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Dopamine autoreceptors and the effects of drugs on locomotion and dopamine synthesis

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1 Criteria for distinguishing dopamine autoreceptor agonism from other mechanisms of inhibiting locomotion were examined, together with the relationship between inhibition of locomotion and dopamine synthesis.

2 ED_{50} potencies to inhibit locomotion of mice were established for drugs from a number of categories. Spiperone 0.02 mg kg^{-1} significantly ($P < 0.05$) reversed inhibition of locomotion by known dopamine agonists but not that by the other types of drug. Idazoxan antagonized inhibition of locomotion due to α_2-agonists but not dopamine agonists. RU 24926 (N-propyl-N,N-di[2-(3-hydroxyphenyl)ethyl]amine) was antagonized by both spiperone and idazoxan.

3 Only for dopamine agonists was there good correlation ($r = 0.97$) between potencies to inhibit locomotion in mice and L-dihydroxyphenylalanine (L-DOPA) accumulation in the nucleus accumbens of rats treated with γ-butyrolactone and 3-hydroxybenzylhydrazine. The specific dopamine D_1-agonist, SK&F 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine), was inactive in both tests at doses up to 10 mg kg^{-1}. The mixed dopamine agonist/antagonist, (−)-3-(3-hydroxyphenyl)-N-propylpiperidine, commonly known as (−)-3-PPP, acted as a dopamine agonist in both tests but inhibited locomotion more potently than L-DOPA accumulation.

4 The inhibitory effects of dopamine agonists on locomotion were not prevented by α-methyl-*p*-tyrosine pretreatment.

5 The data suggest that spiperone-reversible inhibition of locomotion in mice is a good criterion for dopamine autoreceptor agonists. The receptors involved are affected by low doses of both dopamine agonists and antagonists and seem similar to those involved in the autoreceptor mediated inhibition of dopamine synthesis. However, inhibition of locomotion is not due simply to suppression of dopamine release brought about as a secondary consequence of effects on synthesis; a separate mechanism for inhibiting dopamine release is probably involved.

Introduction

Stimulation of presynaptic dopamine receptors, located on the dendrites, soma or axonal terminals of dopamine neurones within the central nervous system, results in suppression of locomotion in rodents (Di Chiara *et al.*, 1976; Strombom, 1976). Suppression of locomotion does not define the mechanism of drug action because this behaviour can be reduced by a range of drugs acting via mechanisms other than stimulation of presynaptic dopamine receptors (eg. α_2-agonism, sedation etc.). Consequently confirmation of dopamine agonist activity requires that the effect be antagonized by a specific antagonist (e.g. by non-sedative doses of neuroleptics, Costall *et al.*, 1981). Since apomorphine reduces the synaptic release (Farnebo & Hamberger, 1971) and the rate of synthesis of dopamine (Raiteri *et al.*, 1978), it is thought that apomorphine and other dopamine autoreceptor agonists suppress locomotion by inhibiting synthesis and/or release of dopamine. Thus if a drug acts at certain doses to suppress locomotion via dopamine autoreceptor agonism, then at corresponding doses, it is expected to inhibit synthesis and/or release of dopamine. The inhibition of L-dihydroxyphenylalanine (L-DOPA) accumulation in rats treated with γ-butyrolactone (GBL; which inhibits impulse flow in dopaminergic neurones and suppresses feedback from events at postsynaptic dopamine receptors) and 3-hydroxybenzylhydrazine (NSD 1015; which inhibits L-aromatic amino acid decarboxylase) is used as an index of the degree of suppression of dopamine

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synthesis mediated via presynaptic dopamine receptor activation *in vivo* (Walters & Roth, 1976).

The purpose of the present study was to examine criteria for distinguishing between drugs acting via dopamine autoreceptors and drugs acting via other mechanisms. Additionally we tested whether the ability to inhibit dopamine synthesis is a prerequisite for the dopamine agonist-induced suppression of locomotor activity. The first criterion for considering a drug as a dopamine autoreceptor agonist was that it should inhibit locomotion in mice and that this effect should be antagonized by pretreatment with the dopamine antagonist spiperone. The second criterion was that the potency of a drug to suppress locomotor activity in mice should correspond with its potency to suppress L-DOPA synthesis in rats using the GBL/NSD 1015 model.

