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Schedule-Induced Polydipsia and Operant Licking: Effects of Chlorpromazine, Methamphetamine and Secobarbital

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SCHEDULE-INDUCED POLYDIPSIA AND OPERANT LICKING:
EFFECTS OF CHLORPROMAZINE, METHAMPHETAMINE AND SECOBARBITAL

by

Paul Tobin Maginnis

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Submitted to the
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in Partial Fulfillment
of the
Degree of Master of Arts

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INTRODUCTION

Rats receiving dry food pellets under schedules of intermittent food reinforcement, and allowed free access to water, will ingest large amounts of water after each pellet delivery. Falk (1961) was the first to report this phenomenon of schedule-induced polydipsia. It has since been observed in the rhesus monkey (Schuster and Woods, 1966) and the pigeon (Shanab and Peterson, 1969). The drinking behavior occurs during the first third of the interfood interval, with a local lick rate that does not seem to vary from a constant four to five times per second.

Licking behavior is influenced by a number of parameters. First, size of the food pellet is important. Falk (1967) increased reinforcement magnitude from 45 mg to 90 mg Noyes pellets in variable-interval one and two minute schedules and found an average 50% increase in drinking per interval. Second, the food deprivation level of the subject affects schedule-induced polydipsia. As weights are increased through the 95 to 105% range, schedule-induced polydipsia decreases linearly, while responding for food will not substantially decrease until weights of 104 to 105% free feed are reached (Falk, 1969). Third, fixed or variable non-contingent intervals of food delivery produce higher water ingestion values than response-dependent schedules with similar interfood intervals (Falk, 1964). Fourth, quality of the food pellet will affect polydipsia. Food pellets adulterated with non-nutritive
substances do not produce schedule-induced polydipsia (Falk, 1967). Fifth, intermittent delivery of liquid food reinforcers does not produce polydipsia, and will interrupt existing polydipsia initially produced on schedules using dry food reinforcement (Stein, 1964). These parameters are subject to yet another factor, the interfood interval. As the interval is increased, the amount of water consumed increased until a 90 to 120 second interfood interval is reached, and then water consumption begins to decrease until a nominal value is reached at an interval of approximately 240 seconds (Falk, 1966; Flory, 1971).

Changes in physiological functions were originally considered a possible cause of schedule-induced polydipsia, but extensive investigations did not prove them to be significantly involved (See Falk, 1964, for review). Of other hypotheses that have been proposed to explain schedule-induced polydipsia, the first concerns adventitious reinforcement of licking (Clark, 1962; Segal, 1965). The hypothesis is that licking is controlled by the same reinforcing properties of the pellet as is the operant response which produces the pellet, e.g. that licking is the first member of a chain of responses whose terminal components are under the direct control of reinforcement. This view has been challenged by Falk (1964) and Hitzing (1968), both of whom used delay of reinforcement procedures and concluded that adventitious reinforcement was not a necessary condition for either acquisition or maintenance of schedule-induced polydipsia.
A second hypothesis originates from an ethological viewpoint, and suggests that polydipsia is an activity of high probability (because of genetic endowment) that has been displaced because of "thwarting" (not being able to complete a meal of sufficient size to result in satiation). This displacement activity (schedule-induced polydipsia) is released when the animal is under a high drive condition, engaged in eating and is prevented from continuing to eat by the intermittency of the reinforcement schedule (Falk, 1971). Such an account of polydipsic behavior lacks independent evidence, such as a measure for the amount of "thwarting" necessary before the intermittency of the schedule releases drinking, and the amount of "dynamic change" that is needed between food, no food and not enough food to result in drinking.

Another possible approach to this problem is to consider pellet delivery a discriminative stimulus. Pellets could serve a dual role, reinforcing food responding and also take on discriminative properties by signalling a time period during which food will not be available (the period immediately after food delivery being furthermost in time from the next pellet delivery). Behaviors other than polydipsia, such as schedule-induced aggression and escape, also occur during schedules of intermittent food reinforcement and, like schedule-induced polydipsia, occur most frequently during the first portion of the interfood interval. Increases in the interfood interval produce aggressive behavior following a non-monotonic function similar to that of polydipsia (Flory, 1969), and
responding for escape into a time-out situation (Azrin, 1961; Thompson, 1964). Thus, it would seem that the initial portion of the interfood interval can be considered aversive. If this is true, one might predict that any experimental manipulation which would decrease the aversiveness of the interfood interval, such as drug administration, would result in a decrease in schedule-induced behavior.

