0022-3565/82/2212-0289$02.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

Vol. 221, No. 2
Printed in U.S.A.

Effects of *d*-Lysergic Acid Diethylamide, *d*-2-Bromolysergic Acid Diethylamide, *dl*-2,5-Dimethoxy-4-Methylamphetamine and *d*-Amphetamine on Classical Conditioning of the Rabbit Nictitating Membrane Response[1]

J. A. HARVEY, I. GORMEZANO and V. A. COOL
Departments of Psychology and Pharmacology, The University of Iowa, Iowa City, Iowa
Accepted for publication January 22, 1982

ABSTRACT

Harvey, J. A., I. Gormezano and V. A. Cool: *Effects of d-lysergic acid diethylamide, d-2-bromolysergic acid diethylamide, dl-2,5-dimethoxy-4-methylamphetamine and d-amphetamine on classical conditioning of the rabbit nictitating membrane response.* J. Pharmacol. Exp. Ther. **221:** 289–294, 1982.

Classical conditioning of the rabbit nictitating membrane response was accomplished by presenting tone and light conditioned stimuli for 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. The rate of acquisition of conditioned responses to both tone and light conditioned stimuli was significantly increased by both *d*-lysergic acid diethylamide (LSD) and *dl*-2,5-dimethoxy-4-methylamphetamine (DOM). *d*-Amphetamine (AMP) differed from LSD and DOM in that it enhanced the rate of acquisition to the light but not to the tone conditioned stimulus. There was no effect of *d*-2-bromolysergic acid diethylamide on acquisition of conditioned responses to either conditioned stimulus. The order of potency for increasing the rate of conditioned response acquisition was: LSD > DOM > AMP for the light-conditioned stimulus; and LSD > DOM for the tone-conditioned stimulus. Separate groups of rabbits received explicitly unpaired presentations of stimuli (tone alone, light alone and shock alone) in order to determine the nonassociative effects of these drugs on response production. LSD and AMP produced no increase in either base-line responding, responding to the tone and light stimuli or the amplitude of the unconditioned response to shock. Therefore, the increased rate of acquisition of conditioned responses produced by LSD and AMP could be attributed to an effect on associative factors. DOM also had no effect on the amplitude of the unconditioned reponse to shock, but the highest dose used (3 μmol/kg) did increase both base-line rate of responding and responding to tone and light stimuli. Therefore, the increased rate of acquisition of conditioned responses produced by DOM appeared, at least at the highest dose, to be due to some combination of effects on both associative and nonassociative factors. Thus, while LSD, DOM and AMP had the common effect of increasing the rate of acquisition of conditioned responses, AMP differed from LSD and DOM by having a selective effect on acquisition to the light conditioned stimulus and DOM differed from LSD and AMP by its effects on nonassociative contributors to conditioned response production.

LSD increases the rate of acquisition of the classically conditioned rabbit NMR to both tone and light CSs and enhances the excitatory properties of the CS (Gimpl *et al.*, 1978; Gormezano and Harvey, 1980). The ED_{50} of LSD for enhanced acquisition of CRs to both tone and light CSs was 1.1 μg/kg, as the base (Gimpl *et al.*, 1978), a value that compares favorably with the dose of 1 μg/kg of LSD required to produce reliable hallucinations in humans (Abramson *et al.*, 1955; Rothlin, 1957). These results suggest that there might be a relationship between the potency of a drug for producing hallucinations in humans and its potency for enhancing the acquisition of classically conditioned responses in the rabbit. Such a relationship might exist if the perceptual changes, including an enhancement in the sensory processing of stimuli, are involved in both the hallucinogenic effects noted in humans and the increased ability of the CS to enter into conditioning (Gormezano and Harvey, 1980). In order to further explore this relationship between hallucinogenic potency and enhanced acquisition of CRs we compared the effects of LSD on acquisition of CRs to both tone and light CSs with the effects of three other drugs that differ in hallucinogenic potency in humans: DOM, AMP and BOL.

DOM has been reported to be a potent hallucinogen with a

Received for publication December 3, 1979.
[1]This work was supported by National Institute on Drug Abuse Grant DA 01759.

