Psychopharmacology 60, 125–130 (1979)

Psychopharmacology

An Analysis of Some Perceptual Effects of Morphine, Chlorpromazine, and LSD

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Abstract. Male albino rats were trained to detect either a pure tone or a weak footshock embedded in white noise by utilizing a discrete-trial two-choice, successive discrimination procedure. The effects of morphine, chlorpromazine (CPZ), and lysergic acid diethylamide (LSD) were then analyzed on several measures of performance. Morphine (2.5–10 mg/kg) produced a nonspecific decrease in accuracy of discrimination on trials when the stimulus was presented as well as on trials when no stimulus occurred. Morphine was also followed by dose-dependent decreases in speed to initiate trials and by increases in intersubject variability. CPZ (1.0–4.0 mg/kg) caused a decrease in accuracy only on no-stimulus trials and, like morphine, decreased speed to initiate trials. LSD (0.04–0.16 mg/kg) decreased overall accuracy in a nonspecific manner (i.e., when shock and tone discriminations were considered together) and decreased speed by producing periods of nonresponding.

Key words: Discrimination – Perception – Morphine – Chlorpromazine – LSD

Among the psychoactive drugs that are known to alter perception (i.e., responding under the control of discriminative stimuli) are opiates, neuroleptics, and hallucinogens. Opium, and later its primary derivative, morphine, have been used to attenuate pain throughout man's history (Appel and Dykstra, 1977; Jaffe, 1970), and the phenothiazines, of which chlorpromazine (CPZ) is the prototype, produce a general loss of 'behavioral tone' and responsivity to environmental stimulation (Iversen and Iversen, 1975). Hallucinogens such as lysergic acid diethylamide (LSD) have been reported to enhance or distort perception in both humans and animals (Appel, 1968; Appel and Dykstra, 1977; Bradley and Elkes, 1957; Brawley and Duffield, 1972; Hollister, 1968; Key, 1961; Key and Bradley, 1960).

Unfortunately, the mechanisms of action underlying these effects are not well understood. We have argued elsewhere (Appel and Dykstra, 1977) that this lack of understanding may be, at least in part, the result of the complex nature of 'perception,' which always involves two distinct, but often confounded, components (Goldiamond, 1962), i.e., sensory effects of environmental stimulation and the organism's response to these effects, both of which can be altered by drugs. For example, the clinically significant (analgesic) effects of opiates might be: 1) the result of action of these compounds on central pain mechanisms (Sinitsin, 1964; Killam, 1968; Pert and Yaksh, 1974; Yaksh and Rudy, 1976); 2) a correlate of the euphorigenic effects of the same compounds on pain-induced suffering, affect, or mood (Beecher, 1959, 1968; Jaffe, 1970; Levine, 1973); or 3) a combination of (1) and (2).

One way to analyze the mechanisms of action of drugs such as opiates is to compare the effects of these compounds on behavior that is differentially controlled by noxious or other stimuli. Unfortunately, little is known about such effects. In squirrel monkeys, morphine does not appear to alter the differential rates of food-reinforced bar-pressing that occur in the presence or absence of an electric shock of low intensity (McMillan and Morse, 1967). However, this compound does decrease the ability of rats to detect shock in a discrete-trial, two-choice situation; this effect is due primarily to a decrease in accuracy (percent correct) on trials when shocks were presented and is an inverse function of shock intensity (Lloyd et al., 1978). The same authors reported that CPZ also lowered accuracy, but that this decrease was due almost entirely to a decrease in percent correct on trials in which shocks were not presented. It was therefore concluded that morphine

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0033-3158/79/0060/0125/$01.20

may affect sensory aspects of the perception of the shock stimulus (sensitivity) whereas CPZ probably affects higher-order, 'attentional' processes (Lloyd et al., 1978).

Since virtually nothing is known about the effects of either of these compounds on the perception of nonaversive stimuli, and since a relatively narrow dose range of morphine (4.0 – 6.0 mg/kg) was studied by Lloyd et al., 1978), it seemed desirable to (1) repeat their experiment with CPZ and a wider dose range of morphine (2.5 – 10 mg/kg), (2) compare the effects of both of these compounds on the discrimination of both potentially aversive (shock) and nonaversive (tone) stimuli, and (3) examine the effects of an additional drug, LSD (0.04 – 0.16 mg/kg). While this hallucinogen is not generally viewed as having analgesic properties, it has been used to attenuate pain (or suffering) in various areas of medicine (Sankar, 1975). Such effects could, however, be the result of drug-induced alterations in the organism's response to sensory stimulation, e.g., response perseveration or 'bias' (Dykstra and Appel, 1970, 1974).

