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Effects of LSD on Learning as Measured by Classical Conditioning of the Rabbit Nictitating Membrane Response[1]

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ABSTRACT

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Acquisition of the classically conditioned, nictitating membrane response was used to assess effects of LSD on learning. Tone and light conditioned stimuli (CS) were presented 800 msec before delivery of the unconditioned stimulus, consisting of a 100 msec electric shock to the skin over the paraorbital region of the head. Extension of the membrane to the CSs in the 800 msec prior to shock onset was recorded as a conditioned response (CR), while extension to shock onset was recorded as an unconditioned response (UCR). LSD (1, 10, 30, 100 or 300 nmol/kg) was injected i.v., 30 min before each daily conditioning session. Dosages of 1 to 100 nmol/kg of LSD produced a dose-dependent enhancement of CR acquisition. Acquisition to a criterion of 10 successive CRs required 184 trials at 30 nmol/kg of LSD as compared to 293 trials with controls. Separate groups of rabbits received explicitly unpaired presentations of stimuli (tone alone, light alone and shock alone). The frequency of responding within 800 msec of CS onset or in the 800 msec before shock onset was low (2–3%) and was not affected by any dosage of LSD, indicating that the effects of LSD on acquisition were not due to sensitization, pseudoconditioning or changes in baseline responding. LSD also had no effect on UCR amplitude. Hence, the systematic effects of LSD on acquisition of CRs reflects the action of the drug on learning.

Little is known concerning the possible effects of hallucinogens on the acquisition of learned behaviors. Operant procedures for the examination of drug effects on behavior were first reported by Skinner and Heron (1937) and subsequently applied in a systematic fashion beginning with the classic study of Dews (1955). These studies have provided a great deal of valuable information but have primarily examined the effects of drugs, including hallucinogens (Freedman *et al.*, 1964; Appel, 1971; Harris *et al.*, 1978), on well established behaviors. Studies of drug action in classical (Pavlovian) conditioning situations, although first initiated as early as 1908 in Pavlov's laboratory (Pavlov, 1960), have been relatively rare. Moreover, the one study employing a hallucinogen, mescaline, focused primarily on the performance of already established conditioned responses in well trained animals (Bridger and Gantt, 1956). Thus, operant and classical conditioning procedures have not been employed to examine the effects of hallucinogens on learning.

The effects of hallucinogens on learning have been examined in a few studies employing the conditioned avoidance response (CAR) which can be viewed as combining elements of both classical and operant conditioning techniques. Mescaline and *d*-lysergic acid diethylamide (LSD) have been reported to produce both enhanced and retarded acquisition of the CAR depending on dosage and apparatus employed (Domino *et al.*, 1965; Bignami, 1972; Stoff *et al.*, 1974; Bridger, 1975; Izquierdo, 1976). However, these effects of LSD or mescaline on CAR acquisition have not provided an unambiguous assessment of drug effects on learning since changes in rates of CAR acquisition were not separated from possible effects of the drugs on such factors as pseudoconditioning, sensitization or alteration in baseline rate of responding. Thus, various investigators have interpreted changes in CAR acquisition produced by LSD as due to an effect on learning (Bridger, 1975), pseudoconditioning (Izquierdo, 1976) and motivation (Bignami, 1972).

We used a classical conditioning procedure employing the rabbit nictitating membrane response to examine the effects of LSD on the acquisition of conditioned responses (CRs). This preparation, which has been extensively described (Gormezano, 1966, 1972), has several advantages. Electric shock to the skin of the paraorbital region or a brief air puff to the cornea (the unconditioned stimuli, UCS) reliably elicit an unconditioned response (UCR) of eyeball retraction, *via* the action of the retractor bulbus muscle, which results in the passive extension of the nictitating membrane over the globe. The extension of the nictitating membrane is thus solely controlled by the abducens nucleus of the brainstem *via* the sixth cranial nerve (Cegavske *et al.*, 1976). More importantly, the rabbit, when

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properly restrained, remains relatively passive in the conditioning situation and the baseline frequency of membrane extensions is quite low (1–3 responses/hr). In addition, there are no unconditioned responses of the nictitating membrane to tone or light conditioned stimuli (CS) and control procedures consisting of the unpaired presentations of CSs and UCSs reveal, essentially, no change in baseline responding and the absence of sensitization or pseudoconditioning effects to the CS. Also, in classical conditioning preparations, the CR and UCR occur within the same response system (Gormezano and Kehoe, 1975), and one can determine whether changes in CR production are related to changes in the reflex system itself (Gormezano, 1966). The present study examined acquisition of the classically conditioned, rabbit nictitating membrane response under five dosages of LSD.

