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# Dopamine $D_2$ Mechanisms in Canine Narcolepsy

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**Narcolepsy is a sleep disorder characterized by abnormal manifestations of rapid-eye-movement (REM) sleep and excessive daytime sleepiness. Using a canine model of the disease, we found that central $D_2$ antagonists suppressed cataplexy, a form of REM-sleep atonia occurring in narcolepsy, whereas this symptom was aggravated by $D_2$ agonists. The effect on cataplexy was stereospecific for the *S*(−) enantiomer of sulpiride (a $D_2$ antagonist) and the *R*(+) enantiomer of 3-PPP (a $D_2$ agonist). There was also a significant correlation between the *in vivo* pharmacological potency and *in vitro* drug affinity for $D_2$ receptors (but not for $D_1$ and $\alpha_2$ receptors) among the seven central $D_2$ antagonists tested. Selective $D_1$ compounds were also tested; however, the results were inconsistent because both antagonists and agonists generally suppressed cataplexy. Our current results demonstrate that central $D_2$-type receptors are critically involved in the control of cataplexy and REM sleep. Furthermore, the finding that small doses of $D_2$ antagonists suppressed cataplexy and induced behavioral excitation, while small doses of $D_2$ agonists aggravated cataplexy and induced sedation, suggests that this effect is mediated presynaptically. However, considering the fact that selective dopamine reuptake inhibitors did not modify cataplexy and that our previous pharmacological results demonstrated a preferential involvement of the noradrenergic system in the control of cataplexy, we believe that the effect of $D_2$ compounds on cataplexy is mediated secondarily via the noradrenergic systems.**

Human narcolepsy is an incurable sleep disorder characterized by sleep-onset periods of rapid-eye-movement (REM) sleep, recurring bouts of flaccid muscular paralysis (cataplexy), which are often initiated by emotional stimuli, and excessive daytime sleepiness (Guilleminault, 1976). Canine narcolepsy is a spontaneous animal model of this condition that presents behavioral, pharmacological, and electrophysiological similarities to the human disorder (Baker and Dement, 1985; Mignot et al., 1991). As with primary human narcolepsy, no morphological abnormalities in the CNS have been found in affected canines, and it is therefore suggested that subtle neurochemical dysfunctions are involved in the pathophysiology of this disorder (Baker et al., 1982; Baker and Dement, 1985).

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In the canine model, several neurochemical abnormalities have been found, including fluctuations in the levels of dopamine (DA) and norepinephrine (NE) and their metabolites in the cerebrospinal fluid (Faull et al., 1982) and localized brain regions (Mefford et al., 1983; Miller et al., 1990), and regional upregulations of adrenergic $\alpha_1$, $\alpha_2$, and dopaminergic $D_2$ receptors in the narcoleptic canine CNS (Bowersox et al., 1987; Mignot et al., 1988a; Fruhstorfer et al., 1989). Furthermore, we have studied the effect on cataplexy of various pharmaceutical compounds acting on the central catecholaminergic systems, and have demonstrated a preferential involvement of the noradrenergic system in the control of cataplexy; specifically, enhancing the activity of central noradrenergic systems results in a suppression of cataplexy, while decreased central noradrenergic activity is associated with an aggravation of this symptom (Babcock et al., 1976; Foutz et al., 1981; Mignot et al., 1988a,b; Nishino et al., 1990). In contrast to these clearly demonstrated pharmacological results, the effect of dopaminergic compounds on cataplexy reported in a previous study (Foutz et al., 1981) was inconclusive, and further studies were needed to clarify the role of this monoamine in the modulation of cataplexy. In the present study, by means of both *in vivo* and *in vitro* pharmacological approaches using new selective dopaminergic ($D_1$ and $D_2$) compounds, we have demonstrated that dopamine $D_2$-type receptors are critically involved in the control of cataplexy.

## Materials and Methods

### In vivo *pharmacological studies*

*Animals.* Six genetically narcoleptic Doberman pinschers were used for this study. All dogs were housed in the Stanford University Department of Animal Laboratory Medicine in individual stainless-steel cages (100 × 180 $cm^2$), and all experiments were carried out in strict accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals.* Dogs were fed daily at 9 A.M. and exposed to a 12-hr:12-hr light/dark cycle (lights on at 7 AM, off at 7 PM). Room temperature was maintained at 22.2 ± 1.1°C, and relative humidity, at 40%. Mean age and weight of the six narcoleptic dogs were 3.6 ± 0.6 yr and 27.2 ± 0.8 kg (mean ± SE), respectively.

