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The Effects of Apomorphine on the Acquisition of Schedule-Induced Polydipsia in Rats

SAMUEL H SNODGRASS AND JOSEPH D ALLEN[1]

Department of Psychology, University of Georgia, Athens, GA 30602

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SNODGRASS, S H AND J D ALLEN *The effects of apomorphine on the acquisition of schedule-induced polydipsia in rats* PHARMACOL BIOCHEM BEHAV **29**(3) 483–488, 1988 —Injections of the dopamine agent, apomorphine, at the doses of 0 05, 0 50 and 1 0 mg/kg were given to three different groups of rats while a fourth group received an injection of the drug vehicle The injections preceded each of 15 schedule-induced polydipsia (SIP) acquisition sessions in which the subjects bar-pressed for food pellets on a fixed interval 60-sec schedule of reinforcement The vehicle-injected group developed SIP over sessions while each dose of apomorphine suppressed the acquisition of SIP Bar-press rates were also depressed at the higher doses, while response patterning was affected at the lower dose The results support the contention that a normally functioning dopamine system is necessary for the acquisition of SIP, but they do not support the view that this neurotransmitter system is specifically involved in the generation of SIP

Schedule-induced polydipsia Apomorphine Dopamine Fixed interval schedule Operant bar-pressing Rats

WHEN a food deprived rat is allowed free access to water while receiving small allotments of food on an intermittent basis, adjunctive drinking, also known as schedule-induced polydipsia (SIP), develops over a few sessions [10] During the acquisition of SIP, rats develop a characteristic drinking pattern such that they drink immediately after the ingestion of the food reinforcer with the peak in drinking occurring early in the interfood interval and then declining over the interval [12,13] Large volumes of water are consumed during SIP sessions even though the rats are never deprived of water nor are they experiencing any known form of physiological water deficit [12, 13, 36] For this reason, SIP has been classified as a non-homeostatic form of drinking [12]

It has been known for some time that dopamine antagonists, such as haloperidol, suppress established SIP [3, 19, 20, 22] as do the dopamine agonists, d-amphetamine [22, 24, 30, 33, 40] and apomorphine [34] Lesions of the dopamine rich nucleus accumbens with 6-hydroxydopamine (6-OHDA), while not suppressing established SIP or operant bar-pressing, do alter the temporal patterning of these behaviors [30] Recent evidence from this laboratory has shown that either pharmacological over- or under-activation of the dopamine system in rats resulted in decreases in established SIP as well as operant bar-pressing and deprivation-induced drinking Furthermore, all three behaviors were affected to the same degree by increasing doses of apomorphine or haloperidol [34]

The acquisition of SIP has also been reported to be altered by manipulations of the dopamine system Chemical lesions of the lateral septal nucleus with 6-OHDA have been reported to accelerate the rate of acquisition of SIP [37] However, 6-OHDA lesions of the nucleus accumbens suppress its development [29,39] while not influencing deprivation-induced drinking [29] or daily water or food intake [39] A similar behavioral specificity has been reported by Porter *et al* [26] concerning the administration of the dopamine antagonists, pimozide and spiperone Neither operant bar-pressing nor deprivation-induced drinking were reportedly affected by these drugs, while the acquisition of SIP was effectively blocked

In none of the above studies was the possibility entertained that the apparent behavioral selectivity of the drugs or lesions was due to the fact that SIP had not been established prior to administration of the drug or chemical In the Porter *et al* [26] study, for instance, rats were given prior experience with bar pressing for pellets on various schedules leading to a terminal FI 1-min schedule before drug administration and SIP testing began. Injections of pimozide (0 5 or 1 0 mg/kg) or spiperone (0 62 or 0 125 mg/kg) were initiated with SIP testing and lasted for 15 sessions Data on drinking and bar pressing were reported only for the final 3 test days, at which time SIP had not developed, but bar press rates were similar to control rates There is ample evidence [14, 16, 18, 23, 25, 31, 38, 41] to suggest that, at the dosage levels used, the two dopamine blockers should have also disrupted operant responding It is quite

