Pharmacology Biochemistry & Behavior, Vol. 19, pp. 211–217, 1983. © Ankho International Inc. Printed in the U.S.A.

Effects of Agonists and Antagonists of D1 and D2 Dopamine Receptors on Self-Stimulation of the Medial Prefrontal Cortex in the Rat

J. M. R. FERRER, A. M. SANGUINETTI, F. VIVES AND F. MORA[1]

Department of Physiology, Faculty of Medicine, University of Granada, Granada, Spain

Received 28 August 1982

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**(2) 211–217, 1983.—The possible participation of D1 versus D2 dopamine receptors in mediating dopaminergic neurotransmission of self-stimulation (SS) in the medial prefrontal cortex (MPC) of the rat was studied neuropharmacologically. Intracerebral as well as intraperitoneal injections of agonists and antagonists of dopamine receptors were used in this study. In all experiments performed with systemic injections, spontaneous motor activity (SM) was measured parallel to self-stimulation behavior as control for non specific effects of the drugs. Intracranial injections were done unilaterally serving SS of the contralateral side (not injected or injected with 0.9% NaCl) as control in the same animals. Spiroperidol and pimozide were used as D1-D2 dopamine antagonists, while sulpiride was used as a specific D2 antagonist. Apomorphine was used as D1-D2 agonist, while bromocriptine and lergotrile were used at doses in which these ergot drugs are considered predominantly D2 agonists. Sulpiride, intraperitoneally or intracerebrally injected at the same locus at which the stimulating electrode was located produced no effect on SS. On the contrary, the D1-D2 antagonists, spiroperidol and pimozide intraperitoneally or intracerebrally injected produced a dose-dependent decrease on SS. On the basis of these data it is suggested, that the dopamine neurotransmission involved in SS of the MPC is mediated via D1 dopamine receptors. This suggestion is further emphasized by the results obtained with the agonists, apomorphine, bromocriptine and lergotrile. Apomorphine produced a dose-related decrease on SS and a decrease at lower doses and an increase at higher doses on SM. Bromocriptine and lergotrile had, on the contrary, no effect on SS and a dose-related decrease on SM.

Self-stimulation Prefrontal cortex Dopamine D1-D2 dopamine receptors Spontaneous motor activity
Spiroperidol Pimozide Sulpiride Apomorphine Bromocriptine Lergotrile

THERE is strong evidence in support of the idea that dopamine [16] and possibly acetylcholine [21] are part of the neurochemical substrates underlying self-stimulation (SS) in the medial prefrontal cortex (MPC) of the rat [3, 17, 23, 25, 27]. There is also evidence for the existence of two different types of dopamine receptors (D1, D2) in the medial and sulcal prefrontal cortex [8,29] being their main differential characteristic that D1 receptors are linked to cyclic-AMP and D2 receptors are not [9].

Mapping brain areas for regional distribution of these two types of receptors has shown that both coexist, although in different proportion, in the majority of brain areas analyzed [8]. Tassin *et al.* [29] have reported that the highest concentration of dopamine activity in sulcal and medial prefrontal cortex was linked to cyclic-AMP, that is to D1 receptors. Iversen [8] has confirmed this observation showing that there are a high density of D1 receptors versus barely detectible D2 receptors in the prefrontal cortex of the rat.

In view of the above mentioned reports showing, first, that dopamine is involved in SS of the MPC [17] and second, that there are both types of receptors (D1 and D2) in that same area of the brain [8,29], the purpose of the present investigation was to determine neuropharmacologically whether the dopaminergic neurotransmission involved in SS of the MPC is mediated via D1 or D2 or both types of receptors.

METHOD

Male Sprague-Dawley rats, weighing 200–250 g at the time of operation were used in these experiments. The rats were housed in individual wire mesh cages with food and water ad lib. Fifty nine rats were implanted under Equithesin anaesthesia (2 ml/kg IP) with bilateral monopolar stimulating electrodes made of 00 ga stainless steel pins. The electrodes were implanted in the MPC. The coordinates, derived from the atlas of König and Klippel [11] and using bregma as the reference point, were 2.4 mm anterior to bregma, 0.8 mm lateral to the midline and 4.0 mm beneath the dura. Another group of twelve rats were implanted with electrodes plus guide cannulae placed bilaterally into the MPC. The tip of

[1]To whom requests for reprints should be addressed.

the cannulae were positioned 1 mm in front and 2.5 mm above the tip of the ipsilateral electrode. The cannulae were made of 23 ga stainless steel tubing.

One week after surgery the animals were daily tested for SS and spontaneous motor activity (SM) in boxes that were 26×29×36 cm. In SS, the reinforcer for every lever press consisted of a train (0.3 sec duration) of monphasic rectangular negative pulses (0.5 msec duration) at 100 Hz, provided by a Letica stimulator LI-200. Current intensity (ranging among animals between 0.1–0.6 mA) was monitored on an oscilloscope (Telequipment D61a) and adjusted individually for each animal after a rate-intensity curve was performed. The current for SS was set to be at the middle point in the rate-intensity curve (see [18,19] for an example). Prior to a SS session, SM was recorded automatically for each animal from contacs in the floor of a motility chamber. Since in this study, drugs which interfere with dopaminergic mechanisms were injected, SM was measured as control for nonspecific effects such as sedation or motor impairment.

