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# Effect of Dopamine Agents on Schedule- and Deprivation-Induced Drinking in Rats

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SNODGRASS, S H AND J D ALLEN *Effect of dopamine agents on schedule- and deprivation-induced drinking in rats* PHARMACOL BIOCHEM BEHAV **27**(3) 463–475, 1987 —The dopamine agonist, apomorphine, or its antagonist, haloperidol, was administered to rats whose drinking was induced by fixed-interval schedules of pellet delivery or by water deprivation The first study revealed that both drugs produced dose-dependent decreases in bar-pressing and schedule-induced polydipsia (SIP) At higher doses, haloperidol also depressed the rate of pellet delivery The second study demonstrated that the suppression in SIP obtained in the first study was primarily due to the direct effect of the drugs and not to changes they produced on the underlying food reinforcement schedule The third study showed that both drugs suppressed water deprivation-induced drinking during a ten-minute session Apomorphine delayed the onset of drinking, while haloperidol accelerated the cessation of drinking The results indicated that apomorphine produced motor deficits that interfered with consummatory behavior, and that haloperidol interfered with the sensory feedback necessary to sustain consummatory behavior

Schedule-induced polydipsia Deprivation-induced drinking Dopamine Haloperidol Apomorphine Operant bar-pressing Rats

SCHEDULE-INDUCED polydipsia (SIP) occurs when a food-deprived animal is allowed free access to water while receiving small allotments of food on an intermittent basis [11,13] Typically, drinking behavior is initiated immediately after the subject ingests the food reinforcer, reaches its peak early in the inter-pellet interval and gradually decreases to the end of the interval [13] Large amounts of water are consumed by subjects exposed to the above conditions even though they are not experiencing any known type of fluid deficit or physiological imbalance [13,14]

While the reasons for the occurrence of SIP are still unclear, there has been some recent evidence linking the central dopamine system to the generation and maintenance of adjunctive behavior Specifically, it has been reported that 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens attenuates the development of SIP while not affecting deprivation-induced drinking [29,35] It has also been reported that 6-OHDA lesions of the nucleus accumbens, while not depressing the overall amount of established SIP, does alter its temporal patterning The high rates of licking which occur immediately post-pellet are reduced, while the lower rates of licking which occur further into the inter-pellet interval are increased [30] However, the effect of this lesion was not specific to SIP in that the high rates of operant responding which occur near the end of a fixed-interval 60-second schedule of reinforcement were also reduced

Pharmacological manipulation of the dopamine system has also been reported to influence the production of SIP by rats The indirect dopamine agonist d-amphetamine blocks both the acquisition of SIP [40] and suppresses established SIP [23, 24, 30, 31, 37], as does the direct dopamine agonist apomorphine [30] Administration of the dopamine antagonists, chlorpromazine [3,23] and haloperidol [20,21], produces suppression of established SIP, while it has been reported that the dopamine antagonists, pimozide and spiperone, block the acquisition of this behavior without affecting operant bar-pressing or deprivation-induced drinking [28]

From the above reports it is clear that drug- or lesion-produced changes in the activity of the dopamine system affect the production and maintenance of SIP What is not clear is whether SIP is more sensitive to dopaminergic disruption than goal-oriented behaviors, such as drinking when water deprived or bar-pressing for food It appears, from the studies cited above, that the acquisition of SIP can be suppressed by manipulation of the dopamine system without goal oriented behaviors being similarly affected [28, 29, 35] However, as noted above, alterations of this neurotransmitter system have been reported to influence both established adjunctive drinking and goal oriented behaviors

There are several possible explanations for this discrepancy One is that there is a level of disruption of the dopamine system which interferes with the acquisition of all behaviors, not just SIP, while not affecting their mainte-

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nance Another possibility is that, unlike goal oriented behaviors, adjunctive drinking arises specifically from activity of the dopamine system and is therefore more sensitive to disruptions within the system Thus, it is possible that the doses of the dopamine agonists and antagonists used in previous studies were not appropriate to produce a selective suppression of established SIP The research reported here is primarily concerned with this latter possibility The first study determined whether established SIP is more sensitive to dopaminergic disruption than operant bar-pressing by establishing the dose-response effect for the dopamine agonist, apomorphine and the antagonist, haloperidol The second study determined the influence of drug-produced changes in reinforcer density on SIP, while the third study investigated the effects of apomorphine and haloperidol on deprivation-induced drinking in rats

## EXPERIMENT 1

The purpose of this study was to provide a detailed analysis of the effects of a dopamine antagonist and agonist on operant bar-pressing and on established SIP Haloperidol was chosen as the antagonist because of its pharmacological specificity for the dopamine receptor [4, 5, 32], and apomorphine was chosen as the agonist because of its direct effect on these receptors [6, 10, 32] A wide range of doses for both drugs was used in order to maximize the possibility of observing selective drug effects on SIP

As was previously mentioned, SIP typically occurs as an immediately post-pellet phenomenon [13,14] However, it has been reported that increasing the inter-pellet interval produces an increase in the amount of time from ingestion of the food reinforcer until the initiation of SIP by the organism [33] Therefore, a relatively long fixed-interval value was used so that the peak in the temporal pattern of licking would be shifted towards the mid-portion of the inter-pellet interval It was thought that because 6-OHDA lesions of the dopamine rich nucleus accumbens produced alterations in the temporal patterning of both SIP and operant bar-pressing [30] that more general alterations of the dopaminergic system might similarly produce temporal changes in these behaviors Having drinking behavior located more centrally in the interval would thus facilitate the detection of drug produced shifts in this peak

### METHOD

*Subjects*

Fourteen male Long-Evans hooded rats were obtained from the University of Georgia breeding colony and were approximately 90 days of age at the start of the experiment They were reduced to, and maintained at, 80% of their free-feeding weight for the duration of the study The subjects were individually caged and were housed in a colony room with a 12-hr light-dark cycle (8 00 a m to 8 00 p m light period) in effect Animals had continuous access to water

*Apparatus*

Sessions were conducted in Lehigh Valley Electronics (Model 1714) operant conditioning chambers, 30×25×28 cm in diameter, with sound attenuating cubicles In each of the two chambers a lever was mounted on the front wall 3 cm from the left wall of the chamber and 4 cm above the floor Standard formula 45 mg Noyes food pellets were delivered by a Ralph Gerbrands pellet dispenser to the food magazine which was located in the center of the front wall Water was available through a drinking tube which was recessed behind 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 Licks at the tube were recorded with Grason-Stadler drinkometers The drinking tube was connected to a 100 ml graduated cylinder through which the amount of water consumed by the subject was measured

A PET/CBM 4032 microcomputer was used to program the behavioral contingencies and record the licking and bar-pressing behavior of the subjects

*Procedure*

The 14 subjects were randomly assigned to two groups of seven subjects each They were trained to bar press for the food reinforcer using a fixed-interval one-second schedule of reinforcement (FI 1-sec) in which the first bar-press after one second had elapsed since the last reinforcer delivery produced the reinforcer This baseline condition lasted for five sessions during which the subjects could acquire a total of 12 reinforcers per session Twelve was the total number of reinforcers that the subjects would be able to earn during control and test sessions, and the amount of water consumed during these five sessions was used to calculate the baseline amount of consumption for each subject

After the baseline sessions, the FI value was gradually increased to FI 240-sec by the following stages 15, 60, 120, 180 and 240-sec Each subject remained at each FI value for three sessions before it was shifted to a longer interval The terminal FI 240-sec schedule was chosen so as to maximize the possibility of observing shifts in either direction of the temporal location of SIP

All training and test sessions lasted 47 minutes or until 12 pellets were delivered The first pellet was delivered non-contingently at the beginning of each session Each subject received one session daily, seven days a week Water was available in the chamber at all times

