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Comparison of Behavioral Effects of Systemic L-DOPA and Intracranial Dopamine in Mesolimbic Forebrain of Nonhuman Primates

RUSSELL E. DILL, DANIEL L. JONES, J. CHRISTIAN GILLIN AND GREER MURPHY

Department of Anatomy, Baylor College of Dentistry, Dallas, TX 75246 and National Institute of Mental Health, Bethesda, MD

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DILL, R. E., D. L. JONES, J. C. GILLIN AND G. MURPHY. *Comparison of behavioral effects of systemic L-DOPA and intracranial dopamine in mesolimbic forebrain of nonhuman primates.* PHARMAC. BIOCHEM. BEHAV. **10**(5) 711–716, 1979.—The systemic administration of L-DOPA and carbidopa to six rhesus and four squirrel monkeys produced an initial period of depressed activity followed by increased locomotion, hypervigilance, involuntary oral-facial movements and a gnawing syndrome. The squirrel monkey exhibited a depressed phase, locomotor stimulation, searching behavior, stereotypic grooming and gnawing syndrome. Most of these activities were prevented by pretreatment with 0.1 mg/kg haloperidol. Bilateral injection of 100 μg dopamine into the mesolimbic forebrain of four squirrel monkeys also produced an initial depression followed by hyperactivity similar to that produced by L-DOPA, but without gnawing. A stereotyped submissive or juvenile posturing occurred in three animals. These DA-induced activities were blocked by 0.1 mg/kg haloperidol. Similar injection of 100 μg L-norepinephrine produced a profound depression followed by moderate activity coupled with loss of extensor muscle strength in the legs. Bilateral injection of 300 μg dopamine into the nucleus accumbens of a rhesus monkey produced stereotypic pacing. These data confirm in primates the importance of dopaminergic mechanisms of the mesolimbic forebrain in locomotor activity and behavior.

Primates L-DOPA Mesolimbic area Intracranial injections Dopamine Norepinephrine Locomotor stimulation Depression Submissive posturing Compulsive gnawing

LARGE doses of L-DOPA (L-3, 4-dihydroxyphenylalanine) produce locomotor stimulation of monkeys [24, 27, 28], rats [5,6], mice [3], and dogs [32] and increase the mobility of parkinsonian patients [4,11]. This drug may also induce involuntary oral-facial and limb movements in primates, including man [18, 22, 23, 27, 28, 33]. Mice [21] and monkeys [23,28] may develop a compulsive gnawing syndrome following L-DOPA administration.

One current theory associates L-DOPA-induced dyskinetic movements and behavioral changes with excessive stimulation of dopaminergic receptors in the striatum. The excessive stimulation is thought to be the result of conversion of large amounts of L-DOPA to dopamine (DA) in the striatum and in the case of parkinsonian, increased sensitivity of the dopamine receptor [1, 20, 30, 31].

The principal focus of research on L-DOPA-induced dyskinesia has been on the effects of DA in the striatum. However, it is now clear that DA has locomotor-stimulating properties when administered directly to the mesolimbic nucleus accumbens of rats [9, 19, 25, 26]. Further, intraaccumbens injection of DA has been shown to reverse the akinesia induced by reserpine in rats [2]. The markedly reduced levels of DA in the nucleus accumbens of parkinsonian patients [16] may be in part responsible for the akinesia of this disease. The effects of direct application of DA to the mesolimbic area (MA) of a primate has not been reported.

We hypothesize that the locomotor stimulating and possibly other effects of systemically administered L-DOPA in primates is due to increased dopaminergic activity in the MA, and more specifically the nucleus accumbens. Thus, a preliminary study was carried out to compare the gross motor and behavioral effects of systemically administered L-DOPA and the direct application of DA to the MA in two species of primates, *Macaca mulatta* (rhesus) and *Saimiri sciureus* (squirrel monkeys). Additionally, primates were chosen to evaluate these effects because of their closer phylogenetic relationship to man and more diversified motor behavior repertoire.

METHOD

Six rhesus monkeys (five male and one female) were given 100 mg/kg of L-DOPA plus 20 mg/kg carbidopa (*alpha*-methyldopa hydrazine) and 5 mg/kg ascorbic acid IP in 0.1 N HCl (pH adjusted to about 6.0 with NaOH), placed in their home cage and all activity recorded by one to three observers. Behavioral activities were ranked according to

procedures given in the RESULTS section. Latency was the time elapsed from injection to the first appearance of dyskinesia or active behavioral change, whereas duration was the time elapsed between onset of these activities and recovery. Recovery is defined as that point where activity diminished to control levels.

