Psychopharmacology of Hallucinogens

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PRECLINICAL IDENTIFICATION OF HALLUCINOGENIC COMPOUNDS

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INTRODUCTION

New compounds are being synthesized daily for both medicinal and research purposes. Lacking are reliable preclinical tests for identifying possible hallucinogenic activity in new compounds. As mentioned recently by several authors (Dixon, 1968; Brawley and Duffield, 1972; Silva and Cahil, 1975; Shah et al., 1975), this lack requires remedy. We undertook to meet this need under a contract from the National Institute on Drug Abuse (NIDA).*

The rationale for establishing discriminative tests for hallucinogens includes the following:

1. The hallucinogenic drug-induced state in humans resembles that manifested during the acute phases of psychotic episodes in many ways. Thus, the identification of hallucinogenic compounds specifically synthesized for theoretical purposes and the subsequent elucidation of their mechanisms of action could be useful to researchers attempting to determine the etiology of certain mental illnesses. Indeed, several theories have been suggested purporting that abnormal production or metabolism of endogenous putative central neurotransmitters yielding hallucinogenic compounds may be responsible for the onset and maintenance of aberrant mental function. For example, Saavedra and Axelrod (1972) demonstrated that the human brain is capable of synthesizing hallucinogenic compounds by way of N-methylation of endogenous tryptamines to yield DMT and bufotenin--compounds that have been reported to be present in the urine of schizophrenic patients (Tanimukai et al., 1967).

2. The ability to differentiate between the hallucinogenic properties of CNS drugs and those characteristically induced by other agents would aid in evaluating theories purporting a continuum of CNS excitable states. These theories hypothesize that hallucinogens induce a hyperexcited brain syndrome localized on a continuum between stimulant activation and frank epileptiform seizures (Winters and Wallach, 1970; Fischer, 1971).

3. Pharmaceutical houses would benefit from a battery of preclinical tests that would reliably identify hallucinogenic properties of psychoactive drugs since these properties would render an otherwise promising compound nonmarketable.

The overall goal of this research was to select--on the basis of a review of the literature and other sources--the fewest, simplest, most economical preclinical tests that would reliably identify compounds with hallucinogenic activity and to validate these test procedures in our laboratory. Since several of the newer hallucinogens are amphetamine derivatives, we concentrated on identifying preclinical tests that discriminated such compounds, as well as the classic hallucinogens, from classic stimulants. Our

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aim was to derive a battery of tests that sorted unknown drugs into one of three classes: Hallucinogen, Stimulant or Other.

TEST SELECTION

Fifty-six test procedures were identified from the literature as promising. These were culled to 12 on the basis of the size of the data base, the specific research interests of staff members, and a set of criteria that emphasized reliability, simplicity of execution, and low cost. Following preliminary laboratory research, these 12 were narrowed to six, which were investigated extensively in our laboratory.

In the order of their simplicity and economy, the six procedures selected for further evaluation were:

1. Rat body temperature
2. Rabbit body temperature
3. A modified version of the Irwin Mouse Screen
4. Photocell activity of the rat
5. Spontaneous beating rabbit atrial preparation
6. Fixed-ratio lever-pressing in the rat

LABORATORY RESEARCH

Twenty-one representative drugs (shown in subsequent tables) selected from the major CNS drug classes were used as standards to evaluate the discriminatory power of the six procedures. The number of drugs used to evaluate each procedure varied, however, since tests that proved unreliable during the course of their investigation were dropped before all 21 drugs had been utilized.

A minimum of three doses of each drug was used during evaluation tests. The dose range was selected from the literature, although in our tests we found that in some cases the highest dose was not effective. When time permitted, higher doses were subsequently run. All laboratory evaluations were run blind.

Of the six procedures selected for intensive laboratory investigation, only three proved sufficiently discriminatory and reliable to be included in the final battery. These were rat photocell activity, rat body temperature, and rabbit body temperature. A fourth test, the spontaneous beating rabbit atrial preparation, was tentatively included in the battery because it appeared particularly useful for discriminating stimulants from depressants. Since hallucinogens have little or no effect on this preparation, it was expected that they might be discriminable from the other classes of compounds on the basis of their failure to influence the spontaneous rate or contractility of the atria. Their subsequent evaluation in other tests would be expected to further clarify their class membership.

Procedures Investigated and Subsequently Dropped

We did not exhaustively research the methods described below. Our approach was to collect data on a procedure until inconsistencies developed. We then attempted to resolve the inconsistencies by replications using a wider dose-response regimen. If the tests remained unreliable or produced ambiguous results, we discontinued further research and dropped the test from further consideration. This does not imply that the procedure had no utility in helping to identify hallucinogenic activity. It does mean that, balanced against other procedures being investigated simultaneously, it was less reliable.

Irwin Mouse Screen. Certain behaviors are detected in the Irwin screen (see Irwin, 1968, for detailed methods of procedure) that appear to be selectively induced by hallucinogenic agents. These are grouped under the category of "bizarre" behaviors and are manifested during an open-field test procedure. Bizarre behaviors include head twitching (Corne and Pickering, 1967; Yamamoto and Ueki, 1975), prancing forelimbs (Irwin, 1968), visual tracking (Irwin, 1968), retropulsion (Smythies et al., 1969), circling or spinning (Nir et al., 1974), and a scratching response (Kulkarne, 1973; Shah et al., 1975). Other parameters of the primary mouse screen that appear to be selectively sensitive to hallucinogenic drug action include stimulus reactivity whereby animals display a markedly exaggerated response to a sound stimulus or touch (see Smythies, 1970) and a decrease in emotionally induced defecation (Brimblecomb, 1963). In our modification of this screen we reduced the number of observations to about one-half, retaining those that have been shown to be specifically sensitive to hallucinogenic and stimulant activity (Edgewood Arsenal, personal communication).