After 54 sessions of the FI 240-sec schedule, the bar-pressing and drinking behavior of all the subjects was considered stable and the drug testing procedure was begun For all non-drug sessions, i e , control sessions, subjects received a vehicle injection, and the session which preceded a drug-injection session served as the control for that subsequent drug session Each drug session was followed by control sessions until the subjects' behavior had stabilized, with a minimum of two control sessions separating successive drug sessions A subject's behavior was deemed stable when the level of the behavioral measures, after a drug session, returned to the pre-drug baseline level Also, if there were increasing or decreasing trends in a subject's behavioral measures, control sessions were run until the trend was no longer apparent

To assess for differences in the sensitivity of SIP and operant bar-pressing to each drug, an ascending series of doses followed by a descending series of doses was used For the apomorphine group, the ascending series began with a dose of 0 05 mg/kg with the next dose being 0 10 mg/kg The doses were then successively increased by 0 10 mg/kg until the terminal dose of 1 3 mg/kg was reached The descending series of doses was then begun with the initial dose being 1 1 mg/kg and successive doses being decreased by 0 20 mg/kg until the terminal dose of 0 10 mg/kg was reached

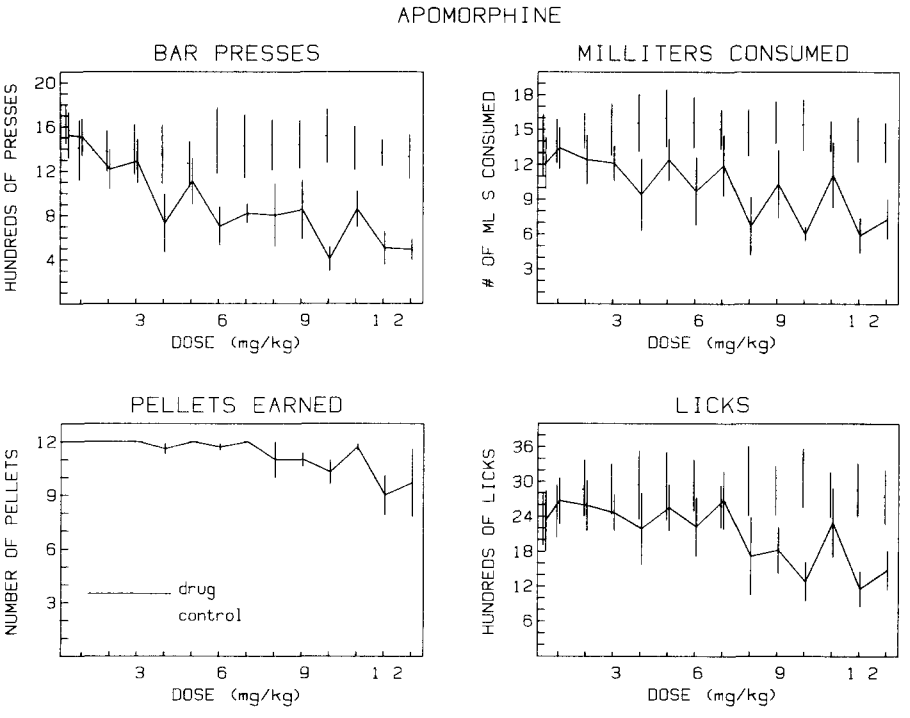


FIG 1 Dose effect curves of the ascending series of apomorphine on bar-pressing, pellets earned, water intake and licking SEMs are depicted by vertical lines

The ascending series of doses of haloperidol was begun with a dose of 0 05 mg/kg and successive doses were raised by 0 05 mg/kg until the terminal dose of 0 35 mg/kg was reached This ascending series of doses produced wide fluctuations in the behavior of the subjects The reason for the behavioral variation was thought to be the precipitation of haloperidol out of the solution To correct for this precipitation, the drug vehicle was altered and the solution containing haloperidol was prepared for each subject immediately before each drug session Control sessions were carried out using the new drug vehicle and when the subjects' behavior was again stabilized, a descending series of doses was begun The initial dose was 0 30 mg/kg and each subsequent dose was decreased by 0 05 mg/kg until the terminal dose of 0 05 mg/kg was reached

The effects of drug administration on the distribution of licks and bar-presses during the inter-pellet interval were assessed by dividing the four-minute interval into 24 discrete time periods of ten seconds each and recording the number of licks and presses per period The recording of behavior into successive time bins allowed for the determination of changes in the temporal distribution of SIP and bar-pressing during the test and control sessions The total number of licks and presses was also recorded The number of bouts, defined as one burst of five or more licks during an interpellet interval, was recorded as well as the number of milliliters of water consumed Milliliters consumed were divided by bouts to provide a measure of bout size during test and control sessions These measures were used to assess the stability of the subjects' behavior The number of food pellets earned by the subjects was also recorded

*Drugs*

The appropriate dose (mg/ml) of apomorphine hydrochloride (Sigma Chemical Co , St Louis, MO) was prepared on the day of administration The solution was administered in a constant volume of one ml/kg Apomorphine was dissolved in a vehicle of distilled water and approximately 1 ml of solution was placed in seven individual containers and stored on dry ice to prevent oxidation of the solution Five minutes prior to the administration of the solution, a container was removed from the dry ice and the solution was thawed The stock apomorphine was continuously stored on dry ice to prevent oxidation of the drug All doses of apomorphine are expressed as the salt

The appropriate dose (mg/ml) of haloperidol free base (McNeil Pharmaceutical, Spring House, PA) was prepared for each subject immediately prior to the subjects' drug session The drug was dissolved in 1 ml of warm lactic acid, mixed with 42 ml of distilled water and buffered to a pH of 4 6 by the addition of 7 ml of a 5% sodium hydroxide solution All doses of haloperidol are expressed as the free base

## RESULTS

As can be seen from Fig 1, the effects of apomorphine were to suppress the output of both SIP and operant barpressing in a dose-dependent manner From inspection of the panels for licks (bottom right), milliliters consumed (top right) and for presses (top left) it can be seen that SIP and barpressing were affected at approximately the same dose of the drug There were no consistent drug effects on the temporal pattern of SIP As a measure of drug effects on the scalloped

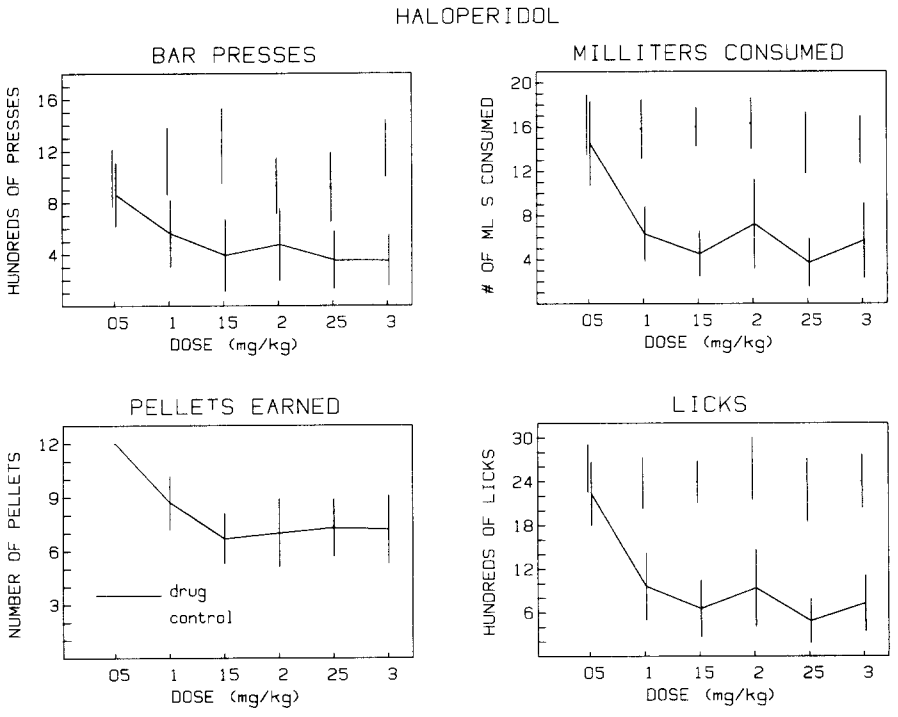


FIG 2 Dose effect curves of the descending series of haloperidol on bar-pressing, pellets earned, water intake and licking SEMs are depicted by vertical lines

pattern of responding of the subjects, an index of curvature [18] was calculated for the control and drug sessions It was found that apomorphine administration did not produce any systematic effects on the pattern of bar-pressing by the subjects The average index of curvature value was 0 47 for the control sessions and the low and high values for drug sessions were 0 37 and 0 57, respectively

