Pharmacology Biochemistry & Behavior, Vol. 25, pp. 503–509, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

Behavioral Deficits Induced by Low Doses of Apomorphine in Rats: Evidence for a Motivational and Cognitive Dysfunction Which Discriminates Among Neuroleptic Drugs

P. CARNOY, S. RAVARD, B. WEMERMAN, PH. SOUBRIE[1] AND P. SIMON

Département de Pharmacologie, Faculté de Médecine, Pitié-Salpêtrière 91, Bd de l'Hôpital 75634 Paris 13, France

Received 2 May 1986

CARNOY, P., S. RAVARD, B. WEMERMAN, PH. SOUBRIE AND P. SIMON. *Behavioral deficits induced by low doses of apomorphine in rats: Evidence for a motivational and cognitive dysfunction which discriminates among neuroleptic drugs*. PHARMACOL BIOCHEM BEHAV 25(3) 503–509, 1986.—In order to further assess the alterations (motor, motivational or cognitive) that might underlie animal behavioral deficits associated with a reduced dopamine transmission, the effects of apomorphine at doses thought to stimulate dopaminergic autoreceptors were studied on rat operant behavior. Apomorphine (30 μg/kg SC) decreased the number of food rewards obtained, when rats trained on a continuous reinforced schedule were shifted to schedules of fixed ratio higher than 2:FR3, FR4, and FR8. In rats shifted to a FR4 schedule, apomorphine (7.5, 15, 30, 60 μg/kg SC) dose-relatedly reduced the number of rewards obtained. In rats subjected to previous extinction sessions, apomorphine (30 μg/kg) did not affect lever pressing reinstated on presentation of primary reinforcers but inhibited responding renewed on presentation of secondary reinforcers. Under a FR(3+1) schedule where the last (rewarded) response was distinct from the initial (non-rewarded) responses, the detrimental effect of apomorphine on response rates was considerably weaker than under a conventional FR4 schedule. The reward deficits caused by apomorphine under the FR4 schedule were dose-dependently and completely reversed by amisulpride (0.125, 0.25, 0.5, 1 and 2 mg/kg), pimozide (0.125 mg/kg), sulpiride (8, 16, 32 and 64 mg/kg), but not by conventional neuroleptics (namely chlorpromazine, fluphenazine, haloperidol, metoclopramide and thioridazine). It is suggested that behavioral deficits associated with a reduced dopamine transmission such as that caused by low doses of apomorphine involve motivational and cognitive dysfunctions rather than motor impairments. In account of its differential sensitivity to neuroleptic drugs, apomorphine-induced deficit might have some relevance for a further delineation of the mechanisms of action of these compounds.

Dopamine Presynaptic DA receptors Apomorphine Neuroleptic drugs Operant behavior
Anhedonia Cognitive deficits Rat

BLOCKADE of dopaminergic transmission with neuroleptic drugs reportedly induced various behavioral deficits, including reduced locomotor activity or decreased performance in positively and negatively reinforced operant tasks [1, 9, 16, 23]. In agreement with lesion studies, this has led to the implication of dopaminergic neurons in motor capability, motivational processes and cognitive functions [1, 16, 23].

However, when using neuroleptic drugs, and despite considerable investigation, there is still difficulty in sorting out the relative importance of motor vs. motivational or cognitive impairments in the behavior-modifying effects of blocking dopaminergic transmission. [5, 6, 9, 12, 13, 23]. This prompted us to investigate in rats whether a reduced dopaminergic transmission as that thought to result from a stimulation of dopamine (DA) autoreceptors [3, 4, 15, 17] may deteriorate operant behavior via a disruption of motivational or cognitive processes rather than of motor capabilities.

With that aim, the effects of apomorphine at doses (low doses) thought to exert a preferential stimulation of DA autoreceptors were studied on a positively reinforced operant behavior. It has been proposed that a drug which primarily affects motivational processes, must have a more profound suppressant effect, on performance maintained by low rather than high reinforcement frequencies [9,12]. Hence, the effects of apomorphine on the performances of rats subjected

[1]Requests for reprints should be addressed to Ph. Soubrie at above address.

to schedules of food presentation of varying fixed ratio: 1(CRF), 2(FR2), 3(FR3), 4(FR4) or 8(FR8), were first compared. A second set of experiments was carried out to investigate whether, in rats trained to press for food and then subjected to extinction sessions, apomorphine differentially affected the pressing behavior reinstated by secondary vs. primary (food) reinforcers. On FR schedules, the animals must repeat a specified number of times the same response for reward to be obtained, thus with reward or non-reward being associated with the performance of identical responses. Whether apomorphine might alter the cognitive processes involved in the treatment of such an ambiguous situation was evaluated thirdly. For that purpose, we studied the effects of this drug on a FR schedule in which the response that was followed by the reward delivery was distinct from the non-rewarded, prerequisite presses. Finally, the action of various neuroleptic drugs on apomorphine-induced performance deficit under the FR4 schedule was examined in order to compare the sensitivity of this deficit with the reported hypokinesia produced by low doses of apomorphine [2–4, 10, 11, 20].