In order to establish whether these were appropriate criteria a range of drugs was tested. These were taken from different pharmacological classes including dopamine agonists and antagonists, α_2-adrenoceptor agonists, an α_2-antagonist, an α_1-antagonist, and anxiolytic, sedative, hypnotic drugs (see section on 'Drugs' for categorization). If only dopamine agonists in general satisfy the criteria, then the criteria are useful. If more than the occasional drug from other classes satisfy the criteria, then they are inappropriate. In some cases where a drug inhibited locomotion without being antagonized by spiperone, further characterization of the mechanism of the inhibition was tested by using the α_2-antagonist idazoxan and the benzodiazepine antagonist Ro 15-1788.

In order to test the importance of inhibition of dopamine synthesis in the locomotion inhibitory effect of dopamine agonists their effects on locomotor activity were tested in mice pretreated with the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine. If the drugs retain their ability to inhibit locomotion when dopamine synthesis is blocked, then their capacity to inhibit locomotion is not directly dependent on their ability to inhibit synthesis.

Methods

Locomotor activity

Male CD1 strain mice (Charles River) 25–30g were taken from stock maintained at 21 ± 1°C with lights on 07 h 00 min–19 h 00 min and access to food and water *ad libitum*. Locomotor activity was measured in a microcomputer controlled activity monitor containing 5 activity chambers (one mouse per chamber) each with 3 infra-red photocell units (Francis *et al.*, 1983). Testing was carried out between 13 h 00 min and 17 h 00 min. Food and water were removed and the mice were treated with the test drug or vehicle (s.c. unless otherwise specified) and the locomotor activity measured during the 5 min period immediately following introduction into the activity monitor. Drug treatment times were 10 min except Ro 15-1788 (15 min) haloperidol, prazosin, idazoxan, meprobamate (30 min) spiperone and sulpiride (60 min). Antagonism by spiperone, idazoxan or Ro 15-1788 of drug-induced inhibition of locomotion was assessed by pretreating with the respective antagonist (intraperitoneally) at a dose which did not by itself significantly suppress locomotion. These doses were spiperone 0.02 mg kg^{-1}, idazoxan 1.6 mg kg^{-1}, Ro 15-1788 10 mg kg^{-1} at 60 min, 30 min and 15 min, respectively, before introduction into the activity monitors. When the role of dopamine synthesis was tested, 250 mg kg^{-1} α-methyl-*p*-tyrosine methylester hydrochloride was given i.p., 60 min before introducing the mice into the activity monitor.

L-DOPA synthesis

Male CFY strain rats (Hacking and Churchill) 175–300g were used and maintained under identical conditions to those previously described for mice. GBL, 750 mg kg^{-1}, and NSD 1015, 50 mg kg^{-1}, were co-administered 30 min before killing except when 3-phenethyl-PP was tested. In this case the pretreatment time for GBL and NSD 1015 was 45 min. A dose of 50 mg kg^{-1} NSD 1015 was used to inhibit L-DOPA decarboxylation since under our conditions doses of 25, 50, 100 and 150 rng kg^{-1} did not cause significantly different accumulation of L-DOPA. Other drugs were administered to groups of 5 rats 1 h before killing. Brains were removed to an ice-cold glass plate. The corpus striatum and nucleus accumbens were rapidly dissected and stored at − 20°C until analysis.

L-DOPA concentrations were assayed using high performance liquid chromatography with electrochemical detection (h.p.l.c.-e.c.d.) following partial purification using a Sephadex 610 column method adapted from Westerink & Mulder (1981). L-DOPA was eluted from an ODS APEX reverse phase column using a 0.1 M sodium dihydrogen phosphate buffer (pH 2.8) containing 0.2 mM EDTA, 30 mg l^{-1} octane sulphonic acid and 8.5% methanol. Electrochemical detection was carried out using a glassy carbon electrode (LC-17) linked to an LC4 control module (Bioanalytical systems, U.S.A.) operating at + 0.7 v potential. A constametric III pump (LDC) was operated at a flow rate of 1 ml min^{-1} with a typical back pressure of 1500 psi.

