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Psilocybin as a Discriminative Stimulus: Lack of Specificity in an Animal Behavior Model for 'Hallucinogens'

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Abstract. Fifteen rats were trained to discriminate between the tryptamine hallucinogen psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine; 1.0 mg/kg) and saline in a two-lever choice task. Dose-response and time-response curves were obtained. The psilocybin cue generalized to psilocin (the dephosphorylated congener of psilocybin) and to the prototypical indoleamine hallucinogen LSD, but not to the phenylethylamine hallucinogen mescaline. These results indicate that the hallucinogenic effects of these drugs in humans may not be identical with their discriminative stimulus functions in animals, and that these four compounds may not be members of a single drug class. The term 'hallucinogen' may thus be a misnomer in the context of drug discrimination studies in nonhumans.

Key words: Psilocybin – Psilocin – LSD – Mescaline – Hallucinogens – Stimulus properties of drugs – Drug discrimination – Rats

Psilocybin is a tryptamine-derivative hallucinogen present in about 40 mushroom species (Schultes and Hofmann 1980) that occur in North America, Europe, Australia, and Southeast Asia. This compound was first isolated from *Psilocybe mexicana* Heim by Hofmann et al. (1958) and identified as 4-phosphoryloxy-*N*,*N*-dimethyltryptamine, a uniquely structured natural indole by virtue of both the position 4 substitution and the phosphoric acid radical. A substantial experimental literature concerning pharmacological, biochemical, and metabolic aspects of psilocybin has been reviewed by Hofmann (1968).

The extent of current psilocybin use is not reported in federally sponsored nationwide drug use surveys (e.g., Abelson and Fishburne 1976). Several indicators, including the proliferation of popular books on identification, cultivation, and use of the mushrooms (e.g., Castaneda 1969; Harris 1976; Norland 1976; Oss and Oeric 1976; Menser 1977; Stamets 1978), occasional medical reports of reactions to mushroom ingestion (e.g., Benjamin 1979), and the frequency of submissions to 'street' drug analysis services [e.g., in a recent 4-month period, 66% of alleged samples actually contained psilocybin (Anonymous 1979)], suggest that incidence and prevalence of illicit use are increasing.

Despite the apparent increase in use, behavioral aspects of psilocybin have received little scientific attention in comparison with LSD and mescaline. Delay et al. (1959) and Böszörményi (1961) examined the therapeutic potential of psilocybin in normal subjects and psychiatric patients. Several studies have revealed similar unconditioned reactions to psilocybin, LSD, and mescaline in humans (Isbell 1959; Hollister and Hartman 1962; Hollister and Sjoberg 1964; Rinkel et al. 1961; Wolbach et al. 1962b) and to psilocybin and LSD in animals (Jacobs et al. 1976, 1977). Chronic administration to both humans and animals results in development of tolerance to the effects of psilocybin, and also in cross-tolerance to LSD (Abramson et al. 1960; Isbell et al. 1961; Appel and Freedman 1968).

In contrast to the behavioral techniques employed in the above studies, which examined either unconditioned responses following drug administration or effects of the drug on some ongoing operant behavior, an alternative approach involves measuring the ability of drugs to function as cues or discriminative stimuli. In the drug discrimination procedure, availability of reinforcement contingent on a specific response covaries with the presence or absence of a drug. Animals trained to discriminate a given dose of one compound are then tested after administration of different doses of the same compound or novel compounds to determine degree of similarity (generalization or transfer) between the training and test drug stimuli. This strategy has proven useful because it detects relatively specific drug effects, thus providing a means for classification (Barry 1974), it is robust in that comparable results have been obtained in several different tasks using a variety of reinforcers (Schuster and Balster 1977; Winter 1978a), and it is sensitive to small drug doses (Greenberg et al. 1975a; Overton 1979) that are ineffective in other behavioral procedures.

Winter (1974a) suggested that drug discrimination might prove especially profitable in the case of drugs such as hallucinogens, where ethical and legal considerations prohibit human experimentation. It is important for several reasons (e.g., screening of new pharmaceutical compounds and study of hallucinatory behavior) to develop an animal model that selectively detects those drugs having hallucinogenic effects in humans. Models based on unconditioned behavior, such as the cat limb-flick test proposed by Jacobs et al. (1976, 1977), have recently been shown to be nonspecific for hallucinogens (Marini and Sheard 1981; Marini et al. 1981).

