Pharmacology Biochemistry and Behavior, Vol 46, pp. 51-60, 1993
Printed in the U S A.

0091-3057/93 $6.00 + .00

Effects of Ibotenic Acid Lesion of the Medial Prefrontal Cortex on Dopamine Agonist-Related Behaviors in the Rat

A. R. BRAUN,[1] G. E. JASKIW,† K. VLADAR,‡ R. H. SEXTON,‡
B. S. KOLACHANA‡ AND D. R. WEINBERGER‡

Voice, Speech and Language Branch, National Institute on Deafness and Other Communication Disorders, Building 10, Room 5D38, National Institutes of Health, Bethesda, MD 20892
†Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland OH 44106
‡Clinical Brain Disorders Branch, National Institute of Mental Health, NIMH Neuroscience Center at St. Elizabeths, Washington, DC, 20032

Received 4 June 1992

BRAUN, A. R., G. E. JASKIW, K. VLADAR, R. H. SEXTON, B. S. KOLACHANA AND D. R. WEINBERGER. *Effects of ibotenic acid lesion of the medial prefrontal cortex on dopamine agonist-related behaviors in the rat.* PHARMACOL BIOCHEM BEHAV **46**(1) 51-60, 1993.—Behavioral responses to apomorphine and to the selective D_1 and D_2 dopamine receptor agonists SK&F38393 and quinpirole were evaluated in rats following ibotenic acid (IA) or sham lesion of the medial prefrontal cortex (MPFC). IA-lesioned rats showed an increased responsiveness to the postsynaptic effects of all of the dopamine agonists. Patterns of the responses to the selective agonists administered alone and in combination suggest that these effects might be due to selective increases in the sensitivity of postsynaptic D_1 receptor-associated mechanisms. In addition, IA-lesioned rats pretreated with saline were hyperactive in comparison to sham-lesioned rats when animals were exposed to a novel open field, but spontaneous motor activity did not differ between these two groups when animals were pretreated with low doses (0.03 mg/kg) of quinpirole. The fact that hyperreactivity observed in lesioned animals is inhibited by a dose of quinpirole that is felt to act presynaptically, selectively attenuating endogenous dopaminergic tone, suggests that effects of the MPFC lesion may be mediated presynaptically as well.

Dopamine Dopamine agonists Medial prefrontal cortex Presynaptic Postsynaptic D_1 receptor D_2 receptor Rat Behavior Stereotypic behavior Locomotion Grooming Open-field behavior Behavioral disorganization

THE classical behaviors induced by the postsynaptic action of dopamine (DA) agonists depend upon concurrent stimulation of D_1 and D_2 receptors (2,6,16). While both receptor subtypes contribute to overall increases in arousal as measured by motor activity (38) and desynchronization of electrocortical potentials (39), the level of D_1 receptor tone appears to be critical in the transition from functional to dysfunctional levels of arousal (5). A low level of D_1 receptor stimulation—when accompanied by activation of the D_2 receptor—appears to be necessary for the expression of organized motor activity. Increasing stimulation of the D_1 receptor, on the other hand, results in progressive disorganization of motor activity, emergence of stereotypic behaviors, and failure of attentional mechanisms (2,5,6). These responses have been proposed as animal models for neuropsychiatric disorders that are characterized by behavioral disorganization and are associated with apparent increases in dopaminergic tone.

While these pharmacological principles are relatively well established, it is not yet clear which regions of the brain participate in this functional interaction between D_1 and D_2 receptors. The medial prefrontal cortex (MPFC) of the rat would appear to be of particular interest in this regard. It has a relatively high concentration of D_1 receptors relative to other cortical areas (15,42). Although the absolute density of D_1 receptors is higher in the striatum, globus pallidus, and substantia nigra pars reticulata, the MPFC has the highest D_1/D_2 receptor ratio measured in the brain (4). The MPFC, moreover, is known to participate in cognitive processes and in the integration of complex sequences of motor behaviors (33). Accordingly, it is possible that stimulation of D_1 receptors

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

within the MPFC plays a critical role in regulating the nature of the behavioral output that follows combined administration of D_1 and D_2 agonists.

Alternatively, because the medial prefrontal cortex appears to participate in the modulation of subcortical dopaminergic activity (26,30,34,41,43) it is possible that this region of the cortex, via its influence upon extracortical dopaminergic mechanisms, might modify the effects of dopamine agonists acting elsewhere in the brain.

To characterize the role played by the medial prefrontal cortex in the generation of postsynaptic dopamine agonist-induced behaviors, animals received either ibotenic acid (IA) or sham lesions of this area and behavioral responses were evaluated following SC administration of vehicle, various doses of apomorphine, and the selective D_1 and D_2 receptor agonists SK&F38393 and quinpirole administered alone or in combination.

To assess the effects of the MPFC ibotenic acid lesion on presynaptic dopaminergic parameters, a second set of experiments was performed. IA- and sham-lesioned animals were pretreated with SC injections of vehicle or 0.03 mg/kg quinpirole—a dose believed to act preferentially on presynaptic dopamine receptors, thereby reducing endogenous dopaminergic tone—and spontaneous motor activity was evaluated following exposure of animals to a novel open field.

METHOD

Animals

Sixty male Sprague–Dawley rats (Zivic Miller), weighing between 250 and 300 g at the outset, were utilized in these experiments. Animals were housed in a temperature-controlled room illuminated on a 12 L : 12 D cycle. Food and water were provided ad lib throughout the course of the study.

Cortical Lesions

After induction of anesthesia with intramuscular ketamine (70 mg/kg) and xylazine (6 mg/kg), rats were positioned in a stereotaxic frame (Kopf Instruments, Topanga, CA, Model 900), with the incisor bar set at 2.5 mm below the interaural line. Ibotenic acid (5 μg in 0.5 μl delivered over 2.5 min) or an equal volume of vehicle (0.1 M phosphate-buffered saline, pH 7.4) were stereotaxically administered bilaterally through 26-ga stainless steel cannulae at the coordinates AP +3.5 mm and ML +0.7 mm to bregma and VD −3.5 mm from dura according to the atlas of Paxinos and Watson (40). The cannulae remained in place for 5 min after the end of the infusions.

Ten animals with ibotenic acid (IA) lesions were randomly selected after the final testing session, anesthetized with chloral hydrate (300 mg/kg, administered IP), and decapitated. After immersion in a 4% buffered formalin solution, brains were dehydrated in xylene and embedded in paraffin wax. Cresyl violet sections, 25 μm thick, were prepared. The outermost area of neuronal cell loss as determined by light microscopy was used to define the boundaries of the lesion.

