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Sensory and Associative Effects of LSD on Classical Appetitive Conditioning of the Rabbit Jaw Movement Response

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Abstract. Three experiments were conducted to determine the effects of LSD (30 nmol/kg) in classical appetitive conditioning of the rabbit jaw movement response (JMR). In experiment 1, LSD significantly enhanced the acquisition of conditioned responses (CRs). The performance of control groups receiving unpaired presentations of the conditioned stimulus (CS) and unconditioned stimulus (UCS) demonstrated that LSD's enhancing effect on conditioning could not be attributed to an elevation in baseline responding, sensitization, or pseudoconditioning. Accordingly, experiments 2 and 3 were conducted to determine whether LSD's enhancement of conditioning could have arisen from its altering the sensory processing of either the CS or UCS, or both. In experiment 2, LSD was found to have no significant effect on the functions relating UCS magnitude to the frequency, amplitude, or number of sinusoidal peaks comprising each unconditioned response (UCR). In contrast, experiment 3 revealed that LSD significantly enhanced the frequency of CRs to an extended range of CS intensities and lowered the CS intensity threshold. It was concluded that the enhancing effect of LSD on the acquisition of CRs is attributable, at least in part, to the drug's enhancement of the sensory processing of the CS.

Key words: LSD – Classical conditioning – Rabbit – Learning – Sensory processing

Gormezano and Harvey (1978), in a brief review and critique, argued for the methodological and conceptual utility of the classical (Pavlovian) conditioning paradigm for analyzing the effects of LSD, and other hallucinogens, on associative, sensory, and motor processes. Subsequently, Gimpl et al. (1978) reported the results of a classical defense conditioning study designed to establish a dose-response function for LSD (1, 10, 30, 100, or 300 nmol/kg) on the acquisition of the rabbit nictitating membrane response (NMR). The study revealed a biphasic dose-response function in which dosages of 1–100 nmol/kg LSD significantly enhanced the acquisition of conditioned responses (CRs), with a peak enhancement occurring at 30 nmol/kg, whereas, 300 nmol/kg LSD retarded the acquisition of CRs. The performance of control groups given unpaired presentations of the conditioned stimulus (CS) alone and the unconditioned stimulus (UCS) alone revealed that the effect of LSD on CR acquisition could not be attributed to the drug affecting such nonassociative factors as the baseline of responding, sensitization (i.e., augmentation of an already present unconditioned response to the CS), or pseudoconditioning (i.e., responses to the CS resulting from prior UCS-alone presentations). Specifically, LSD did not operate to differentially affect the presence of factors in conditioning preparations that may occur independent of the temporal pairing of the CS and UCS (see Gormezano 1966; Gormezano and Kehoe 1975). Furthermore, the absence of any effect of LSD on the amplitude of the unconditioned response (UCR), to a fixed shock intensity of the UCS, in the unpaired control group, suggested that the drug was not affecting the motor response.

Gimpl et al. (1978) postulated that the more rapid acquisition of NM CRs produced by LSD might be due to an enhancement of the sensory processing of either the UCS or CS, or both. Subsequently, Gormezano and Harvey (1979) examined this sensory enhancement hypothesis and found that UCR amplitude to a shock UCS was not significantly affected by 30 nmol/kg LSD, nor did the drug significantly affect the psychophysical functions relating UCS intensity to the frequency or amplitude of UCRs, or the UCS intensity threshold for evoking UCRs. Accordingly, since both NM CRs and

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UCRs involve the abducens nucleus, the final common pathway, via the sixth cranial nerve (Cegavske et al. 1976), LSD's effects upon NM CRs cannot be attributed to an alteration in the motor response system. On the other hand, the finding that LSD significantly enhanced the frequency of CRs to an extended range of CS intensities and lowered the CS intensity threshold, led Gormezano and Harvey (1979) to conclude that the enhancement of NMR acquisition produced by 30 nmol/kg LSD could be attributed to the enhancement of the sensory processing of the CS. Such an interpretation of LSD's conditioning effects is consistent with reports of enhanced auditory and visual evoked potentials in the cat (Purpura 1956) and rabbit (Burian et al. 1958) at low dosages of LSD and with the knowledge that CS intensity manipulations can substantially affect the acquisition of NMRs (Gormezano and Moore 1969).