Investigation of the mouse screen was discontinued after 11 compounds* were evaluated because several drugs from other classes, including chlorpromazine and chlordiazepoxide, produced so-called bizarre responses presumably characteristic of hallucinogens only. The results obtained after administration of amphetamine derivatives having hallucinogenic properties (MDA, TMA-2 and DOM) were also equivocal, both stimulant and hallucinogenic behavioral changes being evident. Further, since mouse screen data are based primarily on subjective observations and since the variability of results was excessive, we did not consider this procedure sufficiently promising, at least in our hands, to continue evaluation of additional compounds.

Fixed-ratio responding of the rat. A number of operant procedures have been utilized to differentiate hallucinogenic agents from other classes of compounds. These include the Sidman Shock Avoidance technique (Bovet and Gatti, 1963; Smythies et al., 1967; 1969), discriminated Sidman Avoidance (Morin et al., 1975; Beaton et al., 1969), and differential reinforcement of low rates of response (DRL) (Smythies et al., 1967, 1965; Marquis et al., 1973, 1974).

Another operant schedule that has been reported to be selectively sensitive to differential disruption by hallucinogenic drugs is the fixed-ratio

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*DOM, LSD-25, MDA, mescaline, psilocybin, TMA-2, d-amphetamine, cocaine, methylphenidate, chlordiazepoxide and chlorpromazine.

(FR) responding pattern. Hallucinogens given in relatively low doses have been reported to induce a reversible pause in a rat's FR response pattern. This has been demonstrated for LSD, psilocybin, mescaline, DMT, DOM, Δ^9-THC, and DET (Appel and Freedman, 1968; Marquis, 1974; Rech et al., 1975; Tilson et al., 1975; Winter, 1969). The duration of the pause is a function of the dose and consists of a period of no responding that usually lasts from 5 to 40 minutes during a 40-minute to one-hour test period. The effect appears to be an all-or-none phenomenon as intermediate rates of responding are not manifested during the session. In contrast, physiological doses of d-amphetamine and other stimulants typically reduce the overall rate of responding during the major portion of a 40-minute session without inducing a pause of any appreciable duration, i.e., more than 5 minutes (Marquis, 1974; Rech et al., 1975; Tilson et al., 1975).

The FR operant procedure was discontinued after 14 compounds* were evaluated because pauses were induced by d-amphetamine, cocaine, and diethylpropion as well as by hallucinogens. Also, contrary to previous reports (Rech et al., 1975), pretreatment with cinanserin, a 5-HT receptor blocking agent, produced inconsistent results with respect to selectively blocking hallucinogen-induced pauses. These data are consistent with recent findings by Silva and Cahil (1975). They evaluated several CNS compounds using the FR procedure and concluded that the pause induction was not specific to hallucinogens.

Rabbit atrial preparation. The spontaneous beating rabbit atrial preparation (Levy, 1970) appeared to be a simple *in vitro* test for making a first-line differential approximation of possible hallucinogenic compounds. In preliminary experiments we found that stimulants tended to increase, depressants decrease, and hallucinogens have no effect on the rate and contractility of this preparation.

Following standardization tests, all twenty-one reference drugs were investigated using blind procedure. The test was unusually successful in correctly identifying compounds with depressant properties, but misidentified DOM, MDA and tranylcypromine as stimulants, and cocaine and ethanol as hallucinogens. Nevertheless, we considered this procedure sufficiently sensitive to be of use during the second of two validation tests which will be described subsequently.

Successful Procedures

Of the six procedures investigated in our laboratory the three described below proved adequate to identify hallucinogenic compounds. A combination

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*DOM, LSD-25, MDA, mescaline, TMA-2, d-amphetamine, cocaine, diethylpropion, methamphetamine, methylphenidate, phenmetrazine, chlordiazepoxide, chlorpromazine, and morphine.

of other procedures--procedures that we did not investigate--might also have proven effective. It is doubtful, however, that they would have proven as simple, economic and reliable as those described in this section.

Spontaneous motor activity. It is well documented that stimulants markedly increase motor activity in several animal species (Van Rossum, 1970; Rech and Stolk, 1970; Smith, 1965). Although little data are available regarding the effects of hallucinogenic drugs on this measure, high doses of the few studied have been reported to markedly depress this behavioral parameter (Huang, 1972; Szara and Hearst, 1962).

In our studies, we used male Fischer rats (150-170 g) that were housed two per cage and were provided with food and water ad libitum. We measured spontaneous motor activity by placing each rat individually into a black, cylindrical chamber 12 inches in diameter and 11 inches high. Six photocells located 0.5 inches above the floor and oriented 60° around the periphery recorded the animal's movements on a digital counter. The photocell activity chamber was housed inside a ventilated, sound-attenuated box equipped with a 7.5-W light located above the center of the chamber.

On a given day, we used 24 rats to assess drug effects on spontaneous nonhabituated motor activity. Intraperitoneal injections of saline were given to 6 rats, which served as controls, and 18 received the drug ip (each drug at three dose levels). The drugs were administered about 15-20 min before exposure of the rats to the activity chamber. Activity counts were recorded after 2, 5, and 10 min.

Table 1 shows the lowest effective dose that resulted in a significant change in photocell activity or the highest dose tested that failed to produce significant results. Motor activity was significantly increased by all of the stimulants tested and significantly decreased by all of the hallucinogens. Significant decreases are also evident for all of the drugs from other CNS classes except for ethanol and morphine--probably because high enough doses were not used.

