Psychopharmacologia (Berl.) 13, 81—88 (1968)

Self Administration of Minor Tranquilizers as a Function of Conditioning

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Received April 14, 1967
Final Version: December 16, 1967

Summary. An attempt was made to develop pronlonged preferences in rats for quinine, LSD, nicotinic acid, meprobamate and chlordiazepoxide. It was found that forced ingestions of the drugs had no enduring effects on subsequent free choice preference intakes. When the animals were conditioned to drink the drugs in order to obtain food pellets, it was found that they developed increased preferences for meprobamate and chlordiazepoxide which endured over a 21 day free choice period. The results are interpreted as showing that through pairing with food several of the drugs acquired secondary reinforcing properties which were responsible for their sustained drinking by the animals.

Key-Words: Psychiatry — Psychology — Drug Addiction — Reinforcement, Learning — Conditioning — Animal Behavior.

It is well established that animals which have become physically dependent on opiate drugs will self-administer the compounds in order to forestall abstinence effects (NICHOLS *et al.*, 1956; WEEKS, 1961). Further, WIKLER (1961) has demonstrated that even when once addicted subjects have been returned to a drug free state they often continue to consume the compound. An extension of these techniques to non-opiate drugs has been demonstrated (DENEAU, YANAGITA and SEEVERS, 1964) and results obtained which confirm that it is not only the opiate drugs which animals will self-administer. Each of these cases may be viewed as an instance of operant conditioning and the drugs considered to be primary reinforcers because they are ingested by animals solely for their physical properties.

The purpose of the present study was to examine a possible additional type of reinforcing function which drugs might serve—that of secondary reinforcers.

Traditionally, secondary reinforcing stimuli are developed by a pairing within a classical conditioning paradigm of such environmental stimuli as lights and tones with any number of primary reinforcing stimuli, e.g., food or water. Similarly, it seemed reasonable to expect that the physical properties of ingested drugs, when paired with a

primary reinforcer like food could also acquire secondary reinforcing properties and thus, be chronically self-administered by experimental subjects for this effect. This notion was readily tested by conditioning animals to drink various drug solutions for food and then allowing them to self-administer the compounds in choice tests which employed water as an alternative drinking solution. An increased preference for drugs was anticipated as a result of the pairing of the drugs with food, i.e., the secondary reinforcing properties of the compounds.

Subjects and Apparatus

The subjects were thirty adult female rats (Spague-Dawley) weighing between 250 and 310 g. They were maintained at 85% ad libitum weight throughout experimentation and supplied with drinking solutions from 250 ml calibrated bottles attached to the home cage. During the conditioned drinking phase of the study the animals were trained in commercial conditioning chambers, $8 \times 9^1/_2 \times 9^1/_2$ inch, equipped with dispensers which delivered 45 mg food pellets into trays located in the chambers. The delivery of the pellets was contingent on licks from a steel spout which eminated from a bottle placed in the chamber. Electronic controlling and recording units were used to monitor training sessions.

The drug concentrations used in all procedures were 0.5 mg/ml of chlordiazepoxide (Librium), 6 mg/ml meprobamate (Miltown), 2 μg/ml lysergic acid diethylamide (LSD), 1 mg/ml nicotinic acid and 0.1 mg/ml quinine. All drug concentrations contained 0.01 mg/ml of quinine as a control for taste.

Procedure 1. The 30 animals were housed in individual cages and for 25 days presented with a choice between tap water and a drug solution. The positions of the water and drug bottles were varied to control for preferences. The purpose of this procedure was to determine the extent to which the drug solutions would be consumed by the animals prior to their having experienced them.

Procedure 2. Fifteen rats then had their water bottles removed and were forced to obtain their fluid requirements from the drug solutions. Three rats were placed on each drug. After 25 days of forced drug consumption, water bottles were again added to home cages and each animal tested 21 days for preference between water and the drug which it had been forced to drink. The cycle of forced drinking for 25 days and choice for 21 was repeated. The purpose of this procedure was to determine if an increased preference of drugs would result from a period of their chronic ingestion.

Procedure 3. The remaining 15 rats were trained in chambers for a period of 25 days to drink drug solutions in order to receive food pellets.

Each daily session lasted until an animal had consumed 15 ml of a particular drug solution (animals trained to drink water for pellets drank 15 ml in 20 to 30 min) Initially, a 45 mg food pellet was delivered with every fifth lick of the spout (Fixed Ratio 5) and then gradually extended to one pellet per 50 licks (FR 50). Three animals were trained on each drug. Water was available to the animals in the training chambers and in home cages. Following 25 days of training, the rats were tested in their home cages for 21 days for drug and water preferences. Fluid intakes were recorded daily and the positions of the bottles switched frequently. The cycle of trained drinking for 25 days and choice for 21 was repeated. The purpose of this procedure was to determine if an increased preference by the animals for drugs would result from a period of pairing of the compounds with food.