ABBREVIATIONS: LSD, *d*-lysergic acid diethylamide; NMR, nictitating membrane response; CS, conditioned stimulus; CR, conditioned response; DOM, *dl*-2,5-dimethoxy-4-methylamphetamine; AMP, *d*-amphetamine; BOL, *d*-2-bromolysergic acid diethylamide; UCS, unconditioned stimulus; UCR, unconditioned response.

dose of 50 μg/kg, as the base, producing perceptual, associative and affective changes in humans that are quite similar to those seen after LSD (Snyder *et al.*, 1967, 1968; Shulgin *et al.*, 1969). In contrast, AMP is a weak hallucinogenic agent in humans. A single i.v. injection of 10 mg of AMP sulfate or administration of oral doses at the rate of 5 to 50 mg/hr, leading to daily intakes of up to 300 mg, failed to reveal reliable evidence of hallucinations in humans, although there were associative and affective changes characteristic of a paranoid psychosis (Angrist and Gershon, 1970; Griffith *et al.*, 1972). However, hallucinations have been reported by amphetamine abusers who have consumed 500 to 1000 mg daily for a week or more (Connell, 1958). Finally, BOL is a nonhallucinogenic congener of LSD (Brawley and Duffield, 1972). The purpose of the present study was to determine how the order of hallucinogenic potency of these drugs in humans, LSD > DOM > AMP, would compare with their potency for enhancing the acquisition of the classically conditioned NMR in the rabbit.

Methods

Subjects. This study used 288 male and female rabbits (New Zealand white albino) obtained from Morrison Rabbitry (West Liberty, IA). The rabbits weighed approximately 2 kg on arrival and were housed individually with free access to Purina Rabbit Chow and tap water.

Apparatus and general procedure. The apparatus and procedures used in conditioning of the rabbit NMR have been described (Gormezano, 1966; Gormezano *et al.*, 1962; Gormezano and Harvey, 1980). Two CSs were used: an 800-msec, 75-db (0.0002 dynes/cm^2 reference), 1 kHz tone delivered through a speaker by an audio-oscillator (Hewlett-Packard model 201CR) and an 800-msec flashing light stimulus produced by interruption of two 6-w, 24-V d.c. houselights at 10 Hz to yield a change in illumination, measured at the animal's eye level, from 32.0 to 8.0 lux. The UCS was a 100-msec, 3-mA, 60-Hz shock delivered by a laboratory-constructed, constant current shock generator through two-wound clips attached to the skin over the paraorbital region of the head at a distance 10 mm posterior to the canthus and 15 mm apart in the vertical direction. A phototransistor assembly, attached to a loop of nylon sutured into the right membrane, converted nictitating membrane movements into electrical signals that were recorded on an Offner oscillograph operating at a paper speed of 250 mm/sec and a 2:1 amplification.

Paired CS-UCS procedure. Two days after the nictitating membrane was sutured, 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. In the adaptation session, responses were recorded during intervals in which CSs would have been presented on subsequent acquisition sessions in order to provide a base-line measure of the frequency of membrane extension in the absence of any explicit presentation of stimuli. One day later, animals received 10 days of acquisition training. Each daily (60 min) acquisition session 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 no 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 0.5-mm extension of the nictitating membrane. Response occurring during the tone or light CS, but before shock onset, were recorded as CRs, while those occurring after the shock-UCS onset were recorded as UCRs.

Unpaired stimulus procedure. A 60-min adaptation session occurred 2 days after the placement of sutures and responses were recorded as described above. On the following day, animals were given the first of 10 daily sessions. Each session consisted of 120 trials composed of 30 tone-alone, 30 light-alone and 60 shock-alone trials, so that the total number of tone, light and shock presentations and the duration of the session (60 min) was equal to that used in the paired CS-UCS procedure. These trials were 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 (average interval 30 sec). The duration and intensity of each stimulus was as described above. A response was recorded when it occurred during the 800-msec presentation of the tone or light stimulus. In addition, a response occurring during the 800-msec interval preceding each shock UCS was recorded as a base-line response. For each of the 10 days of training, the amplitude of the UCR was recorded on each of the UCS alone trials and for each day, 11 trials were chosen for statistical analysis. These were trials 1 through 5, trial 10 and then every 10th trial thereafter.

Drugs and injection procedure. LSD tartrate, BOL tartrate and DOM hydrochloride were obtained from the National Institute on Drug Abuse (Bethesda, MD) and AMP sulfate was obtained from Sigma Chemical Co. (St. Louis, MO). LSD and BOL were dissolved in sterile nonpyrogenic distilled water, while DOM and AMP were dissolved in sterile nonpyrogenic physiological saline. LSD (0.003, 0.030 and 0.300 μmol/kg), BOL (0.003, 0.030 and 0.300 μmol/kg), DOM (0.3, 1.0 and 3.0 μmol/kg), AMP (3, 10 and 30 μmol/kg) or the appropriate vehicle were injected in a volume of 0.4 mg/kg *via* the marginal ear vein at a rate of 3 ml/min by means of a Harvard infusion pump (model no. 975). No drug or vehicle was injected during the 60-min adaptation sessions. During either the paired CS-UCS or unpaired stimulus procedures, vehicle or drug was injected 30 min before each of the 10 daily 60-min sessions. Animals were run in squads of 12 animals with three animals in each squad receiving vehicle and three animals receiving each of the three doses of one drug. In the paired CS-UCS procedure there were 12 animals at each dosage of the four drugs, 24 animals injected with the distilled water vehicle and 24 animals injected with the saline vehicle. In the unpaired stimulus procedure, there were 6 animals at each dosage of the four drugs, 12 animals injected with the distilled water and 12 animals with the saline vehicle.