It should be pointed out that the lowest effective doses shown in this and subsequent tables are not necessarily the lowest possible doses that might produce a significant change in the variable investigated. Conversely, lack of effect at the highest doses we used does not imply that still higher doses would not have been effective. Since we were guided in our selection of doses by those reported in the literature as effective, some of these may have been either too low or, conversely, higher than necessary to show a significant effect.

Body temperature evaluation in rabbits, rats, and mice. Investigations have indicated that a wide range of stimulants tend to induce an increase in the body temperature of rats and mice as measured by a rectal probe thermistor (Borison and Clark, 1967; Pryor and Mitoma, 1974). Hallucinogens and other classes of drugs, when effective, have been reported to induce a decrease in body temperature (Winter, 1972; Ladefoged, 1973). In the rabbit, however, hallucinogens as well as stimulants tend to induce an increase in body temperature (Shemano and Nickerson, 1958; Elder and Shellenberger, 1962; Horita and Delle, 1954). Accordingly, if these results are reliable, compounds that induce an increase in body temperature in rats and rabbits

TABLE 1. Effects of Hallucinogens, Stimulants and Other CNS Classes of Drugs on Photocell Activity of Rats (Counts)

Treatment	N	Dose† (mg/kg)	Test Interval 0-2 min	2-5 min	5-10 min
Saline	126	--	173 ± 25.4‡	153 ± 26.6	183 ± 62.0
LSD-25	6	0.50	49 ± 13.7**	45 ± 12.5	84 ± 41.4**
TMA-2	6	2.5	141 ± 19.9**	171 ± 21.3	162 ± 35.8
DOM	6	1.0	133 ± 19.4**	110 ± 19.1**	142 ± 44.1
MDA	6	1.25	155 ± 16.2*	178 ± 43.1	207 ± 57.1
Mescaline	6	20.0	102 ± 25.2**	104 ± 50.5*	109 ± 55.6**
Psilocybin	6	1.0	150 ± 23.3*	96 ± 43.1**	79 ± 44.8**
d-Amphetamine	6	0.5	211 ± 27.2**	221 ± 47.3*	297 ± 103.4*
Methylphenidate	6	10.0	230 ± 41.7**	318 ± 92.1**	489 ± 160.2**
Phenmetrazine	6	20.0	163 ± 19.4**	212 ± 41.9	246 ± 75.5
Diethylpropion	6	10.0	191 ± 35.0*	208 ± 69.4**	246 ± 53.9
Caffeine	6	10.0	198 ± 5.9**	206 ± 27.0**	269 ± 35.2*
Methamphetamine	6	2.0	167 ± 25.2	201 ± 27.2**	348 ± 53.8**
Chlorpromazine	6	1.0	158 ± 25.0	107 ± 42.9*	89 ± 51.5**
Diazepam	6	5.0	161 ± 26.7	100 ± 35.8**	42 ± 39.2**
Pentobarbital	6	2.5	178 ± 22.8	142 ± 65.9	119 ± 48.3*
Phenobarbital	6	10.0	158 ± 16.9	90 ± 18.9**	71 ± 29.2**
Ethanol	6	2.0§	125 ± 14.2	130 ± 44.1	123 ± 55.1
Morphine	6	10.0	177 ± 22.3	193 ± 56.4	190 ± 92.1
Imipramine	6	10.0	145 ± 32.1	105 ± 58.6	61 ± 49.7*
Tranylcypromise	6	2.5	131 ± 39.7	67 ± 23.5*	63 ± 40.2**
Haloperidol	6	5.0	129 ± 26.0	90 ± 70.1	50 ± 56.4*

†Drug injected ip.
‡Mean ± standard deviation.
*$p \leq 0.05$} Significance by t-test.
**$p \leq 0.01$}
§Dosage units g/kg.

should have some reasonable probability of being a stimulant; those that induce a decrease in rats and an increase in the rabbit mimic effects induced by a wide range of hallucinogens. Psychoactive agents that induce a decrease in body temperature in both rats and rabbits would most likely belong to classes other than Hallucinogen or Stimulant.

Table 2 presents our results for the rabbit. The table shows the lowest effective doses that resulted in significant hyperthermia or hypothermia, or the highest dose used that failed to produce significant results. Hallucinogens and stimulants both increased body temperature, whereas drugs from other classes either had no effect or decreased body temperature as expected.

Results for mice and rats were equivocal and generally unreliable for stimulants. Although we consistently found in the mouse screen (temperature was measured) and in preliminary rat experiments that hypothermia resulted when effective doses of hallucinogens or drugs from other classes were tested, the temperature response to stimulants was variable. An earlier decision to reject the rat body temperature test was later reversed on the basis of considerations discussed below. It was combined with the rat photocell test and immediately followed it. Nevertheless, the response to stimulants was still variable. This was most probably the case because the effective doses to produce hyperthermia were probably considerably higher, at least for some drugs, than those required to produce significant changes in motor activity.

Table 3 shows that, as before (see Table 1), all of the stimulants induced a significant increase in activity, whereas body temperature did not differ from control levels. The hallucinogens, however, caused the expected decrease in activity and a pronounced decrease in body temperature. With the exception of morphine (which had no effect on either measure) and phenobarbital (which had no effect on activity), all other compounds also induced a decrease in activity and in body temperature. Accordingly, measurement of rat body temperature changes at doses that induce significant changes in motor activity appears to have limited utility for discriminating stimulants from other classes of compounds. However, the test is useful for identifying compounds that are <u>not</u> stimulants and, combined with an increase in rabbit body temperature, for identifying hallucinogens. On the basis of these results and our experience with this test in another project that showed that very high doses of stimulants consistently induced hyperthermia, the test was retained in the battery.

