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BRIEF COMMUNICATION

Drug-Induced Conditioned Suppression: Specificity Due to Drug Employed as UCS[1]

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CAMERON, O. G. AND J. B. APPEL. *Drug-induced conditioned suppression: specificity due to drug employed as UCS.* PHARMAC. BIOCHEM. BEHAV. 4(2) 221–224, 1976. – The classical conditioning potential of several drugs was tested in rats by pairing a light CS with the drug UCSs; these stimuli were superimposed on a variable-interval 30 sec schedule for water reinforcement. Conditioning (suppression of bar-pressing in the presence of the CS) was definitely demonstrated with psilocybin (2.0 mg/kg), was suggested but not clearly shown with LSD (0.13 mg/kg), and was not evident with methyl atropine nitrate (50 mg/kg) or pentobarbital (25 mg/kg). These results indicate that previously demonstrated drug-induced conditioned suppression is not a nonspecific effect of unconditioned suppression but depends on the type of drug employed.

Conditioned suppression LSD Psilocybin Methyl atropine nitrate Pentobarbital
Variable interval

BY using biochemical agents as unconditioned stimuli (UCSs) in classical or Pavlovian conditioning paradigms. altered behavioral states can be elicited by previously neutral stimuli. For example, stimuli associated with morphine and nalorphine, a morphine antagonist [5,6], amphetamine [14], scopolamine [7], LSD [2,3], and chlorpromazine [2] will induce decreases in response rate (drug-induced suppression) when presented to animals performing an operantly conditioned task. Moreover, conditioned rate increases to appropriate doses of at least one compound, amphetamine, have also been reported [10,11]. In addition, at least one drug, LSD, produces a gradient of response suppression similar to that observed when a nondrug UCS, shock, is used in a stimulus generalization paradigm involving conditioned suppression [3,8]. The research to be reported here extends the above work in the following ways. First, other compounds are employed as UCSs, including (a) psilocybin, a hallucinogenic drug similar to LSD, (b) pentobarbital, and (c) methyl atropine nitrate, an anticholinergic which has its effects primarily on the peripheral nervous system [9]; and second, a lower dose of LSD, a drug previously demonstrated to be effective at 0.20 mg/kg [2], is used.

METHOD

Animals

Sixteen male Sprague-Dawley rats were used. Animals were run 6 days per week with tap water as the reinforcer, followed by 24 hr of free access to water and then 24 hr of water deprivation. No other water was given. Food was always available in individual home cages, housed in a room maintained at constant temperature (24°C) and humidity (40–50%). All animals had stable weights of 250–350 g during the study, and remained in good health throughout.

Drugs

The fluid used for saline injections and for preparing drug dilutions was 0.9% sodium chloride and 0.9% benzyl

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alcohol in distilled water. D-lysergic acid diethylamide (LSD) and psilocybin were obtained from NIMH, Center for the Study of Narcotics and Drug Abuse; sodium pentobarbital was obtained from Abbott Laboratories, North Chicago, Illinois; and methyl atropine nitrate was obtained from Sigma Chemicals, Chicago, Illinois. All injections were intraperitoneal (IP), and of equal volume adjusted for weights (1.0 ml/kg).

Procedure

The procedure has been described extensively elsewhere [2]. Briefly, all animals were initially deprived of water for 48 hr. They were then shaped to press a bar with water as a reinforcer (each reinforcer was 0.05 ml) and were stabilized on a variable-interval 30 sec schedule (VI 30); each session was 30 min in duration and was conducted in the presence of 2 dim red house lights.

Prior to conditioning (below) 7–10 habituation sessions were run during which a saline injection was given 1 min following the onset of a 2 min white 28 V light (CS). By the last of these sessions no behavioral suppression was observed either after the injection was given or in the presence of the white light.

Conditioning consisted of presenting the 2 min CS and the appropriate pharmacological UCS once per 30 min session at a random time during the session, excluding the first or last 5 min. Five groups of animals were run with different compounds as UCSs: (1) 0.13 mg/kg of LSD (N of 3), (2) 2.0 mg/kg of psilocybin (N of 2), (3) 50 mg/kg of methyl atropine nitrate (N of 3), (4) 25 mg/kg of pentobarbital (N of 3), and (5) saline (N of 5). The appropriate drug UCS was given 1 min after CS onset in Groups 1–4 (hence, full drug effect, as indicated by behavioral suppression, had usually occurred by CS offset); saline (in saline group) was given at 1 min (N of 3) or at 2 min (CS offset; N of 2). The saline animals were controls for determining whether or not conditioning was being produced by the injection procedure per se, and not the drug. Drugs and saline were administered by removing the animal from the experimental chamber for 15 sec, and administering an intraperitoneal injection of the appropriate solution. Non-drug sessions were randomly interspersed approximately twice per week with conditioning sessions; on these days no CS or UCS was presented.