[1]Requests for reprints should be addressed to Joseph D Allen, Visiting Professor, Department of Psychology, University of Guelph, Guelph, Ontario, Canada N1G 2W1

possible, however, that the drugs did initially affect bar-pressing, which then slowly recovered over the two-week course Since no time-course data were presented for either drinking or bar-pressing, it is not possible to affirm this possibility The present study was therefore conducted as a systematic replication of the Porter *et al* [26] study, and included the needed time course data along with a wider range of drug dosages

The pharmacological agent apomorphine was used because of its dose-dependent effects At low doses, apomorphine has been reported to selectively bind with autoreceptors located on the pre-synaptic terminals of dopamine containing neurons The physiological effect of this binding is a decrease in the amount of synthesis and a decreased release of dopamine during neurotransmission [4,32] Higher doses of apomorphine bind with both pre- and post-synaptic dopamine receptors [4,32] Behaviorally, it has been reported that low doses of apomorphine cause inhibition of motor activity [2, 4, 8, 35] as well as a decrease in bar-pressing maintained on small fixed ratio schedules, i e , fixed ratios of one to four [5] Higher doses of apomorphine cause behavioral activation and, at appropriate doses, stereotypies [6, 9, 35]

The doses of apomorphine used in this study were chosen so as to encompass the range of these behavioral effects The dose of 0 05 mg/kg was chosen because it is in the range of doses reported to produce selective binding with the dopamine autoreceptors and, thus, behavioral inhibition [2, 4, 8, 35] Two higher doses, 0 50 and 1 0 mg/kg, were chosen on the basis of previous research which has shown that the 0 50 mg/kg dose causes moderate suppression of established SIP and operant bar-pressing while the 1 0 mg/kg dose produces a large suppression of these behaviors [34] The 1 0 mg/kg dose has also been observed in our laboratory to produce stereotyped head weaving and sniffing in rats

METHOD

Subjects

Twenty-four male Long Evans hooded rats, approximately 100 days old, were obtained from the University of Georgia breeding colony and served as subjects The rats were individually housed in a large colony room with a 12 hour light-dark cycle (8 00 a m /8 00 p m light cycle) in effect The subjects had continuous access to water in the home cage for the duration of the study

Apparatus

Sessions were conducted in three Lehigh Valley Electronics (Model 1714) operant conditioning chambers Each chamber was 30×25×28 cm in diameter and was enclosed in a sound attenuating cubicle In each chamber a response lever was mounted on the front wall 3 cm from the left wall and 4 cm above the floor A food magazine was located in the center of the front wall into which a Ralph Gerbrands pellet dispenser delivered Standard Formula 45 mg Noyes food pellets which served as the reinforcer Water was available through a drinking tube which was connected to a 100 ml graduated cylinder located on the outside of the front wall Access to the drinking tube was via a 1 5 cm opening in the front wall 5 5 cm to the right of the food magazine and 1 5 cm above the floor The drinking tube was recessed behind this opening so that incidental contact of the subjects with the tube was avoided and only licks would be recorded Licks at the tube were recorded with Grason-Stadler drinkometers and the amount of water consumed by each subject was measured to the nearest milliliter by visual inspection of the graduated cylinder

A Sym-1 microcomputer was networked with a PET/CBM 4032 microcomputer [1] and was used to control the behavioral contingencies and to record the licking and bar-pressing behavior of the subjects

Procedure

Upon arrival at the colony room, the subjects were randomly assigned to one of four treatment groups of six subjects each The subjects were then weighed once a day for five consecutive days and these weights were used to calculate the 80% free feeding weights which the subjects were subsequently reduced to over the next seven days The subjects were maintained at these 80% free feeding weights for the duration of the study by supplemental feedings given immediately after each session

