Pharmacology Biochemistry & Behavior, Vol. 37, pp. 387–392. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Unilateral Injections of a D2 But Not D1 Agonist Into the Frontal Cortex of Rats Produce a Contralateral Directional Bias

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Received 15 February 1990

BENINGER, R. J., M. A. MUSGRAVE AND P. R. DICKSON. *Unilateral injections of a D2 but not D1 agonist into the frontal cortex of rats produce a contralateral directional bias*. PHARMACOL BIOCHEM BEHAV **37**(3) 387–392, 1990.—Unilateral manipulations of frontocortical dopamine have been found in previous studies to produce a directional bias in the circling behaviour of rats. Agonists produced contralateral circling and antagonists produced ipsilateral turning. To examine the role of dopamine receptor subtypes, the present studies investigated the ability of unilateral intrafrontal cortical microinjections of the D1 agonist, SKF 38393 or the D2 agonist, quinpirole to produce contralateral circling in rats. The antagonist, *cis*-flupenthixol was also tested and was expected to produce ipsilateral circling. In 3 separate experiments, rats received 7 50-min sessions in a circular arena separated by at least 48 hr. The first and final sessions were preceded by no injection, the second and sixth by saline [or the inactive *trans* isomer (25 μg) in the flupenthixol experiment] and the middle 3 sessions by doses of *cis*-flupenthixol (1, 10, 25 μg in 0.5 μl), quinpirole (3, 6, 12 μg) or SKF 38393 (2, 4, 8 μg), the order being counterbalanced across rats. *cis*-Flupenthixol and quinpirole produced dose-dependent ipsi- and contralateral circling, respectively, whereas SKF 38393 was without significant effect. No reliable directional bias was seen in any no-injection, saline or *trans*-flupenthixol sessions. Results suggested that the D2 receptor may mediate the motor effects of frontal cortical dopamine.

Dopamine receptors SKF 38393 Quinpirole *cis*-Flupenthixol Circling Frontal cortex

DOPAMINE (DA) contributes to the control of unconditioned motor activity. Numerous studies have shown that increases and decreases in DA neurotransmission lead to respective increases and decreases in locomotion (3, 7, 28). The role of specific DA systems and terminal areas in this function also has been extensively investigated. Results have shown that the nigrostriatal and mesoaccumbens systems both appear to contribute to the control of unconditioned motor activity (5,15).

One approach that has been very useful in the investigation of the role of DA terminal regions in motor behaviour involves the study of circling or turning. When there is an imbalance in the level of DA activity on the two sides of the brain, rats typically circle away from (contralateral to) the side of higher DA activity (21). This approach has been employed to study frontal cortical DA. Results have shown that unilateral intrafrontal cortical microinjections of the DA agonists, apomorphine, (+)-amphetamine or cocaine produced contralateral circling (10, 17, 18). Although the effect did not involve a large number of turns, results were highly reliable in supporting the hypothesis that frontal cortical DA may play an excitatory role in the control of locomotor behaviour.

In recent years there has been great interest in the possible contribution of DA receptor subtypes to the behavioural functions mediated by DA (4, 6, 16). Results of studies involving systemic treatments with pharmacological agents relatively specific for D1 or D2 receptors have generally shown that stimulation of both receptor subtypes seems to be necessary for the observation of locomotor stimulation in normosensitive animals (30). Although both D1 and D2 agonists can produce locomotor stimulation, the effects of D2 agonists are usually larger (29).

The effects of D2-specific compounds have been investigated following unilateral microinjection into the frontal cortex. It has been found that the D2 agonist, LY 141865 produced contraversive circling (26), whereas the D2 antagonists, metoclopramide and sulpiride produced ipsiversive circling in animals pretreated systemically with amphetamine (10, 17, 18, 26). Sulpiride also antagonized circling produced by cocaine (18). The role of D1 receptors has not been investigated.

The purpose of the present investigation was to evaluate the effects of intrafrontal cortical injections of the D1 agonist, SKF 38393, on circling behaviour. The active isomer of LY 141865, quinpirole (LY 171555), also was tested to replicate the D2 agonist effect. Finally, a group was tested with the DA antagonist, *cis*-flupenthixol. It was expected that the agonists would produce contraversive circling and that the antagonist would produce ipsiversive circling.

