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European Journal of Pharmacology 280 (1995) 159–166

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Antiparkinsonian action of dextromethorphan in the reserpine-treated mouse

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Received 19 December 1994; revised 20 March 1995; accepted 28 March 1995

Abstract

Dextromethorphan has been reported to be a weak antagonist of the ion channel associated with the NMDA receptor, and to have putative antiparkinsonian activity in man. This study looked at the effects of dextromethorphan in normal and monoamine-depleted mice, to determine whether it exhibited a behavioural profile with regard to motor activity that was consistent with NMDA receptor blockade. In normal mice, 5–80 mg/kg i.p. dextromethorphan caused modest muscle relaxation at the highest dose in all animals; hyperlocomotion and stereotypy were evident at 40 mg/kg i.p. in a fraction of mice (4/14). In 24 h reserpine-treated mice, locomotion was reinstated by the dopamine D_1 receptor agonist 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrochloride (SKF 38393, 30 mg/kg i.p.), the dopamine D_2 receptor agonist *N*-n-propyl-*N*-phenylethyl-*p*-(3-hydroxyphenyl)ethylamine (RU 24213, 5 mg/kg s.c.) and L-3,4-dihydroxyphenylalanine (L-DOPA, 150 mg/kg i.p. in conjunction with benserazide 100 mg/kg i.p.). Dextromethorphan alone (10–40 mg/kg i.p.) caused non-significant arousal of monoamine-depleted mice, but potentiated synergistically movements elicited by SKF 38393 and L-DOPA, though not RU 24213. The possible use of dextromethorphan as an adjunct to L-DOPA in the treatment of Parkinson's disease in man, is discussed.

Keywords: Reserpine; Motor behavior; Dextromethorphan; Dopamine D_1 receptor; Dopamine D_2 receptor; L-DOPA (L-3,4-dihydroxyphenylalanine); (Mouse)

1. Introduction

Dextromethorphan is the dextrorotatory morphinan analogue of codeine and a clinically well-tolerated antitussive. Dextromethorphan has a complex profile of binding to central nervous tissue and has been found to act as a ligand for a variety of receptors (for review see Tortella et al., 1989). It recognises the same receptive sites as phencyclidine and behaves as a weak, non-competitive antagonist of the NMDA receptor. The latter property could account for dextromethorphan's anticonvulsant (Ferkany et al., 1988) and neuroprotective actions (Choi, 1987), or these might be due to its metabolic conversion to dextrorphan, which binds with high affinity to the NMDA receptor-associated channel site (Franklin and Murray, 1992).

Other therapeutic possibilities for this drug include the pharmacological management of Parkinson's disease, where the primary loss of nigrostriatal dopamine neurones leads to secondary glutamatergic hyperactivity within basal ganglia motor circuits (Albin et al., 1989). It has been hypothesised that the akinesia of parkinsonism might be relieved by agents which block glutamate receptors, since these would help to normalise the excessive impulse traffic that develops in motor-inhibitory basal ganglia pathways (Gerfen, 1992; Greenamayre and O'Brien, 1991; Starr, 1995).

Behavioural experiments with monoamine-depleted rodents and primates bear out this prediction, by demonstrating that a wide variety of NMDA and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-type glutamate receptor antagonists, whilst having little antiakinetic action of their own, greatly potentiate that of the traditional antiparkinsonian drug L-3,4-dihydroxyphenylalanine (L-DOPA; Kaur et al., 1994; Klockgether et al., 1991; Klockgether and Turski, 1990; Löschmann et al., 1991; Maj et al., 1993; Morelli et al., 1992; Wüllner et al., 1992). Thus adjunctive treatment of human parkinsonian patients with gluta-

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SSDI 0014-2999(95)00200-6

mate receptor antagonists could conceivably increase the useful lifetime of L-DOPA therapy, as well as slow the inexorable progression of the underlying neurodegenerative process itself.