The subjects were trained to bar-press for the food reinforcers on a fixed ratio 1 (FR 1) schedule of reinforcement in which each bar-press produced a 45 mg pellet Then three baseline sessions were conducted by allowing the subjects access to water in the chamber with the FR 1 schedule in effect Each subject could earn 30 reinforcers during the 30-min session, after which water intakes were recorded Following the last baseline session, the water bottles were removed from the experimental chambers and the schedule of reinforcement was changed to a fixed interval (FI), in which the first response after a specified period of time has elapsed since the delivery of the last reinforcer produces the next reinforcer The subjects were exposed to FI values of 15 and then 30 seconds for one session each The FI value was then shifted to 60 seconds where it remained for the duration of the study

Subjects were exposed to the FI 60-second schedule for two sessions after which SIP acquisition sessions were initiated Water was again made available to the subjects, and administration of the appropriate dose of apomorphine, or vehicle solution, was given 15 minutes prior to the beginning of the acquisition session The dose of apomorphine administered to a subject depended upon the group to which the subject had been assigned The groups were designated by dose of apomorphine, i e , 0 05 mg/kg, 0 50 mg/kg, 1 0 mg/kg or control (drug vehicle) group

The 30 minute acquisition sessions continued for 15 consecutive days, during which time the number of bar-presses, pellets earned, licks emitted and milliliters of water consumed for each subject during each session was recorded The number of bouts, defined as five or more licks during an interpellet interval, was also recorded In order to determine the effects of apomorphine on the temporal pattern of licking and bar-pressing, the number of licks and presses which occurred in each consecutive 10-second bin of the 60-second interval was recorded

The commercially available form of apormorphine hydrochloride (Eli Lilly and Company) was used in this study The drug vehicle was distilled water, which also served as the solution for the vehicle injections All injections were administered by the IP route 15 minutes pre-session in a constant volume of 1 ml/kg The drug solutions were prepared daily and the doses are expressed as the salt

RESULTS

One subject from the 1 0 mg/kg group developed an inner ear infection and was euthanized Because the acquisition

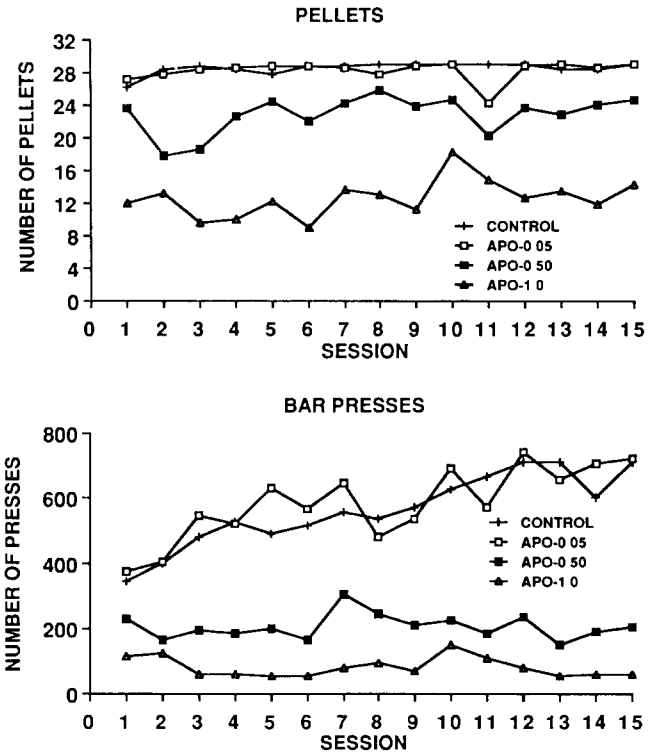

FIG 1 Number of pellets earned (top panel) and number of bar-presses emitted (bottom panel) over 15 acquisition sessions by groups receiving either 0 05, 0 50 or 1 0 mg/kg of apomorphine or drug vehicle

sessions had not yet begun it was possible to switch a subject from the control group to replace it During the acquisition sessions a control subject developed the behavior of shaking the water tube instead of drinking and for this reason its data were not included in the results for the control group The data for one subject in the 0 05 mg/kg dose group were also excluded from the results of its group This subject did not consume any water during the baseline or acquisition sessions All other subjects consumed at least a few milliliters of water during one or more of these sessions It was therefore concluded that this subject would not have become polydipsic even without the drug administration