VALIDATION TESTS

The rat photocell activity and the rat and rabbit body temperature data presented in Tables 1-3 indicate that, if a series of unknown compounds were evaluated using these procedures, those that produced a <u>decrease</u> in rat photocell activity and body temperature and an <u>increase</u> in rabbit body temperature would have a high probability of being hallucinogens. Those that produced an increase in all three measures would most likely belong to the class Stimulant, and compounds that produced a <u>decrease</u> in all three measures would most likely belong to some other class of CNS drugs. These expectations were tested in two double-blind validation tests.

TABLE 2. Effects of Hallucinogens, Stimulants and Other CNS Classes of Drugs on Body Temperature in the Rabbit

Treatment	N†	Dose § (mg/kg)	Preinjection	15 min Postinjection	30 min Postinjection	60 min Postinjection	120 min Postinjection
LSD-25	6	0.05	38.5 ± 0.49‡	(39.3 ± 0.29)††	39.3 ± 0.39**	39.8 ± 0.54**	(40.4 ± 0.47)*
TMA-2	6	2.5	39.1 ± 0.29	39.3 ± 0.29*	39.3 ± 0.34**	39.1 ± 0.51	(38.6 ± 0.76)
DOM	6	0.5	38.7 ± 0.39	39.0 ± 0.20	39.1 ± 0.20*	38.9 ± 0.20	(38.7 ± 0.91)
MDA	6	5.0	38.9 ± 0.22	39.2 ± 0.32*	39.3 ± 0.32*	39.2 ± 0.37	(39.2 ± 0.54)
Mescaline	6	5.0	39.2 ± 0.34	(39.4 ± 0.29)*	39.3 ± 0.37	39.3 ± 0.49	(38.9 ± 0.71)
Psilocybin	6	5.0	39.1 ± 0.61	(39.7 ± 0.38)	39.8 ± 0.66**	40.2 ± 0.71**	(40.2 ± 0.68)
d-Amphetamine	6	0.5	38.4 ± 0.22	(38.7 ± 0.08)	38.7 ± 0.22*	38.8 ± 0.25**	(38.8 ± 0.37)
Cocaine	6	20.0	38.2 ± 0.27	(38.7 ± 0.12)	39.3 ± 0.78*	39.4 ± 0.91*	(38.6 ± 0.59)
Methylphenidate	6	5.0	39.3 ± 0.49	39.3 ± 0.69	39.9 ± 0.91*	39.7 ± 0.93	(38.7 ± 0.29)
Phenmetrazine	6	20.0	38.8 ± 0.27	39.0 ± 0.32*	39.0 ± 0.42	38.9 ± 0.29	38.7 ± 0.27
Methamphetamine	6	5.0	38.9 ± 0.17	39.0 ± 0.27*	39.2 ± 0.34**	39.3 ± 0.81	39.3 ± 0.74
Phentermine	3	1.0	38.9 ± 0.00	--	39.6 ± 0.17**	39.4 ± 0.37	--
Chlorpromazine	6	2.5	38.7 ± 0.27	38.7 ± 0.37	38.6 ± 0.37	38.5 ± 0.51	(38.7 ± 0.31)
Chlordiazepoxide	6	10.0	39.0 ± 0.44	39.2 ± 0.56	39.3 ± 0.61	38.4 ± 0.42	(38.4 ± 0.81)
Diazepam	6	10.0	38.7 ± 0.27	38.9 ± 0.20	38.9 ± 0.20	38.9 ± 0.20	38.7 ± 0.20
Pentobarbital	6	40.0	39.2 ± 0.61	39.3 ± 0.49	39.4 ± 0.54	39.4 ± 0.56	(38.6 ± 0.21
Phenobarbital	6	10.0	39.0 ± 0.22	39.1 ± 0.20	39.0 ± 0.25	38.8 ± 0.17*	38.8 ± 0.25
Morphine	6	1.0	39.1 ± 0.27	38.6 ± 0.34**	38.7 ± 0.39*	38.1 ± 0.51	38.7 ± 0.51
Imipramine	6	5.0	38.9 ± 0.29	38.9 ± 0.56	38.9 ± 0.64	38.8 ± 0.71	(38.0 ± 0.23)*

†Ns are for two replications of three animals each.
§All drugs were injected ip.
‡Mean ± standard deviation.
††Values in parentheses are for three animals.

*p ≤ 0.05, **p ≤ 0.01 Significance by t-test.

TABLE 3: Effects of Various Drugs on Photocell Activity and Body Temperature in the Rat

Treatment	N	Dose† (mg/kg)	Photocell Activity (10-min counts)	Body Temperature (C°)
Experiment 1				
Saline	10	--	496 ± 123§	37.0 ± 0.19
Tranylcypromine	10	5.0	173 ± 79*	35.2 ± 0.32
Haloperidol	10	5.0	258 ± 167*	36.7 ± 0.32*
Diethylpropion	10	20.0	1501 ± 594*	36.7 ± 0.56**
Experiment 2				
Saline	10	--	556 ± 184	37.1 ± 0.43
Imipramine	10	20.0	220 ± 92*	35.5 ± 0.35*
Caffeine	10	25.0	752 ± 146**	37.3 ± 0.22
Phenmetrazine	9	20.0	1162 ± 495*	37.1 ± 0.39
Experiment 3				
Saline	10	--	547 ± 79	37.0 ± 0.15
Phenobarbital	10	20.0	512 ± 72	36.8 ± 0.27*
Morphine	10	10.0	541 ± 142	36.8 ± 0.33
Diazepam	10	10.0	333 ± 163*	36.2 ± 0.56*
Experiment 4				
Saline	10	--	478 ± 176	36.9 ± 0.27
Methamphetamine	10	2.5	1031 ± 309*	36.7 ± 0.51*
Mescaline	10	40.0	145 ± 69*	34.9 ± 0.44*
Pentobarbital	9	20.0	89 ± 64*	35.1 ± 0.61*
Experiment 5				
Saline	10	--	527 ± 67	36.9 ± 0.24
Methylphenidate	9	10.0	1189 ± 315*	37.0 ± 0.28
TMA-2	10	10.0	139 ± 81*	34.9 ± 0.66*
Psilocybin	10	2.5	173 ± 52*	35.6 ± 0.60*

†Drug injected ip 15 min pretest.
§Mean ± standard deviation.

