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Lifetime Monoamine Oxidase Inhibition and Sleep

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MENDELSON, W B , R M COHEN, I C CAMPBELL, D L MURPHY, J C GILLIN AND R J WYATT *Lifetime monoamine oxidase inhibition and sleep* PHARMAC BIOCHEM BEHAV 16(3) 429–431, 1982 —The effects of clorgyline, a type A monoamine oxidase (MAO) inhibitor, on the sleep of the rat were examined after subacute and lifetime administration When 2 mg/kg/24 hours were given for 60 hours, type A MAO was inhibited by 92% and a significant reduction in REM sleep time was noted When fetal rats were exposed to maternal dosage of 1 mg/kg/24 hours and then received this dose from one to 6 weeks postnatally, type A MAO was inhibited by 99%, but there were no alterations in the EEG sleep stages In summary, subacute administration of clorgyline resulted in decreases in both Type A MAO and REM sleep, during chronic administration in a developing animal, Type A MAO was again decreased but there was no corresponding change in REM sleep

Clorgyline Sleep REM Sleep Monoamine oxidase

MONOAMINE oxidase (MAO) inhibitors, clinically used in the treatment of depression and narcolepsy, have been shown in a variety of human studies to produce profound reductions in Rapid Eye Movement (REM) sleep [2] It has been argued that this effect results very specifically from the MAO inhibition itself, insofar as biochemically similar agents without this property (e g , isoniazid) do not affect REM [7] Sleep studies with MAO inhibitors, however, have largely been performed with agents possessing mixed type A and B inhibition and are usually from only a few days' to a few weeks' duration In the present study have examined the effects of clorgyline, a relatively specific type A inhibitor [1] on sleep in rats, upon whom MAO activity determinations were performed The study includes (1) an examination of subacute administration in order to determine if adult rats, like humans, show decreased REM sleep in response to MAO inhibitors, and (2) a sleep and biochemical study of adult rats who have been continuously exposed to clorgyline since fetal life, to determine the effects of MAO inhibition in the developing brain on subsequent adult sleep

METHOD

In the subacute study, 22 male Sprague-Dawley 225 g rats (about 6 weeks of age) were assigned to one of two groups One (N=12) received 2 mg/kg of clorgyline IP, given in daily injections for 3 days at 8 45 a m , while the other (N=10) received equivolume saline An eight-hour sleep study was begun 15 minutes after the third such injection In the "lifetime" study Sprague-Dawley rats 7 days pregnant were assigned to one of two groups, each containing 7 animals Following halothane anaesthesia, both groups were implanted subcutaneously with Alzet minipumps with concentrations determined individually to administer 1 mg/kg/24 hours or equivolume saline, based on weight at time of implantation (Previous experience had indicated that 2 mg/kg subacutely and 1 mg/kg chronically are needed to achieve approximately equal MAO inhibition of 90%, which was the desired goal) Following birth and weaning (until which time the experimental animals received milk from their mothers who were continued on the drug regimen), recording electrodes were surgically implanted, and the rats were maintained with minipumps Dosages were individually determined and based on weight at time of implantation Every 2 weeks the pumps were replaced, with drug concentrations being determined by the new weights of the animals so as to continue to deliver 1 mg/kg/24 hours At 6 weeks of age they had an eight-hour sleep recording starting at 9 00 a m In all studies animals were maintained in a room with lights on from 8 00 a m to 8 00 p m

Sleep studies were performed by implanting 0–80, 1/8 in stainless steel dural screw electrodes for the electroencepha-

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TABLE 1
SUBACUTE STUDY—EFFECTS OF CLORGYLINE ON SLEEP

	Clorgyline (N=12)		Saline (N=10)		
	Mean	SE	Mean	SE	Significance
Total Recording Period	483 0	3 1	487 0	1 7	
Total Sleep Time	265 0	11 2	294 0	13 6	
Non-REM Time	243 5	9 9	260 4	13 1	
REM Time	21 5	3 0	33 6	2 7	$p<0$ 01
Intermittent Waking Time	171 8	12 3	151 0	12 4	
Disconnect Time	5 2	2 2	5 4	2 5	
% Non-REM	92 0	1 0	88 4	1 1	$p<0$ 02
% REM	8 0	1 0	11 6	1 1	$p<0$ 02
% Intermittent Waking	39 2	2 5	34 0	2 9	
Sleep Latency	41 8	8 8	53 2	14 4	
REM Latency	159 0	32 6	100 8	20 0	
Number REM Episodes	8 2	1 1	15 7	1 2	$p<0$ 001
REM Episodes Length	2 5	0 2	2 1	0 1	
REM Efficiency	91 6	2 4	94 8	0 6	
REM—non-REM Cycle Length	39 0	6 2	24 2	2 2	$p<0$ 05
Number Intermittent Waking Episodes	19 8	1 7	18 3	1 8	