Methods

This study employed 120 rabbits of either sex (New Zealand White albino) obtained from Morrison Rabbitry, West Liberty, Iowa. Animals weighing between 1.9 to 2.4 kg during the course of the experiments were housed individually with free access to Purina Rabbit Chow and tap water.

Apparatus and general procedure. The apparatus and procedures employed in conditioning of the rabbit nictitating membrane response have been described in detail (Gormezano *et al.*, 1962; Gormezano, 1966). A small loop of monofilament nylon was sutured into the right nictitating membrane. The hair was removed from the skin of the paraorbital region and two stainless steel wound clips were applied to the skin 10 mm posterior to the canthus and 15 mm apart in the vertical direction. Each rabbit was placed in a Plexiglas restrainer and fitted with a muzzle-like headmount that supported a resistive photocell transducer assembly for recording nictitating membrane responses. Each rabbit was then positioned in a ventilated, sound attenuated, conditioning chamber containing an 11.4 cm speaker positioned above and in front of the animal. Houselights were provided by two panels, one located to each side of the speaker, each illuminated by a 6 w, 24 V d.c. light bulb (2.6 mL). The nylon suture was coupled to an angled piano-wire rod protruding from the transducer assembly. The transducer converted the rabbit's nictitating membrane movements into electrical signals that were recorded on a Beckman type R oscillograph at a paper speed of 100 mm/sec and an amplification of 2 mm pen deflection to 1 mm membrane extension. Two CSs were employed: an 800 msec, 84 db (0.0002 dynes/cm^2 reference), 1 kHz tone delivered through the speaker, and a 800 msec light stimulus produced by interruption of the houselights at 10 Hz. A 100 msec, 3 mA, 60 Hz electric shock delivered to the paraorbital region through the two wound clips served as the UCS. A punched paper tape, fed through a tape reader, programmed intertrial intervals and the stimuli whose durations were controlled by an Iconix timebase (model 6255), preset controller (model 6010) and storage and relay unit (model 6087).

Drug. *d*-Lysergic acid diethylamide tartrate (LSD, MW 430.5), obtained from the National Institute of Drug Abuse was dissolved in sterile distilled water and injected into the marginal ear vein at dosages of 1, 10, 30, 100 and 300 nmol/kg. Animals were injected with vehicle or drug in a volume of 0.4 ml/kg at a rate of 3 ml/min.

Experiment 1

Paired CS-UCS training. This training procedure employed 72 rabbits divided into six groups of 12 animals per group. Two days after suturing of the nictitating membrane, animals were placed into each of 12 individual, experimental chambers for a 60-min adaptation session during which no stimuli were presented and no drug or vehicle was injected. Responses were recorded during the intervals in which conditioned stimuli would have been presented (see below) to provide a baseline measure of the frequency of membrane extension in the absence of any explicit presentation of stimuli. One day later, the first of 10 daily conditioning sessions was initiated. Vehicle or drug was injected 30 min before each conditioning session. Within each group of 12 rabbits, two animals were injected with vehicle and two with each of the five dosages of LSD. The 12 rabbits at each dosage of LSD or vehicle were completely counterbalanced with respect to the 12 conditioning chambers. Each daily conditioning session was 60 min in duration and consisted of 60 trials composed of 30 tone-shock and 30 light-shock trials presented in a randomized sequence within 10 trial blocks with the restriction that not more than three consecutive tone or light trials could occur. On each conditioning trial, the offset of the 800 msec tone or light CS occurred simultaneously with the onset of the 100 msec shock UCS. Trials occurred at intervals of 50, 60 and 70 sec (the average interval was 60 sec). A response was defined as at least a 1 mm pen deflection (0.5 mm membrane extension) and its onset latency was measured from the point at which the deflection departed from baseline. Response latencies occurring during the tone or flashing-light CS (onset latencies less than 800 msec) were recorded as CRs, while those occurring after UCS onset were recorded as UCRs.