Materials and Methods

Subjects. Six male albino rats of Sprague-Dawley strain (obtained from ARS Sprague-Dawley, Madison, Wisconsin) were used. They were housed in a room maintained on a 12-h light/dark cycle with constant temperature (24° C) and humidity (50%). Water was continuously available in the individual home cages. The subjects were maintained at 80% of their free-feeding body weights (375 – 425 g) by augmenting food consumed during the experimental sessions with an additional 10 – 15 g per day of Purina lab chow. The animals were fed 1 h after completion of the test sessions, which were conducted 5 days per week, Monday to Friday.

Apparatus. The apparatus consisted of a modified, commercially available rat chamber (BRS/LVE, Model 1316) housed in a picnic chest (Coleman) equipped with a blower for air circulation. The chamber was equipped with two levers located 3 cm to the left and right of a food cup, and a commercially available pellet feeder (R. Gerbrands Co., Model D), which delivered one 45 mg Noyes pellet per reinforcement. An overhead house light and two green pilot lights located 5 cm above each lever were also provided. The chamber also contained a 15 cm chain, which hung from the ceiling opposite the wall containing the levers and food cup, and a speaker directed downward from the ceiling. Additional apparatus were commercially available Audio-Oscillator (Hewlett-Packard, Model 200AB), which emitted an 8.0 Hz tone, a white noise generator (Grason-Stadler, Model 455C), and a shock generator and scrambler (Grason-Stadler, Model E6070B), which delivered shock through the chain, levers, walls, and grid floor of the chamber.

All experimental events were programmed by electromechanical switching and timing circuits in an adjoining room. Cumulative latencies for all subjects for each session (house lights to chain pull and chain pull to lever press), as well as choice responses and food reinforcements, were recorded.

Behavioral Procedure. The animals were first trained to respond differentially on a two-choice auditory discrimination task in which the stimuli to be discriminated were the presence of an 8.0 kHz tone embedded in white noise (Sd1), or the white noise alone (Sd2). They were initially trained to press the right lever in the presence of Sd1. During this phase, the chamber was dark, and the chain and the left lever were removed. Each right lever press was followed immediately by food and a 0.3-s flash of the pilot light located above the lever (conditioned reinforcer).

The animals were then trained to respond in the presence of Sd1 and to withhold lever pressing for 10 s when the house lights were on and no auditory stimuli (except the masking noise produced by the blower) were present. At the end of 10 s the house lights went out and Sd1 was presented, until a single right lever press occurred and was reinforced. When all animals had learned to respond correctly on 50 consecutive trials, the chain was inserted and chain pulling in the presence of the house lights was shaped by successive approximation. Pulling the chain resulted in extinguishing the house lights and the occurrence of Sd1. A right lever press rapidly followed and was reinforced with food and pilot light. Reinforcement was followed immediately by the onset of the house lights, the cue for initiation of the next trial.

The left lever press was then established in the same manner by removing the chain and the right lever, extinguishing the house lights, and reinforcing (with food and pilot light) left lever presses in the presence of the white noise alone (Sd2). The chain and house lights were then reintroduced, with the right lever removed as above. Chain pulling now resulted in Sd2, the conditions associated with a left lever press.

Finally, both levers were presented. The chain pull now resulted in extinguishing the house lights, and in the presentation of either Sd1 or Sd2. A correction procedure was initially used in which Sd2 was presented on trial 1 and remained in effect until five trials with correct (left) lever choices occurred. This was followed by Sd1 until five correct (right) trials occurred. An incorrect response resulted in a 10-s time-out (TO 10″), during which the box was dark and chain-pull or lever-press responses had no programmed consequences. Each correct response was immediately reinforced with food and pilot light. An experimental session continued for 200 trials. When the animals reached a criterion of 90% correct responses, the correction procedure was replaced by a random procedure in which Sd1 and Sd2 trials occurred 50% of the time in random order, with the restriction that not more than three successive trials under the same conditions were allowed to occur.