Schedule-induced polydipsia has recently been studied using a method which makes food reinforcement contingent upon a licking response (Hitzing, 1968; Segal and Deadwyler, 1964). Using this procedure results in the occurrence of both postpellet licking (schedule-induced polydipsia) and prepellet licking (operant responding). Pausing between postpellet bursting and "scalloped" licking for the next pellet is a common occurrence. The two resulting local rates correlate well with the usual bursting and scalloping patterns found in polydipsia and fixed-interval responding for food reinforcement.

Psychopharmacological research is often instigated for one of two reasons: (1) behavior is utilized as a means of analyzing the actions of a drug, or (2) drugs are utilized as a means of analyzing the mechanisms of behavior. Since the response topography of the schedule-induced and operant behavior are the same in the above-mentioned lick-contingent reinforcement procedure, this design, in combination with the second pharmacological approach, lends itself to further investigations into the controlling mechanisms of polydipsia. Results from such research may provide evidence concerning the plausibility of the aversive control hypothesis of schedule-induced licking.
Further, drug effects may suggest one or more general physiological mechanisms involved in the control of schedule-induced and operant licking. A differential effect on the two patterns of responding would tend to suggest that more than one common controlling mechanism exists. A coincident change in both patterns of responding following a drug manipulation could suggest several possibilities: (1) only one controlling mechanism is present for both patterns of behavior, (2) two or more mechanisms involved in the control of licking are common to both schedule-induced and operant responding, (3) possible mechanisms distinct to one pattern of licking are not affected by the administration of the given drug such that a differential effect is seen.

Falk (1964) found that rats, pressing a lever for food on a variable-interval one-minute schedule, decreased polydipsic responding following one dose of methamphetamine administration, while Teitelbaum and Derks (1958) reported that d-amphetamine administration increased rates of operant licking when each lick postponed the onset of an electric shock. These data suggest that amphetamine administration differentially effects schedule-induced and operant licking. The present study attempts to demonstrate such differentiation within the same experimental session using several drugs.
METHODS

Subjects

Six male albino rats, obtained from the Upjohn Company, Kalamazoo, Michigan, ranging in weight from 379 to 453 grams, were reduced to 80% of their free feeding weight. Subjects were allowed constant access to water throughout the experiment except for two days during early training.

Apparatus

The interior of the chamber measured 23 x 36 x 17.5 cm with a hardware cloth floor supported 8 cm above the catch tray. Three of the walls and the ceiling were covered with Fiberglas. The fourth wall was a steel plate. On this wall a 1.25 cm hole and Gerbrands food cup were placed 2.5 cm from the chamber floor and 6.5 cm from the left and right of center. A stainless steel drinking tube was placed 0.6 cm behind the hole and attached to a calibrated reservoir. A drinkometer (Zucker, 1969) attached to the tube and chamber floor allowed an average of three microamperes to pass through the subjects' tongue to their feet, which operated a relay. The chamber lighting was provided by three, 2.5 Watt bulbs placed next to each other in the ceiling. The experiment was controlled with electromechanical equipment.
Procedure

All six subjects initially received 60 pairings of chamber light flash and pellet feeder click with each food delivery. After 22 hours of water deprivation, each subject was shaped to lick the tube for food reinforcement. Every tenth reinforcement increased the interreinforcement interval by 10 seconds until a fixed-interval of one minute was reached. Thirty reinforcements were presented for the first seven sessions, but all subsequent sessions were run until 60 reinforcements were produced. The subjects were allowed three hours to complete the session or it was terminated.

Water consumption was measured to the nearest milliliter for each session. After approximately 35 sessions, the records were inspected for reliable changes in local rate of responding during the one-minute interfood interval. This interval was subdivided into six, ten-second intervals (bins) and licks during these successive bins were separately recorded. The bin which contained the smallest number of responses was defined as separating postpellet licking (schedule-induced polydipsia) from prepellet licking (operant responding). If the majority of responses within this bin occurred during the first few seconds, it was considered to contain schedule-induced polydipsia. If most responses recorded in this bin occurred during the last few seconds, it was considered to contain operant licking.