*Food-Elicited Cataplexy Test.* The Food-Elicited Cataplexy Test (FECT), a standardized biological assay for quantifying the severity of cataplexy, was originally developed by Babcock et al. (1976) and has been successfully used by several investigators to assess symptom severity in narcoleptic canines (Foutz et al., 1981; Mignot et al., 1988b; Nishino et al., 1989, 1990). Food, which is equivalent to an emotional stimulus in humans, precipitates multiple cataplectic attacks in these animals, sometimes resulting in full-blown REM-sleep periods. In our experimental procedure, 12 pieces of wet food (1 $cm^3$) were placed 30 cm apart in a line on the floor. The dogs previously had been trained to eat all pieces of food in serial order. The experimenter recorded the number of cataplectic attacks that occurred while the dog ate the pieces of food and the time required for the dog to eat all 12 pieces of food. FECTs were always administered in duplicate (two tests on the same dog).

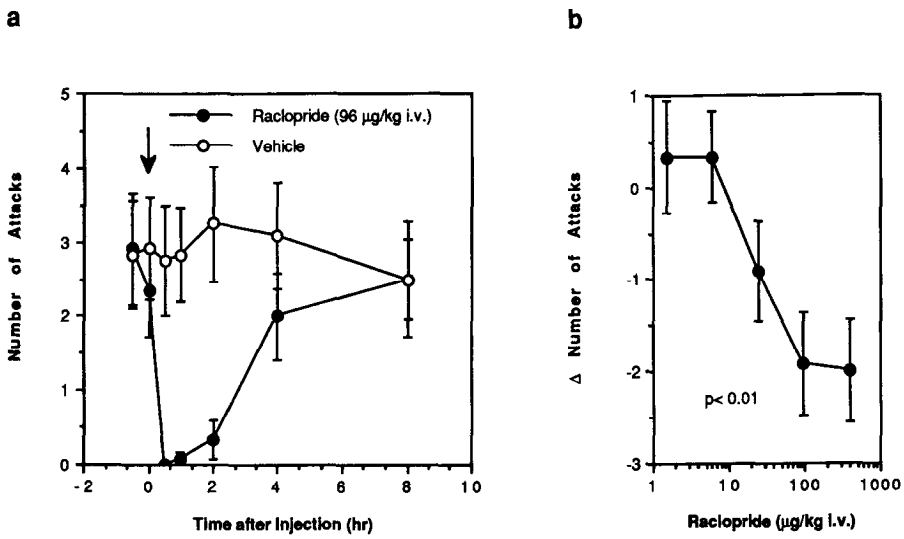


*Figure 1.* Effect of raclopride, a $D_2$ antagonist, on canine cataplexy. Effect on cataplexy was assessed by the FECT. Each *point* represents the mean ± SEM (*vertical bars*) of six narcoleptic dogs. *a*, Time course for the effect of raclopride on cataplexy. Drug or vehicle was injected at time 0 (*arrow*). In the overall model, raclopride significantly suppressed cataplexy ($p < 0.001$, repeated-measures ANOVA with drug treatment as a grouping factor). *b*, Dose–response curve for the effect of raclopride on cataplexy. Drug doses were progressively increased, and the effect on cataplexy was measured after each dose. Significance of dose–response effects ($p < 0.01$) was assessed using a repeated-measures one-way ANOVA.

*Experimental designs.* Two types of experimental design were used: (1) time-course studies in which the long-term effects of the drugs on cataplexy were recorded, and (2) cumulative dose–response experiments in which drug doses were progressively increased and the effect on cataplexy was measured after each dose. A minimum of six drug-free days was allowed for each dog between pharmacological experiments.

For the time-course studies, two baseline FECTs were performed at −0.5 hr (−15 min for quinpirole) and just before (0 hr) drug administration. The drug or vehicle was injected intravenously through the right cephalic vein at 10:30 A.M., and postdrug FECTs were performed 0.5, 1, 2, 4, and 8 hr (5, 15, 30, 60, and 120 min for quinpirole) after drug administration.