METHOD

Animals

Male albino Wistar (n = 11) and Sprague Dawley (n = 47) rats weighing 200–250 g, obtained from Charles River Canada, were individually housed in a climatically controlled (21 ± 1°C) colony room on a 12-hr light (0600–1800 hr)/dark cycle. Food and water were available ad lib in the home cages.

Surgery

Rats were anesthetized with sodium pentobarbitol (60 mg/kg, IP) and implanted unilaterally with chronic indwelling stainless steel guide cannulae (0.64 mm dia.) aimed at the medial prefrontal cortex with coordinates: 4.5 mm anterior to bregma, 0.8 mm lateral to the midline and 3.0 mm ventral to the dura mater with the incisor bar set at 5.0 mm above the horizontal plane passing through the interaural line (20). Cannulae were anchored to the skull using stainless steel screws and acrylic cement. Stainless steel obturator pins were used to seal the cannulae between injections. For Experiments 1 and 2, 23 and 18 Sprague-Dawley rats were cannulated, respectively. For Experiment 3, 17 rats were implanted, 11 Wistar and 6 Sprague-Dawley. For all experiments, the side of cannulation was balanced with an equal number of rats being implanted in the right and left frontal cortices.

Apparatus

Three polyurethane-sealed circular wooden bases, 30 cm in diameter, enclosed within a cylinder of wire mesh 30 cm high were fitted with Plexiglas covers.

Behavioural Testing

Beginning approximately 1 week after surgery, each animal was tested 7 times using the following protocol: 1) no central injection; 2) central injection of 0.9% saline (except in Experiment 1; see below); 3,4,5) central injection of each of 3 drug doses order being counterbalanced across rats over the 3 sessions; 6) replication of the saline condition; 7) replication of the no central injection condition. Sessions occurred during the light period at approximately the same time each day and were separated by a minimum of 48 hours.

A test session began with an intracerebral injection and placement into the circular arena. All complete turns (360°), ipsiversive and contraversive to the side of the cannula, were counted during each observation period. Three animals were scored during each 50-min session, observation periods being at 0–5, 15–20, 30–35 and 45–50 min. Animals were started at staggered intervals such that only 1 animal was being scored at any time. The clock was stopped during the time taken to administer the central injection (maximum of 2 min). Thus, each animal was scored for a total of 20 min in four 5-min blocks at approximately equal intervals throughout the session.

For Experiment 1, rats were pretreated with (+)-amphetamine (1.5 mg/kg, IP) 15 min prior to every session. No central injection was given prior to sessions 1 and 7. Immediately prior to sessions 2 and 6, central injections of the inactive geometric isomer of *cis*-flupenthixol, *trans*-flupenthixol were delivered in a dose of 25 μg, while prior to sessions 3, 4 and 5, *cis*-flupenthixol was injected in doses of 1, 10 and 25 μg, the order being counterbalanced across rats.

In Experiment 2, rats received no central injections prior to sessions 1 and 7. Saline was injected immediately prior to sessions 2 and 6 and prior to sessions 3, 4 and 5, quinpirole was injected in doses of 3, 6 and 12 μg, the order being counterbalanced across rats.

Experiment 3 was like Experiment 2 except that immediately prior to sessions 3, 4 and 5 rats were centrally injected with SKF 38393 in doses of 2, 4 and 8 μg.

Drugs

(+)-Amphetamine sulphate (Smith, Kline and French), *cis*- and *trans*-flupenthixol (H. Lundbeck), quinpirole (Eli Lilly and Co.) and SKF 38393 (Research Biochemicals Inc.) were dissolved daily in distilled water prior to behavioural testing.

Central Injections

Microinjections were delivered in a volume of 0.5 μl using a 5 μl Hamilton microsyringe attached via polyethylene tubing to an injection cannulae constructed of stainless steel tubing (0.30 mm in diam) cut to extend 0.5 mm beyond the tip of the guide cannulae. The injection was delivered manually over a period of 30 sec and the injection cannula was left in place for an additional 60 sec to ensure sufficient drug diffusion. Following infusion, obturator pins were inserted into the guide cannulae.