Psilocybin has been used with limited success as a training stimulus in drug discrimination experiments. Harris and Balster (1971) attempted to train a psilocybin versus saline discrimination and found that 0.2 and 0.4 mg/kg psilocybin produced only weak, if any, stimulus control. Cameron and

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Appel (1973) found that psilocybin (0.8 mg/kg) and LSD (0.08 mg/kg) were not discriminable from each other when used as training stimuli. However, using psilocybin (1.0 mg/kg) versus Δ^9-THC (1.0 mg/kg), good discriminative control was obtained (Greenberg et al. 1975b), although response rates were substantially lower following psilocybin administration.

Psilocybin has also been examined as a test compound in animals trained to discriminate a variety of other drugs. Animals trained to discriminate *d*-amphetamine (Harris and Balster 1970; Kuhn et al. 1974; Silverman and Ho 1980), Δ^9-THC (Järbe and Henriksson 1974), or the hallucinogen DOM (2,5-dimethoxy-4-methyl-phenylisopropylamine) (Silverman and Ho 1980) did not generalize to test injections of psilocybin. In rats trained with LSD (0.08 mg/kg), Cameron and Appel (1973) found that test injections of psilocybin (0.4 and 0.8 mg/kg) were followed by random responding: In contrast, Schecter and Rosecrans (1972) showed complete generalization to a psilocybin (2.56 mg/kg) test stimulus in animals trained to discriminate LSD (0.048 mg/kg).

The present experiment was designed to determine whether rats could be trained to discriminate between injections of psilocybin and saline, and, if so, to examine dose and time parameters of the psilocybin cue (interoceptive stimulus conditions associated with psilocybin administration) and the degree to which several other hallucinogenic drugs share the same discriminative stimulus properties.

Materials and Methods

Twenty-four naive adult male Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, MA) were housed individually and maintained on a 12-h light-dark cycle in a room with constant ambient temperature (21 – 23°C) and humidity (50%). Food was freely available in home cages throughout the experiment. Rats were initially deprived to 90% of their free-feeding weights (370 – 470 g) by restricting water access. During training and testing, water access was limited to that obtained during experimental sessions plus 15 min free access postsession each day and 12 h on weekends. Under these conditions, the rats weighed 430 – 580 g at the conclusion of the experiment. Fifteen rats completed the experiment: Six rats were dropped from the study as described below; the remaining three animals died of respiratory infection.

The experiment was conducted in eight rat operant chambers (Lehigh Valley Electronics model 143-24) that were housed in sound- and light-attenuating boxes (LVE model 132-04). Each chamber contained two operant levers mounted on one wall, separated by a liquid dipper that delivered 0.1 ml water. Chambers were ventilated and illuminated by a 6 W white house light. Electromechanical and solid state programming and recording equipment was located in an adjacent room.

IP injections were given 15 min prior to the beginning of a training or test session (except during time-course tests with psilocybin). All drugs were dissolved in physiological saline (0.9% NaCl) in concentrations such that constant volume injections of 1.0 ml/kg body weight were required. The following compounds were used: psilocybin, psilocin, and *d*-LSD tartrate (all obtained from NIDA, Washington, DC); mescaline HCl (Sigma Chemical, St. Louis, MO). The doses of psilocybin and psilocin refer to free bases and the doses of LSD and mescaline refer to the salts.

Training

Stage 1. Errorless shaping was conducted to establish stable patterns of lever pressing maintained by water reinforcement provided on a fixed ratio (FR) schedule. Rats were injected with psilocybin (1.0 mg/kg) or saline (vehicle) and placed in the chambers with only the stimulus-appropriate (psilocybin or saline) lever present, and were initially shaped to lever press under a continuous (FR 1) reinforcement schedule. The sequence of psilocybin and saline injections was randomly programmed, with the restriction that neither condition was administered for more than 3 consecutive days. The left lever was designated as psilocybin-appropriate (right as saline-appropriate) for half of the subjects, and lever designations were reversed for the remaining rats to control for possible position-related preferences. The FR requirement (lever presses per reinforcement) was gradually increased to FR 32. Sessions were 30 min long and were conducted 5 days per week. Errorless shaping continued until responding of all rats stabilized at FR 32 (i.e., a total of 28 sessions).

