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Brain Stimulation as the Reinforcer in Alcohol-Saline Discrimination

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DEWITTE, PH. *Brain stimulation as the reinforcer in alcohol-saline discrimination.* PHARMAC. BIOCHEM. BEHAV. 17(6) 1093–1096, 1982.—Male Wistar rats were trained to discriminate intraperitoneal injections of 1 g/kg alcohol from saline injections. The reward that reinforced correct choices was an electrical brain stimulation which the animals self-administered according to a FR10 schedule of bar pressing; the stimulation was given in the postero-lateral hypothalamus. Quantitative generalization experiments revealed a mean ED 50 of 0.39 g/kg. The main advantages of this method using direct intracranial stimulation as the reward would seem to be: (1) quantitative and qualitative generalization experiments can be carried out in non-deprived rats having a normal body weight and (2) the possibility of estimating, in addition to the analysis of their discriminative properties, the effects of drugs on self-stimulation rate.

Drug discrimination Alcohol Brain stimulation Reward Self-stimumation Rats

A WIDE variety of substances having CNS stimulant, tranquilizing, analgesic, hallucinogenic or other effects on the central nervous system can serve to control discriminative responding. In a discrimination paradigm, the discrimination made by the organism of the presence of one of these substances is a condition to obtain reward or to avoid punishment [3]. In establishing such drug-discrimination behavior, at least three variables are to be controlled, i.e., the pharmacological class of the drug, the animal's behavior, and the unconditioned stimulus which reinforces the behavior [1,4]. These variables are not perfectly independent. Drugs can produce motor effects which interfere with the acquisition of the discrimination, and some of the drugs which can be discriminated also possess reinforcing properties. It therefore would seem useful to establish a method in which the discriminative and the reinforcing properties of drugs can be assessed at the same time. Rewarding brain stimulation can be used as an unconditioned stimulus to evaluate the rewarding value of numerous drugs [9]. The phenomenon of intracranial self-stimulation gives access to the reward centers in the brain. The modification of the activity of these reward centers by drugs becomes apparent by the changes in the rate of bar presses for brain stimulation. The purpose of this paper was to determine the feasibility of using direct electrical brain stimulation as the reinforcer in a drug discrimination paradigm.

METHOD

Subjects, Electrodes and Histology

Male albino Wistar rats weighing approximately 300 g at the time of surgery, were implanted with a monopolar nickel-chrome electrode (0.25 mm) insulated except for the cross section of the tip. The electrodes were implanted stereotaxically according to the following coordinates: A3.5 mm behind bregma; L1.2 mm; H 8.3 mm below the skull surface (lateral posterior hypothalamus). This brain area was chosen for the high rate of self-stimulation that can be obtained there. The indifferent electrode was placed 2 mm in front of the bregma. The animals were allowed one week to recover and were then trained to self-stimulate. Upon completion of the experiment, subjects were killed and the brain removed and placed in 10% formalin in saline for 10 days. The brains were then frozen, cut at 100 μ, and the section stained with cresyl violet.

Animals were allowed to self-stimulate in modified Skinner boxes using brain stimulations of 0.2 sec train duration, 0.2 msec negative pulses being delivered at a frequency of 100 Hz. The current intensity varied between 60 and 200 μA from rat to rat with a mean of 130 μA. An experimental group of 8 rats showing consistent self-stimulation behavior, was established.

Apparatus

After the injection of drug or vehicle, animals were placed in an illuminated and sound-attenuating chamber (modified Campden Box); the chamber contained two levers (3.5×2.5 cm) separated by 11 cm on one wall. The appropriate lever was connected to the brain stimulator which automatically delivered one stimulation train after the required number of lever presses had been made; this number varied from 1 to 10 in the acquisition process of the FR requirement. The electrical parameters of the rewarding brain shock were always monitored by means of an oscilloscope, and the number of bar-presses on both levers was recorded.