Statistics. A repeated measures analysis of variance was performed on the data of each experiment with follow-up analyses carried out by the method of Dunnet (Winer, 1971).

Results

Under the paired CS-UCS procedure, vehicle controls and animals at each dosage of LSD, BOL, DOM and AMP showed a significant acquisition of CRs to both the tone and light CS ($P < .001$), reaching asymptotic levels of 73 to 99% CRs by the last 2-day block of conditioning sessions (fig. 1). LSD produced a significant ($p < .001$) and biphasic effect on CR acquisition, with doses of 0.003 and 0.030 μmol/kg producing enhanced acquisition to both the tone CS (panel A) and light CS (panel B) and the highest dose (0.300 μmol/kg) producing a retarded CR acquisition to the tone CS and no effect on acquisition to the light CS. DOM also produced a significant ($P < .001$) and dose-dependent enhancement of CR acquisition to both the tone (panel C) and light (panel D) CSs. In contrast to LSD and DOM, the effect of AMP on CR acquisition was a function of CS modality. Thus, AMP had no effect on acquisition of CRs to the tone CS (panel C) but did produce a significant ($P < .001$) enhancement of acquisition to the light CS (panel D). AMP also differed from LSD and DOM in that its enhancement of CR acquisition to the light CS was not significantly dose-dependent. BOL produced some small but nonsignificant effects on CR acquisition to the tone (panel A) and light (panel B) CSs.

In order to obtain a measure of drug effect on the rate of CR acquisition, we calculated, for each animal, the number of tone-shock trials and the number of light-shock trials required to

