Pharmacology Biochemistry & Behavior, Vol. 22, pp. 309–315, 1985. 0091-3057/85 $3.00 + .00

Dopaminergic Agents Including 3-PPP and its Enantiomers on Medial Septal Self-Stimulation

A. J. GOWER AND C. L. E. BROEKKAMP

CNS Pharmacology Department, Organon International B.V., P.O. Box 20, 5340 BH, OSS, The Netherlands

Received 19 March 1984

GOWER, A. J. AND C. L. E. BROEKKAMP. *Dopaminergic agents including 3-PPP and its enantiomers on medial septal self-stimulation.* PHARMACOL BIOCHEM BEHAV 22(2)309–315, 1985.—The effects of several dopamine agonists were determined on medial septal self-stimulation in rats and compared with selected dopamine antagonists and with the psychostimulants, d-amphetamine and nomifensine. Apomorphine, 3-PPP, TL-99, N,N-dipropyl-5,6-ADTN and N,N-dipropyl-6,7-ADTN inhibited self-stimulation at dose ranges selective for the dopamine autoreceptor as indicated by biochemical studies. Haloperidol and molindone produced dose-related inhibition but sulpiride increased self-stimulation. D-amphetamine and nomifensine also increased responding. The agonist-induced inhibition differed from neuroleptic-induced inhibition of self-stimulation. Both (+) and (−) 3-PPP inhibited responding by a similar amount over the dose range 0.25–1.0 mg/kg. At higher doses, (−) 3-PPP further decreased responding whereas the effects of (+) 3-PPP plateaued at approximately 55% of controls. These studies show that dopamine agonists, like neuroleptics, inhibit medial septal self-stimulation. This effect appears to be mediated via autoreceptor activation. Differences between neuroleptic- and agonist-induced inhibition and the 3-PPP stereoisomer data accord with the hypothesis that behavioural inhibitory effects caused by autoreceptor activation are less severe than those caused by dopamine postsynaptic blockade.

Self stimulation Dopamine agonists 3-PPP Dopamine antagonists

OVER the past few years evidence has been accumulating for the existence of dopamine autoreceptors which are located on the dopamine neurones and regulate the output of dopamine [1, 13, 26]. Thus, stimulation of the autoreceptors by dopamine agonists inhibits the synthesis and release of dopamine [22,28]. Such a mechanism of action, which effectively reduces dopaminergic transmission, may provide a new class of antipsychotic drugs for clinical use [22,29].

Dopamine autoreceptor agonists including 3-PPP and TL-99 have been shown to share some behavioural actions of dopamine blocking agents such as haloperidol. Thus, they reduce locomotor activity and disrupt conditioned avoidance responding [3, 7, 12, 15]. In view of the sensitivity of intracranial self-stimulation (ICSS) to inhibitory actions of neuroleptics, it might be expected that dopamine autoreceptor agonists should likewise suppress responding. 3-PPP and TL-99 have recently been reported to reduce self-stimulation of the lateral hypothalamus [7]. Low doses of apomorphine, also considered selectively active on the autoreceptor [4], have likewise been found to reduce self-stimulation of the lateral hypothalamus [20] and the medial frontal cortex [8]. However, the inhibitory effects of this drug on lateral hypothalamic self-stimulation are not always obtained [7].

Septal self-stimulation is characteristically different from lateral hypothalamic (L.H.) self-stimulation. For example, it sustains a lower rate of responding which, unlike L.H. self-stimulation, declines with time during a prolonged test session [11,24]. The differences could be related to the neuronal pathways involved. The medial septum forms part of the mesolimbic system which appears to be particularly sensitive to dopamine autoreceptor agonists [2,15]. We therefore tested the effects of several dopamine autoreceptor agonists including 3-PPP on medial septal self-stimulation. The two stereoisomers of 3-PPP were of especial interest in view of reports that while both activate the autoreceptor, the two isomers have opposite actions on the postsynaptic dopamine receptor: (+) 3-PPP acts as an agonist and (−) 3-PPP as an antagonist [15]. We also investigated the effects of SKF 38393, a dopamine agonist which is considered selective for the postsynaptic D1 dopamine receptor [25,27]. Finally, for comparative purposes, we determined the effects of some dopamine antagonists, including sulpiride reputedly selective for the presynaptic dopamine receptor [18,23].

METHOD

Animals

Male Wistar rats (Cpb: WU; TNO, Zeist, The Netherlands) were used which weighed 140–170 g at the time of surgery and 300–450 g at the time of drug testing. Following surgery, the rats were housed singly and maintained on a 12 hr light-dark cycle with ad lib access to standard cube diet and water.