Drugs and Behavioral Testing

Six weeks after surgery, sham- and ibotenic acid-lesioned animals were randomized into groups and their behavioral responses were assessed following a series of acute drug treatments.

Animals were individually housed and acclimated to observation cages for at least 1 h prior to injection of drugs in the first portion of the study. Apomorphine HBr (Sigma Chemical Co., St. Louis, MO), SK&F38393 (Research Biochemicals, Inc., Natick, MA), and quinpirole (Research Biochemicals) were dissolved in distilled water immediately before SC administration. Behaviors were observed in a series of 18 15-s intervals over the course of a 90-min period of observation that began 5 min following injection of drug or vehicle.

A behavioral checklist similar to that described by Fray et al. (14) was utilized, permitting independent quantification of movements of the head, mouth, trunk, and limbs. Total motor activity represented the frequency of intervals in which any motor behaviors were observed. Individual behaviors such as sniffing, locomotion, or grooming were scored as present or absent in an interval, and the associated behavioral scores were expressed as the percent of the total number of intervals in which that behavior was observed.

Intensity of oral stereotypies was scored using a modification of the Ernst scale (32). Ernst scores for each animal were expressed as percent of the maximum possible value. Frequency of stereotypic behavior per se was calculated as well and again expressed as the percentage of the total number of intervals in which these behaviors were observed. For these purposes, stereotypy was rated as present in an interval when the animal received a score of 3 or greater on the Ernst scale or when characteristic repetitive and invariant patterns of head and limb movements were present.

In the first testing session, all animals received injections of vehicle alone. One week later, animals were randomized into groups and received one of the following doses of apomorphine: 0.125, 0.375, or 1.25 mg/kg. Seven days later, animals were re-randomized to control for the potentially confounding effects of prior drug exposure. Groups of 10 animals each were treated with either the selective D_1 agonist SK&F38393 (32 mg/kg), the selective D_2 agonist quinpirole (3 mg/kg), or both drugs administered in combination at these same doses. In cases of combined administration of agonists, quinpirole was administered first and SK&F38393 5 min later. Animals that received only one selective agonist were given a second injection of vehicle.

Four weeks after the completion of these experiments, animals were again randomized with respect to prior drug exposure. Spontaneous motor activity in a novel open field (42 × 42 × 30 cm) was evaluated over 20 min immediately following pretreatment with SC quinpirole, 0.03 mg/kg, or vehicle. Activity was measured with an Omnitech RXYZCM(16) system (46), which quantified vertical and horizontal motor activity and total distance traveled. Spontaneous motor activity was independently assessed using a checklist similar to that described above. In this case, behaviors were scored in a series of 12 10-s intervals over the 20-min period of observation.

Behavioral scores derived by observation in either portion of the study were analyzed for statistical significance by nonparametric analysis of variance (ANOVA). For this purpose, the absolute number of intervals in which individual behaviors were observed was utilized. Scores for all animals were ranked for each experiment and tested using the Kruskal–Wallis statistic. Data collected by the photocell-based activity monitoring system were analyzed by parametric ANOVA. In both cases, mean differences were tested using posthoc multiple-range tests designed to control for type I error.

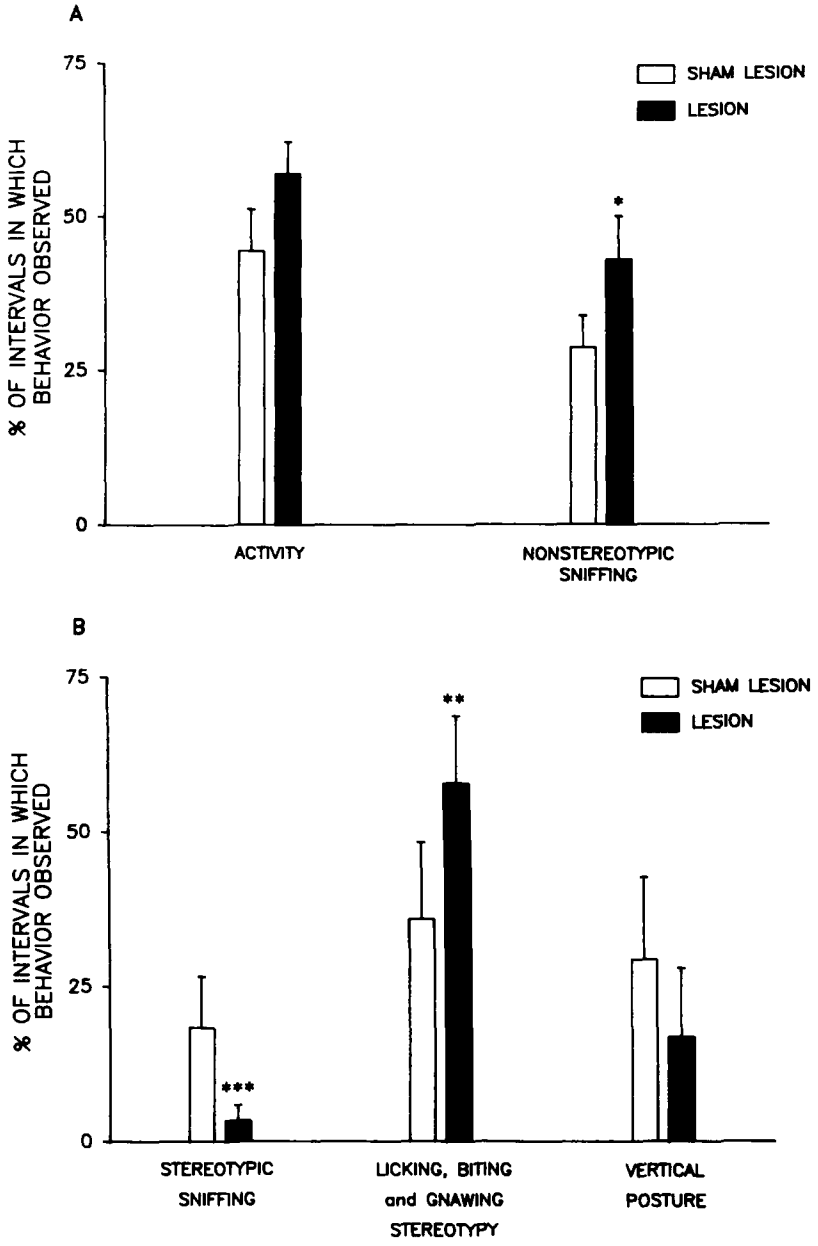

FIG. 1. Behaviors induced by apomorphine in sham- (n = 10) and ibotenic acid (n = 10)-lesioned animals. Behavior was monitored over a period of 90 min following SC injection of 0.125 mg/kg (a) and 1.25 mg/kg (b) apomorphine. Bars represent the mean frequencies of individual behaviors ± SEMs. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs. sham-lesioned animals.