A one-way repeated measures analysis of variance was performed for each of the dependent measures and, if a statistically significant effect was found, a Dunnett test was used to locate the doses of the drug which produced this effect It was found that at doses of 1 mg/kg and above licks were significantly depressed below control levels, $F(14,84)=3\ 59$, $p<0\ 001$ Presses were also found to be affected, $F(14,84)=6\ 66$, $p<0\ 05$, at doses of 0 40 mg/kg and above Although the overall analysis for bouts was significant, $F(14,84)=2\ 59$, $p<0\ 01$, the Dunnett test did not reveal any specific differences Milliliters consumed and milliliters consumed per bout were both found to be significantly affected by apomorphine, $F(14,84)=3\ 23$, $p<0\ 001$ and $F(14,84)=3\ 50$, $p<0\ 001$, respectively Milliliters consumed dropped below control levels at doses of 0 80 mg/kg and above, while milliliters consumed per bout were suppressed at doses of 0 40 mg/kg and above The number of pellets earned by the subjects was significantly affected by the administration of this drug, $F(14,84)=5\ 80$, $p<0\ 001$, however, the Dunnett test did not reveal any specific differences The descending doses of apomorphine produced a systematic dose-response relationship that was highly comparable to that of the ascending series

Figure 2 depicts the descending series of doses of haloperidol It should be noted that because subject Hal-4 failed to develop SIP his data were not included in any of the graphs or analyses From Fig 2 it can be seen that this drug produced a dose-dependent decrease in each of the dependent measures The licking behavior of the subjects was decreased, $F(6,30)=6\ 49$, $p<0\ 001$, at all doses above 0 05 mg/kg Bouts were significantly depressed, $F(6,30)=6\ 04$, $p<0\ 001$, again with all doses above 0 05 mg/kg producing a decrease The reductions in milliliters consumed and the number of milliliters consumed per bout were also found to be significant, $F(6,30)=4\ 07$, $p<0\ 01$ and $F(6,30)=2\ 79$, $p<0\ 05$, respectively All doses were found to decrease the number of milliliters consumed except 0 05 and 0 20 mg/kg For the number of milliliters consumed per bout the doses which produced a decrease were 0 25 and 0 30 mg/kg Even though bar-press rates are seen to be diverging at higher doses, the analysis of variance did not reveal a significant difference for this measure, $F(6,30)=2\ 18$, $p>0\ 05$ The number of food pellets earned by the subjects was found to be significantly depressed by this drug, $F(6,30)=2\ 64$, $p<0\ 05$

The effect of haloperidol on SIP was typically to reduce its level of occurrence without producing a shift in its temporal pattern Although this was typically the case, there were instances when SIP was shifted to, or restricted to, the latter part of the inter-pellet interval Also, at higher doses, haloperidol produced a disruption in bar-pressing for most subjects The index of curvature for the control sessions was 0 44 and for the dose of 0 05 mg/kg it was 0 39 At higher doses many of the subjects failed to emit over 100 responses during the sessions, rendering the index of curvature analysis meaningless

## DISCUSSION

The effect of apomorphine was to dose-dependently suppress SIP and bar-pressing by the subjects There was no

evidence that this drug, at any dose, selectively affected SIP However, because SIP is generated by the subject's ingestion of the food reinforcer, it is possible that the suppression of this behavior was at least partially caused by the drug-produced decrease in the number of food pellets which were earned While a decrease in reinforcer density may have contributed to the suppression of SIP, it can be seen from inspection of Fig 1 that SIP was suppressed at doses that produced only a slight decrease in the number of pellets earned by the subjects Therefore, it is not likely that suppression of drinking was caused solely by a decrease in reinforcer density

Haloperidol administration also reduced the number of pellets earned by the subjects (Fig 2, lower left) Since SIP is influenced by the rate of food delivery [12,16], a decrease of one third or more in the number of food pellets earned by the subjects, as occurred with this drug, would normally produce large reductions in drinking Thus, it is difficult to determine what proportion of the suppression of SIP was caused by the pharmacological effect of the drug and what proportion was due to drug-produced changes in reinforcer density

Rate of bar-pressing was not found to be significantly affected by haloperidol While this result supports the possibility that haloperidol selectively affected SIP, such a conclusion would seem to be premature for two reasons The first, which was discussed above, is that the suppression of SIP may have been due to the decrease in food pellets earned by the subjects and not a direct drug effect The second is that while the suppression of bar-pressing seen after haloperidol administration (Fig 2, top left) may indeed be due to chance fluctuations, it is also possible that some factor caused large between-subject variability in response rates which masked the depressant effect of this drug An inconsistent drug vehicle and/or the short pre-session injection time may have produced this variability That even the highest dose of haloperidol did not reliably suppress bar-pressing lends support to this possibility, since it is well known that the neuroleptics depress the output of this behavior [2, 7, 15, 38]

It will be recalled that a four-minute fixed-interval was used so that the peak in drinking would occur towards the middle of the inter-pellet interval However, the peak in drinking occurred within the early portion of the inter-pellet interval, which is in contradiction to the results of Segal, Oden and Deadwyler [33] They reported that the peak in drinking was a function of the length of the inter-pellet interval One possible explanation for the differing results of these two studies is that Segal *et al* used response-independent fixed-time (FT) schedules of reinforcer delivery while the schedule used in this study was a response-dependent fixed-interval Therefore, operant responding may have limited the occurrence of SIP to the initial part of the inter-pellet interval

Because the peak in SIP occurred in the early portion of the inter-pellet interval it was difficult to discern shifts to the left in the peak of drinking It appears unlikely, however, that a shift to the left occurred Typically, both drugs decreased SIP without any consistent alterations in the peak of the temporal pattern of the behavior

To further investigate the effects of haloperidol on bar-pressing and also to separate the pharmacological actions of the drugs on SIP from the effects of decreased reinforcer density, a second study was conducted using subjects as their own "yoked-controls"

## EXPERIMENT 2

The purpose of this study was to partial out the effects on SIP that are attributable to the direct pharmacological actions of the drugs from those effects that are due to drug-produced changes in reinforcer density For each drug session of this study, the elapsed time between successively earned food pellets was recorded This modified schedule of reinforcement was then played back to the subject during a non-drug session In this manner, each subject served as its own yoked-control Thus, the extent to which suppression of SIP resulted from decreased reinforcer density alone could be determined by comparing the subjects' behavior between the yoked and control sessions, whereas the amount of suppression resulting from the pharmacological action alone could be analysed by comparing behavior between yoked and drug sessions

