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Schedule-induced Narcotic Ingestion

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FOR several years, we have been interested in developing models of oral self-administration of narcotic solutions by rats. In the early research on oral ingestion of narcotics, rats usually were made physiologically dependent upon morphine by injection before exposure to solutions of narcotics (18, 25). Later studies showed that it was not necessary to premedicate rats, or to make them physiologically dependent, to induce them to drink solutions containing narcotics (10, 20, 22). Daily doses of 60 mg/kg (1) to 100 mg/kg (13, 22) have been ingested when morphine was dissolved in the only drinking fluid available to rats on free-feeding in their home cages.

Falk (3, 5) first reported that rats would drink excessive amounts of water when small food pellets were presented on an intermittent schedule. This pattern of excessive drinking which occurs after pellet presentations has been called schedule-induced polydipsia. Occasionally, the method of schedule-induced drinking has been used to induce rats to drink drug solutions rather than water. For example, schedule-induced polydipsia has been used to induce drinking of ethanol (2, 6, 8, 11), or barbiturate solutions (9, 16). In one report, schedule-induced polydipsia was used to induce morphine drinking in a rat (21, p. 203).

In the present series of experiments we investigated the use of schedule-induced polydipsia to induce chronic drinking of several narcotics. One of our objectives was to determine whether the schedule-induced polydipsia method could be used to induce rats to drink larger doses of narcotics than they drink when the drug solution is the only solution available under free-feeding conditions (1, 13, 22). Another objective was to determine which schedules of food-pellet presentation would be most successful in inducing rats to drink narcotic solutions. Finally, we were interested in describing the effects of chronic narcotic drinking on the behavior of rats to determine whether the availability of a narcotic solution can function as a positive reinforcer.

Three different schedules of food presentation were studied as inducers of narcotic ingestion. The first schedule that will be described is one under which lever presses by the rat produce the food pellet; under the second schedule, the rat's licking of the spout of a bottle produces the food pellet; and under the third schedule, the food pellet was automatically presented without requiring the rat to make any specific response.

Schedule-induced Licking and Fixed-interval Lever Pressing

These experiments were conducted with Sprague-Dawley rats housed in a Lehigh Valley Electronics rat test cage within a sound-attenuated and ventilated chamber. The inside dimensions of the test cage were 21 cm wide by 31 cm long with a height of 19 cm. In the middle of the front panel (21 cm) was mounted a receptacle into which 90 mg Noyes rat pellets could be dispensed. To the left (5.5 cm) of the food receptacle and 4 cm off of the grid floor was a Gerbrand's rat lever; each press of more than 30 g on the lever was recorded as a lever-press response. To the right (6 cm) of the food receptacle and 10 cm off of the floor was a hole which allowed access to the metal spout of a bottle. The spout was recessed 1 cm behind the front panel of the cage and access was controlled by an elec-

trically operated door. Each contact on the spout was detected by a Grason-Stadler Drinkometer and recorded as a licking response. The bottle was weighed before and after each session to estimate the amount of solution drunk by the rat (assuming 1 ml of solution = 1 g) and corrected for spillage. The programming and recording equipment were electromechanical and were housed in a room separated from the test chambers. Each rat was maintained at approximately 300 g by the food received during the session and by postsession supplemental feedings. Water was always available when the rats were not in the test cage.

Under the fixed-interval schedule where lever presses were required, the rats received a food pellet for the first lever-pressing response after 90 sec had elapsed. Under this fixed-interval 90-sec schedule of food presentation, there was an initial period of about 20 to 40 sec in which very few lever-pressing responses occurred, followed by an increasing frequency of lever-pressing responses until pellet delivery. When a drinking bottle containing water or saline was available, licking responses occurred at a high rate for about 20 to 30 sec after virtually every pellet delivery (*schedule-induced licking*); licking responses seldom occurred during the remainder of the 90-sec interval. Similar patterns of licking and lever-pressing under fixed-interval schedules of food presentation have been described previously (4).

The effects of adding either morphine or methadone to a saline (0.9% NaCl) solution in the bottle were studied under this schedule of pellet delivery after the patterns of lever-pressing and spout-licking had stabilized. In figure 1 are shown the effects of increasing the concentration of morphine HCl in the saline solution for 2 rats (15 and 42) that were tested for a 4-hr session daily. Generally, as the morphine HCl concentration was increased, the rates of licking and the volume ingested decreased, while the total ingested dose increased; doses averaged 140 to 160 mg/kg per session (35 to 40 mg/kg per hr) with the 1 mg/ml concentration. The rates of lever-pressing varied across morphine concentrations, but under the fixed-interval 90-sec schedule, the rate of pellet delivery was fairly steady. After the sessions shown in figure 1, both rats stopped licking the spout when the 1 mg/ml concentration was present and did not lick when tap water was subsequently presented. Both rats died within a few days; respiratory infection was suspected, but not verified, as the cause of death.

The lever-pressing and licking patterns of two other rats were stabilized under the fixed-interval 90-sec schedule of pellet delivery with only a saline solution in the bottle; later 0.5 mg of morphine HCl per ml was added. Representative cumulative-response records of licking-responding from one of these rats under each condition of the experiment are shown in figure 2. With the saline solution in the bottle, the rat licked the spout after almost every pellet delivery, except in the 3rd and 4th hr of the session. In the 71st session with the 0.5 mg of morphine HCl per ml solutions, the pattern of licking after the delivery of each of the first 10 food pellets was similar to that seen with saline, but subsequently the licking episodes became less frequent but more prolonged. By session 188 the latter pattern of licking was predominant. Most licking responses occurred in five episodes that were about evenly spaced through the 3 hr, while the lever-pressing response occurred at a low rate throughout the session. Thus, during repeated exposure to morphine HCl solutions, the pattern of licking that has been originally induced by the schedule of food presentation became dissociated from this schedule.