METHOD

The experiments were carried out on male Wistar A.F. rats (Centre d'élevage R. Janvier, France) weighing 170–190 g on the day of the experiment. The animals were housed in groups of 10, under standard conditions (room temperature: 21±1°C, light/dark cycle: 12 hr/12 hr) with free access to water and food. During training, food was restricted in order to maintain the animals at about 80% of their normal body weight.

Training Procedure

The experiments were performed using operant chambers (Campden Instruments, London, UK) housed in a ventilated sound attenuated cubicle, with an automatic dispenser delivering 45 mg noyes pellets. The operant chambers were equipped with two levers (5.5 cm above the floor) which required a vertical force of at least 12 g to operate the microswitch. Pellets were delivered into a recess between the two levers. The rats were trained (one daily session of 15 min over 2 weeks) to press the right lever of the operant chamber in order to obtain pellets according to a continuous reinforcement schedule (CRF).

Effects of Apomorphine and Reinforcement Frequency

At the end of the training phase, rats of separate groups (n=20 per group) were either maintained on CRF or shifted from CRF to schedules of different fixed ratios (2,3,4,8). For each of these groups, rats were injected subcutaneously (SC) with either apomorphine HCl 30 μg/kg or saline, 15 min before a test-session that took place after the rats were habituated or not habituated to their FR testing condition. In a second set of experiments, separate groups of rats (n=10 per group) were injected SC 15 min before testing with apomorphine HCl: 0, 7.5, 15, 30 or 60 μg/kg before a 15 min FR4 (first exposure) or CRF session. Thirdly, we investigated the effects of apomorphine under high response rate demands. After training, rats (n=10 per group) underwent seven daily FR4 sessions and then were subjected to a 15 min FR16 session, after receiving 0 or 30 μg/kg of apomorphine (SC 15 min before testing).

Effects of Apomorphine and Nature of the Reinforcement

These experiments were performed to examine whether apomorphine might affect the rewarding value of secondary rather than primary reinforcers. After the training phase, rats were subjected to two consecutive 30 min daily extinction sessions during which lever pressing was no longer followed by either reward delivery or the noises associated with the activation of the pellets dispenser. Rats were then divided into 3 sub-groups and subjected to a single experimental session conducted under one of the following conditions. In condition 1, after completion of an initial 2 min extinction period, lever pressing was associated with the contingent activation of the unloaded food dispenser, whereas in condition 2 the first two presses performed after the 2 min period were followed by pellet delivery. In the third condition, rats were maintained under non-reward. Fifteen minutes before the experimental session, rats were given 0 or 30 μg/kg apomorphine SC (n=10 per group). The number of lever presses during the 3 min after the onset of changes during extinction were recorded for each rat; bar pressing of rats maintained on extinction was recorded during an equivalent 3 min period.

Effects of Apomorphine and Reinforcement Contingency

As distinct from the usual training procedure, rats were trained to push open the flap preventing access to the tray in order to obtain food pellets. After one week of training, rats were progressively required (over a 3 week-period) to perform 1, and 2 and finally 3 successive presses on the right lever before pushing the flap to be reinforced. Therefore, a specified number of responses (4) was required of the rats but, as distinct from conventional FR4 schedules, the 3 initial non-rewarded responses of the sequence were distinct from the response that was followed by pellet delivery—FR(3+1) stands for this schedule. The effects of apomorphine (30 μg/kg SC, 15 min before test) on responding during a 15 min session, were compared on rats trained under FR4 or FR(3+1) schedules.

Reversal by Neuroleptic Drugs of the Effects of Apomorphine

On the day of the experiments, rats were switched from CRF to FR4 schedule. Before being subjected to a 15 min FR4 session, separate groups of rats were pretreated with varying doses of neuroleptics IP (8 to 16 animals per dose) and then challenged with 30 μg/kg apomorphine SC 15 min before test. The following neuroleptics, amisulpride (0.125 to 4 mg/kg), pipotiazine (0.125 to 2 mg/kg), sulpiride (4 to 128 mg/kg), and thioridazine (0.06 to 2 mg/kg), were administered in suspension in acacia gum, 1 hour before testing, and pipotiazine 30 min before testing. Haloperidol (0.015 to 0.125 mg/kg) and pimozide (0.06 to 0.25 mg/kg) dissolved in tartaric acid (1.5%) were injected 30 min before testing. Chlorpromazine HCl (0.125 to 0.5 mg/kg), fluphenazine 2 HCl (0.015 to 0.125 mg/kg) and metoclopramide HCl (0.25 to 1 mg/kg) were administered in bidistilled water, 30 min before testing. As a control, the ability of sulpiride (8, 16, 128 mg/kg), pimozide (0.125 mg/kg) and haloperidol (0.125 mg/kg) to modify by themselves FR 4 responding was investigated.