Unpaired CS,UCS training. This training procedure used 42 animals with seven animals at each dosage of LSD or vehicle. An adaptation session occurred 2 days after placement of sutures as described above. During this session, responses were recorded during the intervals in which conditioned stimuli would have been presented as well as in the 800 msec period before the time in which the UCS would have been presented. On the following day, animals were injected with vehicle or one of the five dosages of LSD and 30 min later were exposed to explicitly unpaired CS and UCS presentations. Each daily session consisted of 30 tone, 30 light and 60 shock trials presented in a randomized sequence within 20 trial blocks with the restriction that no more than three consecutive tone, light or shock trials could occur. Trials occurred at 25, 30 and 35 sec intervals (the average interval was 30 sec). The duration and intensity of the stimuli were as described above. A response was recorded when it occurred during the 800 msec presentation of either CS. In addition, a response occurring during the 800 msec interval preceding each UCS was recorded as a baseline response. The amplitude of the UCR was recorded on each of the 60 daily UCS presentations and expressed as millimeters of membrane extension. This procedure was repeated over 10 daily (1-hr) sessions.

Experiment 2

In this experiment, three rabbits were injected with 300 nmol/kg of LSD and three rabbits with vehicle before each of 12 consecutive conditioning sessions, conducted as described for paired CS-UCS training in experiment 1. Then, rabbits previously receiving the vehicle were injected with 300 nmol/kg of LSD, and rabbits previously receiving LSD were injected with vehicle before each of three more conditioning sessions.

Data Analysis

A repeated measures analysis of variance was performed separately on the percent response data of the paired CS-UCS and unpaired CS,UCS conditions of the first experiment with four main factors of dosage (6), days (10), CS modality (2) and blocks (3). For the analysis of these data, the number of responses to the CSs produced by each animal was expressed as a percent score based on: a) the total number of tone and light trials (600) for all 10 acquisition days; b) all tone (300) and light (300) trials for all 10 acquisition days; c) the total number of tone and light trials on each day (60); d) the tone (30) and light (30) trials on each day; and e) the first, second and third 20-trial blocks of tone and light trials within each daily session. In addition, for the unpaired CS,UCS experiment, responding during the 800 msec before UCS was analyzed by a repeated measures analysis of variance with three main factors: dosage (6); days (10); and blocks (3). The UCR amplitude data (expressed as millimeters of membrane extension) were analyzed by a repeated measures analysis of variance with three factors: dosage (6); days (10); and trials (16). For each day, the 16 trials chosen

for analysis of UCR amplitude were trials 1 through 5, and then every 5th trial thereafter. All follow-up analyses of significant effects were performed by the method of Tukey or Dunnet (Winer, 1971). In the second experiment, the number of conditioned responses for each animal was expressed as a percent score based on: a) the total number of trials (720) for all 12 conditioning sessions; and b) the number of trials (180) during each of the three conditioning sessions immediately following drug reversal. The significance of group differences during both acquisition and drug reversal was calculated by Student's *t* test (two-tailed).

Results

Experiment 1, effects of LSD on the acquisition of conditioned responses. Figure 1 presents the percent responding to tone and light CSs combined, for all 10 days of conditioning, as a function of LSD dosage. In the paired CS-UCS procedure, LSD (1–100 nmol/kg) produced a dose-dependent increase in percent CRs as compared with vehicle controls, with the maximum effect occurring between 30 and 100 nmol/kg (upper curve, fig. 1). Separate analyses revealed that LSD (1–100 nmol/kg) increased responding to both the tone and light CSs ($P < .05$) as compared with vehicle controls. The highest dose of LSD, 300 nmol/kg, produced a small and nonsignificant decrease in CR responding as compared with vehicle controls. The frequency of responding to tones and lights under the unpaired CS,UCS procedure was low for vehicle controls (1.6%) and was not significantly affected by any dosage of LSD (lower curve, fig. 1). The small and nonsignificant increase in responding at 30 and 100 nmol/kg of LSD represent only 2.9 and 3.8% increases over vehicle controls.