Cerebellar tissue from untreated animals was used for blank values and (with 100 ng of L-DOPA added) for internal standards. The volume of the samples after the initial purification was 3 ml, of which 0.1 ml was taken for h.p.l.c. assay. The coefficient of variation of the internal standards was 1.1 ± 0.74%, s.d. cal-

culated over 5 separate assays. The recovery through the whole procedure was typically greater than 90%.

Statistical analysis

Regression data were analysed and ED_{50} values with 95% confidence limits determined by analysis of variance including correction for variance of controls. Significances in the single and multiple comparisons data were analysed using Student's *t* test and Dunnett's test, respectively.

Drugs

Drug doses refer to base except were stated otherwise in the text. (±)-3-PPP ((±)-3-(3-hydroxyphenyl)-N-propylpiperidine hydrobromide), its enantiomers, the N-2-phenylethyl analogue of 3-PPP called 3-phenethyl-PP, ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4-H-imidazo [1,5-a][1,4] benzodiazepine-3-carboxylate (Ro 15-1788) and sulpiride were synthesized in our laboratory. Other drugs were obtained from the following sources, either commercially or, where

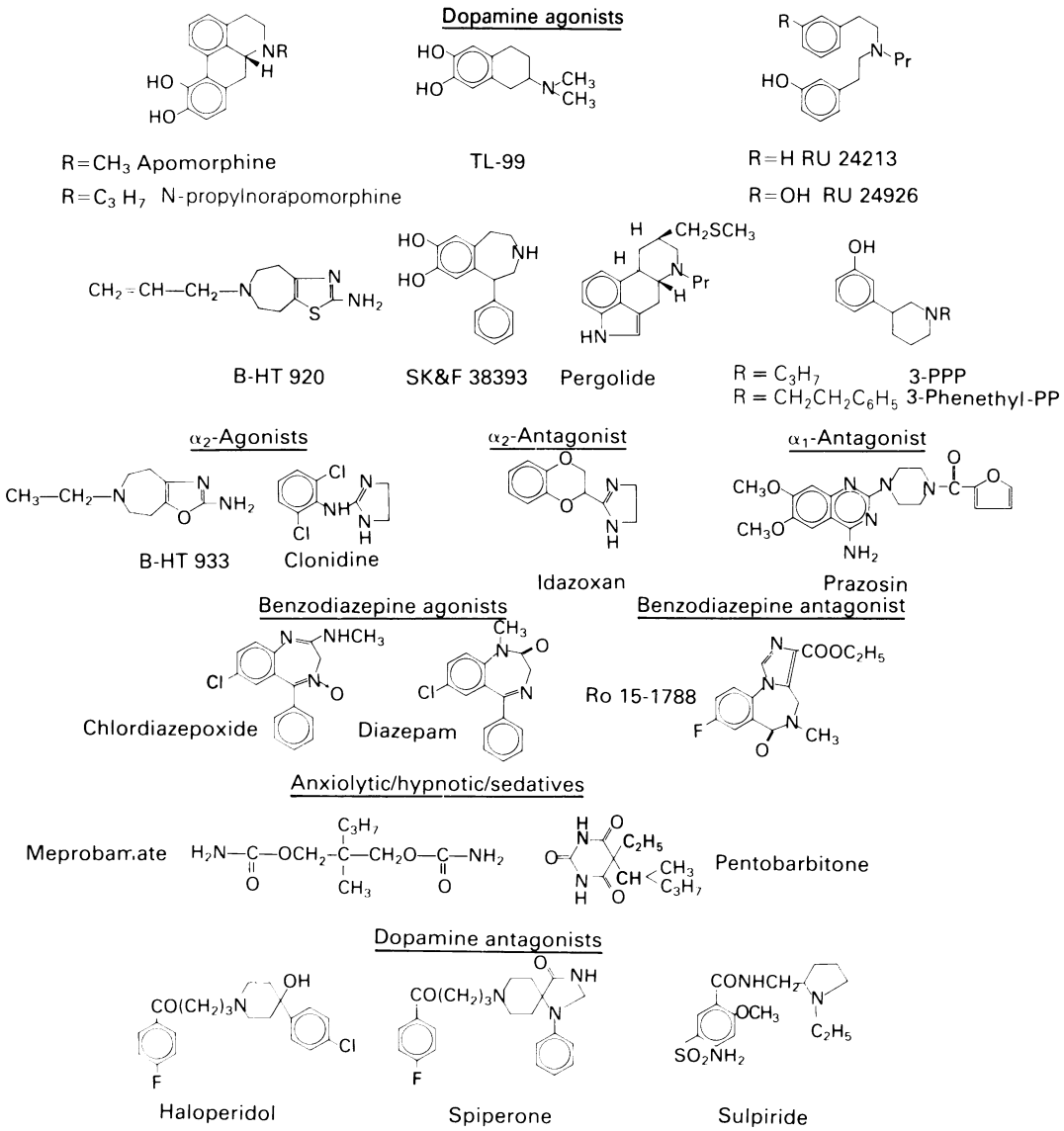

Figure 1 Drug structures.

marked *, as generous gifts which we gratefully acknowledge: 3-hydroxybenzylhydrazine dihydrochloride (NSD 1015; Aldrich); 2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo [4,5-d] azepine dihydrochloride (B-HT 920), 2-amino-6-ethyl-5,6,7,8-tetrahydro-4H-oxazolo [4,5-d] azepine dihydrochloride (B-HT 933 or azepexole) and clonidine hydrochloride (Boehringer FDR*); pergolide mesylate (Eli-Lilly*); spiperone (Janssen*); pentobarbitone