A major objection to administering NMDA receptor antagonists to man is that they can cause unacceptable side effects. These include pyschostimulation and memory impairment, as well as muscle relaxation and ataxia. From theoretical considerations, however, compounds which have a low affinity for the NMDA receptor-associated ion channel may be the most effective (Lipton, 1993) and the least toxic of the many NMDA receptor antagonists that are currently available. Dextromethorphan closely matches this theoretical ideal and has been tested in small groups of idiopathic parkinsonian patients with mixed success. Thus dextromethorphan significantly increased the motor improvement obtained with L-DOPA in two open-label trials (Bonuccelli et al., 1992; Saenz et al., 1993), the additional mobility being comparable in magnitude to that achieved with amantadine, another weak NMDA receptor antagonist (Bonuccelli et al., 1992; Kornhuber et al., 1991). A later attempt to reproduce this finding was unsuccessful (Montastruc et al., 1994).

The present study considers the experimental basis for a possible antiakinetic action of dextromethorphan in the reserpine-treated mouse model of parkinsonism. The motor effects of dextromethorphan have been investigated by administering the drug on its own, and in conjunction with L-DOPA or selective agonists of dopamine D_1 and D_2 receptors.

2. Materials and methods

2.1. Animals

Male albino mice (TO strain, A.R. Tuck), weighing 27–35 g, were housed in groups of 25 at $22 \pm 1°$ C, under fluorescent lighting from 07.00 to 17.00 h, and allowed free access to food and water. Experiments were conducted between 10.00 and 17.00 h, and each animal was used once only.

2.2. Behavioural measurements

To establish a working dose range for dextromethorphan in mice, the drug was first administered to naive animals (5–80 mg/kg i.p.). The mice were then placed singly onto the floor of a Perspex container ($29 \times 26 \times 21$ cm high) without prior acclimatization, and their locomotor activity monitored for the next 2 h by a Radiospares 8960 Microwave Doppler Module, connected to a combined amplifier, timer and LED display unit, constructed in this laboratory to our own design. The assembly was previously calibrated to detect horizontal movements and to provide 10 min locomotor scores in arbitrary units. The presence of other behaviours was recorded by a trained observer, with reference to a checklist, but these were not systematically quantified.

Subsequent experiments were conducted with mice pretreated with reserpine (5 mg/kg i.p.), 20–24 h beforehand. These animals were injected with dextromethorphan (10–40 mg/kg i.p.), L-DOPA (150 mg/kg i.p.) plus the peripheral DOPA decarboxylase inhibitor benserazide (100 mg/kg i.p. 30 min beforehand), 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrochloride (SKF 38393, 30 mg/kg i.p., a selective dopamine D_1 receptor agonist) or *N*-*n*-propyl-*N*-phenylethyl-*p*-(3-hydroxyphenyl)ethylamine (RU 24213, 5 mg/kg s.c., a selective dopamine D_2 receptor agonist), either alone or in various drug combinations (see text). The motor activity of the animals was then monitored every 10 min for 2 h, together with any other behaviours as described above.

2.3. Statistics

Locomotion was recorded as cumulative 2 h counts. These data were analysed by one- or two-way analysis of variance (ANOVA). Post-hoc analysis of individual dose points was made with Scheffé's multiple range test. In all cases significance was taken as $P < 0.05$.

2.4. Drugs

Reserpine, L-DOPA and benserazide were obtained from Sigma; dextromethorphan and SKF 38393 were obtained from Research Biochemicals International (Natick, MA, USA). RU 24213 was generously provided by Roussel. All drugs were dissolved in distilled water and administered in a dose volume of 5 ml/kg. The solution of reserpine was aided with a minimum quantity of glacial acetic acid.

3. Results

3.1. Motor effects of dextromethorphan in normal mice

Two hour locomotor scores for non-habituated mice averaged 3327.6 ± 832.4 ($n = 13$). Over the dose range 5–20 mg/kg, dextromethorphan did not visibly affect motor performance (Fig. 1). At 40 mg/kg dextromethorphan, the animals were clearly divisible into two populations, with one group appearing no different from controls (mean 2 h motor counts = 2955.1 ± 673.4, $n = 10$) and the other exhibiting clear signs of motor excitement (mean 2 h motor counts = $21\,212.8 \pm 6005.7$, $n = 4$). The locomotor scores for these responders and non-responders are shown separately in Fig. 1. Re-