*$p \leq 0.05$
**$p \leq 0.01$ Significance by t-test.

First Validation Test

Two replications of a double-blind experiment were performed. Three hallucinogens, three stimulants, and three drugs from other CNS drug classes were selected randomly from the list of standard compounds by a staff member not directly associated with the project. A second staff member not associated with the project then prepared coded formulations of each of the nine drugs according to the dosage/ml data provided to him. The single dose selected for each drug was based on prior demonstration in our laboratory studies that it was an effective dose for the selected procedures. The coded solutions then were given to the technician for use. The code was known only to the disinterested staff member who prepared the formulations until after the experiment was terminated.

The same blind study procedure was followed for both replications. Since the data for the two replications were equivalent, they have been combined for presentation in this paper.

For the rat photocell activity/temperature test, the photocell activity scores of 9 nonfasted male Fischer rats, weighing approximately 180 g, were recorded after administration of each coded compound. Each subject was placed individually into the photocell apparatus 15 min after ip injection of the test compound. Ten min later, the animal was removed, the accumulated counts were recorded, and the animal's body temperature was recorded to the nearest tenth of a degree Centigrade over a 1-min interval, using a calibrated, transistorized telethermometer.

The data recorded for each drug are shown in Table 4. Compared with saline controls, motor activity and body temperature clearly were decreased in the test animals by all of the drugs except the stimulants, although the results were not significant in every case. Activity was increased by each of the stimulants; body temperature, however, was increased only slightly by d-amphetamine and cocaine but was decreased by phentermine. With the exception of this anomaly, the results were as predicted; the test identified compounds that were not stimulants (i.e., all compounds that induced a decrease in both photocell activity and body temperature).

For the rabbit body temperature test, we used as subjects a total of 6 nonfasted New Zealand male albino rabbits, weighing approximately 3.7 kg each, for each coded compound. Since three separate experiments were required to complete the two replications, a total of 18 rabbits served as controls.

The rabbits were equilibrated in head stockades for 15 min, and preinjection rectal temperatures were determined to the nearest tenth of a degree over a 1-min period using a calibrated transistorized telethermometer. The compound was then injected ip, and rectal temperatures were determined 30 and 60 min later.

The data are shown in Table 5. Temperature changes were evaluated statistically by comparing temperatures at 30- and 60-min postinjection with preinjection values. The differences were evaluated by t-test against the mean of all preinjection scores using the residual error variance and degrees of freedom from an analysis of variance.

TABLE 4. Effects of Selected CNS Drugs on Photocell Activity and Body Temperature in the Rat—First Validation Study

Treatment	N	Dose† (mg/kg)	Photocell Activity (10-min counts)	Body Temperature (°C)
Saline	9	--	417 ± 160 §	37.0 ± 0.20
DOM	9	2.5	230 ± 163 **	36.3 ± 0.51*
LSD-25	9	1.0	118 ± 33 *	35.8 ± 0.35*
MDA	9	5.0	210 ± 68 *	36.4 ± 0.53*
d-Amphetamine	9	1.0	645 ± 207 **	37.2 ± 0.27
Cocaine	9	20.0	688 ± 388	37.1 ± 0.47
Phentermine	9	20.0	557 ± 332	36.7 ± 0.36**
Chlordiazepoxide	9	10.0	207 ± 151 **	36.1 ± 0.38*
Chlorpromazine	9	5.0	135 ± 109 *	35.9 ± 0.71*
Imipramine	9	20.0	152 ± 48 *	35.8 ± 0.36*

†Drugs were injected ip 15 min pretest.
§Mean ± standard deviation.

*$p \leq 0.05$}
**$p \leq 0.01$} Significance by t-test.

TABLE 5: Effects of Selected CNS Drugs on Body Temperature in the Rabbit--First Validation Study

Treatment	N	Dose † (mg/kg)	Preinjection	30 min Postinjection	60 min Postinjection
Saline	18	--	39.0 ± 0.25§	39.0 ± 0.36	39.0 ± 0.36
DOM	6	1.0	39.0 ± 0.34	39.2 ± 0.38**	39.1 ± 0.56
LSD-25	6	0.2	39.0 ± 0.19	39.7 ± 0.22*	40.1 ± 0.24 *
MDA	6	5.0	38.9 ± 0.26	39.6 ± 0.71 **	40.1 ± 1.23 **
d-Amphetamine	6	1.0	39.0 ± 0.35	39.1 ± 0.43	38.9 ± 0.28
Cocaine	6	20.0	38.9 ± 0.15	39.0 ± 0.31	38.8 ± 0.17
Phentermine	6	20.0	39.0 ± 0.50	39.1 ± 0.54	39.5 ± 0.56**
Chlordiazepoxide	6	10.0	39.0 ± 0.20	38.8 ± 0.52	38.8 ± 0.71
Chlorpromazine	6	5.0	38.8 ± 0.15	38.3 ± 0.53**	37.8 ± 0.87 **
Imipramine	6	20.0	38.8 ± 0.26	38.6 ± 0.22**	38.5 ± 0.25 **

†Drugs were injected ip.
§Mean ± standard deviation.

*$p \leq 0.05$}
**$p \leq 0.01$} Significance by t test.

