Role of Central Alpha-1 Adrenoceptors in Canine Narcolepsy

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Abstract

The role of central alpha-1 adrenergic receptors in cataplexy was investigated in genetically narcoleptic Doberman pinschers. Treatment of narcoleptic dogs with 25–600 μg/kg prazosin, a selective alpha-1 adrenergic receptor blocker, exacerbated cataplexy, whereas treatment with the alpha-1 agonist, methoxamine, ameliorated it. Subsequent studies showed that the beneficial effects of classical treatments of human narcolepsy (amphetamines and tricyclic antidepressants) are antagonized by prazosin, suggesting that these drugs are active through an indirect alpha-1 stimulation (via an increase of norepinephrine in the synaptic cleft). Other studies confirmed that the observed effects were not due to peripheral alpha-1 cardiovascular involvement. Atropine, a central anticholinergic agent, but not methylatropine, a peripheral one, completely suppressed the prazosin effect, which suggests that adrenergic and cholinergic systems act sequentially and not independently to generate cataplexy. Little is known about the physiological role of central alpha-1 adrenoceptors. This series of experiments implicates these receptors in narcolepsy-cataplexy.

Introduction

Human narcolepsy is a disabling sleep disorder of unknown origin, characterized by sudden attacks of partial or complete flaccid paralysis (cataplexy) and excessive daytime sleepiness. These attacks can strike spontaneously or be elicited by emotional experiences such as laughter, excitement, or fear. Sleep recording studies in narcoleptic patients show an abnormally rapid transition from wake to rapid eye movement (REM)[1] sleep during the day and a drastically shortened REM latency at night (1). Since a state of muscular paralysis similar to cataplexy normally occurs during REM sleep, narcolepsy is considered an REM sleep disorder (1).

Considerable attention has centered on the role of central cholinergic systems in the regulation of REM sleep. Cataplexy and REM sleep are controlled by known cholinergic mechanisms located in the brainstem (2–7). Cholinergic neurons of the dorsal pontine tegmentum tonically inhibit muscle tone during REM sleep. This muscle inhibition involves projections to the reticular formation in the medial medulla and from there to motor neurons in the spinal cord (2–7). Consistent with these anatomical findings, central cholinergic stimulation by physostigmine or arecoline has been reported to aggravate the symptoms in narcoleptic dogs, whereas central anticholinergic drugs, such as atropine or scopolamine, improve them (8). The use of anticholinergic drugs has, however, been very disappointing in human narcolepsy, particularly because of their numerous side effects.

The pharmacological manipulations of the central cholinergic network have been coupled with investigations of the role of monoamines in controlling REM sleep (9–11) and cataplexy. Noncholinergic, monoaminergic (especially norepinephrine) reuptake blockers (tricyclic antidepressants, viloxazine, and nisoxetine) and monoamine-releasing drugs (amphetamine and methylphenidate) are REM sleep suppressants and have beneficial effects in human and canine narcolepsy (8). However, it is difficult to assess which of their multiple pharmacological actions is responsible for their therapeutic effect and/or side effects. All these drugs act presynaptically on monoaminergic systems, and supposedly increase norepinephrine levels in the synaptic cleft. If such an increase in norepinephrine takes place, a postsynaptic adrenoceptor stimulation should occur, and such stimulation is probably involved in the therapeutic effects seen in narcoleptics.

Reports of changes in REM sleep in animals (12–15) and humans (16) after treatment with alpha-1 adrenergic agents (increase with blockade and decrease with stimulation) provided further rationale for our hypothesis. The role of central alpha-1 mechanisms in narcolepsy was examined by in vivo pharmacology in narcoleptic Doberman pinschers, an autosomal recessive animal model of human narcolepsy (8, 17–19).

Methods

Animals. Dogs were exposed to a 12/12 dark/light cycle. They had free access to food between 1300 and 0700 hours. Changes in cataplexy, BP, and heart rate (HR) induced by pharmacological treatments were evaluated in six affected Dobermans, four controls, and four heterozygotes. The six homozygous Dobermans were four adults (3–7 yr) and two puppies (6 mo). Their mean age and weight were 3.1 yr and 18.7 kg, respectively. Heterozygous and control Dobermans were all adult dogs (> 8 mo old) and had no attacks. Mean age and weight of heterozygous dogs were 10.8 mo and 26.0 kg. All control Dobermans were at least 11 mo old (two were born at an unknown date; mean weight was 28.1 kg).

Food-elicited cataplexy test. The food-elicited cataplexy test (FECT) was used for the pharmacological investigations (8). Food precipitates multiple cataplectic attacks in these animals, sometimes followed by REM sleep. In our experimental procedure, 12 successive pieces of wet food (1 cm³) were placed on the floor and spaced 30 cm apart. Dogs were previously trained to eat the food one piece after another. The experimenter recorded (a) the time required for the dog to eat all the pieces of food (elapsed time) and (b) the number of complete and partial cataplectic attacks. An attack was considered complete when the dog dropped to the floor with head resting on the

1. *Abbreviations used in this paper:* DBP, diastolic blood pressure; E_{max}, maximal effect; FECT, food-elicited cataplexy test; HR, heart rate; REM, rapid eye movement; SBP, systolic blood pressure.

Table I. Effect of Placebo, Prazosin, and Methoxamine on Food-elicited Cataplexy Test