Unless otherwise noted, the number of food rewards obtained by each rat during 15 min was recorded in all the

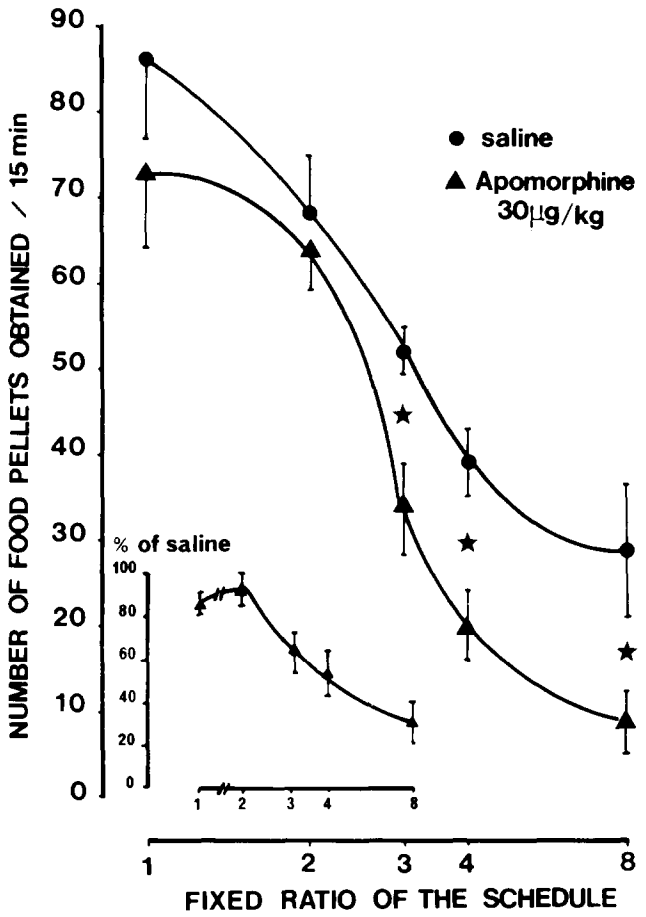

FIG. 1. Effects of apomorphine on food rewards (mean±SEM) obtained in 15 min by rats subjected to operant schedules of varying fixed ratio (FR1, FR2, FR3, FR4, FR8). Separate groups of rats were trained under continuous reinforced schedule and then, either maintained under this condition (FR1) or shifted to a given FR schedule, 15 minutes after receiving a single injection of apomorphine (30 μg/kg SC) or saline. The inset graph depicts the number (mean±SEM) of pellets obtained by apomorphine-treated rats as a percent of saline injected controls. ★Indicates significant differences ($p<0.05$) between apomorphine- and saline-treated rats.

