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Unique Influences of Ten Drugs Upon Post-Shock Biting Attack and Pre-Shock Manual Responding

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EMLEY, G. S. AND R. R. HUTCHINSON. *Unique influences of ten drugs upon post-shock biting attack and pre-shock manual responding.* PHARMACOL BIOCHEM BEHAV **19**(1) 5–12, 1983.—Delivery of a fixed-time, response-independent electric tail shock to the squirrel monkey generated bites on a rubber hose immediately following shock and manual responses on a lever immediately preceding shock; two temporally and topographically different responses in a single organism in a single experimental session. d-Amphetamine, cocaine, and caffeine each had the effect of elevating both bite and lever press responses; nicotine, chlorpromazine, chlordiazepoxide, and diazepam each elevated lever press responding while depressing bite responding across a portion of the dosage range; phenobarbital, alcohol, and morphine had the effect of depressing both bite and lever press responses but lever pressing was selectively more depressed than biting. The results parallel previous research with these drugs on other measures of aggression and on other behavioral paradigms. The responses are contingency free so that the effect of a drug does not interact with response produced environmental consequences. The recording of two separate responses related to distinct emotional states from one organism in a single experimental session allows for the objective measurement of selective and differential drug effects.

d-Amphetamine Cocaine Caffeine Nicotine Chlorpromazine Chlordiazepoxide Diazepam Phenobarbital Alcohol Morphine Attack Bite Aggression Response-independent fixed-time shock Lever press

BEHAVIORAL pharmacology has employed many procedures for testing drugs that may be useful clinically in altering certain emotion-related behaviors. With the discovery of behaviorally active drugs, experimental methods for testing of infrahuman subjects and predicting a drug's behavioral action in humans are needed and are being perfected. The purpose of the present studies was to assess the suitability of a new method for testing and predicting the actions of drugs upon several emotional states.

The presentation of response-independent shock on a four minute fixed-time schedule generated bite responses immediately following the shock and lever press responses preceding the delivery of shock. These two responses are topographically and temporally separate and occur in a single organism in a single experimental session [27,28].

The bite and lever press responses produced in the present experiment though consequence-free are similar in motivation basis to certain responses studied by other investigators. The bite response is a sensitive and valid index of attack in more naturalistic settings [25]. The lever press, anticipatory manipulative responding is an index related to escape or flight in natural settings and has performance characteristics which are similar to laboratory escape and avoidance performance [26,27].

The present experiment examined the effects of ten compounds, d-amphetamine, cocaine, caffeine, nicotine, chlorpromazine, chlordiazepoxide, diazepam, phenobarbital, alcohol and morphine, on the response-independent, fixed-time shock-induced bite and lever press responding. Previous reports [16, 17, 18] have presented preliminary data on five drugs on the response-independent shock procedure with several subjects each. Additional testing has allowed confirmation of the general patterns of action suggested in early studies. The effects of ten drugs tested and the behavioral categorization for each drug class are presented here. The study employed the squirrel monkey subject and determined a dose-response function for each drug. Obtained effects were then compared to previously reported effects of these drugs obtained by other procedures.

METHOD

Subjects

Subjects were nineteen male (700–1000 grams) and four female (575–675 grams) squirrel monkeys (*Saimiri sciureus*). Subjects were individually housed in a large, humidity, temperature and illumination controlled colony room, were fed Wayne monkey diet, and had free access to water in the home cage.

Apparatus

Primate restraint chairs (Plas Labs mfg., Lansing, MI) equipped with brass tail electrodes [22] were used during the experimental tests. The subject was restrained at the waist with the tail held in a stockade device. A latex rubber bite