Procedure 4. Four rats, additional to the 30 studied for the drinking response, were trained for 30 days to press a lever for pellets delivered on a FR 50 schedule of reinforcement. The conditions of training were identical to those of the drug-trained animals with the exception of the substitution of the lever pressing response for the licking response. Concurrent with training, and during subsequent extinction, the animals were forced to drink drug solutions in the home cage. Following training, daily sessions of extinction of the lever pressing response were undertaken. Forced drinking of drugs was continued during this period. Two rats, each under meprobamate and chlordiazepoxide, were used in this test. The purpose of this procedure was to determine the effects of the two compounds on extinction of a response other than licking.

Results and Discussion

Spontaneous Drinking of Drugs vs. Water

Only one of the 30 animals presented with a choice of a drug and water drank more than a few millilitres (average of 10) of the drug solution per day and in that case its drug intake (meprobamate) was considerably less than its water consumption (average of 45 ml). These data are not presented graphically since they approximate zero. The rats frequently sampled the quinine flavored drug solutions because of the shifts in bottle positions but, then, quickly shifted to water. This result demonstrates that the drug solutions were not primary reinforcers for the animals, i.e., they would not be consumed for their effects *per se*. It is highly probable, of course, that the bitter taste (to humans) of chlordiazepoxide, meprobamate and quinine was sufficient cause for refusal of the compounds by the animals. Obviously, these results do not bear on the possibily primary reinforcing characteristic which may derive from the physio-pharmacological effects of the drugs, once ingested.

Spontaneous Drinking of Drugs Following Forced Drinking

Fig. 1 shows that during the period of forced drinking of the drugs the animals in all group drank between 30 and 40 ml per day, which represents about a 30% reduction in the average daily tap water intake for rats of this age and species. Consumed in these quantities, the daily mg/kg dosages of each drug are considerably greater than the average

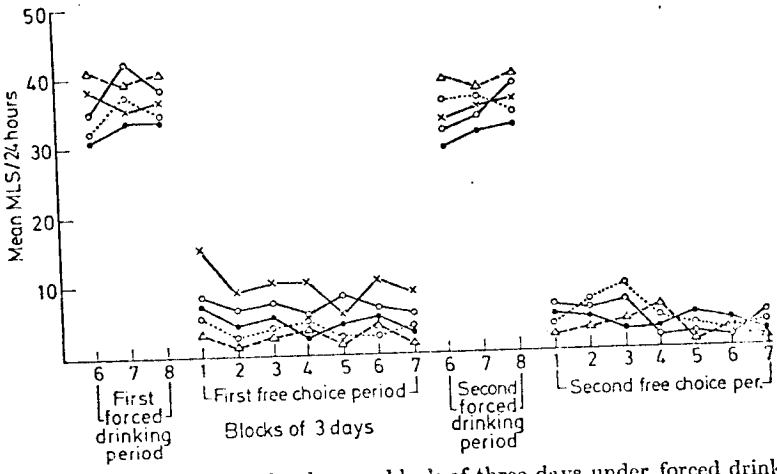

Fig. 1. Mean volumes of drug intake sper block of three days under forced drinking conditions (left points) and free choice tests (right points). ×——× Meprobamate; o——o Chlordiazepoxide; o····o Nicotine Acid; •——• LSD; ▵---▵ Quinine

dose necessary to produce discriminable effects in humans. The animals given LSD sometimes demonstrated locomotor disturbances associated with this drug, but in the main, none of the groups could be considered to have been markedly affected pharmacologically by the drugs.

The period of forced drinking did not appreciably influence the animals' consumption of the majority of the drugs in subsequent choice drinking tests (Fig. 1). Only the meprobamate group drank more than token amounts of its respective drug, and in that case one animal was primarily responsible for the elevated group curve, it having drunk almost exclusively from the drug bottle for the entire 21 day test period. The drug quantities consumed during the choice period by the meprobamate and chlordiazepoxide groups, while small, are nevertheless greater (0.01 level of significance) than the amounts consumed by their counterparts during the initial choice drinking period.

These results show that with the possible exception of meprobamate, the pharmacological effects derived from ingestion of these dose levels of the drugs were not primarily reinforcing to the animals. Dose-response

relationships, tolerance developments and other standard pharmacological measures will have to be obtained before any generalizations can be made on the physically addictive potentials of this group of drugs; but, for the purposes of this study, the results suffice to demonstrate that the increased drug preferences of the conditioned drinking groups shown in Fig. 2 cannot be attributed to such physical effects as addiction or taste adaptation.