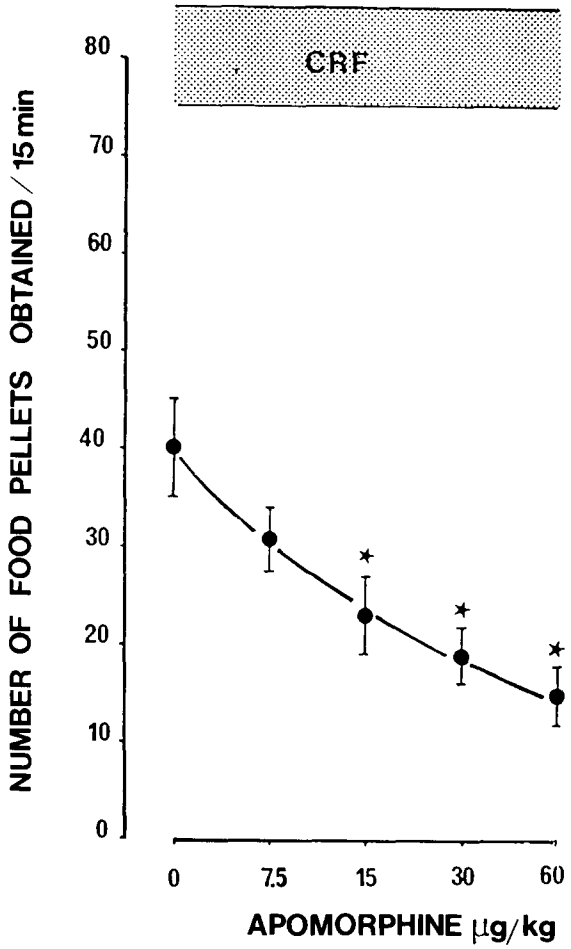

FIG. 2. Dose-response curve of apomorphine in worsening reward deficits in rats shifted from continuous reinforced schedule (CFR) to FR4 schedule. Data are the mean (±SEM) number of food pellets obtained in 15 min. Rats were trained under CRF conditions and shifted to a fixed ratio 4 schedule of food presentation 15 minutes after receiving apomorphine SC. ★Indicates significant differences ($p<0.05$) between apomorphine- and saline-treated rats.

experiments. Statistical significance was determined by analysis of variance followed by Dunnet's t test for multiple comparisons.

RESULTS

Effects of Apomorphine and Reinforcement Frequency

Rats trained on a CRF schedule and shifted to a fixed ratio (FR) schedule showed a decrease in the number of reinforcements obtained, the magnitude of the decrement being more important as the ratio of the schedule elevated (Fig. 1). Under these conditions, apomorphine 30 μg/kg induced a further detrimental effect, the intensity of which correlated positively with the value of the ratio of the schedule. Whereas no significant difference was observed between saline- and apomorphine-treated rats under FR1(CRF) or FR2 schedules, the number of reinforcements obtained by apomorphine-treated rats was significantly ($p<0.05$) decreased under the FR3, FR4 and FR8 schedules as compared with saline-treated rats (Fig. 1). In rats shifted to the FR4 schedule, apomorphine dose-dependently decreased (linear regression $F(1,49)=11.26$, $p<0.01$), the number of reinforcements obtained (Fig. 2). In rats maintained under the CRF schedule, apomorphine did not significantly affect responding up to the dose of 60 μg/kg which produced a limited (30%) though significant ($p<0.05$) reduction in the number of food pellets delivered (data not shown). In animals shifted to FR16 schedule after 7 daily FR 4 sessions, apomorphine 30 μg/kg significantly reduced the number of pellets obtained in the session: 39±4.8 vs. 23.7±5.2 ($p<0.05$) and thus did not prevent the animals from performing a number of presses (372±83) that would not result in a significant reward deficit under FR3 or FR4 conditions.

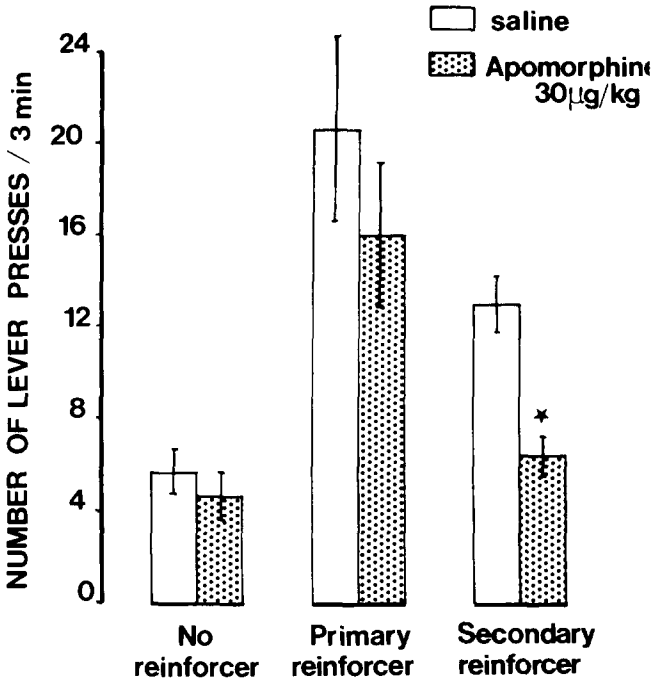

FIG. 3. Effects of apomorphine on lever pressing previously extinguished and then reinstated either by presentation of response-contingent reward (2 pellets = primary reinforcer) or by activation of the unloaded food dispenser (secondary reinforcer). The data are the mean number (±SEM) of presses during 3 minutes. ★Indicates significant differences ($p<0.05$) between apomorphine- and saline-treated rats.

Effects of Apomorphine and Nature of the Reinforcement

In rats previously subjected to extinction sessions and maintained under non-reward condition at the beginning of the experimental session, the delivery of two response-contingent pellets or the activation of the unloaded food dispenser produced (during 3 min) a substantial renewal of responding as compared to rats maintained under extinction conditions. Apomorphine 30 μg/kg did not significantly affect responding temporarily reinstated by presentation of 2 food-pellets but significantly depressed ($p<0.01$), responding renewed by presentation of secondary reinforcers such as the noises inherent in the activation of the food dispenser (Fig. 3).