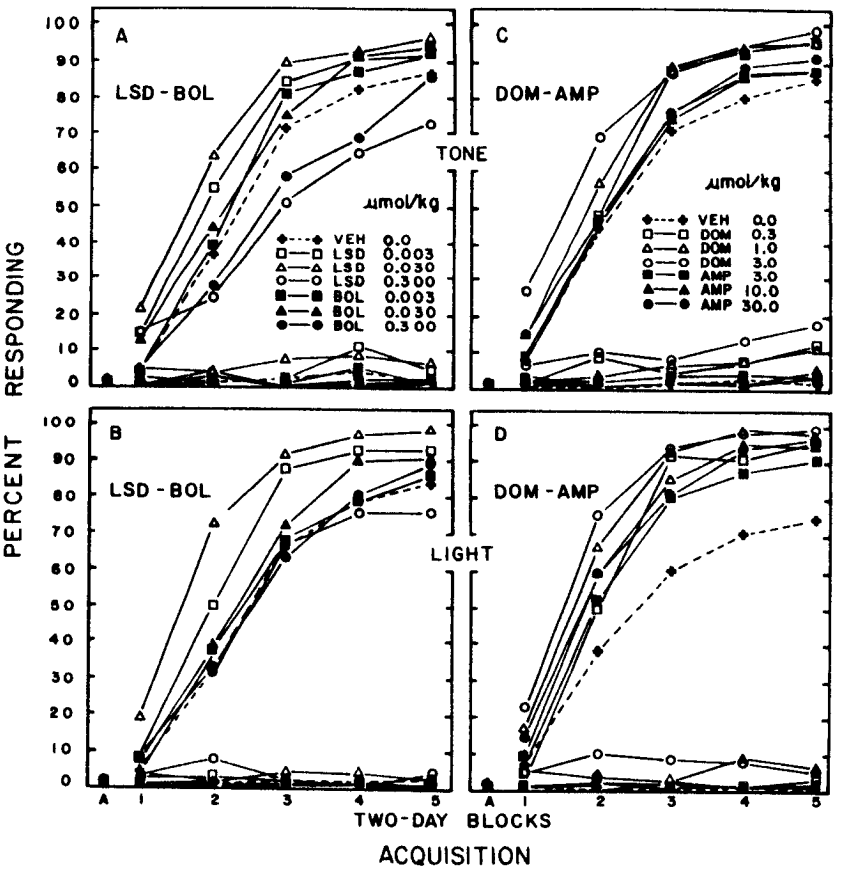

Fig. 1. Effects of LSD, BOL, DOM and AMP on acquisition of CRs. Data are expressed as mean percent responding during adaptation (A) when no stimuli were presented and responding to the tone and light CSs as a function of 2-day blocks of training sessions under both the paired CS-UCS procedure (the seven upper curves in each panel) and the unpaired stimulus procedure (the seven lower curves in each panel). The effects of LSD and BOL are presented in panel A for the tone stimulus and in panel B for the light stimulus, and the effects of DOM and AMP are presented in panel C for the tone stimulus and in panel D for the light stimulus. For the paired CS-UCS procedure, each point for the combined LSD and BOL vehicle (VEH) controls (panels A and B) and the combined DOM and AMP VEH controls (panels C and D) is the mean of 24 animals, whereas all other points are based on 12 animals. In the unpaired stimulus procedure, each point for the combined LSD and BOL or DOM and AMP vehicle controls is the mean of 12 animals and all other points is the mean of 6 animals.

achieve a criterion of five consecutive CRs to the tone and light CSs, respectively. This criterion measure of the rate of CR acquisition was quite similar for the two vehicle control groups. Thus, the combined LSD and BOL vehicle controls ($N = 24$) required 117 and 128 trials to reach criterion to the tone and light CS, respectively, whereas the combined DOM and AMP vehicle controls ($N = 24$) required 110 trials for the tone CS and 123 trials for the light CS. We then calculated a trials to criterion difference score as the number of trials required to attain the criterion of five consecutive CRs by the appropriate vehicle control group minus the number of trials required at each dose of drug (fig. 2). Doses of 0.003 and 0.030 μmol/kg of LSD (panels A and B) and 0.3 to 3.0 μmol/kg of DOM (panels nd D) significantly ($P < .05$) decreased the number of trials required to achieve the criterion to both the tone and light CS. Animals receiving 0.030 μmol/kg of LSD or 3.0 μmol/kg of DOM required 52 to 62 fewer trials to reach this criterion to tone and light CSs, which represents a 46 to 49% decrease from the number of trials (110–128) required by vehicle controls. In agreement with previous results (Gimpl *et al.*, 1978), the highest dose of LSD (0.300 μmol/kg) had no effect on the criterion difference score measure of CR acquisition. Although the shape of the BOL dose-effect curve was somewhat similar to that of LSD (panels A and B), the differences from vehicle control were not significant. Finally, 3 to 30 μmol/kg of AMP significantly ($P < .05$) decreased the number of trials to reach criterion to the light CS (panel D), but had no significant or consistent effect on attainment of the criterion to the tone CS (panel C). The magnitude of the AMP effect on CR acquisition to the light CS was also less than that obtained with LSD and DOM and the dose-effect curve was flatter. Animals receiving 30 μmol/kg of AMP required 40 fewer trials to reach criterion to the light CS or only 32% fewer trials than required by their vehicle controls.

In the unpaired stimulus presentation procedure, the percent responding of the vehicle controls during the presentation of tone and light stimuli was quite low and did not change across days of training (fig. 1). The mean percent responding, averaged for all 10 days of training, for the combined LSD and BOL vehicle controls ($N = 12$) was: tone, 2.5%; and light, 1.6%. For the combined DOM and AMP vehicle controls ($N = 12$), these values were: tone, 1.6%; and light, 1.0%. LSD, BOL and AMP had no significant effect on the percent responding to the tone and light stimuli as compared with their respective vehicle controls (fig. 1). However, the highest dose of DOM (3 μmol/kg) produced a significant ($P < .05$) increase in responding to both stimuli; the actual values, averaged for all 10 days of training, were: tone, 11.0%; and light, 7.8%. The elevated percent responding to the light remained constant across all 10 days of training (fig. 1, panel D), but responding to the tone increased from 6.7% in the first 2-day block to 17.8% in the last 2-day block of training sessions (fig. 1, panel C).

Base-line responding, as measured by the percent occurrence of NMRs during the 800 msec before UCS delivery when no stimuli were presented, was also low for vehicle controls and did not change across days (fig. 3, panels A and C). The actual values, averaged for all 10 days, were: combined LSD and BOL vehicle controls, 1.1%; and combined DOM and AMP vehicle controls, 0.7%. Moreover, these values were not significantly different from the base-line rate of NMRs obtained with all animals during the adaptation session (1.2%) when no stimuli were presented and no drug was injected (fig. 1). LSD, BOL

