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BRIEF COMMUNICATION

Protection From Pentobarbital Lethality Mediated by Pavlovian Conditioning

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VILA, C. J. *Protection from pentobarbital lethality mediated by Pavlovian conditioning.* PHARMACOL BIOCHEM BEHAV 32(1) 365–366, 1989.—The lethal effects of pentobarbital overdose were dependent upon the context in which the drug was administered. Rats received repeated injections of pentobarbital (30 mg/kg), in a distinctive environment and saline in the home room. At test, rats received a large dose (95 mg/kg) of pentobarbital. Fewer deaths occurred in a contex previously associated with drug administration. The results are consistent with a Pavlovian model of drug tolerance.

Pentobarbital Overdose Tolerance Pavlovian conditioning

TOLERANCE has been defined as a decrement in the effect of a drug as a consequence of repeated administration (1). The role of contextual cues on the development and maintenance of tolerance has been recently emphasized (8). The effect of context on tolerance is based upon a Pavlovian conditioning model in which the administration of a drug constitutes a conditioning trial.

The context present at the moment of the drug administration functions as a conditioned stimulus (CS) and the drug effect is considered the unconditioned stimulus (US). According to the conditioning theory of drug tolerance the CS comes to elicit a compensatory conditioned response (CR) which is opposed to the effects of the drug. With the continued pairing of drug administration and the context (CS) a CR develops progressively and opposes the effects of the administered compound producing tolerance. This model of tolerance, based on associative procedures, has been demonstrated with several drugs, e.g., morphine (7), ethanol (3), scopolamine (5), haloperidol (4), pentobarbital (2,10) and amphetamine (6). In all these cases it has been demonstrated that tolerance occurs in the context associated with a history of drug administration but not in other environments.

Recently this model of Pavlovian conditioning has been applied to the lethal effects of an overdose of heroin. In study by Seigel *et al.* (9) fewer animals died when an overdose was administered in the environment associated with previous drug administration than when the overdose was administered in an environment previously associated only with saline injections.

The purpose of the present experiment was to evaluate the role of Pavlovian conditioning in the lethal effects of pentobarbital.

METHOD

Subjects

The subjects were 48 Long-Evans male rats approximately 90 days old at the beginning of the experiment. The subjects had free access to water and food, and were maintained on a dark-light cycle of 12 hours, the light cycle beginning at 7:00 hr.

Apparatus, Environments; Home and Drug Rooms

Each subject was housed in individual acrylic boxes (37×27×15 cm). The experiment was conducted in two separate rooms, the Drug room and the Home room. In the Home room the subjects were housed in their home cages. A white noise of 75 dB was present in the Drug room during the drug administration. The subjects were tested daily beginning at 14:00 hr.

Procedure

Table 1 shows the experimental design for the experiment. The subjects were randomly assigned to two groups of 24 rats each. Groups received 40 sessions alternated in the two environments.

When the session was in the Drug room the animals were transported in their boxes from the Home room to the Drug room; When the session was in the Home room the animals were tested in the same place they were housed. For the experimental group, pentobarbital (30 mg/kg) was administered intraperitoneally 15 min after being placed in the Drug room. Saline only was injected in the Home room (vol. eq.). In the control group the procedure was similar except that

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TABLE 1
EXPERIMENTAL DESIGN FOR PENTOBARBITAL OVERDOSE

Control N=24		Experimental N=24	
Train		Train	
Saline	Saline	Pento (30 mg/kg)	Saline
Home Room	Drug Room	Drug Room	Home Room
Test N=12 Each		Test N=12 Each	
Pento (95 mg/kg)	Pento (95 mg/kg)	Pento (95 mg/kg)	Pento (95 mg/kg)
Home Room	Drug Room	Drug Room	Home Room

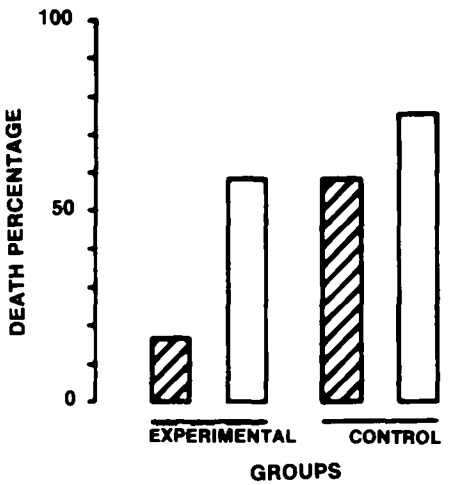

FIG. 1. The percentage of deaths by pentobarbital overdose for the experimental and control groups in the Home (hatched columns) and Drug (open columns) rooms.

saline was administered in both the Drug and Home rooms. There were 20 administrations of pentobarbital in the Drug room and 20 administrations of saline in Home room for the experimental group, and 40 administrations of saline on the Drug and Home rooms for the control group.

On session 41 pentobarbital at a dose of 95 mg/kg was administered to half of the experimental group and half of the control group in the Drug room. The number of deaths in each place was recorded. A subject was considered dead when it was immobile and without detectable heart rate (via palpation) for two hours.

RESULTS AND DISCUSSION

Figure 1 shows the percentage of deaths for both groups in the Drug and Home rooms. Significantly fewer deaths occurred in the experimental group in the Drug room than in the Home room ($\chi^2=4.42$, $p>0.05$). In the control group the pentobarbital lethality was not different in both environments ($\chi^2=0.75$, $p<0.05$). Also there was no significant difference in the number of animals that died in the Home room in the experimental and control groups ($\chi^2=0.187$, $p<0.05$).

These results indicate that the probability of pentobarbital-induced lethality is substantially diminished in an environment previously associated with pentobarbital administration.

Recently Siegel *et al.* (9) have proposed that death by overdose of a drug in tolerant subjects could be due to the absence of predictive cues that normally signal the drug and thus tolerance does not not occur. Death by pentobarbital overdose in the experimental group supports this analysis since the lethal effect of pentobarbital in the Home and Drug environments was dependent on a differential history of pentobarbital exposure in these two environments.

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