RESULTS

Vehicle Injections

Following injection of vehicle, no significant differences were observed in the frequency or duration of any behaviors in IA- and sham-lesioned animals that had been acclimated to test cages.

Apomorphine

Nonstereotypic sniffing was increased in frequency in IA-lesioned animals treated with 0.125 mg/kg ($p < 0.05$, Fig. 1a).

While the frequency of other individual nonstereotypic behaviors was increased in lesioned animals treated with this dose of apomorphine, increases in the frequency of these be-

haviors or of total motor activity did not reach statistical significance. There was, however, an apparent increase in spontaneous motor activity following the initial postsynaptic drug effect in lesioned animals (Fig. 2a).

Stereotypic behaviors were observed more frequently in lesioned animals treated with 0.375 mg/kg apomorphine ($p < 0.01$) when scores were compared with sham-lesioned controls (Fig. 2b). The lesion did not appear to alter the duration of action of apomorphine.

Intense compulsive oral stereotypies were increased, both in frequency ($p < 0.01$, Fig. 1b) and intensity ($p < 0.01$, Fig. 3), in IA-lesioned animals that received 1.25 mg/kg apomorphine, while less intense stereotypic sniffing was reduced ($p < 0.001$, Fig. 1b).

Selective Agonists

The frequency of stereotypic behaviors was increased in IA-lesioned animals treated with the D_2 agonist quinpirole

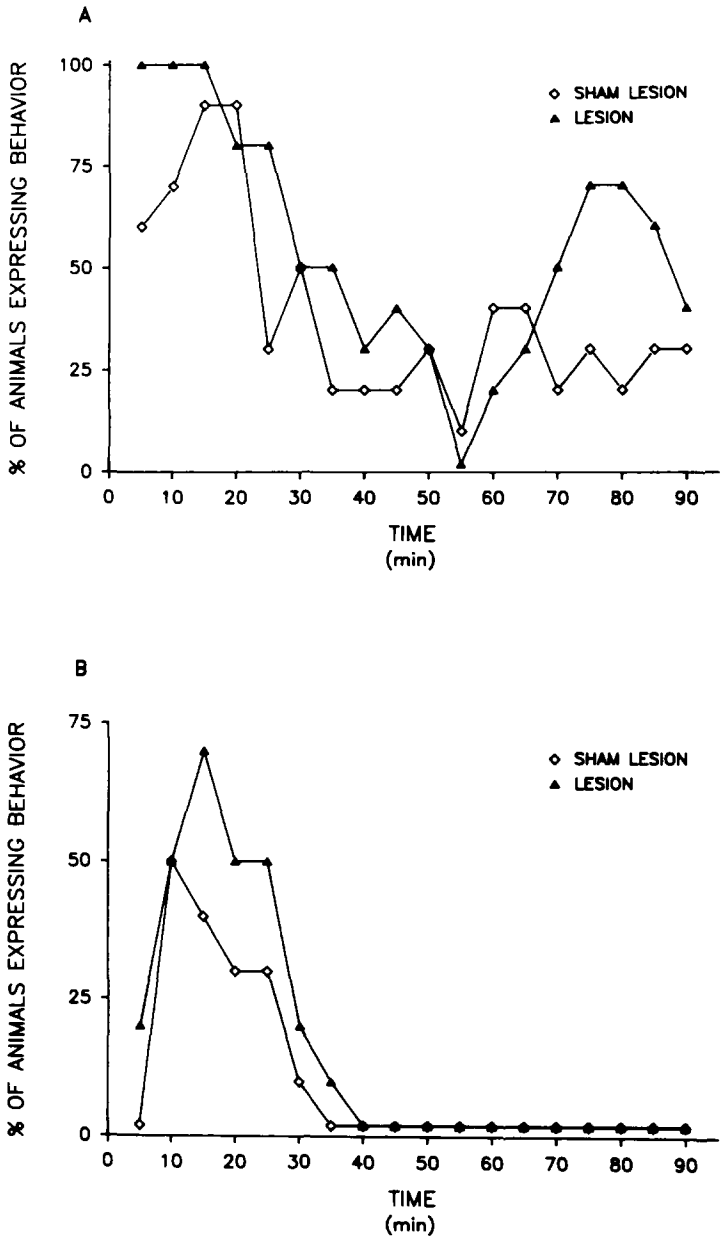

FIG. 2. Behaviors induced by lower doses of apomorphine in sham- and ibotenic acid-lesioned animals ($n = 10$, each case). (a). Proportion of animals expressing any motor activity in consecutive 15-s observation intervals following the SC injection of 0.125 mg/kg apomorphine. (b). Proportion of animals expressing compulsive oral (continuous licking, biting, and gnawing) stereotypy in each observation interval following SC injection of 0.375 mg/kg apomorphine.

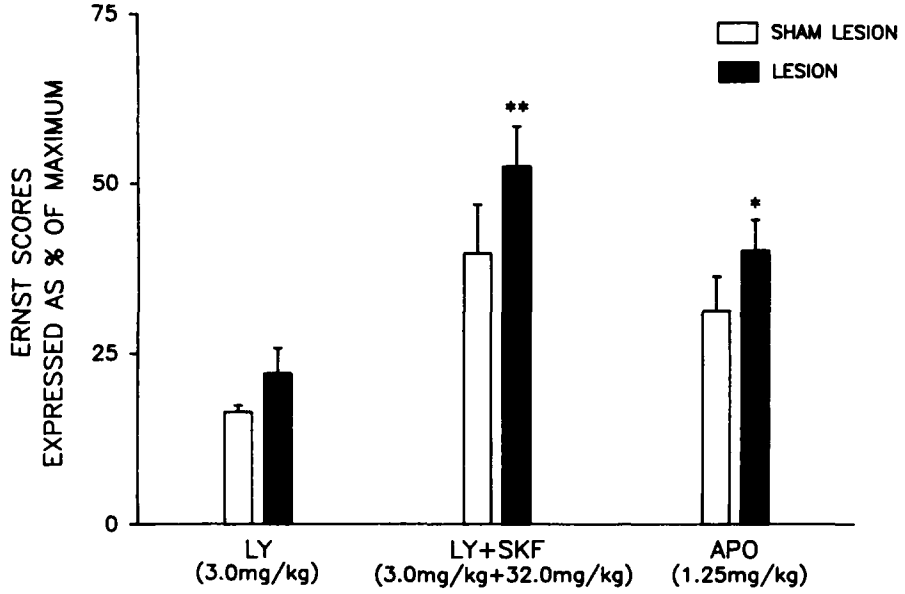

FIG. 3. Comparison of Ernst stereotypy scores following three drug treatments in sham and ibotenic acid-lesioned animals (n = 10, each case). Bars represent modified Ernst scores expressed as percent of the maximum possible score ± SEMs following administration of quinpirole (LY), quinpirole + SK&F38393 (LY+SKF), and high-dose apomorphine (APO). SK&F38393 administered alone elicited no stereotypies in either IA- or sham-lesioned animals and did not contribute to Ernst scores. *$p < 0.01$, **$p < 0.001$ vs. sham-lesioned animals.