In the dose–response studies, an indwelling catheter was implanted in the right cephalic vein at 9:00 A.M. on the day of the experiment, and baseline FECTs were performed. Increasing concentrations of the drug were injected, and cataplexy testing by FECT was performed 30 min (5 min for $D_2$ agonists) after each drug dose. The first drug dose injected was calculated to be pharmacologically inactive, as deduced from the data available in the literature or from drug affinities obtained by radioreceptor binding assays. The drug dose was increased two- or fourfold each time, until a maximal effect on cataplexy was observed on two successive doses, or when interfering side effects (emesis, anorexia, major behavioral changes) were present. The injection volume at each concentration for all drugs was adjusted to 0.2 ml/kg.

In vivo *data analysis.* Results are expressed as mean values ± SEM of six dogs. For the dose–response curve analysis, the significance of drug effects was assessed using a repeated-measures one-way analysis of variance. When dose-dependent drug effects were statistically significant ($p < 0.05$), the maximal effect ($E_{max}$) and the dose producing 50% of the maximal effect [$ED_{50}$ (μg/kg, i.v.)] were calculated by nonlinear regression analysis (Quasi-Newton procedure) on the dose–response curve using the equation $E = E_{max}/(1 + (ED_{50}/\text{dose}))$ as described in Pliska (1987).

For time-course experiments, drug effects were compared with control values (vehicle injection) using a repeated-measures analysis of variance with drug treatment as a grouping factor. All computations were performed using the software program SYSTAT® (Systat Inc., Evanston, IL) on a personal computer.

### In vitro *radio receptor binding assays*

Drug affinities for canine $D_2$, $D_1$, and $\alpha_2$ receptors were assessed by radio receptor binding assay using $^3$H-raclopride (New England Nuclear, Boston, MA; specific activity, 72.7 Ci/mmol), $^3$H-SCH-23390 (Amersham, Arlington Heights, IL; specific activity, 83.0 Ci/mmol), and $^3$H-yohimbine (New England Nuclear; specific activity, 79.5 Ci/mmol) as ligands, respectively. The tissue used for this study was canine caudate (for $D_2$) and frontal cortex (for $D_1$ and $\alpha_2$) obtained from brain tissue purchased from Pel-Freez (Rogers, AR). Brain tissue homogenates were used for receptor binding assays, and the $\alpha_2$, $D_2$, and $D_1$ binding studies were carried out as described in Fruhstorfer et al. (1989) and Hall et al. (1988; with 40 nM of ketanserin for the $D_1$ assay). Specific binding for $D_2$, $D_1$, and $\alpha_2$ receptors was defined as that radioactivity that could be displaced by 1 μM *cis*-flupenthixol, 1 μM (+)-butaclamol, and 0.1 mM (−)-norepinephrine, respectively. Under the above assay conditions, the dissociation constant ($K_d$) (mean ± SEM; $n = 3$) of $^3$H-raclopride (1.93 ± 0.31 nM), $^3$H-SCH-23390 (0.78 ± 0.26 nM), and $^3$H-yohimbine (0.76 ± 0.18 nM) were obtained from saturation studies, and the final concentration of these ligands used for displacement studies ranged from 2.20 to 2.40 nM, from 0.77 to 0.86 nM, and from 0.67 to 0.88 nM, respectively. The data were analyzed using LIGAND (Munson and Rodbard, 1980), an iterative nonlinear least-squares curve-fitting program, with a one-site model. Values were expressed as the mean of three separate determinations for each compound tested.

### *Drugs*

The compounds used for this study were obtained from the following sources: raclopride and *S*(−)- and *R*(+)-sulpiride, Astra Research Center AB, Södertälje, Sweden; UH-232, AJ-76, and U-8617OE, The Upjohn Company, Kalamazoo, MI; haloperidol, pimozide, domperidone, quinpirole, *S*(−)- and *R*(+)-3-PPP, apomorphine, bromocriptine, SKF-83566, SKF-38393, SKF-77437, SKF-82958, (+)-butaclamol, and ketanserin, RBI, Natick, MA; YM-09151-2, Yamanouchi Pharmaceutical Co., Tokyo, Japan; EMD-23448, Merck E, Darmstadt, Germany; SCH-23390, Schering Corp., Bloomfield, NJ; *cis*-flupenthixol, Lundbeck A/S, Copenhagen, Denmark; and (−)-norepinephrine, Sigma Chemical Company, St. Louis, MO. All drug solutions were freshly prepared each experimental day.