When the animals again responded correctly in 90% of the trials, they were divided randomly into two groups to counterbalance the order of testing with tone and shock stimuli. For one group, the intensity of the 8.0 kHz tone was decreased gradually to 57 dB, and the intensity of the noise was increased to 70 dB. The probability of food reinforcement for the tone discrimination was then lowered gradually to 0.30 on each lever, independently.

For the other group, shock was introduced slowly on Sd1 trials. On day 1 of this phase, the shock intensity was 0.05 mA (at the source) and on succeeding days was increased gradually to 0.10 mA. The tone was then faded out until, on Sd1 trials, the chain pull resulted in presentation of the noise and shock whereas, on Sd2 trials, the chain pull resulted in noise alone. In order to equate asymptotic performance of the two groups at 80% correct (overall) the shock intensity was then reduced to 0.06 mA, and the probability of food reinforcement for the shock discrimination was reduced to 0.70 on each lever, independently. For both groups, each correct lever press resulted in reinforcement with the pilot light, and each incorrect response resulted in TO 10″.

Pharmacologic Procedure. Once training was completed, the animals were tested for one session (200 trials) per day until stable baseline performance was established (2 – 3 weeks). A drug regimen was then begun under which, on drug days, each rat received a drug or saline prior to testing. Drug days were spaced such that at least two nondrug days preceded each drug day. The drugs used were morphine,

administered 10 min prior to testing, CPZ, and LSD, both administered immediately prior to testing. Morphine was prepared from 15 mg/ml ampuls of morphine sulfate solution (Eli Lilly, Indianapolis) diluted with 0.9% isotonic saline to a concentration of 5.0 mg/ml, and was administered in doses of 2.5, 5.0, and 10.0 mg/kg. CPZ was prepared from 30 mg/ml vials of Thorazine (Smith, Kline, and French, Philadelphia) diluted to a concentration of 2.0 mg/ml with saline, and was administered in doses of 1.0, 2.0, and 4.0 mg/kg. LSD was prepared from LSD tartrate powder (obtained from NIDA), dissolved in saline to a concentration of 0.08 mg/ml. Doses used were 0.04, 0.08, and 0.16 mg/kg. Saline was always given in a volume of 1.0 ml/kg, immediately prior to testing. All drugs and saline were administered intraperitoneally in random order, with the restriction that an animal receive the lowest dose of a drug first and the highest dose last.

Crossover Replication. Once the full drug regimen was completed by each subject, the two groups were crossed over. That is, for those rats tested initially with tone Sd1, the shock was faded in and the tone faded out as described above. For those animals tested initially with shock Sd1, the tone was gradually reintroduced and the shock faded out. When stable baselines were reestablished (1–2 weeks), the complete drug regimen was repeated for each animal in reverse order of drugs and dosages.

Analysis of Data. One rat, which was tested initially with the tone Sd1, died shortly after the crossover was completed; its data have not been included in the analysis. Three measures of discrimination performance were calculated for each animal for each drug day, and for the 2 days immediately preceding each drug day, in the manner of Lloyd et al. (1978): overall percent correct lever choice (PC); percent correct on trials when Sd1 was presented (PCS); and percent correct on trials when Sd2 was presented (PCN). It should be noted that PCS and PCN can thus vary independently, although PC is dependent on both PCS and PCN. Two measures of response speed were also calculated for each subject for each drug and baseline day: the mean reaction speed for trial initiation (responses per second between trial completion and chain pull, RSCP) and mean reaction speed for lever choice (responses per second between chain pull and lever press, RSLR). Changes from baseline scores were then calculated for each measure for each drug and saline injection, as the difference between mean performance on the two baseline days and performance on the drug day. To determine whether each psychoactive drug had an overall effect on 'perception' relative to saline controls, PC, PCS, and PCN change scores were pooled over stimulus conditions (shock and tone Sd1) and doses, and confidence intervals based on Dunnet's test for differences from a control (Bruning and Kintz, 1977) were constructed about each overall drug mean. Overall effects of the psychoactive drugs on speed of responding were similarly assessed by pooling RSCP and RSLR change scores over stimulus conditions and dose, and constructing Dunnet's intervals relative to saline about each drug mean.

To determine the effects of Sd1 vs. Sd2, shock vs. tone, and dose on accuracy of discrimination, mean PCS and PCN change from baseline scores under each drug condition were submitted to separate, completely within subject analyses of variance (Sd by stimulus by dose by subjects). To determine the effects of shock vs. tone and dose on reaction speeds, mean RSCP and RSLR change from baseline scores for each drug condition were submitted to separate, completely within subject analyses of variance (stimulus by dose by subjects).

