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Discriminative Stimulus Control with Imipramine: Transfer to other Anti-depressants

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SCHECHTER, M. D. *Discriminative stimulus control with imipramine: Transfer to other anti-depressants.* PHARMACOL BIOCHEM BEHAV **19**(5) 751–754, 1983.—Discriminative stimulus control with the tricyclic anti-depressant imipramine was attempted in three groups of rats; two of which were subjected to artificially stressful conditions. Only the unstressed group were shown capable of discriminating between the stimulus properties of intraperitoneal 10 mg/kg imipramine and saline in a two-lever, food-motivated operant task. Discriminative performance with decreasing doses of imipramine was shown to be dose-responsive. The ability to discriminate the interoceptive cue produced by imipramine was observed to transfer to a 10 mg/kg dose of both amitriptyline and desmethylimipramine. The results suggest a common tricyclic anti-depressant cueing property.

Drug discrimination Desmethylimipramine Imipramine Amitriptyline Tricyclic anti-depressants

A BEHAVIORAL paradigm which is particularly suited for assessing the subjective effects of psychoactive drugs is the drug discrimination procedure. The ability to assume discriminative control of behavior has been observed to be the property of virtually every psychoactive drug tested, and thus, most centrally acting drugs have effects that may be termed "discriminable" [2]. Within a discriminative stimulus (DS) paradigm, a subject comes under stimulus control of a drug whereby correct operant responses in a choice situation is contingent upon which drug was previously administered. Thus, a hungry rat is trained to emit one response, i.e., to press one lever of a two lever operant box for a food reward, following the administration of a drug. The same subject must make the opposite response, i.e., press the other lever, following the injection of a vehicle solution (saline). Research that employs the DS procedure indicates a direct relationship between the central effects of the drug and its ability to serve as a DS [11]. Although the specific basis of these drug discriminations is unknown, it is commonly assumed to reflect interoceptive stimulus consequences of drug actions, perhaps including events that might also be called changes in mood or affect. Some drugs are said to be more discriminable than others referring to the fact that drug discriminations are much more readily acquired with these drugs than with others [12].

Although many classes of psychoactive drugs have been used successfully as discriminative stimuli in operant tasks, very little information is available concerning the stimulus properties of anti-depressant compounds. Although rats have been trained in a shock-escape T-maze task to discriminate between doxepin, imipramine or amitriptyline and saline [12] and to discriminate desipramine from saline in a two-lever operant task [14], reports of extensive mortality rates among experimental subjects, before extensive transfer testing could be conducted, has limited the classification of a broad range of anti-depressants in the DS paradigm. Thus, exploration of a common cue property for various anti-depressant agents is at present lacking [8].

The intent of the present study was to determine the discriminative cueing properties of a prototype anti-depressant imipramine in three groups of animals; two of which were put under artificially stressful conditions in hopes of increasing the interoceptive cueing ability of this compound, and to evaluate other tricyclic anti-depressants in those animals successfully trained to discriminate imipramine from saline.

METHOD

Subjects

Subjects were 21 male ARS/Sprague-Dawley rats which weighed between 280 and 350 g at the beginning of the experiment. They were housed in individual cages in a vivarium facility kept at a constant temperature of 20–22°C with a daily cycle of 12 hours light and 12 hours dark. Standard laboratory chow was rationed such that subjects' weights remained at 80±5% of the free-feeding weight as determined by daily weighing of 3 free-feeding control rats purchased from the supplier (Zivic-Miller, Allison Park, PA) at the same time. Water was available ad lib.

Apparatus

Training was carried out in 4 standard two-lever operant chambers (Lafayette Instrument Co.). Two levers were lo-

cated 7 cm above the grid floor of the chambers and were 7 cm from each other with a food tray centered between the levers at an equal distance from them. The chambers were contained in sound-attenuating boxes in which were located 9 W houselights and exhaust fans. Reinforcement schedules were controlled, and subjects' responses were recorded, by solid-state programming equipment (LVB Corp.) located in a room adjoining the training room.

Stress Procedures

Rats were randomly divided into three equal groups of 7 animals each. One group, designated the "foot-shock" group, received 3 noncontingent foot-shocks (NCFS) of 0.80 mA of 1 sec duration each in a 1 min period while confined in a box similar to that used in training. The second group, designated the "restraint" group, were placed in wire tubes for 14 hr (1800–800 hr) and were removed immediately before training. The last group, the control group, were placed in the NCFS box for 1 min just prior to discrimination training. These treatments were begun 1 week prior to any discrimination training and were maintained throughout the training period.