## Results

### *Effect of $D_2$ antagonists on cataplexy*

Raclopride, a selective $D_2$ antagonist, produced a significant dose-dependent suppression of cataplexy (Fig. 1*a,b*), and the effect was associated with moderate behavioral excitation, aggressiveness, and tachypnea. The effect on cataplexy occurred within 30 min after drug administration and disappeared within 4 hr after drug administration (Fig. 1*a*). These effects on cataplexy and general behavior were similar to the effects of $\alpha_2$ antagonists and $\alpha_1$ agonists previously reported by our group (Mignot et al., 1988a,b; Nishino et al., 1990). A total of seven centrally active $D_2$ antagonists (YM-09154-2, $ED_{50} = 0.063$ μg/kg, i.v.; haloperidol, $ED_{50} = 0.43$ μg/kg, i.v.; pimozide, $ED_{50} = 10.8$ μg/kg, i.v.; raclopride, $ED_{50} = 32.8$ μg/kg, i.v.; UH-232, $ED_{50} = 329.9$ μg/kg, i.v.; AJ-76, $ED_{50} = 539.6$ μg/kg, i.v.; *S*(−)-sulpiride, $ED_{50} = 1083.0$ μg/kg, i.v.) were found to suppress cataplexy significantly. On the other hand, a peripheral $D_2$ an-

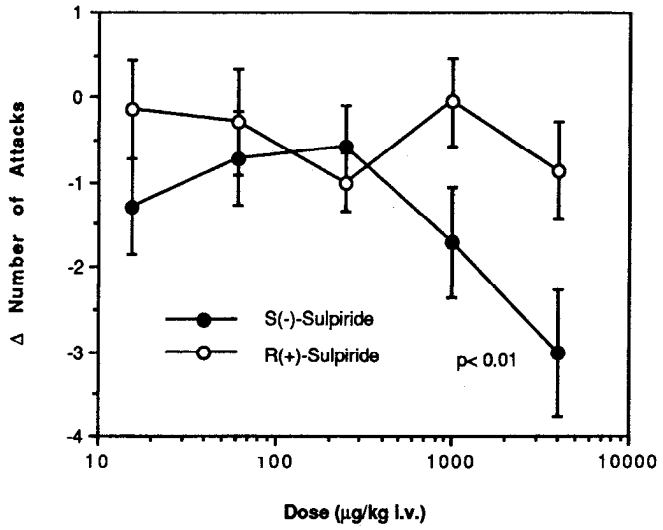


*Figure 2.* Stereospecificity of the effect of *S*(−)- and *R*(+)-sulpiride on cataplexy *in vivo*. Effect on cataplexy was assessed by FECT. Each *point* represents the mean ± SEM (*vertical bars*) of six narcoleptic dogs. Drug doses were progressively increased, and the effect on cataplexy was measured after each dose. Significance of dose–response effects ($p < 0.01$) was assessed using a repeated-measures one-way ANOVA.

tagonist, domperidone, did not modify cataplexy at intravenous doses up to 384.0 μg/kg. The effects of $D_2$ antagonists on cataplexy were stereoselective for the enantiomers of sulpiride; *S*(−)-sulpiride suppressed cataplexy, while *R*(+)-sulpiride had no effect on cataplexy across the dose range tested (15.7–4000.0 μg/kg, i.v.; Fig. 2).

*Effect of $D_2$ agonists on cataplexy*

A selective $D_2$ agonist, quinpirole, significantly and dose-dependently aggravated cataplexy (Fig. 3*a,b*). The effect occurred immediately after drug administration, but lasted less than 30 min (Fig. 3*a*). The effect was very dramatic, and all six dogs responded with increased cataplexy at very low doses (<6 μg/kg, i.v.) before the occurrence of emesis, which is considered a classical $D_2$ agonist effect. After the administration of 6 μg/kg of quinpirole, all dogs were sleepy, and three of six dogs had