Four squirrel monkeys (two male and two female) were given 50 mg/kg L-DOPA plus 20 mg/kg carbidopa and 4 mg/kg ascorbic acid IP, placed in a clear plastic observation cage 30×28×60 cm with a horizontal rod centered 22 cm from the floor, and all activity recorded by one or two observers. All animals were placed in the observation cage 30 min prior to drug injections and activity was recorded prior to and following drug treatment as described previously. Cinematographic (16 mm) records were made of representative activities of both species.

L-DOPA injections were repeated several days later but the monkeys were given 0.1 to 0.5 mg/kg haloperidol IP 30 min prior to L-DOPA. Activity was recorded as before.

Subsequently, the four squirrel monkeys were permanently cannulated bilaterally in the head of the caudate nucleus and dorsal tuberculum olfactorium near its border with the nucleus accumbens septi at stereotoxic coordinates A + 12.5, L 2.5, V 8.5 mm and A+ 15.0, L 2.75, V 1.2 mm respectively according to procedures described elsewhere [13]. Similar procedures were used to cannulate the nucleus accumbens septi in the female rhesus monkey. The stereotoxic coordinates were AP + 18.5, L 3.0 and V 4.5 mm [29].

Following a recovery period of at least one week, the squirrel monkeys were injected intracranially (IC) in the MA bilaterally with 100 μg dopamine hydrochloride (DA) 16–18 hr after pretreatment with the monoamine oxidase (MAO) inhibitor, tranylcypromine, 1 mg/kg SC. An MAO inhibitor was used to prolong the effects of DA, a procedure used by many workers studying the effects of DA on the MA of rats [10, 19, 26]. One week later the IC DA injections were repeated as before, but 0.0075 to 0.1 mg/kg haloperidol was given IP 30 min earlier. Other IC injections included L-norepinephrine hydrochloride (NE) and 3-methoxytyramine hydrochloride (3-MT). The latter two amines were injected into the MA to test for the possibility that a metabolic product of DA could be responsible for the initial period of depressed activity produced by DA and L-DOPA. The head of the caudate nucleus in the squirrel monkey was injected with similar amounts of DA as a site control. The nucleus accumbens of the rhesus monkey was injected with 100 and 300 μg DA bilaterally.

All drugs for IC injection were made up fresh daily in sterile physiologic saline in concentrations such that the injection volume did not exceed 4 μl. Equal volumes of saline were injected into all sites following drug pretreatment for control purposes.

Upon completion of the study, each animal was anesthetized with 35–40 mg/kg sodium pentobarbital and perfused intravascularly with ammonium bromide-Formalin fixative. The brain was removed and prepared for histologic verification of cannula placement.

RESULTS

The behavioral effects of systemically administered L-DOPA and carbidopa in rhesus monkeys appeared in the following general pattern: (1) An initial period of slightly depressed activity of rapid onset (less than 5 min) continuing until the onset of active behavioral changes; (2) atypical oral-facial movements; (3) hypervigilance characterized by rapid and frequent changes in visual fields, locomotor stimulation and hyperexcitability; and (4) compulsive gnawing (Fig. 1). The gnawing was usually centered on one or two localized areas of the cage and on one occasion resulted in the loss of two incisors. The animal seemed oblivious to the trauma. It was sometimes possible to induce an animal to gnaw on a surgical towel. Occasionally, myoclonic twitches or jerking movements of the shoulder and limbs were seen in some animals. One animal displayed paradoxical taming, i.e., Y 345, a normally aggressive male allowed the investigator to rub his finger along the animal's nose.

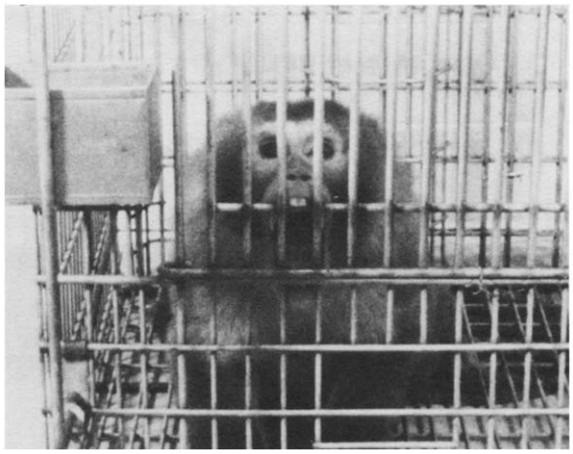

FIG. 1. Rhesus Monkey D2 three hr following 100 mg/kg L-DOPA plus 20 mg/kg carbodopa IP. Illustrated is the typical gnawing syndrome produced in these animals by L-DOPA. All figures are taken from 16 mm color movie film.