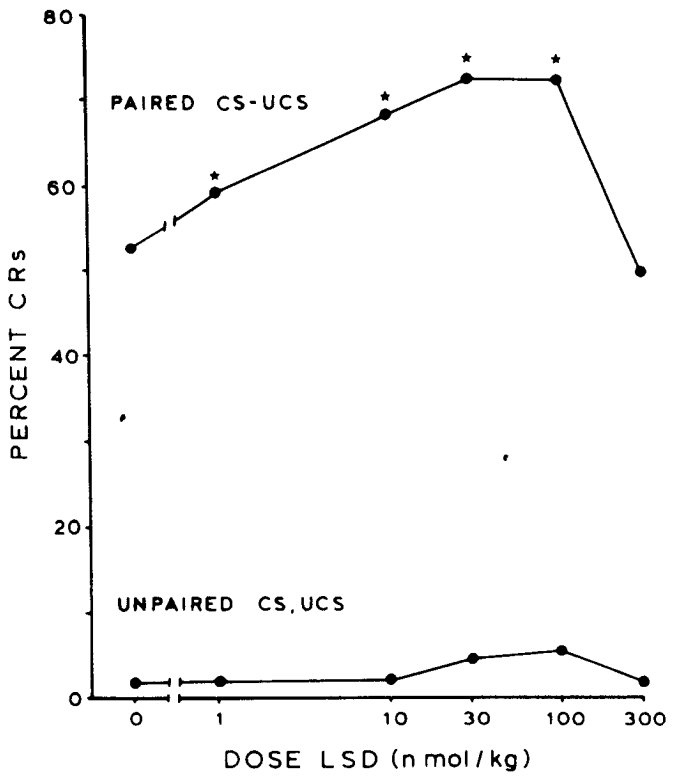

Fig. 1. Effects of LSD on conditioned responding. Data are expressed as mean percent conditioned responses (CRs), based on the total number of tone plus light trials (600) for all 10 days of conditioning. The zero dosage represents vehicle controls. The upper portion of the figure presents data obtained from the paired CS-UCS condition. Each point is the mean of 12 animals. The lower portion of the figure presents data obtained from the unpaired CS,UCS condition. Each point is the mean of seven animals. ★, significant mean difference from vehicle control ($P < .05$) as calculated by the method of Tukey (Winer, 1971).