sodium (Sagatal; May and Baker); prazosin hydrochloride (Pfizer*); idazoxan (RX 781094 hydrochloride; Reckitt and Colman*); N,N-dimethylamino-6,7-dihydroxytetraline hydroboromide (TL-99) and N-propyl-norapomorphine hydrochloride (NPA; Research Biochemicals Inc. U.S.A.); chlordiazepoxide hydrochloride and diazepam (Roche*); N-propyl-N-2-phenylethyl-N-[2-(3-hydroxyphenyl) ethylamine hydrochloride (RU 24213) and N-propyl-N,N-di[2-(3-hydroxyphenyl)ethylamine (RU 24926; Roussel-UCLAF*); haloperidol (Searle*); apomorphine hydrochloride, γ-butyrolactone (GBL) and α-methyl-*p*-tyrosine methylester hydrochloride (Sigma); 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine hydrochloride (SK&F 38393; Smith, Kline & French*); meprobamate (Wallace*). Drugs were dissolved in 0.9% w/v NaCl solution (saline) with the following exceptions. GBL, NSD 1015, pergolide and SK&F 38393 were dissolved in distilled water; meprobamate, prazosin and Ro15-1788 were suspended in 1% methyl cellulose; 3-phenethyl-PP, sulpiride and haloperidol were dissolved in saline with a minimum amount of tartaric acid; diazepam and spiperone were dissolved in distilled water with a minimum amount of tartaric acid and acetic acid respectively; apomorphine solutions were protected from oxidation by sodium metabisulphite. Where necessary, vehicle and drug solutions were adjusted to pH 5.5–8.0 with sodium hydroxide. Compounds were injected s.c. (except idazoxan, prazosin, spiperone, haloperidol and sulpiride i.p.) in a volume of 0.1 ml per 100g body weight in rats, and 1.0 ml per 100g body weight in mice. Animals not receiving drugs were administered the respective drug vehicle at the corresponding times of the injection schedule.