The purpose of the present series of investigations was to determine the generality of LSD's effects on classical conditioning by employing classical (appetitive) conditioning of the rabbit's jaw movement response (JMR), which involves a reflex system with a different anatomical organization (Doty 1968) and, perhaps, different behavioral laws of conditioning (Gormezano 1972; Poulos et al. 1971) from those of the classical (defensive) conditioning of the NMR. In particular, the present series of investigations determined whether 30 nmol/kg LSD would affect the course of classical appetitive conditioning of the JMR (experiment 1) and, if so, whether the effects could be attributed to alterations in the sensory processing of the UCS (experiment 2) or the CS (experiment 3).

Materials and Methods

Subjects. The three experiments were performed on a total of 86 New Zealand white albino rabbits, 80–100 days old, that weighed between 1.8 and 2.8 kg during the course of the experiments. The animals were obtained from Morrison Rabbitry, West Liberty, Iowa, USA, and, upon their arrival, were housed individually with free access to Purina Rabbit Chow and tap water.

Apparatus and General Procedure. The apparatus and procedures for conditioning of the rabbit JMR have been described in detail by Mitchell and Gormezano (1970), who describe the departures from earlier procedures (Smith et al. 1966). The preparation, depicted in Fig. 1, portrays the rabbit restrained in a Plexiglas box and fitted with a headmount supporting a jaw-movement transducer and a liquid delivery system for presentation of water to the animal's oral cavity.

The jaw-movement transducer assembly (A) consists of an opaque Plexiglas cylinder housing a Z-shaped piano-wire armature (B), the one end of which is inserted into the channel of a wound clip permanently implanted to the tip of the rabbit's lower jaw. The other end of the armature serves as an axle supporting a disc of polarized film mounted on a Teflon bushing and positioned in the Plexiglas cylinder between a constant intensity LED (Litronix Model RLC201) and a photocell (Vactec Model VT212-L) positioned in chamber covered by a fixed plate of polarized film.

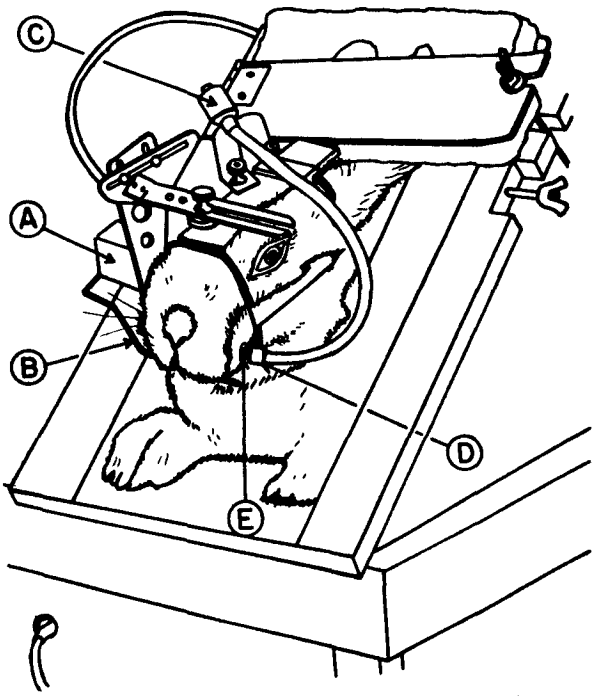

Fig. 1. A restrained rabbit prepared for recording the jaw-movement response: (A) photoresistive transducer, (B) piano-wire armature, (C) Luer-Lock connector, (D) blunted hypodermic needle, and (E) polyethylene cannula

The transducer converts the rabbit's jaw movements into an electrical signal by rotating the disc of polarized film on the Teflon bushing to produce changes in the amount of illumination from the LED falling on the photocell through the fixed polarized plate. The accompanying variations in the electrical signal from the photocell is amplified to yield 1 mm of pen deflection for 0.5 mm of jaw movement on an Offner (Type R) oscillograph. As revealed by the oscillograph tracings, the topography of UCRs and CRs tend to be sinusoidal (Smith et al. 1966, Fig. 1).

A length of Tygon tubing, connected to a pressurized liquid reservoir, couples to the Luer-Lock (C) on the rabbit's headmount. A solenoid valve operated by direct current interrupts the Tygon tube just below the reservoir and, when activated, delivers water to the animal's oral cavity through a length of tubing that terminates in a blunted hypodermic needle (D) inserted into a permanently implanted polyethylene cannula (E) in the rabbit's cheek.