Again the results were as expected. Body temperature was markedly reduced by chlordiazepoxide, chlorpromazine, and imipramine--compounds that belong to classes other than Stimulant or Hallucinogen--while hyperthermia occurred for the hallucinogens and, to a lesser degree, for the stimulants. The lack of significant hyperthermia for the stimulants may have been due to the low doses used.*

The data were transformed to Z-scores** to permit comparisons among drugs for both activity and temperature scores using a common scale of measurement (standard deviation units). Rat Z-scores were based on a comparison between the drug groups and a saline control group (N=9). Rabbit Z-scores compared pre- and postdrug temperatures at 60 min postdrug using the pooled standard deviation of all predrug scores.

The Z-scores for the coded compounds are shown in Table 6 and their comparison with saline controls is indicated by + (greater than) or - (less than). Saline was disclosed as Code D after completion of the blind tests and before any predictions were attempted. The predicted pattern of +s or -s did not occur for every drug. Retrospectively, we decided that we should have selected the highest instead of the lowest effective dose for this study. Ideally, stimulants should have a pattern of +/+/+ for the three measures, hallucinogens should have a pattern of -/-/+, and drugs from other classes, a pattern of -/-/-. Nevertheless, the data were sufficient to allow three of us (L.S.O., G.T.P., and K.P.) to independently predict drug class membership. All compounds having a pattern that included a + for photocell activity and at least one other +, were designated stimulants, those with three -s were designated "other," and those with a pattern of -,-,+ were designated hallucinogens. All nine drugs were correctly identified as to class membership by all three staff members.

Second Validation Test

The cooperation of the National Institute on Drug Abuse (NIDA) was solicited in running the second validation test.

Nineteen compounds in powder form from different CNS drug classes were selected by NIDA, and were procured, coded, and shipped to our laboratory by the Research Triangle Institute. No biological or chemical information was requested or provided for any of the compounds except that they were water soluble.

Since the amount of each compound supplied was limited to 500 mg, it was necessary to modify our usual procedure somewhat and use fewer animals (especially rabbits) in the tests than we would normally employ.

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*The doses used in these tests were the lowest that produced a significant change in temperature during our laboratory studies.

**$Z = \frac{\bar{X}_e - \bar{X}_c}{SD_c}$; the mean of the experimental group subtracted from the mean of the control group divided by the standard deviation of the control group.

TABLE 6: Z-Scores for Drugs Evaluated in the First Validation Study

Coded Drugs	Rat: Photocell Activity	Rat: Body Temperature	Rabbit Body Temperature	Z-Score Profile	Predicted Drug Class	Actual Drug	Dose (mg/kg)
A	1.69*	0.50*	- 0.57*	+/+/-	Stimulant	Cocaine	20
B	- 1.87	- 6.00	3.57	-/-/+	Hallucinogen	LSD-25	1, 0.2†
C	- 1.66	- 6.00	- 1.95	-/-/-	Other	Imipramine	20
D‡	0.00	0.00	0.00	0/0/0	--	Saline	--
E	1.42	1.00	- 0.57	+/+/-	Stimulant	d-Amphetamine	1
F	- 1.29	- 3.00	3.57	-/-/+	Hallucinogen	MDA	5
G	- 1.76	- 5.50	- 4.36	-/-/-	Other	Chlorpromazine	5
H	0.87	- 1.50	1.50	+/-/+	Stimulant	Phentermine	20
I	- 1.17	- 3.50	0.12	-/-/+	Hallucinogen	DOM	2.5, 1§
J	- 1.31	- 4.50	- 0.91	-/-/-	Other	Chlordiazepoxide	10

*Rat Z-scores are based on a comparison between the drug groups and a saline control group; rabbit Z-scores compare pre- and post-drug scores of the same animals.

†Dose was 1.0 mg/kg for the rat and 0.2 mg/kg for the rabbit.

‡Code D was disclosed as saline after completion of the experiment but before predictions were attempted. Saline control groups contained 9 rats and 18 rabbits.

§Dose was 2.5 mg/kg for the rat and 1.0 mg/kg for the rabbit.

We first ran all of the coded drugs through the rabbit atrial preparation at 5 mg/kg/drug. This test was selected as the first one to run because of the low amount of compound needed to evaluate the drugs. Based on the results of this test, a preliminary classification of the coded drugs was attempted.

Those classified as stimulants were then run in the photocell activity and body temperature test, and those classified as hallucinogens, in the rabbit body temperature test. Discrepancies between the results of these tests and the results of the in vitro test suggested that all drugs should be evaluated in all tests using a wide range of doses. The doses used began at 1 mg/kg and were scaled upward to 2.5,5,10,20, and 40 mg/kg until a significant (or interpretable) effect occurred, or we ran out of the drug.

Tables 7 and 8 show the results for the most effective dose or the highest dose attempted. The drugs are grouped on the basis of their identification by NIDA following our submission of our predictions regarding class membership.

As shown in Table 7, a significant decrease in photocell activity occurred for all the hallucinogens except PCP, and for pentobarbital and naltrexone. Lactose did not affect motor activity. All of the stimulants increased photocell activity.

Body temperature tended to decrease or was unaffected by the hallucinogens and by pentobarbital, lactose and naltrexone. Stimulants either increased or had no effect on body temperature. PCP induced hyperthermia.

The increase in photocell activity and body temperature by PCP (coded Compound O) was accompanied by marked ataxia which was noted when the animals were removed from the activity chamber. Since we had not previously observed such high activity scores associated with ataxia in animals given stimulants at the dose indicated, we flagged this compound for special attention.

After all of the tests were completed, we suspected that Compound O was, in fact, PCP, and ran PCP through each of our procedures. The results, which mirrored those of Compound O, are shown for the rat in the table following PCP in parentheses (PCP).