	Time (hours)				
	0	2	4	8	
Controls (n = 4)					
Placebo					
Elapsed time (s)	12.3±1.3	11.8±2.4	11.8±1.3	12.2±1.2	
Prazosin (600 µg/kg)					
Elapsed time (s)	12.8±1.1	12.2±0.7	11.8±0.6	12.1±0.6	
Heterozygotes (n = 4)					
Placebo					
Elapsed time (s)	11.3±0.4	11.6±0.2	11.2±0.5	11.4±0.3	
Prazosin (600 µg/kg)					
Elapsed time (s)	11.3±0.4	11.5±0.3	11.4±0.3	11.2±0.3	
Homozygotes (n = 6)					
Placebo					
No. of attacks	2.13±1.12	1.87±1.06	1.80±0.91	1.35±0.60	
Elapsed time (s)	33.2±12.0	23.3±5.3	21.9±5.0	23.9±5.4	
Prazosin (2.5 µg/kg)					
No. of attacks	2.83±1.55	2.38±1.28	2.83±1.46	2.83±1.67	
Elapsed time (s)	27.1±9.1	27.4±9.0	29.4±9.8	33.2±14.1	
Prazosin (7.5 µg/kg)					
No. of attacks	3.50±1.64	2.83±1.45	3.55±1.23	3.33±1.62	
Elapsed time (s)	35.0±11.0	28.6±8.3	35.9±9.3	36.7±12.2	
Prazosin (25 µg/kg)					
No. of attacks	2.20±0.90	5.00±1.48	4.88±1.78	3.37±1.54	
Elapsed time (s)	28.3±8.4	44.3±11.4	50.07±13.52	38.2±12.2	
Prazosin (75 µg/kg)					
No. of attacks	2.93±0.93	11.43±2.76	11.62±2.90	9.77±1.35	(4)
Elapsed time (s)	37.5±7.7	125.0±33.2	137.8±42.0	73.4±11.5	(3)
Prazosin (225 µg/kg)					
No. of attacks	3.00±1.37	13.50±2.18	14.25±1.59	9.83±1.09	(3)
Elapsed time (s)	35.2±13.30	170.3±54.0	203.9±39.3	119.4±21.7	(6)
Prazosin (600 µg/kg)					
No. of attacks	1.65±0.98	14.15±2.08	13.95±3.57	10.05±2.79	(5)
Elapsed time (s)	33.6±13.8	209.9±47.0	169.3±52.3	98.2±8.9	(5)
Methoxamine (0.1 mg/kg)					
No. of attacks	3.92±0.97	3.17±0.62	3.33±1.26	3.33±0.82	
Elapsed time (s)	37.6±6.4	45.3±8.4	53.7±11.6	35.0±7.2	
Methoxamine (0.2 mg/kg)					
No. of attacks	4.83±0.73	3.00±1.11	3.09±1.11	3.25±1.23	
Elapsed time (s)	67.0±12.1	44.2±15.6	39.1±11.7	36.6±11.7	
Methoxamine (0.5 mg/kg)					
No. of attacks	4.10±1.64	0.27±0.21	0.27±0.21	1.67±0.71	(1)
Elapsed time (s)	39.2±9.9	17.1±3.5	13.2±1.3	32.0±11.7	(2)
Prazosin (600 µg/kg) plus methoxamine (0.5 mg/kg)					
No. of attacks	2.23±1.06	12.73±2.62	8.98±1.18	5.83±0.83	(7)
Elapsed time (s)	33.4±8.4	206.6±56.0	150.3±55.3	81.1±13.2	(8)

Data shown are the mean±SEM of six dogs for each treatment. FECT and statistical procedures are described in Methods. A statistically significant prazosin dose-dependent increase in elapsed time and number of attacks was obtained ($P < 10^{-9}$). (1), $P < 0.05$ vs. placebo; (2), $P < 0.01$ vs. placebo; (3), $P < 10^{-5}$ vs. placebo; (4), $P < 10^{-6}$ vs. placebo; (5), $P < 10^{-7}$ vs. placebo; (6), $P < 10^{-8}$ vs. placebo; (7), $P < 10^{-4}$ vs. 0.5 mg/kg methoxamine; (8), $P < 10^{-8}$ vs. 0.5 mg/kg methoxamine.

floor, and partial in other cases (when the dog dropped to the ground on hindquarters, forequarters, or both, but with head above the floor). This test has been used previously with poodles and Dobermans and is very sensitive to drugs known to modify human narcolepsy (8).

Cardiovascular measurements. Systolic and diastolic BP (SBP and DBP) and HR were measured directly by an auscultatory method comparable to that described in reference 20. The dogs were trained to stand quietly in a sling that supports most of their weight and did not show cataplexy during the measurements. BP was taken on the forelimb after detection of the humeral artery pulse. HR was taken by thoracic auscultation. Materials used included a child-size cuff, a diaphragm-type stethoscope, and a standard sphygmomanometer.
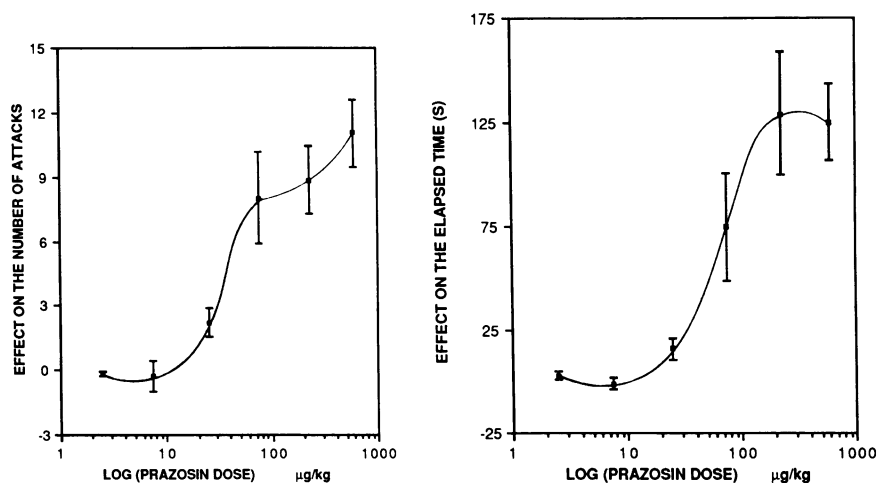
Figure 1. Dose-response curves of the effects of prazosin on cataplexy. Cataplexy was measured using the food-elicited cataplexy test (FECT, elapsed time and number of attacks) (2, 4, and 8 h) before and after drug administration. The dose dependence was examined on the mean of the three postdrug data points collected after various doses of prazosin (2.5, 7.5, 25, 75, and 600 μg/kg p.o.). The term effect relates to the difference between pre- and postdrug values. Technical aspects are described in detail in the text. Each point is the mean of six narcoleptic dogs and vertical bars depict SEM.

Locomotor activity. To appreciate simultaneously the effects of the administered drugs on overall behavior of the dogs, an open field measurement of locomotor activity was also performed. The testing room was divided into squares of $\sim 50 \times 50$ cm^2 (~ 25 squares for the room used). The experimenter, located outside the room, watched the animal through the window for 2 min 30 s and recorded the number of times the dog's forelegs crossed a line separating two squares. The number and the duration of spontaneous cataplectic attacks that could occur during the test were recorded (under basal conditions these spontaneous attacks are unusual). The number of crossings was also expressed by minutes of wake (2 min 30 s − time spent in cataplexy) to exclude changes in this parameter due to an increase in cataplexy. This test was used to exclude any nonspecific effects and excessive sedation due to overdosage.

Experimental design. The FECT was administered (three tests in 20 min; all subsequent data analysis used the mean of the three tests) before and after drug administration. Testing began at 9 a.m. and the experimenter who recorded the results was aware of the drug that had been given. Drugs were administered immediately after the first baseline testing of each dog (prazosin, hydralazine, methoxamine, and protriptyline) and/or 1 h later (metaraminol, dextroamphetamine, nisoxetine, atropine, and methylatropine). Postdrug FECTs were performed 2, 4, and 8 h after the first test in all the cases. Comparative control sessions were also performed by administrating placebo by way of the mouth (p.o.) and/or saline intramuscularly (two placebo sessions). BP, HR, and locomotor activity were measured with FECT administration during the first two tests ($t = 0$ and 2 h). Because the same dogs were used for several drug administration experiments, a correct washout (five times the half-life of the compound previously given) was always allowed.