Effects of Apomorphine and Reinforcement Contingency

As shown in Table 1, apomorphine 30 μg/kg significantly depressed responding for food in rats trained under a conventional FR4 schedule. In rats required to bar press 3 times and then to push open the flap of the tray in order to obtain pellets (FR3+1), apomorphine significantly reduced the number of pellets delivered. This reduction, however was significantly lower ($p<0.01$) as compared with that observed under the FR4 schedule (Table 1). Interestingly, under the FR(3+1) schedule, apomorphine did not affect the efficiency (ratio: reward/press) of the animals: controls: 69.3/393.7 = 0.18 vs. 52.2/336.7 = 0.16 in apomorphine-treated rats.

TABLE 1

EFFECTS OF APOMORPHINE ON FOOD OPERANT BEHAVIOR ARE DEPENDENT UPON REINFORCEMENT CONTINGENCIES

	Number of rewards obtained by trained rats (mean ± SEM)			
	in FR4		in FR(3 + 1)	
Controls	(28)	85.8 ± 8.0	(26)	69.3 ± 4.0
Apomorphine (30 μg/kg)	(28)	45.2 ± 5.1*	(26)	52.2 ± 3.8*
Difference (controls vs. apomorphine)		40.6 ± 6.5		17.1 ± 2.3
				$p<0.01$

Under the fixed ratio 4 (FR4) schedule, rats were trained to press the lever 4 times to obtain pellets whereas, under the FR(3 + 1) schedule, rats were required to press the lever 3 times and then, push open (once) the flap preventing access to the tray to be reinforced.

Apomorphine was given subcutaneously 15 min before a single 15 min test-session.

Statistical comparisons were made by using ANOVA followed by Dunnett's t test. *$p<0.01$ as compared with controls. Number of animals under each condition are given in parenthesis.

Reversal by Neuroleptic Drugs of the Effects of Apomorphine

The deficit provoked by 30 μg/kg of apomorphine on the first FR4 session was significantly reversed (Table 2) either completely and dose-dependently by amisulpride (active doses: 0.125–0.25–0.5–1 and 2 mg/kg), pimozide (0.125 mg/kg), sulpiride (8–16–32 and 64 mg/kg) or partially by pipotiazine (0.5 mg/kg). The antagonistic activity of all these drugs waned at high doses, probably because their ability to decrease FR 4 performance, since by itself, sulpiride for instance (128 mg/kg) decreased by 45% the number of pellets obtained during a 15 min FR4 session (37.0±4.0 vs. 17.0±5.2, $p<0.05$). At none of the doses tested, were the effects of apomorphine antagonized by the following neuroleptics: chlorpromazine, fluphenazine, haloperidol, metoclopramide and thioridazine (Table 2). Fluphenazine (0.125 mg/kg), haloperidol (0.125 mg/kg), and chlorpromazine (0.5 mg/kg) significantly enhanced the deficit caused by apomorphine. This was probably the result of an addition of the effects of apomorphine and of these neuroleptics in depressing FR4 responding since, for instance, haloperidol (0.125 mg/kg) was found to reduce the number of pellets obtained during a 15 min FR4 session in saline-treated rats (41.5±5.1 vs. 9.7±4.2, $p<0.01$). At doses which completely reversed the apomorphine-induced reward deficit, sulpiride (8 and 16 mg/kg) or pimozide (0.125 mg/kg) were not able to enhance FR4 performance in animals not treated with apomorphine (number of food pellets: controls: 38.5±4.9; sulpiride 8: 42.7±2.3; sulpiride 16: 30.5±3.4; pimozide 0.125: 32.7±3.6).

In a complementary experiment was observed that the inhibitory effect of apomorphine (30 μg/kg) on responding renewed by secondary reinforcers was significantly reversed by sulpiride 16 mg/kg (controls: 16.6±2.0; apomorphine alone: 8.5±1.4; apomorphine + sulpiride: 13.2±1.7, $t=2.13$, $p<0.05$.) but not by haloperidol 30 μg/kg.