Table 1 Inhibition of locomotor activity in mice and of L-DOPA accumulation in nucleus accumbens of GBL/NSD 1015 treated rats

Compound	*Inhibition of locomotor activity ED_{50} (95% limits)*	*Inhibition of L-DOPA accumulation ED_{50} (95% limits)*
N-Pr-norapomorphine	0.004 (0.002–0.005)	0.005 (0.002–0.031)
L-Apomorphine	0.02 (0.003–0.15)	0.060 (0.01 –0.16)
B-HT 920	0.01 (0.004–0.023)	0.028 (0.002–0.124)
Pergolide	0.09 (0.017–1.68)	0.125 (0.05 –0.83)
RU 24926	0.13 (0.057–0.32)	0.21 (0.096–0.381)
RU 24213	0.17 (0.038–0.77)	0.517 (0.349–0.845)
TL-99	0.44 (0.300–0.64)	1.172 (0.642–2.664)
(±)-3-PPP	1.34 (0.57 –4.44)	3.14 (0.62 –12.36)
(+)-3-PPP	1.97 (0.71 –9.69)	5.3 (2.30 –14.0)
(−)-3-PPP	1.81 (0.53 –7.82)	29.6 (10.4 –279)
3-Phenethyl-PP	0.25 (0.076–0.96)	2.337 (0.822–19.54)
SK&F 38393	Inactive at 10 Increased at 30**	Inactive at 10
Clonidine	0.043 (0.022–0.08)	Inactive at 8.6
B-HT 933	7.7 (2.2 –27.0)	37% decrease at 21.4*
Chlordiazepoxide	6.88 (5.44 –9.2)	Inactive at 17.9
Diazepam	13.5 (7.9 –26.4)	Inactive at 30
Pentobarbitone Na	31.1 (19.2 –48.5)	Inactive at 100
Meprobamate	230 (147 –398)	Inactive at 250
Idazoxan	33.9 (10.3 –>111)	Inactive at 59
Prazosin	2.89 (1.34 –7.79)	Inactive at 27.4
Spiperone	0.14 (0.069–0.29)	68% increase at 5*
Haloperidol	0.11 (0.090–0.14)	81% increase at 3*
Sulpiride	118 (42.1 –>330)	Inactive at 200

ED_{50} values and doses in mg kg^{-1} s.c. (i.p. haloperidol, spiperone, prazosin, idazoxan, sulpiride).
* $P<0.05$, ** $P<0.01$, Dunnett's test.

Table 2 Antagonism of drug-induced inhibition of locomotion in mice by specific pharmacological antagonists

Compound	*Spiperone*	*Idazoxan*	*Ro 15-1788*
N-Pr-norapomorphine	**	NS	
Apomorphine	**	NS	
B-HT 920	**	NS	
Pergolide	**	NS	
RU 24926	**	**	
RU 24213	**	NS	
TL-99	**	NS	
(±)-3-PPP	*	NS	
(+)-3-PPP	*	NS	
(−)-3-PPP	*	NS	
3-Phenethyl-PP	*	NS	
Clonidine	NS	**	
B-HT 933	NS	**	
Chlordiazepoxide	NS		**
Diazepam	NS		**
Pentobarbitone-Na	NS		
Meprobamate	NS		
Idazoxan	NS		
Prazosin	NS		
Spiperone	NS		
Haloperidol	NS		
Sulpiride	NS		

* $P < 0.05$; ** $P < 0.01$; NS, not significant; Student's t test.

Drug categorization

Pharmacological categorization of the compounds, apart from those of long established standing, is based on the following references. B-HT 920 and B-HT 933, dopamine and α_2-agonists respectively, (Anden *et al.*, 1982; 1983). Idazoxan (RX781094), α_2-antagonist (Doxey *et al.*, 1984); 3-phenethyl-PP and 3-PPP, dopamine agonists (Hacksell *et al.*, 1981); Ro 15-1788, benzodiazepine antagonist (Hunkeler *et al.*, 1981); RU24213 and RU24926, dopamine D_2-agonists (Euvrard *et al.*, 1980); TL-99, dopamine agonist (Seeman, 1981); SK&F 38393, dopamine D_1-agonist (Setler *et al.*, 1978).

The structures of the drugs used are shown in Figure 1.