Drugs. The following drugs were used for these experiments: prazosin HCl an alpha-1 antagonist, (1 and 5 mg Minipress, Pfizer Chemicals Div., Hoffman Estates, IL; 2.5–600 μg/kg p.o.), methoxamine HCl, an alpha-1 agonist, (2% Vasoxyl, Burroughs Wellcome & Co., Raleigh, NC; 0.1–0.5 mg/kg i.m.), hydralazine HCl, a peripheral vasodilator, (10 and 50 mg Aprezoline, Ciba-Geigy Corp., Pharmaceuticals Div., Summit, NJ; 4 mg/kg p.o.), metaraminol bitartrate, a peripheral vasoconstrictor, (1% Aramine, Merck Sharp & Dohme, West Point, PA; 0.1 mg/kg i.m.), nisoxetine HCl, a selective norepinephrine uptake inhibitor (Eli Lilly Research Laboratories, Indianapolis, IN; 0.5 mg/kg p.o.), protriptyline HCl, a tricyclic antidepressant (5 and 10 mg Vivactil, Merck Sharp & Dohme, 1.2 mg/kg p.o.), dextroamphetamine sulfate, (an amphetamine, 5 mg Dexedrine, SmithKline Corp., Philadelphia, PA; 0.5 mg/kg p.o.), atropine sulfate, an anticholinergic agent with central effect (Sigma Chemical Co., St. Louis, MO; 0.1 mg/kg i.m.), methylatropine nitrate, a peripheral anticholinergic drug (Sigma Chemical Co.; 0.1 mg/kg i.m.). Drugs (tablets, capsules, or powder)

were given orally mixed with wet dog food or intramuscularly as obtained or dissolved in saline. Placebo sessions were performed by giving only the wet dog food (placebo session of the dose response curve of prazosin) or by giving wet dog food and one injection of 0.5 ml saline i.m. 1 h later (placebo session of the drug combination experiments).

Statistics. Drug effects were analyzed using the computerized statistical program SYSTAT on an IBM XT computer (Systat Inc., Evanston, IL). Data were transformed (ranked) to obtain the homogeneity of variance within groups (Bartlett's test). Placebo and drugs sessions were compared by analysis of variance on repeated measures with grouping factors (treatment). One placebo session was used for prazosin dose-response analysis. The second placebo session was used for all the other comparisons. P values of the univariate F test statistics were considered only when they were in agreement with the results of the multivariate statistics (Wilks' Lambda likelihood ratio criterion, Pillia's Trace statistics, and Hotelling-Lawley trace and their corresponding F statistics), which was the case most of the time. If the univariate and multivariate F statistics led to different conclusions, the P considered was the one obtained with the multivariate profile analysis (mean of the three tests) because this test does not require the compound symmetry assumption (equivalence of the covariances across all pairs of cells). The Bonferroni adjustment was applied to the P values obtained in case of multiple comparisons.

Dose-response dependence of the prazosin effect was first tested as described previously, by analysis of variance using each dose and placebo as grouping factors. The second step used a simple linear regression between the effect of the drug on the parameter (postdrug-predrug values) and the log decimal of the prazosin dose. The dose dependence of the effect of prazosin on FECT was calculated on the mean of the three postdrug data points (2, 4, and 8 h) to condense the data. Maximal effects (E_{max}) and the doses producing 50% of the maximal effect (ED$_{50}$) were approximated by nonlinear regression analysis on the following equation: effect = $E_{max}/[(ED_{50}/\text{prazosin dose}) \mu + 1]$ with $\mu = 1$, according to Pliska (21). Minimization algorithms used were the Quasi-Newton method (Systat).

Results

Significance of the different parameters used in this study to quantify cataplexy. Four parameters directly assessed the severity of the cataplexy in narcoleptic dogs: the number of attacks and the elapsed time of the FECT were measures of elicited cataplexy and the number of spontaneous attacks and the time spent in cataplexy during the locomotor activity test were measures of spontaneous cataplexy. FECT elapsed time was highly correlated with the number of attacks occurring

Table II. Effect of Placebo, Prazosin, and Methoxamine on Locomotor Activity and Spontaneous Cataplexy

		No. of crossings	No. of attacks	Time spent in cataplexy	No. of crossings per minute of wake
				s	min^{-1}
Controls (n = 4)					
Placebo	Before	60.1±9.4	—	—	24.4±7.5
	After	61.4±10.7	—	—	26.25±5.2
Prazosin (600 µg/kg)	Before	63.6±9.0	—	—	25.5±3.6
	After	51.3±6.1	—	—	20.0±2.4
Heterozygotes (n = 4)					
Placebo	Before	54.0±9.3	—	—	21.6±3.7
	After	57.6±4.7	—	—	23.0±1.9
Prazosin (600 µg/kg)	Before	57.5±7.2	—	—	23.0±2.9
	After	62.5±10.9	—	—	25.0±4.3
Homozygotes (n = 6)					
Placebo	Before	60.1±9.4	0.17±0.17	0.33±0.33	24.2±3.8
	After	61.4±10.7	0.08±0.08	0.17±0.17	24.6±4.3
				$P < 0.05$	
Prazosin (2.5 µg/kg)	Before	55.5±7.9	0.75±0.04	1.50±0.81	22.4±3.2
	After	54.7±9.3	0.33±0.21	0.67±0.42	22.0±3.8
Prazosin (7.5 µg/kg)	Before	75.5±6.0	1.08±0.82	5.25±2.14	31.5±2.8
	After	67.5±4.3	0.75±0.57	1.50±1.15	27.3±4.3
Prazosin (25 µg/kg)	Before	62.3±7.2	1.50±1.31	3.50±3.12	25.6±3.0
	After	42.0±7.8	1.50±1.15	4.17±2.99	17.2±3.1
Prazosin (75 µg/kg)	Before	51.5±11.0	1.42±0.86	4.67±2.13	21.1±4.3
	After	37.0±4.2	4.58±1.74*	45.58±18.97*	24.1±4.1
Prazosin (225 µg/kg)	Before	79.8±21.4	0.50±0.22	5.33±2.33	29.6±7.2
	After	48.0±14.8	1.50±0.72	27.00±18.78*	20.9±6.4
Prazosin (600 µg/kg)	Before	60.3±6.5	0.00±0.00	0.00±0.00	24.1±2.6
	After	33.8±2.7*	1.17±0.53*	19.92±5.33*	17.3±3.2
Methoxamine (0.1 mg/kg)	Before	48.2±6.9	0.50±0.34	6.67±4.34	20.5±3.2
	After	50.0±7.7	0.50±0.22	9.00±8.21	21.0±2.7
Methoxamine (0.2 mg/kg)	Before	59.0±13.7	1.50±0.62	21.33±8.76	26.6±5.3
	After	57.0±14.5	0.50±0.34	19.00±17.83	25.3±4.2
Methoxamine (0.5 mg/kg)	Before	67.3±9.6	0.58±0.41	2.83±2.14	27.5±3.8
	After	70.8±15.3	1.00±0.68	3.33±2.17	28.8±6.0
Methoxamine plus prazosin	Before	61.1±10.1	0.17±0.17	0.33±0.33	24.5±4.1
	After	35.6±7.9	2.67±1.12‡	37.00±15.78‡	18.2±2.4