The effects of methadone HCl were also studied under the fixed-interval 90-sec lever-pressing schedule of food presentation during 4-hr sessions. The effects of intro-

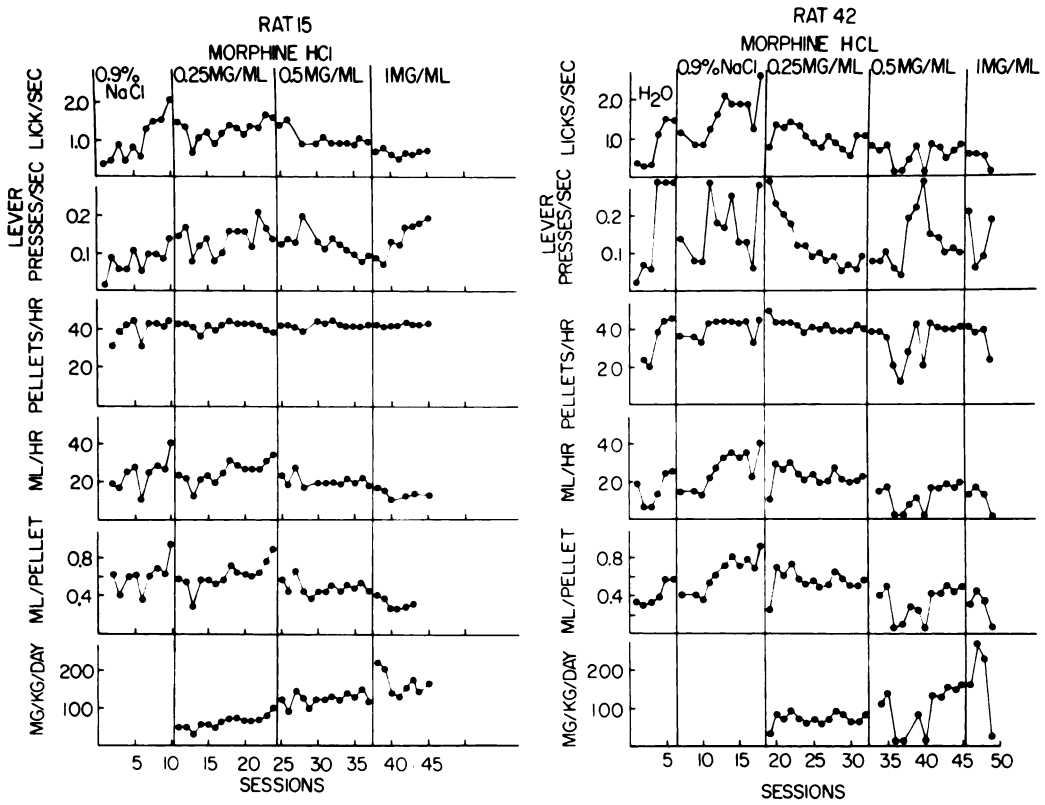

FIG. 1. The effects of increasing morphine HCl concentrations in the drinking solutions of two rats that were tested daily for 4-hr sessions. Ordinates: Licks on the drinking tube per sec, lever presses per sec, pellets received per hr, ml of solution consumed per hr, ml consumed relative to the number of pellets received, and the mg/kg dose of morphine consumed during the 4-hr daily session. Abscissae: Consecutive daily sessions, starting with the first session of training in the experimental chamber. The solutions available for drinking are indicated at the top of each graph. Changes in the drinking solution are indicated by the vertical lines in both graphs.

ducing increasing concentrations of methadone in the saline solution are shown in figure 3, and the effects of 1 mg of methadone per ml are compared with the effects of 1 mg of morphine SO_4 per ml for two rats. The addition of 0.3 mg of methadone per ml to the saline solution decreased the rate of licking and the volume ingested. A more concentrated methadone solution (1 mg/ml) further decreased the rate of licking and the volume ingested, while increasing the dose of methadone ingested. During the 4-hr sessions with the 1 mg/ml solution, doses of methadone of more than 100 mg/kg (25 mg/kg per hr) were often ingested. Replacing the 1 mg of methadone per ml solution with a 1 mg of morphine SO_4 per ml solution increased the rates of licking and the volume of solution ingested. Doses of more than 150 mg of morphine per kg were ingested during 4-hr sessions (approximately 40 mg/kg per hr), which exceeded the doses of methadone ingested by these same rats. The intake of morphine SO_4 was similar to that of morphine HCl at a similar concentration (fig. 1).

Chronic methadone drinking also disrupted the relationship between the pattern of licking responses and food pellet presentation. Under the saline solution condition, most licking responses occurred between 18 and 27 sec after pellet delivery. After exposure to the methadone solutions, most licking responses occurred between 36 and 45 sec after pellet delivery for one rat,