Figure 1 illustrates the effects of the differing doses of apomorphine on the number of pellets earned (top panel) and the number of bar-presses (bottom panel) emitted by the different groups over the 15 acquisition sessions From this figure, it can be seen that the functions for the control (vehicle) group and the group which received 0 05 mg/kg of apomorphine are similar for these measures Depression of the behavior for the other two groups was immediate, constant and dependent upon the dose of apomorphine administered

For pellets earned, a two-way mixed analysis of variance with dose as the fixed factor and sessions as the repeated factor revealed that the interaction was not significant, $F(42,238)=0\ 637$, $p>0.25$, but that the main effect for dose was, $F(3,17)=49\ 09$, $p<0\ 001$ A post-hoc analysis of the main effects of dose by the Tukey HSD test revealed that the groups which received vehicle, 0 05 and 0 50 mg/kg of apomorphine differed significantly ($p<0\ 05$) from the group which received 1 0 mg/kg of apomorphine, but were not different from each other For bar-presses, the analysis of variance again revealed only a significant effect for dose, $F(3,17)=11\ 143$, $p<0\ 001$ The Tukey HSD test of the marginal means for dose revealed that the control group and the 0 05 mg/kg group differed significantly ($p<0\ 05$) from the two groups which received the higher doses of apomorphine, but not from each other The groups which received 0.50 and 1 0 mg/kg also did not differ significantly from each other

TABLE 1

INDEX OF CURVATURE FOR THE VEHICLE GROUP AND THE GROUPS WHICH RECEIVED 0 05 mg/kg AND 0 50 mg/kg OF APOMORPHINE

	Session			
Group	13	14	15	Mean
Control	520	567	565	550
0 05 mg/kg	436	457	464	452
0 50 mg/kg	326	331	346	335

An index of curvature [17] was applied to the intrainterval bar-press behavior for the control, 0 05 and 0 50 mg/kg groups for the final three sessions of acquisition in order to determine the effects on the temporal pattern of bar-pressing of these doses of apomorphine An index of curvature quantifies the amount of positive or negative acceleration in the rate of behavior over a time interval A high positive index of curvature (i e , 0 80) indicates the majority of behavior occurred near the end of the interval, i e , a scalloped pattern, while a high negative index of curvature, (−0 80), indicates that most of the behavior occurred near the beginning of the interval An index of zero indicates that the rate of behavior is constant throughout the interval The 1 0 mg/kg group was excluded from this analysis because the low rate of responding by its subjects (typically less than 100 bar-presses) did not permit the calculation of a reliable index From Table 1 it can be seen that response patterns were scalloped for all groups, however, apomorphine produced progressive flattening in the response pattern for subjects assigned to the 0 05 and 0 50 mg/kg conditions

The mixed analysis of variance yielded a significant main effect for dose, $F(2,12)=8\ 373$, $p<0.006$, with the Tukey HSD test revealing that the index for each group differed significantly ($p<0\ 05$) from that of each of the other groups

Figure 2 illustrates the effects of dose of apomorphine on the development of SIP across sessions By inspection of the top panel (licks), middle panel (bouts) and the bottom panel (milliliters consumed) it can be seen that the control group acquired SIP over the 15 sessions It can also be seen that all three doses of apomorphine suppressed the acquisition of SIP, and again suppression was ordered roughly by dosage These results were confirmed by statistical analyses of the data For licks, the two-way interaction (dose × session) was significant, $F(42,238)=8\ 54$, $p<0\ 001$, and the post-hoc analysis of the cell means by the Tukey HSD test revealed that the control group began licking significantly more ($p<0\ 05$) than the other groups by the third session Over sessions 13–15, it was found that the control group licked significantly more than did any other group On sessions 13 and 14 the number of licks emitted by the 0 05 mg/kg group was significantly different than that of the 1 0 mg/kg group, while the number of licks of the 0 50 mg/kg group did not differ from either group On session 15, the groups receiv-