Results

Baseline performance (no drug or saline injection) showed no differences between accuracy of shock and tone discriminations or between Sd1 and Sd2 trials. Overall mean PC of baseline days was 81.8 ± 0.6 (SEM) for shock discriminations and 81.9 ± 0.6 for tone discriminations. Mean baseline PCS was 82.6 ± 1.1 and PCN, 80.9 ± 0.8 for shock discriminations; mean baseline PCS was 83.5 ± 1.0 and PCN, 80.2 ± 0.9 for tone discriminations. Mean baseline RSCP was 0.155 ± 0.006 responses/s for shock discriminations and 0.147 ± 0.007 for tone discriminations; mean baseline RSLR was 0.427 ± 0.008 responses/s for shock discriminations and 0.507 ± 0.004 for tone discriminations. As no differences were observed between performance of animals tested first with tone Sd1 and those tested first with shock Sd1, the data have been pooled for all subjects.

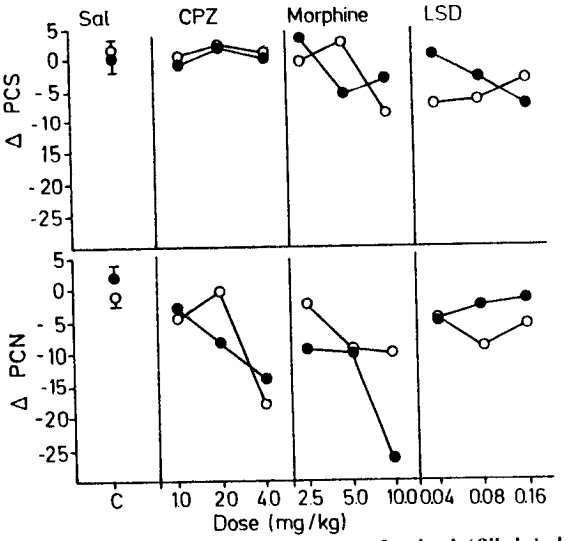

Fig. 1. Mean change from baseline scores for shock (*filled circles*) and tone (*open circles*) detection under saline (Sal), CPZ, morphine, and LSD as a function of dose. Negative change scores indicate decrease in accuracy of detection. *PCS*, percent correct on trials when the stimulus was presented; *PCN*, percent correct on trials when no stimulus was presented. *Saline points:* mean of three administrations per animal per stimulus condition. *Variance estimates:* ±SEM. $N = 5$

The effects of saline and of the three drugs studied on performance of both the shock and tone discrimination problems are shown in Figure 1, and the effects on speeds of responding are shown in Figure 2. When the data were pooled over dose and stimulus modality (above), confidence intervals showed no overall effects of saline administration on any measure of performance, relative to baseline performance. The analyses of variance revealed that there were no differential effects of saline on any variable for any measure of accuracy of discrimination or their interactions (Fig. 1). Thus, discrimination performance under saline conditions was comparable on (1) Sd1 and Sd2 trials and (2) shock and tone discrimination problems.

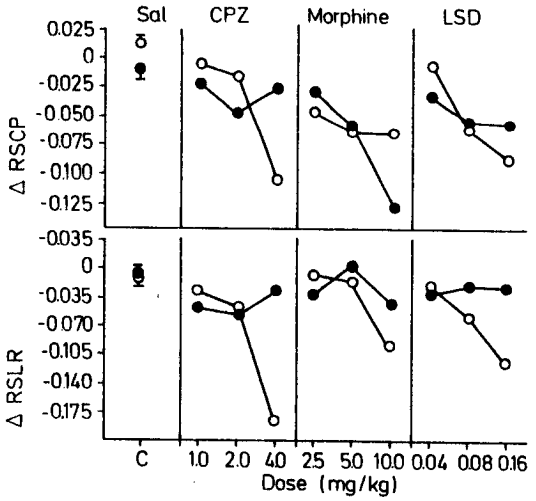

Fig. 2. Mean change from baseline scores for response speeds under saline (Sal), CPZ, morphine, and LSD as a function of dose. *Filled circles:* response speeds for shock; *open circles:* response speeds for tone-detection problems; *negative change scores:* decrease in response speeds. *RSCP*, speed to trial initiation (responses/s); *RSLR*, speed between trial initiation and lever choice (responses/s). *Saline points:* mean of three administrations per animal per stimulus condition. *Variance estimates:* ± SEM. $N = 5$

