Pharmacology Biochemistry & Behavior, Vol. 19, pp. 755–758, 1983. © Ankho International Inc. Printed in the U.S.A.

Interference by a Nonpharmacological Factor on the Action of Psychoactive Drugs in Rats. A Comparative Study[1]

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Received 23 February 1983

SILVA-FILHO, A. R., H. M. LODDER AND J. MASUR. *Interference by a nonpharmacological factor on the action of psychoactive drugs in rats. A comparative study.* PHARMACOL BIOCHEM BEHAV **19**(5) 755–758, 1983.—The interaction of 5 psychoactive drugs (ethanol, chlorpromazine, diazepam, pentobarbital and THC) with a nonpharmacological factor was studied in rats. The nonpharmacological variable studied was the level of motivation to overcome the depressant action of the drugs administered. Rats highly motivated to perform a learned escape response (high intensity footshocks during training) required significantly higher doses of ethanol to become impaired when compared to low motivated animals (low intensity footshocks during training). However, the level of motivation did not interact with the action of the other 4 drugs, as the doses required to impair the escape response were the same in the low and high motivated rats. The greater susceptibility of ethanol to a nonpharmacological factor when compared to the other psychoactive drugs is discussed.

Nonpharmacological influence on ethanol Ethanol and nonpharmacological interference
Psychoactive drugs and nonpharmacological factors Chlorpromazine Diazepam Pentobarbital THC

THE importance of nonpharmacological variables on the effects of psychotropic drugs has been demonstrated in several experimental situations. The setting in which the drug is ingested [11] and subject's expectancy [13] are some of the variables shown to interfere with drug action.

The specific question of whether or not a person can exercise self-control over the effects of drug intoxication has also been investigated. Thus, it was reported that properly motivated subjects were able to compensate for some of the effects of marihuana intoxication [1]. Similarly, Young and Pihl [14] demonstrated that alcoholized subjects when instructed to "try to stay sober" were less affected by the drug when compared to a control group without such an instruction.

The demonstration that drug intoxication is at least partially under volitional control leads to the question whether in animals a similar effect could also be observed. Such a finding would further demonstrate the importance of nonpharmacological factors when the effect of a drug is being considered.

The present experiment was designed to test whether rats trained to perform an escape response are able to overcome the depressant effects of ethanol, pentobarbital, chlorpromazine, diazepam and Δ^9-*trans*-tetrahydrocannabinol (THC).

METHOD

Animals

Male Wistar rats were used. After weaning at 25 days of age they were kept in groups of 3 in wire cages. They were 90 days old at the beginning of the experiment.

Apparatus

Two chambers (28×25×31 cm) were connected to each other through a 7×8 cm opening at the top, situated 23 cm from the floor. Moving from one chamber to the other required a jumping response. The floor of one of the chambers had a grid floor connected to a shock generator while the other chamber was provided with a wooden floor.

Drugs

Ethanol, prepared as a 15% (w/v) solution in saline, Diazepam (Vallium®, Roche) and Chlorpromazine (Amplictil®, Rhodia) in ampoules, (−) Δ^9-*trans*-tetrahydrocannabinol-THC (kindly supplied by NIH) suspended in 0.7% Tween 80-saline, and Pentobarbital sodium (Abbott) dissolved in water were used.

[1]Funded by Financiadora Nacional de Estudos e Projetos (FINEP) and Associação Fundo de Incentivo à Psicofarmacologia (AFIP).
[2]With a fellowship from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).
[3]Researcher 1-A from Conselho Nacional de Desenvolvimento Cientifico e Tecnológico (CNPq).

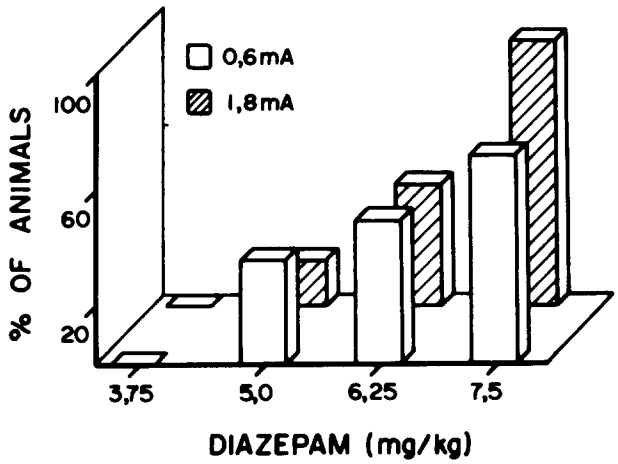

FIG. 1. Impairment by diazepam of a learned jumping response of rats trained under 0.6 or 1.8 mA footshocks. The columns indicate the percentage of animals which failed to perform the response. The ED_{50s} for the 0.6 and 1.8 mA groups were 6.7±0.6 mg/kg and 6.0±0.3 mg/kg, respectively. No significant difference was found.