Only schedule-induced licks were used in calculating a stability measure. Stability was defined as 10 consecutive sessions.
during which the first and last five sessions' means did not differ by more than 10% from the mean of the entire 10 sessions. After the first drug injection, the first five control sessions for the next dosage were the last five control sessions of the previous injection, thus, no less than five days passed between two successive drug administrations. The one exception is subject B5, whose last ten sessions did not include the previous drug control days.

**Drug Administration**

Subjects B4 and B5 received methamphetamine hydrochloride, B2 and B6 received secobarbital and chlorpromazine was administered to B1 and B3. All drugs were injected in an elixor form and each dosage was diluted with normal saline to "x" mg/cc. Drugs were administered to each subject in proportion to its body weight and no one subject received overall volume changes of greater than 0.02 cc throughout the experiment. Amounts and sequence of dosage administration for each subject can be seen in Table I.

Starting with session 31, each subject was weighed and injected intraperitoneally approximately eight minutes before each session. On control days, the subject received 1 cc/kg of normal saline. On drug days, the appropriate drug and dosage was administered. Subjects received approximately 90 daily injections over the course of the experiment without any noticeable cutaneous irritation.
RESULTS

Chlorpromazine

The effects of chlorpromazine administrations on both schedule-induced and operant licking are shown in Figure 1. Dosages of below 1 mg/kg for B3 and below 2 mg/kg for B1 produced little or no change in either response measure. At dosages of 1 and 2 mg/kg, subject B3, which received dosages in an ascending order (excluding replications) showed either no differential effect or a greater decrease in operant than in schedule-induced licking. This inconsistency was seen both at different dosages and on replications of the same dosage. Administrations of 3 mg/kg resulted in an absence of responding, and the subject was observed during both of these sessions and found to be immobile.

Subject B1, which received the drug dosages in a descending order (excluding replications), showed inconsistent effects similar to but not of the same degree as B3. Dosages of 2 and 3 mg/kg produced equal decrements in both response measures once, a greater decrease in operant licking four times and a total absence of responding twice. The subject did initiate responding following the first administration of 3 mg/kg, but failed to produce 60 reinforcers within the three-hour criterion.

Methamphetamine

The effects of methamphetamine on both schedule-induced and operant...
licking are shown in Figure 2. Dosages below 1 mg/kg produced little or no change in either response measure. Dosages between 1 and 3 mg/kg produced a much greater effect on schedule-induced licking than on operant.

Subject B4, which received drug dosages in an ascending order, showed a minimal decrease to 25% of control responding for schedule-induced licking in the range of 1 to 3 mg/kg. No deviation from control range was observed in operant licking at 1 and 2 mg/kg, but 3 mg/kg produced a consistent decrease in operant responding. This decrease in operant licking, except for the second dosage of 3 mg/kg, was not as great as those seen in schedule-induced licking.

Subject B5, which received drug dosages in descending order (excluding the 5 mg/kg dosage), showed a similar change in schedule-induced licking following 1 to 3 mg/kg injections, with a minimal decrease to 33% of control responding. However, the greatest effect on operant licking was seen following 1 mg/kg methamphetamine, which produced a decrease in responding to 30% of control rate. Due to intersession variability and a consistent decline in schedule-induced licking during control days, dosage replications were not possible.

At a dosage of 5 mg/kg, neither subject met criterion for session completion, and both schedule-induced and operant licking were almost completely suppressed. During these sessions, subjects were observed periodically and found to be extremely active, and thus, the decreases in licking cannot be attributed to immobility.
Secobarbital

The effects of secobarbital on both schedule-induced and operant licking are shown in Figure 3. Low dosages of secobarbital, e.g. those below 7 mg/kg, produced little or no change in either response measure for both subjects. Subject B6, which received drug administration in ascending order, showed a greater decrease in schedule-induced than in operant licking at all dosages above 10 mg/kg. Schedule-induced licking showed a greater depression with each increasing dosage, while operant licking showed little or no depression even at the highest dosage levels.