Histology

At the conclusion of behavioural testing, animals were sacrificed for histological confirmation of cannulae placements. Rats were injected with a lethal dose of sodium pentobarbitol, exsanguinated with intracardial 0.9% saline followed by 10% formalin. Brains were extracted and coronal sections (40–50 μm), taken through the frontal cortex, were mounted and stained with thionin.

Statistical Analyses

For each rat, turns were summed over the 4 observation periods. Circling behaviour was expressed as a turning ratio, viz., number of ipsiversive turns over total number of turns (ipsiversive + contraversive). Ratio values of 0.5 indicated equal turning in both directions. Values greater or less than 0.5 indicated a tendency towards ipsiversive or contraversive circling, respectively. The total number of turns per session served as the second dependent measure.

For each experiment for each dependent variable, the first analyses were a pair of *t*-tests for related measures comparing the first and second no-injection session and the first and second saline (or *trans*-flupenthixol) sessions. Where significant differences were not found, these pairs of sessions were combined. The 5 treatments, viz., no-injection, saline (or *trans*-flupenthixol) and the 3 drug doses were then analyzed using one-way repeated measures analyses of variance (ANOVA) followed by Dunnett's *t*-tests if the main effect was significant. As the ANOVAs involved repeated measures, the more conservative Greenhouse-Geisser adjusted degrees of freedom were used (12).

RESULTS

The number of rats included in the statistical analyses for Experiments 1, 2 and 3 was 10, 10 and 8 (5 Wistar and 3 Sprague-Dawley), respectively. Cannulae placements are indicated in Fig. 1. The remaining rats were discarded due to defective cannulae or inaccurate placements. It is noteworthy that the discarded animals with placements dorsal, lateral or anterior to the target area failed to show significant effects.

