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European Journal of Pharmacology 459 (2003) 231–237
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Motor effects of a dopamine stabilizer (GMC1111) in primate models of Parkinson and hemiparkinsonism

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Received 25 July 2002; received in revised form 13 November 2002; accepted 19 November 2002

Abstract

The effects on motor behavior of a new potential dopamine stabilizer: 2-amino-6-(*N*,*N*-di-*n*-propylamino)thiazolo[4,5-*f*]indan (GMC1111) were investigated in common marmosets with 6-hydroxydopamine lesions within the median forebrain bundle (12 unilateral, 6 bilateral). GMC1111 was administered orally or subcutaneously (s.c.) to unilaterally 6-hydroxydopamine lesioned monkeys, either alone or together with s.c. injections of apomorphine (0.2 mg/kg) and the effect on rotational behavior was examined. GMC1111 (0.03–3.0 mg/kg) alone, orally or s.c., did not induce rotational behavior. When apomorphine and GMC1111 were injected simultaneously, rotations were nearly abolished in three monkeys with a baseline apomorphine-induced rotation rate below 13/min, whereas GMC1111 did not modify the rotations in three high-rotating animals (>17/min). Oral administration of GMC1111 (1.0 and 3.0 mg/kg) abolished the apomorphine-induced rotations in another six unilaterally dopamine-denervated monkeys, indicating a good oral bioavailability. A low dose of GMC1111 (0.3 mg/kg) administered s.c. to marmosets with bilateral nigrostriatal lesions produced a reduction of Parkinson symptoms of approximately the same degree as with levodopa/benserazide (15/3.75 mg/kg), while higher doses of GMC1111 were less effective. When levodopa/benserazide was administered together with various doses of GMC1111 (0.3–3.0 mg/kg), the levodopa-induced peak-dose dyskinesias were reduced with the highest dose of GMC1111 (3 mg/kg). Taken together, GMC1111 modifies dopaminergic activity in a normalizing direction. Parkinson symptoms, as well as levodopa-induced dyskinesias are both reduced. This suggests the arrival of another member of the new dopamine stabilizer family.

Keywords: GMC1111; Parkinson's disease; Dyskinesia; 6-Hydroxydopamine; Levodopa; Apomorphine; Dopamine stabilizer

1. Introduction

Neurodegeneration of the dopaminergic system in substantia nigra is the single most important factor in the underlying cause of Parkinson's disease leading to a dopamine deficiency in the striatum and to the clinical features of the disease (Kish et al., 1988). The predominant therapy for Parkinson's disease is based on restoration of the dopaminergic neurotransmission by administration of levodopa, the precursor of dopamine, and administration of dopamine receptor agonists. However, as the disease progresses, the levodopa therapy often results in the emergence of motor complications, e.g. on–off phenomena and levodopa-induced dyskinesias (Nutt, 2001).

The underlying pathophysiology of the motor fluctuations is largely unknown, but severity of the disease, as well as the duration of levodopa treatment, appears to be contributing factors (Horstink et al., 1990). It has also been suspected that pro-oxidant properties of levodopa may contribute to the progression of the disease (Martignoni et al., 1999; Weiner, 2000). Moreover, it has been hypothesized that oxygen-derived free radicals may be involved in the pathophysiology of Parkinson's disease (Jenner and Olanow, 1996). Therefore, a combination of dopamine receptor agonistic and radical scavenging properties in the same molecule may provide a drug that both reduces the symptoms of the disease and prevents further neurodegeneration. In the new drug 2-amino-6-(*N*,*N*-di-*n*-propylami-

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doi:10.1016/S0014-2999(02)02817-0

no)thiazolo[4,5-*f*]indan (GMC1111), these characteristics have been sought to be combined (Van Vliet et al., 2000a,b).