### METHOD

*Subjects*

Four male Long-Evans hooded rats, obtained from the University of Georgia Breeding Colony, served as subjects The rats were approximately 100 days old at the beginning of the study Housing and feeding conditions were the same as in experiment one

*Procedure*

Ad lib weights were recorded for five days and then the subjects were gradually reduced over a seven-day period to 80% of this weight The subjects were then exposed to a continuous reinforcement schedule for five days, one hour per day Forty Noyes 45 mg food pellets could be earned during this hour and on the last three days of this condition water intake was measured for each subject to provide a baseline measure of drinking After baseline water intake had been recorded, the subjects were exposed to increasing FI schedule values, two one-hour sessions for each value, until the terminal FI value of 90 seconds was reached The subjects were exposed to 28 sessions on the FI 90-sec schedule, at which time their behavior had stabilized and testing was begun Two rats received doses of apomorphine and the other two received doses of haloperidol Each drug session was preceded by a vehicle control session and followed by a yoked-control session The yoked session was separated from its drug session by two or more sessions, depending on the stability of the subject's behavior At least two sessions separated the yoked session from the next vehicle control session, again depending on the stability of the behavior During yoked sessions the drug vehicle was not administered to the subject

A SYM-1 microcomputer was networked with a PET/CBM 4032 microcomputer [1] in order to control the behavioral contingencies and record the data from two identical operant chambers During drug sessions, the computer recorded the inter-pellet interval associated with each pellet delivery into sequential memory locations For each yoked session, the sequentially ordered inter-pellet intervals of the preceding drug session determined when reinforcers for bar-pressing became available to the subject Therefore, a subject was exposed to the same schedule conditions that had occurred during the directly preceding drug session

As in the first experiment, the subject's licking and bar-pressing behavior was recorded in 10-second bins to permit the examination of their temporal patterns The total number

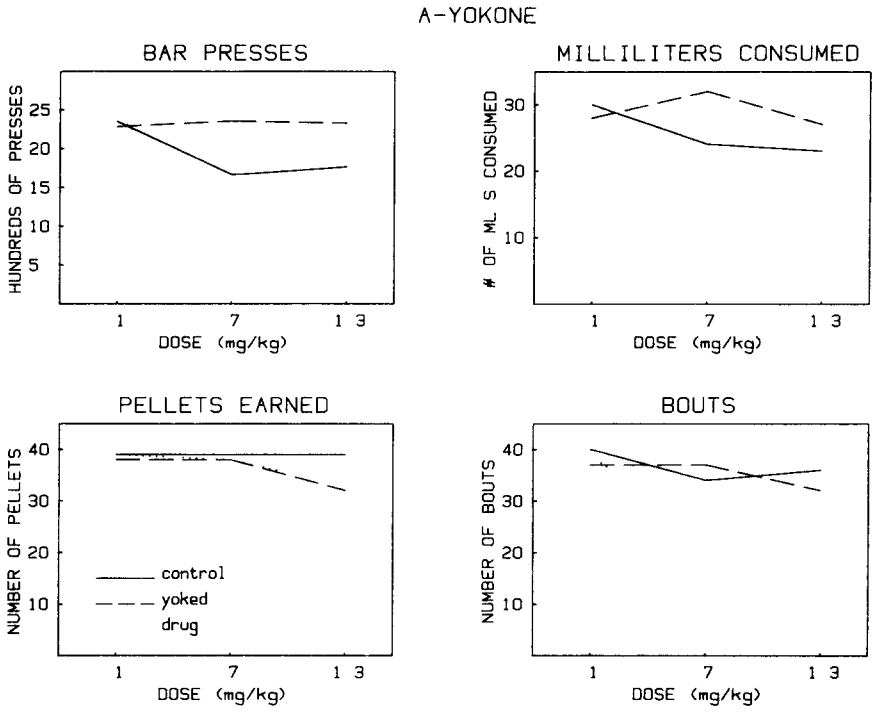


FIG 3 Bar press, pellet delivery and drinking rates for A-Yokone during apomorphine-administered, yoked and control sessions

of licks, bar-presses, bouts and milliliters consumed was also recorded Sessions were conducted six days per week, one hour per day

All drugs and vehicles were administered by IP injections Two rats received three dose levels of apomorphine, which were injected 15 minutes pre-session The commercially available form of apomorphine hydrochloride (Eli Lilly and Company) was used in this study and was dissolved in distilled water The vehicle alone was used for control injections Three doses of apomorphine, 0 10, 0 70 and 1 3 mg/kg, were selected from the first study's dose-effect function to produce light, medium, and heavy suppression of lever pressing behavior The doses were administered in counterbalanced order across subjects Using the same logic, two other rats received the following doses of haloperidol 0 1, 0 2, and 0 3 mg/kg Haloperidol free base (McNeil Pharmaceuticals) was crushed and then suspended in a solution of three to four drops of Tween 80 (Sigma Chemical Corporation) per 10 milliliters of distilled water This vehicle was also used for control sessions Because it is known that the behavioral effects of haloperidol peak approximately one hour after systemic administration [19], a pre-session injection time of 30 minutes was used so that the peak effect would occur near the mid-point of the session

## RESULTS

The effects of apomorphine were quite similar for both subjects, so that only the behavior of A-Yokone is depicted in Figs 3 and 4 As can be seen in Fig 3, apomorphine produced dose-dependent decreases in water intake and rate of bar-pressing while producing only slight decreases in pellets earned Inspection of the upper and lower panels reveals that the subject earned most of the scheduled pellets during the drug sessions even though its bar-pressing rates were greatly reduced compared to control values It can also be seen that drinking and bar-pressing rates were comparable during yoked and control sessions

Figure 4 illustrates the effects of apomorphine administration on the temporal pattern of behavior of A-Yokone The temporal patterns of licking and pressing were comparable for the yoked and control sessions However, beginning with the dose of 0 70 mg/kg a flattening of the temporal pattern of drinking occurred compared to that produced during yoked and control sessions As in the first study, the index of curvature analysis did not reveal any systematic dose effects on the temporal pattern of bar-pressing The control indices ranged from 0 61 to 0 68, and indices for the drug sessions ranged from 0 54 to 0 66

Haloperidol also produced similar effects on the behavior of its subjects so only the behavior of H-Yokone is illustrated in the following figures From Fig 5 it can be seen that haloperidol produced dose-dependent decreases in both SIP and bar-pressing Unlike the results obtained with apomorphine, a decrease in bar-pressing was accompanied by a substantial decrease in the number of pellets earned by the subject Also, during yoked sessions, decreases in water intake and bouts paralleled decreases in pellet delivery rate

If the difference in pellets delivered is taken into account by expressing drinking and pressing measures as ratios of the number of pellets earned, then Fig 6 shows that haloperidol produced suppression of pressing and drinking over and above the effects produced by the reduction in pellet delivery rate On a pellet by pellet basis the behavioral output of the subject during yoked sessions was equal to or greater than that during the respective control session, whereas it was usually below the control rate during drug sessions