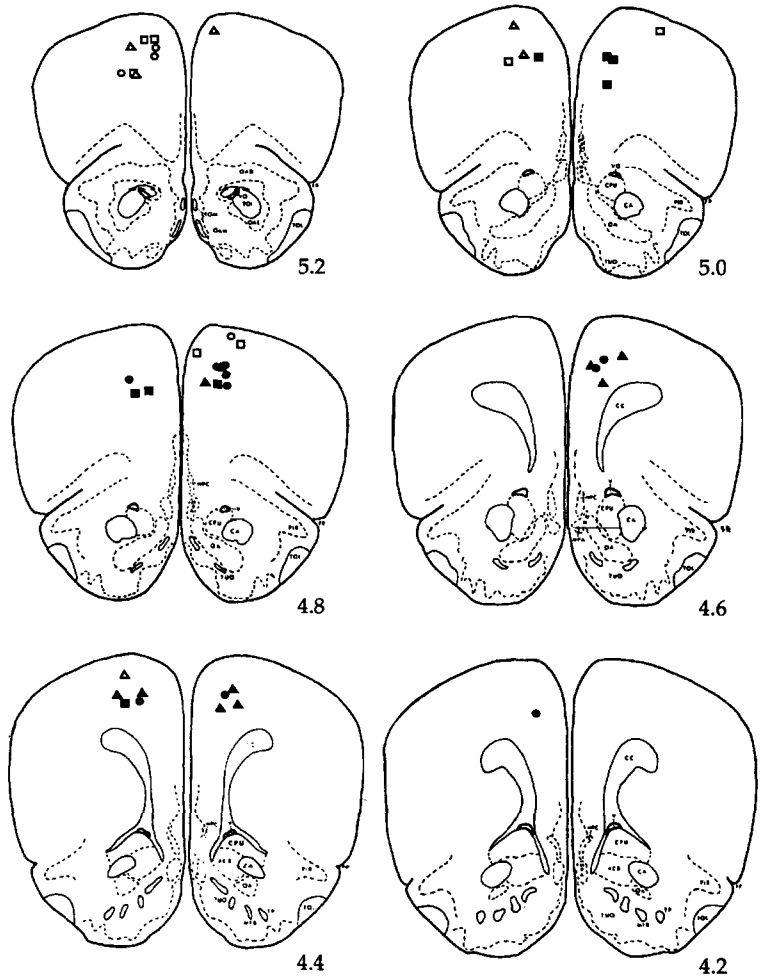

FIG. 1. Cannulae placements for the rats included in Experiments 1 (▲), 2 (●) and 3 (■). Filled symbols indicate sites included in data analyses and open symbols indicate misses. In general, misses were anterior, dorsal or lateral to the dopaminergically innervated region of the frontal cortex. Coronal sections were reproduced from Pellegrino *et al.* (20) and the distance anterior to bregma is indicated below each section. Sixteen of the 23 rats from Experiment 1, 14 of the 18 rats from Experiment 2 and 15 of the 17 rats from Experiment 3 are shown. The brains of the remaining rats failed to reveal cannulae tracts probably because the cannulae were either too medial or too dorsal. The data from these latter animals were not included in any of the analyses.

Experiment 1: cis-*Flupenthixol and Circling*

The mean (±SEM) turning ratios for the first and second no-injection sessions were 0.49±0.06 and 0.50±0.06, respectively and those for the corresponding *trans*-flupenthixol sessions were 0.55±0.08 and 0.48±0.06. *t*-Tests revealed no significant differences for no-injection, $t(9)<1$, $p>0.05$, and for *trans*-flupenthixol, $t(9)<1$, $p>0.05$; therefore, each animal's scores from the pairs of sessions were combined for subsequent analyses.

The mean turning ratios for no-injection, *trans*-flupenthixol, and 1, 10 and 25 μg doses of *cis*-flupenthixol are shown in Fig. 2A. ANOVA revealed a significant treatment effect, $F(4,36)=9.68$, $p<0.001$, and Dunnett's tests showed the mean ratio scores for the 25 μg dose to be significantly different from the *trans*-flupenthixol treatment, $p<0.01$.

The mean (±SEM) number of total turns for the first and second no-injection sessions were 21.1±3.3 and 19.3±2.7, respectively and those for the corresponding *trans*-flupenthixol sessions were 26.8±5.0 and 17.6±2.8. *t*-Tests revealed no significant differences for no-injection, $t(9)<1$, $p>0.05$, and for *trans*-flupenthixol, $t(9)=-1.99$, $p>0.05$; therefore, each animal's scores from the pairs of sessions were combined for subsequent analyses.

The mean total turns for no-injection, *trans*-flupenthixol, and 1, 10 and 25 μg doses of *cis*-flupenthixol are shown in Table 1. ANOVA revealed no significant treatment effect, $F(4,36)=1.02$, $p>0.05$.

Experiment 2: Quinpirole and Circling

The mean (±SEM) turning ratios for the first and second no-injection sessions were 0.53±0.06 and 0.57±0.05, respectively and those for the corresponding saline sessions were 0.57±0.05

and 0.51 ± 0.04. *t*-Tests revealed no significant differences for no-injection, $t(9) = -1.10$, $p > 0.05$, and for saline, $t(9) < 1$, $p > 0.05$; therefore, each animal's scores from the pairs of sessions were combined for subsequent analyses.

The mean turning ratios for no-injection, saline, and 3, 6 and 12 μg doses of quinpirole are shown in Fig. 2B. ANOVA revealed a significant treatment effect, $F(4,36) = 3.63$, $p < 0.05$, and Dunnett's tests showed the mean ratio scores for the 12 μg dose to be significantly different from the saline treatment, $p < 0.05$.

The mean (±SEM) number of total turns for the first and second no-injection sessions were 12.3 ± 2.3 and 9.5 ± 1.6, respectively and those for the corresponding saline sessions were 9.8 ± 1.6 and 9.9 ± 1.4. *t*-Tests revealed no significant differences for no-injection, $t(9) = -1.11$, $p > 0.05$ and for saline, $t(9) < 1$, $p > 0.05$; therefore, each animal's scores from the pairs of sessions were combined for subsequent analyses.

The mean total turns for no-injection, saline, and 3, 6 and 12 μg doses of quinpirole are shown in Table 1. ANOVA revealed no significant treatment effect, $F(4,36) < 1$, $p > 0.05$.