Surgery

Each rat was anaesthetized with pentobarbital 60 mg/kg IP and a bipolar stimulating electrode (MS 303, Plastic Products Co., Roanoke, VA) insulated except at the tip, im-

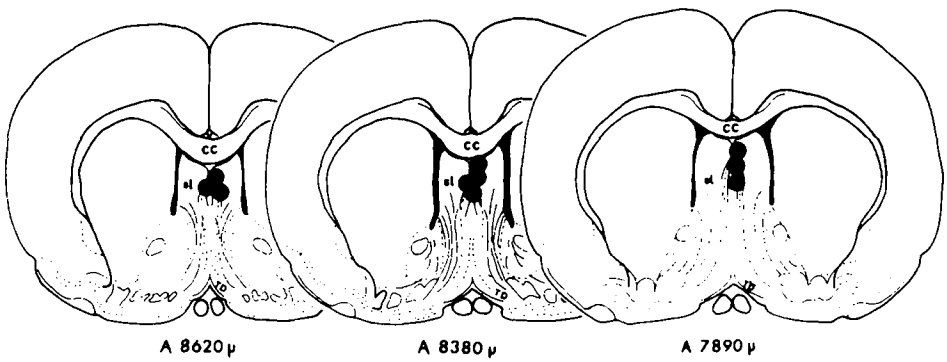

FIG. 1. Typical electrode placements, confirmed by histological examination following termination of experiments. Coronal sections are adapted from König and Klippel [19]. CC=corpus callosum; TD=diagonal band of Broca; sl=lateral septum.

planted stereotaxically into the medial septum. The coordinates used were A 8.4; L 0.0; H 0.0 according to the rat brain atlas of König and Klippel (1963). The electrode was positioned at an angle of 7° to the midsagittal plane. At least one week post-operative recovery time was allowed before self-stimulation training began. The positions of the electrodes were verified post-mortem. Fig. 1 illustrates typical successful electrode placements.

Procedure

Experiments were carried out in grey perspex Skinner boxes (30×18×41 cm). Each box was equipped with a single lever 4 cm wide × 1 cm long protruding from one end wall at a height of 4.5 cm above the bar floor level. The opposite end wall was clear perspex and constituted the door. Stimulation was delivered via a commutator located in the lid of the box. Depression of the lever produced a 0.3 sec train of negative impulses (100 p.p.s; 0.2 msec pulse duration). The Skinner boxes were sponged clean immediately after testing each rat, using a solution of Desogen (Ciba-Geigy).

The rats were trained using standard operant procedures; rats failing to acquire the response after two 30 min sessions were rejected. Training was continued for at least 8 more 30 min sessions until consistent day to day responding was achieved at a submaximal rate of not less than 300 responses per hour, maintained by a current intensity ranging from 150 to 300 μA.

Agonist and Antagonists

Each drug was investigated individually using groups of 6 to 9 rats per dose-level. For any given drug except the 3-PPP stereoisomers, the effects of each dose-level were determined separately over 2 consecutive days using a cross-over procedure. In this procedure, half the rats in the group received drug injections on day 1 and control vehicle on day 2; the remaining animals received control injections on day 1 and drug injections on day 2. In this way each rat served as his own control and control results were obtained for each dose-level of each drug.

For the two 3-PPP stereoisomers, the procedure was modified to a 3-day test for each dose-level so that the same dose-level of each isomer plus a vehicle control were investigated in the same experiment. A balanced design was used in which on each of 3 consecutive test days, a third of the group received (+) 3-PPP, a third received (−) 3-PPP and a third received vehicle control. Thus, by the end of the experiment, each rat in the group had received all 3 treatments.

Following injections the rats were returned to their home cage for the duration of the dose-test interval; these times are given in the results section. For testing drug effects, each rat was connected into the Skinner box and self-stimulation responses recorded over consecutive 10 min periods for either ½ or 1 hr.

Interaction Studies

The effects of pretreatment with the dopamine antagonists, haloperidol and sulpiride or the α_2 adrenergic antagonist, idazoxan, on (±) 3-PPP-induced decreases in self-stimulation and the effects of idazoxan on clonidine-induced decreases in self-stimulation were determined in separate experiments. Each interaction experiment was carried out over 4 consecutive days using a different group of rats for each experiment. On any one day of the 4 test days, each rat received one of the following treatment combinations: (1) saline + saline, (2) saline + agonist, (3) antagonist + saline, (4) antagonist + agonist. The order of treatments was semi-randomized and arranged so that by the end of the experiment each rat had received each of the 4 treatments. During the dose-test interval the rats were replaced in their home cages. Self-stimulation responding was measured over the half hour of peak activity of the agonist.

Drugs Used

The following drugs were used: apomorphine HCl (O.P.G., The Netherlands); 3-(3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP and both isomers); N,N-dimethylamino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (TL-99) (R.B. Inc. Wayland, USA); N,N-di-n-propylamino-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (N,N-dipropyl-5,6-ADTN); N,N-di-n-propylamino-6,7-dihydroxy-1,2,3,4-tetranaphthalene (N,N-dipropyl-6,7-ADTN); 2,3,4,5-tetrahydro-7,8-dihydroxy-l-phenyl-1H-3-benzazepine HCl (SKF 38393); d-amphetamine sulphate (O.P.G., The Netherlands); nomifensine maleate (Hoechst, West Germany); haloperidol (Janssen, Belgium); sulpiride (Delagrange, France); molindone hydrochloride (Endo Laboratories); clonidine hydrochloride and idazoxan (RX 781094; Reckitt and Coleman, Hull, U.K.). Clonidine, 3-PPP and its stereoisomers, N,N-dipropyl-5,6-ADTN, N,N-dipropyl-6,7-ADTN and SKF 38393 were synthetised in the chemical R and D Laboratories at Organon.