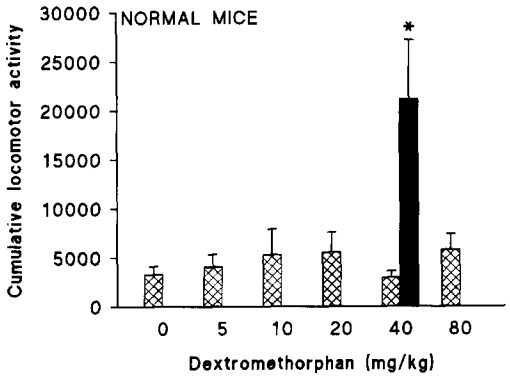

Fig. 1. Effects of dextromethorphan on locomotor activity of normal mice. Animals were injected i.p. with dextromethorphan (5–80 mg/kg) or vehicle (controls), then placed singly onto the floor of a Perspex observation box, without prior acclimatisation. Motor activity, consisting principally of forward locomotion, was recorded every 10 min for 2 h by means of Radiospares 8960 Doppler Modules. Each column is the mean 2 h cumulative motor score ± S.E.M. for 6–14 experiments. Data for 40 mg/kg i.p. dextromethorphan have been divided into 'non-responders' (hatched column, $n = 10$), which appeared no different from controls, and 'responders' (solid column, $n = 4$), which exhibited clear signs of hyperlocomotion and stereotypy. $^{*}P < 0.05$ versus controls.

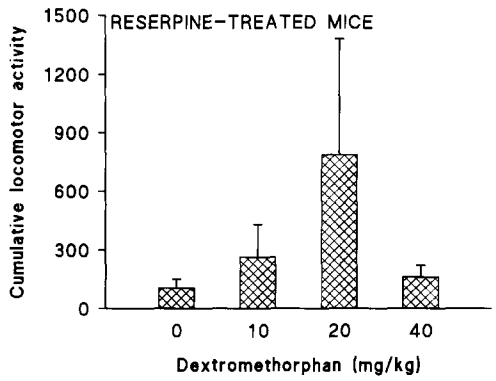

Fig. 2. Effects of dextromethorphan on locomotor activity in reserpine-treated mice. Animals were injected with 5 mg/kg i.p. reserpine, and 24 h later with dextromethorphan (10–40 mg/kg i.p.) or vehicle (controls). Locomotor scores were then recorded every 10 min for 2 h as described for Fig. 1. Each result is the mean ± S.E.M. of 7–10 experiments.

sponders were continuously active over the period 10–100 min post-injection, displaying fast forward walking, rearing, sniffing and occasional grooming. Non-responders and vehicle-treated control mice were active during the early exploratory phase (10–40 min), which then gave way to increased bouts of whole body grooming and stillness. No such behavioural dichotomy was evident at 80 mg/kg i.p. dextromethorphan, which caused a modest flattening of the hind quarters suggestive of mild muscle relaxation, but this did not appear to interfere with locomotion and the animals were not ataxic. Statistical analysis revealed a significant drug main effect by one-way ANOVA ($F(5,41) = 11.23$, $P < 0.0001$), and a significant increase in locomotion at 40 mg/kg dextromethorphan in the 'responder' group ($P < 0.05$ versus controls by Scheffé's multiple range test).

3.2. Motor effects of dextromethorphan in reserpine-treated mice

Control mice receiving 5 mg/kg i.p. reserpine were almost completely immobile 24 h later (2 h locomotor score = 105.8 ± 45.8, $n = 10$). Dextromethorphan, 10 mg/kg i.p., was without effect on reserpine-induced akinesia, but higher doses appeared to cause some arousal (Fig. 2). This was most pronounced at 20 mg/kg, which elicited sniffing, grooming, rearing and some forward locomotion. However, locomotion was accompanied by hind limb abduction during the first hour, giving variable locomotor counts, which were not significantly increased for the group as a whole (drug main effect by one-way ANOVA $F(3,42) = 1.80$, $P = 0.16$). Muscle relaxation of the hind quarters was more pronounced at 40 mg/kg dextromethorphan and may have impeded motor recovery, as indicated in Fig. 2.

3.3. Effect of dextromethorphan on SKF 38393-induced locomotion in reserpine-treated mice

Based on earlier experiments (Starr et al., 1987), a fixed dose of 30 mg/kg i.p. SKF 38393 was used to elicit dopamine D_1 receptor-dependent locomotion in reserpine-treated mice. Movements were fluent and well-coordinated, and were accompanied by abundant rearing, sniffing and grooming. The locomotion evoked by SKF 38393 was long-lived (> 2 h), as shown in Fig.