Stage 2. Discrimination training (after the method of Kuhn et al. 1976a) commenced immediately following completion of stage 1 shaping. Animals were injected 5 days per week and, 15 min later, placed in the operant chambers for 30 min with both levers present. Responses on the 'correct' (stimulus-appropriate) lever were reinforced on a FR 32 schedule, while incorrect responses had no consequences. Injections were randomly sequenced as described above. Data were collected on the total number of presses on each lever during the entire session and on the number of responses on each lever prior to delivery of the first reinforcer. Discrimination training continued until each rat achieved criterion performance of at least 85% correct for 10 consecutive days. The majority (13) of the 24 rats met this criterion within 20 days of discrimination training, and the 15 reported on here achieved criterion as of day 58. However, discrimination training continued for a total of 107 days, during which time 3 additional animals died and the 6 remaining animals (having failed to meet criterion due to drug-induced response suppression) were excluded from the testing phase.

Testing

All generalization testing was conducted in extinction (i.e., no reinforcement) to prevent spurious learning of non-training-condition cues. Extinction sessions ended upon completion of 32 responses on either of the levers or after a specified period of time, whichever occurred first. Each generalization test was conducted only once with all 15 rats. Interspersed between test sessions, animals received 2 – 7 days additional discrimination training. Injections of psilocybin and saline were random in these retraining sessions, except that extinction tests always followed a saline session to minimize possible residual drug effects. Generalization tests were conducted following psilocybin administration to determine the (1) temporal and (2) dose parameters of the psilocybin cue, and (3) transfer to other compounds.

Temporal parameters were ascertained by varying the interval between psilocybin injection and placement of rats in the operant chambers. Intervals tested were 1.875, 3.75, 7.5, 15.0, 30.0, 60.0, 120.0, and 240.0 min: These time tests were administered in random order. Each test epoch was limited in duration to either 15 min or a length of time equal to the interval from injection to the beginning of the test, whichever

was less: Thus, for example, the 1.875-min test epoch lasted 1.875 min, beginning at 1.875 min and ending at 3.75 min postinjection. This ensured that the drug cue being discriminated was that present at the interval being tested and not at some longer interval.

Dose parameters were determined by injecting psilocybin in a range of doses and testing for lever choice 15 min later. Doses of 0.0 (saline), 0.0312, 0.0625, 0.125, 0.25, 0.5, 1.0, and 2.0 mg/kg were tested in random order. Test sessions were limited to 15 min.

Transfer tests were conducted by injecting animals with psilocin (0.125, 0.25, and 0.5 mg/kg), *d*-LSD (0.02, 0.04, and 0.08 mg/kg), or mescaline HCl (5.0, 10.0, 15.0, and 20.0 mg/kg) and testing for lever choice 15 min later. This postinjection interval is known to produce effective discriminative stimuli with *d*-LSD (Cameron and Appel 1973) and mescaline (Winter 1978b). Test sessions were limited to 15 min. Tests of these compounds were interspersed randomly throughout the testing period to avoid order effects.

Data Analysis

For training sessions, a percent correct score (100 × 32 correct responses ÷ total responses prior to first reinforcer) was determined for each subject; these scores were averaged to obtain a group mean. For test days, a percent psilocybin-responding score (100 × number of psilocybin-lever responses ÷ total responses prior to 32 responses on either lever) was similarly derived for each subject and averaged. If a subject was 'disrupted' (failing to complete at least one FR 32 on the correct lever during training days or on either lever during test days), no percent lever-choice score was computed.

In addition to these percent lever-choice scores, a response rate measure (mean number of responses/min) was computed from whole-session correct and incorrect responses for each training session. Response rates from the last 21 saline and 21 psilocybin training sessions prior to testing were compared with a paired two-tailed Student's *t*-test.

Three scores were obtained for each test, one in the test condition and one from the immediately preceding saline and psilocybin training conditions (subsequently referred to as saline-control and psilocybin-control sessions). Subjects who were disrupted in any one of these sessions were excluded from the analysis. Also, subjects failing to meet criterion accuracy (85% correct) during either of the preceding training sessions were excluded. Scores from each test condition were compared with scores from both preceding control sessions by means of a Student's *t*-test for correlated samples. No statistic was calculated if fewer than seven animals completed a FR 32 under the test condition. In order to compare dose-effect curves for psilocybin and the test drugs, calculated ED_{50} values, 95% confidence intervals ($C_{0.95}$), slopes, and slope function ratios were determined by the probit versus log-dose method of Litchfield and Wilcoxon (1949).