Subject B2, which received the first three drug dosages in descending order, showed no consistent effects following secobarbital administrations. Medium dosages (10 to 12 mg/kg) produced greater overall response suppression than higher dosages. When suppression did occur, it appeared approximately equal in both response measures.
DISCUSSION

Both schedule-induced and operant licking by subjects B3 and B1 were suppressed following chlorpromazine administration. A general decrement in responding would seem to contradict the idea of an aversive quality being associated with the interfood interval, yet this decrement is consistent with results from other studies concerning chlorpromazine (Herz, 1960; Dews and Morse, 1961; Gollub and Brady, 1965). This suppression of responding has been shown regardless of type, quality or magnitude of reinforcement when drug effects are compared between several response rates (Kelleher and Morse, 1968).

Other studies concerned with pre- and postevent behaviors have shown differential effects with chlorpromazine (Hutchinson and Emley, 1970; 1971). Squirrel monkeys were given unavoidable fixed-time electric shocks. The subjects pressed a lever before and bit a hose following shock delivery. Neither behavior had any programmed consequences. Hutchinson found chlorpromazine to suppress biting and to facilitate lever pressing. Assuming chlorpromazine does not facilitate extremely low response rates and the intershock interval is aversive, the drug produced the expected results. The present study did not show a sign or degree change between licking measures following chlorpromazine administration. Results from both studies, however, could also be interpreted as specificity of drug action between behaviors induced by aversive stimuli and those
induced by positive stimuli (Hutchinson, personal communication), but comparable control rates between studies would be needed before this possibility could be verified.

Methamphetamine subjects B4 and B5 (see Figure 2) showed a differential separation of operant and schedule-induced licking. At dosages of 1 to 3 mg/kg, schedule-induced licking is always decreased to at least 25% of control rate, while operant licking is inversely related to dosage size for B4 and to a lesser extent for B5.

The concept of rate-dependent effects offers an interesting analysis of these data. In general, low local rates are increased and high local rates are suppressed following amphetamine administration. Such results have been observed across species, and the initial quantitative data was reported by Kelleher and Morse (1968), who analyzed a squirrel monkey's local rates under fixed-interval and fixed-ratio avoidance schedules. At the only dosage employed in this study (0.3 mg/kg of d-amphetamine) they found rates below one per second to be facilitated by as much as 1,000%. Rates of one per second showed no change, while rates above one per second showed a gradual decrease to approximately 30% of control rates. Similar data have been reported by McKearney (1971) who used a pigeon and a squirrel monkey.

In the present study, the lowest rate of responding was two per second, which generally occurred before pellet delivery (operant licking), while the highest rate was five per second, which generally followed pellet delivery (schedule-induced licking).
Yet, facilitation and suppression can be seen in both response measures at different dosages (see Figure 2). Therefore, the rate-dependent effects seen by Kelleher and Morse, as well as by McKearney, cannot account for the changes seen here in licking unless it can be assumed that the specific drug-rate relationship is dependent upon species and response topographies. This does not seem an unreasonable assumption at this time, in view of the very limited data available concerning the rate-dependent effects of amphetamine.

In the Kelleher and Morse (1968) study, as response rates increased from one per second to 2.4 per second, a larger degree of suppression occurred following drug administration. This is also the case in the present study. Subject B4's operant rate of 1.3 per second was reduced to 0.8 per second (58% of control) while the schedule-induced rate of 4.7 per second was reduced to less than 0.3 per second (7% of control) at 2 mg/kg. Subject B5 showed a generally higher operant than schedule-induced licking rate, and following drug administration, more depression occurred in the schedule-induced measure. Typical *averaged* schedule-induced licking rates were approximately 0.8 per second, and this decreased to 0.03 per second (3% of control) following amphetamine administration, while operant rates averaged three per second and were decreased to 1.3 per second (43% of control) at 2 mg/kg. Close inspection of the cumulative records indicated that B4 showed steady responding patterns, but B5 did not, especially in schedule-induced licking. This subject would typically show bursting following some pellet deliveries and none at all following others. Thus, a low *averaged*
rate decreased more than a higher averaged rate relative to control values. Perhaps this seeming contradiction of rate-dependent effects of amphetamine can be explained by the initial inconsistency of schedule-induced licking by subject B5. However, the fact that both subjects showed a greater decrease in schedule-induced than in operant licking leaves open the possibility of specific drug actions on schedule-induced behavior, or a possible reduction of aversiveness associated with the interfood interval. Clearly, further research into this area is needed before any definitive explanations are found for these results.