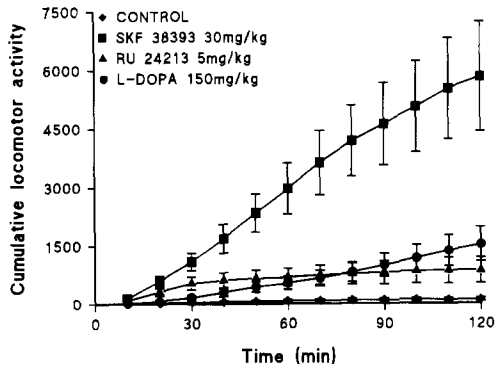

Fig. 3. Time course of locomotor activity induced by dopaminergic treatments in 24 h reserpine-treated mice. Animals were injected with 5 mg/kg i.p. reserpine, and 24 h later with the dopamine D_1 receptor agonist SKF 38393 (30 mg/kg i.p., solid squares), the dopamine D_2 receptor agonist RU 24213 (5 mg/kg s.c., solid triangles), or a combination of L-DOPA (150 mg/kg i.p.) and benserazide (100 mg/kg i.p., solid circles). Controls received vehicle (5 ml/kg i.p., solid diamonds). Each result is the mean ± S.E.M. of at least six experiments.

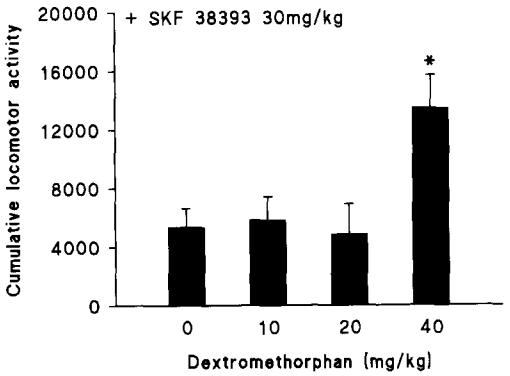

Fig. 4. Effects of dextromethorphan on locomotor activity induced by SKF 38393 in 24 h reserpine-treated mice. Treatments as for Fig. 3. Each column is the mean ± S.E.M. of at least six experiments. $^{*}P < 0.0001$ versus controls.

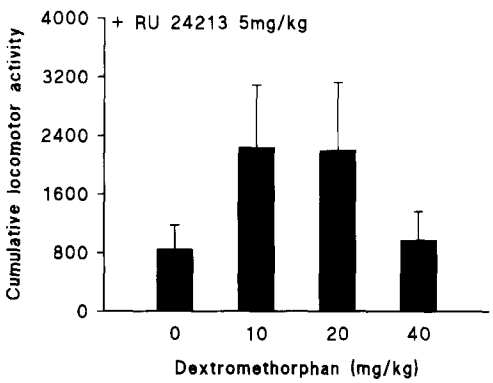

Fig. 5. Effects of dextromethorphan on the locomotor activity induced in 24 h reserpine-treated mice by RU 24213. Treatments as for Fig. 3. Each column is the mean ± S.E.M. of at least six determinations.

3. Cumulative 2 h motor counts for SKF 38393-treated mice (5361.5 ± 649.2, $n = 10$) were significantly different from vehicle-treated controls (drug main effect by one-way ANOVA $F(1,26) = 113.9$, $P < 0.0001$; Fig. 4). The effect of coadministration of SKF 38393 (30 mg/kg) with dextromethorphan (10–40 mg/kg) is shown in Fig. 4. Low doses of dextromethorphan (10–20 mg/kg) did not influence the animals' response to SKF 38393, whilst 40 mg/kg dextromethorphan interacted synergistically with SKF 38393 to enhance locomotion (interaction term by two-way ANOVA $F(1,37) = 69.2$, $P < 0.0001$). These animals walked rapidly and fluently around the perimeter of the test box, and showed no signs of hind-limb abduction or postural collapse. Other dopamine D_1 receptor-mediated behaviours appeared not to be affected by dextromethorphan.