alone, at a dose of 3 mg/kg ($p < 0.05$, Fig. 4a), while nonstereotypic behaviors such as sniffing and grooming were observed less frequently ($p < 0.001$ and $p < 0.01$, respectively).

IA-lesioned animals treated with SK&F38393 alone, at a dose of 32 mg/kg, expressed more intense grooming—a behavior characteristically produced by selective D_1 receptor stimulation—than did animals that had received sham lesions ($p < 0.05$, Fig. 4b).

The frequency of compulsive oral (licking, biting, and gnawing) stereotypies was increased in IA-lesioned animals treated with the combination of quinpirole and SK&F38393 at the above doses ($p < 0.001$, Fig. 4c), while the frequency of less intense stereotypic sniffing was reduced ($p < 0.001$). The frequency of complex stereotypies (repetitive head and limb patterns and self-mutilation) did not appear to be affected by the lesion, however (Fig. 4c).

Stereotypic Behavior Across Treatments

Ernst stereotypy scores were increased in IA-lesioned animals treated with the nonselective agonist apomorphine ($p < 0.01$, Fig. 3) and the selective D_2 agonist quinpirole administered in combination with the selective D_1 agonist SK&F38393 ($p < 0.001$, Fig. 3). Intensity of oral stereotypic behaviors was increased in animals treated with quinpirole alone, but did not reach statistical significance.

Open-field Behaviors

When exposed to a novel open field, IA-lesioned animals displayed significantly more spontaneous horizontal locomotor activity than sham-lesioned controls ($p < 0.05$, Fig. 5). Results were similar for indices of vertical activity, as well as for total distance traveled. Horizontal and vertical activity, however, were uncorrelated. Similarly, increased open-field locomotor activity was unaccompanied by or correlated with significant increases in rearing, nonstereotypic sniffing, or other elements of observed motor activity.

Pretreatment with 0.03 mg/kg quinpirole was equally effective in inhibiting spontaneous motor activity in IA- and sham-lesioned animals ($p < 0.05$, Fig. 5). The frequency of spontaneous motor activity was indistinguishable in the two groups that had received this dose of the D_2 agonist.

Histology

In agreement with previously reported histology (26), the lesion induced by IA infusion consisted of a small central region of occasional cavitation surrounded by a larger area of gliosis and neuronal absence. The lesion was confined to the region traditionally defined as the MPFC and in all 10 animals produced neuronal loss extending rostrally from the genu of the corpus callosum to a region just caudal to the frontal pole, mediolaterally from the midline to the forceps minor, and ventrodorsally from the shoulder of the infralimbic cortex and cingulate cortex area 1 to the lower border of cingulate cortex area 3 (40). In addition, there was a more variable degree of involvement of medial and ventral orbital cortices, frontal cortex area 2, and cingulate cortex area 2 (40). In no cases were the corpus striatum or nucleus accumbens directly involved. Although we used doses of IA that are reported to be axon sparing, the integrity of fibers of passage in the lesion area was not independently assessed. There was no correlation between the extent of the lesion and either spontaneous or drug-induced behavioral responses.

DISCUSSION

Postsynaptic Mechanisms

Behaviors typically elicited by the nonselective dopamine agonist apomorphine and selective D_1 and D_2 agonists quinpir-