Results

A dose-dependent inhibition of locomotor activity of mice was produced by all of the test compounds with the exception of the dopamine D_1-agonist, SK&F 38393. This compound increased locomotion (+24%, $P < 0.01$) at 30 mg kg^{-1} but no inhibition was seen at doses down to 0.01 mg kg^{-1}. The ED_{50} values for inhibition of locomotion are summarized in Table 1. The inhibitory effects on locomotion of dopamine agonists were in every case significantly antagonized by spiperone. In no case was the inhibitory effect of a compound not acting on dopamine receptors antagonized by spiperone. The α_2-antagonist, idazoxan, counteracted the inhibitory effects of the α_2-agonists, clonidine and B-HT 933, but did not affect those of the dopamine agonists, with the exception of RU 24296 (Table 2). The benzodiazepine antagonist Ro 15-1788 antagonized the effects of chlordiazepoxide and diazepam.

The potencies of the drugs at inhibiting L-DOPA accumulation in the nucleus accumbens of rats are also shown in Table 1. All the dopamine agonists, except SK&F 38393, strongly inhibited L-DOPA accumulation. B-HT 933 caused weak inhibition; other compounds caused no inhibition at the doses tested. The dopamine antagonists haloperidol and spiperone increased L-DOPA accumulation. Results for the corpus striatum (not shown in Table 1 for brevity) were similar to those for the nucleus accumbens, except that idazoxan and prazosin caused slight inhibitions.

A high order of correlation only for dopamine agonists ($r = 0.97$) was observed between the ED_{50} values for inhibition of L-DOPA synthesis and inhibition of locomotion (Figure 2). (−)-3-PPP deviated slightly from the regression; it was less potent on L-DOPA accumulation than predicted from inhibition of locomotion. Other compounds were inactive

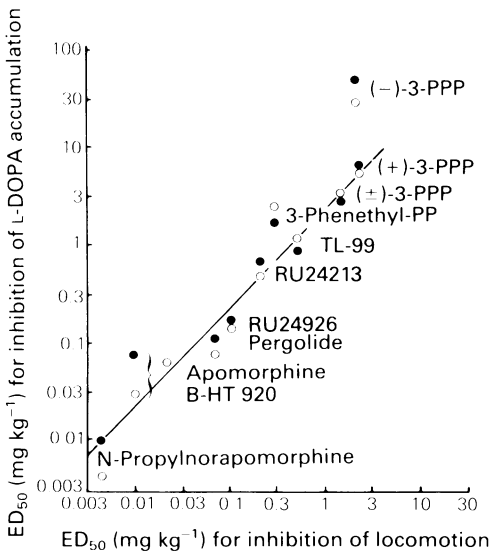

Figure 2 Correlation between potencies of dopamine agonists to inhibit locomotion and L-DOPA synthesis. Abscissa scale: ED_{50} doses (s.c.; treatment time 10 min) to inhibit locomotion in mice. Ordinate scale: ED_{50} doses (s.c.; treatment time 1 h) to inhibit L-DOPA accumulation in (○) nucleus accumbens and (●) corpus striatum of dopamine agonist + GBL + NSD 1015 treated rats as % of that in saline + GBL + NSD 1015 treated rats. The correlation coefficients, $r = 0.97$ (accumbens), $r = 0.96$ (striatum), exclude data for (−)-3-PPP.

on L-DOPA accumulation or only caused less than 50% inhibition at doses higher than their ED_{50} values for inhibition of locomotion.

α-Methyl-*p*-tyrosine treatment for 1 h inhibited locomotion by 23% but did not prevent most of the dopamine agonists from exerting inhibition of locomotion similar to that exerted in the absence of α-methyl-*p*-tyrosine (Figure 3). However, pergolide caused significantly less inhibition, and B-HT 920 significantly greater inhibition, in the presence of α-methyl-*p*-tyrosine.