All animals were conditioned until either a clear suppressive effect to the CS was observed or it was evident that no conditioning was occurring (all animals were given 14 conditioning pairings, twice the number found to be necessary in previous research [2]). Finally, 4 extinction sessions, in which the CS was again paired with saline, as in the habituation sessions, were given to all drug groups.

Raw data were used to calculate suppression ratios; ratios equaled number of CS responses divided by CS responses plus pre-CS responses. Pre-CS responses equaled number of response in 1 min and 45 sec period immediately preceding the CS period, therefore equal to 2 min CS period less 15 sec for the injection during the CS period. (The raw data from which these ratios were calculated can be obtained from Dr. Cameron upon written request.) A ratio of 0.50 indicated no change in rate during the CS; a value of 0.0 indicated complete suppression.

RESULTS

For the 3 animals given 0.13 mg/kg of LSD there was suggestive evidence of conditioning (Fig. 1). The ratios demonstrated a trend indicating a conditioned effect (decreasing values) over the first four conditioning trials. This trend was inconsistant during subsequent training trials, and there was much variability of the calculated ratios. However, the suppression ratios of the LSD group were consistantly lower than those of the control group. And the first 3 extinction trials were clearly below those of the control animals. No behavioral tolerance to the unconditioned suppressive effect of the drug occurred during this regimen of drug administration, to LSD or any of the other drugs employed.

The animals which were given psilocybin (Fig. 1) showed a clear conditioned effect. By the seventh conditioning trial, the average suppression ratio was below 0.20 and the trend was consistant with progressive conditioning – a decrease from earlier to later trials. While these animals were run for 7 more training trials, as well as 4 extinction trials, the data obtained were not included in Fig. 1 because the baseline rates had been suppressed so much that the suppression ratios were unreliable (see Discussion).

The animals which received methyl atropine nitrate initially appeared to show some conditioning; for the first 5 conditioning sessions no suppression was apparent, but the suppression ratios decreased on the next 4 days. However, after the eleventh session, the suppression disappeared even though the conditioning procedure was continued for 6 more sessions. And no characteristic pattern of extinction was observed when saline injections were again paired with the CS. Therefore, it was unlikely that conditioning had occurred. In addition, suppression of baseline response rates was not seen with this drug, as it had been with psilocybin, another indication that conditioning had not occurred (see Discussion).

No characteristic conditioning pattern was observed when the suppression ratios of the animals given pentobarbital were compared to those of the control animals. And only a minimal amount of generalized baseline suppression was observed with this drug, again suggesting that no conditioning had occurred.

Comparison of the animals given saline injections early in the CS with those given injections at the end of the CS period (not shown in Fig. 1) showed that there was little difference between these groups. This indicated that, even with many CS-saline pairings, little permanent conditioning occurs to the aversive characteristics of the injection procedure itself.

DISCUSSION

This study has extended the list of drugs capable of producing conditioned suppression to another hallucinogen, psilocybin. And it has suggested that LSD at 0.13 mg/kg, approximately two-thirds the dose which was previously demonstrated to be effective [2], may be a weakly effective or threshold dose for conditioning. But, more importantly, it had indicated that a high dose of a drug with unquestioned central nervous system action, pentobarbital, as well as a drug which has only minimal central activity, methyl atropine nitrate, probably do not produce significant conditioning. And this was true even though these agents produced clearly observable unconditioned suppression of bar pressing, albeit not strongly in the case of methyl atropine nitrate. Therefore, it appears that mere suppression itself is not a sufficient condition to produce conditioning. Another, as-yet-unknown, mechanism must