Drug-Discrimination Procedure

The subjects were placed in the test chamber for a 15 min session, 10 min after an intraperitoneal injection of ethyl

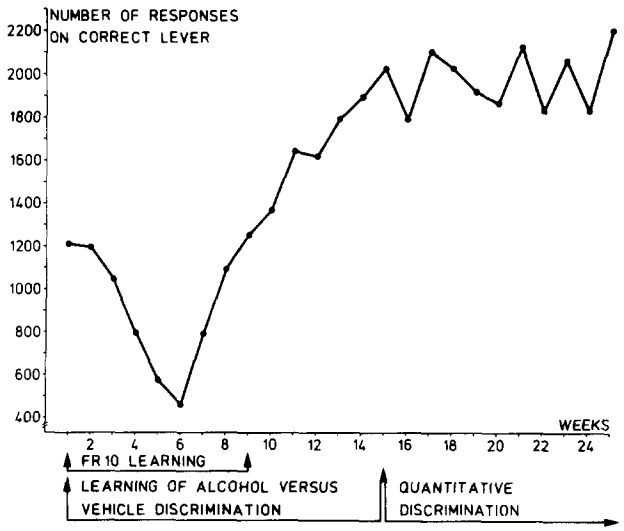

FIG. 1. Acquisition of FR10 responding and of the discrimination of 1 g/kg alcohol.

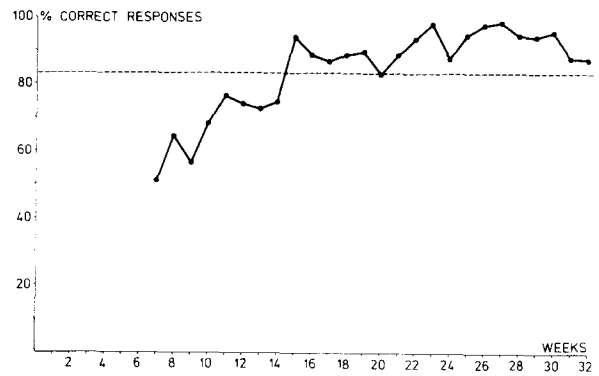

FIG. 2. Percentage of correct responses (ordinate) as a function of the number of weeks that expired in acquisition.

alcohol (1 g/kg, comprising 12,64 ml/kg of a 10% solution v/v in isotonic saline) or saline.

Injections of alcohol (A) or vehicle (V) were given according to two weekly alternating sequences, i.e.:V-A-A-V-A and the week 2: V-V-A-V-A.

Discrimination training began simultaneously with training on the FR10 schedule. The sample of rats was divided into two groups, the first having the alcohol lever on the right side and the second having it on the left.

Recorded were the number of bar presses on the incorrect lever before the first reward was delivered, the number of bar presses for the entire session, and the number of rewards received during each session.

Once FR10 responding was acquired, discriminative performances was evaluated using the percentage of correct responses, i.e. $(10/N)\times 100$, where N is the total number of bar presses made on both levers before the first reinforcement had been delivered. Averages of these percentages were calculated per rat and per week.

A correct choice was defined as a percentage of correct responses beyond 82% (no more than 2 presses on the incorrect lever before obtaining the first reward). The criterion of the discrimination acquisition was set at 8 such correct choices out of ten consecutive training sessions.

After having reached this criterion, dose-response effects were tested using doses of alcohol lower than the training dose (from 0.1 to 1 g/kg alcohol with increments of 0.1 g/kg).

On test days, one per week, an extinction period of 3 minutes was run. Between the test days, regular training sessions were continued to maintain the drug discrimination. Three successive correct drug discrimination training sessions were required before each test. The number of bar presses on each lever was recorded when there had been at least 10 presses on either lever. The percentage of responses on the drug lever was then calculated.

RESULTS

Six animals acquired the FR10 lever press response for brain stimulation reward after a mean period of 9 weeks (range: 7–12). Figure 1 shows that responses rate initially decreased as the FR requirement increased from one to ten. Once the FR10 was acquired, responding increased till about the 15th week and then remained stable at a mean number of 2.000 responses per 15 min session. Two of the 8 animals never acquired the FR10 and were discarded.

The mean percentage of correct responses increased from 56% at the end of the FR10 learning (9th week) to attain criterion (82%) in the 15th week (Fig. 2). From this week on, the percentage always remained above criterion. One animal died during this period.

The dose-response gradient for ethanol in the 5 remaining subjects trained with 1 g/kg of alcohol was then established. Figure 3 shows the individual percentage of responses on the drug lever during 3 minute extinction tests. It was found that the rats progressively discriminated lower doses of ethanol from the training dose; the gradients were generally similar among four of the five animals tested. Figure 3 also shows the mean gradient for the entire sample. The mean ED50 was 0.39 g/kg (range: 0.23–0.60).