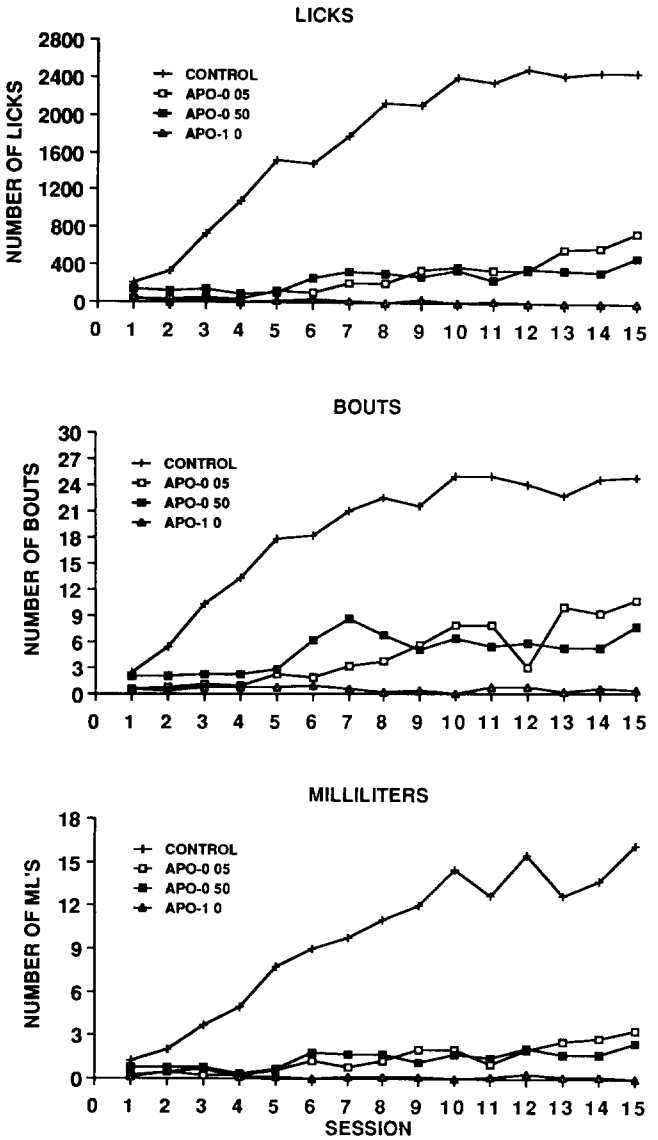

FIG 2 Number of licks emitted (top panel), number of bouts engaged in (middle panel) and the number of milliliters consumed (bottom panel) over 15 acquisition sessions by groups receiving 0 05, 0 50 or 1 0 mg/kg of apomorphine or drug vehicle

ing 0 05 and 0 50 mg/kg did not differ from each other, but licked significantly more than the 1 0 mg/kg group

The statistical analyses for bouts revealed a significant two-way interaction, $F(42,238)=4\ 36$, $p<0\ 001$ Post-hoc analysis of the simple main effects by the Tukey HSD test showed that the control group engaged in significantly more bouts than the other three groups by the third session For sessions 13–15 the post-hoc analysis revealed that the control group differed from all other groups, and that the number of bouts for the 0 05 and 0 50 mg/kg groups, while not different from each other, was significantly greater than that of the 1 0 mg/kg group