Table 8 shows that rabbit body temperature was increased by all of the hallucinogens and stimulants--in most cases, significantly. Conversely, a slight nonsignificant hypothermia was induced by pentobarbital, lactose and naltrexone. These results are as expected.

Table 9 compares the effects of each drug on the three tests by transforming the data to Z-scores as before. Our predictions of class membership and the actual drug, as disclosed by NIDA, are also shown.

The Z-score profiles allowed unequivocal prediction of drug class membership for all of the compounds except Compound I. The rabbit hyperthermia suggested that Compound I was more likely a drug other than a stimulant or hallucinogen. Examination of the raw data indicated that the changes in motor activity and temperature were slight and nonsignificant. Also, the

TABLE 7: Effects of Selected CNS Drugs on Photocell Activity and Body Temperature in the Rat--Second Validation Study

Treatment	N	Dose† (mg/kg)	Activity (10-min count)	Body Temperature (C°)
Saline	32	--	620 ± 140	37.0 ± 0.20
PMA	6	5	482 ± 186 *	36.4 ± 0.57 **
MMDA-2	6	10	180 ± 53 **	36.3 ± 0.35 **
Mescaline	6	5	596 ± 143 *	37.1 ± 0.29
DMA-2,5	6	10	311 ± 106 **	36.6 ± 0.38
DMT	6	5	314 ± 181 *	35.9 ± 0.50 *
MDA	6	5	381 ± 129 *	37.0 ± 0.57
DET	6	10	192 ± 31 **	35.8 ± 0.31 **
DOM	6	10	32 ± 23 **	35.3 ± 0.32 **
LSD-25	6	5	286 ± 79 **	35.7 ± 0.60 **
PCP	6	10	2042 ± 693 **	37.7 ± 0.38 **
DPT	6	10	418 ± 184 *	37.2 ± 0.23
(PCP)	6	10	1956 ± 555 **	37.5 ± 0.22 **
d-Amphetamine	6	5	955 ± 280 *	37.6 ± 0.32 **
Cocaine	6	10	1059 ± 237 **	37.2 ± 0.32
Methamphetamine	6	1	843 ± 158 **	37.2 ± 0.37
Methylphenidate	6	5	1184 ± 269 **	36.9 ± 0.28
l-Amphetamine	6	10	778 ± 211	37.2 ± 0.27
Pentobarbital	6	20	196 ± 68 **	35.1 ± 0.13 **
Lactose	5	5	675 ± 152	37.2 ± 0.27
Naltrexone	6	5	394 ± 94 **	36.7 ± 0.28

†Dose was injected ip. Dose shown is the most effective or highest dose used.
§Mean ± standard deviation.

*$p \leq 0.05$}
**$p \leq 0.01$} Significance by t-test.

TABLE 8: Effects of Selected CNS Drugs on Body Temperature in the Rabbit--Second Validation Study

Treatment	N	Dose† (mg/kg)	Preinjection	30 min Postinjection	60 min Postinjection
PMA	4	5	39.0 ± 0.30	41.4 ± 0.99**	-- ††
MMDA-2	4	5	39.0 ± 0.36	39.9 ± 0.57**	39.9 ± 0.66**
Mescaline	3	1, 5, 10 (ip)	39.1 ± 0.07	39.3 ± 0.12	39.3 ± 0.12
DMA-2,5	2	5	38.8 ± 0.00	39.5 ± 0.40*	40.4 ± 0.85**
DMT	4	10 (ip)	38.9 ± 0.10	39.3 ± 0.22	39.0 ± 0.39
MDA	3	5	38.8 ± 0.15	41.7 ± 0.81**	--
DET	3	5	38.9 ± 0.31	41.5 ± 0.70**	--
DOM	3	3	38.9 ± 0.10	40.0 ± 0.06**	--
LSD-25	3	1, 5, 10 (ip)	38.9 ± 0.14	39.7 ± 1.10**	40.1 ± 1.22**
PCP	3	2.5	38.7 ± 0.12	39.6 ± 0.53**	39.7 ± 0.42**
DPT	3	5	38.9 ± 0.11	40.9 ± 0.58**	--
(PCP)	3	2.5	38.9 ± 0.16	39.9 ± 0.46**	--
d-Amphetamine	3	5	38.7 ± 0.38	39.5 ± 0.31**	40.5 ± 0.57**
Cocaine	3	2.5	38.9 ± 0.19	39.2 ± 0.15	38.8 ± 0.25
Methamphetamine	2	5	38.7 ± 0.14	41.7 ± 0.64**	--
Methylphenidate	2	5	38.7 ± 0.35	39.4 ± 0.57*	39.3 ± 0.42
l-Amphetamine	3	2.5	38.9 ± 0.47	39.5 ± 0.06*	39.5 ± 0.10*
Pentobarbital	3	5, 10† (ip)	38.9 ± 0.22	38.8 ± 0.40	38.7 ± 0.40
Lactose	3	2.5	38.9 ± 0.06	38.9 ± 0.23	38.5 ± 0.42
Naltrexone	3	2.5	38.9 ± 0.23	38.8 ± 0.69	38.7 ± 0.79

†Dose was injected iv (ear vein) unless otherwise noted. Dose shown is the most effective or highest dose used.
§Mean ± standard deviation.
*$p \leq 0.05$} Significance by t-test. Differences tested against mean
**$p \leq 0.01$} of all preinjection scores.
††Two rabbits received 5 mg/kg and one received 10 mg/kg ip.
††Two or more animals died.