The injections of drugs began after a period of 14 days in which control of SM and SS was reproduced every day. In the first series of experiments we investigated the effects of intraperitoneal injections of spiroperidol and sulpiride on SS of the MPC and SM. Spiroperidol dissolved in 1/100 M tartaric acid was used at the doses of 0.016, 0.032, 0.064 and 0.128 mg/kg. Sulpiride, dissolved in 0.9% NaCl with a few drops of acetate/acetic buffer, was used at the doses of 1, 5, 10, 20 and 40 mg/kg. Spiroperidol, a specific dopamine receptor blocker at the doses used in this study [1], is an antagonist of both D1 and D2 receptors [9]. Sulpiride at the doses mentioned above, is considered to be a selective D2 antagonist [5,8].

The rats were tested as follows: (a) SS and SM were recorded every day at the same time in the morning. The animals were tested first for fifteen minutes (min) for SM followed by fifteen min for SS, measurements being recorded for the last ten min of each session. (b) The animals were injected with spiroperidol every four days and with sulpiride every three days. (c) On the day of injection, spiroperidol was administered two hours and sulpiride four hours before SM and SS session started [20,28].

In a second series of experiments investigations were carried out to analyze the effects of intracerebral administration of pimozide [1] and sulpiride [5,8] into the MPC, at the same location of the tip of the electrode (see above). Sulpiride in these experiments, was used at the doses of 10, 20 and 40 μg/μl and dissolved as described previously. Pimozide (an antagonist of both D1 and D2 receptors) was used at the doses of 1, 2 and 4 μg/μl and dissolved in 1/100 M tartaric acid. For microinjections an inner 27 ga injector cannula was lowered into the guide cannula. The injector was connected by way of a polyethylene tubing (PE20) to a 10 microliter Hammilton syringe mounted on a Harvard infusion pump. The microinjections were made unilaterally fifteen min before SS test started [15]. As a control for possible motor impairment caused by the drugs, SS, contralateral to the injected side was also tested in the same animals. All drugs were delivered in a total volume of 1 μl over a period of 30 sec [22].

A third block of experiments consisted of investigating the effects of subcutaneous injections of apomorphine, lergotrile and bromocriptine on SS of the MPC and SM. Apomorphine was used at doses of 0.075, 0.15, 0.3, 0.6 and 1.2 mg/kg dissolved in 0.9% NaCl with 0.5 mg/ml of ascorbic acid. Lergotrile and bromocriptine were used at doses of 1, 2, 4 and 8 mg/kg dissolved in distilled water with a few drops of 70% ethanol. SM and SS were recorded ten min after apormorphine administration [13] and twenty min after lergotrile and bromocriptine administration, using the same time, experimental design and testing procedures as the ones described for the systemic injections of dopamine antagonists. At the doses used in these experiments apomorphine is considered an agonist of both D1 and D2 receptors [8,9] and lergotrile and bromocriptine are predominantly D2 agonists [8].

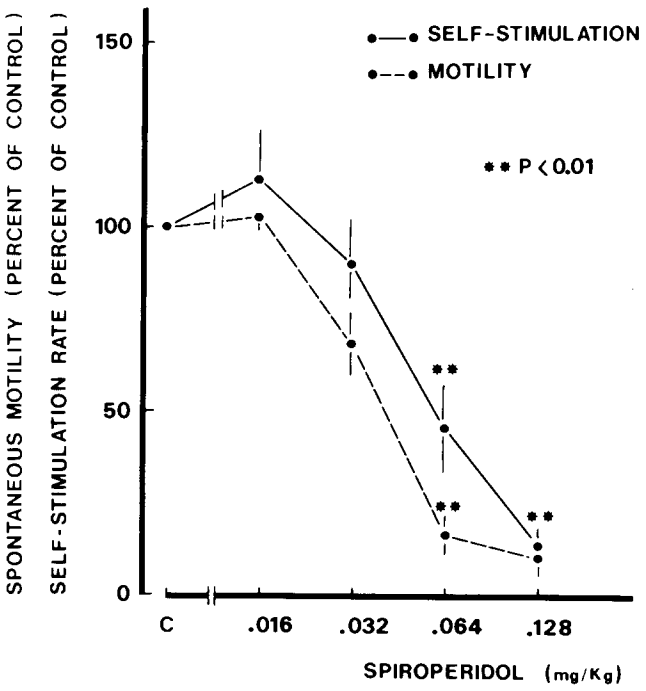

FIG. 1. Dose-related decrease produced by intraperitoneal injections of spiroperidol on SS obtained from the MPC and SM in a group of 4 rats. The vertical lines indicate the standard error of the mean.

At the end of the experiments the location of the electrodes and cannulae was verified histologically [10] (see Figs. 8 and 9 for a histological example and a schematic representation of the stereotaxic planes at which the electrodes and cannulae were located). The results were statistically analyzed using analysis of variance and Dunnett's test.

RESULTS

In order to compare the effects of drugs on SS and SM on the same scale, the results are expressed in percentage of control. The rate for SS ranged from 305 to 509 presses in 10 min. The counts for SM in 10 min ranged from 180 to 295.