TABLE 2

DIFFERENTIAL ABILITY OF NEUROLEPTIC DRUGS IN REVERSING THE APOMORPHINE-INDUCED REWARD DEFICITS IN RATS SHIFTED FROM CRF TO FR4 SCHEDULE OF FOOD DELIVERY

	Active Neuroleptic (NL) Drugs				Inactive Neuroleptic (NL) Drugs				
	AMIS	PIMO	PIPO	SULP	CHLO	FLUP	HALO	METO	THIO
Apo alone	14 ± 1	19 ± 3	33 ± 2	18 ± 4	20 ± 2	20 ± 3	13 ± 3	23 ± 2	13 ± 2
+ NL mg/kg									
0,015						22 ± 2	20 ± 7		
0,03						22 ± 3	16 ± 6		
0,06		24 ± 5				22 ± 4	14 ± 6		
0,125	22 ± 3*	29 ± 4†	38 ± 4		21 ± 3	11 ± 2	3 ± 1		16 ± 4
0,25	22 ± 3*	14 ± 3	33 ± 3		25 ± 3			26 ± 4	13 ± 2
0,5	31 ± 2†		39 ± 2*		14 ± 3			24 ± 4	16 ± 4
1	23 ± 4†		34 ± 2						9 ± 6
2	19 ± 3		32 ± 4						8 ± 2
4	19 ± 3			29 ± 3					
8				33 ± 2*†					
16				35 ± 2*†					
32				44 ± 3*†					
64				33 ± 6*†					
Saline	31 ± 6	35 ± 4	50 ± 1	37 ± 4	38 ± 3	35 ± 2	40 ± 4	40 ± 6	42 ± 3

Data are the mean number (± SEM) of pellets obtained in 15 minutes. Apomorphine (30 μg/kg) was injected SC 15 minutes before the session, either in rats pretreated with saline (Apo alone) or with neuroleptics (+ NL) injected intraperitoneally. Amisulpride (AMIS), sulpiride (SULP) and thioridazine (THIO) were given 1 hour before testing. Pimozide (PIMO), pipotiazine (PIPO), chlorpromazine (CHLO), fluphenazine (FLUP), haloperidol (HALO) and metoclopramide (METO) were administered 30 minutes before testing.

The number (± SEM) of food pellets obtained in 15 minutes by the separate saline-saline treated groups of rats are given in the last line of the table (saline).

*Significant increase as compared with rats treated with apomorphine alone ($p<0.05$, Dunnett's t test).

†No significant difference vs. saline-treated rats.

While this article was in the editorial process, some experiments were performed with ritanserine and imipramine. Ritanserine, a 5-HT receptor blocker was given IP 30 min before apomorphine challenge at doses ranging from 0.06 to 8 mg/kg. Imipramine was injected twice daily (8 mg/kg IP) during seven days, the last injection being performed 1 hr before apomorphine challenge. Neither drug was found to antagonize the deficits produced by apomorphine under the FR4 schedule.

DISCUSSION

This study shows that low doses of apomorphine disrupted rat operant responding under fixed ratio schedules of food delivery. This detrimental effect was increasingly marked as the imposed ratio of the schedule elevated. From the results of the present experiment, attempts can be made to sort out the various (motor, motivational or cognitive) disturbances that might account for the observed effects of apomorphine. Since, at the doses studied, apomorphine is thought to reduce dopaminergic transmission through a stimulation of DA autoreceptors [2, 3, 11, 15, 17], this study may shed further light on the role of DA-containing neurons in the control of behavior and on the neuropsychological processes that could primarily be affected by a reduced dopaminergic transmission.

Motor Impairment

Low doses of DA agonists have abundantly been reported to reduce locomotor activity in rodents [3, 4, 10, 11, 20]. The decline in response rate produced by apomorphine on operant behavior might be related to motor impairment. Two facts militate against such a hypothesis. Apomorphine 30 μg/kg did not significantly alter performances of rats working on CRF, but abolished responding reinstated by secondary reinforcers whereas this drug almost spared renewal of pressing caused by food delivery. It is still conceivable, however, that motor impairment might only be observed under high response demands (FR as opposed to CRF schedule). Two facts lend little support for this motor debilitation hypothesis: first under FR16 schedule, apomorphine-treated rats can perform a number of presses (400 over a 15 min session) that would result in no reward deficit under the FR3 or FR4 schedules, and second, apomorphine-treated rats are capable to emit about 340 presses in 15 min under the FR(3+1) schedule.

Motivational Processes and Cognitive Functions

In agreement with the hypothesized motivational bluntness caused by DA receptor blockade [23], our data may suggest that the rate decreasing effect of apomorphine involves a reduction in the rewarding value of reinforcers. In

particular, the more marked effect of apomorphine on schedules of elevated fixed ratio is concordant with the anhedonia hypothesis such as that based on a mathematical model of the law of effect [9,12]. This hypothesis posits that a drug which induces an anhedonic state, must have a more profound suppressant effect on performance maintained by low reinforcement frequencies than on performance maintained by high reinforcement frequencies. Above and beyond a possible primary reinforcement deficit, the fact that apomorphine exerted a differential effect on responding reinstated by primary vs. secondary reinforcers (only the latter being blocked by this drug) tends to indicate that, in apomorphine-treated rats, incentive stimuli or secondary reinforcements themselves have a blunted impact. This possibility offers a plausible explanation for apomorphine-induced reward deficits under elevated FR schedules since, in conditions (including FR schedules) in which reward is temporarily omitted, secondary reinforcers play a critical role in maintaining responding [20]. Moreover the detrimental effects of apomorphine on elevated FR schedules and on pressing renewed by secondary reinforcement exhibited an identical, differential sensitivity to neuroleptic drugs such as sulpiride and haloperidol.

