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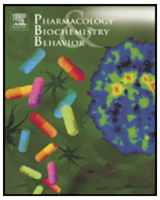

Increasing food deprivation relative to baseline influences *d*-amphetamine dose–response gradients

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ABSTRACT

Several studies using non-pharmacological discriminative stimuli have found that stimulus control, as evident in generalization gradients, changes when motivation for (i.e., deprivation of) the relevant reinforcer is altered. Drug-discrimination studies, however, have not consistently revealed such an effect. A procedural detail that may account for the lack of a reliable effect in drug-discrimination studies is that motivation was characteristically reduced relative to the training condition in these studies. The present experiment examined how substantially increasing motivation affects *d*-amphetamine discrimination. Rats initially were trained to discriminate *d*-amphetamine (1.0 mg/kg) from vehicle (0 mg/kg) injections under 22-h food deprivation conditions. Dose–response gradients were then obtained under 22-h and 46-h deprivation levels. The ED_{50} was significantly higher with greater deprivation. This finding suggests that increasing motivation relative to the training condition may reduce stimulus control by drugs, while decreasing it may sharpen stimulus control.

1. Introduction

Motivating operations (MOs) are changes in the environment, such as instituting food deprivation, that alter the reinforcing effectiveness of specified stimuli, such as food (Laraway et al., 2003). A recent review (Lotfizadeh et al., 2012a) summarized the effects of MOs on stimulus control exerted by drug and non-drug stimuli. The authors reviewed the experiments that obtained generalization gradients under various levels of food or water deprivation. Generalization gradients are graphic depictions of responding when a discriminative stimulus is presented and when other untrained stimuli that vary by differing amounts from the discriminative stimulus are presented; they take the form of dose–response curves in drug-discrimination studies. Results of published studies suggest that deprivation often influence stimulus control by altering the range of stimuli that evoke responding (i.e., the width of generalization gradients), by altering the evocative strength of various test stimuli differently (i.e., the height and slope of generalization gradients), and by exerting these effects in a graded fashion. While these results were obtained in all non-drug discrimination studies and in one drug-discrimination study (Gaiardi et al., 1987), three drug-discrimination experiments failed to demonstrate statistically significant effects of deprivation on stimulus control (Li et al., 1995, Experiments 1 and 2; Massey and McMillan, 1987). The drug-discrimination studies were not specifically designed to evaluate the effects of changes in motivation on generalization gradients, however, and differed in several aspects from one another and from the studies that examined the effects of altering deprivation on stimulus control by non-drug stimuli.

In an attempt to control for some procedural differences across the drug-discrimination studies reviewed by Lotfizadeh et al. (2012a,b) conducted an experiment to examine the influence of pre-feeding and no-pre-feeding conditions on *d*-amphetamine discrimination using rats as subjects. The purpose of the study was to assess whether (a) the dependent variables that were used in the previous experiments (quantal vs. graded), (b) the species, and (c) the testing procedures accounted for the discrepant results across studies. The authors concluded that the measurement system, the species, and the testing procedures were not responsible for the discrepant results that were obtained in previous drug-discrimination studies. In the Lotfizadeh et al. (2012b) study, pre-feeding did not affect *d*-amphetamine dose–response gradients, which was consistent with the results of most other drug-discrimination studies but inconsistent with the results of studies using non-pharmacological discriminative stimuli.

A difficulty in comparing drug-discrimination studies with other discrimination studies that altered deprivation is that the primary response measure in drug-discrimination is a relative measure of responding (e.g., percentage of responses on one of two levers, the drug-appropriate lever during training), whereas the primary measure in other discrimination studies is an absolute measure (e.g., response rate, force, or latency) of responding on one operandum. In order to make better comparisons between drug-discrimination and other studies, it may be helpful to convert the absolute response measures into

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percentage (relative) measures by expressing the absolute response measure obtained at a given test stimulus (e.g., 10 responses in 1 min) by the corresponding measure obtained with the training discriminative stimulus (e.g., 20 responses in 1 min) or all stimuli and multiplying by 100 (yielding a value of 50% in our example).

Coate (1964) presented gradients of relative generalization under 5-, 12-, 40-, and 48-h water deprivation conditions using a standard stimulus generalization procedure (not drug-discrimination). We also derived gradients of relative generalization similar to those presented by Coate (1964) from two other non-drug-discrimination studies that were reviewed in the Lotfizadeh et al. (2012a) paper. This was done for studies that reported response frequency and tested responding across more than four stimulus values (Kalish and Haber, 1965; Thomas and King, 1959) at two or more deprivation levels. Both the gradients from the Coate (1964) study and the transformed gradients yielded sigmoidal (s-shaped) gradients at higher deprivation levels (i.e., with a stronger MO in effect) and curvilinear (steeper) gradients at lower deprivation levels (i.e., with a weaker MO in effect). Interestingly, a similar pattern was also obtained in the only drug-discrimination study that demonstrated a statistically significant effect of motivation level on stimulus generalization (Gaiardi et al., 1987).