Data shown are the mean±SEM of six dogs for each treatment. Locomotor activity was measured using an open field divided into 25 squares (see Methods). The number of times the dogs crossed a line separating two squares in 2.5 min was counted. The raw number (number of crossings) was also expressed by minute of wake to distinguish changes in this parameter due to a change in cataplexy. The mean number and duration of spontaneous attacks that occurred during the test are also reported. Statistical analysis is described in Methods. $P < 0.05$: Statistical dose-dependent increase in spontaneous cataplexy after prazosin (overall analysis of variance on repeated measures with placebo and prazosin doses as grouping factors). * $P < 0.05$ vs. placebo. ‡ $P < 0.05$ vs. methoxamine.

during all the drug-free tests (six dogs, $n = 150$, $r^2 = 0.554$, $P < 10^{-9}$) with a constant (extrapolation of elapsed time when the number of attacks is zero) of 15.81±2.71 s (mean±SEM) and a slope (approximates the mean duration of one cataplectic attack) of 8.76±0.65 s (mean±SEM). Similarly, the time spent in cataplexy during the locomotor activity procedure was correlated with its corresponding number of attacks during the same drug-free tests ($n = 150$, $r^2 = 0.184$, $P < 10^{-7}$). The drug-free number of attacks during FECT (elicited cataplexy) was also slightly correlated with the time spent in cata-

plexy during the locomotor activity test (spontaneous cataplexy) ($n = 150$, $r^2 = 0.035$, $P < 0.05$).

Effect of prazosin on the cataplexy of homozygous Dobermans. The first compound tested on cataplexy was prazosin, a very selective alpha-1 adrenergic receptor antagonist (22, 23) that easily crosses the blood brain barrier (24). Prazosin is the most potent cataplexy-inducing compound we have yet tested. Dosages as low as 75 µg/kg p.o. lead to a long-lasting (up to 8 h) exacerbation of cataplexy during FECT (number of attacks and elapsed time, Table I) in all homozygous Dobermans

Table III. Cardiovascular Changes Induced by Prazosin and Methoxamine

		Heart rate	SBP	DBP
		beats/min	mmHg	
Controls (n = 4)				
Placebo	Before	115.0±4.0	170.0±4.0	108.8±9.2
	After	122.8±2.6	170.0±7.9	105.0±7.4
Prazosin (600 µg/kg)	Before	120.0±4.1	165.0±6.5	106.3±11.1
	After	137.5±7.8	147.5±10.3*	81.3±6.6‡
Heterozygotes (n = 4)				
Placebo	Before	126.0±2.7	175.0±11.9	93.8±3.8
	After	126.0±1.2	177.5±10.9	92.5±6.3
Prazosin (600 µg/kg)	Before	121.5±4.1	172.5±8.5	95.0±6.5
	After	151.5±6.9	147.5±11.1‡	72.5±4.8‡
Homozygotes (n = 6)				
Placebo	Before	126.8±6.0	171.7±8.3	98.3±8.2
	After	123.3±9.9	171.7±8.0	101.7±7.6
		P < 0.05	P < 0.01	P < 0.05
Prazosin (2.5 µg/kg)	Before	108.8±6.1	178.3±10.1	92.5±4.8
	After	115.0±6.7	177.5±8.2	95.8±5.4
Prazosin (7.5 µg/kg)	Before	127.7±7.1	181.7±8.0	86.7±4.4
	After	125.7±7.1	175.0±7.5	86.7±4.0
Prazosin (25 µg/kg)	Before	120.0±10.2	184.2±7.0	90.0±4.3
	After	116.0±11.4	179.2±6.6	83.3±5.6
Prazosin (75 µg/kg)	Before	136.0±10.1	169.2±8.1	92.5±4.2
	After	160.0±8.5*	156.7±4.9	85.0±5.0
Prazosin (225 µg/kg)	Before	132.0±8.5	179.2±9.3	87.5±4.0
	After	178.0±10.2*	157.5±6.8*	74.2±3.3‡
Prazosin (600 µg/kg)	Before	119.8±7.6	165.0±4.1	96.7±7.4
	After	135.7±8.4*	141.7±6.9‡	81.7±7.6*
Methoxamine (0.1 mg/kg)	Before	130.0±5.9	177.5±7.9	100.8±6.9
	After	141.0±10.2	174.2±7.8	90.0±3.4
Methoxamine (0.2 mg/kg)	Before	136.0±9.1	175.8±10.0	89.2±4.2
	After	110.0±9.5	181.7±11.2	98.3±1.7
Methoxamine (0.5 mg/kg)	Before	122.0±8.4	170.0±5.9	96.7±1.7
	After	115.0±9.7	174.2±6.3	101.7±4.0
Methoxamine (0.5 mg/kg) plus	Before	118.3±4.1	175.8±6.2	89.2±4.4
prazosin (600 µg/kg)	After	115.3±10.2	171.7±6.1§	88.3±4.2

Data shown are the mean±SEM. Systolic and diastolic BP and HR were taken by an auscultatory method. Schedules of drug administration and statistical procedures are described in the text. $P < 0.05$ and $P < 0.01$: Statistical dose-dependent changes in HR and BP (overall analysis of variance on repeated measures with placebo and prazosin doses as grouping factors). * $P < 0.05$ vs. placebo. ‡ $P < 0.01$ vs. placebo. § $P < 0.05$ vs. prazosin.

