ELSEVIER

European Journal of Pharmacology 325 (1997) 137–144

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Talipexole or pramipexole combinations with chloro-APB (SKF 82958) in MPTP-induced hemiparkinsonian monkeys

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Received 12 December 1996; revised 12 February 1997; accepted 18 February 1997

Abstract

The effects of two predominant dopamine D_2-like receptor agonists, talipexole (6-allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo [4,5-*d*]-azepine dihydrochloride, B-HT 920 CL_2) and pramipexole (*S*(−)2-amino-4,5,6,7-tetrahydro-6-propyl-aminobenzothiazole dihydrochloride, SND 919 CL_2Y), were studied alone and in combination with the selective dopamine D_1-like receptor agonist chloro-APB ((±)6-chloro-7-8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzazepine hydrobromide, SKF 82958) in five chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned hemiparkinsonian *Macaca nemestrina* monkeys. Talipexole induced contraversive rotation in a dose-dependent manner up to 32 μg/kg, i.m. Talipexole was more potent than pramipexole (10 vs. 32 μg/kg, i.m.), but pramipexole was more efficacious in producing contraversive rotational behavior and significant hand movements in the afflicted limb. Larger doses of chloro-APB also produced contraversive rotation. Combinations of each dopamine D_2-like receptor agonist in a median effective dose with chloro-APB (23.4 and 74.8 μg/kg, i.m.) had synergistic effects, producing either addition or potentiation, depending upon the dose used. The effects noted with these combinations were less than the effect of a large dose (100 μg/kg) of pramipexole. Talipexole, in the largest dose studied (100 μg/kg, i.m.), produced sedation which was not seen with the same dose of pramipexole. No significant extrapyramidal side effects were noted with either agent.

Keywords: Talipexole; Pramipexole; Chloro-APB; MPTP-induced hemiparkinsonism; (Monkey); SKF 82958; Dopamine D_1-like receptor agonist; Dopamine D_2-like receptor agonist

1. Introduction

Two potential therapeutic agents in the treatment of Parkinson's disease have become available: talipexole (6-allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo [4,5-*d*]-azepine dihydrochloride, B-HT 920 CL_2) and pramipexole (*S*(−)2-amino-4,5,6,7-tetrahydro-6-propyl-aminobenzothiazole dihydrochloride, SND 919 CL_2Y). Talipexole, which is a potent dopamine D_2-like receptor agonist both pre- and postsynaptically, as well as an α_2-adrenoceptor agonist and a weak 5-HT_3 receptor antagonist (Kobinger and Pichler, 1981; Pichler and Kobinger, 1981; Andén et al., 1982, 1983; Hinzen et al., 1986; Nishio et al., 1996), was effective in the treatment of Parkinson's disease in controlled clinical trials (Nakanisi et al., 1993).

Electrophysiological studies have demonstrated that talipexole acts on caudate neurons of cats and rats as a dopamine D_2-like receptor agonist (Matsubayashi et al., 1994, 1995; Todo et al., 1994). This drug induces yawning behavior in rats (Yamada et al., 1990) and an improvement of motor movements in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated marmosets (Irifune et al., 1993, 1994). Pramipexole is primarily a dopamine D_2 receptor agonist with negligible α_2-adrenoceptor activities (Mierau and Schingnitz, 1992; Nishio et al., 1996) and 5-HT_3 receptor antagonistic properties (unpublished observations). Further studies were performed on MPTP induced hemiparkinsonian monkeys to determine the acute antiparkinsonian effects of talipexole in comparison with those of pramipexole. The role of dopamine D_1 receptors in the treatment of Parkinson's disease remains to be determined. Therefore, whether each of these agents alone or in combination with a selective dopamine D_1 receptor agonist such as chloro-APB ((±)6-chloro-7-8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzazepine hydrobromide, SKF 82958; Pfeiffer et al., 1982; Murray and Waddington,

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PII S0014-2999(97)00129-5

1989; O'Boyle et al., 1989) produces an additive or potentiating effect was also examined. An additive action is defined as the two drugs together having the sum of the effects of the two drugs alone. A potentiating action is when the two drugs together have an effect greater than the sum of the effects of the two drugs alone. A synergistic action is when the two drug effects together are either additive or potentiating.