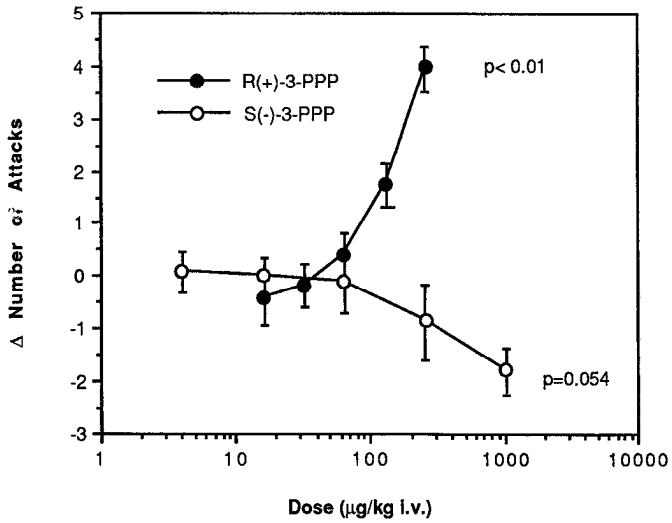


*Figure 4.* Stereospecificity of the effect of *R*(+)- and *S*(−)-3-PPP on cataplexy *in vivo*. For details, see Figure 2 caption.

short-lasting (<5 min) emesis. This compound also induced a significant behavioral sedation, based on assessment of locomotor activity by an open-field measurement described in Nishino et al. (1990); the motor activity had decreased to 18.7% of the predrug activity level at 10 min after drug administration ($p < 0.001$, paired *t* test). The effects of quinpirole on cataplexy and general behavior were similar to the effects of $\alpha_2$ agonists and $\alpha_1$ antagonists reported in our previous studies (Mignot et al., 1988b; Nishino et al., 1990). A total of seven $D_2$ agonists were tested, and five of these (U-86170E, $ED_{50}$ = 2.9 μg/kg, i.v.; apomorphine, $ED_{50}$ = 3.7 μg/kg, i.v.; quinpirole, $ED_{50}$ = 5.1 μg/kg, i.v.; EMD-23448, $ED_{50}$ = 20.3 μg/kg, i.v.; *R*(+)-3-PPP, $ED_{50}$ = 817.7 μg/kg, i.v.) were found to aggravate cataplexy significantly. One potent $D_2$ agonist, bromocriptine (0.18–12.0 μg/kg, i.v.), had no clear effect on cataplexy and induced long-lasting vomiting (up to 8 hr) and anorexia, an effect not observed after administration of other $D_2$ agonists. The cataplexy aggravating effect of *R*(+)-3-PPP was stereospecific because its enantiomer, *S*(−)-3-PPP, instead suppressed cataplexy ($p = 0.054$; Fig. 4).

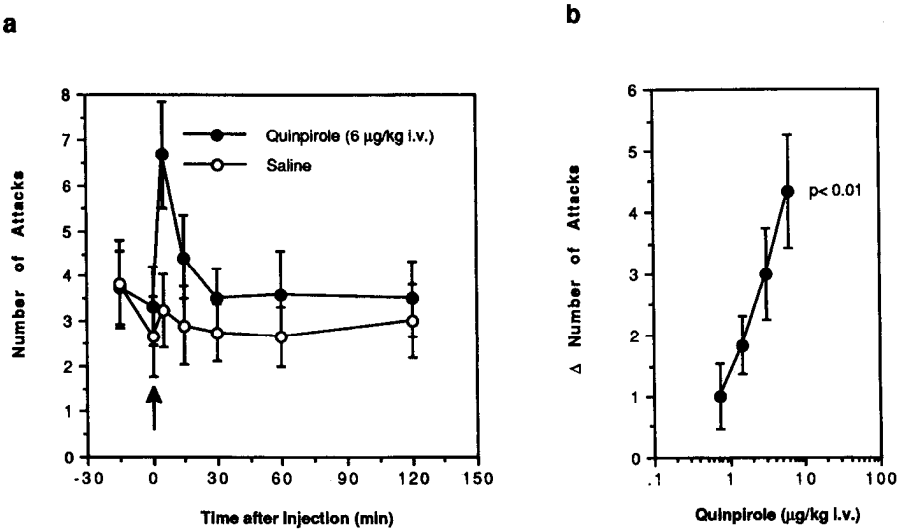


*Figure 3.* Effect of quinpirole, a $D_2$ agonist, on cataplexy. *a,* Time course for the effect of quinpirole on cataplexy. In the overall model, quinpirole significantly aggravated cataplexy ($p < 0.05$). *b,* Dose–response curve for the effect of quinpirole on cataplexy. For details, see Figure 1 caption.