tested. Prazosin even triggered attacks in the oldest animal of our group, who normally showed no cataplexy during FECT. The dose dependence of the effect of prazosin on FECT was calculated on the mean of the three postdrug data points collected after various doses of prazosin (2.5–600 µg/kg). This mean effect is shown on Fig. 1. A high correlation was obtained between the effect of prazosin on the number of attacks or the elapsed time and the logarithm of the prazosin dose [number of attacks vs. log (dose of prazosin): $n = 36$ (six dogs × six doses), $r^2 = 0.760$, $P < 10^{-9}$; elapsed time vs. log (dose of prazosin): $n = 36$, $r^2 = 0.702$, $P < 10^{-9}$]. Estimations of the maximal effects and ED_{50} for the number of attacks were $E_{max} = 12.49$ attacks, $ED_{50} = 73.55$ µg/kg (correlation between pa-

rameters estimates $r = 0.787$, $n = 36$) and for elapsed time were $E_{max} = 159.9$ s, $ED_{50} = 97.61$ µg/kg (correlation between parameters estimates $r = 0.800$, $n = 36$). Prazosin was also able to increase the number of cataplectic attacks and the time spent in cataplexy during simple observation without emotional stimuli (locomotor activity measurements, Table II). The drug also produced a significant decrease in the number of line crossings by the narcoleptic dogs during the locomotor activity test (Table II), but the effect disappeared when the number of crossings was corrected for the time the dogs were awake (Table II). A correlation was obtained between the effect of a given dose of prazosin on the number of attacks or the time spent in cataplexy during the locomotor activity test and

Table IV. *Cardiovascular Effects of Monoaminergic and Cholinergic Drugs*

		HR	SBP	DBP
		beats/min	*mmHg*	
Placebo	Before	125.8±5.3	168.3±6.3	94.2±4.9
	After	130.2±9.7	168.8±4.6	95.4±3.4
Prazosin (*600 µg/kg*)	Before	119.8±7.6	165.0±4.1	96.7±7.4
	After	135.7±8.4*	141.7±6.9‡	81.7±7.6*
Hydralazine	Before	122.0±2.7	175.0±11.9	93.3±8.1
	After	236.9±16.4§	146.7±8.7*	70.6±4.5*
Metaraminol	Before	119.0±6.8	165.8±8.9	86.7±3.3
	After	91.0±7.0*	193.3±4.0*	112.5±8.6*
Metaraminol + Pz	Before	127.0±9.4	170.8±9.5	95.8±4.4
	After	112.3±9.4	172.5±8.3‖	89.2±3.8
Nisoxetine	Before	131.0±8.1	176.7±9.6	79.2±4.9
	After	130.0±9.9	179.2±9.4	75.0±1.8
Nisoxetine + Pz	Before	126.0±8.2	174.2±14.0	81.7±6.0
	After	150.0±8.8¶	145.0±8.5	63.3±4.8
Protriptyline	Before	137.0±10.5	177.5±11.2	77.5±3.1
	After	128.0±10.5	185.0±13.2	85.0±6.7
Protriptyline + Pz	Before	133.0±12.3	186.7±9.1	79.2±4.9
	After	178.7±16.6**	154.2±9.5	70.0±5.0
Dextroamphetamine	Before	128.7±11.7	175.0±9.2	90.8±4.9
	After	134.3±20.8	192.5±8.0*	96.7±5.9
Dextroamphetamine + Pz	Before	128.0±10.8	179.2±11.6	93.3±4.8
	After	161.0±16.3	170.8±12.5‖	84.2±2.7
Atropine	Before	132.7±12.5	175.0±10.3	96.7±8.7
	After	207.0±22.1‡	164.2±8.4	96.7±4.9
Atropine + Pz	Before	129.7±13.2	166.7±11.4	94.2±5.2
	After	190.0±17.5	145.8±7.1	79.2±2.7
Methylatropine	Before	123.7±9.2	173.3±10.4	90.0±5.3
	After	243.3±26.7‡‡	182.5±14.7	105.0±4.1
Methylatropine + Pz	Before	119.3±13.9	169.2±9.0	95.8±3.3
	After	221.3±16.2	141.7±8.4	79.2±3.3

Data shown are the mean±SEM of six narcoleptic dogs for each treatment. BP and HR were taken by an auscultatory method. Schedules of drug administration and statistical procedures are described in the text. Pz, * $P < 0.05$ vs. placebo. ‡ $P < 0.01$ vs. placebo. § $P < 0.001$ vs. placebo. ‖ $P < 0.05$ vs. prazosin. ¶ $P < 0.05$ vs. nisoxetine. ** $P < 0.05$ vs. protriptyline. ‡‡ $P < 10^{-4}$ vs. placebo.

the logarithm of the prazosin dose [number of attacks vs. log (dose of prazosin): $n = 36$, $r^2 = 0.270$, $P < 0.001$; time spent in cataplexy vs. log (dose of prazosin): $n = 36$, $r^2 = 0.256$, $P < 0.01$]. Estimations of the maximal effects and ED$_{50}$ for the number of attacks were $E_{max} = 1.71$ attacks, ED$_{50} = 30.99$ µg/kg (correlation between parameters estimates $r = 0.833$, $n = 36$) and for time spent in cataplexy were $E_{max} = 28.13$ s, ED$_{50} = 35.34$ µg/kg (correlation between parameters estimates $r = 0.644$, $n = 36$).

Effect of prazosin on BP and HR. Prazosin taken orally produced a dose-dependent decrease in SBP and DBP and a dose-dependent increase in HR (Table III). Estimations of the maximal effects and ED$_{50}$ for SBP, DBP, and HR were, respectively, $E_{max} = 27.00$ mmHg, ED$_{50} = 75.59$ µg/kg (correlation between parameters estimates $r = 0.913$, $n = 36$), $E_{max} = 17.06$ mmHg, ED$_{50} = 74.22$ µg/kg (correlation between parameters estimates $r = 0.748$, $n = 36$), and $E_{max} = 33.88$ beats/min, ED$_{50} = 60.32$ µg/kg (correlation between parameters estimates $r = 0.616$, $n = 36$). 600 µg/kg prazosin p.o. also produced a

statistical decrease in SBP and DBP and an increase in HR in the control and heterozygous Dobermans (Table III). The magnitude of changes appeared similar in the three groups of animals (homozygous, heterozygous, and control dogs) (Table III).

Effect of prazosin on FECT in control and heterozygous Dobermans. Prazosin had a noticeable effect on BP (see above) and control experiments were then needed to eliminate the role of the cardiovascular system in the effect observed on FECT. Control and heterozygous Dobermans did not present any spontaneous or emotionally induced cataplectic attacks and were able to eat all the pieces of food in < 20 s (Table I and II). Prazosin, at a dose of 600 µg/kg (7 to 20 times the ED$_{50}$ in narcoleptic dogs), did not produce any cataplectic attacks in these normal dogs, despite the fact that potent vasodilation and hypotension were observed (Table III) as a consequence of the blockade of alpha-1 vascular receptors (25).