The 2-aminothiazole moiety in GMC1111 has been shown to be a successful bioisoteric replacement of a phenol group in dopamine receptor agonists, such as pramipexole. Some compounds with this functional group have been found to have antioxidant properties. GMC1111 was shown to possess both good oral availability and hydroxyl-free radical scavenging properties in studies on rats and in in vitro experiments (Van Vliet et al., 2000a,b).

Moreover, GMC1111 has been shown to have similar properties to the partial dopamine receptor agonist *S*-(−)-3-(3-hydroxyphenyl-)-*N*-*n*-propylpiperidine ((−)-3-PPP), which may act as a full agonist, partial agonist or a weak antagonist at dopamine receptors depending on the functional state of the receptors studied (Hjorth et al., 1988). In in vitro evaluations, GMC1111 was found to possess a high affinity for dopamine D3 receptors (Van Vliet et al., 2000a,b). GMC1111 displayed partial agonism at dopamine D2 receptor sites and antagonism at dopamine D3 sites (Van Vliet et al., 2000b). Hence, the pharmacological properties of GMC1111 are interesting and the new drug might prove useful not only as an antiparkinsonian agent, but also as a potential atypical neuroleptic or in conditions where both a reduction and an elevation in dopamine neurotransmission are necessary.

To further evaluate the properties of racemic GMC1111 and its potential use in Parkinson's disease, the present study was performed. The effect of GMC1111 on motor behavior was investigated in two primate models of Parkinson's disease. First, the apomorphine-induced contralateral turning behavior in the unilaterally 6-hydroxydopamine lesioned marmoset monkey was studied. Second, the behavioral effects of GMC1111 were examined in bilaterally 6-hydroxydopamine lesioned marmosets. The 6-hydroxydopamine-induced destruction of nigrostriatal dopamine neurons results in supersensitivity of dopamine receptor function, which in the unilateral model is evaluated by the rotational behavior provoked by administration of dopamine receptor agonists (Ungerstedt, 1971). When 6-hydroxydopamine is given to both hemispheres a bilateral parkinsonian syndrome is established, which means that more complex motor behaviors can be studied.

2. Materials and methods

2.1. Animals

Eighteen adult in-house bred common marmosets (*Callithrix jacchus*) of either sex (nine males and nine females) were used in these experiments. Twelve of the marmosets were included in the experiments on unilaterally lesioned animals (n=6 for the s.c. administration of GMC1111, and n=6 for the oral administration of GMC1111). Six monkeys were bilaterally dopamine denervated by 6-hydroxydopamine injections in the median forebrain bundle on both hemispheres. The monkeys weighed between 290 and 460 g each and were housed in pairs in a temperature (27±1 °C) and humidity (relative 50%) controlled environment with a 12-h light–dark cycle (the light was on between 6 am and 6 pm). They received fortified milk solution, bread, monkey pellets and fresh fruit everyday and had free access to water. This study was approved by the Ethical Committee on Animal Research at Uppsala University and followed the N.I.H. guidelines detailed in the Guide for the Care and Use of Laboratory Animals and the Federal Animal Welfare Act. All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Lesions

At least 1 month before the start of the study, the neurotoxin 6-hydroxydopamine (6-OHDA HBr with ascorbic acid, RBI, MA, USA) was infused into the right nigrostriatal bundle (unilateral lesions) or into both right and left hemispheres (bilateral lesions) under ketamine (80 mg/kg, Ketalar®, Parke-Davis) and xylazine (4.5 mg/kg, Rompun vet®, Bayer) anaesthesia according to the method of Annett et al. (1992). A time period of 8 weeks was allowed between the first and the second lesion in the bilaterally treated animals.