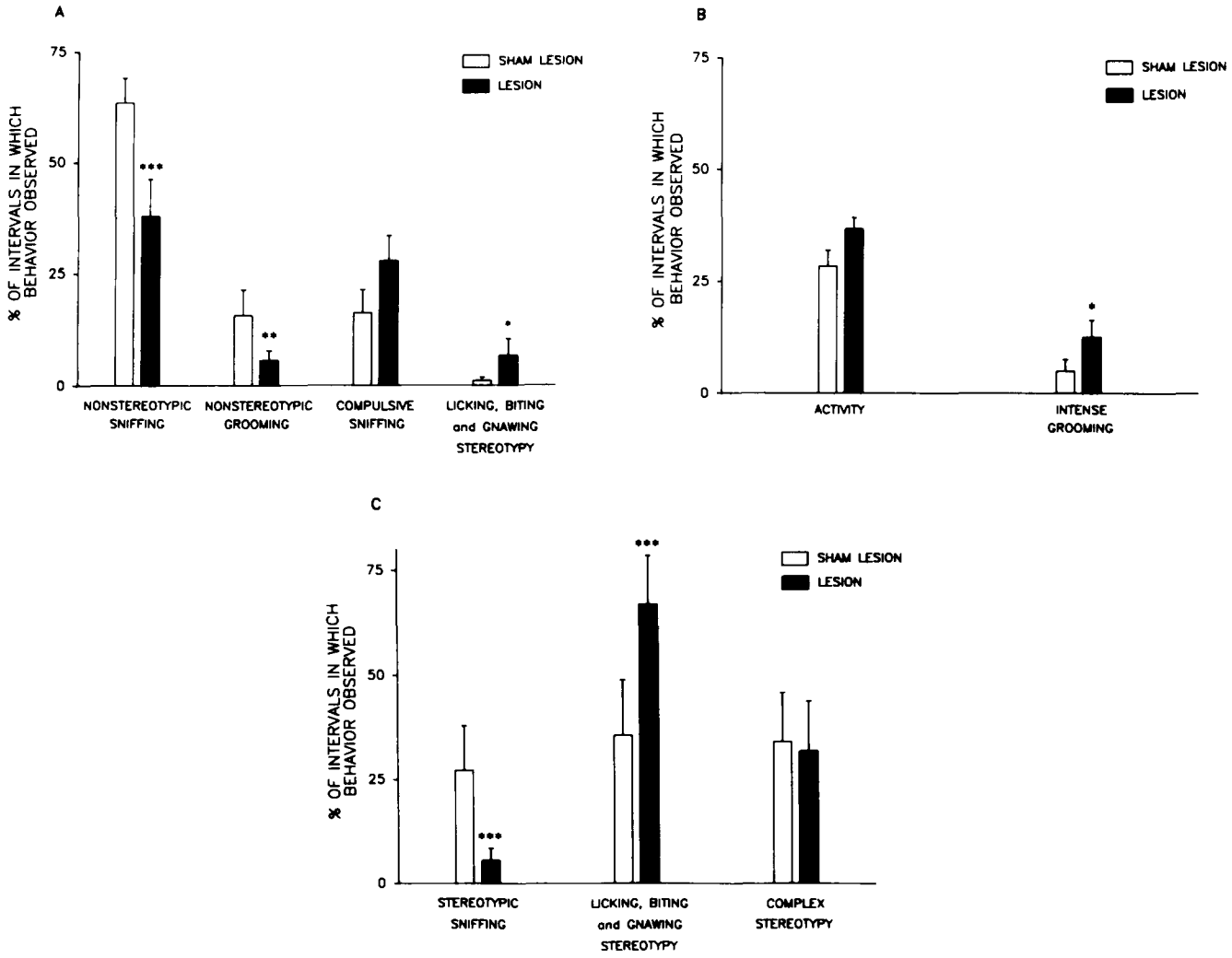

FIG. 4. Behaviors induced by selective dopamine agonists administered alone and in combination to sham- and ibotenic acid-lesioned animals (n = 10, each case). (a). Relative frequency of behaviors observed following SC administration of 3 mg/kg of the selective D_2 agonist quinpirole (LY171555); compulsive sniffing is synonymous with stereotypic sniffing as used in the text. (b). Frequency of total motor activity and of the characteristic intense grooming behavior elicited by 32 mg/kg of the selective D_1 agonist SK&F38393 administered SC; this agent elicited no stereotypic behaviors in either IA- or sham-lesioned animals. (c). Relative frequency of individual stereotypic behaviors observed following combined administration of these same doses of quinpirole and SK&F38393, administered SC and IP, respectively. Bars represent the mean frequencies of individual behaviors ± SEMs. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs. sham-lesioned animals.

ole and SK&F38393 were neither inhibited nor attenuated by ibotenic acid lesion of the medial prefrontal cortex, nor did these behaviors differ qualitatively from those observed in sham-lesioned animals. These results indicate that stimulation of either D_1 or D_2 receptors in the MPFC is not necessary for the generation of classical dopamine agonist-induced behaviors and that D_1 receptors within this region are not directly implicated in the D_1 receptor-dependent behavioral disorganization that follows coadministration of appropriate doses of selective agonists (5).

On the contrary, IA-lesioned rats exhibited enhanced behavioral responses to both selective agonists and apomorphine. These results suggest that while stimulation of dopamine receptors within the medial prefrontal cortex may not play a primary role in the generation of dopamine agonist-induced behaviors neurons within the MPFC may play a role in modulating dopamine receptor-associated mechanisms elsewhere in the brain.

It must be mentioned that because only single doses of both selective D_1 and D_2 receptor agonists were used our results should be interpreted cautiously. While these doses were selected for their ability to produce characteristic postsynaptic behavioral responses in unlesioned animals (5,6), other doses could have produced different results in IA-lesioned animals.

Enhanced behavioral responses to apomorphine (9,47) and amphetamine (1,17,18,23–25,35) have been reported after a variety of ablative frontocortical lesions. In most of these

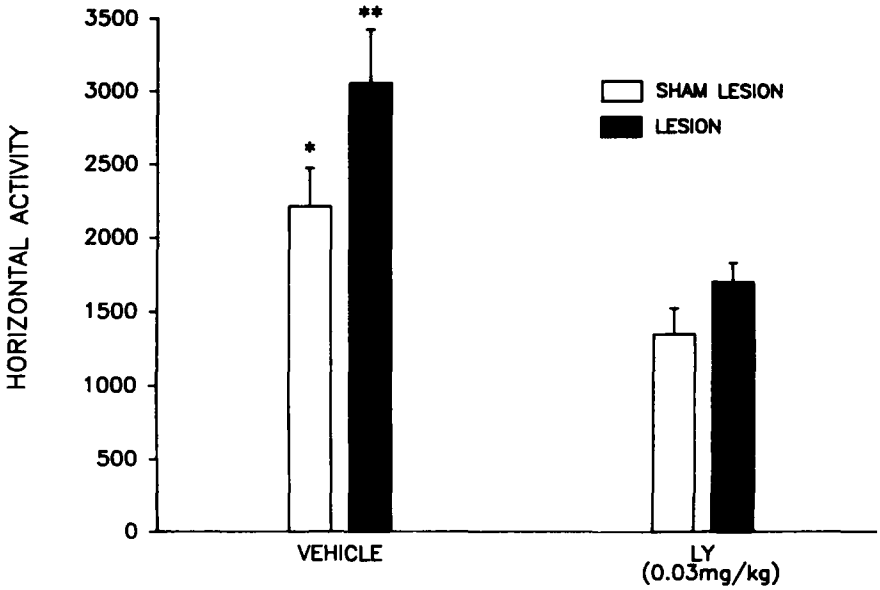

FIG. 5. Spontaneous locomotor activity observed in sham- and ibotenic acid-lesioned animals following exposure to a novel open field. Half the animals in each group (n = 15 in each case) were pretreated with 0.03 mg/kg quinpirole (LY) and the other half (n = 15, each case) received vehicle. Bars represent horizontal activity (mean ± SEMs), a correlate of distance traveled, recorded in photocell monitors over a 20-min period immediately following exposure to the novel field. *$p < 0.05$ vs. sham-lesioned animals pretreated with quinpirole, **$p < 0.05$ vs. all other groups.

cases, the lesion extended beyond the confines of the MPFC or predominantly affected other regions of the frontal cortex. Our data confirm these earlier studies and demonstrate specifically that intrinsic MPFC neurons modulate the expression of behaviors induced by dopamine agonists. The present results suggest that projections from the MPFC to subcortical or other cortical regions may normally play an inhibitory role that is interrupted when intrinsic neurons in this region are lesioned. The finding that behavioral responses to direct-acting dopamine agonists are augmented in IA-lesioned animals suggests that the modulatory effect of the MPFC must operate, at least in part, at a postsynaptic level.