For milliliters consumed, a significant dose × session interaction, $F(42,238)=7\ 93$, $p<0.001$, was also revealed The Tukey HSD test showed that the vehicle group consumed significantly more water than the other groups by the fourth session Over the last three sessions, the control group consumed significantly more water than any of the other groups During sessions 13 and 14, apomorphine groups did not differ from each other, however, 0 05 mg/kg group drank more than the 1 0 mg/kg group on session 15

It has been known for some time that a limiting condition on the induction of SIP is the length of the interpellet interval (IPI) If the IPI is either too short or too long, SIP will not be generated [11, 12, 15] While the IPI was not directly recorded in this study, it was possible to calculate an average value for each of the groups by dividing the session length by the number of pellets earned Since the analysis of variance for number of pellets earned revealed only a significant main effect, the average number of reinforcers which were delivered over the 15 sessions was used to calculate the average IPI for each group For the control group an average IPI of 63 seconds was found while the 0 05 mg/kg group had a mean IPI of 64 seconds The 0 50 mg/kg group had an average of 79 seconds and the 1 0 mg/kg group produced a mean of 143 seconds Thus, all IPI values are within the range of intervals which generate a high, near maximal rate of drinking [11,15]

During baseline sessions, the control group drank 2 5 ml while the 0 05, 0 50, and 1 0 mg/kg groups averaged 2 1, 2 5, and 1 9 ml of water consumed respectively By the fifteenth session, the 0 05 mg/kg group was drinking 3 4 ml, or only 1 3 ml over its baseline intake, while the 0 50 mg/kg group remained at its baseline intake While it is possible that the 0 05 mg/kg group was starting to acquire SIP, as evidenced by the increasing trends in the drinking measures (Fig 2), the development of the behavior was severely delayed and retarded

DISCUSSION

All three doses of apomorphine affected at least one measure of operant bar-pressing and effectively blocked the acquisition of SIP While the doses of 0 50 and 1 0 mg/kg were found to suppress the bar-press rates, the dose of 0 05 mg/kg did not However, the temporal pattern of operant responding was affected by the 0 05 mg/kg dose as revealed by the decreased index of curvature compared to that of the control group Thus, these doses of apomorphine produced behavioral effects which were general in nature, i e , not specific to SIP

By visually comparing the effects of each of the doses of apomorphine on bar-pressing and the acquisition of SIP (Figs 1 and 2), it is apparent that apomorphine did have a greater effect on SIP than on operant responding. However, the first drug administration occurred on the first SIP acquisition session Therefore, the subjects had not had an opportunity to establish this behavior before they were exposed to the pharmacological actions of the drug From inspection of the lower graph of Fig 1 it can be seen that bar-pressing, while not stabilized by the first acquisition session, was relatively well established in the control and 0 05 mg/kg groups and, by inference, in the groups which received the higher doses of apomorphine Thus, the appearance of a greater effect of apomorphine on SIP than on lever pressing is most likely the result of the different levels to which the behaviors had been established at the time that drug administration began

Porter *et al* [26], reported that the dopamine antagonists, pimozide and spiperone, blocked the acquisition of SIP in their subjects, but did not affect operant bar-pressing The

authors offered two possible explanations for the lack of a drug effect on the subjects' bar-pressing behavior One is that, because they used a relatively short pre-session injection time (one hour), the drugs had not exerted their peak behavioral action during the time the subjects were engaged in bar-pressing Another factor the authors felt might have contributed to the lack of effect was that the subjects were engaged in both a schedule-controlled and a schedule-induced behavior during these sessions (although they report that SIP did not develop) However, as in the present study, the bar-pressing behavior of the subjects in the Porter *et al* [26] study would have been relatively well established at the onset of the acquisition sessions It may well be then, that the selective suppression of SIP that they reported was not due to the effects of the drugs per se, but rather to the differing levels to which the behaviors had been established prior to drug administration It may also be, as with the dose of 0 05 mg/kg of apomorphine in the present study, that while the rate of bar-pressing was not affected, the temporal pattern of responding was altered Because only response rates were reported, the question is moot