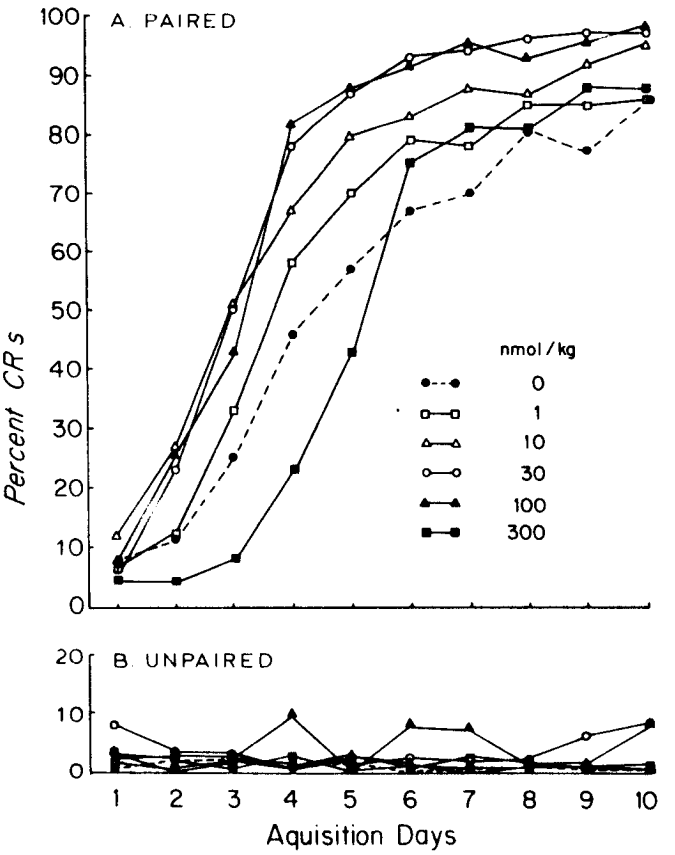

Fig. 2. Effects of LSD on acquisition of conditioned responses over days. Data are expressed as mean percent conditioned responses (CRs), on each of the 10 acquisition days, calculated for the 60 daily trials irrespective of CS modality. A, data for the paired CS-UCS condition. Each point is the mean for 12 aminals. B, data for the unpaired CS,UCS condition. Each point is the mean for seven animals.

Figure 2 presents the percent responding to tone and light CSs combined on each of the 10 days of conditioning, for both the paired CS-UCS procedure (A) and the unpaired CS,UCS procedure (B). Under the paired CS-UCS procedure, animals at each dosage level showed significant acquisition of the conditioned nictitating membrane response ($P < .01$), and reached asymptotic levels ranging from 86 to 98% by the 10th day of training. LSD produced significant differences in rate of CR acquisition as revealed by the dosage × days interaction ($P < .01$). Dosages from 1 to 100 nmol/kg enhanced acquisition, whereas 300 nmol/kg retarded acquisition as compared with vehicle controls. All animals acquired CRs within daily sessions ($P < .01$), and LSD similarly altered the rate of CR acquisition within daily sessions as indicated by the blocks × dosage interaction ($P < .01$). Under the unpaired CS,UCS procedure, levels of responding to CSs were low and showed no significant or consistent changes during the 10 days of acquisition. Also, LSD produced no significant or systematic effects on these levels of responding either across or within daily sessions.

To assess further the altered rates of acquisition produced by LSD, we calculated for each animal the number of trials preceding the occurrence of a criterion of 10 consecutive conditioned responses. Since the mean number of trials preceding

the occurrence of the first CR (45.0) was not differentially affected by LSD, this criterion provides a measure of the rate of transition from initiation of conditioned responding to attainment of a high terminal level of acquisition. With this stringent criterion, LSD can be seen to have had a biphasic effect on the rate of acquisition (fig. 3). Peak enhancement of acquisition occurred at 30 nmol/kg of LSD, at which dosage animals required 109 fewer trials than vehicle controls to reach criterion.

The frequency of baseline responding during adaptation, when neither CSs nor UCSs were presented and no drug was injected, was 1.7%. Moreover, the frequency of baseline responding during the 800 msec before UCS delivery, during the 10 days of the unpaired CS,UCS procedure, was also quite low and was not affected by LSD dosage. The mean frequency of such responding for all 10 days was 1.1% for vehicle controls and for the various dosages of LSD (nanomoles per kilogram) was: 1, 2.0%; 10, 1.9%; 30, 2.7%; 100, 2.9%; and 300, 1.4%. Frequency of baseline responding showed a small but statistically significant decline across days ($P < .01$), from values of 5.7% on day 1 to 2.9% on day 10. LSD had no effect on this decline in responding.

LSD had no significant effect on UCR amplitude in the unpaired CS,UCS procedure. However, the mean UCR amplitudes of the 42 animals for all 10 days showed a small but statistically significant decline over trials ($P < .01$), from a mean value of 6.8 mm membrane extension on trial 1 to 5.8 mm on trial 60. A similarly small decrease in UCR amplitude was seen across days ($P < .01$), from an initial value of 7.1 mm on day 1 to 6.6 mm on day 10. LSD had no significant effect on these modest decreases in UCR amplitude.

Experiment 2, effects of LSD on acquired responding. In agreement with the results of experiment 1 (fig. 2), 300 nmol/kg of LSD again produced a significant retardation of CR acquisition ($P < .01$) across the 12 days of conditioning (fig. 4). However, the reversal of drug conditions beginning on the 13th day of conditioning produced only a small and nonsignificant decrement in CR responding to both the tone and light CSs. More importantly, the modest decrement in responding was not significantly different between animals shifted from vehicle to LSD and those shifted from LSD to vehicle.