Augmented responses to all postsynaptically active doses of apomorphine were observed in IA-lesioned animals. The lowest dose of apomorphine produced more nonstereotypic sniffing, while higher doses produced an increase in the frequency and intensity of stereotypic behavior. The striatum and nucleus accumbens have been implicated in the expression of stereotypy and nonstereotypic locomotor/exploratory activity, respectively, although some functional overlap appears to exist (10,31,49). Accordingly, our findings would suggest that MPFC efferents may modulate postsynaptic responsiveness in both regions of the basal ganglia.

In addition, behavioral responses to the selective agonists suggest that the modulatory effects of the MPFC may selectively involve D_1 receptor-associated mechanisms. IA-lesioned animals showed increases in the frequency of compulsive oral stereotypies and decreases in the frequency of less intense stereotypic behaviors following combined administration of the selective D_1 and D_2 receptor agonists SK&F38393 and quinpirole. Previous studies demonstrated that this behavioral pattern is specifically associated with an augmentation of postsynaptic D_1 receptor tone (2,6). Further, because licking, biting, and gnawing stereotypies were also significantly—albeit modestly—increased in IA-lesioned animals receiving the selective D_2 agonist alone, a lesion-induced increase in D_1 receptor-mediated activity appears likely: These behaviors are almost never observed in unlesioned animals treated with quinpirole alone (2,5,6) and generally appear only when the D_1 receptor is stimulated concurrently.

Several mechanisms could explain the apparent augmentation of D_1 receptor-mediated transmission in IA-lesioned animals. An increase in the release of endogenous DA may be involved. Alternatively, the lesion could produce an increase in the sensitivity of D_1 receptors or D_1 receptor-linked intraneuronal mechanisms. The latter possibility is supported by the fact that direct stimulation of the D_1 receptor by SK&F38393 administered alone resulted in augmentation of the intensive grooming response—a behavior specifically related to selective D_1 receptor stimulation (37)—in IA-lesioned animals.

IA lesion of the MPFC therefore produces an increased responsiveness to dopamine agonists that appears to be mediated, at least in part, by an increase in the sensitivity of postsynaptic, D_1 receptor-associated mechanisms. Previous work established neuroanatomic and biochemical processes that could subserve these effects.

The MPFC provides direct (48), presumably glutamatergic (36,52), innervation of intrinsic cells of the basal ganglia (3). A competitive relationship has been demonstrated in striatal cells between the local effects of D_1 receptor stimulation and glutamatergic stimulation (20). Accordingly, partial loss of

corticostriatal glutamatergic projections following an IA lesion of the MPFC might result in a functional disinhibition of postsynaptic D_1 receptor-mediated effects. Indeed, it is interesting to note that discrete electrolytic lesions of the MPFC enhance DA-stimulated adenylate cyclase activity within the basal ganglia (43), an effect mediated by the D_1 receptor.

Presynaptic Mechanisms

The present results suggest that the effects of the MPFC lesion on dopaminergic activity may be mediated presynaptically as well. While no differences between vehicle-treated IA- and sham-lesioned animals were observed when behaviors were monitored in cages to which animals had become acclimated, lesioned animals that received injections of vehicle showed significantly more locomotor activity than unlesioned animals when placed in a novel open field.

Increased open-field locomotor activity in these instances was not accompanied by or correlated with significant increases in rearing, nonstereotypic sniffing, or other elements of observed motor activity. Similarly, horizontal and vertical activity monitored automatically were uncorrelated. These findings suggest that the hyperreactive response to novelty seen in these animals does not represent the expression of organized exploratory activity. An apparent hyperreactivity of MPFC-lesioned animals to novel environments has been demonstrated previously (21,22,26).

In the present study, hyperactivity was abolished by pretreatment with 0.03 mg/kg quinpirole—a dose thought to act preferentially on presynaptic D_2 dopamine receptors, causing a reduction in the firing rate of mesencephalic DA neurons and in the synthesis and release of DA in terminal fields (8). This observation suggests, first, that novelty-induced hyperreactivity observed in MPFC-lesioned animals is mediated, at least in part, by increases in presynaptic DA release. Further, the fact that IA-lesioned animals appear to be more sensitive to the activity-decreasing effects of the low dose of quinpirole suggests that removal of the MPFC may modify the presynaptic, as well as the postsynaptic, effects of the D_2 agonist.

The MPFC is clearly in a position to regulate presynaptic dopaminergic activity within the forebrain. In addition to the striatal efferents outlined above, the MPFC projects directly to the substantia nigra and ventral tegmental area (48), the nuclei of origin of the forebrain DA systems (13). The MPFC may normally play a role in modulating the responsiveness of the mesencephalic DA systems to novelty or to other environmental stressors.

Both we and others found that experimentally induced dysfunction of the MPFC alters stress-induced neurochemical and behavioral indices of DA transmission within the basal ganglia (12,27,28,29). It has been postulated (28,29) that the MPFC contributes significantly to compensatory mechanisms that dampen environmentally driven changes in basal ganglia DA release. Accordingly, the "cost" of an MPFC lesion may include exposure to abnormally high levels of DA in the basal ganglia during stressful experiences.

Brief, repeated episodes of increased DA release during routine environmental stresses could also account for some of the apparent postsynaptic DA receptor-mediated changes observed in the present study. It is known, for example, that chronic treatment with DA agonists can induce behavioral sensitization to the effects of these drugs in rats, a phenomenon that has been used as a model for the psychotomimetic effects of chronic DA agonist exposure in humans [for review, see (45)]. While alterations in drug-induced release of DA are suspected (45), increases in the sensitivity of intraneuronal, postsynaptic mechanisms have also been implicated (19,44). Indeed, repeated administration of the direct D_1 agonist SK&F38393 (but not the D_2 agonist quinpirole) results in the development of behavioral supersensitivity (7,11) and an enhanced sensitivity of striatal neurons to DA agonists (51). Repeated stimulation of the D_1 receptor through stress-induced DA release in rats with MPFC lesions (e.g., in the course of routine handling and injections) might produce similar effects.

CONCLUSIONS

Results of the present study demonstrate that stimulation of either D_1 or D_2 receptors in the medial prefrontal cortex is not necessary for the generation of classical dopamine agonist-induced behaviors. Nor is activation of D_1 receptors within the MPFC responsible for the behavioral fragmentation that follows systemic administration of D_1 and D_2 dopamine agonists in the appropriate ratios.