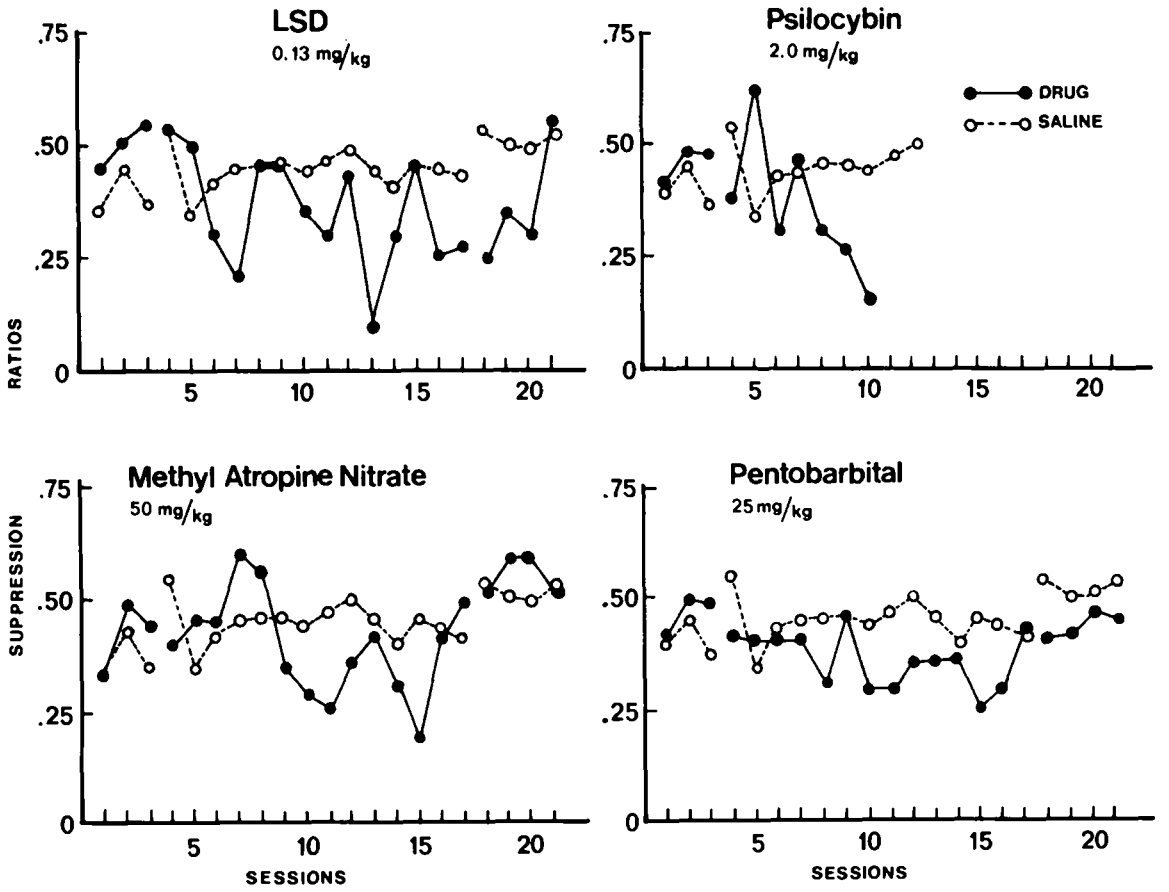

FIG. 1. The habituation (pairings of CS and saline), conditioning, and extinction data for the 4 drug groups. Dotted line – saline control group; solid line – experimental groups. Last 3 control days, followed by 14 conditioning pairings with several randomly interspersed nondrug days on which no CS or UCS was presented (nondrug days not shown), and finally 4 extinction (CS-saline) pairings. Ordinate – calculated suppression ratios: (number of responses during 2 min CS)/(number of responses during 1 min and 45 sec immediately preceding CS plus number of CS responses).

be selectively affected by those drugs which produce conditioning, but not by those which do not. And effect on the central nervous system per se, versus peripheral effect only, is not the relevant variable, as the barbiturate animals demonstrated, although a more specific or localized change in the central nervous system undoubtedly mediates this selective response.

In the group which clearly demonstrated conditioning, the psilocybin group, a further apparent conditioning phenomenon was noted. Over the course of conditioning a generalized drop in baseline response rate was observed, almost to the point of complete suppression by the fourteenth conditioning day. These decreased rates may have been caused by either a partial debilitation produced by physiological changes due to chronic drug administration, or to the drug state becoming conditioned to many of the environmental cues in the experimental situation, not just the experimentally-defined CS. However, since it has been demonstrated that chronic administration of a hallucinogenic drug leads to the development of tolerance, not sensitization or debilitation [4], the first explanation seems unlikely. On the other hand, it has been shown that animals can be conditioned to incidental cues in various experimental situations [13]. In fact, a similar effect has been found when a conditioned suppression paradigm was employed with a shock UCS [12]. The second hypothesis thus seems more plausible to explain the suppression which did occur, especially considering that this effect was also observed when 0.20 mg/kg of LSD was used as the UCS [2], and that 2.0 mg/kg of psilocybin and 0.20 mg/kg of LSD are of approximately equal potency [1]. This generalized suppression of baseline is further evidence of a specific conditioning effect of specific drugs; it was not at all evident in the methyl atropine nitrate group and only weakly so with pentobarbital or 0.13 mg/kg of LSD.

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