Effects of Intraperitoneal and Intracerebral Injections of Spiroperidol and Pimozide on SS of the MPC and SM

Figure 1 shows the effects of intraperitoneal injections of spiroperidol on SS and SM. As it can be seen in that figure, spiroperidol produced in both parameters, SS and SM, a decrease which was dose-related. On the contrary, microintracranial injections of pimozide at the same locus at which the tip of the electrode was located, produced a dose-related decrease of SS in the injected side, while the contralateral

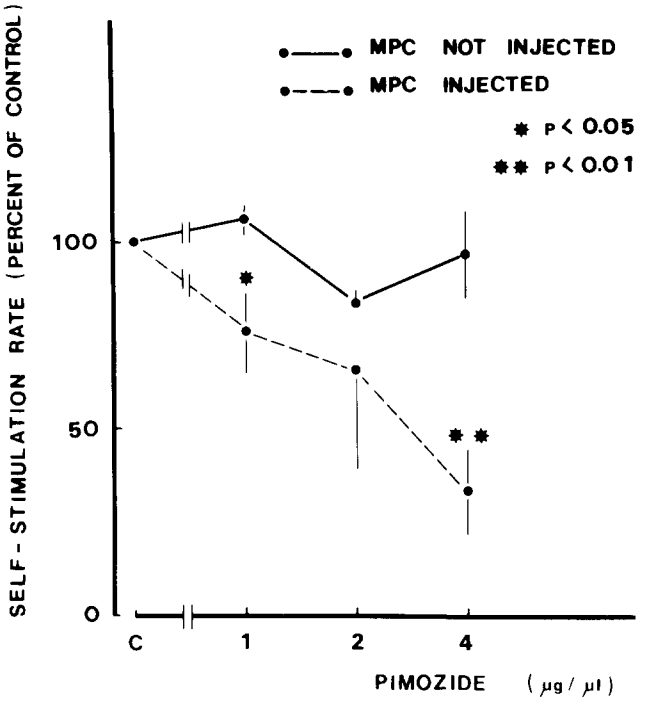

FIG. 2. Effects of intracranial injections of pimozide into the medial prefrontal cortex on SS of the ipsilateral and contralateral (not injected) MPC in a group of 4 rats. The vertical lines indicate the standard error of the mean.

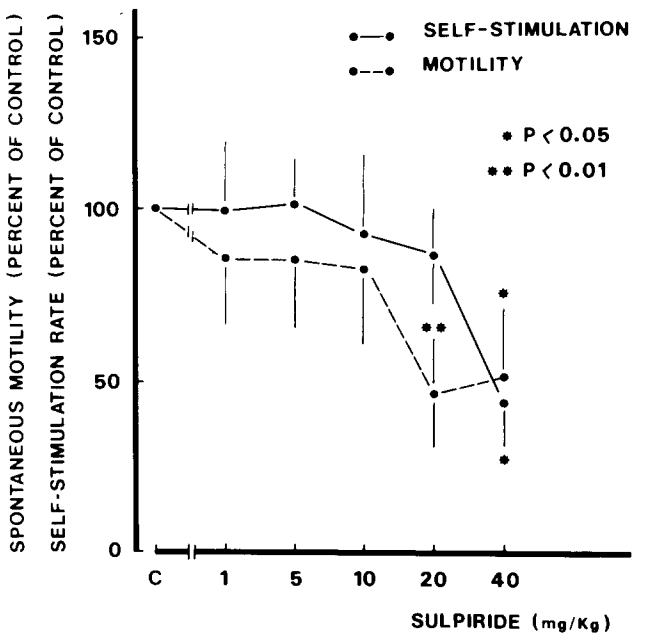

FIG. 3. Effects of intraperitoneal injections of sulpiride on SS of the MPC and SM in a group of 6 rats. The vertical lines indicate the standard error of the mean.

side (not injected) was not significantly affected by the drug (see Fig. 2).

Effects of Intraperitoneal and Intracerebral Injections of Sulpiride on SS of the MPC and SM

Figure 3 shows the effects of intraperitoneal injections of sulpiride on SS and SM. Sulpiride produced no effects on SS at the doses of 1, 5, 10 and 20 mg/kg. However at the dose of 40 mg/kg SS was significantly decreased ($p<0.05$). Similar effects were produced by sulpiride on SM. This parameter was not affected at the doses of 1, 5 and 10 mg/kg, however was significantly decreased at the following doses of 20 and 40 mg/kg ($p<0.01$ and $p<0.05$ respectively).

Figure 4 shows the effects of microintracranial and unilateral injections of sulpiride on SS of the MPC. No significant effects were found on SS in either side after unilateral microinjections of 10, 20 and 40 μg/μl (see Fig. 4).

Effects of Subcutaneous Injections of Apomorphine, Bromocriptine and Lergotrile on SS of the MPC and SM

Figure 5 shows the dose-related decrease produced by apomorphine on SS of the MPC. SM, on the contrary, had clear biphasic effects depending on the range of doses used. Thus, at the doses of 0.075 and 0.15 mg/kg SM was significantly decreased ($p<0.01$) while at the doses of 0.3, 0.6 and 1.2 mg/kg motility was clearly facilitated reaching statistical significance at the highest dose ($p<0.01$).