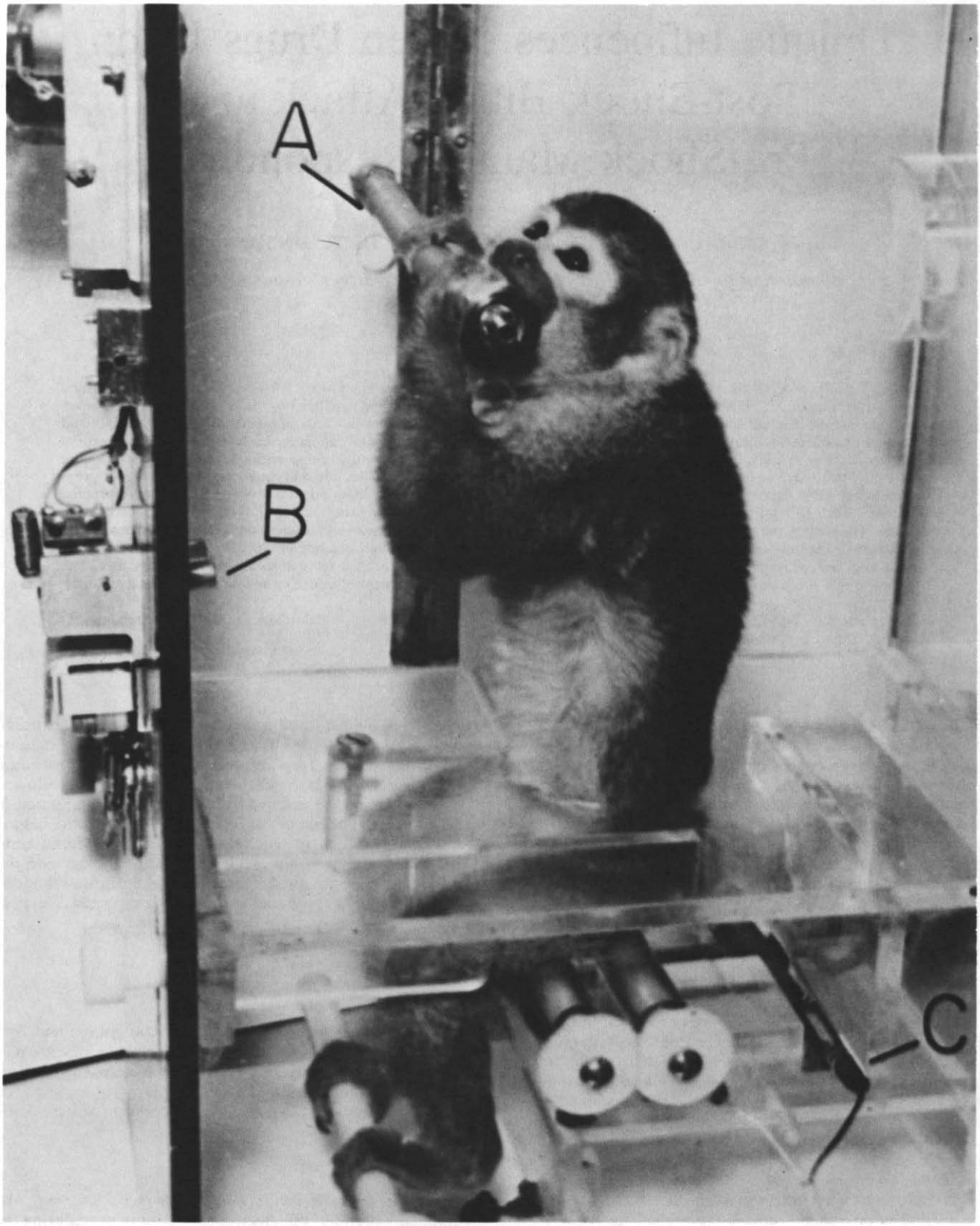

FIG. 1. Squirrel monkey seated in the restraint chair: A. indicates the bite hose; B. indicates response lever; C. indicates the tail electrodes.

TABLE 1

SUMMARY TABLE OF DRUGS ADMINISTERED, NUMBER OF SUBJECTS FOR EACH DRUG, ROUTE OF ADMINISTRATION AND PRETREATMENT TIME

Drug	N	Route	Pretreatment Time
d-amphetamine sulfate	5	SC	30 min
cocaine hydrochloride	5	SC	30 min
caffeine sodium benzoate	4	SC	30 min
nicotine tartrate	4	SC	5 min
chlorpromazine hydrochloride	6	SC	30 min
chlordiazepoxide hydrochloride	5	SC	30 min
diazepam	4	SC	30 min
phenobarbital	4	SC	60 min
ethyl alcohol	6	IP	30 min
morphine sulfate	4	SC	30 min