Effect of BP changes on cataplexy. That hypotension did not induce cataplexy in normal dogs did not, however, exclude
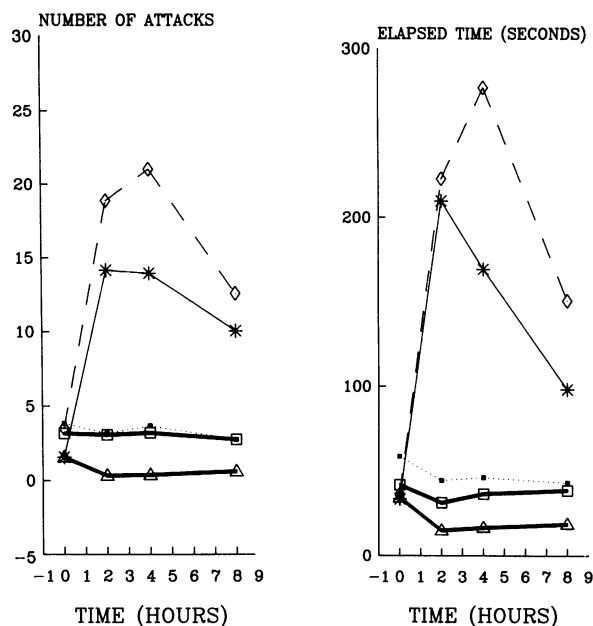
NUMBER OF ATTACKS

ELAPSED TIME (SECONDS)

TIME (HOURS)

TIME (HOURS)

Figure 2. Effect of placebo, prazosin (600 μg/kg p.o.), metaraminol (0.1 mg/kg i.m.), or prazosin plus metaraminol on cataplexy in homozygous Dobermans. Cataplexy was measured using the FECT (see Methods and Fig. 1). Data shown are the mean of 6 narcoleptic Dobermans for each treatment. SEM have been omitted for the clarity of the figure. Placebo, prazosin (Pz), and hydralazine were given *per os* just after the baseline testing ($t = 0$ h). Metaraminol was injected intramuscularly 1 h after the first testing. Comparisons between groups were made using analysis of variance. Statistical procedures are described in detail in Methods. Number of attacks: $P < 10^{-7}$ prazosin vs. placebo; $P < 0.05$ hydralazin vs. placebo; $P < 10^{-6}$ Pz + metaraminol vs. metaraminol. Elapsed time: $P < 10^{-7}$ prazosin vs. placebo; $P < 10^{-5}$ Pz + metaraminol vs. metaraminol. ➤, prazosin; ⊟, placebo; ⊿, hydralazine; ⊖, pz + metaraminol; ···■···, metaraminol.

the possibility that changes in BP might improve or aggravate cataplexy in the narcoleptic Dobermans. Some complementary experiments directly addressed this issue. We examined the effect of peripheral vasoconstriction induced by metaraminol, an alpha-1 stimulant with no central effect (26-28) on cataplexy. Administration of metaraminol induced hypertension and bradycardia (Table IV) and did not change cataplexy (Fig. 2), demonstrating that peripheral alpha-1 stimulation does not explain the beneficial effects of methoxamine. We also tried to dissociate the central from the peripheral alpha-1 effects by administering prazosin in the absence and presence of metaraminol to counteract the hypotensive effect of prazosin (25). The two drug regimens effectively normalized the blood pressure (Table IV), whereas the aggravation of spontaneous and food-elicited cataplexy induced by prazosin persisted (Fig. 2, Table V). These results demonstrate that the peripheral cardiovascular effects have little participation in the overall anticataplectic effect of the centrally acting drugs described in this work. A last control experiment examined the effect of another potent hypotensive agent, hydralazine (29), on cataplexy. Administration of hydralazine induced hypotension and tachycardia (Table IV) without large changes in cataplexy (Fig. 2). A statistically significant improvement was even noticed after hydralazine administration (Fig. 2).

Effect of methoxamine alone and associated with prazosin. Methoxamine was selected as a central alpha-1 receptor agonist because it crosses the blood brain barrier (13) and has been reported to have some effect on REM sleep (14, 30). Methoxamine also has some other pharmacological properties, such as a beta-blocking action (27), which cannot be neglected in vivo. Methoxamine improved number of attacks and elapsed time on the FECT when administered at 0.5 mg/kg i.m. (Table I). A combination of methoxamine (0.5 mg/kg i.m.) and prazosin (600 μg/kg p.o.) did not modify blood pressure and HR (Table III), but did increase elicited and spontaneous cataplexy similar to that obtained with prazosin alone (Table I and II), confirming the alpha-1 mediation of the methoxamine effect (Tables I and II).

Effect of dextroamphetamine, nisoxetine, and protriptyline alone and associated with prazosin. Dextroamphetamine alone significantly decreased cataplexy during FECT (Fig. 3), increased locomotor activity (number of crossings, even when corrected for the time spent in cataplexy and sleep/number of crossings by minute of wake) (Table V) and produced systolic hypertension (Table IV). Nisoxetine and protriptyline also decreased food-elicited cataplexy (Fig. 3) but did not change cardiovascular parameters and locomotor activity significantly (Table IV and V). Dextroamphetamine, nisoxetine, or protriptyline when combined with prazosin (600 μg/kg p.o.) produced a large increase of spontaneous and elicited cataplexy similar to the one obtained with prazosin alone (Fig. 3, Table V). Coadministration of dextroamphetamine with prazosin also reduced the hypotension produced by the alpha-1 blocking agent (Table IV).

Effect of prazosin in combination with atropine and methylatropine. As expected from the literature, atropine, which crosses the blood-brain barrier, ameliorated food-elicited cataplexy (Fig. 4, Table V), whereas methylatropine, a peripheral anticholinergic drug, was ineffective on FECT (Fig. 4). Both compounds produced tachycardia but did not modify significantly SBP or DBP (Table IV). The aggravating effect of prazosin (600 μg/kg p.o.) on elicited and spontaneous cataplexy was completely abolished by a coadministration of atropine (Fig. 4, Table V) and the combination of both drugs even improved the dogs, as did atropine alone (Fig. 4). On the other hand, methylatropine, when associated with prazosin, did not modify the prazosin effect, and the combination of both drugs aggravated the dogs, as did prazosin alone (Fig. 4). Atropine and methylatropine both produced a similar tachycardia when associated with prazosin (Table IV).

Discussion

Alpha-1 adrenoceptors are widely distributed within the central nervous system (31), but little is known about their physiological role. Alpha-1 adrenergic agents have no overt central effects in waking animals (26, 32, 33) and humans (34), and reports conflict over their effects on REM sleep (12-16, 30). Our data demonstrate a crucial role of these receptors in canine narcolepsy, which is considered an animal model of human narcolepsy.