On the contrary, behavioral responses to apomorphine, SK&F38393, and quinpirole indicate that the loss of intrinsic MPFC neurons results, instead, in increased sensitivity to the postsynaptic effects of dopamine agonists. Responses to the selective agonists suggest that such an effect may be due at least in part to increases in the sensitivity of postsynaptic D_1 receptor-associated mechanisms. Glutaminergic projections from the MPFC have an inhibitory influence upon D_1 receptor mediated processes at the level of striatal neurons. The MPFC lesion may, in removing this influence, result in augmentation of behavioral effects of D_1 receptor activation. While D_1 receptors within the MPFC may not be directly responsible for induction of dopaminergic behaviors, MPFC neurons may play a significant role by modulating D_1 receptor tone elsewhere in the brain.

Additionally, the hyperactivity observed in IA-lesioned animals exposed to a novel open field and the inhibition of this activity by presynaptic doses of quinpirole suggest that effects of the MPFC lesion might also be mediated presynaptically. Destruction of intrinsic MPFC neurons may result in enhancement of the phasic increases in dopamine release that accompany acute exposure to novelty or stress. This might itself lead to some of the postsynaptic effects observed in lesioned animals: Repeated stress-induced increases in DA release could result in gradual sensitization of postsynaptic DA receptor-associated mechanisms. If this were the case, the MPFC lesion might produce behavioral sensitization in the same fashion as chronic intermittent administration of dopamine agonists such as amphetamine, treatments that have themselves been used as models for psychosis.

Overall, our results are consistent with increasing evidence that the MPFC, itself the target of mesocortical dopamine projections, plays a critical role in modulating dopaminergic mechanisms in subcortical regions of the brain, particularly in the anteromedial striatum and nucleus accumbens septi. The modulatory role of the MPFC may be of significance in certain neuropsychiatric illnesses. For instance, prefrontal cortical dysfunction—especially under conditions of novelty or during the performance of specific cognitive tasks—is observed in patients with schizophrenia, an illness also characterized by dopaminergic dysregulation (50). The results of the present study—suggesting that MPFC dysfunction could result in functional disinhibition of both pre- and postsynaptic dopaminergic mechanisms—may provide a heuristically useful model for this disorder.