Experiment 3: SKF 38393 and Circling

The mean (±SEM) turning ratios for the first and second no-injection sessions were 0.55 ± 0.07 and 0.41 ± 0.15, respectively and those for the corresponding saline sessions were 0.43 ± 0.06 and 0.42 ± 0.15. *t*-Tests revealed no significant differences for no-injection, $t(7) = 1.22$, $p > 0.05$, and for saline, $t(7) < 1$, $p > 0.05$; therefore, each animal's scores from the pairs of sessions were combined for subsequent analyses.

The mean turning ratios for no-injection, saline, and 2, 4 and 8 μg doses of SKF 38393 are shown in Fig. 2C. ANOVA revealed no significant treatment effect, $F(4,28) = 1.34$, $p > 0.05$. As the rats included in this study were of two different strains, the ANOVA of turning ratios was repeated with strain as a factor. Neither the main effect of strain, $F(1,6) < 1$, $p > 0.05$, nor the interaction, $F(4,24) < 1$, $p > 0.05$, was significant.

The mean (±SEM) number of total turns for the first and second no-injection sessions were 14.6 ± 1.5 and 12.5 ± 1.9, respectively and those for the corresponding saline sessions were 13.9 ± 2.8 and 13.0 ± 2.5. *t*-Tests revealed no significant differences for no-injection, $t(7) < 1$, $p > 0.05$ and for saline, $t(7) < 1$, $p > 0.05$; therefore, each animal's scores from the pairs of sessions were combined for subsequent analyses.

The mean total turns for no-injection, saline, and 2, 4 and 8 μg doses of SKF 38393 are shown in Table 1. ANOVA revealed no significant treatment effect, $F(4,28) = 1.50$, $p > 0.05$.

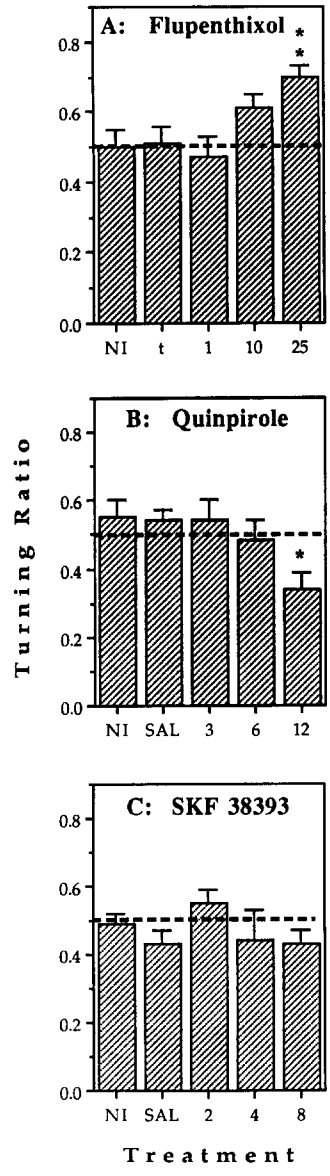

FIG. 2. Mean (+SEM) turning ratios (total ipsilateral turns/total ipsilateral + contralateral turns) for the two no-injection (NI) sessions combined, the two saline (SAL) [or *trans*-flupenthixol (t)] sessions combined and the three doses (μg in 0.5 μl) of *cis*-flupenthixol (A), quinpirole (B) or SKF 38393 (C). Analyses of variance revealed significant treatment effects for flupenthixol ($p < 0.001$) and quinpirole ($p < 0.05$) but not SKF 38393. Post hoc tests indicated that the high dose of *cis*-flupenthixol (**) differed from the *trans*-flupenthixol treatment and the high dose of quinpirole (*) differed from its saline control.

DISCUSSION

In each experiment, the series of 5 central injection sessions was bracketed with no-injection sessions. Mean turning ratios were seen to be near 0.5 in each case and in no case did the first no-injection score differ significantly from the last. These results demonstrated that neither chronic cannulation nor the series of 5 central injections had enduring effects on the directional bias shown by the rats. Similar results were reported by Morency *et al.* (17,18) and Stewart *et al.* (26).