2. Materials and methods

The methods used in this study have been described previously by Domino and Sheng (1993a,b).

2.1. Animals

Five adult female *Macaca nemestrina* (pig-tailed macaque) monkeys, ranging in weight from 5.4 to 7.6 kg at the time of this study, were initially obtained from the Charles River (Port Washington, NY, USA). Upon arrival at our facilities, the animals were subjected to a 3 month quarantaine period. During that time they were treated for whipworm (*Trichuris*), lung worm, etc., with the broad spectrum antiparasitic avermectins (Ivermectin) in a dose of 0.02 mg/kg s.c. Inasmuch as monkeys are carriers of herpes virus simiae (B virus), The B Virus Working Group Guidelines for Prevention of Herpes Virus Simiae Infection in Monkey Handlers (The Virus Working Group, 1988) were followed. Similar appropriate procedures were instituted to prevent spreading tuberculosis from monkeys to handlers and vice versa. Animal husbandry was provided by the staff of the Unit for Laboratory Animal Medicine (ULAM) under the guidance of supervisors who were certified as Animal Technologists by the American Association for Laboratory Animal Science. Veterinary care was provide by ULAM faculty members and veterinary residents. Three members of the faculty are Diplomats of the American College of Laboratory Animal Medicine. The University of Michigan is fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). The animal care and use program conforms to the standards in The Guide for the Care and Use of Laboratory Animals (1985). This includes regular periodic surveillance of animal facilities, review of all projects for humane use of animals, and the appropriate use of surgical anesthesia, analgesics and sedatives. When used in these experiments, the animals were tuberculosis (1500 units Tuberculin) intradermally nonreactive and their chest X-rays were normal. Each animal was given an enriched environment consisting of ease of visualization of their colleagues, Kong toys, TV entertainment, etc.

The monkeys were placed in a sound quiet, air conditioned certified animal room ($31.5 \times 11.3 \times 8.0$ feet) on a light/dark cycle with lights on from 7:00 a.m. to 7:00 p.m. Food and water were given in the mornings except when a drug was tested, in which case the animals were fed in the afternoon. Monkey chow and water were available ad libitum until consumed. The animals' diet was supplemented with fruit and vegetables as appropriate. Each adult female monkey was housed in a standard individual cage, was not pregnant, and menstruated monthly. At the time of the present experiments, the animals had symptoms of hemiparkinsonism for 5–7 years which did not show any gross change over this period of time. Therefore, these lesioned monkeys represent a chronic animal model designed to resemble the symptoms and pathophysiology of chronic human parkinsonism. During the intervening years, the animals were given various selected dopamine D_1-like and D_2-like receptor agonists i.m., as well as levodopa/carbidopa orally in their fruit. All animals were free of medication for 5 months prior to this study.

2.2. MPTP-induced hemiparkinsonism

The method of Bankiewicz et al. (1986) was used to slowly infuse MPTP unilaterally into one common carotid artery in a total dose of 2.5–3.5 mg, depending upon the size of the monkey, for a total dose of approximately 0.6 mg/kg. Briefly, each animal in her own squeeze cage was anesthetized with ketamine hydrochloride (5–10 mg/kg, base dose) given i.m. Subsequently, each animal was given 30 mg/kg i.v. pentobarbital to maintain deep anesthesia and secured on an operating table in the prone position for exposure of the right or left common carotid artery at its bifurcation. The common artery supplying blood to the dominant cerebral hemisphere was selected. The major vessels of the external carotid were isolated and fine arterial clips were applied temporarily. Surgery lasted approximately 30 min. The wound was then irrigated with H_2O_2 solution and closed with a continuous nylon suture and skin clips. Each animal was given 300 000 units of sterile penicillin G benzathine and penicillin G procaine in an aqueous suspension.

2.3. Drugs

Talipexole and pramipexole were obtained from Boehringer-Ingelheim (Ingelheim, Germany). Chloro-APB was purchased from Research Biochemicals International (Natick, MA, USA). Five percent dextrose in water (D5W) was purchased from Abbott Laboratories (North Chicago, IL, USA).