REFERENCES

1. Adler, M. W. Changes in sensitivity to amphetamine in rats with chronic brain lesions. J. Pharmacol. Exp. Ther 134:214–221; 1961.
2. Arnt, J.; Hyttel, J.; Perregard, J. Dopamine D-1 receptor agonists combined with the selective D-2 agonist quinpirole facilitate the expression of oral stereotyped behavior in rats. Eur. J. Pharmacol. 133:137–145; 1987.
3. Bouyer, J. J.; Park, D. H.; Joh, T. H.; Pickel, V. M. Chemical and structural analysis of the relation between cortical inputs and tyrosine hydroxylase containing terminals in rat neostriatum. Brain Res. 302:267–275; 1984.
4. Boyson, S. J.; McGonigle, P.; Molinoff, P. B. Quantitative autoradiographic localization of the D_1 and D_2 subtypes of dopamine receptors in rat brain. J. Neurosci. 6:3177–3188; 1986.
5. Braun, A. R.; Barone, P.; Chase, T. N. Interaction of D_1 and D_2 dopamine receptors in the expression of dopamine agonist related behaviors. In: Breese, G. R.; Creese, I., eds. Neurobiology of central D_1 dopamine receptors. New York: Plenum; 1986:151–166.
6. Braun, A. R.; Chase, T. N. Obligatory D_1/D_2 receptor interaction in the generation of dopamine agonist related behaviors. Eur J. Pharmacol. 131:301–306; 1986.
7. Braun, A. R.; Chase, T. N. Behavioral effects of chronic exposure to selective D_1 and D_2 dopamine receptor agonists. Eur J. Pharmacol. 147:441–451; 1988
8. Chiodo, L. A. Dopamine-containing neurons in the mammalian central nervous system: Electrophysiology and pharmacology. Neurosci. Biobehav. Rev. 12:49- 91; 1988.
9. Corwin, J. V.; Kanter, S.; Watson, R. T.; Heilman, K. M.; Valenstein, E.; Hashimoto, A. Apomorphine has a therapeutic effect on neglect produced by unilateral dorsomedial prefrontal cortex lesion in rats. Exp. Neurol. 94:683–689; 1986.
10. Costall, B.; Naylor, R. J. The behavioural effects of dopamine applied intracerebrally to areas of the mesolimbic system. Eur. J. Pharmacol. 32:87–92; 1975.
11. Criswell, H.; Mueller, R. A.; Breese, G. R. Priming of D_1 dopamine receptor responses: Long-lasting behavioral supersensitivity to a D_1 dopamine agonist following repeated administration to neonatal 6-OHDA lesioned rats. J. Neurosci. 9:125–133; 1989.
12. Deutch, A. Y.; Clark, W. A.; Roth, R. H. Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res. 521:311–315; 1978.
13. Fallon, J. H.; Moore, R. Y. Catecholamine innervation of the basal forebrain. J. Comp. Neurol. 180:545–580.
14. Fray, P. J.; Sahakian, T. W.; Robbins, T. W.; Koob, G. F.; Iversen, S. D. An observational method for quantifying the behavioral effects of dopamine agonists: Contrasting the effects of *d*-amphetamine and apomorphine. Psychopharmacology (Berl.) 69:253–259; 1980.
15. Fremeau, R. T.; Duncan, G. E.; Fornaretto, M.-G.; Dearry, A.; Gingrich, J. A.; Breese, G. R.; Caron, M. G. Localization of D_1 dopamine receptor mRNA in brain supports a role in cognitive, affective, and neuroendocrine aspects of dopaminergic neurotransmission. Proc. Natl. Acad. Sci. USA 88:3772–3776; 1991.
16. Gershanik, O.; Heikkila, R. E.; Duvoisin, R. C. Behavioral correlates of dopamine receptor activation. Neurology 33:1489–1492; 1983
17. Glick, S. D. Change in sensitivity to *d*-amphetamine in frontal rats as a function of time: Shifting of the dose–response curve. Psychonom. Sci. 19:57–58; 1970.
18. Glick, S. D. Changes in amphetamine sensitivity following frontal cortical damage in rats and mice. Eur. J. Pharmacol. 20:351–356; 1972.
19. Gropetti, A.; Flauto, C.; Parati, E.; Vescovi, A.; Rusconi, L; Parenti, M. Dopamine receptor changes in response to prolonged treatment with *l*-DOPA. J. Neural Trans. 22:33–45; 1986.
20. Halpain, S.; Girault, J.-A.; Greengard, P. Activation of NMDA receptors induces dephosphorylation of DARPP-32 in rat striatal slices. Nature 343:369–372; 1990.
21. Holson, R. R. Mesial prefrontal cortical lesions and timidity in rats. I. Reactivity to aversive stimuli. Physiol. Behav. 37:221–230; 1986.
22. Holson, R. R.; Walker, C. Mesial prefrontal cortical lesions and timidity in rats. II. Reactivity to novel stimuli. Physiol. Behav. 37:231–238; 1986.
23. Itoh, S.; Hsia, S.; Katsuura, G. Dopaminergic behavior in frontal decorticated rats. Physiol. Behav. 35:109–112; 1985.
24. Iversen, S. D. Enhanced amphetamine responses after frontal cortex lesions in the rat. Eur. J. Pharmacol. 13:387–390; 1971.
25. Iversen, S. D. The effect of surgical lesions to frontal cortex and substantia nigra on amphetamine responses in rats. Brain Res. 31:295–311; 1971.
26. Jaskiw, G. E.; Karoum, F.; Freed, W. J.; Phillips, I.; Kleinman, J.; Weinberger, D. R. Effect of ibotenic acid lesions of the medial prefrontal cortex on amphetamine-induced locomotion and regional brain catecholamine concentrations in the rat. Brain Res. 534:263–272; 1990.
27. Jaskiw, G. E.; Karoum, F ; Weinberger, D. R. Persistent elevations in dopamine and its metabolites in the nucleus accumbens after mild subchronic stress in rats with ibotenic acid lesions of the medial prefrontal cortex. Brain Res. 534:321–323; 1990.
28. Jaskiw, G. E.; Weinberger, D. R. Ibotenic acid lesions of the medial prefrontal cortex potentiate FG-7142 induced attenuation of exploratory activity in the rat. Pharmacol. Biochem. Behav. 36:695–697; 1990.
29. Jaskiw, G. E.; Weinberger, D. R. Ibotenic acid lesions of medial prefrontal cortex augment swim-stress induced locomotion. Pharmacol. Biochem. Behav. (in press).
30. Jaskiw, G. E.; Weinberger, D. R.; Crawley, J. N. Microinjection of apomorphine into the prefrontal cortex of the rat reduces dopamine metabolite concentrations in microdialysate from the caudate nucleus. Biol. Psychiatry 29:703–706; 1991.
31. Kelly, P. H.; Seviour, P. W.; Iversen, S. D. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res. 94: 507–522; 1975.
32. Klawans, H. L.; Goetz, C. G.; Carvey, P. M. Animal models of tardive dyskinesia. Clin. Neuropharmacol. 6:129–135; 1983.
33. Kolb, B. Functions of the frontal cortex of the rat: A comparative review. Brain Res. Rev. 8:65–98; 1984.
34. Louilot, A.; LeMoal, M.; Simon, H. Opposite influences of dopaminergic pathways to the prefrontal cortex or the septum on the dopaminergic transmission in the nucleus accumbens. An in vivo voltammetric study. Neuroscience 29:45–56; 1989.
35. Lynch, G. S. Separable forebrain systems controlling different manifestations of spontaneous activity. J. Comp. Physiol. Psychol. 70:48–59; 1970.
36. McGeer, P. L.; McGeer, E. G.; Schurer, U.; Singh, K. A glutaminergic corticostriatal path. Brain Res. 128:369–373; 1977.
37. Molloy, A. G.; Waddington, J. L. Dopaminergic behavior stereospecifically promoted by the D_1 agonist *R*-SK&F38393 and selectively blocked by the D_1 antagonist SCH23390. Psychopharmacology (Berl.) 82:409–410; 1984.
38. Molloy, A. G.; Waddington, J. L. Sniffing, rearing, and locomotor responses to the D_1 dopamine agonist *R*-SK&F38393 and to apomorphine: Differential interactions with the selective D_1 and D_2 antagonists SCH23390 and metoclopramide. Eur. J. Pharmacol. 108:305–308; 1985
39. Ognini, E.; Caporali, M. G.; Massottio, M. Stimulation of dopamine D_1 receptors by SK&F38393 induces EEG desynchronization and behavioral arousal. Life Sci. 37:2327–2333; 1985.
40. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. Orlando, FL: Academic Press; 1986.
41. Pycock, C. J.; Kerwin, R. W.; Carter, C. J. Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. Nature 286:74–77; 1980.
42. Reader, T. A.; Briere, R.; Gottberg, E.; Diop, L.; Grondin, L. Specific [^{3}H]SCH23390 binding to dopamine D_1 receptors in cerebral cortex and neostriatum: Evidence for heterogeneities in affinity states and cortical distribution. J. Neurochem. 50:451–463; 1988.
43. Reibaud, M.; Blanc, G.; Studler, J. M.; Glowinski, J.; Tassin,

J. P nondopaminergic prefronto-cortical efferents modulate D_1 receptors in the nucleus accumbens. Brain Res. 305:43–50; 1984.
44. Roberts-Lewis, J. M.; Welsh, M. J.; Gnegy, M. E. Chronic amphetamine treatment increases striatal calmodulin in rats. Brain Res. 384:383–386; 1986.
45. Robinson, T. E.; Becker, J. B. Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Res. Rev. 11:157–198; 1986.
46. Sanberg, P. R.; Hagenmeyer, S. H.; Henault, M. Automated measurement of multivariant locomotor behavior in rodents. Neurobehav. Toxicol. Teratol. 17:87–94; 1985.
47. Scatton, P ; Worms, P.; Lloyd, K. G.; Bartholini, G. Cortical modulation of striatal function. Brain Res. 232:331–343; 1982.
48. Sesack, S.; Deutch, A. Y.; Roth, R. H.; Bunney, B. S. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study with *Phaseolus vulgaris* leucoagglutinin. J. Comp. Neurol. 290: 213–242; 1989.
49. Sharp, T.; Zetterstrom, T.; Ljunberg, T.; Ungerstedt, U. A direct comparison of amphetamine-induced behaviours and regional brain dopamine release in the rat using intracerebral dialysis Brain Res. 401:322–330; 1987.
50. Weinberger, D. R. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44:660–669; 1987.
51. White, F. J.; Brooderson, R. J.; Hu, X.-T. Repeated stimulation of D_1 dopamine receptors enhances the effects of dopamine receptor agonists. Eur J. Pharmacol. 191:497–499; 1990.
52. Young, A. M. J.; Bradford, H. F. Excitatory amino acid neurotransmitters in the corticostriate pathway: Studies using intracerebral microdialysis in vivo. J. Neurochem. 47:1399–1404; 1986.