3.4. Effects of dextromethorphan on RU 24213-induced locomotion in reserpine-treated mice

The dose of 5 mg/kg s.c. RU 24213 (determined from a previous study – Starr et al., 1987), reinstated dopamine D_2 receptor-dependent locomotion which was less fluent or robust than that evoked by SKF 38393. The cumulative 2 h motor count was 850.6 ± 234.6 ($n = 6$, drug main effect by one-way ANOVA $F(1,24) = 22.9$, $P < 0.0001$). Animals adopted a characteristic head-down posture, with sniffing directed at the floor, while forward locomotion was slower and more ponderous and only lasted 30–40 min (Fig. 3). The apparent increase in RU 24213-induced locomotion caused by 10–20 mg/kg dextromethorphan, was not significantly different from the sum of the two individual drug effects (interaction term by two-way ANOVA $F(3,72) = 1.33$, $P = 0.27$; Fig. 5).

3.5. Effect of dextromethorphan on L-DOPA-induced locomotion in reserpine-treated mice

As indicated previously (Kaur et al., 1994), a high dose of L-DOPA (150 mg/kg i.p.) was required to restore motor activity to reserpine-treated akinetic mice. Locomotion commenced at about 30 min post-injection, after which it was steadily maintained for the next 90 min (Fig. 3). Recovery of movement was incomplete, with clear evidence of residual ataxia, together with some rearing and much sniffing. Two hour cumulative motor counts averaged 1527.1 ± 369.8 (drug main effect by one-way ANOVA $F(1,40) = 9.19$, $P = 0.0041$, $n = 27$; Fig. 6). Addition of dextromethorphan to the L-DOPA treatment dose-dependently enhanced all aspects of motor responding; rearing was facilitated, and the animals exhibited much licking and scrabbling in the corners. Locomotion was potentiated in a synergistic fashion (interaction term by two-way ANOVA

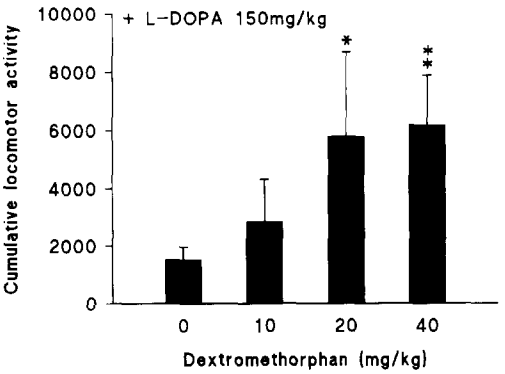

Fig. 6. Potentiation of L-DOPA-induced locomotion in 24 h reserpine-treated mice by dextromethorphan. Treatments as for Fig. 3. Each column is the mean ± S.E.M. of 6–27 determinations. $^{*}P < 0.01$, $^{**}P < 0.001$ versus controls.

$F(3,87) = 5.09$, $P = 0.003$), with significance residing in the 20 mg/kg and 40 mg/kg doses (Scheffé $P < 0.05$, $n = 6$).

4. Discussion

The present results indicate that dextromethorphan is able to stimulate motor activity in a fraction of dopamine-intact (4/14 or 29%) but not monoamine-depleted mice, and to strongly facilitate motor recovery 24 h after reserpine treatment when administered in conjunction with certain dopaminergic treatments. The former property is in agreement with earlier data reported for the rat, where low doses of dextromethorphan (15–30 mg/kg) significantly attenuated haloperidol-induced catalepsy (Scotti De Carolis et al., 1991), and high doses of dextromethorphan (60–120 mg/kg) weakly increased locomotion, stereotypy and ataxia (Szekely et al., 1991). Not all investigators agree with this assessment, however, since Danysz et al. (1994) noted recently that none of these parameters was altered by dextromethorphan, whereas all three were intensified by other low affinity (e.g. memantine, ketamine) or high affinity (e.g. MK 801, phencyclidine) NMDA receptor-channel blockers. It should be added, however, that Szekely et al. (1991) detected hyperlocomotion 45–75 min after administering dextromethorphan i.p. to habituated rats, whereas the experimental conditions employed by Danysz et al. (1994), i.e. non-habituated rats and an overall treatment time of 60 min, would not have allowed a motor stimulant action of dextromethorphan to properly manifest itself.