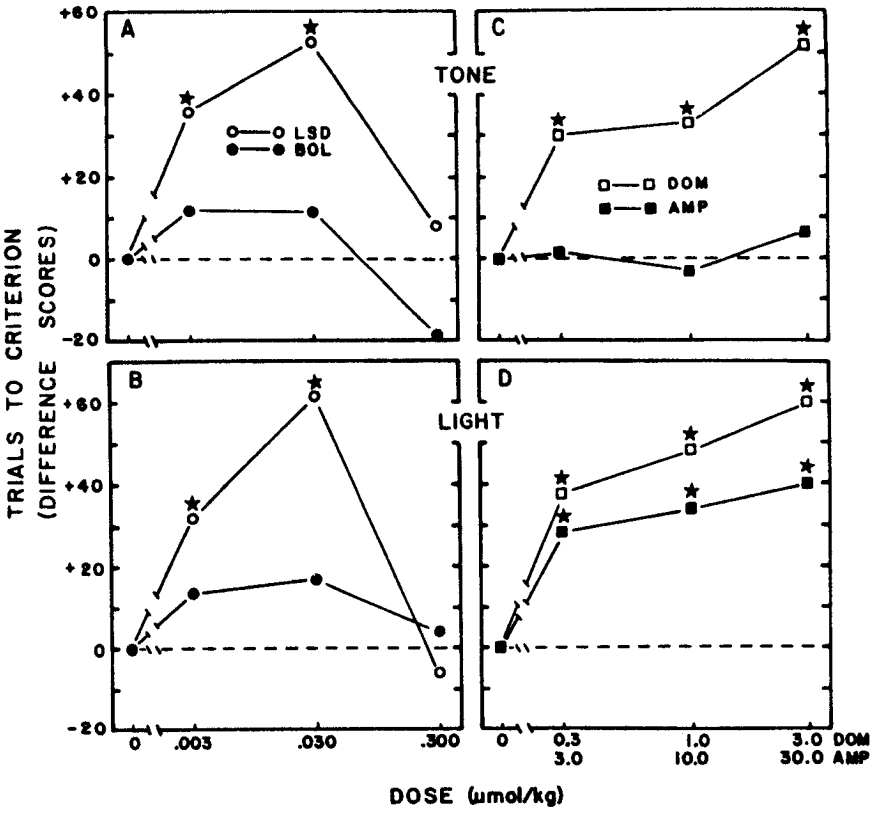

Fig. 2. Effect of LSD, BOL, DOM and AMP on rate of CR acquisition. Data are expressed as the mean number of trials required to the first occurrence of five consecutive CRs by vehicle controls minus the number of trials required after each dose of drug. These differences were calculated separately for tone and light trials. The data for LSD and BOL are presented in panel A for tone trials and panel B for light trials. The data for DOM and AMP are presented in panel C for the tone trials and panel D for the light trials. Each point is the mean of 12 animals. The actual number of trials required by vehicle controls to reach the criterion of five consecutive conditioned reponses were: combined vehicle controls for LSD and BOL (N = 24), 117 trials for the tone CS and 128 trials for the light CS; combined vehicle controls for DOM and AMP (N =24), 110 trials for the tone CS and 123 trials for the light CS. * indicate a significant difference from vehicle controls ($P < .05$) as calculated by the method of Dunnet (Winer, 1971).