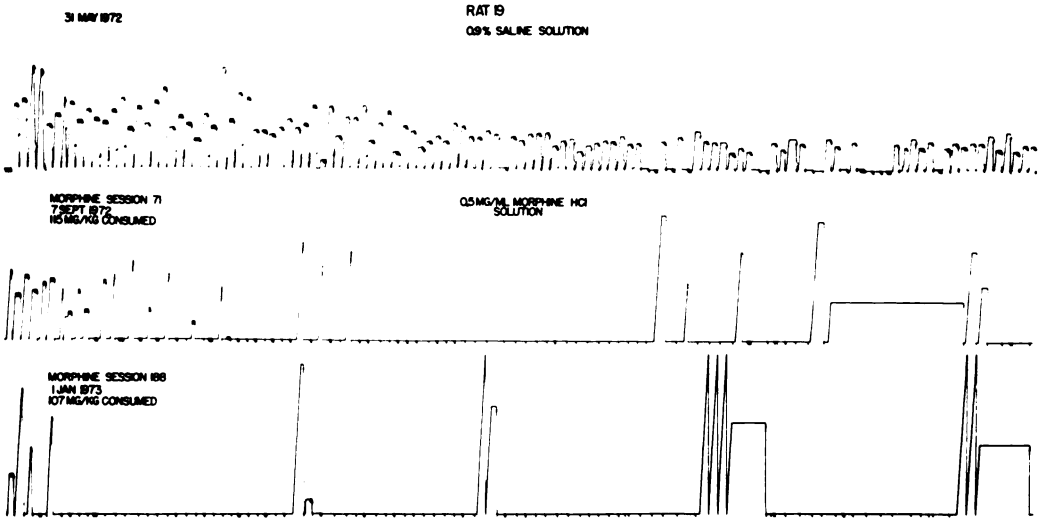

FIG. 2. Representative cumulative licking-response records for rat 19 during an isotonic saline session and two different morphine (0.5 mg/ml of saline) drinking sessions. Each lick on the drinking tube drives the pen upward. Resets of the pen occur at pellet delivery or after 550 successive licks have been made. The deflections indicate lever presses. These records are the first 3 hr of the 4-hr sessions; the 4th hr was similar to the 3rd hr. [From J. D. Leander, D. E. McMillan, and L. S. Harris, J. Pharmacol. Exp. Ther., **195:** 279-287, 1975 (10a).]

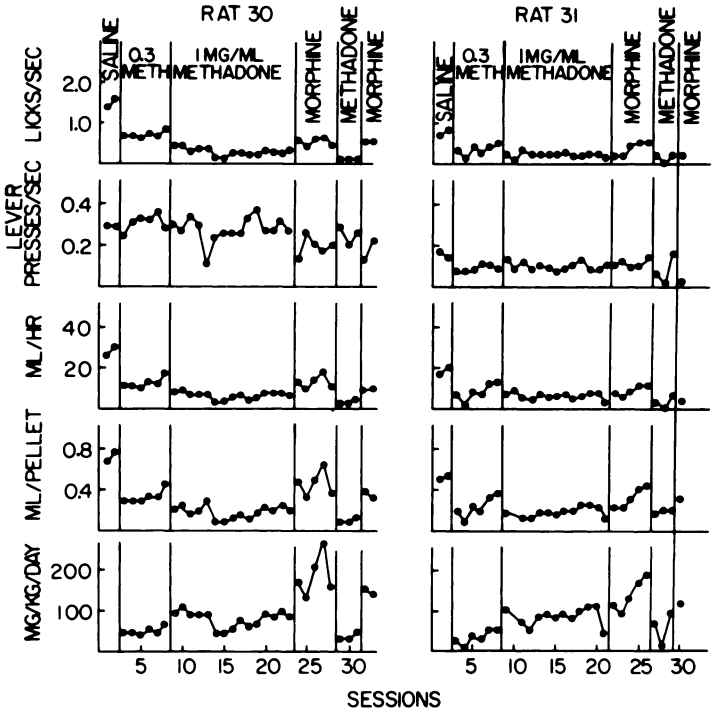

FIG. 3. The effects of increasing methadone concentrations in the drinking solutions and comparison with morphine solutions. The solutions available for drinking are indicated at the top of each graph. The morphine and methadone labels on the right of each graph indicate 1 mg/ml solutions of each. Changes in the drinking solutions are indicated by the vertical lines in both graphs. Ordinates: Licks on the drinking tube per sec, lever presses per sec, ml of solution consumed per hr, ml consumed relative to the number of pellets received, and the mg/kg dose of drug consumed during the 4-hr session. Abscissae: Daily 4-hr sessions. [From J. D. Leander, D. E. McMillan, and L. S. Harris, J. Pharmacol. Exp. Ther., **195:** 279-287, 1975 (10a).]

while the second rat showed no clear pattern from day to day.

During the course of some of these experiments on schedule-induced ingestion of morphine, a pronounced pattern of self-mutilation was observed. The rats, after ingesting large doses of morphine, often gnawed upon their limbs or abdominal wall, resulting in self-mutilation. It has been reported that rats given large daily doses (80 and 160 mg/kg, i.p.) of morphine would often engage in stereotypic gnawing patterns (19). The mutilation in the present experiments with morphine may be a result of such stereotypic gnawing, except that it was directed to the animals' own forepaws. A similar pattern of excessive licking and grooming of the abdominal surface of the rats drinking etonitazene also was observed, but it resulted in a loss of abdominal hair rather than in severe mutilation.

Schedule-induced and Schedule-dependent Licking

The second schedule of food presentation that was studied as an inducer of narcotic ingestion was one under which the rat received a food pellet for the first licking-response after 90 sec had elapsed. The manipulations with this fixed-interval schedule were conducted under generally similar conditions as the earlier described experiments except these were conducted with a Gerbrand's rat test cage with inside dimensions of 20.5 cm wide by 23 cm long with a height of 19.5 cm. In the middle of the front panel was a Gerbrand's rat lever mounted 6 cm off of the grid floor. To the left of the lever was a food receptacle and above it was a hole (11.5 cm from the floor) to provide access to the metal spout of a bottle. Under this schedule of food delivery, lever-pressing responses were not recorded and had no specified consequences. When water or a saline solution was available in the bottle, licking responses occurred at a high rate for about 20 to 40 sec after each pellet delivery (*schedule-induced licking*), then after a pause of variable duration licking responses occurred with increasing frequency until pellet delivery (*schedule-dependent licking*). The patterns of licking were qualitatively similar to those studied by McKearney (15) in rats. Requiring an animal to lick the spout of a bottle to receive food pellets has previously been studied (17) in rhesus monkeys. In that experiment, monkeys would lick the spout of one bottle to produce food pellets (schedule-dependent licking), then lick the spout of a second bottle after pellet delivery (schedule-induced licking). Thus, when licking responses produce food presentations, licking occurred as a composite pattern of both schedule-dependent and schedule-induced licking.