The extent to which response rates were decreased by apomorphine was not dependent on whether the animals were adapted to a certain schedule value or were tested on the day of transition from one schedule to another. This makes it unlikely that disruption in learning processes may greatly account for the apomorphine-induced deficits. Apomorphine-induced deficits might be related to the inability of the drugged rats to deal with a task leading to contradictory information. Typically, FR schedules are situations in which identical responses (lever press) are not associated with identical consequences. In the FR4 schedule, for instance, 3 presses are not rewarded whereas the fourth response is followed by a pellet delivery. The observed lessened ability of apomorphine to disrupt rat performance in a schedule FR(3+1) designed to minimize the ambiguous aspect of FR schedules, might give some credence to this latter hypothesis. Hence, the detrimental action of apomorphine on conventional FR schedule might be accounted for by a disruption of cognitive processes similar to that tentatively associated with an impaired ability to ignore irrelevant stimuli [1, 18, 21]. Indeed, sustained responding under conventional FR schedules requires that non-reward that follows a specified number of presses must in part be tuned-out as irrelevant information. Our data may suggest, in agreement with the role ascribed to DA-containing neurons in information processing, that both an enhanced, as already reported [18,21], but also a reduced DA transmission, produced cognitive deficits in information selection or response processing that have been repeatedly referred to in schizophrenia as one central characteristic of the disease [7,21].

Reversal by Neuroleptics of the Effects Induced by Apomorphine

Among the neuroleptics tested, only some (amisulpride, pimozide, sulpiride and pipotiazine, though to a lesser extent) were found to reverse (at low to moderate doses) the effect induced by apomorphine on the FR4 schedule of food delivery. This contrasts with the well documented ability of the majority of neuroleptics to antagonize the behavioral manifestations linked to a stimulation of post-synaptic DA receptors such as stereotyped movements or climbing behavior [16].

Several investigators [2, 4, 11, 19] have suggested that neuroleptics can be distinguished according to their ability to bind to auto rather than postsynaptic DA receptors, although the possibility to discriminate these receptors pharmacologically has been questioned [8]. One may therefore speculate that the reversal by neuroleptics of apomorphine-induced reward deficit can only be observed with those compounds which, at doses lower than those required to block postsynaptic DA receptors, are able to displace apomorphine bound on autoreceptors. Thus, neuroleptics inactive in reversing apomorphine effects might be compounds which are unable to discriminate auto and postsynaptic DA receptors. A similar hypothesis has been proposed to explain the antagonism by neuroleptics of apomorphine-induced hypokinesia [2, 11, 19], and most neuroleptics found to suppress apomorphine effects in our conditions also reversed apomorphine-induced hypokinesia. However, haloperidol and metoclopramide, which were inactive in reversing apomorphine effects on the FR4 schedule, have been reported to reduce apomorphine-induced hypokinesia [2, 4, 11, 19]. Hence it seems unlikely that response deficit caused by apomorphine can be accounted for by systems mediating sedation or motor impairments nor by a single action such as binding to DA autoreceptors. Additional factors such as preferential action on mesolimbic or mesocortical vs. nigrostriatal neurons [22], or discriminative properties with regards to different DA receptors subtypes [14], may be of critical importance.

Whatever the intimate mechanisms involved, the present study indicates that in rats, low doses of apomorphine thought to reduce DA transmission, induced behavioral deficits similar to those induced by neuroleptics on positively reinforced tasks [1, 9, 23]. These results are consistent with the role ascribed to DA containing neurons in reinforcement and cognitive processes [1, 13, 18, 21, 23]. However, since the contribution of motor impairments in apomorphine-induced reward deficits could be minimal, stimulation of DA autoreceptors seems to be a more convenient condition than post-synaptic DA blockade, to study the respective role of DA neurons in motor vs. motivational or cognitive functions.

REFERENCES

1. Beninger, R. J. The role of dopamine in locomotor activity and learning. *Brain Res Rev* **6:** 173–196, 1983.
2. Costall, B. D., H. Fortune, S. C. Q. Hui and R. J. Naylor. Neuroleptic antagonism of the motor inhibitory effects of apomorphine within the nucleus accumbens: drug interaction at presynaptic receptors. *Eur J Pharmacol* **63:** 347–358, 1980.
3. Costall, B., S. K. Lin and R. J. Naylor. Characterization of the mechanisms by which purported dopamine agonists reduce spontaneous locomotor activity in mice. *Eur J Pharmacol* **73:** 175–188, 1981.
4. Di Chiara, G., M. L. Porceddu, L. Vargiu, A. Argiolas and G. C. Gessa. Evidence for dopamine receptors mediating sedation in the mouse brain. *Nature* **264:** 564–566, 1976.