The conditioning chambers were fabricated from three-drawer legal-sized fireproof filing cabinets to which individual blowers, exhausts, and stimulus panels had been added. Each chamber contained an 11.4 cm speaker positioned above and in front of the animal and houselights were provided by two panels, one located on each side of the speaker, each illuminated by a 6 w, 24 V d.c. light bulb (2.6 ml). Two CSs were used: an 800-ms, 75-db (0.0002 dynes/cm^2 reference), 1-kHz tone delivered through the speaker against a 70-db background noise; and an 800-ms light stimulus produced by interruption of the houselights at 10 Hz to yield a change in illumination, measured at the animal's eye level, from 32.0–8.0 lux. The UCS was a 1-ml squirt of distilled water of 300-ms duration delivered directly into the rabbit's oral cavity. 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).

On the third day after their arrival, the rabbits were anesthetized, a polyethylene cannula was permanently inserted through a fistula in their left cheek, and a wound clip applied to the lower jaw approximately 5 mm posterior to the major curvature of the mandible. After a 48-h recovery period, the rabbits were restricted to 90 ml of water per day for the duration of the experiment. Prior to the availability of water on the fourth day, the rabbits (Basle, Switzerland) were adapted to the apparatus and their spontaneous jaw movements recorded at times corresponding to the observation intervals of subsequent experimental sessions.

Drug. Thirty minutes prior to each experimental session, all animals were injected with *d*-lysergic acid diethylamide tartrate (LSD, molecular weight 430,5), obtained from NIDA, Sandoz, or with the vehicle of sterile distilled water. The drug, dissolved in sterile distilled water, was injected into the animal's marginal ear vein at a dosage of 30 nmol/kg (9.7 µg/kg LSD calculated as the base). Animals were injected with the vehicle or drug in a volume of 0.4 ml/kg at a rate of 3 ml per minute by a Harvard infusion pump.

Data Analysis. A repeated measures analysis of variance and Tukey *hsd* followup analyses (Winer 1971) were performed on the data of each experiment.

Experiment 1: Acquisition of JM CRs under LSD

On the fourth day following the introduction of the 90-ml water maintenance regime, 44 experimentally naive rabbits were adapted to the apparatus. During adaptation, the animals were secured in the Plexiglas restraining box and positioned in the conditioning apparatus for a duration of time (60 min) equal to the length of the subsequent conditioning sessions. No stimuli were presented during the adaptation session, although to obtain an index of base rate of responding, the data records were scored for responses occurring at times corresponding to the usual CS-UCS observation intervals. Following adaptation, all 44 rabbits received 10 days of acquisition training. Two experimental groups (of 11 rabbits each), received 30 CS-UCS paired conditioning trials daily at a CS-UCS interval of 800 ms. The conditioning trials were composed of 15 tone-CS-UCS and 15 light-CS-UCS pairings presented in a randomized sequence within 10-trial blocks with the restriction that not more than three tone or light CS trials could occur consecutively. Trials occurred at intertrial intervals of 100, 120, and 140 s, with a mean of 120 s. In addition, two control groups (of 11 rabbits each) were exposed to explicitly unpaired CS and UCS presentations in which each daily session consisted of 15 tone-CS, 15 light-CS, and 30 water-UCS trials presented in a randomized sequence within 20 trial blocks with the restriction that no more than three trials of tone, light, or water could occur consecutively. Trials in the unpaired controls occurred at 50, 60, and 70 s intervals, with a mean of 60 s. A 60 ml supplement of water was provided in each rabbit's home cage upon the completion of each day's run to bring the total water available up to the prescribed maintenance level of 90 ml.

Thirty minutes prior to each acquisition session, all animals in one experimental and one control group were injected with LSD and the animals in each of the remaining experimental and control groups were injected with the vehicle. Throughout the experiment, a CR was defined as any jaw movement exceeding 0.5 mm and occurring during the 800 ms presentation of either CS. In addition, for the unpaired control groups, a response occurring during the 800-ms interval preceding each UCS was recorded as a baseline response and the amplitude of the UCR (greater than 0.5 mm) was recorded for each of the 30 daily UCS presentations.