In the present experiments, the effects of chronic exposure to morphine SO_4 and methadone HCl in daily 90-sec sessions were studied. The rats were deprived of water 24 hr before the first session to facilitate initiation of the licking pattern; subsequently, the rats had free access to water in their home cages. After 4 days with the saline solution in the bottle, increasing concentrations of morphine were studied without any attempt to stabilize the pattern of licking responses before increasing the morphine concentration. When morphine was introduced, the volume of solution ingested decreased sharply, but it began to recover by the 2nd day in rat 3X and the 3rd day in rat 1C (fig. 4). The volume of drug solution ingested approached saline levels with a morphine concentration of 0.5 mg/ml. After 13 days, rat 3X was drinking more than 100 mg of morphine per kg and rat 1C was drinking more than 50 mg of morphine per kg during a 90-min session. These hourly doses of 49 to 70 mg/kg per hr compare favorably with the doses ingested under the schedule of food presentation in which lever-pressing responses produced food pellets. Another group of five rats was exposed to progressively increasing concentrations of morphine solution and then stabilized on a 1 mg of morphine per ml of saline solution.

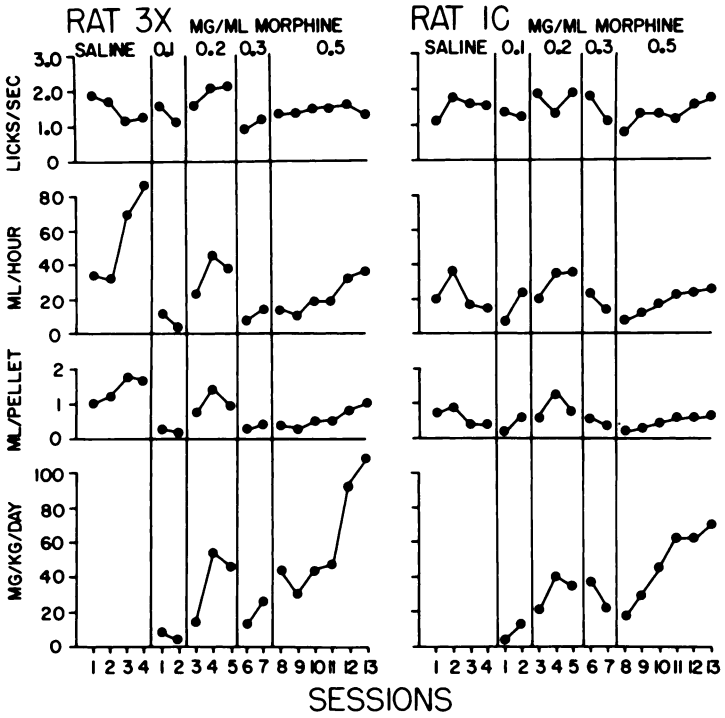

FIG. 4. The effects of increasing morphine concentration in the drinking solution of rats under the fixed-interval 90-sec schedule of food-reinforced licking. The morphine concentrations available for drinking are indicated at the top of each graph. Changes in drinking solutions are indicated by the vertical lines. Ordinates: Licks on the drinking tube per sec, ml of solution consumed per hr, ml consumed per pellet, and the mg/kg dose of drug consumed. Abscissae: Daily 90-min sessions.

These rats ingested an average of 160 mg of morphine per kg in 90 min or an hourly dose of approximately 100 mg/kg per hr. These hourly intakes were larger than those obtained under the schedule of food presentation in which lever-pressing responses produced food.

The fixed-interval 90-sec schedule under which licking responses produced food pellets was also effective in inducing a significant methadone intake. Two food- and water-deprived rats were exposed to increasing concentrations of methadone beginning on their first day in the test cage. After the first session they had access to water in their home cages. The test sessions were 90 min. Increasing concentrations of methadone in the drinking solution did not systematically alter the mean rate of licking or the volume of solution consumed (fig. 5). Daily intakes of methadone reached about 200 mg/kg per 90 min in rat 12 and 80 mg/kg per 90 min in rat 11 (about 130 and 55 mg/kg per hr, respectively).

When either lever-pressing responses or licking responses produced food pellets, the daily doses of morphine and methadone ingested were sufficient to produce signs of physiological dependence immediately before daily test sessions. No formal rating of symptoms was attempted, but signs such as irritability, loose stools and ptosis were often observed under all conditions. A comparison of the amount of drug solution consumed and the doses ingested suggests that the schedule-dependent licking and schedule-induced licking that occur when licking responses produce food pellets can result in larger intakes than the schedule-induced licking that occurs when lever-pressing responses produce food pellets. The licking-response records in figure 6 show why the fixed-interval schedule under which licking produces the food