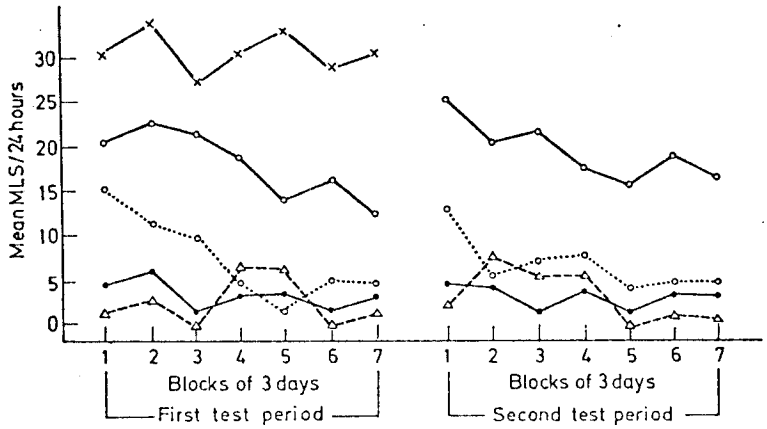

Fig. 2. Mean volumes of drug intakes per block of three days in free choice tests following training. ×——× Meprobamate; ○——○ Chlordiazepoxide; ○····○ Nicotine Acid; •——• LSD; ▵– –▵ Quinine

Spontaneous Drinking of Drugs Following Conditioned Drinking

Greater difficulty was encountered in shaping the drinking response than is usually found with behavior; however, all but the LSD group were trained within a week to readily consume 15 mls of drug solution within 30 min. The animals trained on LSD seldom consumed this amount in less than one hour. Fig. 3 presents a typical cumulative record of one animal's drinking behavior (chlordiazepoxide) during a training session. The animal drank continuously for intervals of five to eight minutes before pausing for brief periods. This performance is similar to that typically obtained on fixed ratio schedules in which other operant responses are reinforced (FERSTER and SKINNER, 1957).

Under this drinking condition, as compared to the previous 24-hour forced drinking procedure, the LSD animals frequently evinced a variety of observable pharmacological effects, probably because they were getting the same drug dosage in a fraction of the time. No attempt was made, however, to systematically quantify and record these effects and, thus, no determinations could be made of toxicity or tolerance development.

Fig. 3. Sample cumulative record of the drinking response of a subject trained on FR 20 to ingest chlordiazepoxide. Later in training, the schedule was extended to FR 50

The principal findings of this study can be observed in Fig. 2, where it is shown that during the preference test period which followed training, the meprobamate, chlordiazepoxide and nicotinic acid groups self-administered considerably greater drug quantities (0.01 level of significance) than had their forced drinking counterparts. The meprobamate and chlordiazepoxide groups averaged approximately 30 and 20 mls, respectively, throughout testing, which represented about 60 and 40 percent of their daily fluid intake (water drinking totals are not graphically presented). The drinking response of the chlordiazepoxide and nicotinic acid groups showed a steady decline over the 21 day test period while the meprobamate animals sustained a high level of drug consumption throughout testing. The meprobamate group was continued on the spontaneous drinking procedure and by the 40th day two of the three animals in this group died.

Drinking patterns for all drug groups during the second training and testing periods were essentially the same as during the first sessions. The meprobamate group, of course, could not be recycled because of the deaths of two of the rats in the group.

These results show that rats can be conditioned to consume drugs which they normally avoid and that the effects of such conditioning

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transfer to subsequent preferences for minor tranquilizers to a marked degree and to nicotinic acid to a lesser extent.

The differential preference by the animals for the drug solutions following conditioning, in conjunction with the virtual absence of drug preferences in the absence of such conditioning, emphasizes the importance of an interactive effect between the conditioning procedure and the physio-pharmacological activity of the drugs in the development of prolonged drug preferences. These data not do, of course, identify the nature of the physical properties of the drugs which may account for their chronic ingestion; however, it is clear from the 24-hour dosages consumed (35 mg/kg chlordiazepoxide and 900 mg/kg meprobamate) that pharmacological effects were experienced by the chlordiazepoxide and meprobamate groups (RANDALL *et al.*, 1960).

Responding in Extinction during Chronic Ingestion of Meprobamate and Chlordiazepoxide

By the 5th day of extinction lever pressing in both groups terminated within five minutes from the beginning of the session (these data are not presented graphically). These results do not differ significantly from rates obtained in extinction without drugs.

These results suggest that the prolonged drinking of meprobamate and chlordiazepoxide shown by the drinking animals was not due to a drug induced inhibition of the extinction process.

Several characteristics of these data indicate that the behavioral mechanism responsible for the sustained drinking levels of meprobamate and chlordiazepoxide can be considered to be the secondary reinforcing properties of the drugs rather than a prolonged extinction of the drinking response or a physical addiction to the compounds. The rapid extinction of drinking in the quinine, LSD and lever pressing groups equivocates interpretations of chronic drug drinking based on a depression of extinction while the absence of sustained drinking following a regimen of forced drug ingestion contraindicates a physical addiction. It would be interesting to determine whether other operant responses, such as lever pressing or maze running could be shaped in the conditioned meprobamate or chlordiazepoxide groups by employing the compounds as reinforcers. By this technique, as well as by others used in tests of generality of secondary reinforcers, the credibility of establishing drugs as secondary reinforcers could be experimentally checked.

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