Experiment 2: UCS-UCR Functions under LSD

Unless otherwise specified, the apparatus, recording technique, and general procedure were identical to that of experiment 1. Twenty-four experimentally naive rabbits were assigned to two groups (of 12 rabbits each), and on the day following a 60-min adaptation session, were injected with LSD or vehicle 30 min prior to each of three daily experimental sessions. In each of the the three daily sessions, all rabbits received 30 trials of UCS alone presentations at randomized intertrial intervals of 100, 120, and 140 s (with a mean of 120 s). The 30 trials were composed of five water-UCS presentations at magnitudes of $^1/_3$, $^2/_3$, 1, $1^1/_3$, $1^2/_3$, and 2 ml obtained by activating the solenoid with a 100-ms pulse 1, 2, 3, 4, 5, or 6 times, respectively, at an interpulse interval of 450 m. Under these parameters of UCS delivery (and water-deprivation level) there was a continuous flow of water into the rabbits' oral cavity for all UCS magnitudes. Moreover, there was no evidence of water loss as revealed by the examination of water collection cups placed under each subject's chin. The frequency, latency, and amplitude of UCRs as well as the number of sinusoidal jaw movements composing each UCR (Smith et al. 1966) was determined for all 30 trials. A 60-ml water supplement upon the completion of each day's run brought each rabbit to a daily water maintenance of 95 ml.

Experiment 3: CS Intensity-CR Frequency Functions under LSD

Unless otherwise specified, the apparatus, recording technique, general procedure, and stimulus parameters were identical to that of experiment 1. Following adaptation, 18 experimentally naive rabbits received 14 days of acquisition training with only the 75 db tone CS for all 30 CS-UCS pairings and no subject was injected with either LSD or vehicle. On the day after the last acquisition session, rabbits were randomly assigned to two groups (of 9 rabbits each) and injected with either LSD (30 nmol/kg) or vehicle 30 min prior to each of five additional daily sessions of 36-tone CS-UCS pairings. In each of these daily sessions, CS intensity was radomly varied over 12 values within each of three, 12-trial blocks. The CS intensities were: 0, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, and 90 db with responding during the 800 ms prior to UCS delivery, when no tone was presented (0 db) providing a measure of baseline responding. A 60-ml daily water supplement brought each animal to a 96-ml maintenance schedule.

Results

Experiment 1

Figure 2 presents the percent JMRs to tone and light CS trials combined across the ten days of acquisition training for the LSD and vehicle injected rabbits under the paired CS-UCS and unpaired CS/UCS conditions. The figure reveals that under the paired CS-UCS condition, LSD substantially enhanced the overall level of CRs as well as the rate of acquisition of CRs. These descriptive aspects of the percent CR data under the paired CS-UCS condition were corroborated by the repeated measures analysis of variance, which revealed significant effects of Groups, and Groups × Days (all P's < 0.01). The mean level of acquisition of CRs to the tone CS was 75% and to the light CS it was 71%, and the analysis revealed that Modality was not a significant source of variation nor did Modality enter into any significant interactions with Days or Groups. To obtain a more detailed assessment of the enhanced rate of acquisition produced by LSD, we determined for each LSD and vehicle injected animal under the paired CS-UCS condition the number of trials required to attain the successively more stringent criterion of 1 to

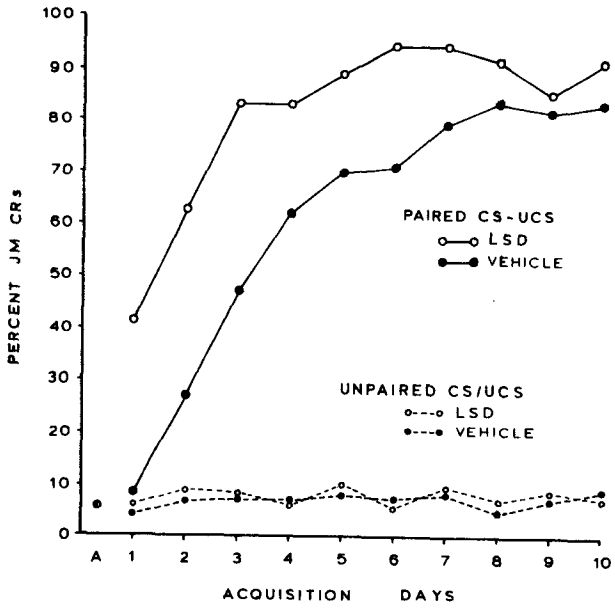

Fig. 2. Effect of LSD (30 nmol/kg) and vehicle on acquisition of conditioned jaw movement responses (*JMRs*) over days. Data are expressed as mean percent JM conditioned responses (*CRs*) on each of the ten acquisition days, calculated for the 30 daily trials, irrespective of CS modality, for both the paired CS-UCS and unpaired CS/UCS groups. Each point is the mean for 11 rabbits