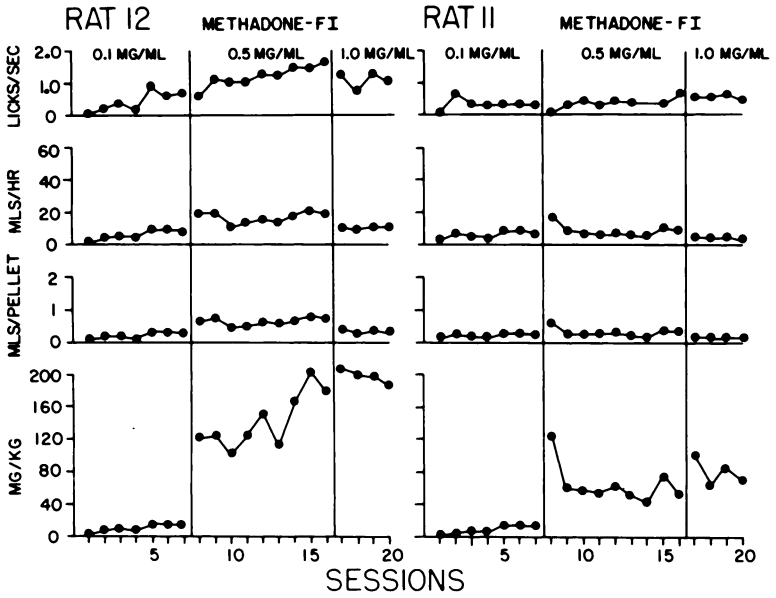

FIG. 5. The effects of increasing methadone concentration in the drinking solution of rats under the fixed-interval 90-sec schedule of food-reinforced licking. Methadone concentrations indicated at the top of the graphs; changes in concentrations indicated by vertical lines. Ordinates and abscissae same as figure 4.

pellets might produce a greater intake of drug solution than the fixed-interval schedule requiring lever-press responding. Both rats under the control condition (licking the spout of a bottle containing tap water) show a high rate of licking after each pellet presentation, then a pause, which is followed by accelerated licking until the next pellet presentation (upper record of fig. 6). For rat 1, on the second day of drinking a solution of 1 mg of morphine per ml of saline (second record of fig. 6), postpellet licking responses seldom occur, whereas prepellet licking responses have been little affected. Rat 2 under control conditions had a short postpellet pattern of licking that either blended into the schedule-dependent licking or was marked by a slight pause before resumption of licking (third record in fig. 6). On the 2nd day of drinking a solution of 1 mg of methadone per ml of saline, the cumulative record (bottom record in fig. 6) shows a loss of postpellet licking with continued maintenance of schedule-dependent licking. Thus for both rats, the narcotic in the drinking solution tended to eliminate the schedule-induced licking while maintaining the schedule-dependent licking. This change in the pattern of licking also produced a decrease in volume of fluid consumed, from 32 ml to 12 ml for rat 1 and from 55 ml to 16 ml for rat 2.

Independently Delivered Food Pellets and Schedule-induced Licking

These experiments were conducted in a Lehigh Valley Electronics rat test cage similar to that described for the experiments on schedule-induced licking and fixed-interval lever-pressing. The schedule of food pellet delivery that was studied as an inducer of narcotic ingestion provided for the food pellets to be automatically delivered every 90 sec independently of the rat's behavior. This schedule generates high rates of schedule-induced licking responses after every pellet delivery with water or saline in the bottle and has been used successfully to induce high levels of ethanol intake in rats (6). In the present experiments, this fixed-time schedule of pellet delivery was used to induce ingestion of etonitazene HCl, a very potent, but short-acting, synthetic narcotic (25).