2.4. Drug administration

All drugs were given i.m. in logarithmic doses to all five monkeys. The drugs were given on the same day each week, usually Thursday a.m. In the combination studies, chloro-APB and talipexole or pramipexole were simultaneously given to each animal. If a drug was given more than once in the same dose, mean data were used for analysis.

The same volume of vehicle (D5W) was injected i.m. as control.

2.5. Behavioral observations

Each monkey was placed in a standard primate cage modified with a clear Plexiglas front for viewing and recording free moving behavior. The upper cages were illuminated with 34 watt fluorescent ceiling lights. The lower cages were illuminated with 20 watt fluorescent lights. Gross animal behaviors were observed via three separate video color cameras. The behaviors of two monkeys in separate cages were recorded with one camera. Thus, a total of three video cameras with zoom autofocus was used, including a Panasonic VHS Model PV-420, Magnavox Model VR 9344-AV01, and Sears LX-1 Model 1934. All three cameras were connected electrically to their own videocassette recorders which were Mitsubishi Model U-32 VCRs. Time and date of each camera were synchronized. The animal was video recorded in its own home cage without human presence for 30 min after vehicle injection, and for an additional 2 h or more, as necessary, following drug or vehicle injection.

The videotapes were scored by two persons blind to the purpose of the study for ipsiversive and contraversive circling to the side of the brain lesion. The number and direction of complete 360° turns during each consecutive 5 min period were counted and recorded. The total number of complete contraversive turns in 2 h after drug administration was computed. This time period was used since all of the drugs studied were relatively short acting. The coefficient of reliably r for two interraters was > 0.9.

2.6. Statistical analysis

The data were analyzed using one-way ANOVA with repeated measures (InStat 2.0 for MacIntosh, 1993) followed by the Tukey multiple-comparison procedure when a significant F ratio was obtained. An alpha level (P value) of 0.05 was used for all statistical tests.

3. Results

3.1. Effects of talipexole

Talipexole was given to each hemiparkinsonian monkey in doses of 3.2, 10, 32, 56, and 100 μg/kg, i.m. at intervals of at least 7 days. Its effects on mean contraversive circling are shown in the bar graph in Fig. 1. As can be seen, this agent significantly increased contraversive circling reaching approximately 200 turns per 2 h with increasing doses up to 32 μg/kg, i.m. Doses of 56 and 100 μg/kg, i.m. significantly decreased ipsiversive circling. Doses of 56 and especially 100 μg/kg, i.m. caused some drowsiness and sedation, and reduced contraversive circling the most. However, the animals could be easily aroused and moving after a light sensory stimulus. Thus, total motor responses were reduced because of sedation and not because of a lack of effect of talipexole. This agent, especially in the lower doses, increased locomotor activity and significant hand movements of the previously rigid and relatively immobile affected limb. The beneficial motor effects of talipexole lasted 1–2 h, depending upon the dose given. Ipsiversive circling was not affected by