The effects of lesions of the nucleus accumbens also had selective effects on the development of SIP in that neither deprivation-induced drinking [29] nor daily food or water intake was disrupted Robbins and Koob [29] concluded that 6-OHDA lesions of the nucleus accumbens result in "reduced motivational excitement" and that it was this lesion effect which resulted in the suppression of SIP (p 411) However, Wallace, Singer, Finlay and Gibson [39] concluded that 6-OHDA nucleus accumbens lesions did not affect food motivation in their subjects, but produced an effect which was specific to the development of SIP

It may also be, however, that a factor in the suppression of SIP was that the behavior was not acquired until after the lesions were produced In other words, the behavioral effect of dopaminergic disturbance may be general and the selective effect on SIP was observed because it was the only untrained behavior tested In support of this hypothesis, Robbins, Roberts and Koob [30] later reported that 6-OHDA nucleus accumbens lesions do not suppress established SIP, but do alter the temporal pattern of the behavior as well as producing an alteration in the temporal pattern of operant bar-pressing Concerning SIP the authors state, "Evidently, prior establishment of this response protects it somewhat from the disruptive effects of 6-OHDA lesions to the N Acc " (p 670)

Also, recent evidence from this laboratory has shown that administration of apomorphine, at doses higher than 0 10 mg/kg, and haloperidol, a dopamine antagonist, affect established SIP, operant bar-pressing and deprivation-induced drinking in rats at approximately the same dose level [34] Thus, when SIP is well established there is no evidence that it is more sensitive to pharmacological disruption of the dopamine system than are other behaviors

It should also be noted that d-amphetamine, at the dose of 1 0 mg/kg, has been reported to suppress the acquisition of SIP, but not to affect SIP when it is established [42]. Other manipulations, such as water pre-loading [7, 21, 27] and conditioned taste aversion [28] have been shown to produce suppression of the acquisition of SIP, but not to affect established SIP

That SIP is more easily disrupted during development than during stable state may be because the acquisition of the behavior is dependent upon different biochemical actions and/or different anatomical locations than is the fully developed behavior However, it would seem that the differential sensitivity that developing SIP has been shown to have for a number of manipulations, as compared to established SIP, simply reflects the general finding that any behavior which is not well established is more easily disrupted than one which is

The major findings of this study were that both over- and under-activation of the dopamine system suppressed the acquisition of SIP in rats and also influenced bar-pressing maintained on a FI 60-second schedule of reinforcement It may be that the reduction in number of pellets earned by the 1 0 mg/kg group played some role in the suppression of SIP for this group However, in a previous study [34], robust SIP developed in rats which earned only 12 food pellets per session while bar-pressing on a fixed interval 240-second schedule of reinforcement In the present study, it was observed that the doses of 0.50 and 1 0 mg/kg of apomorphine produced stereotyped head weaving and sniffing in the subjects It seems probable, as was suggested previously [34], that these stereotyped behaviors interfered with the ability of the subjects to bar-press and also with their ability to drink Stereotopies were not observed, however, in the subjects which received the dose of 0 05 mg/kg of apomorphine, thus stereotypics are not the sole cause of disruption.

The results of this study support the notion that a normally functioning dopamine system is necessary for the development of SIP However, the results are in disagreement with the notion that dopaminergic disruption produces a selective effect on SIP The conclusions reached from these results, and other evidence presented above, is that dopaminergic over- or under-activation is translated to disruption of ongoing behavior and that no one form or type of behavior is exclusively sensitive to this disruption More likely, behavioral disruption is inversely related to the amount of pretraining of the behavior Further evidence pertaining to this hypothesis could be obtained by determining if the acquisition of bar-pressing for food or water, or the acquisition of other learned behaviors, is similarly disrupted at doses of dopamine agents which suppress the acquisition of SIP The research is presently being conducted

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