Each experiment also bracketed the series of 3 central injections of dopaminergic drugs with control injections; in experiment 1 the inactive geometric isomer, *trans*-flupenthixol was used and saline was used in Experiments 2 and 3. Ratio scores were always near 0.5 and they were never seen to differ significantly from pre- to postdrug sessions. The *trans*-flupenthixol results demonstrated that injection of a similar volume of the inactive isomer having the same osmolarity, pH and concentration as the active dose of *cis*-flupenthixol failed to significantly alter the direction of turning. Both the saline and the *trans*-flupenthixol results showed that turning did not result simply from the mechanical effects of making the injections. Nor could the results be attributed to a sensitization to the effects of repeated injections as the pre- and postdrug turning ratios did not differ significantly. These results are consistent with those of previous control studies (17, 18, 26).

The possibility of diffusion of the drug from the frontal cortex to the striatum or nucleus accumbens seems unlikely. It has been shown previously that a 1.0 μl injection volume diffuses

TABLE 1

MEAN (±SEM) TOTAL NUMBER OF TURNS FOR EACH EXPERIMENT

EXP. (N)	NI	SAL	Drug Dose Low	Drug Dose Medium	Drug Dose High
1 (10)	20.2 ± 2.5	22.2 ± 3.4*	23.7 ± 4.4	24.6 ± 4.0	28.0 ± 4.0
2 (10)	10.4 ± 1.4	9.9 ± 1.4	9.2 ± 1.3	8.9 ± 1.3	8.6 ± 2.1
3 (8)	13.6 ± 1.3	12.8 ± 2.2	10.1 ± 1.3	10.3 ± 1.9	12.4 ± 1.9

*Rats in Experiment 1 received *trans*-flupenthixol during these sessions.

Abbreviations: EXP, experiment; NI, no injection; SAL, saline. Drugs (low, medium, high doses in μg delivered in 0.5 μl) in Experiments 1, 2 and 3 were *cis*-flupenthixol (1, 10, 25), quinpirole (3, 6, 12) and SKF 38393 (2, 4, 8), respectively.

into a sphere of approximately 1.0 mm (19). In the rat brain, a distance of at least 3 mm separates the medial prefrontal cortex and these areas. Furthermore, the injection volume used in the present studies was 0.5 μl, further decreasing the probability of widespread diffusion.

It was found that none of the treatments, including those that produced changes in the direction of turning, significantly affected total turns. The animals in the flupenthixol experiment were pretreated with systemic amphetamine to increase their activity and total turn scores reflected this stimulant effect (see Table 1). Previous studies from this lab have reported increases in total turns following treatments with sulpiride, metoclopramide, amphetamine or cocaine, decreases following LY 141865 and no change following procaine (17, 18, 26). The present results showed nonsignificant trends in the same direction, the flupenthixol animals increasing with dose, the quinpirole animals decreasing slightly with dose and the SKF 38393 animals showing no consistent change. Perhaps the use of a wider dose range including higher doses would yield significant effects. The present results clearly demonstrate that it is possible to see a change in *direction* of turning following intrafrontal cortical injection of dopaminergic agents without a large change in total *number* of turns.

The finding that *cis*-flupenthixol and quinpirole produced dose-dependent effects on turning ratios even though the doses were given in a counterbalanced order across rats provided further evidence that the results were not the consequence of repeated central injections to the same animals. The *cis*-flupenthixol effects on direction of turning were consistent with previous reports that the DA antagonists, sulpiride and metoclopramide produced ipsiversive turning and the quinpirole effect was consistent with reports that the DA agonists, apomorphine, cocaine, amphetamine or LY 141865 produced contraversive turning when injected into the medial frontal cortex (10, 17, 18, 26).

Previous and the present studies have shown that DA agonists specific for the D2 receptor produced contraversive turning, whereas D2-specific antagonists produced ipsiversive turning (10, 17, 18, 26). The present study also showed that the D1 agonist, SKF 38393 was without significant effect. These results might suggest that D2 receptors in the frontal cortex mediate the effects of DA on the direction of turning.