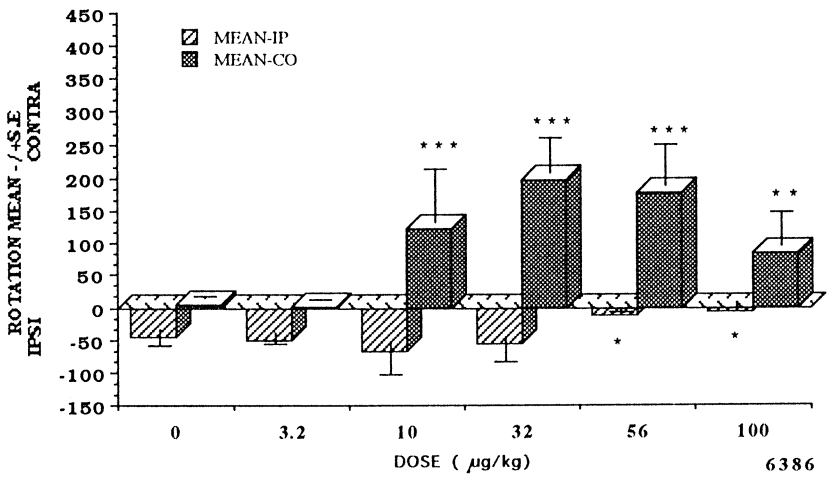

Fig. 1. Effects of talipexole on rotation behavior in MPTP induced hemiparkinsonian monkeys. Increasing doses of talipexole were given i.m. Mean ipsiversive rotation is below and mean contraversive above the x-axis for 2 h after injection. Talipexole has a bell shaped dose-effect curve primarily because of the sedation which occurred with larger doses and not because of a lack of a motor effect. The height of each bar represents the mean ± standard error (S.E.M.). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared to control in this and subsequent figures using one-way ANOVA with repeated measures and a post-hoc Tukey test. IP = ipsiversive, CO = contraversive in this and subsequent figures. $n = 5$.

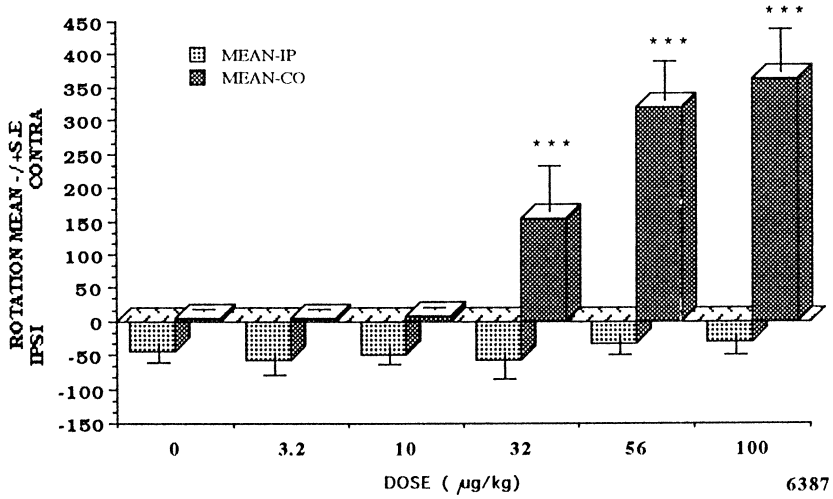

Fig. 2. Effects of pramipexole on rotation behavior in MPTP induced hemiparkinsonian monkeys. Increasing doses of pramipexole produced progressively greater mean contraversive circling which was statistically significant. $n = 5$.

talipexole in doses up to 32 μg/kg. No untoward extrapyramidal effects were noted.

In some animals talipexole caused decreased food and water intake. Sensitive animals did not eat and drink as much as before the talipexole was given. Some monkey chow biscuits, fruit, and water were left in the feeder boxes and drinking bottles, with more remaining after the larger doses. However, in none of the animals was any emetic behavior observed.

3.2. Effects of pramipexole

Pramipexole was given to each hemiparkinsonian monkey in doses of 3.2, 10, 32, 56, and 100 μg/kg, i.m. on the same day of each week. Its effects on mean contraversive circling are shown in the bar graph in Fig. 2. In contrast to talipexole, this agent required a larger dose to produce a similar amount of contraversive circling (32 vs. 10 μg/kg, i.m.). Furthermore, with increasing doses the effects observed were greater and statistically significant and reached approximately 360 turns per 2 h at a dose of 100 μg/kg of pramipexole. They did not show the bell-shaped dose-effect relationships of talipexole. Ipsiversive circling was not affected by pramipexole in doses up to 100 μg/kg. Pramipexole increased general activity and significant hand movements of the previously rigid and relatively immobile affected limb. The beneficial motor effects of pramipexole lasted 1–2 or more hours, depend-