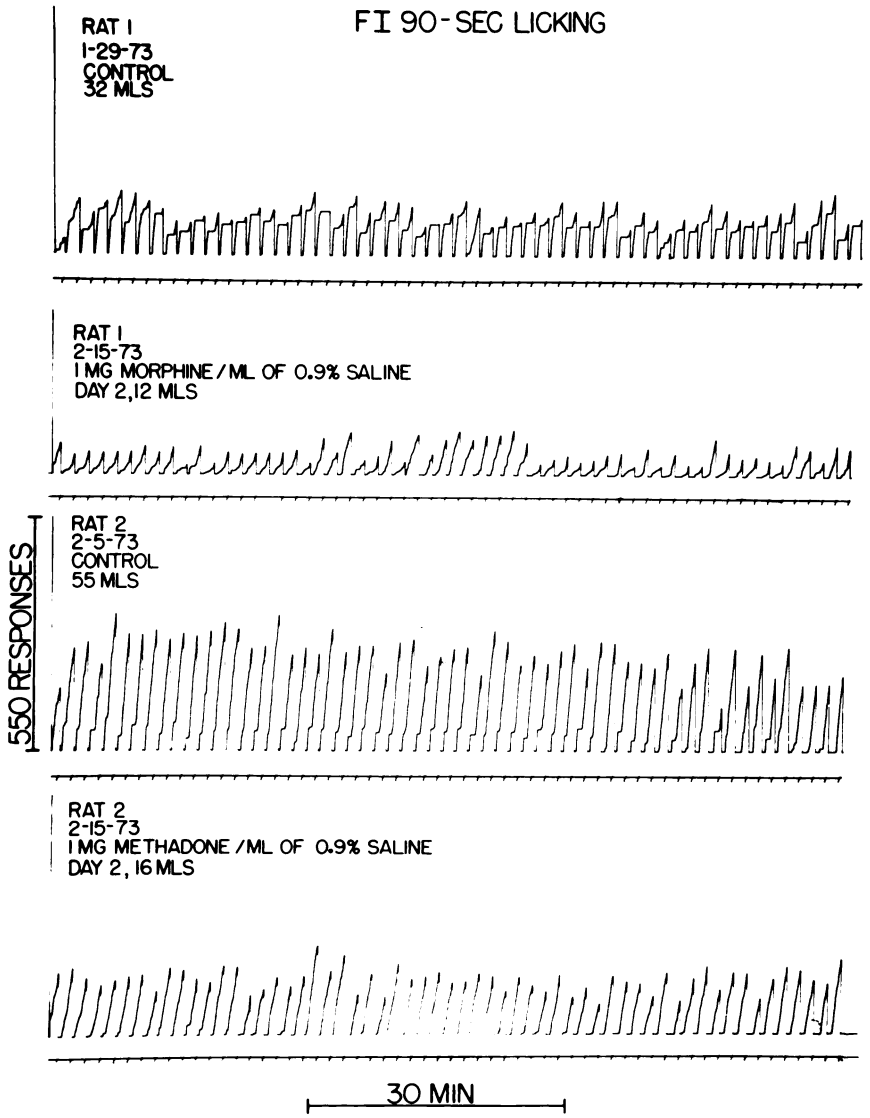

FIG. 6. Cumulative licking-response records for two rats under the fixed-interval 90-sec schedule of food-reinforced licking. Control records were obtained with tap water in the bottle. Drug records were obtained on the 2nd day after the drug solution was introduced into the bottle. Records are for complete 90-min sessions.

In a preliminary experiment with etonitazene, four rats that were lever-pressing under a fixed-interval 90-sec schedule of pellet presentation were exposed to a solution of 5 μg of etonitazene HCl per ml of tap water during a 1-hr session. During the session one rat died of an overdose. The other three rats consumed 5 to 10 ml of the solution during the first 5 to 10 min of the session, then stopped lever-pressing and licking the spout, and collapsed on the cage floor. Neither daily exposure for 6 days to the etonitazene solution or twice daily sessions separated by 6 hr in the home cages produced tolerance to these effects.

It was hoped that more frequent consumption of the etonitazene solution might produce tolerance. To study this possibility we exposed the rats to the fixed-time 90-sec schedule of pellet delivery four times per day for 45 min each time. Each rat received 30 pellets every 6 hr for a daily total of 120

pellets. Initially, the rats were deprived of food for 48 hr and deprived of water for 24 hr before being placed in the test cages, where they lived continuously during the experiment (except for daily weighing of the rats and cleaning of cages). The order of experimental conditions is shown in figure 7. During the first 3 days, water was available in the bottle. This was followed by 15 days exposure to a solution of 5 μg of etonitazene per ml of saline, except for day 4 as indicated by the arrows in figure 7, when water was also available. After 15 days of drinking the etonitazene solution, a bottle containing tap water was introduced at the back of the cage, so that the rats had a choice between consuming the etonitazene solution or tap water. The licks of each rat were recorded in two categories (fig 7). The postpellet licks are those that occurred during the periods when food pellets were being presented every 90 sec. The intersession licks were those licks during the 5¼-hr periods when no pellets were being delivered. The consumption of water during the first 3 days was largely due to licks associated with food pellet delivery. The consumption of the etonitazene solution was also correlated with postpellet licking but there was an increase in intersession licking for rat 41. As noted earlier, a frequent observation when drug solutions are being consumed during schedule-induced polydipsia, is that the

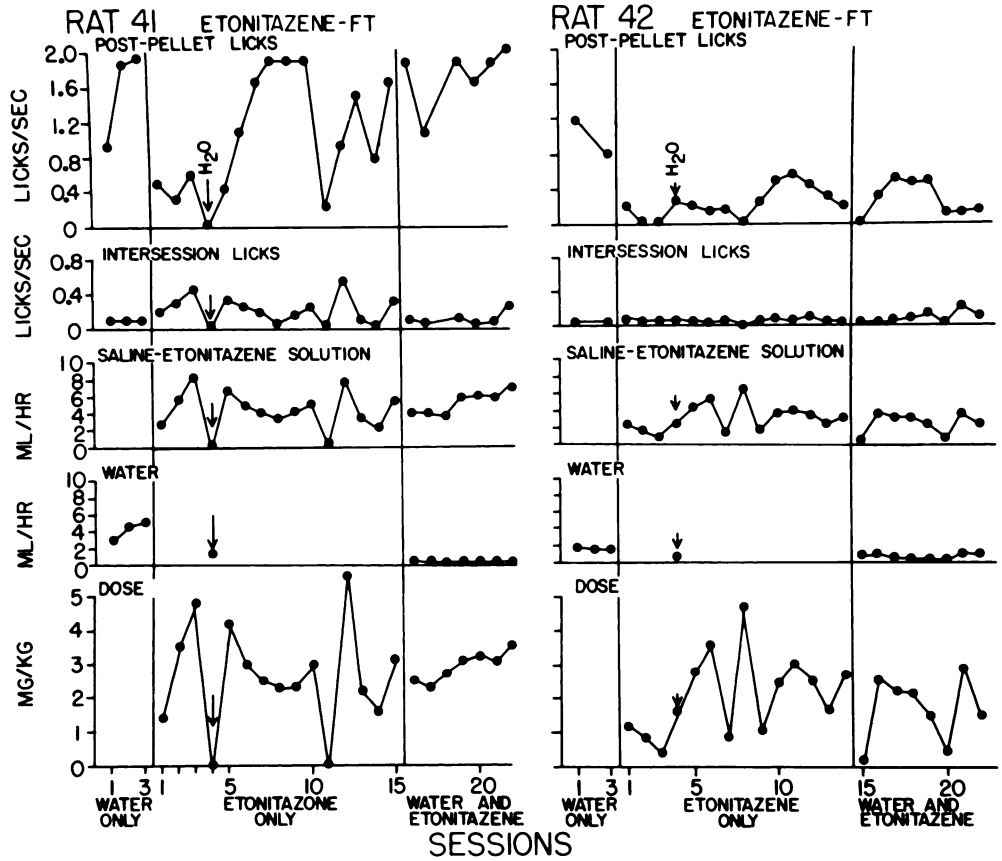

FIG. 7. Effects of etonitazene (5.0 μg/ml of saline) under the fixed-time 90-sec schedule of food presentation. The rats stayed in the test chamber 24 hr per day. Ordinates: Licks per sec of postpellet licks (those licks occurring during the feeding periods) and of intersession licks (those licks occurring between the feeding periods); ml per hr of the etonitazene solution consumed; ml per hr of water consumed. Both rats had only tap water available to drink during the first 3 sessions, then only the etonitazene solution during the next 15 sessions, followed by 8 sessions with both etonitazene solution and tap water available.

drinking of the drug solution becomes dissociated from the schedule of pellet delivery. The tendency for rat 41 to increase his intersession licks may be related to this observation.