DISCUSSION

The present experiment shows that electrical brain stimulation can serve as a reward in a drug discrimination paradigm. While comparison to published results [2, 6, 8, 10] on alcohol discrimination remains difficult, the used of brain stimulation as a reinforcer would seem to delay the FR10 learning (9 week as presented in Fig. 1). Nevertheless, once animals learned the task, discrimination remained stable for the entire experiment.

The median effective dose (ED50) was lower (0.39 g/kg) than that obtained for the same training dose used in other paradigms (0.604 g/kg by Kubena and Barry [6] and 0.610 g/kg by Krimmer [5]). The large number of low doses tested, together with the use of animals having a normal adult weight, probably contribute to this greater sensitivity.

The main advantages of the method using direct intracranial brain stimulation as the reward would therefore seem to be:

(1) The use of non-deprived rats having a normal body weight.

(2)The high number of responses (±2.000 bar presses for a 15 minute session) enables the stabilization of the discriminative conditioning.

(3)Finally, there is the possibility of estimating, in addi-

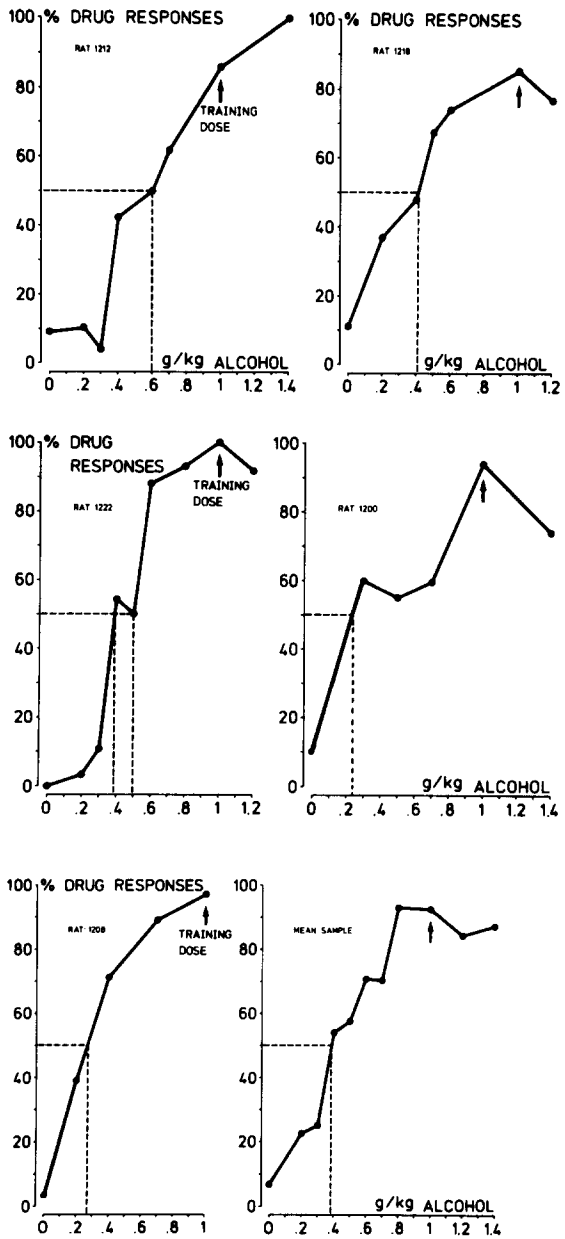

FIG. 3. Individual scores on the drug lever (ordinate) of rats and of the sample after injection of different test doses of alcohol (abscissa).

tion to the analysis of its discriminative properties, the effects of the training drug on self-stimulation.

After lever selection had occurred, the rats in this study self-stimulated for the remainder of the 15 min session. One may thus expect to observe differences between vehicle and drug conditions in terms of their influence on the reinforcing properties of the electrical brain stimulation. In other words, the more the drug interacts with the brain stimulation, the more marked the divergence between vehicle and drug sessions. In our experiment, the number of bar presses in alcohol sessions was lower (mean of 1.976) than that in saline sessions (mean of 2.078), but significance was not obtained for this difference (t-test, $p<0.05$). This probably indicates that the effects of 1 g/kg ethanol on self-stimulation are not very prominent [7].

We now plan to test larger doses of alcohol as well as drugs having strong reinforcing properties combined with modifications in the rewarding value of the brain stimulation.

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