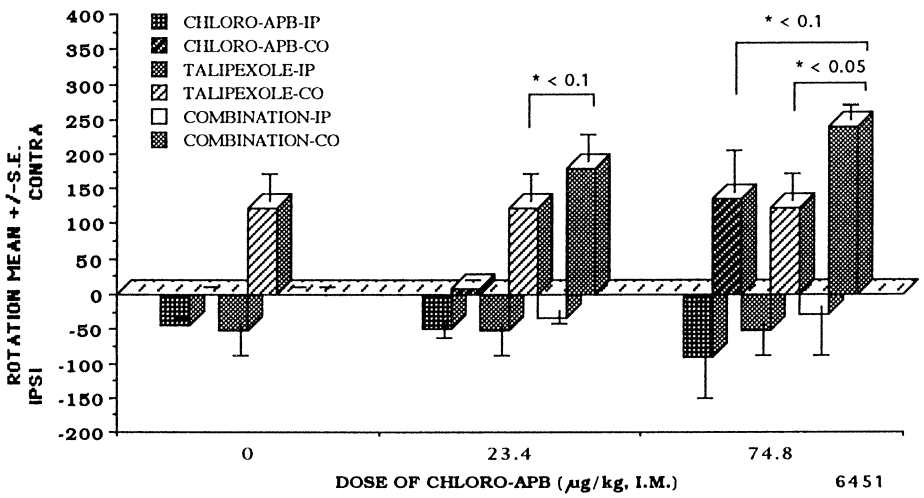

Fig. 3. Effects of increasing doses of chloro-APB and a fixed dose of talipexole (10 μg/kg) on rotation behavior in hemiparkinsonian monkeys. Increasing doses of chloro-APB either potentiated or added to the effects of 10 μg/kg, i.m. talipexole on mean contraversive rotation which was statistically significant ($P < 0.05$, one-tailed, at the largest dose). Mean ipsiversive rotation was not significantly affected. $n = 5$.

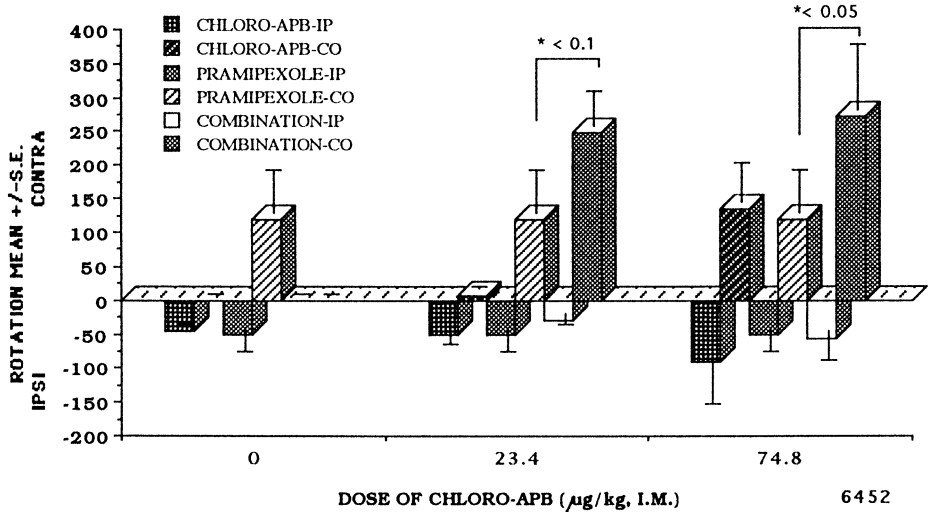

Fig. 4. Effects of increasing doses of chloro-APB and a fixed dose of pramipexole (32 μg/kg) on rotation behavior in hemiparkinsonian monkeys. Increasing doses of chloro-APB had a potentiating or additive effect on mean contraversive rotation with 32 μg/kg, i.m. of pramipexole which was statistically significant ($P < 0.05$, one-tailed, at the largest dose). There was no statistically significant change in mean ipsiversive rotation. $n = 5$.

ing upon the dose given. No untoward extrapyramidal effects were noted. No sedative effect or emetic behavior was observed.

3.3. Effects of chloro-APB

This agent was given to each hemiparkinsonian monkey in doses of 23.4 and 74.8 μg/kg, i.m. the same day of each week. Chloro-APB, in doses of 74.8 μg/kg, significantly increased contraversive circling. Its effects on mean contraversive circling were similar to those reported previously (Domino and Sheng, 1993a,b). The drug was much less potent on an μg/kg basis than either talipexole or pramipexole and its duration was about 1–2 h.