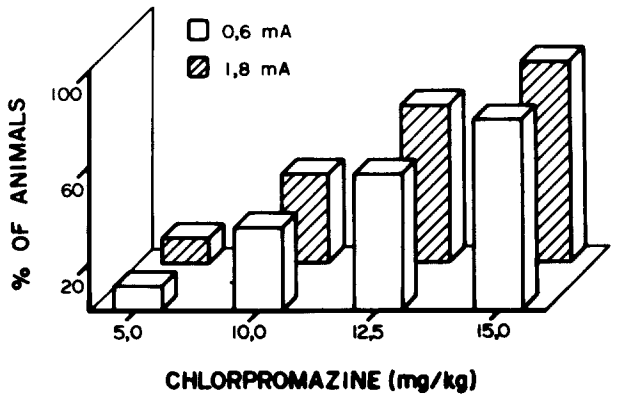

FIG. 2. Impairment by chlorpromazine of a learned jumping response of rats trained under 0.6 or 1.8 mA footshocks. The columns indicate the percentage of animals which failed to perform the response. The ED_{50s} for the 0.6 and 1.8 mA groups were 11.7±0.4 mg/kg and 11.0±0.3 mg/kg, respectively. No significant difference was found.

Procedure

The beginning of the session consisted of placing each rat on the grid floor chamber for at most 2 min. Footshocks were delivered at 5 sec intervals. At each session the rats received at least one shock, delivered at the moment they were introduced into the chamber. Latency to leave the electrified chamber through the jumping response was recorded. Animals were divided into 2 groups, receiving different intensities of footshock (0.6 or 1.8 mA). In our experimental conditions 0.6 mA was the lowest intensity which induced overt behavioral reaction as startle responses while 1.8 mA led to intense vocalization and reflex jumping.

Daily training sessions of one trial each were given until all rats reached a latency time to escape of at most 5 sec. Animals not fulfilling this criterion were excluded from the experiment. Rats of both groups of shock intensities received the same number of sessions.

After reaching the criterion the animals were submitted to a session in which they received an IP injection of the control solution (saline for diazepam, chlorpromazine and ethanol; distilled water for pentobarbital and saline plus Tween-80 for THC) with the shock generator disconnected. This was done in order to verify that the escape response would occur under the non-shock and IP injection conditions. This control session was followed next day by a normal training session under shock and no injection. Finally, on the next day, the animals were submitted to the drug experimental session without shock. Separate groups of 8–10 animals trained under 0.6 and 1.8 mA received either 4 doses of diazepam (3.75, 5.0, 6.25 and 7.5 mg/kg for both shock intensities), 3 doses of THC (5.0, 10 and 15 mg/kg for both shock intensities), 5 doses of ethanol (1.0, 1.25 and 1.5 g/kg for the 0.6 mA group; 1.0, 1.5, 2.0 and 2.5 g/kg for the 1.8 mA group), 3 doses of pentobarbital (10, 15 and 20 mg/kg for both shock intensities), or 4 doses of chlorpromazine (5.0, 10, 12.5 and 15 mg/kg for both shock intensities) as specified in Figs. 1–5. Thus, 35 groups of rats were employed of which 17 were in the 0.6 mA groups and 18 in 1.8 mA groups, corresponding to the 19 dosages of the 5 drugs used. All the animals were used only once, that is they were discarded after receiving one drug dosage.