All values except percentages refer to minutes ± SEM
Definitions of sleep parameters are described in detail in Mendelson *et al* [4]

logram (EEG) and 0 005 in stainless steel nuchal electromyogram (EMG) electrodes, as described by Mendelson *et al* [3] After a one-week surgical recovery period (the animals were, of course, continuously maintained on their drug regimens), recordings were made on a Grass Model 78 polygraph with a paper speed of 10 mm/second and calibrated to 50 μV/10 mm Records were analyzed by one "blind" investigator who determined the state of consciousness (waking, non-REM sleep, REM sleep) for each 30 second epoch according to standard criteria [3,4] In summary, the waking state was defined as a low voltage, mixed frequency EEG with high amplitude EMG, non-REM sleep as comprised of high amplitude, low frequency EEG with somewhat lower EMG amplitude, REM sleep shows a low amplitude, mixed frequency EEG and very low amplitude EMG Statistical analysis of sleep data was performed by *t*-tests for independent groups

Immediately after sleep studies the animals were decapitated and their brains frozen on dry ice MAO-A activity was determined by measuring rate of deamination of serotonin, as described in an earlier publication [1] The specific activity of serotonin in the controls for the subacute study was 135 nmoles/mg protein/hour and in the "lifetime" study was 180 nmoles/mg protein/hour The lack of effect of subacute dosages of clorgyline on type B activity has already been confirmed in this laboratory [1], type B activity in the "lifetime" study was measured by rate of deamination of phenylethylamine, in this case with a control specific activity of 24 8 nmoles/mg protein/hr

RESULTS

Subacute Study

Biochemical analysis revealed that the three injections of clorgyline reduced MAO-A activity 92 4±1 0 (SEM)% ($p<0$ 0001) Sleep EEG data revealed that REM sleep time was significantly ($p<0$ 01) reduced from a control mean of 33 6±2 7 minutes to 21 5±3 0 minutes on clorgyline (Table 1) The percentage of total sleep comprised of REM sleep was also reduced, these changes appeared to be due to a reduction in the number of REM episodes and an increase in REM—non-REM cycle length (the mean time from the beginning of one REM period until the beginning of the next) Total sleep time and sleep latency (the time taken to fall asleep initially) were unaffected

'Lifetime" Study

Biochemical analysis revealed that MAO-A was inhibited by 99 0±2 0% ($p<0$ 0001) There was essentially no type B inhibition Informal observation of the animals suggested that their behavior and neurological status was generally normal The sleep EEG study revealed no significant effects on REM or other sleep measures, although there was a non-significant trend toward decreased REM with clorgyline compared to saline (28 4±6 5 vs 35 3±5 3 min, respectively)

DISCUSSION

These data confirm that clorgyline potently inhibits MAO-A after subacute administration, and may continue to have major and specific effects over 6 weeks in a developing brain It is not known whether norepinephrine and serotonin concentrations remain elevated over this duration, previous work after 3 weeks' administration suggests that, at that point, norepinephrine remained elevated while serotonin did not [1] The subacute EEG data confirms that in rats, like man, an MAO-A inhibitor markedly reduces total and percentage REM sleep When given over many weeks to a developing brain, some sort of dissociation of MAO inhibition

and REM sleep effects appeared to take place Insofar as clorgyline has been reported to readily cross the blood-brain barrier and the placenta, it is presumed (although not definitely known) to have lowered MAO activity over the lifetime of the animal Certainly by adulthood MAO-A activity was suppressed by 99%, yet sleep was normal

The data reported here are reminiscent of another case in which biogenic amine concentrations may be greatly altered without changes in REM sleep Children with phenylketonuria, in whom there are decreased nervous system concentrations of serotonin, may have relatively normal sleep [5] Although the direction of change in serotonin concentrations in the latter study was different (i e , decreased) compared to the present data, all of these observations seem to suggest that during chronic perturbations in biogenic amine metabolism in developing brains there appears to be a compensatory mechanism by which REM sleep characteristics may be relatively normal Whether the compensatory mechanism seen in the present study results from altered synthesis, receptor sensitivity, or some other means, is not yet known

These data differ somewhat form the finding by Wyatt *et al* [6] that phenelzine may suppress REM sleep for up to a year in adult narcoleptics Whether this can be explained by the different biochemical properties of phenelzine (which is a mixed type A and B inhibitor), the clearly abnormal regulation of REM sleep in narcoleptics, or the fact that the drug was given to an adult (not a developing) nervous system remains to be established Finally, any possible effect of the type of drug delivery system in the present study (continuous infusion rather than repeated administration) is, as yet, undetermined

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