Figure 6 shows the effects of subcutaneous injections of bromocriptine. As it can be seen in that figure, SS was not

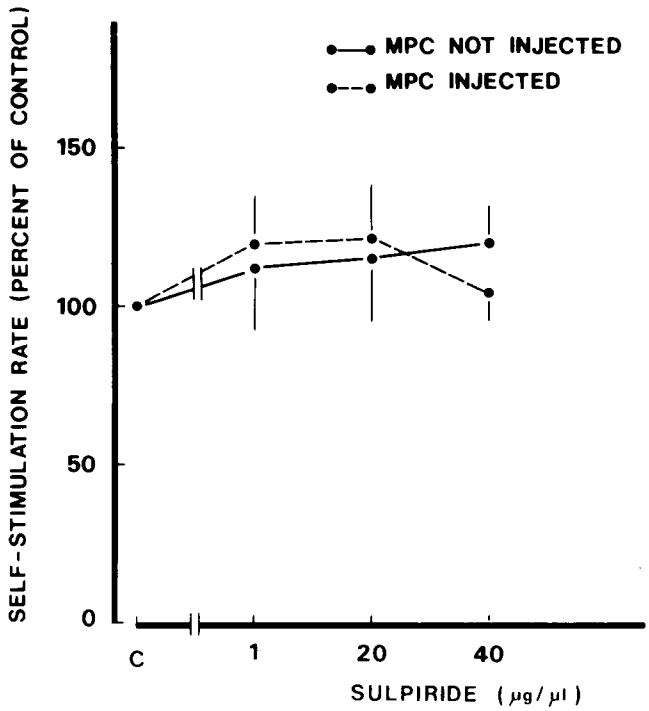

FIG. 4. Effects of intracranial injections of sulpiride into the medial prefrontal cortex on SS of the ipsilateral and contralateral (not injected) MPC in a group of 6 rats. The vertical lines indicate the standard error of the mean.

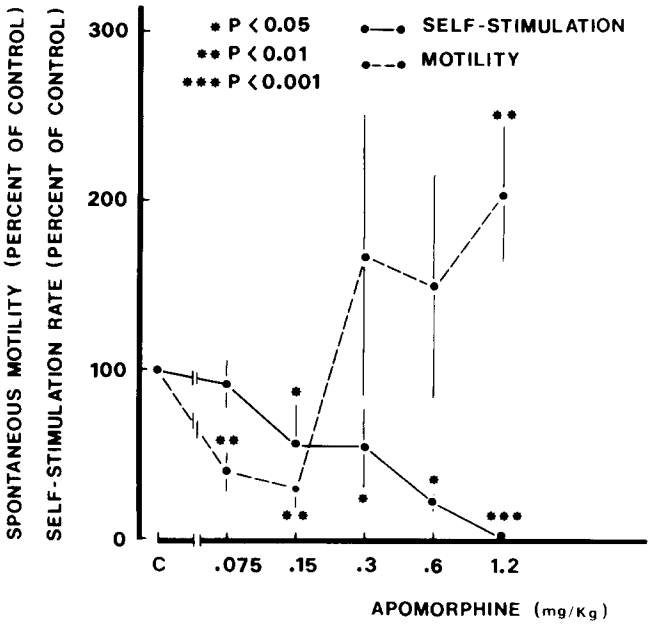

FIG. 5. Differential effects produced by subcutaneous injections of apomorphine on SS of the MPC and SM in a group of 4 rats. As this figure shows apomorphine produced a decrease at the lower doses and a facilitation at the higher doses. The vertical lines indicate the standard error of the mean.

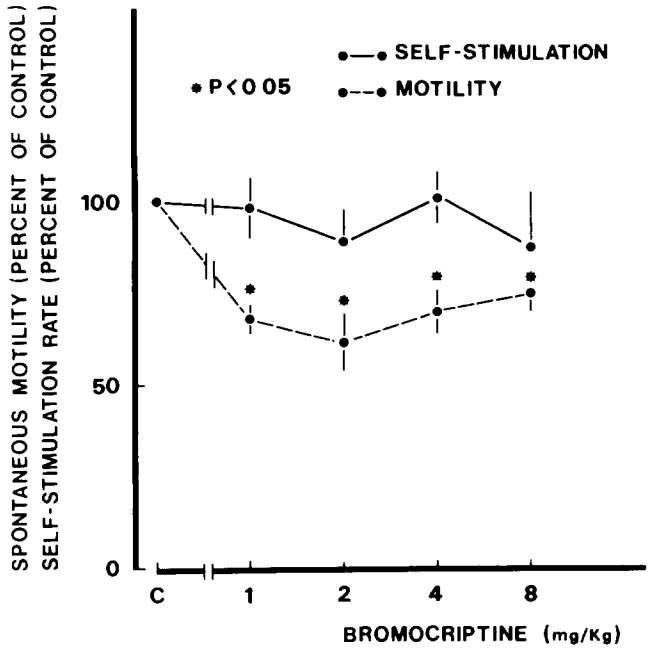

FIG. 6. Effects of subcutaneous injections of bromocriptine on SS of the MPC and SM in a group of 6 rats. The vertical lines indicate the standard error of the mean.

affected by the drug while SM was significantly decreased at the four doses used of 1, 2, 4 and 8 mg/kg ($p<0.05$). Similar effects were found with lergotrile (see Fig. 7) another ergot drug, at the doses of 1, 2, 4 and 8 mg/kg. The decrease of SM