5. Ettenberg, A., G. F. Koob and F. E. Bloom. Response artifact in measurement of neuroleptic-induced anhedonia. *Science* **213:** 357–359, 1981.
6. Franklin, K. B. and S. N. McCoy. Pimozide-induced extinction in rats: Stimulus control of responding rules out motor deficit. *Pharmacol Biochem Behav* **11:** 71–75, 1979.
7. Frith, C. D. Consciousness, information processing and schizophrenia. *Br J Psychiatry* **134:** 225–235, 1979.
8. Helmreich, I., W. Reimann, G. Hertting and K. Starke. Are presynaptic dopamine autoreceptors and postsynaptic dopamine receptors in rabbit caudate nucleus pharmacologically different? *Neuroscience* **7:** 1559–1566, 1982.
9. Heyman, G. M., D. L. Kinzie and L. S. Seiden. Chlorpromazine and pimozide alter reinforcement efficacy and motor performance. *Psychopharmacology (Berlin)* **88:** 346–353, 1986.
10. Misslin, R., P. Ropartz and L. Jung. Impairment of responses to novelty by apomorphine and its antagonism by neuroleptics in mice. *Psychopharmacology (Berlin)* **82:** 113–117, 1984.
11. Montanaro, N., A. Vaccheri, R. Dall-ohio and O. Gandofi. Time course of rat motility response to apomorphine: a simple model for studying preferential blockade of brain dopamine receptors mediating sedation. *Psychopharmacology (Berlin)* **81:** 214–219, 1983.
12. Morley, M. J., C. M. B. Bradshaw and E. Szabade. The effect of pimozide on variable interval performance: a test for the anhedonia hypothesis of the mode of action of neuroleptics. *Psychopharmacology (Berlin)* **84:** 531–536, 1984.
13. Phillips, A. G. and H. C. Fibiger. Decreased resistance to extinction after haloperidol: implications for the role of dopamine in reinforcement. *Pharmacol Biochem Behav* **10:** 751–760, 1979.
14. Protais, P., J. J. Bonnet and J. Constentin. Pharmacological characterization of the receptors involved in the apomorphine-induced polyphasic modifications of locomotor activity in mice. *Psychopharmacology (Berlin)* **81:** 126–134, 1983.
15. Roth, R. H. Dopamine autoreceptors: pharmacology, function and comparison with postsynaptic dopamine receptors. *Cummun Psychopharmacol* **3:** 429–445, 1979.
16. Serra, G., J. M. Van Ree and D. De Wied. Influence of classical and atypical neuroleptics on apomorphine-induced behavioural changes and on extinction of a conditioned avoidance response. *J Pharm Pharmacol* **35:** 255–257, 1983.
17. Skirboll, L. R., A. A. Grace and B. S. Bunney. Dopamine auto and postsynaptic receptors: electrophysiological evidence for differential sensitivity to dopamine agonists. *Science* **206:** 80–82, 1979.
18. Solomon, P. R., A. Crider, J. W. Winkelman, A. Turi, R. M. Kamer and L. J. Kaplan. Disrupted latent inhibition in the rat with chronic amphetamine or haloperidol-induced supersensitivity: relationship to schizophrenic attention disorder. *Biol Psychol* **16:** 519–537, 1981.
19. Sumners, C., J. B. De Vries and A. S. Horn. Behavioural and neurochemical studies on apomorphine-induced hypomotility in mice. *Neuropharmacology* **20:** 1203–1208, 1981.
20. Taylor, J. R. and T. W. Robbins. Enhanced behavioural control by conditioned reinforcers following microinjections of d-amphetamine into the nucleus accumbens. *Psychopharmacology (Berlin)* **84:** 405–412, 1984.
21. Weiner, I., R. E. Lubow and J. Feldon. Abolition of the expression but not the acquisition of latent inhibition by chronic amphetamine in rats. *Psychopharmacology (Berlin)* **83:** 194–199, 1984.
22. White, F. J. and R. Y. Wang. Differential effects of classical and atypical antipsychotic drugs on A9 and A10 dopamine neurons. *Science* **221:** 1054–1057, 1983.
23. Wise, R. A. Neuroleptics and operant behaviour: the anhedonia hypothesis. *Behav Brain Sci* **5:** 39–87, 1982.