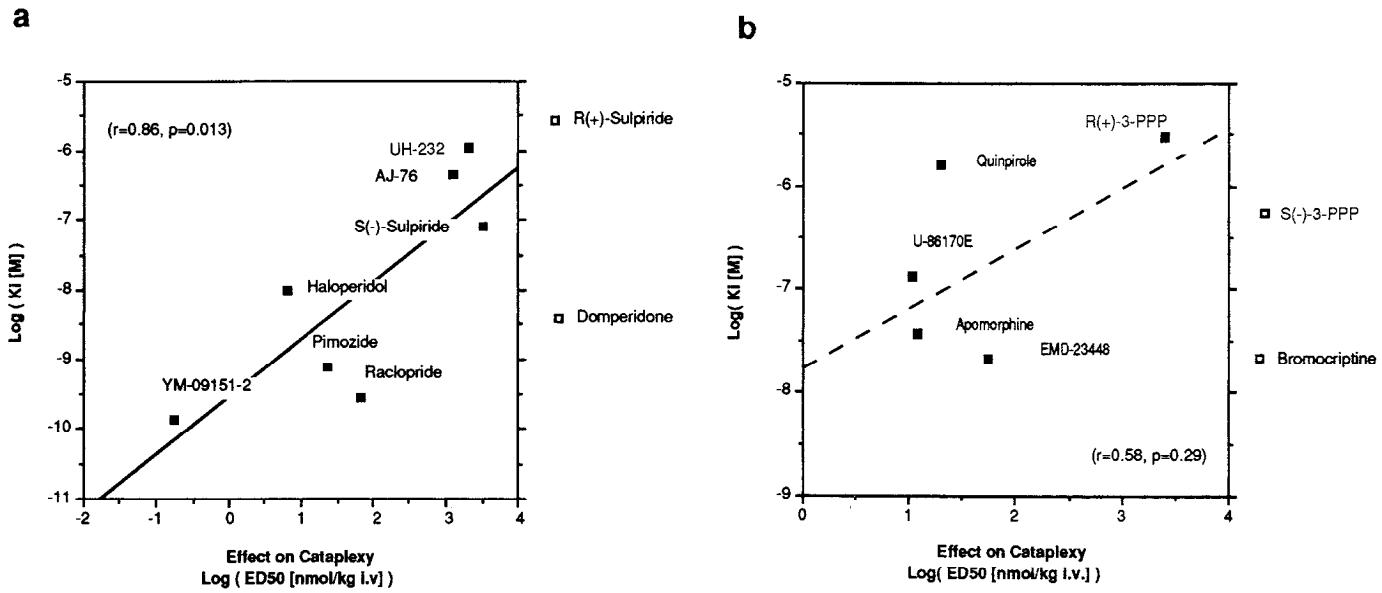


*Figure 5.* Correlation between pharmacological potency on cataplexy *in vivo* and drug affinity for $D_2$ receptors *in vitro*. When dose-dependent drug effects were statistically significant by the ANOVA, $ED_{50}$ (nmol/kg, i.v.) and $E_{max}$ were calculated by nonlinear regression analysis (Quasi-Newton procedure) on the dose–response curve using the equation $E = E_{max}/(1 + (ED_{50}/\text{dose}))$ as described in Pliska (1987). Drugs indicated by *solid squares* had a significant effect on cataplexy, while drugs indicated by *open squares* had no significant effect under the dose range tested. Drug affinities for canine $D_2$ receptors were assessed by radio receptor binding assay using $^3$H-raclopride as a ligand, as described in Materials and Methods. *a,* Correlation between effect on cataplexy and drug affinities among seven central $D_2$ antagonists. The enantiomer of *S*(−)-sulpiride, *R*(+)-sulpiride, had no effect on cataplexy at doses as high as log(nmol/kg, i.v.) = 4.1. The peripheral $D_2$ antagonist domperidone did not modify cataplexy at doses up to log(nmol/kg, i.v.) = 3.0. *b,* Correlation between effect on cataplexy and drug affinities among five central $D_2$ agonists. *S*(−)-3-PPP and bromocriptine did not modify cataplexy at doses as high as log(nmol/kg, i.v.) = 3.6 and 1.3, respectively.

This effect of *S*(−)-3-PPP may be related to a partial agonist property, as suggested by Clark et al. (1985). Our observation that *S*(−)-3-PPP (4.0–1024.0 μg/kg, i.v.) did not induce emesis in any of the dogs supports this hypothesis.