3.4. Effects of a combination of chloro-APB and talipexole

The effects of increasing doses of chloro-APB and a fixed dose of 10 μg/kg of talipexole on mean rotation behavior are shown in Fig. 3. The D5W vehicle alone had no significant effect, with only minimal ipsiversive circling observed. Talipexole in a dose of 10 μg/kg without any chloro-APB produced a mild increase in mean contraversive circling, but no change in ipsiversive circling. Chloro-APB in a dose of 23.4 μg/kg, i.m. produced only minimal contraversive circling, but, when combined with 10 μg/kg, i.m. talipexole, produced a slight decrease in ipsiversive and enhanced contraversive circling, suggesting potentiation. A large dose of 74.8 μg/kg, i.m. of chloro-APB enhanced contraversive circling, while the combination enhanced contraversive circling in an additive manner. This combination produced approximately 250 turns per 2 h, similar to the turns produced by talipexole alone in a dose of 32 μg/kg (see Fig. 1). Similarly, increased locomotor activity and significant hand movements of the previously rigid and relatively immobile affected limb were seen. The beneficial motor effects of the combination were prolonged by about 1 h. No untoward extrapyramidal side effects were observed, but in some animals talipexole decreased food intake with the combined treatment.

3.5. Effects of a combination of chloro-APB and pramipexole

The effects of increasing doses of chloro-APB and a fixed dose of 32 μg/kg, i.m. of pramipexole on mean rotational behavior are shown in Fig. 4, which is arranged in a manner similar to Fig. 3. The D5W vehicle had no significant effect alone, and in combination with 32 μg/kg, i.m. of pramipexole the usual increase in contraversive circling with pramipexole alone was seen. Chloro-APB in a dose of 23.4 μg/kg, i.m. alone had a minimal effect. When combined with 32 μg/kg, i.m. pramipexole, there was a slight decrease in ipsiversive and a marked increased in contraversive circling, indicating a potentiating effect. The larger dose of 74.8 μg/kg, i.m. of chloro-APB, when given with 32 μg/kg, i.m. of pramipexole, had more of an additive than a potentiating effect. This combination produced approximately 300 turns per 2 h, which was still less than the effect (approximately 360 turns per 2 h) produced by pramipexole alone in a dose of 100 μg/kg (see Fig. 2). Similarly, increased locomotor activity and significant hand movements of the previously rigid and relatively immobile affected limb were seen. The beneficial motor effects of the combination were prolonged by about 1 h. No untoward side effects were observed.

4. Discussion

It is generally acknowledged that contraversive circling reflects postsynaptic dopamine D_1/D_2 receptor stimulation in the ipsilateral lesioned nigral input into the striatum. It follows that both talipexole and pramipexole improved parkinsonian symptoms in the hemiparkinsonian monkey by stimulating postsynaptic dopamine receptors in the affected striatum. The effective doses of these drugs in our study are in good agreement with those producing contraversive circling in rats or antiparkinsonian symptoms in monkeys and rodents (Hinzen et al., 1986; Irifune et al., 1993, 1994; Kohno et al., 1997; Mierau and Schingnitz, 1992; Mierau, 1995). Furthermore, talipexole was more potent in vivo than pramipexole (10 vs. 32 μg/kg, i.m.). This can be explained by the displacement activities of talipexole and pramipexole on [^{3}H]spiperone binding to rat striatal membranes in which the K_i (nM) are 144 and 221, respectively (Kohno et al., 1996a). A relatively selective α_2-adrenoceptor agonist like B-HT 933 has no antiparkinsonian effect in MPTP lesioned monkeys except for sedation and slight loss of balance in a very large dose (Hinzen et al., 1986). The α_2 component of talipexole cannot be contributing to its antiparkinsonian activity (Kohno et al., 1997). Both talipexole and pramipexole are well absorbed following oral administration and rapidly penetrate into the brain. Their pharmacokinetic properties are similar. Although pramipexole is less potent in vivo, it is more efficacious than talipexole, probably because its antiparkinsonian effects are not limited by the sedation produced by the latter, an action investigated by Kohno et al. (1996b). The sedative effects of talipexole seem to result from stimulation of α_2-adrenoceptors and dopamine D_2 autoreceptors (Kohno et al., 1996a). When changes in spontaneous EEG activity were evaluated during the dark period with rats housed in a room maintained on a reversed light-dark cycle, talipexole induced a drowsy EEG pattern in doses of 32 and 100 μg/kg. The effects were relatively weak and quite different from those noted with classic sleep inducers (Kohno et al., 1996b). The sedative effects of talipexole evident in our hemiparkinsonian monkeys and in the cynomolgus monkeys with unilateral lesions (Kohno et al., 1997), were not observed in common marmoset or rhesus monkeys treated with systemic MPTP. Clonidine, an α_2-adrenoceptor agonist, does not induce sleepiness in patients with hypertension as much as talipexole does in parkinsonian patients. These findings suggest that part of the sedative effect of talipexole may be related to the neuronal brain damage produced by Parkinson's disease.