Discrimination Training

Training was based upon procedures described by Overton [11]. There were two training phases. In the first phase, food-deprived subjects learned to lever press on both levers for food reinforcement (45 mg Noyes pellets) on an FR 10 schedule. The drug lever was activated first for all subjects. Animals were initially shaped to press this lever on an FR 1 schedule. The schedule was then made progressively more difficult over 10 days until an FR 10 schedule was achieved. Throughout drug-lever training, animals received daily intraperitoneal (IP) injection of imipramine hydrochloride (10 mg/kg, as base) 30 min prior to being placed into the two-lever operant box.

Immediately following attainment of the FR 10 schedule after drug administration, the opposite lever was activated and rats were trained on an FR 1 schedule 30 min after administration of an equal volume (1 ml/kg) of saline. Daily sessions of 30 min were continued over 7 days with saline administration until an FR 10 schedule was attained.

Phase II, discrimination training, then began. Subjects were trained 5 days per week in 15 min sessions with alternation of reinforcement proceeding in a pseudo-random sequence. Thus, in each two-week period there were 5 days with drug lever (D) correct and 5 days with saline lever (S) correct. The pattern was DSSDD; SDDSS. Criterion was set at 8 of 10 consecutive sessions during which the first food pellet was received within 12 or less total responses.

Dose-Response and Transfer Experiments

In those rats that attained training criterion, testing and training sessions of 15 min duration, with alternating administrations of 10 mg/kg imipramine and saline, were continued on Mondays, Wednesdays and Fridays. This procedure endeavored to insure and maintain behavioral discrimination to the trained drug conditions and it was intended that if a rat was observed to make more than 2 incorrect responses on these maintenance sessions, the data on that rat's performance would be deleted from the results of that week. On Tuesdays and Thursdays, the trained rats were injected IP with different doses of imipramine (2.5 and 5.0 mg/kg), amitriptyline hydrochloride (5.0 and 10.0 mg/kg, as base) or desmethylimipramine hydrochloride (5.0 and 10.0 mg/kg, as base) and, 30 min later, they were placed into the experimental chamber and were allowed to lever press until 10 responses were made on either of the two levers. Upon making these 10 responses, the rat was immediately removed to preclude continued training in a condition other than after administrations of 10 mg/kg imipramine or saline.

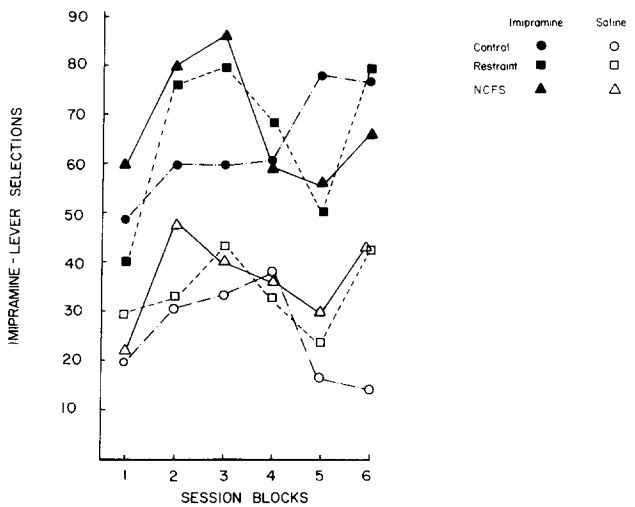

FIG. 1. Learning Curves for Three Groups of 7 Rats Administered Imipramine and Saline. Ordinate: Percent of rats selecting (responding 10 times first upon) imipramine-correct lever after the IP administration of either 10 mg/kg imipramine or saline. Abscissa: Session blocks, each consisting of 5 imipramine and 5 saline trials.

Data Analysis

Results are expressed as the lever first pressed 10 times (selected lever; quantal measurement) and as the number of responses emitted on both levers prior to 10 responses on the selected lever (quantitative measurement). These quantal measurements are expressed as percent selection on the imipramine-correct lever and the quantitative measurements are the number of imipramine-lever responses divided by total responses prior to 10 responses on either lever × 100. The advantages in using these two measurements of discriminative performance are discussed by Stolerman and D'Mello [15].