The canine disorder, documented since 1973, presents striking clinical similarities to its human counterpart. The animals have been shown to be abnormally sleepy (18, 19) and to have fragmented sleep/wake patterns (19). Furthermore, the dogs show loss of muscle tone during feeding, playing, or sex-

Table V. Effect of Monoaminergic and Cholinergic Drugs on Locomotor Activity and Spontaneous Cataplexy

		No. of crossings	No. of attacks	Time spent in cataplexy	No. of crossings per minute of wake
				s	min^{-1}
Placebo	Before	62.3±9.6	0.92±0.46	5.92±3.9	26.4±4.4
	After	46.5±9.1	0.63±0.30	5.92±3.2	19.5±3.9
Prazosin (*600 µg/kg*)	Before	60.3±6.5	0.00±0.00	0.00±0.00	24.1±2.6
	After	33.8±2.7*	1.17±0.53*	19.92±5.33*	17.3±3.2
Hydralazine	Before	75.5±14.4	0.17±0.11	0.33±0.21	30.3±5.7
	After	70.0±14.5	0.08±0.08	0.17±0.17	28.1±5.8
Metaraminol	Before	64.7±10.5	0.83±0.40	11.00±7.31	32.4±4.8
	After	59.8±6.8	1.50±0.72	10.67±5.55	31.4±3.1
Metaraminol + Pz	Before	73.7±14.3	1.42±1.23	22.25±17.2	36.4±5.8
	After	24.5±4.4	3.08±0.97[‡]	43.83±19.0	16.8±2.1
Nisoxetine	Before	71.2±9.7	0.33±0.11	10.67±6.77	30.1±3.2
	After	84.4±17.2	0.00±0.00	0.00±0.00	33.8±6.9
Nisoxetine + Pz	Before	71.7±8.5	0.33±0.21	5.33±3.51	30.0±3.9
	After	33.3±8.3	1.83±0.78[§]	34.17±15.89[‖]	17.4±3.0
Protriptyline	Before	79.0±10.7	0.67±0.33	6.50±3.91	33.2±4.9
	After	78.3±10.1	0.33±0.21	6.67±6.28	33.2±4.4
Protriptyline + Pz	Before	63.5±8.7	0.00±0.00	0.00±0.00	25.4±3.2
	After	43.7±12.1	2.17±1.01[¶]	40.17±11.45[¶]	25.3±6.9
Dextroamphetamine	Before	64.2±10.3	0.67±0.49	5.00±3.26	26.5±4.0
	After	117.7±22.0**	0.00±0.00	0.00±0.00	47.1±8.8[‡‡]
Dextroamphetamine + Pz	Before	58.7±12.9	1.75±1.01	12.42±7.54	26.1±5.8
	After	18.2±1.2[§§]	7.58±3.00[‖‖]	75.42±19.21[‖‖]	21.1±5.6
Atropine	Before	78.8±11.9	1.58±1.05	3.83±2.43	32.4±4.8
	After	78.5±7.9	0.08±0.08	0.17±0.17	31.4±3.1
Atropine + Pz	Before	56.0±9.1	1.50±0.88	5.83±3.38	23.8±4.5
	After	63.8±4.4[¶¶]	0.25±0.25***	0.50±0.50[‡‡‡]	25.6±1.8
Methylatropine	Before	59.2±10.1	0.92±0.58	1.83±1.17	24.0±4.0
	After	57.2±11.8	0.67±0.49	1.33±0.99	23.0±4.7
Methylatropine + Pz	Before	60.7±6.9	0.33±0.25	0.67±0.49	24.4±2.8
	After	54.7±14.4	2.58±1.25***	16.92±9.01***	25.8±7.5

Data shown are the mean±SEM of six narcoleptic dogs. Methods and statistical procedures are described in legend to Table II. * $P < 0.05$ vs. placebo. [‡] $P < 0.05$ vs. metaraminol. [§] $P < 0.05$ vs. nisoxetine. [‖] $P < 0.01$ vs. nisoxetine. [¶] $P < 0.01$ vs. protriptyline. ** $P < 0.01$ vs. placebo. [‡‡] $P < 0.05$ vs. placebo. [§§] $P < 10^{-5}$ vs. amphetamine. [‖‖] $P < 10^{-4}$ vs. amphetamine. [¶¶] $P < 0.05$ vs. atropine. *** $P < 0.05$ vs. methylatropine. [‡‡‡] $P < 0.05$ vs. prazosin.

ual intercourse, a state akin to human cataplexy and similarly generated in an emotional context (8, 17). A familial pattern of narcolepsy has been clearly established in humans but the genetic mechanisms are poorly understood. The causes may be multifactorial, or a single dominant gene with low penetrance may be involved. The canine syndrome is known to affect various breeds of dogs with different genetic mechanisms (8). Doberman pinschers and Labrador retrievers transmit narcolepsy to their offspring through an autosomal recessive mechanism. Narcoleptic poodles and Dobermans are improved by the classical treatments used in human narcolepsy (8).