2.3. Drugs and treatment regimen

2.3.1. GMC1111 subcutaneously to unilaterally 6-hydroxydopamine lesioned animals

At the start of the study, the unilaterally lesioned monkeys were given the mixed dopamine D1/D2 receptor agonist apomorphine (Apoteksbolaget, Sweden) at the dose of 0.2 mg/kg s.c., which induced a contralateral turning behavior in all animals. The number of contralateral rotations was counted in 5-min periods for 60 min after the drug administration. Depending on the number of rotations presented, the animals were assigned into two groups. In the high-rotating group of animals (n=3), more than 17 rotations/min were seen for each animal. In the low-rotating group (n=3), less than 13 rotations per min were recorded (Fig. 1). A strong correlation between the number of rotations induced by apomorphine and the number of remaining tyrosine hydroxylase immunoreactive cells in substantia nigra pars compacta has earlier been shown (Carman et al., 1991). Four doses of GMC1111 were applied (0.1, 0.3, 1.0 and 3.0 mg/kg) with and without concomitant apomorphine to the unilaterally 6-hydroxydopamine lesioned monkeys. In addition, the low-rotating group was given 0.03 mg/kg of GMC1111, alone and together with apomorphine. The response to apomorphine alone was tested three times during the time-course of the study with all animals. No statistically significant difference was seen over time (Fig. 1). All marmosets were also given a control injection of saline s.c.

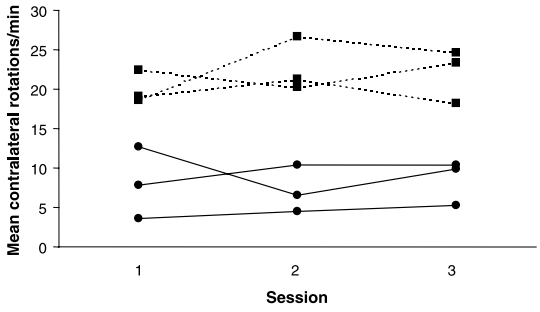

Fig. 1. Subcutaneous injection of apomorphine (0.2 mg/kg) induced contralateral rotations in unilaterally 6-hydroxydopamine lesioned marmosets that were counted for 60 min after administration. Data shown as individual mean rotations/min (n=6) during the observation period immediately after drug administration. No statistically significant effect was established between the three injections over time. As shown in the figure, a low rotating (--) and a high rotating group (-■-) of animals were seen.

2.3.2. GMC1111 orally to unilaterally 6-hydroxydopamine lesioned animals

In another set of experiments, GMC1111 was given orally to unilaterally lesioned marmosets (n=6). The monkeys were starved during the night previous to the drug administration. GMC1111 was dissolved in saline and mixed with orange juice and honey and fed to the monkeys. GMC1111 was administered in three doses (0.3, 1.0 and 3.0 mg/kg orally) and either apomorphine (0.2 mg/kg s.c.) or saline (equal volume s.c.) were given 30 min after GMC1111. The animals were recorded on videotape for 60 min after the apomorphine or saline administration for later evaluation. Apomorphine was given alone at the start, in the middle and after the study to examine the behavioral response over time. The animals rested 1 day between drug injections.

2.3.3. GMC1111 subcutaneously to bilaterally 6-hydroxydopamine lesioned animals

To assess the effect of GMC1111 on motor activity, parkinsonism and peak-dose dyskinesia, GMC1111 was given to marmosets with bilateral 6-hydroxydopamine lesions of the nigrostriatal pathways. Experiments started at least 2 months after the intracerebral lesions. The animals had not been treated with any drugs prior to this study. A baseline was obtained by scoring the animals using the scoring system in Table 1 before treatment. A solution of levodopa and benserazide (Sigma Aldrich) was prepared in saline containing 5% glucose and injected s.c. at a dose of 15/3.75 mg/kg twice daily until the animals had developed peak-dose dyskinesias. The dyskinetic symptoms were stable after 11 days of daily levodopa/benserazide treatment. The marmosets were scored 30 min after the levodopa administration at which time point we had recorded a peak-dose effect of levodopa. Two series of experiments were performed with GMC1111 after the monkeys have developed peak-dose dyskinesia. First, GMC1111 was administered s.c. at three doses (0.3, 1.0 and 3.0 mg/kg) immediately before the levodopa administration. Second, GMC1111 was given s.c. at the same doses, but together with a saline injection instead of the levodopa administration.