At suprathreshold doses (40 mg/kg), dextromethorphan clearly elicited a mixed response in our mice; 10/14 animals were plainly unaffected whilst a smaller number (4/14 animals) were unmistakably activated by this treatment. So-called responders registered locomotor counts that were approximately 7-fold higher than non-responders or controls, as well as a large measure of rearing and stereotypy. This behavioural profile resembles that of phencyclidine (Iwamato, 1984), and also dextrorphan, the demethylated metabolite of dextromethorphan (Szekely et al., 1991). Dextrorphan is a higher-affinity antagonist of the NMDA receptor-ion channel than dextromethorphan, and could owe its potent phencyclidine-like behavioural activity to the release of endogenous dopamine from nigrostriatal axon terminals (Hondo et al., 1994). The reason for the variability in animal response to dextromethorphan in the present study could therefore be due to individual differences in the rate of metabolic conversion of dextromethorphan into dextrorphan, the pharmacologically more active moiety. It is known that large inter-individual differences exist in the demethylation of dextromethorphan in man (Pfaff et al., 1983), and it has been hypothesised that enhanced metabolic activation is the reason for the sporadic abuse of dextromethorphan by some individuals (Musacchio, 1990). Demethylation of dextromethorphan is also reported to be strain-dependent in the rat (Bochner et al., 1994), and so the enhanced biosynthesis of dextrorphan in a fraction of our Tuck strain of mice remains a distinct possibility.

As the dose of dextromethorphan was raised to 80 mg/kg, motor excitation gave way to modest sedation. This curvilinear dose-effect relationship is typical of what one sees with other NMDA receptor-ion channel blockers (Starr and Starr, 1994). Our data are hence consistent with the notion that dextromethorphan, or its metabolite dextrorphan, alter motor responding through the auspices of glutamate antagonism.

From our point of view, the more interesting observation concerns dextromethorphan's behavioural stimulant effects in monoamine-depleted animals. Reserpine is widely used for this purpose, and although it disrupts the vesicular storage of all monoamines, not just dopamine, and does not reproduce the neurodegeneration of parkinsonism, it nevertheless is held to provide a useful test bed for investigating the motor actions of drugs at postsynaptic dopamine and glutamate receptors (for critique see Greenamayre, 1993). Earlier reports have indicated that NMDA receptor blockade can directly restore motility to Parkinson-like mice (Carlsson, 1993; Kannari and Markstein, 1991) and rats (Klockgether and Turski, 1990), but not primates (Domino and Sheng, 1993; Löschmann et al., 1991; Wüllner et al., 1992). However, not all laboratories find this and the matter is subject to some controversy (Carlsson et al., 1991; Carlsson and Svensson, 1990; Starr and Starr, 1993a,b, 1994; Verma and Kulkarni, 1992). Moreover, where motor responses are elicited by NMDA receptor blockers administered alone (e.g. MK 801), these are often weak, patchy and frequently accompanied by severe postural collapse and ataxia, such that animals 'displayed only forward locomotion, their hindlegs dragged behind them and their bodies were flat against the ground' (Carlsson and Svensson, 1990). There was some evidence of motor recovery with dextromethorphan in our reserpine-treated mice, consistent with this compound having low affinity for the channel site on the NMDA receptor complex, but this never approached the frequency or fluency of spontaneous movements in normal animals. To date, then, there is no suggestion that this direct motor stimulant property of NMDA receptor antagonists, even those with low binding affinity, could be exploited to the benefit of parkinsonian patients.

A much more reproducible anti-akinetic action of dextromethorphan was revealed when the drug was administered in conjunction with the dopamine D_1 receptor agonist SKF 38393, or with the dopamine

precursor L-DOPA, but not with the dopamine $D_{2/3}$ receptor agonist RU 24213. This, too, is attributable to the glutamate receptor-blocking property of dextromethorphan, as a closely similar synergistic potentiation of dopamine D_1 receptor-mediated (Goodwin et al., 1992; Morelli et al., 1992; Starr and Starr, 1993a,b,1994) and L-DOPA-induced motor responding (Kaur et al., 1994; Klockgether et al., 1991; Klockgether and Turski, 1990; Löschmann et al., 1991; Maj et al., 1993; Morelli et al., 1992), has been described previously with a range of NMDA and AMPA receptor blocking drugs. This took the form of an intensification of the beneficial motor stimulant actions of SKF 38393 and L-DOPA, with none of the signs of the postural abnormalities that bedevilled the restoration of motor activity induced by more potent NMDA receptor antagonists, such as MK 801 and CGP 40116 (Starr and Starr, 1994).