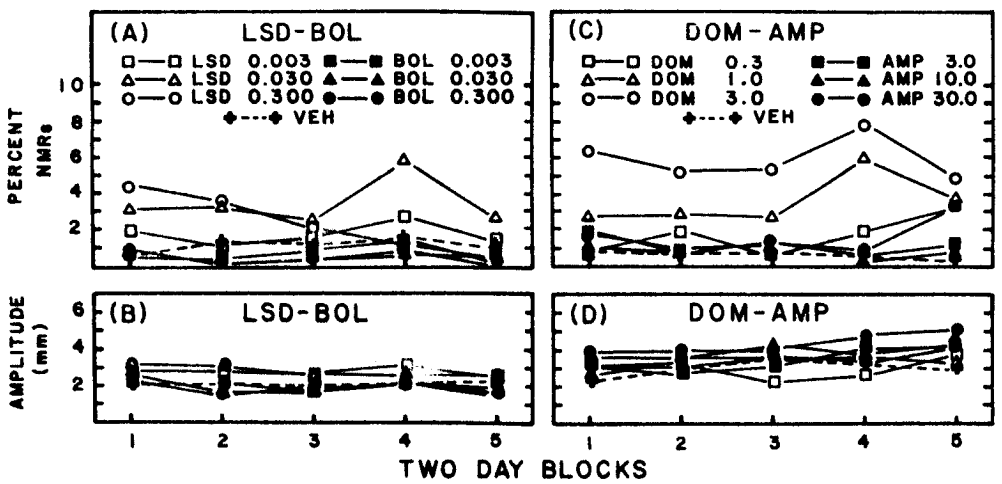

Fig. 3. Effects of LSD, BOL, DOM and AMP on base-line responding and amplitude of the unconditioned NMR as a function of 2-day blocks of training sessions under the unpaired stimulus procedure. The data for base-line responding are expressed as mean percent occurrence of NMRs during the 800 msec before each delivery of the shock UCS with the effects of LSD and BOL presented in panel A and the effects of DOM and AMP in panel C. The amplitude of the unconditioned NMR elicited by the 3 mA shock UCS is expressed as mean millimeters of actual nictitating membrane extension with the effects of LSD and BOL presented in panel B and effects of DOM and AMP in panel D. All points represent the mean of 6 animals, except for the combined LSD and BOL, or DOM and AMP vehicle (VEH) controls, which are the mean of 12 animals.

and AMP had no significant effect on base-line responding as compared with their respective vehicle controls (fig. 3, panels A and C). In contrast, the highest dose of DOM (3 μmol/kg) significantly ($P < .05$) increased base-line responding (fig. 3, panel C) to a mean value of 5.9% for all 10 days of training. This increase in percent base-line responding did not change across the 10 days of training.

There was no significant or consistent effect of any dose of LSD and BOL (fig. 3, panel B) or of DOM and AMP (fig. 3, panel D) on the amplitude of the UCR as compared with their vehicle controls.

Discussion

LSD, DOM and AMP not only increased the overall percent occurrence of CRs during acquisition (fig. 1), but also increased the rate of CR acquisition as measured by a decrease in the number of trials required to achieve the stringent criterion of five consecutive CRs to the CSs (fig. 2). In contrast, BOL was without significant effect on CR acquisition. LSD, DOM and AMP could be distinguished from each other by the precise manner in which they increased acquisition rates. Thus, whereas both LSD and DOM produced an increased rate of CR

acquisition that was equivalent for both the auditory and visual CSs, AMP only increased the rate of acquisition to the visual CS. A further distinction could be made between the actions of these three drugs on the basis of their effects during the unpaired presentations of tones, lights and shocks.

In agreement with previous studies on the nictitating membrane reflex (Gormezano, 1966, 1972), the base-line rate of NMRs during the adaptation session, when no stimuli were presented and no drug injected, was quite low (1.2%). The unpaired presentation of tone, light and shock produced no increase in base-line rate of responding of vehicle controls as measured by the occurrence of NMRs during the 800 msec before UCS delivery, when no stimuli were presented (0.7–1.1%), nor any reliable evidence of an increase in responding during the 800-msec presentation of tone and light stimuli (1.0–2.5%). Therefore, the acquisition of CRs by vehicle controls was associative (occurred only during the paired presentations of CS and UCS). Because LSD and AMP also had no effect on base-line rate of responding or responding to tone and light stimuli in the unpaired stimulus procedure, we conclude that the enhanced rate of CR acquisition produced by these two drugs during the paired CS-UCS procedure was also due to an effect on associative processes.

The increased rate of CR acquisition produced by DOM fered from that produced by LSD and AMP in that it could not be uniquely attributed to an effect on associative processes. Specifically, the unpaired presentation of stimuli indicated that the highest dose of DOM (3 μmol/kg) was producing: 1) a significant increase in base-line responding of 5.2% above vehicle controls; 2) a significant increase in responding to the tone and light stimuli of 9.4 and 6.8%, respectively, above vehicle controls; and 3) a significant monotonic increase in responding to the tone stimulus from 6.7% on the first 2-day block to 17.8% on the last 2-day block of training sessions. Consequently, the increased rate of CR acquisition produced by 3 μmol/kg of DOM in the paired CS-UCS procedure was, at least in part, attributable to its effects on nonassociative determinants of NMR production (*i.e.*, response governing processes that do not require the pairing of a CS with the UCS). However, the effects on CR acquisition at the lower doses of DOM (0.3 and 1.0 μmol/kg) might have been due primarily to effects on associative processes.

It has been demonstrated that both the CR elicited by a tone CS and the UCR elicited by a shock UCS involve an activation of abducens motoneurons which then leads sequentially to a ntraction of the retractor bulbi muscle (*via* the VIth cranial nerve) and retraction of the eyeball. The force of this mechanical action, in turn, produces a passive and correlated extension of the nictitating membrane across the globe (Cegavske *et al.*, 1976, 1979). Our finding that LSD, DOM and AMP had no effect on the amplitude of the unconditioned NMR indicates, therefore, that the enhancement of CR acquisition produced by these three drugs could not be due to either an alteration in the unconditioned reflex or to an alteration in the motoric expression of the conditioned NMR.