Apomorphine, TL-99, N,N-dipropyl-5,6-ADTN and N,N-dipropyl-6,7-ADTN were dissolved in sterile saline solution containing 1.0 mg/ml ascorbic acid. 3-PPP racemate was dissolved in a minimal amount of normal HCl, neutralized to pH 5–5.5 with saturated NaOH solution and made up to volume with sterile saline solution. Haloperidol and sulpiride were prepared respectively from Haldol or Dogmatil ampoules by diluting with sterile saline solution. All other drugs were dissolved in sterile saline solution. Drugs were administered subcutaneously into the loose skin at the back of the neck in a dose volume of 2.0 ml per kg body weight. Doses are expressed in terms of the salt where available as listed above or in terms of the base.

Statistics

Results are given in terms of mean responses per group plus the standard errors of the mean as an indication of variability. Statistical significance was assessed by comparing control and test results using a paired '*t*' test. In order to facilitate comparisons between different drugs and doses the percentage changes in responding relative to control results were also calculated.

RESULTS

Detailed results of the effects of the dopamine agonists and antagonists on mean responding over 1/2 hr at the time of peak drug effect are given in Table 1. Apomorphine, 3-PPP racemate, TL-99, N,N-dipropyl-5,6-ADTN and N,N-dipropyl-6,7-ADTN all reduced the rate of medial septal self-stimulation. Except for N,N-dipropyl-5,6-ADTN, the effects of these drugs were dose-related although complete inhibition was not obtained. The dose-response curve for 3-PPP was shallower than those obtained with apomorphine, TL-99 or N,N-dipropyl-6,7-ADTN. At the doses tested the drugs caused slight depression of general activity but no side effects such as stereotypy which would have disturbed responding. Higher doses were not tested since it was evident from other studies that these would cause disruptive side effects. For example in a separate observation study, apomorphine 0.1 mg/kg was found to cause occasional licking responses in 2 out of 6 rats tested whereas 0.5 mg/kg produced stereotypy in all rats tested. The inhibition in responding caused by N,N-dipropyl-5,6-ADTN increased from 1 to 10 μg/kg but decreases again at 100 μg/kg. Unlike the above agonists in which the inhibition remained fairly constant throughout the testing session, the effects of N,N-dipropyl-5,6-ADTN were optimal during the initial 20–30 min but then declined rapidly (data not shown). At 1 mg/kg N,N-dipropyl-5,6-ADTN responding was completely disrupted by marked stereotypy.

SKF 38393 4.0 mg/kg significantly reduced self-stimulation responding; lower doses were without effect.

In contrast to the dopamine agonists, both d-amphetamine and nomifensine significantly increased responding by approximately 40%. The increases were sustained over the 1 hr test period.

Of the dopamine antagonists, haloperidol and molindone caused dose-related reductions in responding with steep dose-response curves. The highest dose of molindone caused slight catalepsy but no other gross effects, except reduced responsiveness to handling, were observed. Sulpiride increased responding with a peak effect at 20 mg/kg; only slight non-significant increases occurred at 10 and 40 mg/kg. This latter dose also caused slight sedation in 2 rats.

3-PPP Isomers

The results obtained with (+) and (−) 3-PPP are presented graphically in Figs. 2 and 3. From Fig. 2 it can be seen that at low doses, 0.25 to 1 mg/kg, both isomers caused similar dose-related decreases in responding. At higher doses the effects of (+) 3-PPP plateaued at approximately 55% of control values whereas (−) 3-PPP produced further dose-related decreases in responding, reaching almost complete inhibition at 8.0 mg/kg. The within-session patterns of responding are shown in Fig. 3. Following 0.5 or 2.0 mg/kg the inhibition in responding remained fairly constant throughout the 1 hr test session for both isomers. However at 8.0 mg/kg the (+) and (−) patterns of responding were strikingly different. The effects of (+) 3-PPP were optimal during the first 10 min of testing and then declined rapidly. In contrast, the effects of (−) 3-PPP increased to reach an optimal inhibition after 30 min which remained at this level during the second 30 min of the test session.

Interaction Studies

The results of the interaction studies are shown in Fig. 4. At a dose which caused no inhibition on its own, haloperidol did not have any effect on the reduction in responding produced by 0.5 mg/kg 3-PPP racemate. Sulpiride, also at a dose which had no effect on its own, blocked the inhibitory effects of 3-PPP 0.5 mg/kg. The inhibitory effects of either 0.5 or 8.0 mg/kg 3-PPP were unchanged by pretreatment with idazoxan although this antagonist completely prevented the inhibition produced by clonidine. Idazoxan by itself did not change the rate of self-stimulation.