The pattern of results obtained with the gradients of relative generalization and the results of the Gaiardi et al. (1987) study suggest that low deprivation test conditions may enhance discrimination (as evidenced by curvilinear gradients with steeper slopes), whereas high deprivation test conditions may hinder discrimination (as evidenced by sigmoidal gradients of relative generalization). However, these findings were not replicated in any of the other drug-discrimination studies (Li et al., 1995; Lotfizadeh et al., 2012a,b; Massey and McMillan, 1987) and possible causes of the difference in results merit further attention.

Evidence suggests that discriminative performance is less susceptible to changes in deprivation when there is good stimulus control (Powell, 1971). In all of the drug-discrimination studies that did not demonstrate that reducing deprivation altered the generalization gradient (Li et al., 1995; Lotfizadeh et al., 2012b; Massey and McMillan, 1987), generalization tests were conducted when there was good discrimination (e.g., responding on the injection-appropriate lever during 80% or more of opportunities across eight or more consecutive sessions). Gaiardi et al. (1987) utilized a more lenient discrimination criterion than the other experiments before moving on to testing (see Gaiardi et al., 1987 for more details on the discrimination criterion), so discriminative performance may not have been established to the same degree and pre-feeding may have influenced discriminative performance because of the more lenient discrimination criterion. Based on these findings, it is likely that operations that can enhance discrimination (e.g., pre-feeding or increasing body weight) do not do so when there is good discrimination before they are instituted.

Variables that hinder discrimination relative to the baseline condition, such as high deprivation conditions, have rarely been examined in drug-discrimination. This occurred in only one study (Massey and McMillan, 1987) but, as noted previously, the study was not intended to examine the effects of deprivation on generalization and there were methodological limitations that make findings difficult to interpret. Massey and McMillan (1987) trained pigeons to discriminate phencyclidine (PCP) injections from saline injections when the subjects were at 80% of their free-feeding weights. They subsequently obtained dose–response gradients at 70%, 80%, and 90% of their free-feeding weights. However, the animals received discrimination training at all deprivation (i.e., MO) levels prior to testing, which engendered a high degree of stimulus control. For example, when the birds' weights were adjusted from 80% (baseline) to 70% of free-feeding (high deprivation) levels, they continued to receive discrimination training and continued to do so after they reached high deprivation conditions. Given that training was conducted and discriminated responding was established after the body weights were adjusted (i.e., after the MO manipulation had taken place), an effect on generalization should not have been expected and did not occur; there were no apparent differences between dose and response gradients as a function of changes in body weight.

To examine whether changing the level of food deprivation affects generalization gradients, i.e., dose–response relations, in a drug-discrimination procedure when deprivation is increased relative to the training condition and no training is arranged at the higher deprivation level, the present study established 1.0 mg/kg *d*-amphetamine as a discriminative stimulus for rats trained under 22-h food deprivation, then tested (without training) at other doses under 22-h and 46-h food deprivation.

2. Methods

2.1. Subjects

Twelve experimentally naïve male Sprague–Dawley rats were used as subjects. The rats were approximately 50 days old at the beginning of the study. They had unlimited access to water in their home cages and were provided with access to grain-based Purina Rodent Chow (Brentwood, MO) in their home cages according to their feeding schedules, as described below. The experimental animals' body weights were compared to those of members of a control group that were given free access to food to ensure that experimental procedures did not interfere with physical development. The rats were individually housed in 20-cm × 40-cm cages that were kept in a colony room maintained at 20 °C and 20% humidity under a 12-h light/12-h dark cycle. Experimental sessions were conducted six days a week at the same time each day, during the light cycle. The study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 2010) and was approved by the Institutional Animal Care and Use Committee at Western Michigan University.

2.2. Apparatus

Six Med Associates (St. Albans, VT) operant conditioning chambers measuring 31.5 cm (length) × 25.5 cm (width) × 25 cm (height) were used in the experiment. Each chamber contained two retractable response levers located on the right and left sides of the front wall, 3 cm from the nearest sidewall and 6 cm above the chamber floor. Casein-based food pellets (45 mg BioServ, Frenchtown, NJ) were delivered into a metal cup located in a 5-cm × 5-cm opening on the front wall between the two response levers. A 7-W light bulb on the top center of the back wall provided illumination throughout sessions. Each experimental chamber was placed in a sound-attenuating shell with an exhaust fan to provide ventilation and masking noise. Preliminary training was conducted in six similar chambers, which differed only in that a third response lever was located equidistant between the left and right levers. The experimental chambers were connected to a desktop computer via a MED-Associates interface and were operated by MED-PC® software (v. IV for Windows).

2.3. Pharmacological preparation

Sterile 0.9% saline solution was used to dissolve *d*-amphetamine hemisulfate (Sigma Aldrich, St. Louis, MO), which was administered via intraperitoneal injection at a volume of 1.0 ml/kg. Doses were calculated based on the weight of the salt.

2.4. Training

During preliminary training, the rats were acclimated to the chambers and exposed to a fixed-time (FT) 60-s schedule of food delivery during 50-min sessions. Under this schedule, a pellet was delivered every 60 s, regardless of the rat's behavior. Following two such sessions, responding on a center lever (no other levers were present) was initially