Results

Acquisition of differential responding following psilocybin and saline administration was rapid. The group mean of percent correct choices exceeded 90% after 22 training sessions. Mean assymptotic accuracy from day 58 – 107 of discrimination training (after all rats had met criterion) was 91.3% on psilocybin and 96.7% on saline days. Accuracy

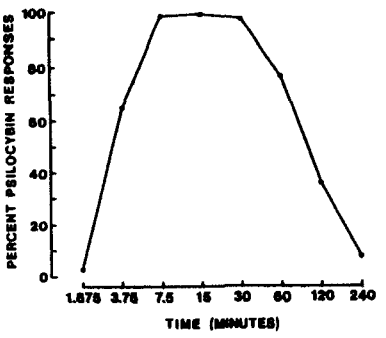

Fig. 1. Temporal parameters of the 1.0 mg/kg psilocybin discriminative stimulus. Abscissa is postinjection time

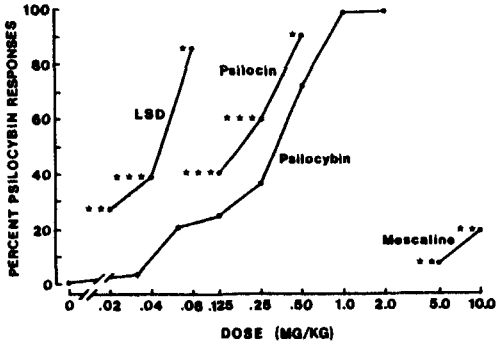

Fig. 2. Generalization gradients of responding controlled by the psilocybin (1.0 mg/kg) stimulus to test doses of psilocybin, psilocin, LSD, and mescaline. Doses plotted on a log scale. * Different from saline control session ($P < 0.05$). ** Different from psilocybin control session ($P < 0.05$). *** Different from both saline and psilocybin control sessions ($P < 0.05$).

continued to improve, averaging 96.5% and 98.6% for psilocybin and saline, respectively, on inter-test retraining sessions (day 108 – 213).

Psilocybin-induced behavioral disruption occurred throughout the study, resulting in the prolonged training and eventual expulsion of six animals as noted. For the 15 animals reported here, each rat failed to respond, on the average, in 1 of 18 sessions, and lever-choice data were not recorded on those occasions. Mean response rates during training (day 58 – 107) after psilocybin administration (36.9/min) was significantly lower than the saline rate (67.1/min) [t (14) = 7.32, $P < 0.01$].

The time-course of the psilocybin discriminative stimulus is shown in Fig. 1. Onset of discriminative control was rapid, i.e., at 3.75 min postinjection 65% of responses were on the psilocybin-appropriate lever. The psilocybin cue reached peak effectiveness (i.e., above 97% psilocybin-appropriate responses) at 7.5 – 30 min after drug administration. Stimulus control declined rapidly thereafter, and was no longer evident at 240 min. Since the drug cue half-life (wash-out time) was found to be this brief, scheduling of each extinction test session after a saline-control session proved to be an unnecessary precaution. However, analysis of accuracy on training sessions following saline sessions compared with training sessions following psilocybin sessions showed little difference, thus no bias was introduced by this scheduling protocol.

Dose-effect relationships for psilocybin are shown in Fig. 2. Percentage of psilocybin-appropriate lever presses

increased in an orderly dose-dependent fashion. At 0.5 mg/kg, half the training dose, the majority of responses (72.3%) were on the psilocybin lever. The training dose (1.0 mg/kg) and a higher dose (2.0 mg/kg) produced 98.9% and 99.3% drug-lever responding, respectively. At the 2.0 mg/kg dose, 6 rats did not respond, so no attempt was made to test larger doses. The calculated ED_{50} for psilocybin was 0.24 mg/kg ($C_{0.95}$: 0.17 mg/kg $\leq ED_{50} \leq$ 0.35 mg/kg).

Generalization test results with the three novel hallucinogens are also presented in Fig. 2. Lever pressing established in the presence of psilocybin also tended to occur following psilocin and LSD administration, and these transfers were dose-related. The calculated ED_{50} for psilocin was 0.17 mg/kg ($C_{0.95}$: 0.1 mg/kg $\leq ED_{50} \leq$ 0.29 mg/kg). The calculated ED_{50} for LSD was 0.038 mg/kg ($C_{0.95}$: 0.025 mg/kg $\leq ED_{50} \leq$ 0.058 mg/kg). Slopes of the dose-effect curves for psilocybin, psilocin, and LSD were 2.38, 2.40, and 2.29, respectively. These slopes were parallel, as indicated by the slope function ratio (SR) for psilocybin and LSD (SR = 1.04) and for psilocybin and psilocin (SR = 0.99).