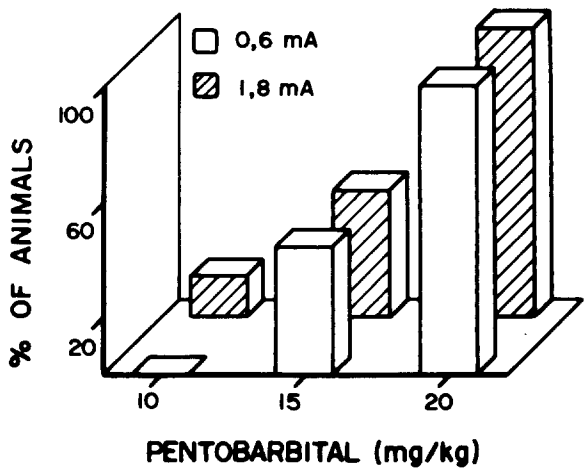

FIG. 3. Impairment by pentobarbital of a learned jumping response of rats trained under 0.6 or 1.8 mA footshocks. The columns indicate the percentage of animals which failed to perform the response. The ED_{50s} for the 0.6 and 1.8 mA groups were 14.8±1.5 mg/kg and 14.0±1.2 mg/kg, respectively. No significant difference was found.

The time interval between the IP injections and testing was 5 min for ethanol, 30 min for chlorpromazine, 60 min for THC, 30 min for diazepam and 10 min for pentobarbital. The maximum time of observation was 2 min.

Statistical Analysis

The percentage of animals failing to escape within the 2 min period was recorded for each dose and drug and the ED_{50s} calculated according to the method of Miller and Tainter [8]. Therefore, 2 ED_{50s} were obtained for each drug, one with rats trained under 0.6 mA and the other under shocks of 1.8 mA.

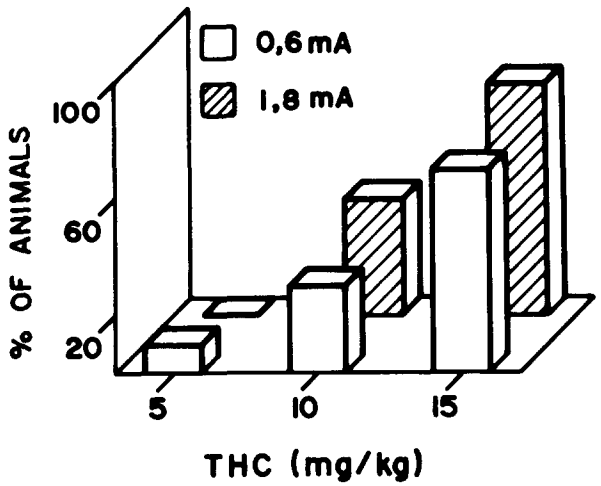

FIG. 4. Impairment by THC of a learned jumping response of rats trained under 0.6 or 1.8 mA footshocks. The columns indicate the percentage of animals which failed to perform the response. The ED_{50s} for the 0.6 and 1.8 mA groups were 12.8±2.4 mg/kg and 11.4±1.5 mg/kg, respectively. No significant difference was found.

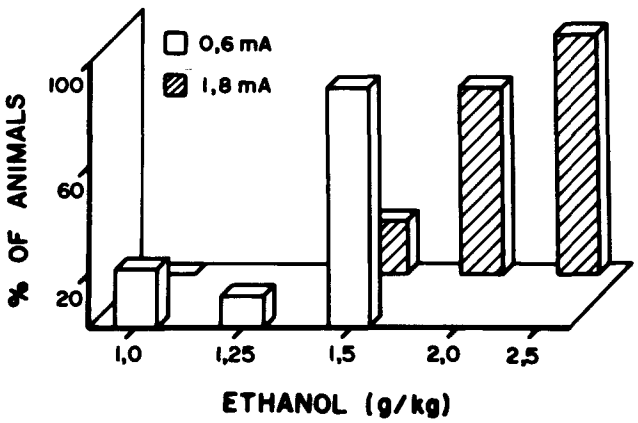

FIG. 5. Impairment by ethanol of a learned jumping response of rats trained under 0.6 or 1.8 mA footshocks. The columns indicate the percentage of animals which failed to perform the response. The ED_{50s} for the 0.6 and 1.8 mA groups were 1.30±0.07 g/kg and 1.72±0.13 g/kg, respectively. Significant difference was found at a level of 0.05.