Discussion

The data obtained in this work demonstrate that locomotor activity of mice is susceptible to inhibition by a range of compounds from a number of different pharmacological classes. In some cases the pharmacological mechanism of action can be determined by the use, where available, of specific pharmacological antagonists. Antagonism by spiperone, in particular, is a good criterion for identifying compounds acting as dopamine autoreceptor agonists. This basis for classification of compounds acting via dopamine autoreceptors receives near complete corroboration from the use of the L-DOPA accumulation test. This suggests that inhibition of locomotion in mice, if it can be reversed by low dose spiperone pretreatment, can be used as a rapid and economical screening test for dopamine autoreceptor agonists,

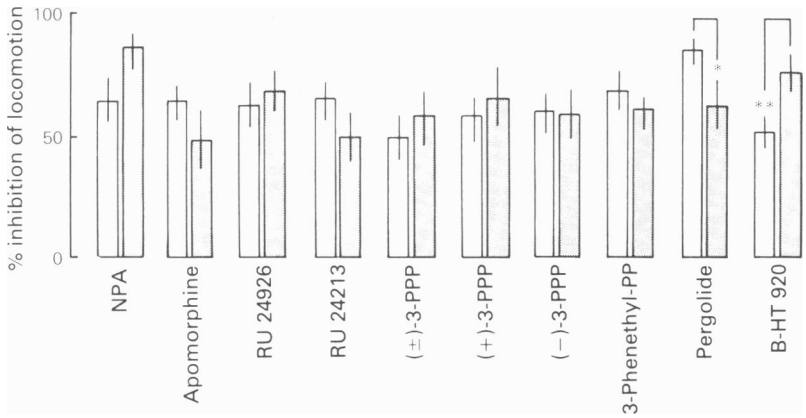

Figure 3 Inhibition of locomotion by dopamine agonists produced independently of inhibition of dopamine synthesis. Columns show mean values for % inhibitions of cumulated locomotor activity over 5 min with vertical lines representing s.e.means, $n = 5$. Open columns: significant inhibitions by saline + dopamine agonists compared with saline + saline; all cases $P < 0.01$, Dunnett's test. Closed columns: significant inhibitions by α-methyl-*p*-tyrosine + dopamine agonists compared with α methyl-*p*-tyrosine + saline; all cases $P < 0.01$. Dunnett's test. Inhibitions by saline + dopamine agonists are not significantly different from inhibitions by α-methyl-*p*-tyrosine + dopamine agonists except pergolide, * $P < 0.05$ and B-HT 920 ** $P < 0.01$, Student's *t* test. α-Methyl-*p*-tyrosine itself inhibited locomotion by 23 ± 7%, $P < 0.01$, Student's *t* test. The dopamine agonists were used at 1-2 × their ED_{50} values for inhibition of locomotion. The pretreatments with saline or α-methyl-*p*-tyrosine methylester hydrochloride 250 mg kg^{-1} for 1 h were given i p.; the challenge doses of saline or dopamine agonists were given s.c. 10 min before measuring locomotor activity. NPA = N-propylnorapomorphine.

without routine recourse to the L-DOPA accumulation test.

The use of a combination of tests is required for accurate characterization of compounds like (−)-3-PPP. This compound inhibits L-DOPA accumulation only at a relatively high dose compared with the dose which inhibits locomotion. This is probably due to a fine balance of dopamine agonist and antagonist properties in this enantiomer of 3-PPP (Hjorth *et al.*, 1983; Brown & Campbell, 1984). The inability of SK&F 38393 to inhibit either locomotion or L-DOPA accumulation is probably due to its dopamine D_1-receptor specificity rather than poor penetration of the brain. In common with a number of other dopamine agonists, it was excitatory at higher doses (in this case 30 mg kg^{-1}). SK&F 38393 has also been shown to be behaviourally active but to differ from dopamine D_2-agonists (Setler *et al.*, 1978; Molloy *et al.*, 1984).