10 consecutive CRs. LSD facilitated not only the initiation of the first CR ($\bar{X}$ = 6.0), relative to vehicle controls ($\bar{X}$ = 21.4), but also the attainment of each successive criterion. An analysis of variance of the number of trials to each of the 10 criteria revealed a significant effect of Groups, Criterion, and Groups × Criterion (all P's < 0.01). Moreover, post tests of the significant Groups contrast revealed LSD injected animals required significantly fewer trials than vehicle controls at each criterion (all P's < 0.05).

The frequency of baseline responding during the 800 ms prior to UCS delivery under the unpaired CS/UCS condition for LSD and vehicle groups over the ten days of training was very low and statistically undifferentiated by drug condition as revealed by mean levels of responding of 3.5% for LSD and 2.8% for vehicle controls. In contrast, the mean level of baseline responding during adaptation when neither CSs or UCSs were presented and no drug had been injected was 5.0%. In addition, as revealed by a reexamination of Fig. 2, under the unpaired condition, the levels of responding to the CSs were low, never exceeding 8.4% on any day, and the overall mean percentage of responding for LSD injected animals (7.2%), relative to vehicle controls (7.0%), showing no significant or systematic drug effects on CS responding. Accordingly, performance under the unpaired CS/UCS condition served to operationally specify that LSD's enhancing effects upon conditioning could not be attributed to the possible contribution to CR measurement of such factors as an elevation in baseline, sensitization, or pseudoconditioning. Furthermore, statistical analysis revealed that under the unpaired CS/UCS condition the amplitude of UCRs to the 1-cc water UCS were virtually identical across days for LSD ($\bar{X}$ = 3.6 mm) and vehicle ($\bar{X}$ = 4.2 mm). Thus, LSD appeared to have no effect upon the sensory processing of the UCS; however, the UCS magnitude used may have been relatively insensitive to the drug's effects. Therefore, in the next experiment, we made a detailed assessment of LSD's effects upon the UCR over a wide range of UCS magnitudes. Specifically, we determined the drug's effects on the psychophysical functions relating UCS magnitude to the frequency, latency, and amplitude of UCRs, as well as to the number of sinusoidal peak jaw movements composing each UCR.

Experiment 2

Panel A of Fig. 3 presents the psychophysical data relating the latency of UCRs, and Panel B the frequency of sinusoidal JMRs (i.e., the number of peaks) comprising each UCR, to UCS magnitude for LSD and vehicle injected animals. Examination of Panel A and statistical analysis revealed that while UCR latency was unaffected by UCS magnitude, LSD markedly decreased UCR latency ($\bar{X}$ = 311 ms) across all UCS magnitudes (P< 0.01), relative to vehicle controls ($\bar{X}$ = 469 ms). Inspection of Panel B indicates the number of sinusoidal peaks comprising each UCR was an increasing function of UCS magnitude for both vehicle and LSD injected animals (P< 0.01); whereas, LSD appears to have decreased the number of peaks, relative to vehicle controls, but the effect was not significant (P = 0.40). On the other hand, neither the frequency nor amplitude of UCRs was affected by UCS magnitude, drug condition, or their interaction.

Experiment 3

Prior to exposing animals to CS intensity testing, all rabbits had been given 14 days of acquisition training to a 75 db tone CS and 1-ml water UCS. By the last four days of acquisition training, the levels of responding averaged about 75%. The subsequently obtained psychophysical functions relating CS intensity to percent CRs for LSD and vehicle injected animals are presented in Fig. 4. As expected from the results of an earlier study of CS intensity effects (Scavio and Gormezano 1974), percent CRs was a direct function of CS intensity (P< 0.01). Moreover, rabbits given LSD demonstrated a higher frequency of CRs at the various CS intensities