Figure 7 depicts the effects of haloperidol on the temporal

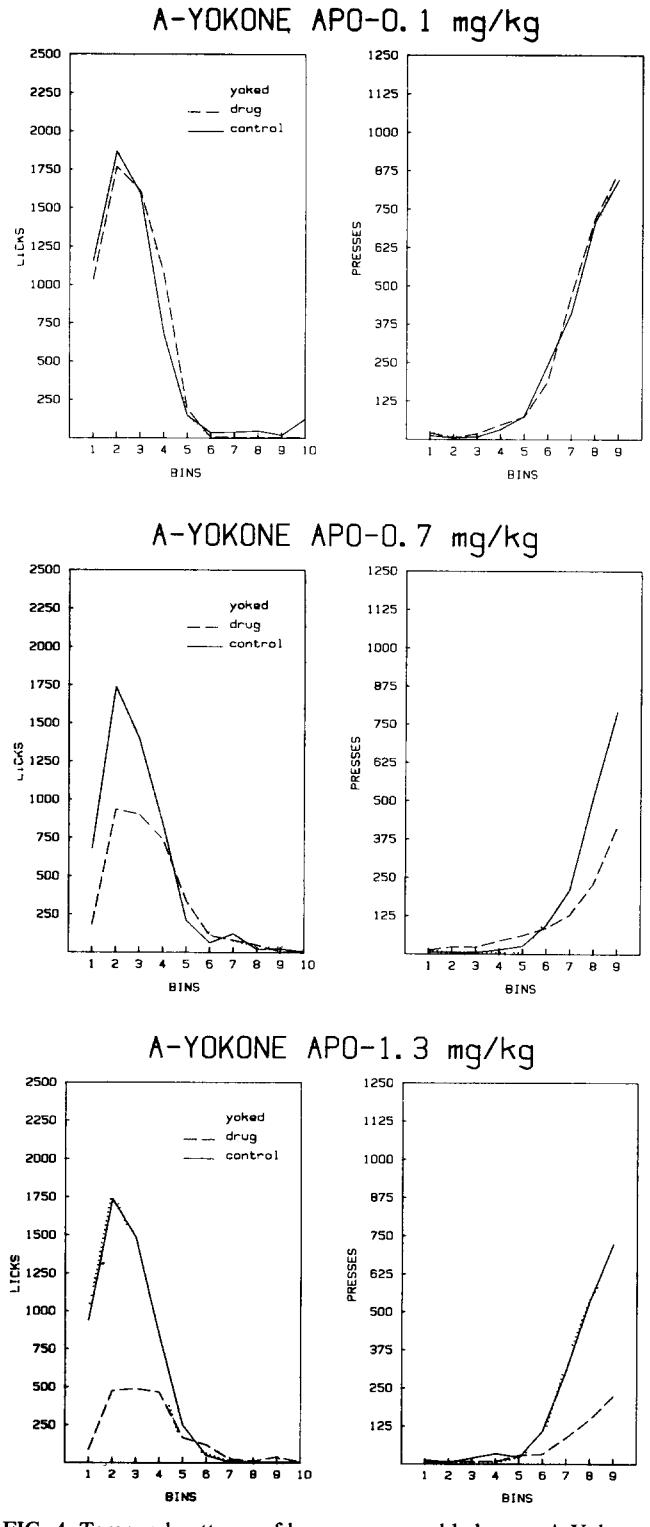


FIG 4 Temporal patterns of bar-pressing and licking in A-Yokone during apomorphine-administered, yoked and control sessions

pattern of SIP and operant bar-pressing for H-Yokone It can be seen that at doses of 0 20 and 0 30 mg/kg the licking behavior of the subject was severely depressed during drug sessions, but that the temporal pattern of licking remained comparable to that which occurred during the control and yoked conditions These doses of haloperidol also resulted in suppression of bar-pressing, which can be seen in the right hand panels of this figure As in the first experiment, response suppression was so severe that quantitative measures of drug effects on temporal patterning are not applicable

## DISCUSSION

For the most part, the results of experiment 2 replicated those of experiment 1 Experiment 2 also provided evidence that the administration of both apomorphine and haloperidol had direct depressant effects on SIP which were separate from any effects produced by disruption of the schedule of reinforcement For apomorphine, the parity in performance during the yoked and control sessions was due to the fact that the subjects earned all, or almost all, of their assigned reinforcers during the drug sessions

Apomorphine caused a flattening of the temporal pattern of licking at the doses of 0 70 and 1 3 mg/kg This pattern of licking was not evident in the first study A possible reason for the difference may be apomorphine's short duration of action [17] The longer session length of the present study, compared to that of the first study (60 versus 45 min), may have allowed drinking to emerge during the latter part of the session The emergent drinking would be temporally post-pellet, but due to a drug-produced ceiling on lick rate, drinking would continue longer into the interval, thus flattening the temporal function

Haloperidol, on the other hand, suppressed the occurrence of SIP without affecting its temporal patterning At the higher doses, SIP disruption was partly caused by severe depression in bar-pressing and concomitant depression in pellet delivery rate Effects which, due possibly to an inconsistent drug vehicle, were not statistically reliable in experiment 1 However, when drinking measures are assessed on a per pellet basis, as depicted in Fig 6, the SIP depressing effects due to the drug itself are clearly evident

## EXPERIMENT 3

The purpose of this experiment was to determine the effects of haloperidol and apomorphine on deprivation-induced drinking by rats It has been reported that the administration of the dopamine antagonists, pimozide and spiperone, block the acquisition of SIP without affecting operant bar-pressing or deprivation-induced drinking [28] However, the results of the preceding experiments have shown that bar-pressing for food is no less sensitive to the effects of dopaminergic disruption than established SIP It therefore seemed possible that drinking induced by water deprivation would be similarly affected at doses of apomorphine and haloperidol which suppressed established adjunctive drinking

It has been hypothesized that haloperidol, like other dopamine blockers, suppresses behavior by decreasing the motivational impact of reinforcing stimuli [38,39] To assess for this possibility, the temporal pattern of licking was recorded during control and drug conditions, and rats were tested at different levels of water deprivation By comparing the pattern of licking established during drug administration to that obtained at differing deprivation levels, it would be

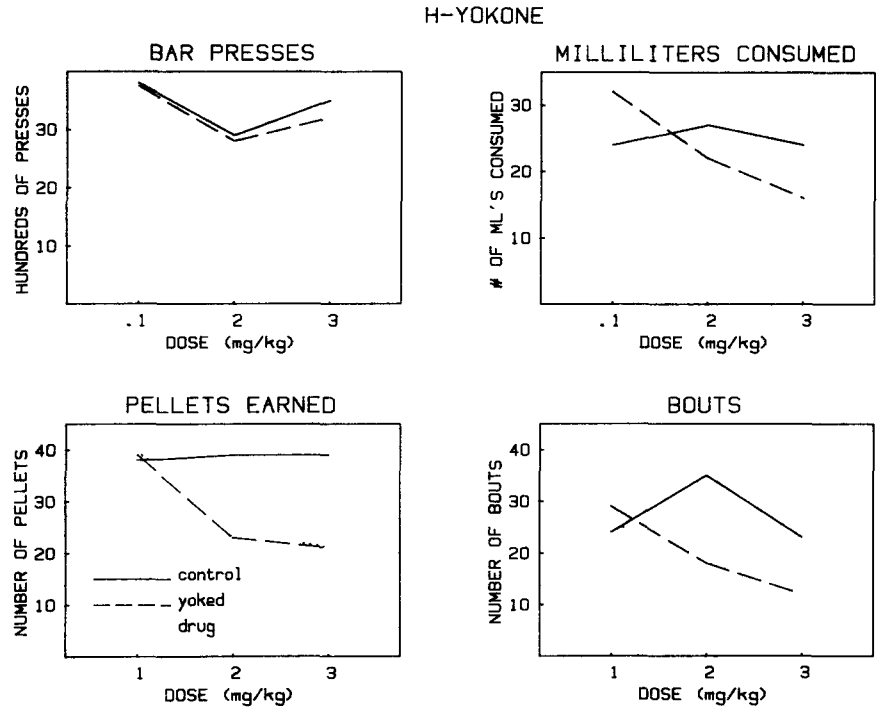


FIG 5 Bar press, pellet delivery, and drinking rates for H-Yokone during haloperidol-administered, yoked and control sessions