Behavioral changes were ranked by assigning values of 1 to 4 to the behavioral signs listed above, in that same order since, in general, there was an ordinal or hierarchical appearance of the signs. The rank of a drug response was the sum of these values. These data are summarized in Table 1. Pretreatment with 0.1 mg/kg haloperidol IP significantly reduced the effects of L-DOPA (Table 1). Higher dose levels of haloperidol (0.5 mg/kg) produced sufficient sedation as to preclude interpretation of the blocking effects.

Squirrel monkeys reacted to systemically administered L-DOPA in a manner similar to the rhesus monkeys. The principal behavioral activities and their general order of occurrence were: (1) depression of locomotor activity with some vomiting; (2) increased locomotor activity; (3) searching activity; (4) face rubbing and stereotyped grooming; and (5) compulsive gnawing. As with rhesus monkeys, gnawing was not ordinarily seen without the appearance of the preceding behavior. Thus, these behavioral activities were ranked 1 to 5 as listed above. A summary of these data are presented in Table 1 along with the effects of prior treatment with haloperidol, which completely blocked the effects of L-DOPA.

One squirrel monkey, given 100 μg DA bilaterally in the MA, exhibited depressed activity for 30 min followed by a return to normal activity. A second monkey similarly treated

TABLE 1

BEHAVIORAL EFFECTS OF SYSTEMIC L-DOPA AND INTRACRANIAL DA

Drug Treatment	Type Monkey	Response Ratio	Behavioral Rank Mean ± SE	Latency in Minutes Mean ± SE	Duration in Hours Mean ± SE
100 mg/kg L-Dopa + 20 mg/kg Carbidopa IP	Rhesus	6/6	8.66 ± 0.73	24.5 ± 2.09	3.50 ± 0.44
Same as above + 0.1 mg/kg Haloperidol IP 30 minutes prior	Rhesus	2/4	3.00 ± 1.22†	77.5	3.0
50 mg/kg L-DOPA + 20 mg/kg Carbidopa IP	Squirrel	4/4	11.50 ± 1.66	22.75 ± 2.66	3.99 ± 0.34
Same as above + 0.1 mg/kg Haloperidol IP 30 minutes prior	Squirrel	0/4	1.00 ± 0	—	—
100 μg DA i.m.a.*	Squirrel	4/4	10.50 ± 1.66	78.75 ± 4.27‡	4.31 ± 0.12
Same as above + 0.1 mg/kg Haloperidol IP	Squirrel	4/4	4.00 ± 1.00	195.00 ± 35.23§	1.37 ± 0.32¶
100 μg NE i.m.a.	Squirrel	4/4	5.50 ± 0.96	107.00 ± 15.07	7–24
Saline, 6 μl i.m.a.	Squirrel	0/4	0	—	—
0.1 mg/kg Haloperidol IP	Squirrel	1/4	0.25	—	—

*i.m.a.=Intracranial injection in the mesolimbic area.
†Differs from animals not treated with Haloperidol, $p<0.05$ by Mann-Whitney U-test, one-tailed.
‡Differs from same animals treated with L-DOPA, $p<0.001$, t-test.
§Differs from same animals treated with i.m.a. DA only, $p<0.02$, t-test.
¶Differs from same animals treated with i.m.a. DA only, $p<0.01$, t-test.

exhibited all the behavioral effects described below for 55 min at which time the animal abruptly went to sleep. Subsequently the animals were pretreated with an MAO inhibitor.

The four squirrel monkeys were injected bilaterally in the mesolimbic area with 100 μg DA per side 18 hr after 1 mg/kg tranylcypromine SC. The animals displayed many of the same behavioral activities produced by systemic L-DOPA; however, there were certain distinctly different activities. As with L-DOPA there was an initial period of depressed activity. During this period the animals spent much of their time in the sleep position and when they were awake they showed obvious ptosis, yet they were responsive to stimuli. The depression phase lasted significantly longer than that produced by L-DOPA, Table 1.