RESULTS

The learning curves of the 3 groups of rats are presented in Fig. 1. Only those animals in the control group reached criterion performance after 60 trials. Of these 7 rats, only 5 survived continued administrations of anti-depressants and, of these, one rat fell below criterion performance.

The dose-response results using lower imipramine doses and the transfer to other anti-depressants are presented in Table 1. The four rats selected the imipramine lever on all maintenance trials with 10 mg/kg imipramine and decreasing doses produced decreased discrimination. The highest (10 ml/kg) doses of both amitriptyline and desmethylimipramine produced imipramine-appropriate lever selection and the discriminative responding to this transfer was dose-responsive both in the quantal and quantitative measurements.

TABLE 1

QUANTAL AND QUANTITATIVE MEASUREMENTS OF DISCRIMINATION AFTER IMIPRAMINE, AMITRIPTALINE AND DESMETHYLIMIPRAMINE

Treatment	Dose (mg/kg)	% Selection on Imipramine-Lever (IL)	Number of Responses on IL/Total Responses X 100
Saline	—	12.5	24.1
Imipramine	10.0	100.0	86.2
	5.0	78.8	61.1
	2.5	25.0	38.9
Amitriptyline	10.0	87.5	75.2
	5.0	37.5	43.1
Desmethylimipramine	10.0	100.0	82.6
	5.0	50.0	51.5

DISCUSSION

In an attempt to increase the discriminability of the anti-depressant compound imipramine, two procedures were employed to stress rats prior to discriminative training, viz., noncontingent foot shock and restraint stress. The use of stress of various types as a precipitant of "depression" in animal models has been reviewed by Murphy and Redmond [10], and the behavioral consequences of stress have been shown to bear some similarity to human depression. In addition to noncontingent foot shock, other stresses such as immobilization [13], forced swimming [4], tumbling [1] and defeat in combat [6] have been studied in several species with many of these stresses producing changes in brain catecholamines [3]. It was hoped that the production of stress by noncontingent foot shock and by restraint would increase the discriminability of the anti-depressant in an analogous way to the use of myobacterium butyricum to produce joint pain increasing the discriminability of aspirin [16] or the use of chronic morphine to increase the discriminability of the opioid antagonist naltrexone [7]. Unfortunately, the two stress procedures employed were unsuccessful in increasing the ability of two groups of rats to discriminate imipramine from saline.

Nevertheless, the control group rats learned to discriminate the 10 mg/kg dose of imipramine from saline after 60 trials. In addition, the four rats who survived the continuous dosing with anti-depressants and maintained criterion performance were observed to discriminate decreasing doses of the training drug in a dose-responsive manner and to transfer the imipramine-appropriate cue to two other tricyclic antidepressants, viz., desipramine and amitriptyline. Shearman *et al.* [14] have reported that 10 mg/kg desipramine was discriminable from saline and that this effect was, likewise, dose-responsive. As in the present study, they, however, reported that continuous administration of this anti-depressant produced disabling effects or mortality in their animals which precluded additional generalization testing with other drugs. Jones *et al* [8] were successful in training animals to discriminate bupropion (20 mg/kg) from saline and reported that amitriptyline, desiprimine and imipramine do not generalize when administered to these animals. In general, the stimulus properties of bupropion in rats appeared to reflect the locomotor stimulant effects of other stimulant agents, such as caffeine and amphetamine. Thus, this report was unable to evidence a common anti-depressant cue between bupropion and tricyclic anti-depressants. Pertinent to this information is the observation that anti-depressants do not produce common subjective effects in non-depressed (normal) human subjects [5,9].

A successful attempt in training rats to discriminate imipramine from saline in a T-maze shock apparatus was reported by Overton and Batta [12]. Both 40 mg/kg imipramine and 20 mg/kg amitriptyline were reported to be successfully used in this report. Unfortunately, drug transfer was not tried in these experiments and the training doses produced both chronic toxic effects and convulsions.

The present observation of the ability of rats to generalize their discrimination from imipramine to two other tricyclic anti-depressants is, to the author's knowledge, the first report of such an occurrence. Thus, there is a possibility of a common anti-depressant cue that may exist. However, the toxicity of imipramine after chronic administration persists and this factor must be kept in mind in future research.

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