In addition to the differences noted above, LSD, DOM and AMP also differed with respect to the potency of their effects. The ED_{50} for producing an increased rate of CR acquisition was estimated from the curves of figure 2 to be: LSD, 0.002 and 0.003 μmol/kg for the tone and light CS, respectively; DOM, 0.26 and 0.24 μmol/kg for the tone and light CS, respectively; and AMP, 1.2 μmol/kg for the light CS. The ED_{50} values for

TABLE 1

Comparison of ED_{50} values for enhanced acquisition of CRs to tone and light stimuli in the rabbit and the dose of drug required to produce reliable hallucinations in humans

Drug	CR Acquisition ED_{50}[a]		Human Hallucinogenic Dose[b]
	Tone CS	Light CS	
	μ/kg		μg/kg
LSD	0.7	0.9	1.0[c]
DOM	55	50	50[d]
AMP	No effect	160	5000[e]
BOL	No effect	No effect	No effect[c]

[a] ED_{50}, as the base, was obtained from dose-effect curves of figure 2.
[b] Lowest dose, as the base, required to obtain reliable hallucinations in humans.
[c] Abramson *et al.* (1955); Rothlin (1957); Brawley and Duffield (1972).
[d] Snyder *et al.* (1967).
[e] Connell (1958).

LSD are in good agreement with our previously reported value of 0.003 μmol/kg for tone and light CSs combined (Gimpl *et al.*, 1978). Thus on a molar basis, LSD was approximately 100 times more potent than DOM in producing enhanced acquisition to the tone and light CSs and 400 times more potent than AMP in producing enhanced acquisition to the light CS.

Table 1 compares the ED_{50} values for producing an increased rate of CR acquisition to tone and light CSs, expressed as micrograms per kilogram of the base, with the minimum dose of drug required to produce reliable hallucinations in humans. It can be seen that the order of potency for producing enhanced acquisition of CRs, LSD > DOM > AMP, is identical with the order of potency of these drugs in producing hallucinations. Moreover, the ED_{50} values of LSD and DOM for enhancing CR acquisition to tone and light CSs were essentially identical with the dosages required to produce reliable hallucinations in humans (table 1). The results with AMP are less clear. Although the ED_{50} of AMP for increasing the rate of CR acquisition to the light CS was considerably below the dose required to produce hallucinations in humans (table 1), even the highest dose (30 μmol/kg or 4100 μg/kg, as the base) had no effect on CR acquisition to the tone CS. However, unlike LSD and DOM which produce hallucinations in humans after a single injection (Abramson *et al.*, 1955; Rothlin, 1957; Snyder *et al.*, 1967), hallucinations produced by AMP have only been reliably obtained in AMP abusers taking multiple daily doses over a period of a week or more and achieving daily intakes of approximately 5,000 to 10,000 μg/kg as the base (Angrist and Gershon, 1970; Connell, 1958, Griffith *et al.*, 1972). Thus, even our highest dose of AMP falls below these values. Higher doses could not be given because they were found, in preliminary experiments, to be lethal in the rabbit. Therefore, it is possible that administration of AMP to the rabbit in a manner comparable to the schedule used by human abusers and hence leading to comparably high daily intakes would produce effects on CR acquisition to a tone CS at doses that more closely approximated the hallucinogenic dose in humans.

Several studies using classical conditioning of the rabbit NMR have demonstrated a relationship between the effects of a drug on CR acquisition and on the sensory processing of the CS. Both haloperidol (Harvey and Gormezano, 1981) and scopolamine (Moore *et al.*, 1976) decrease the rate of CR acquisition to a tone CS and, in previously trained animals, increase the intensity threshold of a tone CS for elicitation of CRs. In contrast, LSD increases the rate of CR acquisition to a tone CS

and decreases the intensity threshold of a tone CS for elicitation of CRs (Gormezano and Harvey, 1980). Identical effects of LSD on CR acquisition and sensory processing of the CS have been demonstrated in rabbits using a classical appetitive conditioning procedure (Gormezano *et al.*, 1980). These results suggest that the changes in the rate of acquisition of classically conditioned responses are, at least in part, due to an alteration in the sensory processing of the CS. Therefore, it is possible that the close correspondence between the order of potencies of LSD and DOM for producing hallucinations in humans and increasing the rate of CR acquisition in rabbits is related to a common effect of these drugs on sensory processing of stimuli. The results with AMP are of interest because they suggest that some drugs may alter sensory processing of stimuli in a modality-specific manner.

Acknowledgments

The authors thank the National Institute on Drug Abuse for supplies of LSD, BOL and DOM hydrochloride. We also thank Linda Saeger Bartels and Ellen Aycock for their invaluable assistance.