Since the dopamine receptors mediating the inhibition of locomotion did not respond to SK&F 38393 (in agreement with Costall *et al.*, 1981) but responded to the agonist rather than antagonist nature of (−)-3-PPP, and as they are sensitive to low doses of dopamine agonists and to spiperone, these receptors appear to be of the D_2-high type (see Grigoriadis & Seeman, 1984). We have shown here that (−)-3-PPP acts as an agonist at dopamine receptors mediating inhibition of both locomotion and L-DOPA accumulation. It also acts as an agonist on those mediating emesis and inhibition of prolactin release but, in contrast, it acts as an antagonist when homovanillic acid (HVA) levels in nucleus accumbens or corpus striatum are used as an index of activity at postsynaptic dopamine receptors (Brown & Campbell, 1984). Again antagonist action is exerted by (−)-3-PPP at postsynaptic dopamine receptors mediating behaviours such as apomorphine-induced climbing in mice (our unpublished data) and apomorphine and amphetamine stimulated locomotor hyperactivity in rats (Hjorth *et al.*, 1983). This indicates that the dopamine receptors involved in mediating emesis, inhibition of prolactin release, the presumed autoreceptor mediated inhibition of locomotion and of L-DOPA accumulation (group a) can be differentiated from those involved in the effects on HVA and apomorphine climbing (group b). Our results are compatible with the classification of the former (group a) receptors as D_2-high, and the latter (group b) as D_2-low (Seeman *et al.*, 1984).

The high correlation between the potencies of dopamine agonists at inhibiting locomotion and L-DOPA accumulation also suggests a close similarity between the receptors mediating these two dopamine agonist-induced effects. It might be thought that activation of dopamine autoreceptors causes inhibition of dopamine synthesis as a primary effect and this leads to reduced release of dopamine and reduced locomotion. This seems not to be the case since the inhibitory effects of the dopamine agonists on locomotion were not directly dependent on suppression of dopamine synthesis, as shown in the α-methyl-*p*-tyrosine experiments. Therefore, it is probable that inhibition of dopamine release operates, independently of effects on synthesis, as the primary mechanism involved in the inhibition of locomotion. In the GBL/L-DOPA accumulation test, where dopaminergic impulse flow is already suppressed, it seems unlikely that dopamine agonist-induced inhibition of dopamine synthesis can occur as a secondary effect of further inhibition of impulse dependent release, e.g. by modulation of impulse flow via soma-dendritic autoreceptors (Aghajanian & Bunney, 1977). Thus despite the good correlation, the effects measured in the L-DOPA accumulation test are difficult to relate directly to the inhibitory effects on locomotion.

Another test for dopamine autoreceptor mediated effects is the synaptosomal tyrosine hydroxylase model. This has been shown by Haubrich & Pflueger (1982) to respond differently to the GBL/L-DOPA accumulation model in terms of the influence of drugs on dopamine synthesis. Their results suggest that dopamine synthesis could be influenced by more than one autoreceptor-like mechanism. Synaptosomal tyrosine hydroxylase, however, also reveals discrepancies between autoreceptor mediated inhibition of dopamine synthesis and inhibition of locomotion. Examples are that in the synaptosomal test pergolide was inactive (Haubrich & Pflueger, 1982) and SK&F 38393 was active (Brown & Nicholass, 1981) which is at variance with their activities on inhibition of locomotion. Investigation of a possible link between dopamine agonist induced inhibition of dopamine release and synthesis therefore remains as a topic for further research.

We are grateful to Mrs B. Trail and Miss M. Kusiak for their skilled technical assistance.

Note added in proof

Clark D. *et al.* (1985, *Eur. J. Pharmac.*, **106,** 185–189) have shown recently that (−)-3PPP acts as a partial agonist at CNS dopamine autoreceptors influencing dopamine synthesis. We have observed that it expresses agonist actions at some sites but agonist actions at others. According to theory the types of actions obtained with a partial agonist would be critically dependent upon the test systems employed since these may involve different endogenous levels of dopamine at the receptors, or even the presence of drugs with completely different intrinsic activities, like neuroleptics or apomorphine. The type of action observed with (−)-3PPP in different tests may not indicate any permanent differences in

receptor states but rather the influence of the experimental conditions. Temporary and localised changes between D_2-high and D_2-low states of the receptors may however be induced by such changes in experimental conditions e.g. via changes in the amount of ternary complex formed between the drug, receptor and guanyl nucleotide binding protein (Wregget, K.A. & De Lean, A. (1984). *Mol. Pharmac.*, **26,** 214—217).

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