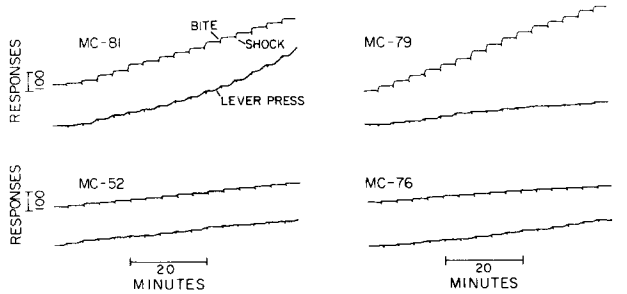

FIG. 2. Sample cumulative records from four squirrel monkey subjects. The upper record of each pair is cumulative bite responses; the bottom record is cumulative lever press responses. Response rate for bites and lever presses respectively on each subject were: MC-81—4.7/min, 6.1/min; MC-52—1.73/min, 2/min, MC-79—6.5/min, 1.9/min; MC-76—1.4/min, 1.8/min.

hose mounted on the removable front panel of the restraint chair (Fig. 1) was connected to an Air Wave switch (Tapeswitch Corp., Farmingdale, NY) which was calibrated to record only bite attacks. Compression of the hose by the teeth caused the air flow switch to trigger; grasping, tugging, squeezing or shaking of the hose with the hands or arms had no effect on the switch. A response lever (LVE No. 1352, Lehigh Valley Electronics, Fogelsville, PA) which required 20 grams of force for a response to be recorded was also mounted on the removable front panel of the restraint chair. The restraint chair was enclosed in an outer chamber providing sound attenuation and ventilation. The chamber was illuminated by four three watt light bulbs and masking noise (84 dB) was provided by a white noise generator. Hose bites and lever presses were recorded on cumulative recorders and counters located in an adjoining room.

Procedure

Experimental sessions were conducted five days each week. During each 64 minute experimental test session, 15 electric shocks (200 msec, 400 V AC) were delivered to the tail on a four minute, fixed-time, response-independent schedule. Shock was delivered through a 50K ohm resistor to the brass tail electrodes. The distal portion of the tail which fit under the electrodes was shaved, cleansed with alcohol and prepared with electrode paste prior to each session.

Baseline Conditions

Subcutaneous injections of 0.5 cc physiological saline were given 30 minutes prior to the experimental session for at least two months before drug administration. The saline control baseline for drug administration was stable responding (10% variation) on four days preceding drug administration. Drug injections were given on Wednesday of the five day experimental test week. Saline control days were Thursday, Friday, Monday and Tuesday preceding the Wednesday drug day.

Drugs

The drugs administered, routes of administration and pretreatment times are indicated in Table 1. Drugs given subcutaneously were prepared in saline and injected in a constant volume of 0.5 cc. Alcohol was given intraperitoneally and was prepared in physiological saline to a 30% v/v concentration and injected in different volumes depending upon the dosage desired. Control intraperitoneal injections were given weekly. Drugs were given in a mixed order of dosages. A range of dosages from minimal to maximal effect was determined individually by behavioral response to the drug. Therefore, the dosage ranges were not constant from subject to subject.

Most subjects were tested on more than one drug and several on three or more, therefore the 23 monkey subjects resulted in a total of 47 subject-drug tests. Behavioral measures from a minimum of one month of saline control baseline were obtained before a new drug regimen was initiated.

RESULTS

The presentation of response-independent tail shock on a four minute, fixed-time, schedule generated a typical pattern of responding. Biting on the rubber hose occurred immediately after the shock while lever pressing occurred prior to the shock. For several seconds most immediately prior to the shock there was an absence or reduction of bite and lever press responding. These behaviors are not shaped or conditioned in any conventional manner, and all animals did not show precisely the same behaviors and patterns. Figure 2 illustrates the pattern of bite and lever press responding for four subjects. The overall temporal distribution of responding is similar for each subject although there are both absolute and relative differences in rates of bite and lever press responses. For each subject, bite responses occur immediately after shock delivery decreasing in time thereafter. Lever presses occur during the last one third or one half of the four minute interval at increasing rates prior to shock delivery, but responding ceases immediately prior to shock delivery. The number of responses per session, as well as the relative number of lever press and bite responses, differs for these four subjects. MC-81 has 303 bite responses in the session illustrated and 391 lever presses. MC-79 has 415 bite responses and 122 lever presses. MC-52, as MC-81, has more lever press responses (128) than bite responses (111) per session but has fewer responses than MC-81. For both MC-52 and MC-76 the number of bite and lever press responses is similar.