DISCUSSION

Medial septal self-stimulation was reduced by dopamine agonists and by the dopamine antagonists, haloperidol and molindone, but was increased by dopamine releasing agents and by sulpiride. Apart from SKF 38393 which will be discussed separately, the effects of the dopamine agonists occurred at doses which inhibit the synthesis and release of dopamine and are therefore considered to selectively activate the autoreceptor [14,21]. The inhibitory effects of 3-PPP could be blocked by pretreatment with sulpiride at a dose which had no effect on its own. Sulpiride by itself at higher doses produced some increase in self-stimulation. These findings suggest that the inhibitory effects of the dopamine agonists are mediated via the autoreceptor. Behavioural evidence is available which suggests that sulpiride preferentially blocks the dopamine presynaptic autoreceptor [18,23]. For example, sulpiride, at doses which have little effect on the postsynaptic receptor, inhibits apomorphine-induced hypoactivity. It was not possible to antagonize the effects of 3-PPP with haloperidol at a low dose claimed to specifically antagonise dopamine autoreceptors. In practice the antagonism is relatively marginal [15] so the lack of effect here does not detract from the above conclusion. The results therefore support the hypothesis [22] that dopamine autoreceptor activation and postsynaptic dopamine receptor blockade have similar inhibitory actions on behaviour, in this case ICSS, by a presumed common net action of reduced dopaminergic transmission.

Haloperidol and molindone both had steep dose-response curves and at high doses were able to completely inhibit responding. However, only partial inhibition was obtained with the dopamine agonists at doses below those causing

TABLE 1

EFFECTS OF DRUGS ON MEAN SELF-STIMULATION RESPONSES (±SE) DURING 30 MIN AT TIME OF PEAK EFFECT

Drug	Dose	n	Mean responses (±SE) Drug	Control	% change
1) *Agonists*					
apomorphine	10 μg/kg	7	317 ± 37*	394 ± 32	−19.5
hydrochloride	25 μg/kg	7	239 ± 28*	333 ± 36	−28.1
(5 min)	50 μg/kg	7	267 ± 14*	406 ± 16	−34.4
	100 μg/kg	7	152 ± 54*	378 ± 30	−59.8
3-PPP racemate	125 μg/kg	8	379 ± 63	417 ± 51	− 9.3
(5 min)	250 μg/kg	9	265 ± 37*	377 ± 48	−29.8
	500 μg/kg	8	183 ± 35*	359 ± 50	−49.1
	1.0 mg/kg	7	167 ± 36*	360 ± 39	−53.5
	2.0 mg/kg	8	135 ± 45*	308 ± 37	−56.2
	4.0 mg/kg	9	171 ± 36*	439 ± 50	−61.0
	8.0 mg/kg	9	92 ± 37*	335 ± 34	−72.6
TL-99	0.25 mg/kg	7	153 ± 32*	303 ± 30	−49.6
(5 min)	0.5 mg/kg	7	95 ± 22*	292 ± 33	−67.6
	1.0 mg/kg	7	58 ± 26*	247 ± 46	−76.4
N,N-dipropyl-5,6-ADTN	1 μg/kg	8	261 ± 33	337 ± 27	−22.7
(5 min)	10 μg/kg	8	138 ± 37*	315 ± 33	−56.1
	100 μg/kg	7	181 ± 79	304 ± 39	−40.5
	1 mg/kg	4	12 ± 6[a]	274 ± 63	−95.7
N,N-dipropyl-6,7-ADTN	0.1 mg/kg	7	404 ± 40	359 ± 37	+12.7
(5 min)	1.0 mg/kg	7	314 ± 29	342 ± 49	− 8.2
	3.4 mg/kg	7	219 ± 19*	361 ± 29	−39.2
	6.8 mg/kg	7	107 ± 29*	389 ± 44	−72.4
SKF 38393	1 mg/kg	7	298 ± 30	339 ± 32	−12.1
hydrochloride	2 mg/kg	7	265 ± 24	289 ± 27	− 8.3
(30 min)	4 mg/kg	7	241 ± 45*	377 ± 43	−36.2
2) *Indirect agonists*					
d-amphetamine sulphate (30 min)	0.3 mg/kg	6	729 ± 73*	526 ± 46	+38.5
nomifensine	1 mg/kg	8	499 ± 71*	358 ± 40	+39.1
maleate	2 mg/kg	7	536 ± 65*	369 ± 32	+45.4
(30 min)					
3) *Antagonists*					
haloperidol	10 μg/kg	7	242 ± 44	302 ± 34	−19.6
(30 min)	25 μg/kg	6	122 ± 27*	415 ± 41	−70.6
	50 μg/kg	6	23 ± 13*	368 ± 64	−93.7
molindone	10 μg/kg	7	381 ± 32	461 ± 44	−17.3
hydrochloride	50 μg/kg	6	273 ± 44*	378 ± 41	−27.7
(15 min)	200 μg/kg	7	104 ± 25*	410 ± 42	−74.7
	500 μg/kg	4	4 ± 3[b]	371 ± 60	−99.0
sulpiride	10 mg/kg	7	445 ± 37	394 ± 55	+13.1
(30 min)	20 mg/kg	8	469 ± 42*	335 ± 29	+40.0
	40 mg/kg	7	395 ± 27	357 ± 18	+10.8

Times given in brackets are the times between injecting and testing.
n=Number of rats per group.
% Change calculated with respect to saline control value.
*Significantly different from saline control ($p<0.05$; 1-tailed).
[a]=Marked stereotypy observed. [b]=Mild catalepsy noted.