The second phase consisted of a period of locomotor stimulation involving almost constant motion. Behavioral activities consisted of intense searching activity, especially the uppermost parts of the observation cage. This activity was periodically interrupted with periods of intense grooming, usually a stereotyped grooming of a particular area such as one area of the tail. The hands were often rubbed together vigorously. Occasionally the face was rubbed on the cage wall. Three of the monkeys developed a stereotyped submissive or juvenile posturing. This occurred in brief bursts of dipping the head from an upright position to one between the legs (Fig. 2). As many as ten dips would be performed in rapid succession. Occasionally, exaggerated startle responses were seen, i.e., sudden jumping and vocalization followed by frenetic searching activity.

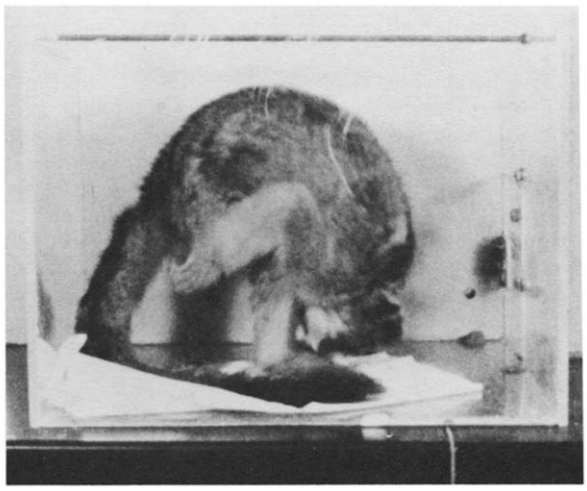

FIG. 2. Squirrel Monkey 7660, 85 min following the bilateral injection of 100 μg dopamine into the mesolimbic forebrain illustrating stereotypic submissive posturing.

These activities were ranked as follows: a rank of 1 for the depressed phase; a rank of 2 for locomotor stimulation or hyperactivity; a rank of 3 for searching behavior; a rank of 3 also for stereotyped grooming and/or face rubbing; a rank of 4 for submissive posturing. The ranks were summed for each animal and the mean is presented in Table 1.

The procedure was repeated following the IP injection of haloperidol. Low levels of haloperidol (0.0075 mg/kg) given to two monkeys or 0.075 mg/kg to one monkey 30 min prior to IC DA had no effect, but 10 to 20 min after the administration of additional haloperidol sufficient to bring the total dose to 0.1 mg/kg, all effects of DA were blocked. DA effects were inhibited in one animal with 0.075 mg/kg haloperidol IP. Pretreatment with haloperidol at 0.1 mg/kg blocked most behavioral effects of DA except the depressed phase and hyperactivity which appeared after a long latency (Table 1).

Some or all of the effects of the exogenous mesolimbic DA could be due to a metabolite of DA, especially since the animals were pretreated with an MAO inhibitor which would increase the 3-methoxytyramine metabolite. Also, some of the effects could be due to increased synthesis of norepinephrine (NE) from DA. Therefore, these two substances were injected into the mesolimbic forebrain of the four squirrel monkeys to determine their effects. NE (100 μg each side) produced a prolonged period of inactivity and sleep. This was followed by brief periods of increased activity usually in the form of moving backwards around the cage while in a sitting position, i.e., a form of retropulsion. These animals could not sit on the bar perch. Apparently all of these phenomena were due to a loss of strength in the extensor muscles of the lower limbs. Manual testing of muscle strength in the lower limbs showed good flexor strength, but marked weakness of the extensors. Stereotyped grooming was seen in the later stages of the response.

The behavioral response to NE was ranked as follows: a rank of 1 was assigned to the depressed phase; a rank of 2 for locomotor stimulation and/or retropulsion; a rank of 2 for demonstrable loss of extensor strength in the legs; and a rank of 3 for stereotyped grooming. The mean of the summed ranks is presented in Table 1.

The intracranial injection of 105 μg of 3-MT into the MA of two squirrel monkeys produced myoclonic twitching and other involuntary movements. A higher dose in one animal (120 μg) lead to increased intensity of the dyskinesias and ultimately to convulsions. A lower dose in one animal (90 μg) produced increased excitability, vocalizations and some retropulsion, but no myoclonic twitching. The mean latency from time of injection to the first appearance of active dyskinesias was 14.0 min $\pm$ s.e.m. of 2.27. No attempt was made to rank these dyskinesias as they were completely different in character from the normal but exaggerated behavior produced by L-DOPA or IC DA.