### *Effect of $D_1$ compounds on cataplexy*

Two selective $D_1$ antagonists and three selective $D_1$ agonists were also tested; however, the results were not consistent for antagonists and agonists. The antagonists (SCH-23390, SKF-83566) and one agonist (SKF-77437) significantly suppressed cataplexy ($ED_{50}$ = 3.2, 21.7, and 227.8 μg/kg, i.v., respectively). These effects were associated with various side effects, such as acute dystonia (following $D_1$ antagonist administration) or anorexia (following $D_1$ antagonist or agonist administration). Furthermore, two other selective $D_1$ agonists, SKF-38393 and SKF-82958, had no clear effect on cataplexy at intravenous doses up to 1024.0 μg/kg and 256.0 μg/kg, respectively.

### *Correlations between* in vivo *effects on cataplexy and* in vitro *drug affinities for receptors*

As shown in Figure 5*a,* a total of seven central $D_2$ antagonists significantly suppressed cataplexy, and there was a significant correlation ($r$ = 0.86; $n$ = 7; $p$ = 0.013) between the $ED_{50}$ for cataplexy *in vivo* and the affinity for $D_2$ receptors *in vitro*. The $ED_{50}$ was not significantly correlated with affinities toward either $D_1$ ($r$ = 0.45; $n$ = 7; $p$ = 0.25) or $\alpha_2$ ($r$ = 0.13, $n$ = 7; $p$ = 0.79) receptors (data not shown). Concerning the effect of $D_2$ agonists, there was a tendency for a positive correlation between the $ED_{50}$ for cataplexy and the affinity for the $D_2$ receptor (Fig. 5*b*) among the five $D_2$ agonists that aggravated cataplexy. This trend, however, was not statistically significant ($r$ = 0.58; $n$ = 5; $p$ = 0.29). Compared to the suppressant effect of $D_2$ antagonists on cataplexy, it was difficult to obtain a maximum enhancing effect for $D_2$ agonists. Higher doses of these drugs induced a dramatic increase in cataplexy (status cataplecticus), and the dogs could not complete the food test. Thus, the calculated $ED_{50}$s for aggravation of cataplexy are probably not as accurate as the $ED_{50}$s for suppression of cataplexy. The binding affinity constant ($K_i$) of most agonists for $D_2$ receptors fell within a narrow range (log[$K_i$M] ranged from −7.9 to −5.8) compared to that of $D_2$ antagonists (log[$K_i$M] ranged from −9.9 to −5.9). This trend may have also made it difficult to obtain a significant correlation between affinity and behavioral effect for $D_2$ agonists. At any rate, the tendency for a positive correlation between the $ED_{50}$ for cataplexy and the affinity for the $D_1$ ($r$ = 0.34; $n$ = 5; $p$ = 0.58) or $\alpha_2$ ($r$ = 0.38; $n$ = 5; $p$ = 0.53) receptor was not statistically significant (data not shown).

## Discussion

In the present study, we found that central dopamine $D_2$ antagonists significantly suppress, whereas most $D_2$ agonists aggravate, canine cataplexy. There was a significant correlation between the *in vivo* pharmacological potency on cataplexy and *in vitro* drug affinities for canine $D_2$ receptors, but not for $D_1$ or $\alpha_2$ receptors, among seven central $D_2$ antagonists. Furthermore, the effect on cataplexy was stereospecific for the *S*(−) enantiomer of sulpiride, a $D_2$ antagonist. These results strongly suggest that the effect on cataplexy was mediated by $D_2$ receptors because both enantiomers penetrate the blood–brain barrier to the same degree (Andersen, 1988) and because the *in vitro* affinity of *S*(−)-sulpiride (log[$K_i$M] = −7.1) for canine $D_2$ receptors is 20 times higher than that of *R*(+)-sulpiride (log[$K_i$M] = −5.9). However, there were reverse stereospecificities for $D_1$ and $\alpha_2$ receptors; the affinity of *S*(−)-sulpiride for $D_1$ (log[$K_i$M] = −4.0)

and $\alpha_2$ receptors ($\log[K_i M] = -5.7$) is lower than that of $R(+)$-sulpiride ($\log[K_i M] = -4.1, -6.2$, respectively). This result suggests that $S(-)$-sulpiride, at least, is not exerting its effect on cataplexy through the $D_1$ or $\alpha_2$ receptor. In contrast to the effect of $D_2$ compounds on cataplexy, the effect of $D_1$ compounds on cataplexy is difficult to interpret because both $D_1$ antagonists and a $D_1$ agonist significantly suppressed cataplexy. This might be due to the lack of structural variation of $D_1$ compounds currently available, because all $D_1$ antagonists and agonists used in this study have a benzazepine structure. Thus, while further studies are necessary to explore the role of $D_1$ mechanisms on cataplexy, this discrepancy of the effect of $D_1$ compounds on cataplexy does not seem to interfere with our interpretation that the effect of $D_2$ compounds on cataplexy is mediated by $D_2$ receptors.