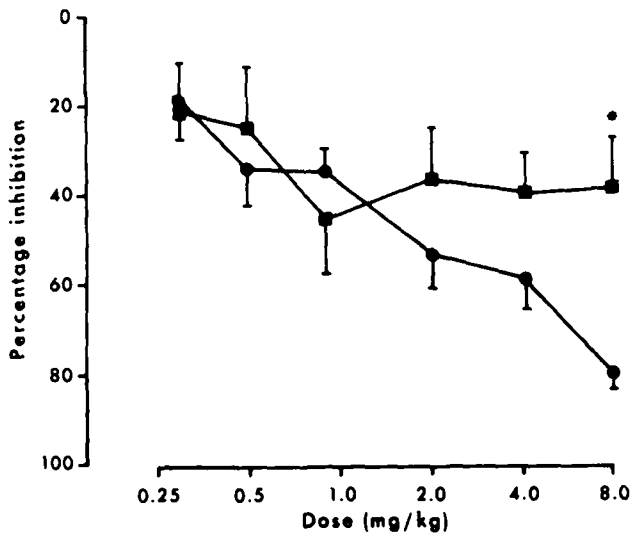

FIG. 2. Percentage inhibition of self-stimulation produced by dose-ranges of (+) and (−) 3-PPP calculated over a 1 hr test session. Squares=(+) 3-PPP; circles=(−) 3-PPP. Solid symbols indicate significantly different from saline control. *Significant difference between (+) and (−) 3-PPP ($p<0.05$; 1-tailed). Vertical bars indicate the standard errors of the mean. Groups of 7 to 9 rats were used. (+) and (−) 3-PPP were injected 5 min prior to testing.

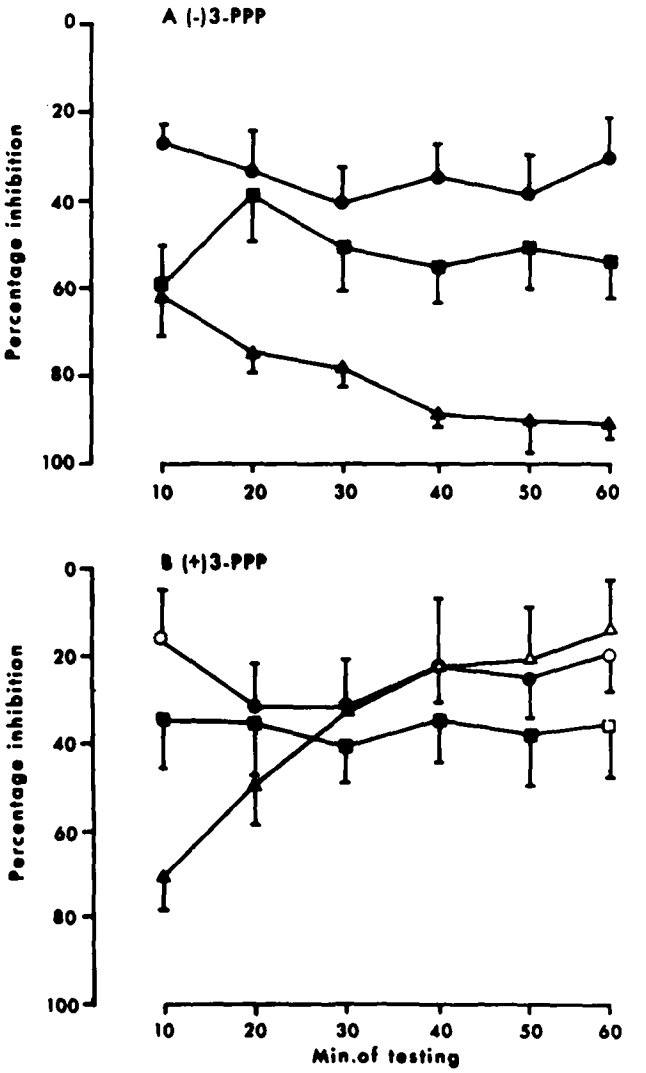

FIG. 3. Within-session patterns of responding shown as percentage inhibition relative to control, of (−) and (+) 3-PPP. Circles=0.5 mg/kg; squares=2.0 mg/kg; triangles=8.0 mg/kg. Solid symbols indicate significantly different from saline control ($p<0.05$; 1-tailed). Vertical bars indicate the standard errors of the mean. Groups of 7 rats used.

disruptive side effects and the dose-response curves for 3-PPP and N,N-dipropyl-5,6-ADTN were comparatively shallow. This shows that dopamine autoreceptor agonists cannot mimic neuroleptics exactly. The reason for this may be that the autoreceptor agonists available are not selective enough or that the behaviour-inhibiting effects of autoreceptor activation are weaker than those produced by postsynaptic blockade [15]. The results obtained with the 3-PPP stereoisomers favour the latter explanation.