The injection of similar amounts of DA into the head of the caudate nucleus in four squirrel monkeys pretreated with 1 mg/kg tranylcypromine produced no observed behavioral effect. The injection of saline into all sites also produced no effect. Since a rank value of 1 was assigned to the depression phase of L-DOPA, DA and NE effects, it was necessary to control for the sedation produced by haloperidol. The IP injection of 0.1 mg/kg of haloperidol in squirrel monkeys pretreated with tranylcypromine produced sedation (rank of 1) in one of four animals (Table 1).

Dopamine, 100 μg, was injected into each nucleus accumbens (NA) of an adult rhesus monkey pretreated 18 hr earlier with 1 mg/kg tranylcypromine SC, without any obvious effect on behavior. One week later, an increase in DA to 300 μg in each NA produced a marked stereotyped pacing. The pacing started 30 min after the injection of DA and occurred 75% of the time during the next one-hr period. Three hours postinjection, this monkey began to bite one area on her leg. This continued intermittently between periods of pacing. This stereotyped biting (three to six rapid bites) stopped suddenly at four hr postinjection. The effects of DA lasted 5 hr, 15 min. An initial period of depression of activity was not observed. Intraaccumbens saline produced no behavioral change in this animal.

Histologic examination of the cannula sites in the squirrel monkeys revealed that the cannulae targeted for the head of the caudate were all in the proper position and those targeted for the mesolimbic area were in all cases located in the most dorsal portion of the olfactory tubercle near its junction with the nucleus accumbens (Fig. 3). Microscopic examination of the injection site revealed only slight tissue damage associated with the repeated injection with the volumes used in this study (Fig. 3). The two cannulae targeted for the nucleus accumbens in the rhesus monkey were in the correct position.

DISCUSSION

The results of the present study have confirmed earlier studies on the locomotor and behavioral effects of systemic L-DOPA in rhesus monkeys [23,28]. These included hyperactivity, hypervigilance and compulsive gnawing. However, the initial period of reduced activity was not previously pointed out. Paradoxical taming was also noted in one animal. This has been reported to occur in two rhesus monkeys treated with methamphetamine following conditioning for several months with methadone [15]. Corson, *et al.*, [8] have demonstrated paradoxical taming in dogs following treatment with amphetamine. The mechanism of this phenomenon is obscure but these findings point toward involvement of dopaminergic pathways.

Earlier observations made on the effects of L-DOPA in squirrel monkeys [24] were also confirmed in part. Our animals developed hypervigilance, hyperactivity, and stereotyped grooming, but did not show obstinate progression as reported by Ng, *et al.*, [24]. Also, our animals displayed considerable searching activities and a compulsive gnawing syndrome similar to that seen in rhesus monkeys. No other involuntary oral-facial movements were noted. The initial period of depressed activity also was not previously reported.

The hypothesis that these effects of systemic L-DOPA are due, in part, to increased dopaminergic activity in the mesolimbic area is compatible with, but not proven by, the results obtained from direct application of DA to the mesolimbic forebrain of the four squirrel monkeys and one rhesus. This hypothesis is further supported by the observation that both the effects of systemically administered L-DOPA in both species and intracranial DA in squirrel monkeys were inhibited by 0.1 mg/kg haloperidol IP.

The initial period of depressed activity produced by direct application of DA to the MA was of longer duration than that produced by systemically administered L-DOPA, suggesting that it was not the result of peripheral effects of L-DOPA or DA. The amount injected IC would hardly seem sufficient to produce the same effects if transported into the general circulation. The depressed phase also did not appear to be due to the DA metabolite 3-methoxytyramine, but was as-