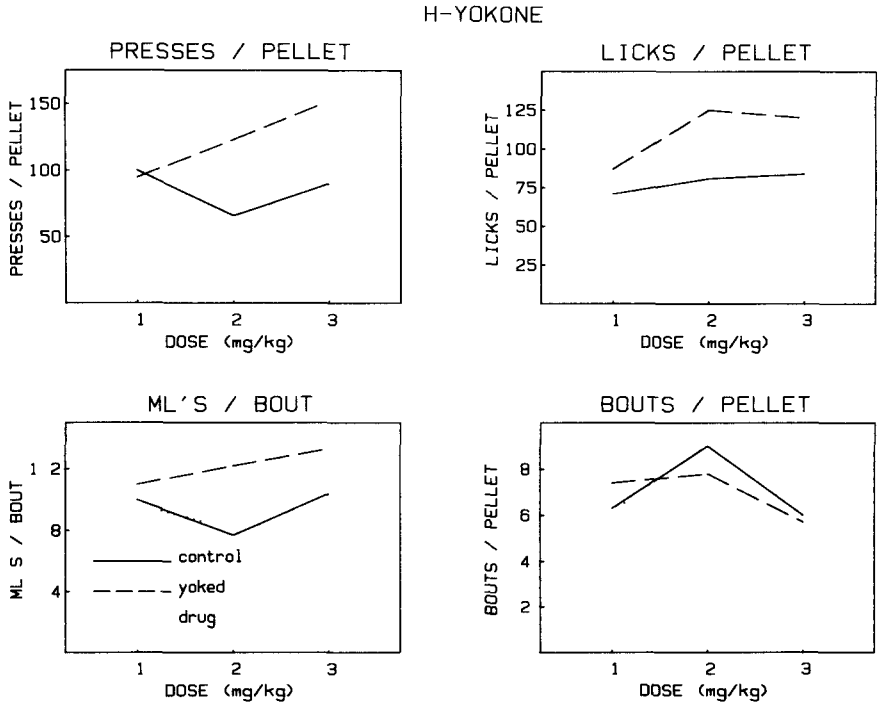


FIG 6 Presses, licks, and bouts per pellet and MLs per bout for H-Yokone during haloperidol-administered, yoked and control sessions

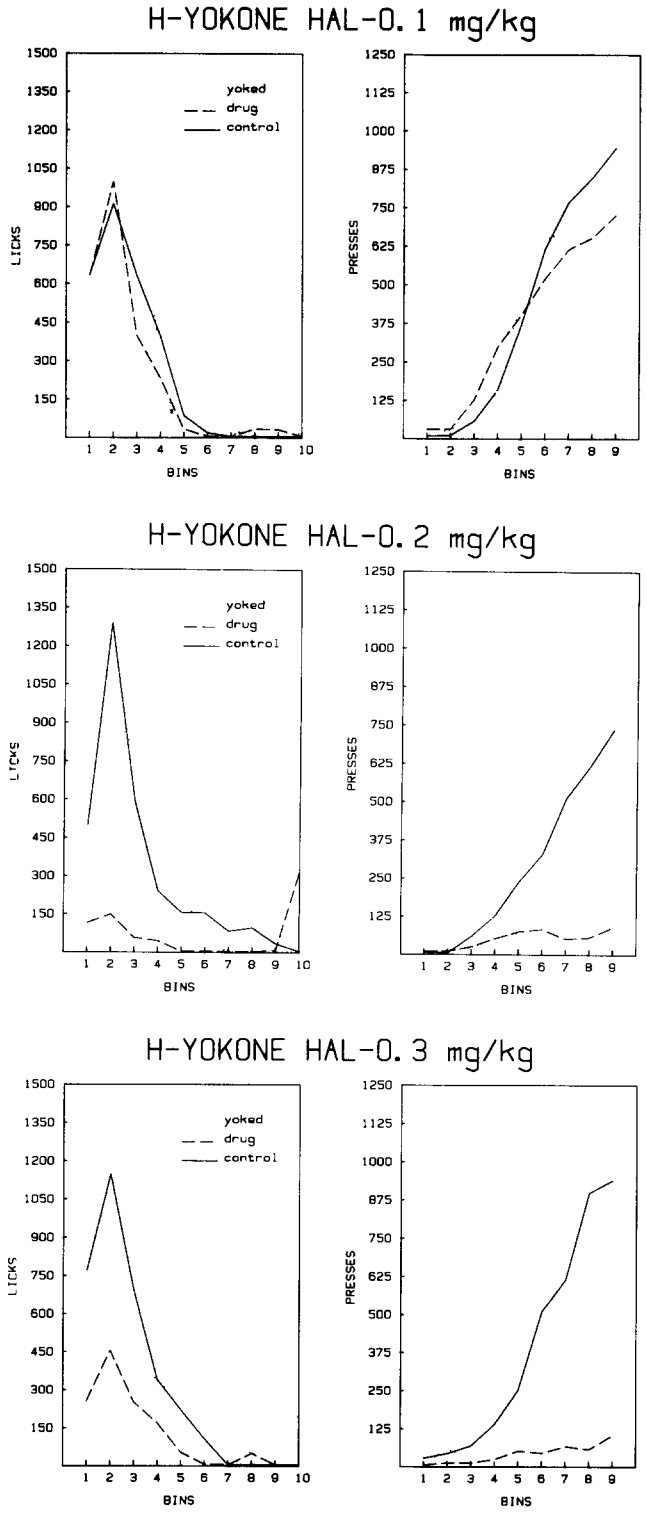


FIG 7 Temporal patterns of bar-pressing and licking in H-Yokone during haloperidol-administered, yoked and control sessions

possible to determine if apomorphine and/or haloperidol produced their effects by a mechanism comparable to decreasing the motivation for water

## METHOD

### *Subjects*

Six male Long-Evans hooded rats, approximately 100 days of age, were obtained from the University of Georgia breeding colony and served as subjects Housing conditions were the same as in the previous experiments

### *Procedure*

The subjects were allowed ad lib access to food and water for one week and during this time were handled and weighed daily On the eighth day the water bottles were removed from the subjects' cages and a 23 hour and 50 minute water deprivation schedule was initiated The subjects continued to have ad lib access to food in the home cage throughout the study

On the ninth day each subject was allowed 10 minutes access to water in one of four identical Lehigh Valley Electronics (Model 1714) operant conditioning chambers, two of which had been used in the previous studies Each contained a lever and a food cup, but food was never present in the chamber and lever presses had no scheduled effect The drinking tube in each chamber was recessed behind a 1 5 cm opening to prevent non-lick contact with the tube The number of licks per 10-sec interval (60 intervals/session) was recorded to provide an analysis of the temporal patterning of licking, and the amount of water consumed per session was recorded for each subject Sessions were conducted six days per week with 10 minutes of water being provided in the home cage on the non-test day Supplemental water was provided immediately after each session so that the weight of the subjects did not fall below 80% ad lib Supplementary water was only necessary for the first two weeks of the deprivation schedule After this time the subjects began gaining weight with 10 minutes daily access to water

The subjects were exposed to 45 sessions in order to assure stability of behavior and drug testing began on session 46 Each drug session was preceded by at least one non-injection session and one control-injection session Three subjects were first exposed to apomorphine while the other three subjects were exposed to haloperidol The doses of apomorphine were 0 10, 0 70 and 1 3 mg/kg while the doses of haloperidol were 0 10, 0 20 and 0 30 mg/kg The doses of the drugs were administered in a counter-balanced order and after the completion of the first series, drug administration was reversed such that the apomorphine treated animals received the doses of haloperidol and vice versa