The synergistic antiparkinsonian effects of a combination of dopamine D_1- and D_2-like receptor agonists have been reported by others (Vermeulen et al., 1993; Vermeulen, 1994; Akai et al., 1995; Domino, 1997). In our study, synergistic effects were noted with the combination of a fixed median dose of talipexole/pramipexole and increasing doses of chloro-APB. The contraversive turns produced by the combination were fewer than the total number of turns produced by the higher 100 μg/kg dose of pramipexole. It was not determined whether the turns produced by 100 μg/kg of pramipexole could be potentiated by chloro-APB. The doses used for the combinations were only on the ascending limb of the dose-effect curves for each drug. Considering the clinical doses of these drugs (the maintenance doses of talipexole and pramipexole are 0.2–3.6 mg/day and 0.3–4.5 mg/day, respectively), either a large dose of a dopamine D_2 receptor agonist or low or median doses of dopamine D_1 plus D_2 receptor agonist might cause similar stimulation and therapeutic effects. Our findings are basically in agreement with those reported by Akai et al. (1995) who demonstrated that the combination of a median dose of quinpirole (*trans*-(−)-4*aR*-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-pyrazolo-[3,4-*g*]quinoline hydrochloride, LY 171555) and chloro-APB produce synergic antiparkinsonian effects in MPTP-lesioned monkeys; the effect was less than that noted with larger doses of quinpirole alone. The combination of large doses of quinpirole and chloro-APB further potentiated the antiparkinsonian effect, but this combination was accompanied by marked excitation of the monkeys. It should be noted that these results, using a full dopamine D_1 receptor agonist like chloro-APB, differ from those using a partial dopamine D_1 receptor agonist like (±)-1-phenyl-1-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrochloride (SKF 38393). Nomoto et al. (1985, 1988) found that SKF 38393 inhibits the antiparkinsonian activity of the dopamine D_2 receptor agonist quinpirole in MPTP treated marmosets, perhaps because the former is a dopamine D_1 receptor partial agonist. Murray and Waddington (1989) also reported on the bidirectional interaction of some dopamine D_1 and D_2 receptor agonists.

The appetite reducing effects of talipexole have been described previously (Honma et al., 1993; Ihara et al., 1993; Kast et al., 1993). The present data are in agreement and suggest the need for additional research into this intriguing effect.

MPTP induced hemiparkinsonian monkeys show both intentional as well as resting tremor, but these are relatively unreliable endpoints (present study) compared to monkeys with unilateral ventromedial tegmental lesions (Kohno et al., 1997). What is clear is that talipexole is very potent in reversing the significant contraversive limb rigidity and increasing contraversive circling, as would be predicted from a dopamine D_2-like receptor agonist. It is clear that talipexole has significant postsynaptic dopamine D_2-like receptor effects (Matsubayashi et al., 1994, 1995; Georgic et al., 1995). Mierau et al. (1995) reported that pramipexole has a 5-fold selectivity for cloned heterologously expressed rat and human dopamine D_2, D_3, and D_4 receptors. Furthermore, Hoffmann et al. (1995) have reported that pramipexole is a dopamine D_3 receptor preferring agonist for the limbic system, raising the issue of

striatal vs. limbic system major sites of action. Clearly the dopamine D_2-like receptor agonist component of talipexole is crucial, as is the case with pramipexole. However, a full dopamine D_1-like receptor agonist potentiates or adds to the dopamine D_2-like receptor agonist effects of both talipexole and pramipexole.

Acknowledgements

The authors would like to acknowledge the efforts of Nai Nan Zhang in this research.

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