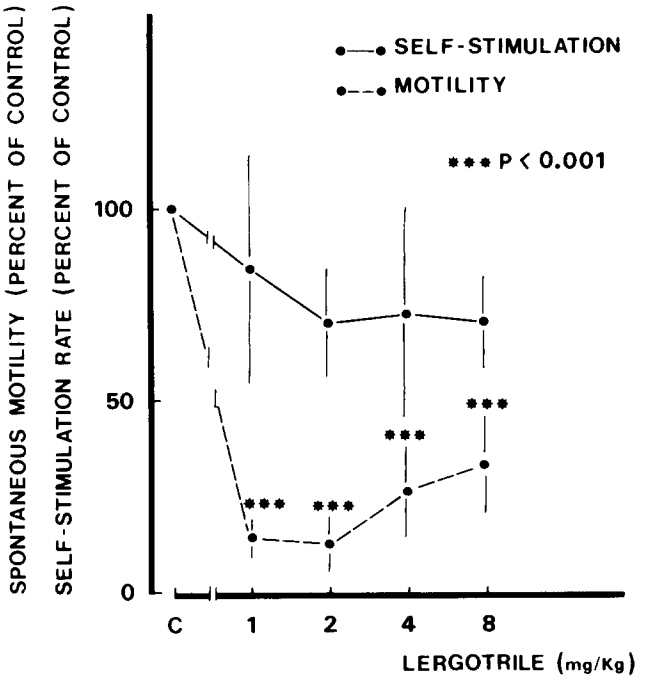

FIG. 7. Effects of subcutaneous injections of lergotrile on SS of the MPC and SM in a group of 4 rats. The vertical lines indicate the standard error of the mean.

under the effects of lergotrile at the same doses than those of bromocriptine was more pronounced ($p<0.001$).

DISCUSSION

The purpose of the present work was to clarify neuropharmacologically the possible selective involvement of D1 dopamine receptors versus D2 or perhaps both altogether in the dopaminergic mediation of SS of the MPC.

Up to date there is no evidence for the existance of selective antagonists of D1 dopamine receptors [8,9]. Spiroperidol (a butyrophenone derivative) and pimozide (a diphenylbutylamine derivative) [31] are both D1-D2 dopamine receptors blockers, therefore, both drugs were used as such in this study.

Spiroperidol produced a dose related inhibition of both SS and SM. The attenuation of SS found in this study is in agreement with previous reports on the effects of this compound on SS of the prefrontal cortex in monkeys as well as SS of other different areas of the brain in the rat [24,26]. The fact that SM was also affected in a dose-related manner suggests that the decrease of SS could be due to a non specific effect (sedation of motor impairment of the animals). This interpretation is emphasized by reports showing a decrease of motor performance in a variety of different operant behaviors under the effects of dopamine receptor blockers [26]. The fact that these drugs (i.e., spirorperidol) block dopamine receptors in the nigrostriatal pathway (known to be involved in extrapyramidal motor mechanisms) further supports such an interpretation [2,30]. However, it is also possible that if blockade of dopamine receptors in the MPC also produces an inhibition of SS this effect could be masked by the motor impairment of the animals. In a recent publica-