2.4. Behavioral assessments

2.4.1. Behavioral assessments in unilaterally 6-hydroxydopamine lesioned animals

Each animal was placed in a stainless steel cage (460×625×455 mm) for the behavioral measurements. An initial time period of 10 min was permitted for habituation to the cage and the observer before drug injection and observation. In the peroral study, the behavior was recorded on videotape for later evaluation by an observer blind to the treatment. All behavioral assessments were performed by trained observers throughout the study.

2.4.2. Behavioral assessments in bilaterally 6-hydroxydopamine lesioned animals

All behavioral assessments were carried out in the home cage of the animals. The observer was present in front of the cage for 10 min to habituate the animals to the observer

Table 1
Behavioral scoring system concerning parkinsonism and dyskinesia for the bilaterally 6-hydroxydopamine treated marmosets

	Behavioral assessments	Score
Parkinsonism scale		
Alertness	Normal/absent	0/1
Reaction to stimuli	Normal/reduced/slow/absent	0/1/2/3
Checking movements	Present/reduced/absent	0/1/2
Attention and eye movements	Normal/abnormal	0/1
Posture	Normal/abnormal (trunk/tail/limbs)/grossly abnormal	0/1/2/3/4
Balance	Normal/unstable/spontaneous falls	0/1/2
Motility	Normal/mild slowing/moderate bradykinesia/akinesia	0/1/2/3
Vocalization	Normal/reduced/absent	0/1/2
Tremor	Absent/present	0/1
Dyskinesia scale		
Perioral	Occasional perioral twitching/grimacing periorally	1/2
Lingual	Tongue protrusion present	1
Periocular	Occasional periocular twitching	1
Masticatory, Frequency	>6 times/6–20 times/>20 times per minute	1/2/3
Arms and legs, Amplitude	Slight dyskinetic movements/pronounced dyskinetic movements	1/2
Arms and legs, Frequency	>6 times/6–20 times/>20 times per minute	1/2/3

before measurements started. The animals were evaluated by visual inspection, using the scoring system in Table 1.

2.5. Statistical analysis

Rotational data on the unilaterally 6-hydroxydopamine lesioned marmosets were analyzed using a one-way analysis of variance (ANOVA). When the *P*-values were less than 0.05, groups were compared using a paired *t*-test. The accepted level of significance was $P<0.05$. The behavioral measurements on bilaterally 6-hydroxydopamine lesioned monkeys were statistically evaluated using a non-parametric test (Kruskal–Wallis). When the *P*-values were less than 0.05, groups were compared using a Mann–Whitney test.

3. Results

3.1. GMC1111 subcutaneously to unilaterally 6–hydroxydopamine lesioned animals

Subcutaneous administration of the dopamine receptor agonist apomorphine induced a marked stimulatory effect on rotational behavior that was stable during the time course of the study in the unilaterally 6-hydroxydopamine lesioned marmoset monkeys (Fig. 1). No statistically significant effect on contralateral rotations different from saline was established when GMC1111 was given by itself in any of the doses tested (Fig. 2). When GMC1111 was given s.c. together with apomorphine, the contralateral rotations decreased in the low rotating group of animals with increasing dose of GMC1111 (Fig. 3). This effect reached statistical significance for the highest doses of GMC1111 (0.3, 1.0 and 3.0 mg/kg). The two lowest doses of GMC1111 (0.03 and 0.1 mg/kg) given with apomorphine caused a rotational behavior that was not statistically significantly different