Analyses of variance of the speed scores (Fig. 2) revealed a significant difference between the effects of saline on speed to initiate trials (RSCP) on the two discrimination problems, $F(1,4) = 11.75$, $P < 0.05$. That is, saline increased RSCP relative to baseline when Sd1 was tone, but decreased RSCP when Sd1 was shock. As can be seen in Figure 2, however, these changes were small compared to those that occurred due to the psychoactive drugs. There were no other effects of saline on RSCP related to any variable or any interaction of variables, and no effects on RSLR.

Dunnet's intervals constructed about the mean overall change from baseline scores following the administration of morphine showed that it significantly decreased overall percent correct ($P < 0.05$) and overall PCN ($P < 0.01$), but had no significant effect on overall PCS. Morphine also produced an overall decrease in RSCP ($P < 0.01$), but had no effect on overall RSLR.

Analysis of variance showed that the decrease in overall percent correct following administration of morphine was dose related, $F(2,8) = 6.86$, $P < 0.025$ (Fig. 1). However, this analysis failed to reveal any significant differences between the effects of morphine on Sd1 (PCS) and Sd2 (PCN) trials or on performance of the shock and tone discrimination problems. There was no interaction between the effect of dose and type of stimulus (shock or tone) or between any other set of variables.

The overall decrease in RSCP following administration of morphine was also found to be related to dose, $F(2,8) = 5.12$, $P < 0.05$; i.e., the slowest speeds occured following the highest dose (10.0 mg/kg). While this relationship appeared to show a tendency to be more pronounced with the shock stimulus (Fig. 2), the stimulus by dose interaction was not significant. There were no effects of morphine on RSCP, or on RSLR, that could be attributed to the nature of the discrimination problem (shock vs. tone).

Dunnet's intervals for the pooled data following administration of CPZ showed that this drug also decreased overall percent correct responses ($P < 0.05$) and overall PCN ($P < 0.05$), but not overall PCS. CPZ had no significant effects on overall speed of responding as measured by RSCP and RSLR.

Analysis of variance showed that the effects of CPZ on overall accuracy of discrimination, in contrast to those of morphine, were not related to dose; while there was a tendency for higher doses of CPZ to produce greater decreases in overall percent correct, these effects were not significant. The decrease in accuracy following CPZ was caused almost entirely by the effects of this compound on Sd2 trials (PCN), $F(1,4) = 42.45$, $P < 0.01$. This effect was dose related, $F(2,8) = 4.46$, $P < 0.05$; there were no differential effects of CPZ on shock and tone discrimination problems, nor were there any further interactions (Fig. 1).

Although Dunnet's intervals indicated that there was no overall decrease in RSCP following CPZ, the analysis of variance did reveal a significant dose effect, $F(2,8) = 6.56$, $P < 0.025$ (Fig. 2). This was caused by the large decrease in speed to initiate trials at the highest dose (4.0 mg/kg). There was no significant effect of stimulus modality on RSCP following CPZ, and no interaction. CPZ had no differential effects on RSLR that could be attributed to any variable.

LSD also decreased overall percent correct discriminative responding, as assessed by Dunnet's intervals on the pooled data ($P < 0.05$). LSD appeared to cause approximately equivalent decreases in overall PCS and PCN, but, when these measures were analyzed separately, the decreases did not prove to be significant ($P > 0.05$). LSD did produce a significant decrease in overall RSCP ($P < 0.05$), but had no effect on overall RSLR.

When performance on the two discrimination problems was compared using analysis of variance, LSD had no differential effect on any measure of accuracy; there was a slight tendency for this compound to decrease accuracy of tone discrimination more than the accuracy of shock discrimination (Fig. 1), but this effect was not significant.

LSD had no significant effects on RSCP related to any variable, although there was a tendency for the overall decrease in this reaction speed, as indicated by Dunnet's intervals, to be dose related, and a tendency

for this effect to be more pronounced for the tone than for the shock stimulus (Fig. 2). Although there were no significant effects of stimulus modality on RSLR following LSD, the data did show a highly significant interaction of stimulus by dose, $F(2,8) = 12.38$, $P < 0.005$. As can be seen in Figure 2, this was due to a dose-related decrease in RSLR following LSD with the tone, but not with the shock, stimulus.