After completion of the second drug series, a series of sessions was conducted in which hours of water deprivation were systematically varied The subjects were maintained on 10 minutes of water in the home cage for three weeks, except for Friday of each week On Fridays the subjects were allowed 1 hr of access to water in the home cage either 12, 5 or 2 hr prior to being placed in the operant chamber for 10 min access to water In this manner, the temporal pattern of licking at differing levels of water deprivation could be recorded so that a comparison could be made with that obtained while the subjects were experiencing the drugs Two SYM-1 microcomputers which were networked with a PET/CBM 4032 microcomputer [1] were used to control the

TABLE 1

THE NUMBER OF LICKS EMITTED AND MILLILITERS CONSUMED BY WATER DEPRIVED SUBJECTS AFTER VEHICLE, HALOPERIDOL OR APOMORPHINE INJECTIONS

| Haloperidol | | | Apomorphine | | |
|---|---|---|---|---|---|
| Dose mg/kg | Licks | ml | Dose mg/kg | Licks | ml |
| 0 00 | 2251 | 13 6 | 0 00 | 2251 | 13 6 |
| 0 10 | 2035 | 11 8 | 0 10 | 2113 | 12 3 |
| 0 20 | 1512 | 8 2 | 0 70 | 1016 | 5 5 |
| 0 30 | 967 | 4 5 | 1 30 | 251 | 1 2 |

operation of the operant chambers and to record the licking behavior of the subjects

All injections were given IP with apomorphine being injected 15 minutes and haloperidol 45 minutes prior to the session The commercially available form of apomorphine hydrochloride (Eli Lilly and Company) was used in this study The drug vehicle was again distilled water which was also used for the apomorphine control injections The drug vehicle for haloperidol free base (McNeil Pharmaceuticals) was the same as in experiment 2 as was the solution used for control injections

## RESULTS

As can be seen from Table 1, both drugs decreased the number of milliliters consumed and the number of licks emitted by the subjects in a dose-dependent manner

A one-way repeated measures analysis of variance showed that apomorphine significantly decreased the total amount of water consumed by the subjects, $F(3,15)=56\ 783$, $p<0\ 001$, and also the total number of licks emitted by the subjects, $F(3,15)=39\ 544$, $p<0\ 001$ A post hoc Tukey HSD test revealed that the doses of 0 70 and 1 3 mg/kg produced decreases in licks and milliliters consumed that were significantly ($p<0\ 05$) different from each other and also from the doses of 0 10 mg/kg and 0 00 mg/kg The effects of 0 10 mg/kg apomorphine on licks and milliliters consumed did not differ from the control data

For haloperidol, total licks were reduced, $F(3,15)=14\ 028$, $p<0\ 001$, as well as total milliliters consumed, $F(3,15)=34\ 662$, $p<0\ 001$ The dose of 0 20 mg/kg decreased the number of licks compared to the control value as did the dose of 0 30 mg/kg, which also produced a decrease in licks compared to the dose of 0 10 mg/kg No other comparisons were significant For milliliters consumed all comparisons, with the exception of the comaprison of the effects of 0 10 mg/kg and vehicle control, were significant

Inspection of the top two panels of Fig 8 reveals that both apomorphine and haloperidol affected the temporal patterning of licking of the subjects, but in different ways At higher doses, apomorphine (top panel) suppressed drinking at the beginning of each session, with the degree of recovery of drinking during the session being inversely related to dose Haloperidol (middle panel) did not affect drinking in the first minute of the access period at any dose However, at the doses of 0 20 and 0 30 mg/kg drinking dropped sharply by the second minute and continued to decline over the session

A two-factor completely repeated analysis of variance

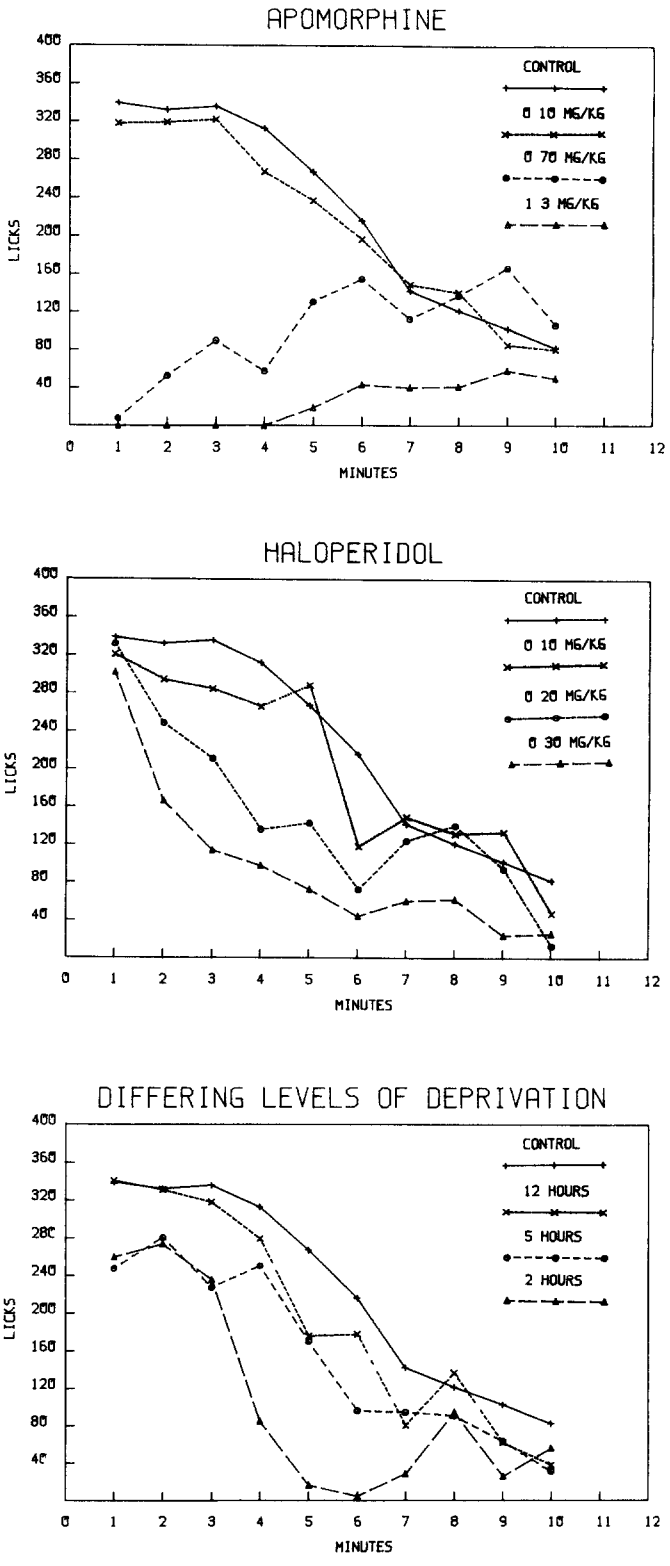


FIG 8 The dose effects of apomorphine (top panel), haloperidol (middle panel), and the effects of differing hours of water deprivation (bottom panel) on the temporal pattern of licking in water deprived subjects during 10-minute sessions

with dose and minutes as the repeated factors was performed on the data for both drugs For apomorphine, the analysis at the 0 10 mg/kg dose revealed only a significant main effect for minutes, $F(9,45)=20\ 448$, $p<0\ 001$ The dose of 0 70 mg/kg produced a 2-way interaction, $F(9,45)=20\ 882$, $p<0\ 001$, with analysis of the simple main effects [22] indicating that licking was significantly ($p<0\ 05$) depressed for the first five minutes compared to the control values A significant, $F(9,45)=14\ 514$, $p<0\ 001$, 2-way interaction was also found for the dose of 1 3 mg/kg Analysis of the simple main effects revealed that licking was significantly depressed for the first eight minutes with this dose of apomorphine