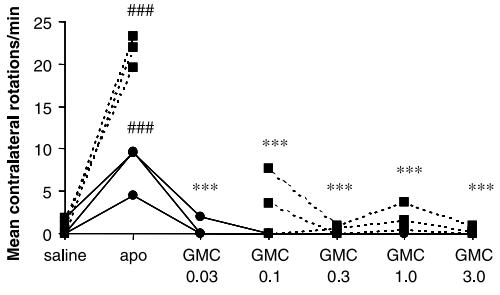

Fig. 2. Graph representing data on contralateral rotational behavior following subcutaneous administration of saline, apomorphine or GMC1111 alone at concentrations of 0.1, 0.3, 1.0 and 3.0 mg/kg in unilaterally 6-hydroxydopamine lesioned common marmosets. The low rotating group of animals (-●-) (n=3) was also given GMC1111 at a concentration of 0.03 mg/kg that the high rotating group of animals (-■-) (n=3) was not. Data shown as individual mean rotations/min (n=6) during the 60-minute observation period immediately after drug administration. One-way analysis of variance (ANOVA) followed by paired *t*-test was used for statistical evaluation. ***$P<0.001$ versus apomorphine. ###$P<0.001$ versus saline.

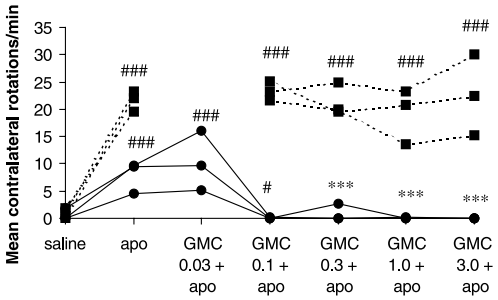

Fig. 3. Graph representing data on rotational behavior induced by apomorphine at baseline or after concomitant subcutaneous administration of GMC1111 at concentrations of 0.1, 0.3, 1.0 and 3.0 mg/kg in unilaterally 6-hydroxydopamine lesioned common marmosets. The low rotating group of animals (-●-) (n=3) was also given GMC1111 at a concentration of 0.03 mg/kg that the high rotating group of animals (-■-) (n=3) was not. Data shown as individual mean rotations/min (n=6) during the 60-minute observation period immediately after drug administration. One-way analysis of variance (ANOVA) followed by paired *t*-test was used for statistical evaluation. ***$P<0.001$ versus apomorphine. #$P<0.05$. ###$P<0.001$ versus saline.

from apomorphine alone. However, in the high rotating group of unilaterally 6-hydroxydopamine lesioned monkeys, no effect on rotations was seen with concomitant GMC1111 administration. No other behavioral effects than rotations were seen with GMC1111 in the unilaterally lesioned animals.

This indicates that GMC1111 may act as a dopamine receptor antagonist in the unilaterally 6-hydroxydopamine lesioned marmoset monkey model of parkinsonism, an effect that is probably attributed to the dopamine D2 receptor partial agonist properties shown by GMC1111 in in vitro evaluations (Van Vliet et al., 2000b).

3.2. GMC1111 orally to unilaterally 6-hydroxydopamine lesioned animals

In order to estimate the oral bioavailability of GMC1111, the drug was administered orally to unilaterally 6-hydroxydopamine lesioned marmosets. When the drug was given together with saline, no rotational behavior was observed with any of the doses of GMC1111 (Table 2). If GMC1111

Table 2
Mean number±S.D. (n=6) of contralateral rotations per minute during 60 min after peroral administration of GMC1111 and concomitant s.c. injection of apomorphine or saline

Drug	Contralateral rotations
Apomorphine 0.2 mg/kg	3.12±3.56
GMC1111 0.3 mg/kg±saline	0.01±0.03[a]
GMC1111 1.0 mg/kg±saline	0.06±0.16[a]
GMC1111 3.0 mg/kg±saline	0.00±0.00[a]
GMC1111 0.3 mg/kg±apomorphine 0.2 mg/kg	2.16±2.72
GMC1111 1.0 mg/kg±apomorphine 0.2 mg/kg	0.00±0.00[a]
GMC1111 3.0 mg/kg±apomorphine 0.2 mg/kg	0.01±0.03[a]

One-way analysis of variance (ANOVA) followed by paired *t*-test was used for statistical evaluation.

[a] $P<0.01$ versus apomorphine.