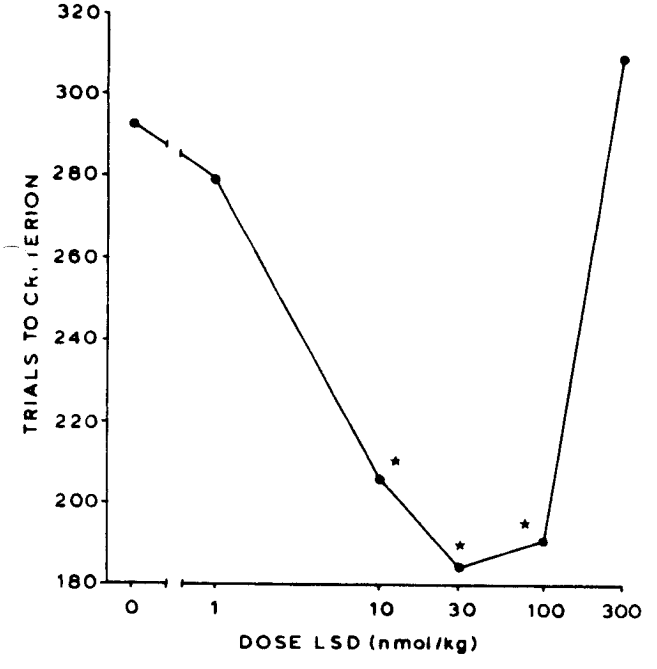

Fig. 3. Effects of LSD on rate of acquisition. Data are expressed as mean number of trials preceding the first occurrence of 10 consecutive conditioned responses as a function of LSD dosage. The zero dosage represents vehicle controls. Each point is the mean of 12 animals. ★, significant mean difference from vehicle control ($P < .05$) as calculated by the method of Tukey (Winer, 1971).

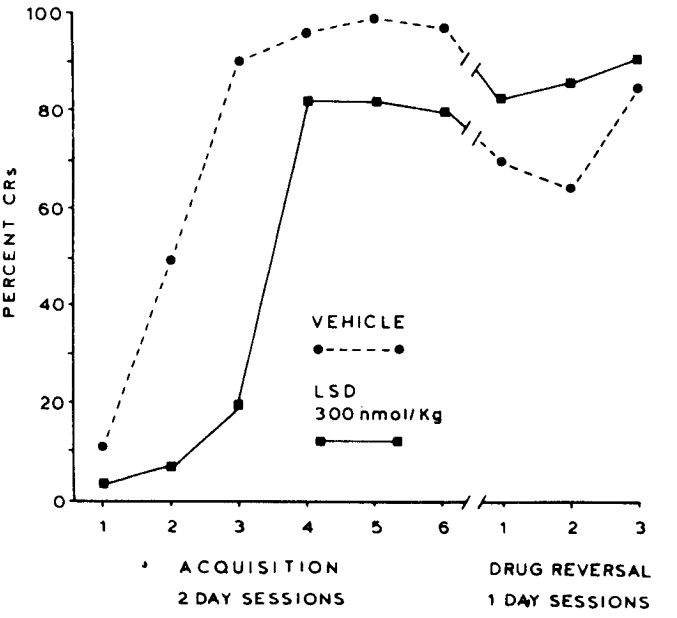

Fig. 4. Comparison between the effects of LSD on conditioned responses during and after acquisition. The left portion of the figure presents mean percent CRs for the 60 daily trials irrespective of CS modality as a function of 2-day acquisition sessions. The right portion presents mean percent CRs for daily sessions during drug reversal. Each point is the mean of three animals.