The pattern of responding developed over a period of

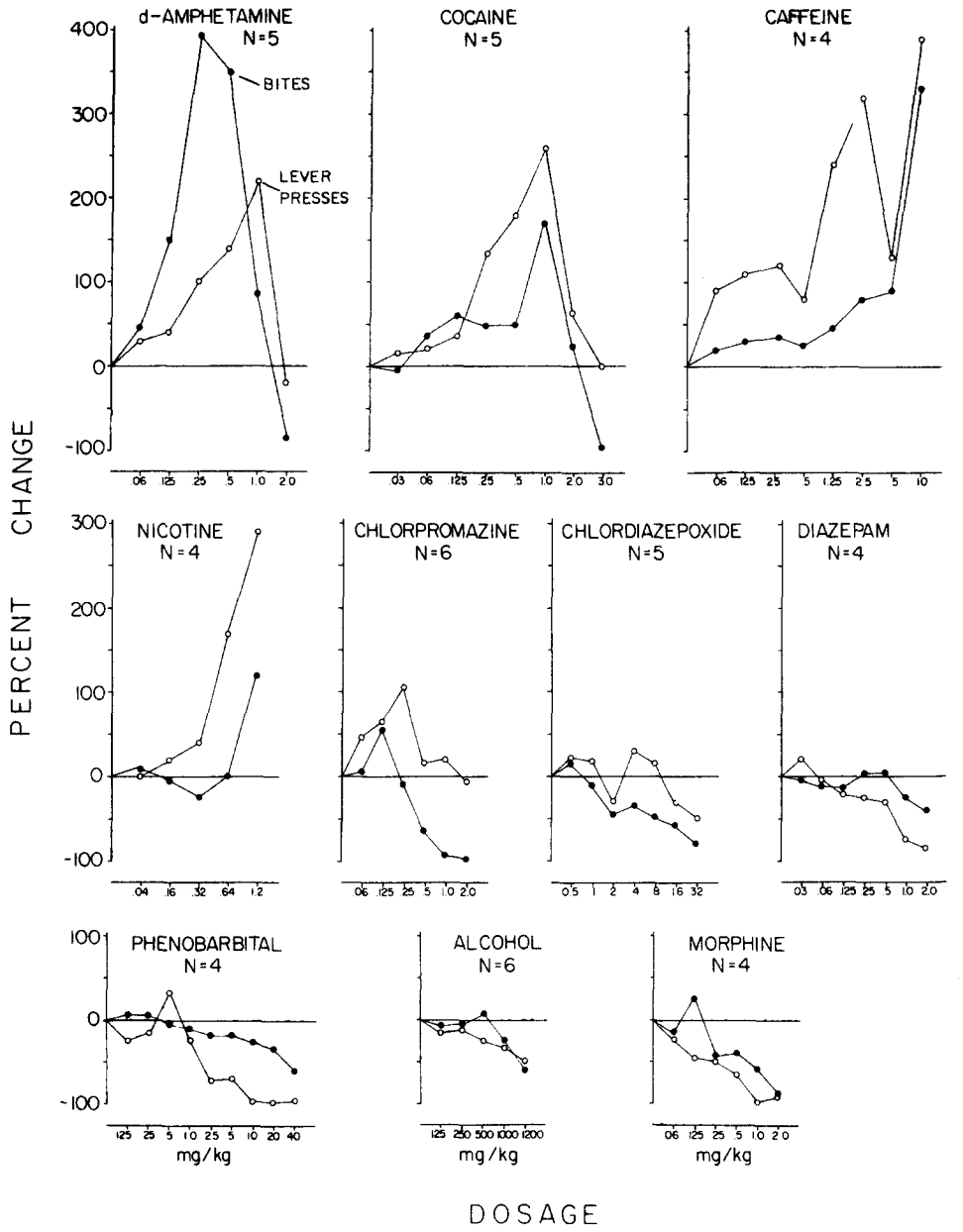

FIG. 3. The effect of ten compounds on fixed-time, response-independent shock produced bite (solid circles) and lever press (open circles) responses in the squirrel monkey. The line at zero is the average of the immediately preceding saline control days. Bite and lever press points are presented as the percent change from the immediately preceding saline control for each drug dosage.

weeks and remained stable thereafter. Though some variation in responding was noted following vacations, weight changes, and changes in animal handlers or experimental test chamber environments, responding on most of the experimental days did not vary by more than ±10–15%.