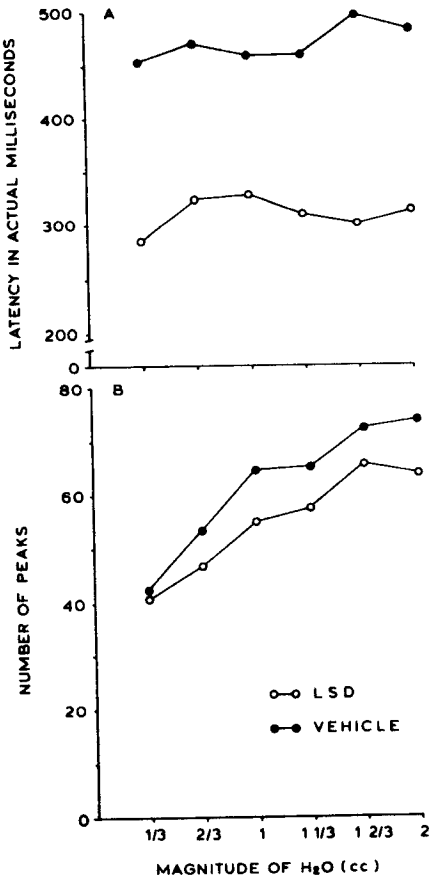

Fig. 3. Effect of LSD (30 nmol/kg) and vehicle on the latency of UCRs (Panel A) and the number of sinusoidal peaks comprising each UCR as a function of water-UCS magnitude. Each point is the mean for 12 rabbits

as compared with vehicle controls, which was reflected in a significant effect of drug condition ($P < 0.01$) and a significant interaction of drug with CS intensity ($P < 0.05$). A subsequent Tukey *hsd* analysis, used to localize the source of the significant interaction, revealed significant enhancing effects of LSD at CS intensities of 45 – 65 db and 75 – 90 db. In addition, a CS intensity threshold was determined for each rabbit by calculating from its own psychophysical function relating CS intensity to CR frequency, the CS intensity at which CRs would occur on 50% of the trials. LSD significantly lowered threshold ($P < 0.01$) in that the mean ± SEM for LSD was 58.0 ± 3.4 db and for vehicle, 69.1 ± 4.6 db.

Discussion

Experiment 1 revealed that LSD (30 nmol/kg) enhanced the acquisition of JM CRs to both visual and auditory CSs with equal facility. Furthermore, baseline responses of 5% during adaptation and 3.5% for LSD and 2.8% for vehicle controls during unpaired CS/UCS training, indicate that LSD's conditioning effects were not due to an elevation in the JMR baseline. In addition, the levels of responding to CSs during unpaired CS/UCS presentations of 7.2% for LSD and 7.0% for vehicle controls, revealed that LSD's enhancing effects upon conditioning could not be attributed to sensitization or pseudoconditioning. The drug also markedly facilitated the initiation of conditioning, as revealed by LSD-injected animals requiring substantially fewer trials to initiate the first CR as well as to

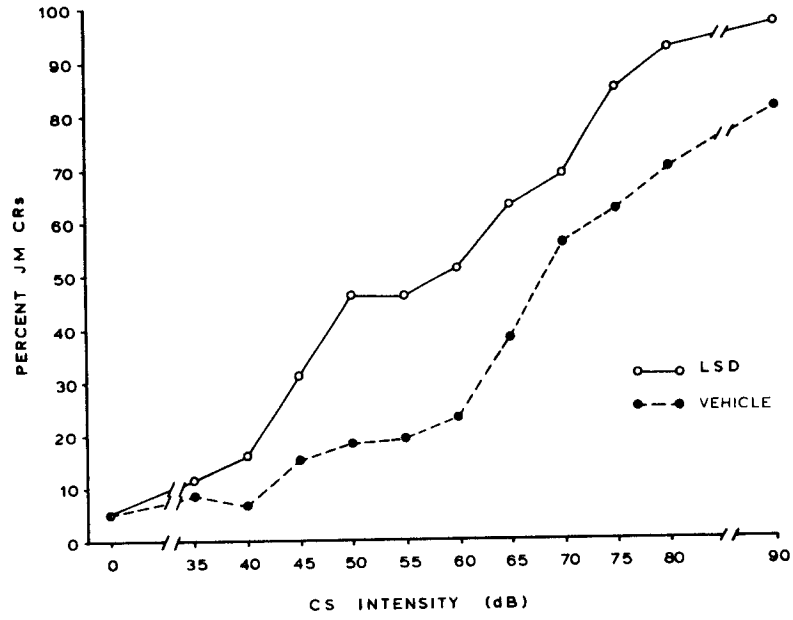

Fig. 4
Effect of LSD (30 nmol/kg) and vehicle on CR occurrence as a function of CS intensity. Data are presented as the mean percent CRs to 15 presentations of a tone conditioned stimulus (*CS*) at each intensity. Each point is the mean for nine rabbits