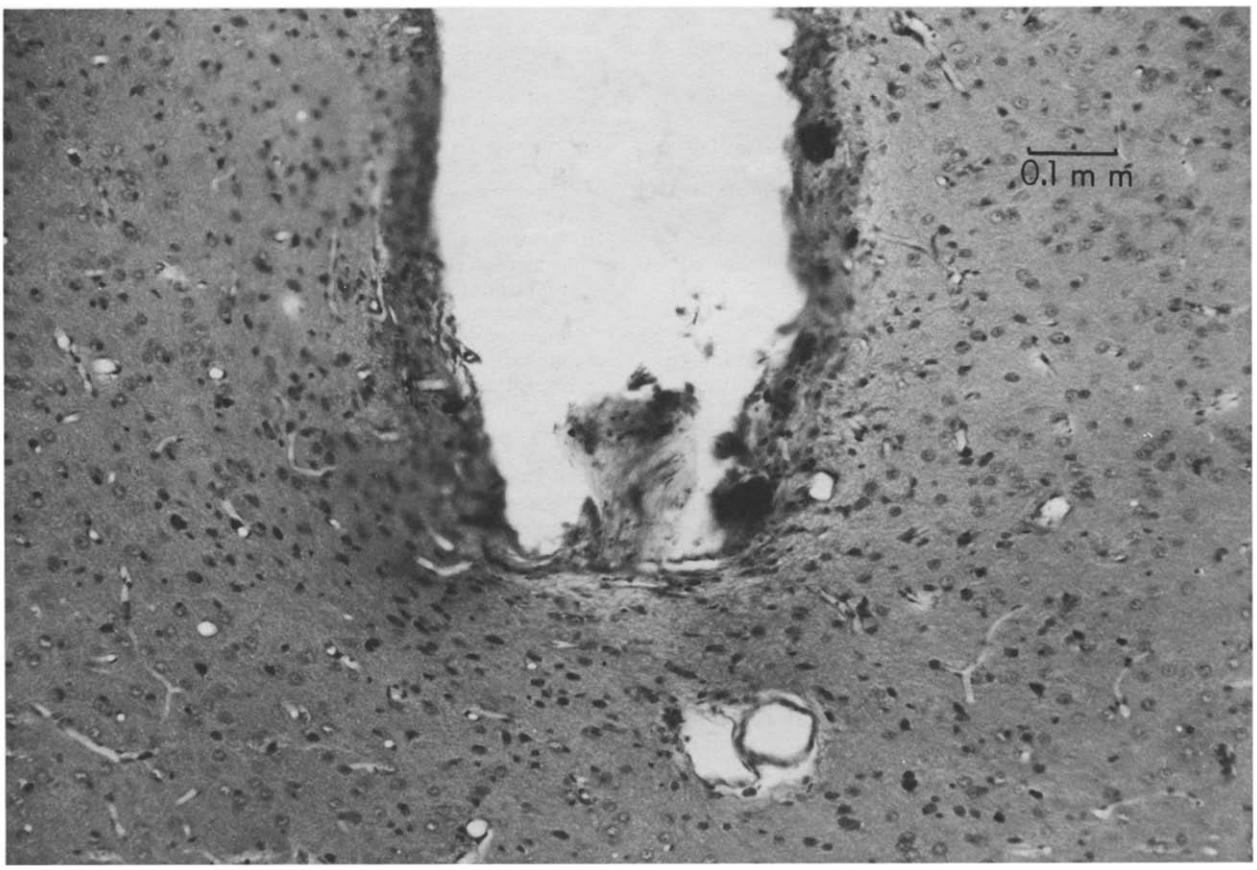

FIG. 3. Photomicrograph of the cannula terminal in the right tuberculum olfactorium, stratum polymorphicum, of Squirrel Monkey 7684. Several pyknotic nuclei, suggesting neuronal death, are seen in an area extending out about 0.2 mm from the injection site and an occasional such nucleus out to 0.4 mm. Otherwise, the tissue appears to be healthy. This animal received seven injections in this site.

sociated with NE. Feldberg [17] has shown that intraventricular administration of adrenalin and noradrenalin produced sedation in cats. Other investigators have demonstrated a similar biphasic response to the DA agonists bromocryptine [14] and apomorphine [12] in mice. The data of Dolphin, *et al.*, [14] strongly suggest an involvement of alpha-adrenergic receptors in the depressed phase. Di Chiara, *et al.*, [12] suggest that the depressed phase is due to activation of DA autoreceptors which are inhibited by some neuroleptics such as haloperidol and pimozide. However, in the present study there was no apparent reversal of the depressed phase by 0.1 mg/kg haloperidol. This could have been due to lack of sensitivity in our method of evaluating depression of motor activity.