The psilocybin stimulus, however, did not generalize to mescaline. Mescaline doses of 5.0 and 10.0 mg/kg yielded only 7.4% and 19.8% psilocybin-appropriate responses, respectively, which was not significantly different from saline responding. Two higher doses of mescaline (15.0 and 20.0 mg/kg) were tested, but these doses so severely disrupted lever pressing that lever-choice data from the small remaining sample (fewer than 4 of 15 rats responded at these doses) could not be analyzed.

Discussion

The present results indicate that 1.0 mg/kg psilocybin paired with saline can exert strong discriminative control over behavior in a two-choice, appetitively motivated task, in contrast with the findings of Harris and Balster (1971) who used smaller doses (0.2 and 0.4 mg/kg). Most rats met, and subsequently maintained an 85% criterion within 20 days of training, although some rats did so only with difficulty (requiring 58 days) and other rats failed by day 90 to acquire or maintain the discrimination. The conclusions of this study are thus limited to those based on subjects capable of performing under the dose and behavioral conditions employed.

At the 1.0 mg/kg psilocybin dose, responding was suppressed and frequently disrupted, suggesting that a slightly lower dose may have discriminative properties with fewer grossly disruptive effects. However, lower training doses may yield less specific results in generalization tests (Shannon and Holtzman 1979).

The dose-effect curve and the time-course of psilocybin stimulus reveal orderly gradients of stimulus control. The time-course is similar to that reported for psilocybin (0.15 mg/kg) in humans (Wolbach et al. 1962b). It should be noted, however, that the shape of such generalization gradients depends on the particular training conditions employed (Overton 1974).

Hydrolysis of psilocybin yields equimolar amounts of phosphoric acid and psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine), which was also isolated from mushroom (Hofmann and Troxler 1959). Horita and Weber (1961) showed that psilocybin is rapidly dephosphorylated to psilocin by alkaline phosphatase in diverse mammalian tissues, suggesting that psilocin is the psychoactive compound. It is, thus, not surprising that psilocybin generalized to psilocin in the present study. Comparison of the two ED_{50} values derived from Fig. 2 suggests that psilocin is 1.41-times as potent as psilocybin, a potency ratio comparable to that obtained in humans (1.48:1) by Wolbach et al. (1962b).

The psilocybin stimulus also transferred to the prototypic hallucinogen LSD, suggesting that the two compounds have similar stimulus properties in agreement with the clinical evidence cited above. ED_{50} values indicate that LSD is 6.32-times as potent as psilocybin, somewhat less than the potency ratio of 10:1 reported by Appel and Freedman (1965) for disruption of bar-pressing behavior in rats. This finding complements the earlier demonstration of LSD generalization to psilocybin (Schechter and Rosecrans 1972).

Further, the fact that the dose-effect curves for psilocybin, psilocin, and LSD are parallel suggests that these three drugs may share a common mechanism of action (a possibility suggested also, perhaps, by their common indolic structural moiety). Indeed, several converging lines of evidence have implicated the serotonergic (5-HT) neuronal system in actions of LSD and psilocybin. For example, 5-HT depletion potentiates LSD-induced limb flicking in cats (Trulson and Jacobs 1976), LSD discriminability (White et al. 1980), and disruption of bar pressing induced by LSD and psilocybin (Appel et al. 1977). Also, 5-HT antagonists block the LSD discriminative stimulus (Kuhn et al. 1978), and binding studies indicate that psilocin (Glennon and Gessner 1979) and LSD (Bennett and Snyder 1976; Snyder and Bennett 1975) have high affinity for 5-HT receptors.

The most unexpected finding of the present study was the failure of the psilocybin stimulus to generalize to mescaline. This conflicts with the traditional conception that psilocybin, LSD, and mescaline are members of a single, homogeneous pharmacological class (i.e., hallucinogens). This conception derives from the drugs' similar clinical effects (cited above), cross-tolerance relationships between them, and results of transfer tests in drug discrimination experiments. Cross-tolerance has been demonstrated between LSD and psilocybin (cited above) and between LSD and mescaline in humans (Balestrieri and Fontanari 1959; Wolbach et al. 1962a). LSD-tolerant rats show cross-tolerance to mescaline and vice versa (Appel and Freedman 1968). However, cross-tolerance between mescaline and psilocybin has never been directly demonstrated, but has been inferred from their mutual cross-tolerance with LSD.