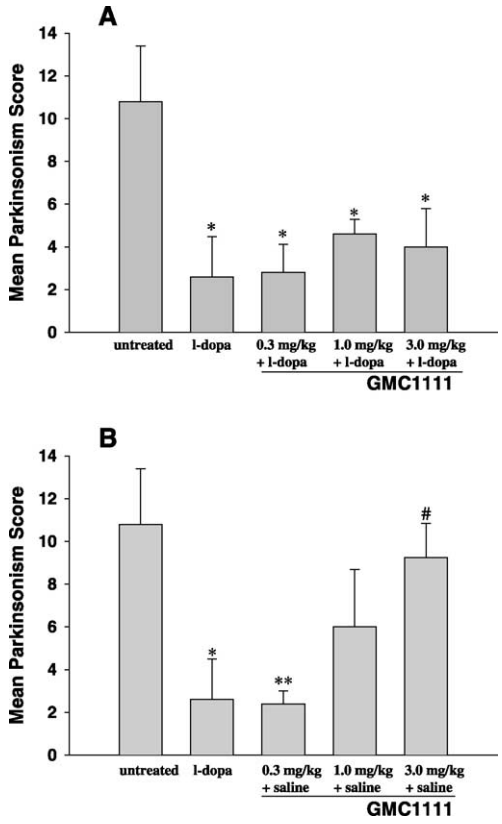

Fig. 4. Mean parkinsonian score (±S.E.M.) in bilaterally 6-hydroxydopamine lesioned marmosets (n=4–6) at baseline and 30 min after a given drug. The effect of concomitant levodopa/benserazide administration and GMC1111 is shown in A. The effect of GMC1111 given with saline is pictured in B. Kruskal–Wallis test followed by Mann–Whitney test was used for statistical evaluation. *P<0.05. **P<0.01 versus untreated. #P<0.05 versus levodopa-treated.

was administered together with apomorphine the rotational response was abolished with the highest doses of GMC1111 (1.0 and 3.0 mg/kg) (P<0.01 if compared to apomorphine injection) (Table 2). This indicates that GMC1111 has a good oral bioavailability and that the drug has mainly antagonistic properties on dopamine receptors if given orally in this primate model. However, these animals did show a much lower mean number of rotations after apomorphine treatment than the animals used in the study where GMC1111 was given subcutaneously. This might be due to a less-pronounced lesion in these animals or because the behavioral scorings were performed without the observer present in the room as the experiments were videotaped for later evaluation.

3.3. GMC1111 subcutaneously to bilaterally 6-hydroxydopamine lesioned animals

To further investigate the effects of GMC1111 on motor behavior, marmosets were bilaterally lesioned with 6-hydroxydopamine and treated sub-chronically with levodopa/benserazide. After 11 days of levodopa administration, when a stable antiparkinsonian effect was established and peak-dose dyskinesia was evident, GMC1111 was given in different regimens. The dyskinesias displayed were mainly located in the oral region or shown as dyskinetic movements in arms and legs. The antiparkinsonian response was satisfactory with all doses of GMC1111, if given together with levodopa/benserazide (Fig. 4A). Except for the lowest dose of GMC1111 given together with saline, the antiparkinsonian effect was higher whenever levodopa/benserazide was part of the drug therapy compared to when it was not. If GMC1111 was given by itself to these animals, the parkinsonian score increased with increasing dose of GMC1111 compared to when levodopa/benserazide was administered (Fig. 4B) and this reached statistical significance for the highest dose of GMC1111 (3.0 mg/kg). With the lowest dose of GMC1111 (0.3 mg/kg), the antiparkinsonian effect was even better than with levodopa/benserazide, indicating a dopamine receptor agonist action of GMC1111 at low concentrations. This indicates that GMC1111 might provide a good antiparkinsonian effect, but only at low concentrations.