The spacing of the four separate periods of food pellet presentation resulted in relatively large doses of etonitazene being ingested, with evidence for tolerance to and physiological dependence on etonitazene becoming readily apparent. The daily doses of etonitazene ingested were quite variable from day to day. On days during which the rats did not ingest much etonitazene they exhibited signs of withdrawal, such as wet shakes (23, 24) and weight loss, and on the following day there was usually a large increase in dose consumed. When the tap water was available concurrently with the etonitazene solutions, the ingestion of drug solution showed little change.

The pattern of postpellet licking for both rats under the fixed-time schedule under the different conditions of the experiment is shown in figure 8. The shaded area is the range of values obtained during the last 2 days with water as the only available solution; the filled circles are the means of values obtained on the 12th and 13th days of exposure to the etonitazene solutions; and the open circles are the means of 2 days when water was also concurrently available (sessions 20 and 21 for rat 41; sessions 18 and 19 for rat 42). Under the three conditions, drinking during the pellet presentation periods was always related temporally to the pellet presentation, and the postpellet drinking never became dissociated from pellet delivery.

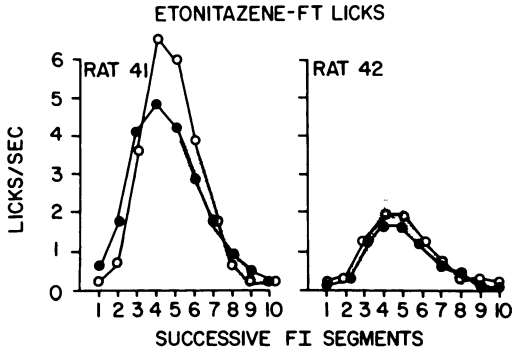

FIG. 8. The mean rates of licking within the 10 consecutive 9-sec segments of the fixed-time 90-sec schedule. The shaded area is the range of values obtained during the last 2 days with water as the only available solution; filled circles are the means of values obtained on the 12th and 13th days on the etonitazene solution; the open circles are the means of 2 days when water was also concurrently available at the back of the test cage (sessions 20 and 21 for rat 41; sessions 18 and 19 for rat 42).

It was striking that the rats continued to drink the etonitazene solution when water was concurrently available. Possibly this occurred because the etonitazene solution was nearest the location where food pellets were delivered. To study this possibility, the positions of the etonitazene and tap water bottles were reversed. In all cases (three rats tested with two different reversals), the rats continued to drink primarily the etonitazene solution. Other control studies comparing saline *vs.* water, however, indicated that when the saline solution was moved to the back of the rat cage, the animals would not continue to drink it, but rather would switch to drinking water near the location of pellet deliveries.

Etonitazene as a Positive Reinforcer

The fact that the rats would follow the etonitazene solution in the cage suggested that etonitazene functioned as a reinforcer. To examine this possibility further, naive rats were placed in the Lehigh Valley Electronics test cages with a plentiful supply of rat chow pellets. For two rats, each lever-pressing response raised a dipper containing 0.2 ml of a 3 μg/ml of etonitazene in water; for two other rats each lever press produced 0.2 ml of a solution of 3 μg/ml etonitazene plus 0.2 mg/ml of quinine (as sulfate) in water. Control rats lever-pressed for 0.2 ml volumes of water or of quinine solutions not containing etonitazene. The only fluid available to the experimental rats for the first six 8-hr sessions were the solutions containing etonitazene. During these six sessions, the rats responding for

the etonitazene solutions responded slightly less often than the control rats responding for water or the quinine solution (fig. 9). Subsequently, all rats were given tap water except during the periods when lever-pressing was studied. Under this condition, the rates of lever-pressing by the rats receiving the etonitazene solutions were well maintained but the rates of responding by the rats receiving quinine or water decreased. In the final condition of this study, a bottle containing tap water was introduced into the test chamber, so that water was freely available at all times. When the tap water was freely available the rate of lever-pressing for quinine solutions or water were sharply decreased (rats Q-1, Q-2, W-1, W-2), whereas the rate of lever-pressing for etonitazene solutions decreased much less (E-1, E-3, E-4) or increased (E-2). Thus, etonitazene functioned as a reinforcer for lever-pressing in the rat, whether the drug was dissolved in water or in a bitter quinine solution.