Of the secobarbital subjects, B2 showed no consistent effects either between measures or dosage levels, while B6 showed a consistently greater decrement of schedule-induced licking with increasing dosages, and at the same time showed little or no change in operant licking. We are currently running another subject on secobarbital and resulting data appear to be similar to that of B6. Barbiturates do show rate-dependent effects, but not to the extent or generality of amphetamines (Kelleher and Morse, 1968). For example, B6's operant and schedule-induced responding are both uniform and of approximately the same rate, yet large differences can be seen between the two measures following secobarbital administration.

Barbiturates increase responding that has been suppressed by immediate punishment (Geller and Seifter, 1960; Geller, 1962; Geller, Bachman and Seifter, 1963). Dosages that result in such an increase do not appear to act as an analgesic agent, as morphine, a classic analgesic, decreases responding to punishment. Further,
disruption of control by discriminative stimuli can be ruled out as causing this increase, as no disruption occurs when a barbiturate is administered under a multiple schedule of shock and no shock (Morse, 1964; Kelleher and Morse, 1964). This increase in response to immediate punishment seems to reflect a motivational change due to drug action, and the present data also suggest such an effect. The progressive decrease in schedule-induced licking, and no significant change in operant licking following secobarbital administration, suggests a decrease in the aversive properties of the interfood interval.

The parameters used in this study deserve further comment. First, if the interfood interval were longer, it would have produced different patterns of schedule-induced and operant responding and, thus, different local rates. If, indeed, the rate-dependent phenomenon of drug action is a critical factor in determining drug actions, a different interfood interval would have possibly resulted in data other than reported here. Secondly, the interpellet interval analysis that was used to separate schedule-induced from operant licking may have provided a more accurate distinction if it utilized smaller response bins. One-second bins would have provided a more precise basis for analyzing local rates and the drug effects seen on these rates. Thirdly, using a lever response as the operant measure, while it would add the uncontrolled variable of two response topographies, would allow a clearer separation of schedule-induced and operant responding, possibly allowing for a more precise differentiation between the two measures. Fourthly, drugs other
barbiturates, such as meprobamate and chlordiazepoxide, seem to demonstrate selective behavioral changes in relation to punishment. Use of such drugs might produce a clearer interpretation of the differential effects seen in this study.
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<td>Chlorpromazine</td>
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<td>Secobarbital</td>
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<td>15  17  20  25</td>
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FIGURE LEGENDS

Figure 1  Effects of chlorpromazine on schedule-induced licking (upper portion) and operant licking (lower portion). Ordinate: rate (responses per 600 seconds times the number of bins) following chlorpromazine administration and expressed as a percentage of control rate. Abscissa: dosage levels of chlorpromazine on a logarithmic scale. Each point represents a single observation and points to the right of the original dosage are further replications. Vertical hash lines represent the range of the five control days prior to drug administration.

Figure 2  Effects of methamphetamine on schedule-induced licking (upper portion) and operant licking (lower portion). Ordinate: rate (responses per 600 seconds times the number of bins) following methamphetamine administration and expressed as a percentage of control rate. Abscissa: dosage levels of methamphetamine on a logarithmic scale. Each point represents a single observation and points to the right of the original dosage are further replications. Vertical hash lines represent the range of the five control days prior to drug administration.

Figure 3  Effects of secobarbital on schedule-induced licking (upper portion) and operant licking (lower portion). Ordinate: rate (responses per 600 seconds times the
number of bins) following secobarbital administration and expressed as a percentage of control rate. Abscissa: dosage levels of secobarbital on a logarithmic scale. Each point represents a single observation and points to the right of the original dosage are further replications. Vertical hash lines represent the range of the five control days prior to drug administration.
FIGURE 1
FIGURE 2
FIGURE 3
REFERENCES