From a theoretical standpoint, the coadministration of drugs like dextromethorphan, as adjuncts to conventional L-DOPA treatment, could represent a major step forward in the pharmacotherapy of Parkinson's disease. Facilitating the induction of voluntary movements by L-DOPA with glutamate receptor antagonists would allow smaller doses of the prodrug to be used. This would be advantageous for several reasons. Firstly, the quantities of potentially neurotoxic oxidation products of dopamine would be reduced (Jenner, 1990), thereby protecting the residual dopamine neurones from accelerated damage and, hopefully, extending the useful lifetime of L-DOPA's effectiveness. Secondly, the administration of lower doses of L-DOPA would reduce the incidence of hallucinatory side effects, and the occurrence of uncontrollable dyskinetic movements by the patient.

With these possible benefits in mind, it is interesting to note that clinicians have already attempted to use add-on therapy with dextromethorphan in this way. Bonuccelli's group (Bonuccelli et al., 1992) reported a significant improvement in tremor, rigidity and finger tapping tests, with single daily supplements of 120 mg or 180 mg dextromethorphan. Saenz et al. (1993) also obtained a modest symptomatic benefit with higher doses (240–360 mg/day), but Montastruc et al. (1994) were not able to repeat these findings. None of the patients participating in these open-label trials was demented, but it may be significant that the average age of the non-improved group (69 years) was considerably higher than those for whom dextromethorphan gave additional benefit (57 years). Sedation and ataxia were occasionally seen as unwanted side effects of dextromethorphan in some parkinsonian patients (Bonuccelli et al., 1992; Montastruc et al., 1994), in common with NMDA receptor blockade in animals (Starr and Starr, 1994). It is too early to make any judgements about the usefulness of dextromethorphan as an antiparkinsonian agent, on the basis of a few uncontrolled trials. It will be interesting to see if dextromethorphan performs favourably in the double-blind, crossover, placebo-controlled trial promised by Bonuccelli et al. (1992), and whether other morphinan analogues having improved efficacy, potency, duration of action and side-effect profile (Tortella et al., 1994), are any better.

The mechanism(s) by which glutamate receptor antagonists potentiate the antiparkinson efficacy of L-DOPA is the subject of continuing investigation (for review see Starr, 1995). Several excitatory basal ganglia pathways, which are postulated to utilise glutamate as their transmitter, are reported to become hyperactive in dopaminergically compromised animals; these include corticostriatal projection neurones, and fibre tracts running to and from the subthalamic nucleus (Albin et al., 1989; Gerfen, 1992; Starr, 1995). Normalisation of neuronal firing in any one of the striatal output circuits would be expected to assist L-DOPA in counteracting parkinsonian akinesia, and this is borne out by the motor activation that accompanies the stereotaxic microinjection of glutamate receptor blockers into the subthalamus or its target nuclei (Brotchie et al., 1991; Carlsson, 1993; Klockgether and Turski, 1990). On the other hand, the fact that dopamine D_1 and D_2 receptors are preferentially localised to the striatonigral and striatopallidal pathways respectively (Gerfen, 1992; Harrison et al., 1990), coupled with the observation that dopamine D_1 receptor-dependent locomotion is accentuated by glutamate receptor blockade, whilst dopamine D_2 receptor-mediated locomotion is not (Starr, 1995; Starr and Starr, 1994), suggests that glutamate receptor blockade could synergistically improve the antiparkinsonian action of L-DOPA by increasing dopamine D_1 receptor efficacy. The flaw in this argument, at least as far as MK 801 is concerned, is that L-DOPA-induced locomotion is potentiated by doses of MK 801 at doses that are 100–1000 times lower than those required to magnify SKF 38393-induced locomotion (Kaur et al., 1994; Starr and Starr, 1993a,b), making it unlikely that dopamine D_1 receptor facilitation is the sole mechanism of MK 801's effect. An alternative explanation is that occluding glutamate receptors might somehow increase the biotransformation of L-DOPA into dopamine, or promote dopamine release, neither of which is properly understood in the parkinsonian brain (Castaneda et al., 1990; Sarre et al., 1992). We are currently investigating this possibility by means of microdialysis.

Acknowledgements

This work was supported by grants from the University of London Central Research Fund and the Parkin-

son's Disease Society. The gift of RU 24213 from Roussel is gratefully acknowledged.

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