Locomotor stimulation has been the consistent finding of those who have applied DA to the nucleus accumbens of rats [9, 19, 25, 26]. Locomotor stimulation was seen in this study to result from the application of DA to the nucleus accumbens in a rhesus monkey and its junction with the olfactory tubercle in four squirrel monkeys. The inhibition of this response by haloperidol further strengthens the specificity of the dopaminergic response. NE produced little locomotor stimulation.

Studies on dopaminergic mechanisms of stereotypy and locomotor activity in rats indicate that dopaminergic stimulation of the nucleus accumbens is more closely associated with increased locomotor activity while stereotypy is more closely associated with dopaminergic stimulation of the striatum [7,10]. Under some conditions dopaminergic agonists produce stereotypy when applied directly to the nucleus accumbens [10]. The present study clearly demonstrated that behavioral changes were more readily elicited in squirrel monkeys by dopaminergic stimulation of the mesolimbic forebrain than by similar stimulation of the head of the caudate nucleus. Particularly striking was the appearance of stereotyped submissive or juvenile posturing following DA injection in the MA. It should be noted that there was a conspicuous absence of gnawing and oral-facial dyskinesias following injection of DA into the MA. Future studies of the role of dopaminergic and noradrenergic systems of the mesolimbic area in primate behavior may provide useful models for human psychotic behavior and therapeutic drug evaluation.