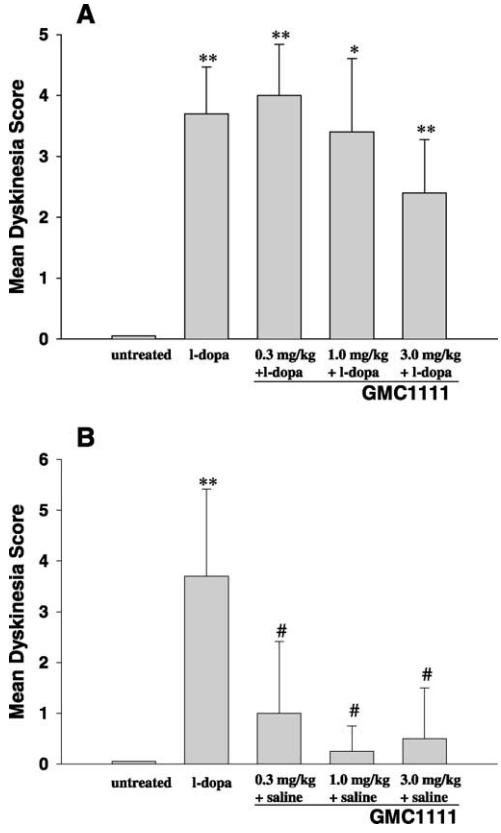

Fig. 5. Dyskinetic response in bilaterally 6-hydroxydopamine lesioned monkeys (n=4–6) at baseline and 30 min after treatment with a given drug. Results shown as mean dyskinetic score±S.E.M. The effect of concomitant levodopa/benserazide administration and GMC1111 is shown in A. The effect of GMC1111 given with saline is pictured in B. Kruskal–Wallis test followed by Mann–Whitney test was used for statistical evaluation. **P<0.01 versus untreated. #P<0.05 versus levodopa-treated.

When examining dyskinesia in the same model, GMC1111 concomitant with levodopa/benserazide caused a decrease in dyskinesia with increasing dose of GMC1111 (Fig. 5A). However, this failed to reach statistical significance. GMC1111 did not induce dyskinesia when given alone (Fig. 5B).

Taken together, the results obtained in bilaterally 6-hydroxydopamine lesioned marmosets imply that GMC1111 would act as a dopamine receptor antagonist at higher doses and as an agonist at lower doses.

4. Discussion

In earlier experiments on unilaterally 6-hydroxydopamine lesioned rats, GMC1111 was found to produce a long-lasting induction of rotational behavior and an increase in dopamine turnover in rat striatum as measured by in vivo microdialysis (Van Vliet et al., 2000a,b). These results may seem contradictory as they indicate both a dopamine receptor agonistic and antagonistic action. However, it has been proposed that the intrinsic activity of a dopamine receptor agonist partly depends on the responsiveness of the receptor, which in turn is determined by the degree of previous endogenous agonist occupancy on that receptor (Carlsson, 1983). This hypothesis is mainly based on the findings with the partial agonist (−)-3-PPP, which acted as an antagonist on normosensitive dopamine receptors and an agonist on supersensitive dopamine receptors (Carlsson, 1983). As it is known that a postsynaptic supersensitivity of dopamine receptors develops in the unilaterally 6-hydroxydopamine lesioned striatum in rats (Ungerstedt, 1971), this would mean that GMC1111 might act as a dopamine receptor agonist in this model. In the present study GMC1111 was shown to display a dopamine receptor agonist action in some situations and a dopamine receptor antagonist action under other experimental conditions.

Moreover, the explanation of the dual action of GMC-1111 might be even more straightforward since the enantiomers of GMC1111 recently have been found to have different affinities and intrinsic efficacies for dopamine receptors, much like the enantiomers of 3-PPP. The minus enantiomer is a full dopamine D2 receptor agonist and a dopamine D3 receptor antagonist. The plus enantiomer is a partial dopamine D2 receptor agonist and a dopamine D3 receptor antagonist. In experiments on unilateral 6-hydroxydopamine lesioned rats, the minus enantiomer of GMC1111 was shown to induce contralateral rotations by itself in coherence with it being a dopamine D2 receptor agonist. The plus enantiomer did not induce any rotational behavior when given to unilateral 6-hydroxydopamine lesioned rats (unpublished results). In view of this, the plus enantiomer of GMC1111 would need to be further studied as a potential atypical antipsychotic and the antiparkinsonian properties of the minus enantiomer need further investigation.