One possible explanation for the negative effects with SKF 38393 in the present study might be that the dose range (2–8 μg) was not wide enough. However, in a recent study, Asin and Montana (1) investigated the effects of intranigral injections of this compound on turning in normosensitive rats and found significant effects with a dose of 5 μg. This showed that doses smaller than the maximum used here could be effective. Furthermore, it has recently been reported, at least in the cat and in humans, that there is a much greater concentration of D1 than D2 receptors in the frontal cortex (8,24). If D1 receptors do mediate directional bias, therefore, the present experiment might have been expected to show it.

It has been suggested previously that frontal cortical dopamine normally inhibits locomotor activity since unilateral or bilateral 6-hydroxydopamine lesions in this area result in hyperactivity 7–10 days postlesion (11, 22, 25). Further evidence supporting this hypothesis is provided by the fact that a high correlation was found between increases in locomotor activity and decreases in frontocortical dopamine 30 days following bilateral electrolytic destruction of the ventral tegmental area (27). In opposition to this, however, are biochemical data which have shown increased levels of dopamine function in the nucleus accumbens and striatum 4 weeks subsequent to frontal cortical dopamine denervation (23). The hyperactivity (11, 22, 25) may be the result of these time-dependent, compensatory subcortical changes, thus demonstrating cortical regulation of subcortical dopaminergic function.

This interpretation is not inconsistent with findings of lesion studies of the frontal cortex. Rotational behavior has been induced in rats with unilateral frontal cortical ablation (2,9). At early postoperative intervals (1–7 days), lesion animals circled ipsilaterally both spontaneously and after systemic amphetamine administration, the intact side being the locus of greater dopamine activity. At later intervals (15–30 days), contraversive circling was observed following systemic amphetamine. Although ablation damage is nonspecific, these data are consistent with the findings of Pycock *et al.* (23). The ipsiversive circling may have been a response to frontal cortical loss, while the contraversive effect could reflect subcortical compensatory changes and is thus suggestive of frontal cortical mediation of subcortical function.

By employing acute unilateral frontal cortical dopaminergic manipulations that would avoid compensatory changes, it has been demonstrated previously in our laboratory that ipsiversive circling resulted from injections of the dopamine antagonists metochlopramide (26), sulpiride (17,18); we now add *cis*-flupenthixol to this list. Contraversive circling was found after (+)-amphetamine (26), LY 141865 (26), and cocaine (18) and now quinpirole. These results suggest that *frontal cortical dopamine is excitatory in its locomotor influence*. In agreement with this conclusion, Klockgather *et al.* (13) recently reported that bilateral intrafrontal cortical microinjections of haloperidol produced catelepsy. It will be the task of future studies to identify more precisely the underlying neurotransmitter interactions and anatomical connections mediating this effect.

Recently, Tassin *et al.* (27) have reported that bilateral microinjections of amphetamine into the frontal cortex, although producing no effect on their own, produced a decrease in the locomotor stimulant effect of bilateral intra-accumbens amphetamine. Others have reported that frontal cortical amphetamine or flupenthixol led to a respective decrease or increase in DOPAC release in the accumbens (14). It is noteworthy that the dose of amphetamine

used by Tassin *et al.* (27) and Louilot *et al.* (14) were 2.5 μg and 3.5 μg in 0.5 μl, respectively, several times lower than the effective dose producing turning by Stewart *et al.* (26); thus, the observation by Tassin *et al.* (27) that 2.5 μg produced no locomotor effects is consistent with our own findings. The suprising observation that this dose of frontal cortical amphetamine decreased locomotor activity produced by accumbens amphetamine awaits explanation.

In conclusion, D2- but not D1-specific agonists produced a contralateral turning bias when injected directly into the medial frontal cortex. This result supports previous findings that DA in the frontal cortex contributes to the control of motor behaviour and further suggests that the effect may be mediated by D2 receptors.

ACKNOWLEDGEMENTS

The authors wish to thank Smith, Kline and French, Canada Ltd., H. Lundbeck and Eli Lilly and Co. for the generous gifts of (+)-amphetamine, *cis*- and *trans*-flupenthixol, and quinpirole, respectively. Supported by grants from the Natural Sciences and Engineering Research Council of Canada and the Ontario Ministry of Health to R.J.B.

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