Drug discrimination studies have yielded a similar pattern of results. Cameron and Appel (1973) showed that rats trained with LSD (0.08 mg/kg) generalized to mescaline (8.0 mg/kg). Likewise, Schechter and Rosecrans (1972) trained rats with 0.048 mg/kg LSD and observed generalization to psilocybin (2.56 mg/kg) and mescaline (22.3 and 29.7 mg/kg). Conversely, Winter (1978b) found that rats trained with mescaline (10.0 mg/kg) generalized to LSD (0.05 mg/kg). Finally, Hirschhorn and Winter (1971) attempted to train for discrimination between LSD (0.028 mg/kg) and mescaline (9.9 mg/kg), but rats did not learn even after extensive training. However, in the drug discrimination studies (as in the case of previously mentioned tolerance studies), there has been no direct test for transfer between mescaline and psilocybin. In two studies (Glennon et al. 1979, 1980), however, rats trained to discriminate 5-methoxy-*N*,*N*-dimethyltryptamine (a psilocybin analog) generalized to LSD (and vice versa), but did not generalize to mescaline to the

extent expected, consistent with the findings of the present report.

The data reported here suggest psilocybin and mescaline may have different neurochemical mechanisms of action. Mescaline, like LSD and psilocybin, has been shown to act on 5-HT neurons (Browne 1978; Winter 1978b), although it binds to 5-HT receptors with considerably less affinity than psilocin (Glennon et al. 1980). Further, while several reports indicate dopamine (DA) receptor involvement in the action of LSD (Pieri et al. 1974; Kelly and Iversen 1975; Nichols 1976; Whitaker and Seeman 1977), psilocybin has negligible affinity for DA receptor binding (Creese et al. 1975) and mescaline has even less (Burt et al. 1976). These findings are difficult to reconcile with the 5-HT hypothesis of hallucinogenesis and with the present results. Fischer and Goldman (1975), however, predicted that mescaline and psilocybin would not show cross-tolerance, since they lack a common structural feature. Their mutual cross-tolerance with LSD was accounted for by the fact that the LSD molecule contains both the phenylethylamine moiety of mescaline and the tryptamine moiety of psilocybin.

While it was originally hoped that the drug discrimination paradigm offered an animal model capable of screening drugs specifically for hallucinogenic activity, numerous experiments lead us to be less sanguine. In a series of experiments, Winter (1973, 1974b, 1975) found that while the nonhallucinogen 3,4-dimethoxy-phenylethylamine was discriminable from mescaline, other nonhallucinogens (2,3,4-trimethoxy-phenylethylamine and 2,5-dimethoxy-4-ethylamphetamine) were not. Winter (1980) recently examined three nonhallucinogenic phenylethylamine derivatives in rats trained to discriminate LSD and found that BL-3912 transferred completely, while fenfluramine and Sch-12679 yielded intermediate transfers. Kuhn et al. (1976b) and White et al. (1977) showed that animals trained to discriminate the nonhallucinogen quipazine generalized to LSD and vice versa.

The present failure of a known hallucinogen to transfer to another hallucinogen provides additional and complementary evidence of the inability of existing drug discrimination procedures to detect 'hallucinogenicity' in drugs. The most plausible explanation for this failure is that these procedures detect something other than hallucinogenicity (e.g., a particular mechanism of drug action); something not necessarily shared by all hallucinogens. While the usefulness of behavioral procedures that identify drug mechanisms is apparent, we clearly must continue the search for an animal behavior model that screens specifically for hallucinogens. The multiple-drug training procedure recently described by Overton (1981) suggests one promising strategy for increasing the specificity of drug discrimination tests. We must also recognize the possibility that this search will be futile, i.e., that hallucinogenicity is *not* a property of drugs but is rather a property of the unique interaction between certain drugs and certain individuals under certain conditions. In the meantime, pending development of animal procedures that afford sensitive and specific detection of such subjective drug effects in humans, the term 'hallucinogen' appears to be a misnomer in the context of nonhuman drug discrimination studies.

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