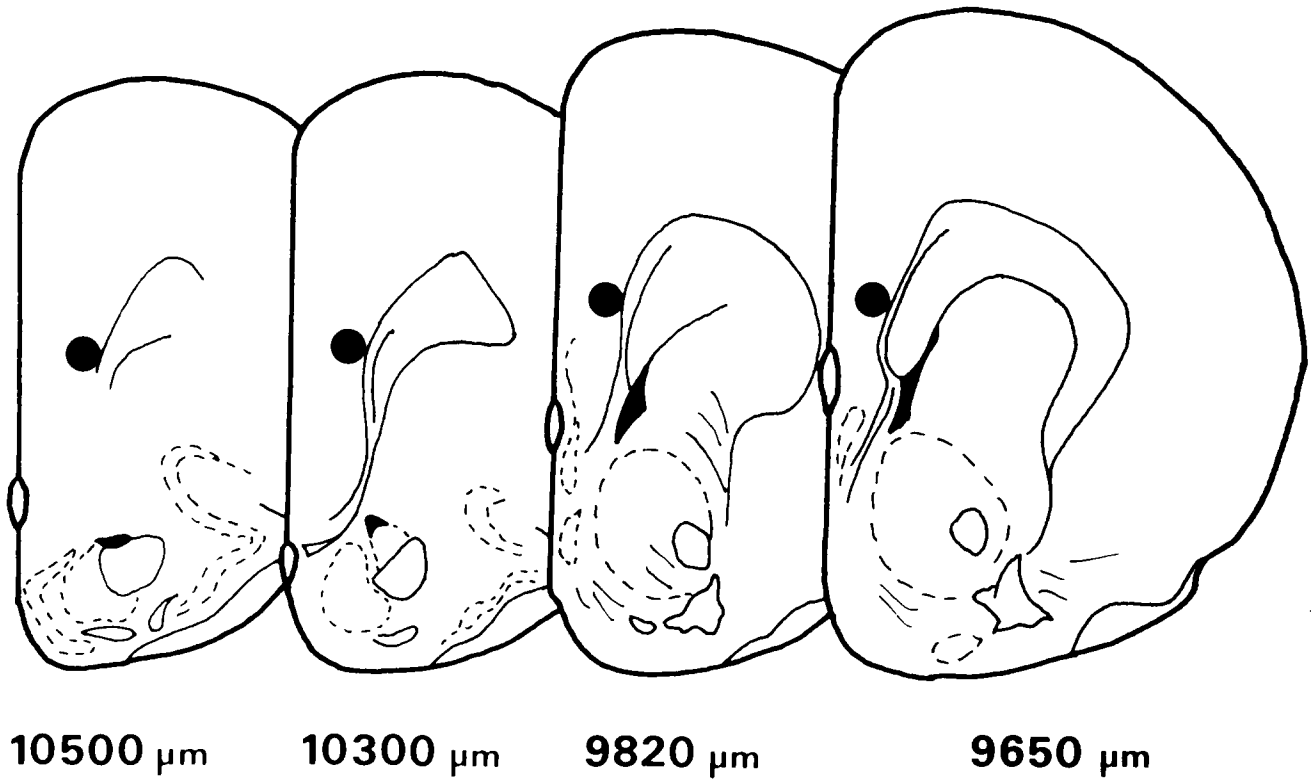

FIG. 8. Schematic representation of the stereotaxic planes at which the electrodes and cannulae were located. The outlines were taken from the atlas of König and Klippel. Dots represent the average location of the tips of electrodes in the MPC in the four different groups of rats used in this study.

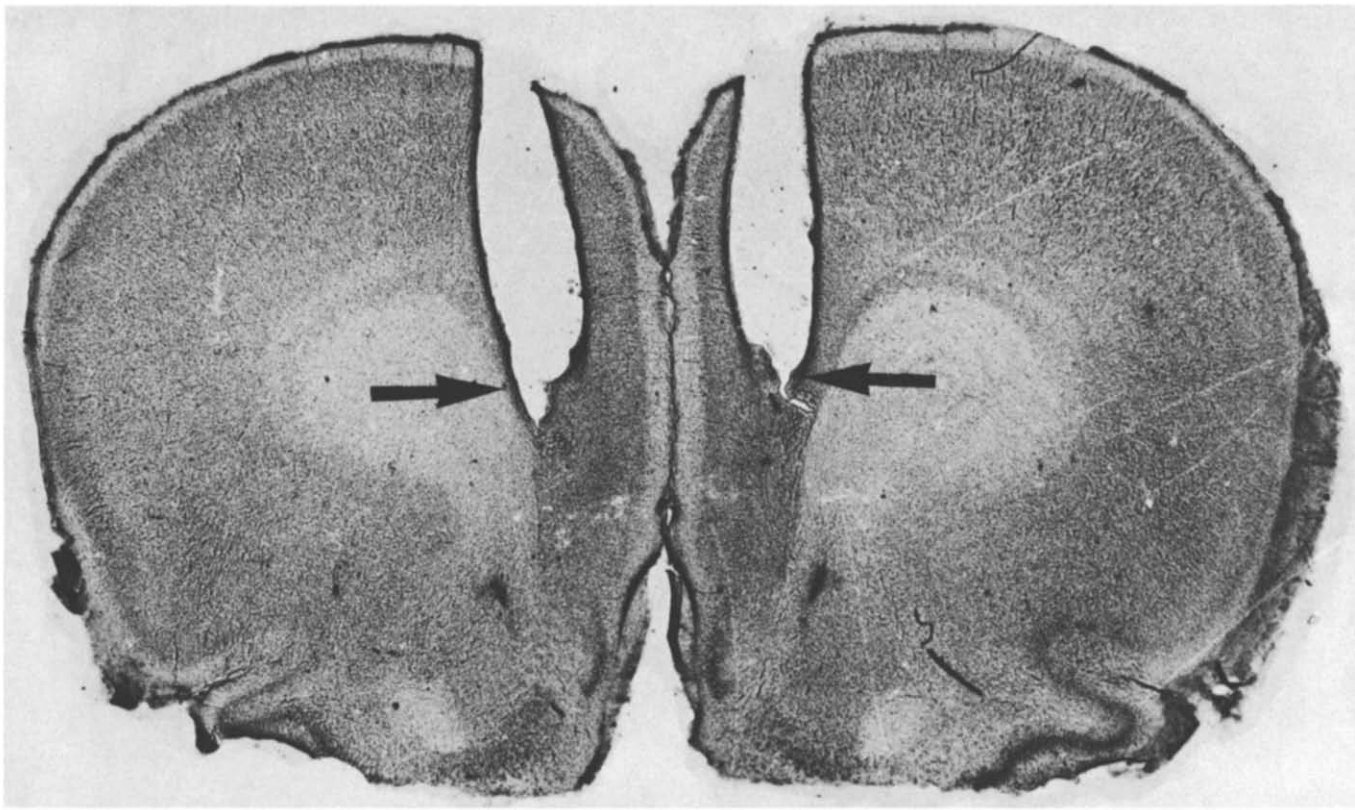

FIG. 9. Photograph showing an example of electrode placement. The arrows indicate the location of the electrodes in the deeper layers of the MPC.

tion [20] we have reported data in favor of such an interpretation. In that last study [20] we showed that an anticholinergic, dexetimide, was able to antagonize the motor inhibition produced by spiroperidol but not SS of the MPC suggesting therefore that spiroperidol could block SS of the MPC selectively and not secondary to motor impairment. Despite of that, we attempted in this study to clarify further this problem injecting pimozide directly into the brain at the same locus where the tip of the electrode is located. This experimental approach would provide a direct evidence on whether the drug is acting directly on the neural substrates of SS in the MPC. As it has been shown in the results section, SS of the injected side was decreased in a dose-related manner while SS contralateral to the injected side was not significantly affected. In conclusion, this last finding would suggest further the specificity of effects produced by D1-D2 receptors antagonists on SS of the MPC.