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REFERENCES

1. Andén, N.-E. Pharmacological and anatomical implications of induced abnormal movements with L-DOPA. In: *L-DOPA and Parkinsonism*, edited by A. Barbeau and F. H. McDowell. Philadelphia: F. A. Davis Co., 1970, pp. 132–143.
2. Andén, N.-E. and B. Johnels. Effect of local application of apomorphine to the corpus striatum and to the nucleus accumbens on the reserpine-induced rigidity in rats. *Brain Res.* **133:** 386–389, 1977.
3. Andén, N.-E., U. Strombom and T. H. Svensson. Locomotor stimulation by L-DOPA: Relative importance of noradrenaline receptor activation. *Psychopharmacology* **54:** 243–248, 1977.
4. Barbeau, A. The pathogenesis of Parkinson's disease: a new hypothesis. *Can. Med. Ass. J.* **87:** 802–807, 1962.
5. Bartholini, G., J. E. Blum and A. Pletscher. Dopa-induced locomotor stimulation after inhibition of extracerebral decarboxylase. *J. Pharm. Pharmac.* **21:** 297–301, 1969.
6. Butcher, L. L. and J. Engel. Behavioral and biochemical effects of L-DOPA after peripheral decarboxylase inhibition. *Brain Res.* **15:** 233–242, 1969.
7. Butcher, L. and J. Gan. Effects on precise motor responding of bilateral intrastriatal application of dopamine. *Behav. Biol.* **12:** 535–539, 1974.
8. Corson, S. A., E. O. Corson, V. Kirilcuk, I. Kirilcuk, W. Knopp and L. E. Arnold. Differential effects of amphetamines on clinically relevant dog models of hyperkinesis and stereotypy. In: *Advances in Neurology*, Vol. 1, edited by A. Barbeau, T. Chase and G. W. Paulson. New York: Raven Press, 1973, pp. 681–697.
9. Costall, B. and R. J. Naylor. The behavioral effects of dopamine applied intracerebrally to areas of the mesolimbic system. *Eur. J. Pharmac.* **32:** 87–92, 1975.
10. Costall, B., R. J. Naylor, J. G. Cannon and T. Lee. Differentiation of the dopamine mechanism mediating stereotyped behaviour and hyperactivity in the nucleus accumbens and caudate-putamen. *J. Pharm. Pharmac.* **29:** 337–342, 1977.
11. Cotzias, G. C., M. H. VanWoert and L. M. Schiffer. Aromatic amino acids and modification of parkinsonism. *New Engl. J. Med.* **276:** 374–380, 1967.
12. DiChiara, G., M. L. Porceddu, L. Vargiu, A. Argiolas and G. L. Gessa. Evidence for dopamine receptors mediating sedation in the mouse brain. *Nature* **264:** 564–567, 1976.
13. Dill, R. E. Induction and measurement of tremor and other dyskinesias. In: *Methods in Psychology*, Vol. 3, edited by R. D. Myers. New York: Academic Press, 1977, pp. 241–257.
14. Dolphin, A. C., P. Jenner, M. C. B. Sawaya, C. D. Marsden and B. Testa. The effect of bromocriptine on locomotor activity and cerebral catecholamines in rodents. *J. Pharm. Pharmac.* **29:** 727–734, 1977.
15. Eibergen, R. D. and K. R. Carlson. Dyskinesias in monkeys: interaction of methamphetamine with prior methadone treatment. *Pharmac. Biochem. Behav.* **5:** 175–187, 1976.
16. Farley, I. J., K. S. Price and O. Hornykiewicz. Dopamine in the limbic regions of the human brain: normal and abnormal. *Adv. Biochem. Psychopharmac.* **16:** 57–64, 1977.
17. Feldberg, W. *A Pharmacological Approach to the Brain from its Inner and Outer Surface*. Baltimore: Williams and Wilkins Co., 1963, pp. 49–52, 71–74.
18. Godwin-Austen, R. B. The long-term therapeutic effects of levodopa in the treatment of parkinsonism. In: *Advances in Neurology*, Vol. 3, edited by D. B. Calne. New York: Raven Press, 1973, pp. 23–27.
19. Jackson, D. M., N.-E. Andén and A. Dahlstrom. A functional effect of dopamine in the nucleus accumbens and in some other dopamine-rich parts of the rat brain. *Psychopharmacology* **45:** 139–149, 1975.
20. Klawans, H. L., P. Crosett and N. Dana. Effect of chronic amphetamine exposure on stereotyped behavior: Implications for pathogenesis of L-DOPA-induced dyskinesias. In: *Advances in Neurology*, Vol. 9, edited by D. Calne, T. N. Chase and A. Barbeau. New York: Raven Press, 1975, pp. 105–112.
21. Molander, L. and A. Randrup. Investigation of the mechanisms by which L-DOPA induces gnawing in mice. *Acta pharmac. tox.* **34:** 312–324, 1974.
22. Mones, R. J. Experimental dyskinesias in normal rhesus monkeys. In: *Advances in Neurology*, Vol. 1, edited by A. Barbeau, T. Chase and G. W. Paulson. New York: Raven Press, 1973, pp. 665–669.
23. Mones, R. J. Levodopa-induced dyskinesias in the normal rhesus monkey. *Mt. Sinai J. Med.* **39:** 197–201, 1972.
24. Ng, L. K. Y., R. E. Gelhard, T. N. Chase and P. D. MacLean. Drug-induced dyskinesias in monkeys: a pharmacologic model employing 6-hydroxy-dopamine. In: *Advances in Neurology*, Vol. 1, edited by A. Barbeau, T. Chase and G. W. Paulson. New York: Raven Press, 1973, pp. 651–655.
25. Pijnenburg, A. J. J., W. M. M. Honig and J. M. van Rossum. Effects of antagonists upon locomotor stimulation induced by injection of dopamine and noradrenaline into the nucleus accumbens of nialamide-pretreated rats. *Psychopharmacology* **41:** 175–180, 1975.
26. Pijnenburg, A. J. J. and J. M. van Rossum. Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens. *J. Pharm. Pharmac.* **25:** 1003–1005, 1973.
27. Sassin, J. F. Drug-induced dyskinesias in monkeys. In: *Advances in Neurology*, Vol. 10, edited by B. S. Meldrum and C. D. Marsden. New York: Raven Press, 1975, pp. 47–54.
28. Sassin, J. F., S. Taub and E. D. Weitzman. Hyperkinesia and changes in behavior produced in normal monkeys by L-DOPA. *Neurology* **22:** 1122–1125, 1972.
29. Snider, R. S. and J. C. Lee. *A Stereotoxic Atlas of Monkey Brain* Macaca mulatta. Chicago: University of Chicago Press, 1961.
30. Thornburg, J. E. and K. E. Moore. Supersensitivity to dopamine agonists following unilateral, 6-hydroxydopamine-induced striatal lesions in mice. *J. Pharmac. exp. Ther.* **192:** 42–49, 1975.
31. Ungerstedt, U. Postsynaptic supersensitivity after 6-hydroxydopamine-induced degeneration of the nigro-striatal dopamine system. *Acta physiol. scand. Suppl.* **367:** 69–93, 1971.
32. Willner, J. H., M. Samach, B. M. Angrist, M. B. Wallach and S. Gershon. Drug-induced stereotyped behavior and its antagonism in dogs. *Communs behav. Biol.* **5:** 135–141, 1970.
33. Yahr, M. D. and R. C. Duvoisin. Drug therapy of parkinsonism. *New Engl. J. Med.* **287:** 20–24, 1972.