That prazosin and methoxamine respectively aggravate and improve cataplexy suggested central alpha-1 adrenergic control of canine narcolepsy, but additional experiments were needed to exclude any participation of peripheral alpha-1 blockade in the observed effects. We therefore showed that prazosin was still able to elicit cataplexy under normal blood pressure conditions (when associated with peripheral sympathomimetic drugs) and that administration of another hypotensive agent, hydralazine, did not increase cataplexy. A slight improvement of cataplexy was even obtained after hydralazine. A possible explanation of this observation may be found in the recent work of Lai et al. (7). These authors have examined the effect of pharmacological manipulations of blood pressure on muscle hypotonia induced by stimulation of the medial medulla in the decerebrate cat (generally considered akin to REM sleep loss of motor tone). Experiments were also performed on a single narcoleptic dog. The findings of Lai et al. indicate a beneficial effect of blood pressure decrease on both medial medulla-induced muscle atonia and cataplexy. These results implicate a role of the autonomic cardiovascular system in the expression of cataplexy and confirmed that the effects observed after prazosin are not due to peripheral alpha-1 blockade.
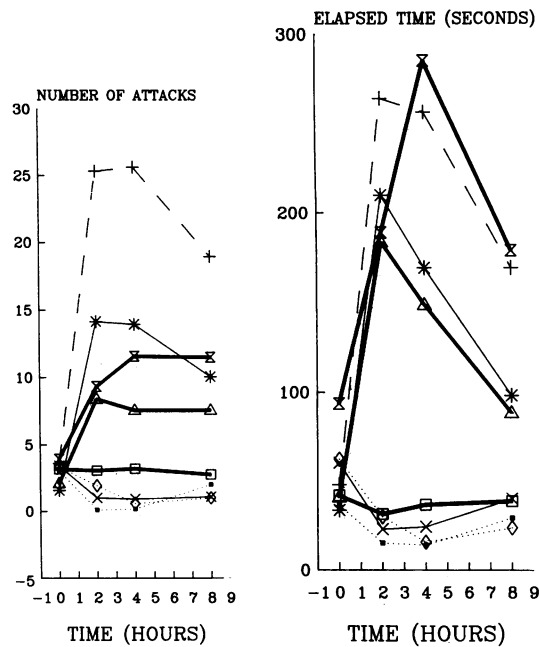
Figure 3. Effect of placebo, dextroamphetamine (0.5 mg/kg p.o.), nisoxetine (0.5 mg/kg p.o.), and protriptyline (1.2 mg/kg p.o.) alone and in combination with prazosin (600 μg/kg p.o.) on cataplexy in narcoleptic Dobermans. Prazosin (Pz) and protriptyline were administered just after the first test. Nisoxetine and dextroamphetamine were given 1 h after the first testing. Data are the mean of six dogs for each treatment. Methods are described in the legend to Fig. 1 and in the text. Number of attacks: $P < 10^{-7}$ prazosin vs. placebo; $P < 0.001$ dextroamphetamine vs. placebo; $P < 0.05$ nisoxetine vs. placebo; $P < 0.05$ protriptyline vs. placebo; $P < 10^{-4}$ Pz + protriptyline vs. protriptyline; $P < 0.001$, Pz + protriptyline vs. prazosin; $P < 10^{-8}$ Pz + dextroamphetamine vs. dextroamphetamine; $P < 10^{-7}$ Pz + nisoxetine vs. nisoxetine. Elapsed time: $P < 10^{-7}$ prazosin vs. placebo; $P < 0.01$ dextroamphetamine vs. placebo; $P < 0.05$ nisoxetine vs. placebo; $P < 0.01$ protriptyline vs. placebo; $P < 10^{-8}$ Pz + protriptyline vs. protriptyline; $P < 10^{-8}$ Pz + dextroamphetamine vs. dextroamphetamine; $P < 10^{-8}$ Pz + nisoxetine vs. nisoxetine. --•--, prazosin; -ᴇ-, placebo; ···■···, dextroamphetamine; -+·, pz + d-amphetamine; -×-, nisoxetine; ···◇···, protriptyline; -▲-, pz + protriptyline; -⬛-, pz + nisoxetine.

Figure 4. Effect of placebo, atropine (0.1 mg/kg i.m.), and methylatropine (0.1 mg/kg i.m.) alone and in combination with prazosin (600 μg/kg p.o.) on cataplexy in narcoleptic Dobermans. Prazosin (Pz) was administered just after the first test. Atropine and methylatropine were given 1 h after the first testing. Data are the mean of six dogs for each treatment. Methods are described in the legend to Fig. 1 and in the text. Number of attacks: $P < 10^{-7}$ prazosin vs. placebo; $P < 0.05$ atropine vs. placebo; $P < 10^{-8}$ Pz + atropine vs. prazosin; $P < 0.001$ Pz + methylatropine vs. methylatropine. Elapsed time: $P < 10^{-7}$ prazosin vs. placebo; $P < 10^{-8}$ Pz + atropine vs. prazosin; $P < 0.01$ Pz + methylatropine vs. methylatropine. --•--, prazosin; -ᴇ-, placebo; -▲-, atropine; -⊕·, pz + atropine; ···■···, methylatropine; ···+···, pz + methylatropine.

We also antagonized the effect of some classical nonspecific therapeutic agents (amphetamine, protriptyline, and nisoxetine) with prazosin, suggesting that, as proposed in the rationale of the study, these drugs could improve narcolepsy by a presynaptic increase in central noradrenergic activity, which then stimulates alpha-1 receptors.

The importance of pontine central cholinergic transmission in REM sleep regulation has been extensively investigated by general pharmacology and local brainstem stimulation (2–7). Cholinergic neurons of the dorsal pontine tegmentum tonically inhibit muscle tone during REM sleep (2–3, 7). Consistent with these anatomical findings, central cholinergic stimulation by physostigmine or arecoline has been reported to aggravate the symptoms in narcoleptic dogs, whereas central anticholinergic drugs, such as atropine or scopolamine, improve them (8). This well-known effect of atropine is shown in Fig. 4 in our group of narcoleptic dogs. This effect is centrally mediated, since methylatropine, a selective peripheral
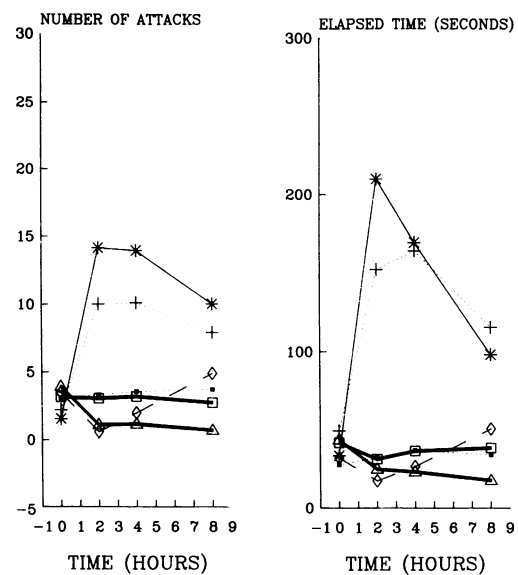
anticholinergic drug, does not modify FECT (Fig. 4). If alpha-1 adrenergic receptors are mainly implicated in narcolepsy, one may ask whether these mechanisms are integrated with these cholinergic mechanisms (i.e., does the monoaminergic system control the cholinergic system or do both systems work in parallel and independently?). To answer this question, we examined the coadministration of prazosin with both atropine and methylatropine, to rule out any peripheral interaction. Atropine, but not methylatropine, completely suppressed the effects of prazosin (Fig. 4). The integrity of a central cholinergic synapse thus is needed for the expression of prazosin effects.

A role for norepinephrine in REM sleep regulation has been documented for many years (9–11). Our data increase the understanding of this monoaminergic control. The very drastic impact of prazosin on our dogs has to be emphasized again: it is the most potent drug that we have ever manipulated. It induces a state close to the human status cataplecticus (1). We also provide evidence for a unknown physiological role of central alpha-1 adrenoceptors: the control of cataplexy, a pathological manifestation of the physiological REM sleep atonia. Results of this work should stimulate the search for more specific alpha-1 adrenergic central agents. These compounds, if available, could improve human narcolepsy treatment and might help us to understand and manipulate abnormal REM sleep patterns of other pathologies, such as depression.

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