Discussion

LSD (1-100 nmol/kg) significantly enhanced the rate of acquisition of a conditioned response in a classical conditioning procedure. The enhancement, which occurred with both visual and auditory stimuli, appears to be due exclusively to an effect of the drug on acquisition processes (*i.e.*, learning). The increased responding to CSs as a function of the repeated pairing of CSs with a UCS can only be attributed to a learning process if there is no comparable increase in responding when CSs and UCSs are presented under an appropriate control procedure. The control procedure chosen for the present study consisted of the unpaired presentations of CSs and UCSs. Changes in responding to CSs in an unpaired CS,UCS procedure can reflect sensititzation, pseudoconditioning, or an increase in overall baseline rate of responding resulting simply from the repeated presentations of CSs and UCSs. In the unpaired CS,UCS procedure responding of vehicle-injected rabbits did not exceed 2%. For example, the baseline of membrane extension during adaptation when animals were neither injected nor exposed to tones, lights and shocks was only 1.7%. In addition, the frequency of responding of vehicle controls in the unpaired CS,UCS condition was equally low, indicating the absence of any sensitization or pseudoconditioning effects. Previous research has also demonstrated that, under a wide variety of conditioning parameters, non-drug-treated rabbits show essentially no contribution of sensitization, pseudoconditioning or

baseline responding to conditioned response acquisition (Gormezano *et al.*, 1962; Gormezano, 1966, 1972). Acquisition of the nictitating membrane response of control rabbits appears, therefore, to provide an unambiguous measure of learning.

In the unpaired CS,UCS condition, LSD did not affect frequency of baseline responding, frequency of responding to tone and light stimuli or amplitude of the unconditioned response. Therefore, the altered rates of acquisition produced by LSD in the paired CS-UCS condition reflect the effects of the drug on learning. Dosages of 1 to 100 nmol/kg enhanced learning whereas 300 nmol/kg retarded learning.

The precise basis for the effects of LSD on the acquisition of CRs is unknown. They could be due to some enhancement of sensory input produced by low dosages of LSD (Bradley and Key, 1958) and a block of sensory input at high dosages. Enhanced auditory and visual evoked potentials have been reported in the cat (Purpura, 1956) and rabbit (Burian *et al.*, 1958) at low dosages of LSD, while at higher dosages there is a decrease in evoked potentials (Purpura, 1956). In the present study, however, LSD did not affect responding to tones, lights or shocks presented alone. Moreover, once CRs had been acquired and maintained, the 300 nmol/kg dosage of LSD did not produce a drug-specific decrease in responding to the visual or auditory CSs (fig. 4). The effects of LSD on conditioning might still be due to an effect on stimulus processing that alters the ability of stimuli to enter into conditioning by a change in CS and UCS excitability functions (Gormezano, 1972; Young *et al.*, 1976; Thompson, 1976).

The enhanced rate of acquisition produced by 1 to 100 nmol/kg of LSD persisted over the entire 10 days of injection and testing, suggesting a relative absence of any development of tolerance to this effect of the drug. In contrast, the retardant effects of 300 nmol/kg of LSD on acquisition began to disappear by the 6th day of training (figs. 2 and 4). Consequently, the retardant effect of 300 nmol/kg of LSD on acquisition was significant only during the initial training sessions and was not reflected by changes in overall CR frequency (fig. 1) or trials to criterion (fig. 3). These data suggest the development of tolerance to the retardant effects of 300 nmol/kg of LSD on learning. Stoff *et al.* (1974) and Bridger (1975) have reported that there was no development of tolerance to the ability of either LSD or mescaline to produce an enhancement of CAR acquisition in the rat. Tolerance does, however, develop to the ability of high dosages of mescaline to produce a retardation of CAR acquisition (Bridger, 1975).

The ED50 of LSD for enhanced CR acquisition (fig. 3) can be estimated as about 3.3 nmol/kg, *i.e.*, 1.1 μg/kg of LSD calculated as the base. This is, to our knowledge, the lowest dosage of LSD ever reported to have behavioral effects. This low ED50 does not appear to be due simple to the known sensitivity of the rabbit to the sympathetic effects of LSD (Aldous *et al.*, 1974) or to the use of intravenous injections. As was pointed out in the Introduction, the behavioral effects of LSD have previously been measured predominantly in terms of changes in the performance of established conditioned responses. In the present experiments, a dosage as high as 300 nmol/kg of LSD had no significant effect on an established CR (fig. 4). Taken together, these data suggest that LSD has a more potent effect on the process of CR acquisition as compared with its effect on previously acquired and well established CRs.

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