3-PPP is a racemate of 2 isomers, both of which activate the dopamine autoreceptor at low doses; the (−) isomer has additional postsynaptic dopamine blocking activity whereas the (+) isomer has additional postsynaptic agonist activity [16]. The effects of the individual isomers on self-stimulation reflect these different profiles. (−) 3-PPP produced dose-related inhibition. The curve was composed of 2 sections: an earlier shallow part from 0.25 to 1.0 mg/kg followed by a steeper part resembling that of the neuroleptics. The within-session pattern of responding obtained at 8.0 mg/kg showing increasing inhibition with time was also similar to that typical of neuroleptics [9]. The effects of (−) 3-PPP are therefore consistent with initial autoreceptor activation producing moderate inhibition followed by postsynaptic blockade producing marked inhibition. In contrast, the effects of (+) 3-PPP can be attributed solely to autoreceptor activation. Although low doses produced dose-related inhibition up to 1 mg/kg, the plateau at approximately 55% of control values shows that no further suppression by this isomer was possible. The effects of (−) and (+) 3-PPP therefore support the suggestion that autoreceptor induced inhibition is weaker than that due to postsynaptic dopamine blockade.

The lack of response enhancing effects of SKF 38393 indicates that stimulation of the postsynaptic D1 receptor cannot mimic the effects of drugs such as amphetamine and nomifensine which increase the release of dopamine and increased ICSS. At 4.0 mg/kg SKF 38393 actually decreased responding. This decrease may be explicable in terms of lowered blood pressure causing general malaise or as showing that continuous stimulation of the postsynaptic receptor reduces the consequence of each self-stimulation response. The stimulant effects of amphetamine on ICSS are well documented [11] but were included here as evidence that the experimental paradigm was sensitive to drug-induced increases. Nomifensine has previously been reported to facilitate medial forebrain bundle (MFB) self-stimulation at doses of 5 and 10 mg/kg IP [17]; the results reported here confirm that this drug has similar enhancing effects on medial septal self-stimulation.

According to recent published data TL-99 and 3-PPP will inhibit lateral hypothalamic SS [7]; low doses of apomorphine have been found to inhibit medial frontal cortex SS and either to inhibit or have no effect on MFB self-stimulation [7, 8, 20]. The present findings not only confirm that these drugs

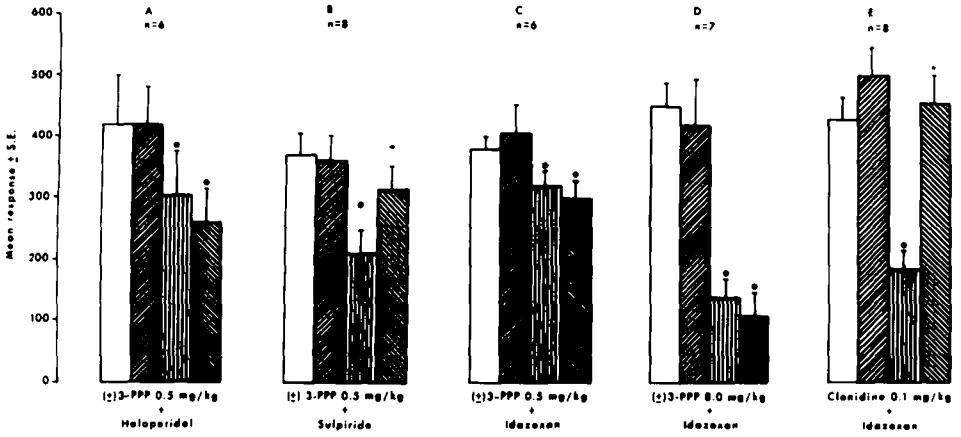

FIG. 4. Effect of pretreatment with antagonists on agonist-induced changes in self-stimulation responding. A=haloperidol 0.01 mg/kg (30 min) vs. 3-PPP 0.5 mg/kg (15 min); B=sulpiride 10 mg/kg (30 min) vs. 3-PPP 0.5 mg/kg (15 min); C=idazoxan 1 mg/kg (30 min) vs. 3-PPP 0.5 mg/kg (15 min); D=idazoxan 1 mg/kg (30 min) vs. 3-PPP 8.0 mg/kg (15 min); E=idazoxan 1 mg/kg (30 min) vs. clonidine hydrochloride 0.1 mg/kg (20 min). Times given in brackets are the intervals between injecting and testing. Open box=Saline + saline; right slanted line box=antagonist + saline; vertical line box=saline + agonist; left slanted line box=antagonist + agonist. *Significantly different from saline + saline ($p<0.01$); +Significantly different from saline + agonist ($p<0.01$); n=number of rats per group. Vertical bars indicate the standard errors of the mean.