TABLE 9: Z-Scores for Drugs Evaluated in the Second Validation Study

Coded Drugs	Rat: Photocell Activity	Rat: Body Temperature	Rabbit Body Temperature	Z-Score Profile	Predicted Drug Class	Actual Drug	Dose* (mg/kg)
A	- 3.02	- 9.65	- 0.89	-/-/-	Other	Pentobarbital	20, †
B	- 0.98	- 3.15	12.63	-/-/+	Hallucinogen	PMA	5, 10
C	- 3.14	- 3.65	4.74	-/-/+	Hallucinogen	MMDA-2	10
D	- 0.17	0.35	2.10	-/+/+	Hallucinogen	Mescaline	5, ‡
E	2.38	2.85	9.47	+/+/+	Stimulant	d-Amphetamine	5
F	- 2.20	- 2.15	7.37	-/-/+	Hallucinogen	DMA-2,5	10, 5
G	- 2.18	- 5.65	2.26	-/-/+	Hallucinogen	DMI	5, 10 (ip)
H	3.12	0.85	1.58	+/+/+	Stimulant	Cocaine	10, 2.5
I	0.39	0.85	- 1.93	+/+/-	Other	Lactose, USP	5, 2.5
J	- 1.14	- 0.65	- 1.05	-/-/-	Other	Naltrexone	10, 2.5
K	- 1.75	- 0.15	15.26	-/-/+	Hallucinogen	MDA	5, 5
L	- 3.05	- 6.15	13.68	-/-/+	Hallucinogen	DET	10, 5
M	- 4.19	- 8.65	11.05	-/-/+	Hallucinogen	DOM	10, 3

TABLE 9: (Concluded)

Coded Drugs	Rat: Photocell Activity	Rat: Body Temperature	Rabbit Body Temperature	Z-Score Profile	Predicted Drug Class	Actual Drug	Dose* (mg/kg)
N	- 2.38	- 6.65	5.79	-/-/+	Hallucinogen	LSD-25	5, †
O	10.12	3.35	4.74	+/+/+	Hallucinogen§	PCP	10, 2.5
P	- 1.44	0.85	18.42	-/+/+	Hallucinogen	DPT	10, 5
Q	1.59	0.85	16.32	+/+/+	Stimulant	Methamphetamine	1, 5
R	4.01	- 0.65	4.21	+/-/+	Stimulant	Methylphenidate	5
S	1.12	0.85	3.16	+/+/+	Stimulant	l-Amphetamine	10, 2.5
PCP	9.51	2.35	4.74	+/+/+	Hallucinogen§	PCP	10, 2.5

*Dose shown is the effective or highest dose used. Rats were injected ip 15 min pretest. Unless otherwise noted, rabbits were injected iv (ear vein). If two doses are shown, the rats received the first dose and the rabbits, the second.

†Two rabbits received 5 mg/kg and one, 10 mg/kg ip.

‡Three rabbits received 1, 5, and 10 mg/kg ip, respectively.

§Although Compound O produced a stimulant profile, observed ataxia suggested that it was PCP. This was verified by testing PCP.

in vitro test classified Compound I as a drug other than a hallucinogen or a stimulant. Accordingly, the drug was classified as such.

DISCUSSION AND CONCLUSIONS

This research has demonstrated that three simple, economical, and reliable preclinical test procedures are sufficient to classify unknown compounds into one of three drug classes--Hallucinogen, Stimulant or Other. The ability to determine whether new compounds belong to the hallucinogen class is particularly useful. This should permit the early preclinical identification of hallucinogenic properties in compounds synthesized for research or for the market. To date, it has been necessary to depend upon clinical data to make this determination.

We do not consider our battery infallible. PCP is a case in point. This compound would have been classified as a stimulant, had we not had previous experience with it in the laboratory. The fact that animals injected with Compound O were highly active but ataxic made them "look like PCP animals" to us. This prior knowledge ultimately led us to evaluate known PCP in our procedures and to correctly classify Compound O as a hallucinogen.

Also, at the time the code was broken, we had misclassified Compound F as an Other. This error occurred because we had not used a high enough dose in the rabbit body temperature test. The dose used (2.5 mg/kg iv) did not significantly affect body temperature. A retest using 5 mg/kg iv that was run subsequently to learning of the error produced marked and significant hyperthermia, allowing us to correct our classification (as shown in the tables) from Other to Hallucinogen.

As it stands, the battery that we have developed has proven sufficient for the classification purposes intended and should prove useful to other researchers, whether for theoretical or market purposes. It correctly identified all 28 compounds submitted for double blind evaluation as belonging to the classes Hallucinogen, Stimulant or Other. Six of the hallucinogens, 1 of the stimulants, and 2 of the drugs from other classes included among the 19 compounds selected by NIDA for our second validation test had not been tested previously in our battery.

Whether or not the battery will stand as is or will require modification* or additional tests in the future can only be established by extending the data base. Evaluation of a wider assortment of extant and newly synthesized compounds would help answer this question. For the present, however, it appears to meet the important need of providing a reliable, economic preclinical battery for establishing whether or not unknown compounds have hallucinogenic properties.

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*The rat body temperature test may prove more useful if it is run as a separate test. This would permit a wider dose-response range that is not limited to the dose range used to evaluate photocell activity. In addition, the measurement of ataxia in such animals might prove useful.

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LIST OF ABBREVIATIONS

Δ^9-THC	Delta-9-Tetrahydrocannabinol
DET	Diethyltryptamine HCl
DMA-2,5	2,5-Dimethoxyamphetamine HCl
DMT	Dimethyltryptamine Fumarate
DOM	2,5-Dimethoxy-4-methylamphetamine HCl
DPT	Dipropyltryptamine HCl
LSD-25	Lysergic Acid Diethylamine
MDA	3,4-Methylenedioxyamphetamine HCl
MMDA-2	2-Methoxy-4,5-methylenedioxyamphetamine HCl
PCP	Phencyclidine
PMA	4-Methoxyamphetamine HCl
TMA-2	2,4,5-Trimethoxyamphetamine