References

ABRAMSON, H. A., JARVIK, M. E., KAUFMAN, M. R., KORNETSKY, C., LEVINE, A. AND WAGNER, M.: Lysergic acid diethylamide (LSD-25). I. Physiological and perceptual responses. J. Psychol. **39:** 3–60, 1955.

ANGRIST, B. M. AND GERSHON, S.: The phenomenology of experimentally induced amphetamine psychosis-preliminary observation. Biol. Psychiatry **2:** 95–107, 1970.

BRAWLEY, P. AND DUFFIELD, J. C.: The pharmacology of hallucinogens. Pharmacol. Rev. **24:** 31–66, 1972.

CEGAVSKE, C. F., PATTERSON, M. M. AND THOMPSON, R. F.: Neuronal unit activity in the abducens nucleus during classical conditioning of the nictitating membrane response in the rabbit (*Oryctolagus cuniculus*). J. Comp. Physiol. Psychol. **93:** 595–609, 1979.

CEGAVSKE, C. F., THOMPSON, R. F., PATTERSON, M. M. AND GORMEZANO, I.: Mechanisms of efferent neuronal control of the reflex nictitating membrane response in rabbit (*Oryctolagus cuniculus*). J. Comp. Physiol. Psychol. **90:** 411–423, 1976.

CONNELL, P. H.: Amphetamine Psychosis, Chapman & Hall, London, 1958.

GIMPL, M. P., GORMEZANO, I. AND HARVEY, J. A.: Effects of LSD on learning as measured by classical conditioning of the rabbit nictitating membrane response. J. Pharmacol. Exp. Ther. **208:** 330–334, 1978.

GORMEZANO, I.: Classical conditioning. *In* Experimental Methods and Instrumentation in Psychology, ed. by J. B. Sidowski, pp. 385–420, McGraw-Hill Book Company, New York, 1966.

GORMEZANO, I.: Investigations of defense and reward conditioning in the rabbit. *In* Classical Conditioning II: Current Research and Theory, ed. by A. H. Black and W. F. Prokasy, pp. 151–181, Appleton-Century-Crofts, New York, 1972.

GORMEZANO, I. AND HARVEY, J. A.: Sensory and associative effects of LSD in classical conditioning of the rabbit (*Oryctolagus cuniculus*) nictitating membrane response. J. Comp. Physiol. Psychol. **94:** 641–649, 1980.

GORMEZANO, I., HARVEY, J. A. AND AYCOCK, E.: Sensory and associative effects of LSD on classical appetitive conditioning of the rabbit jaw movement response. Psychopharmacology **70:** 137–143, 1980.

GORMEZANO, I., SCHNEIDERMAN, N., DEAUX, E. AND FUENTES, I.: Nictitating membrane: Classical conditioning and extinction in the albino rabbit. Science (Wash. DC) **138:** 33–34, 1962.

GRIFFITH, J. D., CAVANAUGH, J., HELD, J. AND OATES, J. A.: Dextroamphetamine. Evaluation of psychomimetic properties in man. Arch. Gen. Psychiatry **26:** 97–100, 1972.

HARVEY, J.A. AND GORMEZANO, I.: Effects of haloperidol and pimozide on classical conditioning of the rabbit nictitating membrane response. J. Pharmacol. Exp. Ther. **218:** 712–719, 1981.

MOORE, J. W., GOODELL, N. A. AND SOLOMON, P. R.: Central cholinergic blockade by scopolamine and habituation, classical conditioning, and latent inhibition of the rabbit's nictitating membrane response. Physiol. Psychol. **4:** 395–399, 1976.

ROTHLIN, E.: Pharmacology of lysergic acid diethylamide and some of its related compounds. J. Pharm. Pharmacol. **9:** 569–587, 1957.

SHULGIN, A. T., SARGENT, T. AND NARANJO, C.: Structure activity relationship of one-ring psychotomimetics. Nature (Lond.) **221:** 537–541, 1969.

SNYDER, S. H., FAILLACE, L. AND HOLLISTER, L.: 2,5-Dimethoxy-4-methylamphetamine (STP); a new hallucinogenic drug. Science (Wash. DC) **158:** 669–670, 1967.

SNYDER, S. H., FAILLACE, L. A. AND WEINGARTNER, H.: DOM (STP), a new hallucinogenic drug, and DOEt: Effects in normal subjects. Am. J. Psychiatry **125:** 113–120, 1968.

WINER, B. J.: Statistical Principles in Experimental Design, McGraw-Hill Book Company, New York, 1971.

Send reprint requests to: Dr. John A. Harvey, Departments of Psychology and Pharmacology, East Hall, E-117, The University of Iowa, Iowa City, IA 52242.