have similar inhibitory effects on medial septal SS but extends the range of drugs to include the N,N-dipropyl-5,6 and 6,7-ADTN compounds. The apparent difficulty in obtaining consistent inhibition by apomorphine of MFB self-stimulation may be explicable in terms of relative insensitivity of the MFB to dopamine autoreceptor agonists; it has been suggested that autoreceptor agonists may have preferential actions on the mesolimbic system [15] of which the medial septum forms part. However when the effects reported by Fenton *et al.* [7] of 3-PPP and TL-99 on low rate but not high rate MFB stimulation are compared with those found in this study using medial septal self-stimulation, the two areas appear similarly sensitive. The low rate stimulation in the Fenton study was obtained by reducing the current intensity; these were therefore submaximal. In the present study the inhibitory effects of the dopamine agonists were also obtained using submaximal current intensities. Hence it appears that it is the use of submaximal intensities rather than the brain area which is important. Leith [20] presented results showing that the inhibitory effects of low doses of apomorphine on MFB self-stimulation were dependent on the current intensity and occurred at submaximal current intensities. Similarly, Wauquier *et al.* [30] reported that the inhibitory effects of various neuroleptics were inversely proportional to the quantity of charge of stimulation.

The lack of antagonism by idazoxan, a selective α_2 adrenoceptor antagonist [5] on low- or high-dose 3-PPP induced inhibition indicates that the inhibition caused by this compound does not involve an α_2-receptor. Conversely clonidine which markedly reduced ICSS, was completely antagonized by idazoxan; this substantiates previous findings that clonidine-induced inhibition of ICSS is α_2-mediated [10].

In the present study we have shown that dopamine agonists, like neuroleptics, will inhibit medial septal self-stimulation. The similarity in the doses producing these effects and doses which according to published biochemical data activate the autoreceptor suggest that the inhibition of self-stimulation is autoreceptor mediated or at least mediated via a receptor with properties similar to the dopamine autoreceptor. Differences between the agonists and neuroleptics in the dose-response characteristics and data obtained with the 3-PPP stereoisomers are in agreement with the hypothesis that the behaviour-inhibiting consequences of autoreceptor activation are less severe than those produced by postsynaptic dopamine receptor blockade.

ACKNOWLEDGEMENTS

The authors thank the various companies for donation of drugs.

REFERENCES

1. Aghajanian, G. K. and B. S. Bunney. Dopamine "autoreceptors": Pharmacological characterization by microiontophoretic single cell recording studies. *Naunyn Schmiedebergs Arch Pharmacol* **297**: 1–7, 1977.
2. Bannon, M. J. and R. H. Roth. Pharmacology of mesocortical dopamine neurons. *Pharmacol Rev* **35**: 53–68, 1983.
3. Clark, D., A. Carlsson, S. Hjorth, K. Svensson, J. Engel and D. Sanchez. Is 3-PPP a potential antipsychotic agent? *Eur J Pharmacol* **83**: 131–134, 1982.
4. Di Chiara, G., M. L. Porceddu, L. Vargiu, A. Argiolas and G. L. Gessa. Evidence for dopamine receptors mediating sedation in the mouse brain. *Nature* **264**: 564–567, 1976.
5. Doxey, J. C., A. G. Roach and C. F. C. Smith. Studies on RX 781094: a selective, potent and specific antagonist of α_2-adrenoceptors. *Br J Pharmacol* **78**: 489–505, 1983.
6. Feenstra, M. G. P., H. Rollema, D. Dijkstra, C. J. Grol, A. S. Horn and B. H. C. Westerink. Effect of non-catecholic 2-aminotetralin derivatives on dopamine metabolism in the rat striatum. *Naunyn Schmiedebergs Arch Pharmacol* **313**: 213–219, 1980.