Discussion

These experiments show that several variations of the schedule-induced poly-

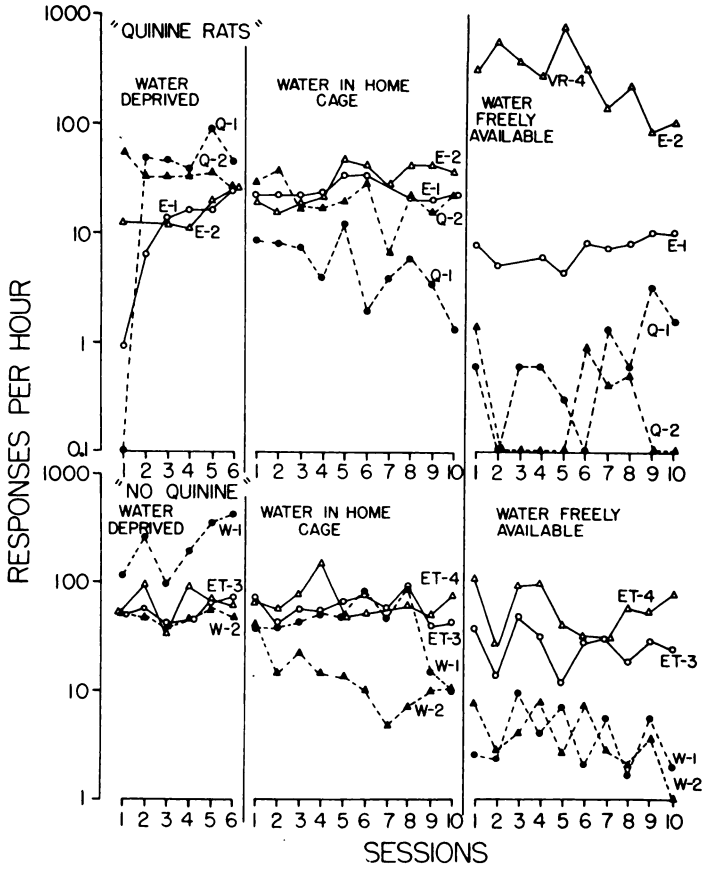

FIG. 9. Lever presses per hr for two rats lever-pressing for water (W-1, W-2), for two rats lever-pressing for quinine solution (Q-1, Q-2), for two rats lever-pressing for an etonitazene-quinine solution (E-1, E-2), and for two rats lever-pressing for an etonitazene solution (E-3, E-4). These 8 rats were trained to lever-press under a water deprivation condition (first 6 sessions; 8-hr sessions); then water was made available at all times except during the 8-hr session; finally water was freely available at all times. Each response produced presentation of 0.2 ml of solution under all conditions for all rats, except rat E-2 under the "water freely available" condition, where after the 3rd session, on the average, every fourth response (variable-ratio 4-response schedule) produced access to the etonitazene-quinine solution. The quinine concentrations were 0.2 mg quinine/ml; the etonitazene concentrations were 3 μg of etonitazene/ml.

dipsia method can be used to induce rats to drink larger doses of narcotic analgesics than they drink when similar concentrations of these drugs are dissolved in the only available drinking solution under free-feeding conditions. For example, when drug solutions were substituted for water for a period of 12 days, the average doses ingested during 24-hr periods were 100 mg/kg of 1 mg/ml of morphine SO_4, 60 mg/kg of 1 mg/ml of methadone, and 1.4 mg/kg of 10 μg/ml of etonitazene (13). The fixed-interval schedule of food-reinforced lever-pressing induced drinking of about 200 mg/kg of 1 mg/ml of morphine (HCl or SO_4) in 4-hr sessions; the fixed-interval schedule of food-reinforced spout-licking induced drinking of similar doses of 1 mg/ml of methadone solution in sessions only 90 min in duration. Similarly, the average ingestion of etonitazene by rats under a fixed-time 90-sec schedule was in excess of 2 mg/kg during four daily 45-min sessions. Thus all three methods induced a higher intake of drug during relatively short experimental sessions than occurred with continuous exposure to the drug solutions in the home cage. Of the two schedules of food presentation that were used with morphine and methadone, the fixed-interval schedule of food-reinforced spout-licking was most effective in producing high drug intakes. The fixed-time schedule with periods of food delivery spaced throughout the 24-hr day was very effective in producing high consumption with marked tolerance to etonitazene, a result that was not attained with once or twice daily exposures to etonitazene in the model with the fixed-interval schedule of food-reinforced lever-pressing.

Schedule-induced drinking of water is a postpellet phenomenon; almost every pellet delivery is followed by rapid licking of the spout. Our experiments showed that during the chronic ingestion of morphine and methadone solutions, the schedule of pellet delivery lost control over the drinking pattern, suggesting that narcotic drinking came to be maintained by variables other than the schedule of food presentation. A similar dissociation of drinking and food pellet delivery has been observed with chronic ethanol drinking "induced" in rats by schedule-induced polydipsia methods (7, 14).

Rats drinking an etonitazene solution in association with the fixed-time schedule did not show this dissociation of drinking and food pellet delivery during chronic exposure to this solution; however, these rats would drink the etonitazene solution in preference to water regardless of the location of the drug solution, whereas rats given a choice between water and saline solution drank whichever solution was closer to the pellet receptacle. In experiments with water freely available, rats pressed a lever to obtain etonitazene solutions more frequently than control rats pressing a lever to obtain solutions not containing etonitazene. These data suggest that etonitazene was functioning as a reinforcer. This suggestion is supported by the results of a recent experiment by Lewis, *et al.* (12), who established morphine dependence in rats with an injection regimen and then trained the rats to lever-press under a fixed-ratio schedule for 0.1 ml volumes of a 5 μg/ml etonitazene solution. Stable patterns of lever-pressing were maintained, even after discontinuation of the morphine injections, with the rats drinking average doses of 20 μg/kg during the daily 40 min sessions.

In summary, these results show that rats which are not physiologically dependent upon narcotics can be induced to drink solutions containing narcotics; that drinking of narcotic solutions can be induced with the method of schedule-induced polydipsia to the extent of consuming large doses of narcotics within relatively short periods of time each day and for many days in succession; and that solutions of narcotics can function as positive reinforcers even when water is concurrently freely available.

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