In the present study, GMC1111 was found to decrease the apomorphine-induced rotations in unilaterally 6-hydroxydopamine lesioned marmosets if given s.c., an effect which was most clearly seen in the low-rotating group of monkeys and which suggests a dopamine receptor antagonist action of the drug. When given orally, GMC1111 almost completely abolished the apomorphine-induced rotations at the two highest doses. Interestingly, this implies a dopamine receptor antagonist action of the racemic GMC1111 and good oral availability of the drug in this primate species.

In order to further study the antiparkinsonian and antidyskinetic actions of GMC1111, another animal model of Parkinson's disease was used. Infusion of 6-hydroxydopamine bilaterally into the medial forebrain bundle provides an animal model of Parkinson's disease that has been characterized elsewhere both for rats (Hayakawa et al., 1999; Roedter et al., 2001) and marmosets (Mitchell and Carroll, 1997). The marmosets show a stable and marked parkinsonian syndrome (Mitchell and Carroll, 1997) and more complex motor behavior can be studied. In this model, GMC1111 seemed to have a good antiparkinsonian action on itself in low concentrations and an antidyskinetic effect at higher concentrations. This suggests that GMC1111 might be a useful antiparkinsonian agent with lesser side effects, such as peak-dose dyskinesia. This might be due to the dual action on dopamine receptors of GMC1111, i.e. it can function both as a dopamine receptor agonist and an antagonist and hence balancing the output of the dopamine system.

The results presented in this study are similar to the actions of another drug, (*S*)-(−)-3-methylsulfonylphenyl-1-propylpiperidine ((−)-OSU6162), a substituted (*S*)-3-phenylpiperidine that has shown promising results as a stabilizer of dopamine neurotransmission (Ekesbo et al., 1997, 1999, 2000; Neu et al., 1997; Tedroff et al., 1998, 1999). (−)-OSU6162 was found to attenuate levodopa-induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated marmosets without appreciably affecting the antiparkinsonian response (Ekesbo et al., 1997). A good antidyskinetic action of (−)-OSU6162 was also reported in a study on MPTP-treated cynomolgus monkeys (Tahar et al., 2001). Moreover, the drug was shown to exert indirect state-dependent effects that differently affect dopamine D1 and dopamine D2 receptor agonist-induced behavior in marmosets (Ekesbo et al., 2000). In a study on rats, (−)-OSU6162 was highly active in vivo on synthesis and turnover of dopamine and showed psychomotor normalizing effects in behavioral tests without inducing hypolocomotion and catalepsy (Sonesson et al., 1994). Moreover, (−)-OSU6162 has shown promising results in the treatment of Huntington's disease (Tedroff et al., 1999). Both (−)-OSU6162 and GMC1111 may represent a novel principle of dopamine stabilizers, normalizing both elevated and reduced dopaminergic neurotransmission. This might prove useful in the treatment of Parkinson's disease. However, GMC1111 has not yet been tested on humans and

species differences between humans and primates may exist in their response to the drug.

In conclusion, the pharmacological properties of GMC-1111 are interesting and the drug seems to be a new addition to the family of drugs that stabilizes dopamine neurotransmission.

Acknowledgements

We wish to thank Leonard A. Van Vliet for synthesizing the drug GMC1111. This study was supported by grants from the Swedish Medical Research Council, no. 11565 (PEA), the Swedish Natural Science Research Council, no. I 1179 (special program 'Signals of Life') (PEA), and the Bank of Sweden Tercentenary Foundation (LG).

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