7. Fenton, H. W., N. R. Hall, S. Gerhardt, L. Noreika, R. Neale and J. M. Leibman. Avoidance and ICSS behavioural models dissociate TL-99 and 3-PPP from dopamine receptor antagonists. *Eur J Pharmacol* **91:** 421–430, 1983.
8. Ferrer, J. M. R., A. M. Sanguinetti, F. Vives and F. Mora. Effects of agonists and antagonists of D1 and D2 dopamine receptors on self stimulation of the medial prefrontal cortex in the rat. *Pharmacol Biochem Behav* **19:** 211–217, 1983.
9. Fouriezos, G., P. Hansson and R. A. Wise. Neuroleptic-induced attenuation of brain stimulation reward in rats. *J Comp Physiol Behav* **92:** 661–671, 1978.
10. Franklin, K. B. J. and L. J. Herberg. Presynaptic α-adrenoceptors: The depression of self-stimulation by clonidine and its restoration by piperoxane but not by phentolamine or phenoxybenzamine. *Eur J Pharmacol* **43:** 33–38, 1977.
11. German, D. W. and D. M. Bowden. Catecholamine systems as the neural substrate for intracranial self-stimulation: a hypothesis. *Brain Res* **73:** 381–419, 1974.
12. Goodale, D. B., D. B. Rusterholz, J. P. Long, J. R. Flynn, B. Walsh, J. G. Cannon and T. Lee. Neurochemical and behavioural evidence of a selective presynaptic dopamine receptor agonist. *Science* **210:** 1141–1143, 1980.
13. Groves, P. M., C. J. Wilson, S. J. Young and G. V. Rebec. Self-inhibition by dopaminergic neurons. *Science* **190:** 522–529, 1975.
14. Hacksell, U., U. Svensson, J. L. G. Nilsson, S. Hjorth and A. Carlsson. N-Alkylated 2-aminotetralins: Central dopamine-receptor stimulating activity. *J Med Chem* **22:** 1469–1475, 1979.
15. Hjorth, S., A. Carlsson, H. Wikström, P. Lindberg, D. Sanchez, U. Hacksell, L.-E. Arvidsson, U. Svensson and J. L. G. Nilsson. 3-PPP, A new centrally acting DA-receptor agonist with selectivity for autoreceptors. *Life Sci* **28:** 1225–1238, 1981.
16. Hjorth, S., A. Carlsson, D. Clark, K. Svensson, H. Wikström, D. Sanchez, P. Lindberg, U. Hacksell, L.-E. Arvidsson, A. Johansson and J. L. G. Nilsson. Central dopamine receptor agonist and antagonist actions of the enantiomers of 3-PPP. *Psychopharmacology (Berlin)* **81:** 89–99, 1983.
17. Katz, R. J., G. Baldrighi and B. J. Carroll. Effects of nomifensine (HOE 984) upon psychomotor activity and intracranial self-stimulation in the rat. *Pharmacol Biochem Behav* **7:** 269–272, 1977.
18. Kendler, K. S., H. S. Bracha and K. L. Davis. Dopamine autoreceptor and postsynaptic receptor blocking potency of neuroleptics. *Eur J Pharmacol* **79:** 217–223, 1982.
19. König, J. F. R. and R. A. Klippel. The rat brain: A stereotaxic atlas of the forebrain and lower parts of the brainstem. London: Balliere Tindall and Cox, 1963.
20. Leith, N. Effects of apomorphine on self stimulation responding: does the drug mimic the current? *Brain Res* **277:** 129–136, 1983.
21. Martin, G. E., M. Williams and D. R. Haubrich. A pharmacological comparison of 6,7-dihydroxy-2-dimethyl-aminotetralin (TL-99) and N-n-propyl-3-(3-hydroxyphenyl)piperidine (3-PPP) with selected dopamine agonists. *J Pharmacol Exp Ther* **223:** 298–304, 1982.
22. Nilsson, J. L. G. and A. Carlsson. Dopamine-receptor agonist with apparent selectivity for autoreceptors: a new prinicple for antipsychotic action? *Trends Pharmacol Sci* **3:** 322–325, 1982.
23. O'Connor, S. E. and R. A. Brown. The pharmacology of sulpiride—a dopamine receptor antagonist. *Gen Pharmacol* **13:** 185–193, 1982.
24. Olds, J. and M. Olds. Drives, rewards and the brain. In: *New Directions in Psychology*, vol 2, edited by F. Barron and W. C. Dement. New York: Holt, Rinehart and Winston, 1965, pp. 327–410.
25. Pendleton, R. G., L. Samler, C. Kaiser and P. T. Ridley. Studies on renal dopamine receptors with a new agonist. *Eur J Pharmacol* **51:** 19–28, 1978.
26. Raiteri, M., A. M. Cervoni and R. del Carmine. Do presynaptic auto-receptors control dopamine release? *Nature* **274:** 706–707, 1978.
27. Setler, P. E., H. M. Sarau, C. L. Zirkle and H. L. Saunders. The central effects of a novel dopamine agonist. *Eur J Pharmacol* **50:** 419–430, 1978.
28. Starke, K., W. Reimann, A. Zumstein and G. Hertting. Effect of dopamine receptor agonist and antagonists on release of dopamine in the rabbit caudate nucleus in vitro. *Naunyn Schmiedebergs Arch Pharmacol* **305:** 27–36, 1978.
29. Tamminga, C. A., M. H. Schaeffer, R. C. Smith and J. M. Davis. Schizophrenic symptoms improve with apomorphine. *Science* **200:** 567–568, 1978.
30. Wauquier, A. and C. J. E. Niemegeers. Intracranial self stimulation in rats as a function of various stimulus parameters II. Influence of haloperidol, pimozide and pipamperone on medial forebrain bundle stimulation with monopolar electrodes. *Psychopharmacologia* **27:** 191–202, 1972.