For haloperidol, the dose of 0 10 mg/kg produced only a significant main effect for minutes, $F(9,45)=25\ 629$, $p<0\ 001$ However, the dose of 0 20 mg/kg produced a 2-way interaction, $F(9,45)=6\ 287$, $p<0\ 001$, with analysis of the simple main effects revealing that this dose reduced licking in the second through sixth and also the tenth minute The two-way interaction for the dose of 0 30 mg/kg was significant, $F(9,45)=7\ 396$, $p<0\ 001$ The analysis of the simple main effects indicated that licking during the second through the sixth and the ninth minute was different from the respective control value

The effects of the differing levels of water deprivation on the subjects licking behavior are illustrated in the bottom panel of Fig 8 It can be seen that the lick rate of the subjects is reduced in the first minute of the 10-minute period at two and five hours post-access to water as compared to the control value It can also be seen that, unlike the functions produced by either drug, drinking remained at this level for the first three minutes of the session before falling in a negatively accelerated fashion

## DISCUSSION

This experiment conclusively demonstrated that both apomorphine and haloperidol produced dose-dependent decreases in water consumed by water-deprived rats and disrupted the pattern of licking These results are in agreement with the reported effects of dopamine agonists and antagonists on water intake in deprived rats [9] It should be noted, however, that the results obtained with haloperidol contradict the reported effects of the neuroleptics, pimozide and spiperone, on drinking induced by water deprivation [28]

Apomorphine, haloperidol and level of water deprivation clearly had different effects on the pattern of licking of the subjects Neither of the drugs produced disruptions in the lick pattern comparable to that produced by changing the deprivation level Therefore, it does not appear that either drug caused a decrease in motivation which was analogous to that produced by decreasing the motivational impact of water

It would also appear that apomorphine and haloperidol affected drinking by different processes It is obvious that apomorphine abolished licking in the initial to mid-portion of the 10-minute access period at the doses of 0 70 and 1 3 mg/kg This suppression could possibly have been caused by a direct effect of this drug on the brain sites which control the drinking behavior of rats However, a more likely explanation is that apomorphine produced behavioral stereotypies [6, 8, 34] which prevented the subjects from licking the drinking tube The recovery of licking in the latter part of the access period is most likely due to the decline in intensity of the drug effects

From inspection of the middle panel of Fig 8 it can be seen that when the subjects received haloperidol at the doses of 0 20 and 0 30 mg/kg they licked at the control rate for only the first minute Licking then declined rapidly over the remaining nine minutes This pattern indicates that neither the ability of the subjects to lick, nor their motivation to do so, was disrupted initially The sharp decline in lick rate beginning with the second minute does not appear to be due to a suppression of water motivation, since this rapid decline is not seeen when the subjects are partially satiated Most likely the subjects were highly motivated to drink, and also physically able to do so What appears to have happened is that the sensory feedback necessary to maintain drinking was disrupted by haloperidol This latter possibility is discussed in more detail in the general discussion section

## GENERAL DISCUSSION

The results of experiments 1 and 2 provided no convincing evidence that established SIP is more sensitive to the effects of dopaminergic disruption than is operant bar-pressing Further, experiment 2 demonstrated that the pharmacological actions of apomorphine and haloperidol produced a suppression of SIP that was separable from the effects of reduced reinforcer density The third experiment showed that the doses of the drugs which affected operant responding and SIP in experiment 2 also suppressed drinking in water-deprived rats The results of all three studies point to the conclusion that established SIP is not any more sensitive to disruption of the dopamine system, at least pharmacologically, than are operant bar-pressing and deprivation-induced drinking It should be recalled that 6-OHDA lesions of the nucleus accumbens also have a general influence on established SIP and operant bar-pressing [30] Thus, while it may be that the acquisition of SIP is selectively suppressed by dopaminergic disruption [28, 29, 35], it seems more probable that drug- or lesion-produced variation in this neurotransmitter system produces a general behavioral effect which interferes with the acquisition of most, if not all, learned behavior It also seems plausable, from the evidence presented above, that an already established behavior is more resistant to the disruptive effects of dopaminergic variation than is a behavior which is being acquired

The studies reported here have shown that while there were similarities in the behavioral effects of apomorphine and haloperidol, there were also important differences Both drugs were shown to suppress bar-pressing, but only haloperidol was shown to produce a concomitant decrease in the number of pellets earned Also, in experiment 3, the effects of the drugs on the drinking pattern of water-deprived subjects were clearly different Therefore, while both drugs suppressed drinking, it appears that they did so through different mechanisms

It is well known that haloperidol produces suppression of motor activity [2,15] This suppression of movement could have caused the decreased bar-pressing found in experiments 1 and 2 However, the results of experiment 3 do not support this conclusion That the subjects licked at control rates in the first minute of access to water indicates that they could lick and that they were motivated to do so The sharp decline in lick rate by the second minute, however, indicates that the subjects were unable to maintain a high rate of licking

It may be, as Wise [38] has suggested, that the neurolep-

tics decrease or block the motivating aspects of a reinforcing stimulus and that it is this block which causes the suppression of reinforced behavior A related, but slightly different, hypothesis is that dopamine mediates between sensory input and motor output [36] Lesions of the nigrostriatal dopamine pathway by chemical or electrolytic means result in a syndrome of sensory neglect [25–27] While subjects are experiencing this syndrome they do not respond to levels of stimulation which, in a normal rat, elicits a marked response [26] It thus seems, as White has suggested [36], that one of the functions of the dopamine system is to activate motor areas of the brain such that a response appropriate to the level of incoming sensory stimulation can be sustained However, if dopamine is blocked from its receptors, then sensory feedback such as that which occurs from the ingestion of food or water should no longer be sufficient to maintain activation of the appropriate behavior

It should be noted that this hypothesis is not new In 1961, Dews and Morse [7] stated that the administration of a neuroleptic produces an uncoupling of environmental stimuli from the behavior of the organism From this viewpoint, the sharp decline in lick rate in experiment 3 and the decrease in bar-pressing and SIP in experiments 1 and 2 were due to a lack of sustained motor activity caused by a disruption of sensorimotor integration It is not that motor behavior or motivation per se were affected, rather it is that the level of sensory stimulation was insufficient to maintain activation of the appropriate behavior

On the other hand, with the administration of apomorphine, the opposite effect would be expected to occur Overactivation of motor systems would result which would interfere with the ability of the subjects to emit the appropriate consummatory behavior The results obtained with apomorphine then, may be due to an increase in the activity of the dopamine post-synaptic receptors which, in turn, produced an increase in the occurrence of behavior which was incompatible with bar-pressing and licking The subjects were still motivated to emit the appropriate behavior but were physically prevented from doing so, at least at control rates However, because the sensory feedback from the ingestion of the food or water was not blocked from maintaining the appropriate motor response, this behavior continued to the extent that it successfully competed with drug-produced motor interference Because the fixed-interval schedule is time based, the subjects were still able to earn the reinforcers when assigned, even though they emitted fewer bar-presses Also, there was some recovery of SIP with the longer session length of experiment 2 as compared to experiment 1, and drinking recovered somewhat near the end of the water-access period in experiment 3 It thus seems that the recovery in both experiments was due to a decline in the interference of the drug-induced behaviors

While the argument for the different mechanisms of action for haloperidol and apomorphine is somewhat post-hoc, it does point to the need for continued research in this area At present the authors are determining the dose-effects of apomorphine, haloperidol and pimozide on the acquisition of SIP Research is also being conducted to determine if changes in incentive value, such as increasing or decreasing the palatability of a drinking solution, or altering the level of food deprivation, influences the behavioral effects of dopamine agonists and antagonists as predicted by the above model

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