RESULTS

A striking difference was noted, in how both groups acquired the escape response, suggesting different strength of motivation. About 30–40% of the rats receiving 0.6 mA footshocks had to be excluded, most of them after the first sessions, as they did not leave the chamber within the 2 min period of observation. In contrast this occurred with only 0–5% of the 1.8 mA group. As this pattern was observed in a previous pilot study designed to determinate the intensities of shock, the initial number of rats of the 0.6 mA group was always larger.

The number of sessions necessary to reach the criterion (leaving the electrified chamber within 5 sec) varied from 6 to 15 sessions. The groups receiving the higher intensity of shock reached criterion after 6 to 8 sessions, while 12 to 15 were required for the 0.6 mA groups (not considering those who were excluded). No difference in performance was observed between the two shock groups in the control session when solvent was injected and no shock delivered.

Figures 1–5 show the dose-response results for the drugs tested. Diazepam (Fig. 1), chlorpromazine (Fig. 2), pentobarbital (Fig. 3) and THC (Fig. 4) were not sensitive to the nonpharmacological factor studied, as the percentage of treated animals which failed to perform the escape behavior was independent of the intensity of the previously received footshocks. Consequently, ED_{50s} were the same for both shock intensities, as indicated in the legend of the Figs. 1–4. Conversely, the ethanol's depressant action was influenced by the nonpharmacological variable employed (Fig. 5). Rats escaping from 1.8 mA shocks overcome the alcohol depressant effect: the dose of 1.5 g/kg that induced impairment of the escape response in nearly 100% of animals of the low-shock group (0.6 mA), affected only a small percentage (20%) of the high-shock animals (1.8 mA). For this latter group it was necessary to increase the dose to 2.5 g/kg in order to abolish the escape response. The comparison of the ED_{50} of the two groups revealed a significant difference at a level of 0.05 as shown in the legend of Fig. 5.

DISCUSSION

As proposed by Edwards [4] in a review article a "fundamental property of any psychotropic substance is manifested in the degree to which its drug related behavior is potentially susceptible to modification." Based on this assumption the concept of plasticity was developed. That is, if a determined action of a psychoactive drug can be modified by nonpharmacological variables (e.g., personality and environment) this effect is considered to be plastic. Conversely, a non plastic effect is not susceptible to modification.

The concept of plasticity is very important to the understanding on how a psychoactive drug exerts its action as the final expression of a drug effect can not be attributed solely to its pharmacological properties. For example, the importance of environmental variables on the development of tolerance to a behaviorally active drug has been extensively demonstrated (e.g., [3, 6, 7, 9, 12]).

In the present paper the effects of a nonpharmacological factor on the acute depressant action of different psychoactive drugs were studied. It was shown that the nonpharmacological variable intensity of footshock did influence the motor depressant effect of ethanol, but did not affect the performance impairment induced by diazepam, chlorpromazine, pentobarbital and THC.

The ability of humans to overcome alcohol intoxication when properly motivated has been described (e.g., [14]). The observation reported here, showing a similar phenomenon in animals, points to the relevance of the nonpharmacological factors when the effects of a psychoactive drug are being considered. The description of the plasticity of the effects of drugs in humans is frequently hindered by confounding variables such as personality characteristics, previous experience with the drug and expectancy of the drug effects. Therefore, animal models can, within their proper limitations, bring further insight to this area of research.

Some important points deserves discussion in the interpretation of the present data. The absence of an effect in laboratory animals as shown for THC, diazepam, pentobar-

bital and chlorpromazine does not preclude the plasticity of their effects in humans. Indeed, there are several evidences of the plasticity of THC effects in humans [2, 5, 10]. However, the demonstration of the nonpharmacological influence on alcohol's effect in rats provides an indication that the degree of plasticity of this drug could be greater when compared to the other psychoactive substances studied. However, an alternative hypothesis, related to task-specificity has to be considered. It is possible that if other drug related behaviors were studied different results could have been attained. Thus, the conclusion of the present paper, on the greater degree of plasticity of ethanol effect has to be limited to the depressant action of this drug.

Another major aspect has to be taken into account. That is, the positive result found for alcohol was obtained with one group receiving the lowest intensity of shock able to induce detectable behavioral reactions. It is possible that by increasing the shock intensity to levels over the threshold one the observed difference in the reaction to ethanol between the low and high shock groups would disappear. Conversely, by increasing still more the strength of motivation of the high-shock group a result similar to the observed with ethanol could be disclosed for the other drugs studied.

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