Central DA receptors are located both pre- and postsynaptically (Langer, 1981), and the effect on cataplexy of $D_2$ compounds could be a function of either receptor. However, our finding that small doses of $D_2$ agonists aggravate cataplexy and induce sedation, while $D_2$ antagonists suppress cataplexy and induce behavioral excitation, suggests that "presynaptic dopamine autoreceptors" (regulatory DA receptors through which the DA system controls its own activity) are involved in the control of cataplexy because it has been reported that behavioral sedation and excitation induced, respectively, by small doses of $D_2$ agonists and antagonists are mediated through these receptors (Di Chiara et al., 1976). Similarly, compounds such as AJ-76, UH-232, or $R(+)$-3-PPP, which are reported to act preferentially on presynaptic dopamine autoreceptors (Clark et al., 1985; Piercey and Lum, 1990), also modified cataplexy in the same way as other $D_2$ antagonists and $D_2$ agonists (Fig. 5*a,b*). Furthermore, this hypothesis could explain why bromocriptine did not aggravate cataplexy, because this drug is reported to be less active at presynaptic dopamine autoreceptors (Lehmann et al., 1983). All of the above results suggest an involvement of "presynaptic dopamine autoreceptors" in the regulation of cataplexy and REM sleep. However, we recently found that selective DA uptake inhibitors (GBR-12909 and amineptine) had no effect on canine cataplexy, in contrast to the potent cataplexy-suppressing effect of the NE uptake inhibitors (nisoxetine, desipramine, and nortriptyline; Renaud et al., 1991). These results are difficult to interpret according to the above hypothesis, because these findings suggest that the activity of the dopaminergic system itself is not important for the regulation of cataplexy. The uptake inhibition data, and the fact that adrenergic $\alpha_1$ agonists and $\alpha_2$ antagonists decrease canine cataplexy (Mignot et al., 1988a,b; Nishino et al., 1990), suggest a preferential involvement of noradrenergic rather than dopaminergic systems in the control of cataplexy. Taken together with the fact that the firing rate of DA neurons does not change during REM sleep in the substantia nigra or ventral tegmental area (Miller et al., 1983; Steinfels et al., 1983), in contrast to the complete suppression of firing of NE-containing neurons in the locus coeruleus during REM sleep (Aston-Jones and Bloom, 1981; Hobson et al., 1983), we believe that the effect of $D_2$ compounds on cataplexy is probably mediated via the noradrenergic system.

Several lines of experimental evidence indicate an interaction between the $D_2$ receptor mechanism and noradrenergic activity. It has recently been reported that peripheral administration of selective $D_2$ agonists reduces, and of $D_2$ antagonists increases, NE release in the rat frontal cortex (Rossetti et al., 1989). Furthermore, a $D_2$ agonist, $R(+)$-3-PPP [and not $S(-)$-3-PPP], suppresses the firing of NE-containing neurons in the locus coeruleus in rats (Elam et al., 1986). This electrophysiological result resembles our current pharmacological results for the enantiomers of 3-PPP; only $R(+)$-3-PPP aggravates canine cataplexy. Considering the similarities between our pharmacological findings *in vivo* and the above findings *in vitro,* we favor the hypothesis that "presynaptic ($D_2$-type) heteroreceptors" [Laduron, 1985; possibly located on NE neuron terminals, regulating synthesis and release of NE (Langer, 1981)], rather than "presynaptic dopamine autoreceptors," are involved in the regulation of cataplexy and REM sleep. Recently, several central dopamine ($D_2$-like) receptor genes have been cloned and expressed (Bunzow et al., 1988; Sokoloff et al., 1990), and it is possible that one of these receptors plays a special role in the regulation of cataplexy and REM sleep. Considering the clarity of the results of our study, in conjunction with accumulated evidence of various neurochemical abnormalities in DA systems in human (Kish et al., 1989) and canine narcolepsy (Mefford et al., 1983; Bowersox et al., 1987; Miller et al., 1990), it appears that altered $D_2$-type receptor mechanisms may be critical in the pathophysiology of narcolepsy.

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