.2)	b

* $P<0.05$ (control vs REMSD) Students' t test (post-hoc)
** Two-way ANOVA: a = group effect ($df=1$) (saline vs biperiden); b = Time effect ($df=1$) (control vs REM sleep deprivation); c = interaction effect
REMSD = REM sleep deprivation

0730 and ended at 1830 hours. Cats were housed in a 12/12 h, dark/light cycle. All the recordings were performed with the cats in a sound attenuated chambers.

The polygraphic states were divided in wakefulness, stage I stage 2 and REM sleep (Ursin and Sterman 1968). Data analysis was performed by one-way ANOVA for the dose-response curve and a two-way ANOVA in the second experiment. Students' t tests for independent measures with a correction to maintain the alpha level at $P<0.05$ (Bonferroni's correction) were performed when indicated (Post-hoc tests).

Results

Experiment 1

Table 1 shows that biperiden produced the following changes in the sleep variables: a reduction of REM sleep percentage (up to 55%) ($F=4.94$; $P<0.004$) and an increase in REM sleep latency ($F=11.1$; $P<0.0001$). Sleep stage II was also increased ($F=5.08$; $P<0.004$), whereas wake time was reduced ($F=3.02$; $P<0.03$). All of these changes were significant for the 0.35 and 0.5 mg doses.

Experiment 2 results are shown in Table 2. REM sleep did not change after biperiden administration in the control conditions, but biperiden reduced the REM sleep recovery after REM sleep deprivation. The two-way ANOVA showed a drug effect (Group effect: $F=5.7$; $P<0.002$) a REM sleep deprivation effect (time effect: $F=33.98$; $P<0.0001$) and interaction effects (group × time effect: $F=4.52$; $P<0.04$). REM sleep increased in the REM sleep deprivation + saline group up to 77% above baseline whereas REM sleep in the REM sleep deprivation + biperiden group was only 24% above control + saline group. REM sleep deprivation produced a shortened REM sleep latency (time effect: $F=11.9$; $P<0.002$). Finally stage II sleep showed a reduction on the two REM sleep deprived groups (time effect: $F=7.1$; $P<0.01$).

Discussion

The present study supports the hypothesis of the involvement of M1 cholinergic receptors in the regulatory process of REM sleep. Differential effects of cholinergic antagonists on REM sleep components have been reported. The study suggests that EEG desynchronization is partially mediated by M1 muscarinic receptors, atonia is mediated by M2 muscarinic receptors and PGO waves have a nicotinic component (Velazquez-Moctezuma et al. 1990).

An alternative explanation to this proposition is that the differential effects reflect a dose-related effect on the different components of REM sleep in the cat. In experiment 2 the same biperiden dose that did not produce any change in REM sleep at baseline showed a reduction in the REM sleep rebound. An enhancement in the release of acetylcholine in the dorsal tegmental field of the cat brain stem has been reported (Kodama et al. 1990). In REM sleep deprivation changes in the release of acetylcholine may occur and in this way some modifications in the sensitivity of muscarinic receptors might produce an increase in the response to the low dose of biperiden and thereby reduce the REM sleep rebound. A similar finding has been reported recently in humans (Salin-Pascual et al. 1991). Another possibility is that REM sleep deprivation modifies other receptor systems that may interact

with biperiden (i.e. Non-M1 receptors) and in that way reduces the REM sleep rebound. Further studies are needed to draw further conclusions regarding the muscarinic regulation of REM sleep.

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