attain each successive CR criterion of two to ten consecutive CRs. The same pattern of LSD effects upon CR acquisition was essentially the same before and after the occurrence of the first CR suggests that whatever may be the mechanism by which LSD enhanced the acquisition of CRs, it must be operative during the CS-UCS pairings that were presented prior to the appearance of the first CR. At the least, therefore, LSD's effects upon conditioning was mediated by a learning mechanism that is independent of CR occurrence.

The above pattern of LSD's effects on classical appetitive conditioning of the rabbit JMR agrees with our previous reports of the drug's effects on classical defense conditioning of the rabbit NMR. However, the pattern of LSD's effects on JM UCS-UCR functions appears to diverge from that obtained with the NMR. Specifically, for the NMR, LSD has been found to have no effect on the (1) UCR amplitude to a fixed shock UCS intensity (Gimpl et al. 1978; Gormezano and Harvey 1979); (2) psychophysical functions relating a wide range of UCS intensities to the frequency, latency, or amplitude of UCRs (Gormezano and Harvey 1979); and (3) UCS intensity threshold for eliciting UCRs (Gormezano and Harvey 1979). On the other hand, the results of experiments 1 and 2 in the present study indicated that while LSD (30 nmol/kg) did not affect the frequency and amplitude of JM UCRs and the number of sinusoidal peaks comprising each UCR, over a range of UCS magnitudes, the drug did substantially decrease UCR latency. Therefore, the enhancing effects of LSD upon conditioning of the JMR may have arisen, in part, from the drug's effects upon UCR latency. Although the effects of CS-UCS/UCR interval on conditioning of the JMR has not been completely specified (Gormezano 1972), the decrease in UCR latency produced by LSD may, for example, yield a more efficacious CS-UCR interval for JMR conditioning. In any event, as opposed to our findings with the NMR preparation, LSD's effect upon the JM UCR latency suggests the drug may affect one or more of several factors: the sensory processing of the water-UCS, motivational state of the organism, or the motor system, i.e., UCR.

Experiment 3 revealed that LSD enhanced the frequency of CRs to an extended range of CS intensities and also lowered the CS intensity threshold. These CS intensity results, also obtained with 30 nmol/kg LSD in a previous NMR study (Gormezano and Harvey 1979), indicate that LSD can enhance the sensory processing of an auditory CS. Moreover, to the extent that these functions were obtained following essentially asymptotic levels of CR acquisition, adherents of a learning-performance distinction would identify LSD's effects to be on performance. Yet, experiment 1 clearly showed that LSD's enhancing effects on CR acquisition were on learning. Although appearing to be contradictory, a number of behavior theorists of conditioning have recognized that an enhanced or more intense CS may operate as a learning or performance variable or both (Grice 1968, 1972; Grice and Hunter 1964; Hull 1943, 1949, 1952; Logan 1956; Perkins 1953: Razran 1957). Specifically, these accounts all contend that both the rate of acquisition of CRs and the energizing (i.e., evoking) of CRs, once conditioning has occurred, will be proportional to the intensity of the CS. Accordingly, to the extent that LSD enhanced the sensory processing of the CS, all of these behavior theories would provide a learning-performance account of CS intensity effects that predicts the drug would facilitate the initiation of CRs, subsequent strengthening of CRs, and post-asymptotic frequency of CRs.

The results of the present study, along with those of Gimpl et al. (1978) and Gormezano and Harvey (1979), indicate that a low dosage of LSD (30 nmol/kg) enhances the rate of learning in both classical defense (NMR) and classical reward (JMR) conditioning. Also, for both preparations, the enhancement of learning appears to be, at least in part, attributable to the enhancement of sensory processing of the CS. In contrast, both 250 µg/kg haloperidol (Harvey et al. 1980) and 1.5 mg/kg scopolamine (Moore et al. 1976) has been found to impair the acquisition of NM CRs and to elevate the auditory CS threshold, while having no detectable effects upon NM UCRs. Hence, consistent with the above behavior theory accounts of CS intensity upon conditioning, all of these drugs appear to be exercising their influence on the acquisition of CRs through their effects upon the sensory processing of the CS.

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