Sulpiride, a selective D2 antagonist and used at doses at which clear effects had been described on dopamine turnover [5, 7, 8, 28], produced no effects on SS. Only at a very high dose, i.e., 40 mg/kg, would an effect be seen. Since spontaneous motor behavior was significantly decreased at doses of 20 and 40 mg/kg it is unlikely that the decrease found on SS at the dose of 40 mg/kg was due to the specific effects of sulpiride on SS. The suggestion, inferred from the intraperitoneal injections, that sulpiride produces no effect on SS was further confirmed by microintracranial injections of sulpiride into the MPC. Contrary to the effects produced by pimozide (D1-D2 antagonist) sulpiride, in the range of doses used, produced no effect on SS, therefore the conclusion of this second block of experiments is that the blockade of D2 dopamine receptors do not interfere with the dopaminergic neurotransmission involved in SS of the MPC and suggests further that the effects of the D1-D2 dopamine receptor blockers on SS of this same area of the brain are due to their action on D1 dopamine receptors. These conclusions are further suggested by the results obtained with dopamine agonists (see below).

Apomorphine used in these experiments as a D1-D2 receptor agonist produced a decrease of SS which was dose-dependent. Motor activity under the effects of apomorphine produced a decrease at lower doses and an increase at higher doses. These effects of apomorphine on SM agrees with previous reports [6]. That the effects produced by apomorphine on SS seem specific or at least, not due secondarily to motor dysfunction or stereotypy, is based on our previous reports in rats and monkeys in which SS of the caudate-putamen under the effects of apomorphine was not affected, and even facilitated, in the same animals at which SS of the MPC had a similar decrease as the one reported here [13,14]. This view would also be supported by experiments in which we showed that the spontaneous firing rate of neurons in the area were the electrodes supporting SS in MPC are located is inhibited by the systemic injections of apomorphine [14].

Bromocriptine and lergotrile, used as D2 agonists [9] had no effects on SS of the MPC. Interestingly, however, SM was significantly decreased in the same animals. The effects of these ergot drugs on SM have been previously described in the literature [6] and agree fully with the effects reported in this study.

The main conclusion from this study is that agonists as well as antagonists that seem to act predominantly on D2 receptors have no effects on SS of the MPC. Since on the other hand, drugs that act on D1-D2 receptors have inhibitory effects on SS of the MPC it is inferred that these effects are mediated through activation of D1 dopamine receptors. This conclusion is not, however, a definitive statement in view of the fact that recently has also been described the existence of a third type of dopamine receptor (D3 receptors) [14]. An interesting and final point which arises from this study is the fact that both, antagonists as well as agonists of D1 receptors, produced the same type of effect, that is, an inhibition of self-stimulation. A theoretical interpretation of such effects have been analyzed in detail and published elsewhere [17].

ACKNOWLEDGEMENTS

We thank professor C. Osorio for the support given to this research and Mrs. R. Montes and Mr. E. Sanchez-Cantalejo for their invaluable help. We would also like to acknowledge the secretarial assistance provided by Mrs. A. Quintana and Mrs. A. Herrera.

REFERENCES

1. Anden, N. E., S. G. Butcher, H. Corrodi, K. Fuxe and U. Ungerstedt. Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur J Pharmacol* **11:** 303–314, 1970.
2. Bernheimer, H., W. Birkmayer, O. Hornykiewicz, K. Jelhinga and F. Seiteberger. Brain dopamine and the syndromes of Parkinson and Huntington: Clinical, morphological and neurochemical correlations. *J Neurol Sci* **20:** 415–455, 1973.
3. Clavier, R. M. and C. R. Gerfen. Self-stimulation of the sulcal prefrontal cortex in the rat: direct evidence for ascending dopaminergic mediation. *Neurosci Sci* **12:** 183–187, 1979.
4. Creese, I. Dopamine receptors explained. *TINS* **5:** 40–43, *Trends Neurosci* **5:** 40–43, 1982.
5. Cross, A. J. and F. Owen. Characteristics of 3H-cisflupenthixol binding to calf brain membranes. *Eur J Pharmacol* **29:** 349–351, 1980.
6. Fuxe, K., B. B. Fredholm, S. Ogren, L. F. Agnati, T. Hokfelt and J. Gustafson. Ergots drugs and central monoaminergic mechanisms: A histochemical, biochemical and behavioural analysis. *Fed Proc* **37:** 2181–2191, 1978.
7. Hoffman, M., G. C. Jommi, O. Montefusco, G. C. Tonon, P. F. Spano and M. Trabucchi. Stereospecific effects of (−) sulpiride on brain dopamine metabolism and prolactin release. *J Neurochem* **37:** 1547–1550, 1979.
8. Iversen, L. L., M. Quick, P. C. Emson, J. K. Dowling and K. J. Watling. Further evidence for the existence of multiple receptors for dopamine in the central nervous system. In: *Receptors for Neurotransmitters and Peptide Hormones*, edited by G. Pepeu, M. J. Kuhar and S. J. Enna. New York: Raven Press, 1980, pp. 193–202.
9. Kebabian, J. W. and D. B. Calne. Multiple receptors for dopamine. *Nature* **277:** 93–96, 1979.
10. Klüver, H. and E. Barrera. A method for the combined staining of cells and fibers in the nervous system. *J Neuropathol Exp Neurol* **12:** 400–403, 1953.
11. König, J. F. R. and R. A. Klippel. *The Rat Brain*. Baltimore, MD: Williams and Wilkins, 1963.
12. Mora, F., A. M. Sanguinetti, E. T. Rolls and S. G. Shaw. Differential effects on self-stimulation and motor behaviour produced by microintracranial injections of a dopamine receptor blocking agent. *Neurosci Lett* **1:** 179–184, 1975.