Discussion

The results indicate that morphine significantly lowers accuracy or ability to detect both shock and tones (in a background of noise), that it lowers speed to initiate trials (but not to make choice responses), and that these effects are dose dependent (2.5 – 10.0 mg/kg). Failure to find significant differences between the effects of this compound on the two kinds of trials (stimulus presented or stimulus not presented) is somewhat surprising in view of the results of Lloyd et al., 1978), and indicates the need for further analysis of the perceptual effects of opiates.

Nevertheless, certain similarities in the present data to those of the earlier study require additional comment. Lloyd et al. (1978) state that while morphine appeared to lower accuracy on no shock trials, the effects were not significant because of the large variability in performance following administration of this compound. In the present experiment, morphine also produced a large increase in variability; in fact, the variability following morphine was twice that induced by CPZ and six times that induced by saline. In particular, the failure to find a significant stimulus vs. no stimulus difference under morphine appears due primarily to a large degree of intersubject variability, with the Sd by subjects' interaction term accounting for 12.6% of the total variance under morphine as compared to 1.6% under CPZ, rather than to pronounced differences between drugs in variability attributable to Sd alone. This variability under morphine is also evidenced by the failure of the decrease in PCS due to morphine to attain significance when assessed by Dunnett's intervals, although PCS and PCN were not found to differ significantly when the two measures were compared directly using analysis of variance.

Other differences between the present results and those of Lloyd et al. (1978) can probably be attributed to pharmacologic parameters such as time between injection and testing and dose.

The most interesting result of the present experiment (concerning morphine) is the lack of significant tone vs. shock differences on any measure of performance. If this finding is not an artifact of increased variability (above), it indicates that this compound has perceptual effects that may not be directly related to its antinociceptive properties (i.e., it attenuates sensitivity to low intensity stimulation, regardless of modality).

The results of the present experiment showed that CPZ (1.0 – 4.0 mg/kg) produced a decrease in overall discrimination performance due entirely to a dose-related decrease in accuracy on trials when the stimulus was not presented and, like morphine, decreased speed to initiate trials. When either shock or tone was presented, animals given CPZ correctly detected the stimulus. These results are in good agreement with those of Lloyd et al. (1978), thus extending previous findings to higher doses, and suggesting that the behavioral effects of this compound are independent of the kind of stimulus the organism is trained to discriminate.

The results of the present experiment indicate that the overall decrease in accuracy of discrimination following LSD was nonspecific with respect to every variable studied, and that this compound does not alter lever preference. These findings are in contrast to those previously reported on the effects of LSD on auditory and visual discriminations (Dykstra and Appel, 1970, 1974; Straub and Appel, 1975) and may reflect differences in the effects of LSD on accuracy in detection vs. difference discrimination tasks. If, as has been suggested, one behavioral effect of LSD is to increase 'arousal' and 'sensory impact' of environmental stimuli (e.g., Appel, 1968), greater disruption of performance in a task (such as the present) involving auditory detection might be expected to occur than in tasks requiring discriminations based on particular stimulus characteristics, such as frequency or duration, which are known to be 'coded' at many levels of the auditory system (e.g., Grossman, 1973).

The decrease in speed to initiate trials following LSD was expected, and is consistent with previous results. Examination of cumulative records revealed that, in general, increased reaction times to trial initiation under LSD were, like those previously reported, due to drug-induced periods of nonresponding (Appel, 1968; Iversen and Iversen, 1975). Morphine and CPZ induced different patterns of disruption in different subjects. Although there was a tendency for this effect of LSD to be dose related and to be more pronounced with the tone stimuli, this difference was not reliable. The finding that LSD decreased the speed of choice responding in a dose-related manner in the tone, but not in the shock detection, problem indicates that this compound did produce specific behavioral effects related to stimulus modality, but that these effects were not reflected in accuracy of discrimination.

Acknowledgements. This research was supported by USPHS Research Grants MH-24,593 from the National Institute of Mental

Health, and 9 R01 DA 01799, from the National Institute on Drug Abuse. We thank Ms. Cheryl Funderburk for her assistance in typing the manuscript.

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Received December 6, 1977; Final Version May 31, 1978