13. Mora, F., A. G. Phillips, J. M. Koolhas and E. T. Rolls. Prefrontal cortex and neostriatum self-stimulation in the rat: Differential effects produced by apomorphine. *Brain Res Bull* **1:** 421–424, 1976.
14. Mora, F., F. Sweeney, E. T. Rolls and A. M. Sanguinetti. Spontaneous firing rate of neurones in the prefrontal cortex of the rat: Evidence for a dopaminergic inhibition. *Brain Res* **116:** 516–522, 1976.
15. Mora, F., R. D. Myers and A. M. Sanguinetti. Self-stimulation of the MFB or VTA after microinjection of haloperidol into the prefrontal cortex of the rat. *Pharmacol Biochem Behav* **6:** 236–241, 1977.
16. Mora, F. and R. D. Myers. Brain self-stimulation: direct evidence for the involvement of dopamine in the prefrontal cortex. *Science* **197:** 1367–1389, 1977.
17. Mora, F. The neurochemical substrates of prefrontal cortex self-stimulation: A review and an interpretation of some recent data. *Life Sci* **22:** 919–930, 1978.
18. Mora, F., A. D. Avrith, A. G. Phillips and E. T. Rolls. Effects of satiety on self-stimulation of the orbitofrontal cortex in the rhesus monkey. *Neurosci Lett* **13:** 141–145, 1979.
19. Mora, F., A. D. Avrith and E. T. Rolls. An electrophysiological and behavioural study of self-stimulation in the orbitofrontal cortex of the rhesus monkey. *Brain Res Bull* **5:** 111–115, 1980.
20. Mora, F., F. Alba, A. M. Sanguinetti, J. M. Rodriguez and F. Vives. Differential effects produced by an anticholinergic on the neuroleptic inhibition of motor behaviour and self-stimulation of the prefrontal cortex in the rat. *Brain Res Bull* **5:** 223–225, 1980.
21. Mora, F., F. Vives and F. Alba. Evidence for an involvement of acetylcholine in self-stimulation of the prefrontal cortex in the rat. *Experientia* **36:** 1180–1181, 1980.
22. Myers, R. D. *Handbook of Drug and Chemical Stimulation of the Brain*. New York: Van Nostrand Reinhold Company, 1974.
23. Phillips, A. G. and H. G. Fibiger. The role of dopamine in maintaining intracranial self-stimulation in the ventral tegmentum, nucleus accumbens and medial prefrontal cortex. *Can J Psychol* **32:** 58–66, 1978.
24. Phillips, A. G., F. Mora and E. T. Rolls. Intracranial self-stimulation in orbitofrontal cortex and caudate nucleus of rhesus monkey: effects of apomorphine, pimozide and spiroperidol. *Psychopharmacology (Berlin)* **62:** 79–82, 1979.
25. Robertson, A. and G. J. Mogenson. Facilitation of self-stimulation of the prefrontal cortex in rats following chronic administration of spiroperidol or amphetamine. *Psychopharmacology (Berlin)* **65:** 149–154, 1979.
26. Rolls, E. T., B. J. Rolls, P. H. Kelly, S. G. Shaw, R. J. Wood and R. Dale. The relative attenuation of self-stimulation, eating and drinking produced by dopamine-receptor blockade. *Psychopharmacologia* **33:** 219–230, 1974.
27. Routtenberg, A. and H. Sloan. Self-stimulation in the prefrontal cortex of the Rattus norvegicus. *Behav Biol* **7:** 567–572, 1972.
28. Tagliamonte, A., G. Moutis, M. L. de Olianas, G. U. Vergiu and G. L. Gessa. Selective increase of brain dopamine synthesis by sulpiride. *J Neurochem* **24:** 707–710, 1975.
29. Tassin, J. P., J. Bockaert, G. Blanc, L. Stinus, A. M. Thierry, S. Lavielle, J. Premont and J. Glowinski. Topographical distribution of dopaminergic innervation and dopaminergic receptors of the anterior cerebral cortex of the rat. *Brain Res* **154:** 241–252, 1978.
30. Wauquier, A. and C. S. E. Niemeegers. The effects of dexetimide on pimozide, haloperidol and pipamperone-induced inhibition of brain self-stimulation in rats. *Arch Int Pharmacodyn Ther* **217:** 280–292, 1975.
31. Wauquier, A. Neuroleptics and brain self-stimulation behavior. *Int Rev Neurobiology*, in press.