The bite and lever press responses generated by this response-independent, fixed-time delivery of electric shock procedure provided a sensitive baseline for assessing unique behavioral effects of different pharmacological compounds. The dose response function established for each of the ten drugs tested on this baseline is illustrated in Fig. 3.

Each drug produced unique orderly changes in each behavioral measure as a function of increasing dosage. These effects ranged from general progressive elevations, selective progressive increases, progressive differential decreases through general progressive decrements. For purposes of emphasis and illustration, the drugs are grouped in Fig. 3 into three categories. The drugs in the top grouping amphetamine, cocaine and caffeine have the common effect of producing increases in both lever press and bite responding over a substantial portion of the dosage range tested. At the high dosages biting is decreased before lever pressing. The second grouping—nicotine, chlorpromazine, chlordiazepoxide and diazepam are presented together because

TABLE 2

THE RESULTS OF THE WILCOXON SIGNED RANKS TEST INDICATING THE LEVEL AND DIRECTION OF SIGNIFICANT DIFFERENCES FROM SALINE CONTROL LEVELS FOR BITE AND LEVER PRESS RESPONSES

	Bite		Lever Press	
Drug	Dosage	Significant	Dosage	Significant
d-amphetamine	0.125–1.0	<0.01 increase	0.125–1.0	<0.02 increase
cocaine	0.03–1.0	<0.01 increase	0.03–1.0	<0.01 increase
caffeine	0.06–10.0	<0.01 increase	0.06–10.0	<0.01 increase
nicotine	0.16–0.64	>0.05 decrease	0.16–1.2	<0.01 increase
chlorpromazine	0.25–2.0	<0.02 decrease	0.06–1.0	<0.05 increase
chlordiazepoxide	1.0–32.0	<0.01 decrease	0.5–8.0	>0.05 increase
diazepam	0.06–2.0	>0.05 decrease	0.06–2.0	<0.01 decrease
phenobarbital	0.5–40.0	<0.02 decrease	0.5–40.0	<0.02 decrease
alcohol	125.0–1200.0	<0.02 decrease	125.0–1200.0	<0.05 decrease
morphine	0.06–2.0	<0.01 decrease	0.06–2.0	<0.01 decrease

they have the common effect through some portion of the dose response function, of elevating lever press responding while simultaneously decreasing bite responses. Phenobarbital, alcohol, and morphine—are grouped because they have the common effect of producing decreases in both lever press and bite responses while differentially decreasing lever pressing more than biting. These data are all expressed as percent change in responding at each drug dosage, determined by comparison with saline control responding for the four days prior to each drug test.

From Fig. 3 it is seen that there are major differences between some drugs while between others less pronounced differences are evident within some portion of the range of dosages tested. Specifically d-amphetamine at low and intermediate doses elevated both responses, differentially elevating biting more than lever pressing. At the highest dosage tested this drug depressed both responses. Cocaine's influence upon responding was somewhat similar to that of d-amphetamine in that both responses were elevated. However, at low doses cocaine produced only moderate differential increases in biting attack but elevated lever pressing relative to biting over a substantial portion of the dosage range. As for d-amphetamine highest dosages of cocaine reduced lever pressing to near control levels while bite responding was essentially eliminated. Caffeine at low and intermediate dosages elevated both responses but consistently elevated lever pressing relative to biting. At high caffeine dosages both responses were elevated. Because of the general elevating effect of both responses these drugs are grouped together. Nicotine, chlorpromazine, chlordiazepoxide and diazepam are here grouped together because of their common unique effect of elevating lever pressing while simultaneously depressing biting over some span of the dosage range, i.e., each was demonstrated to produce the complex effect of simultaneously decreasing an aggression response while coincidentally increasing an alternative non-aggressive response. At low and intermediate dosages nicotine produced elevations in lever pressing while biting attack is depressed. At higher dosages lever press responses were differentially elevated relative to bite responses, though each was increased in a fashion similar to caffeine. Chlorpromazine at low and intermediate dosages selectively elevated lever press responses while biting was reduced at intermediate and high doses. At highest dosages bite responses were eliminated while lever press responses remained slightly elevated or at baseline levels. Chlordiazepoxide at low to intermediate dosages depressed biting attack and elevated lever press responses. Higher dosages depressed biting attack and elevated lever press responses. Higher dosages differentially depressed biting, though each response was depressed. Diazepam at low doses elevated lever pressing and depressed biting. At higher dosages diazepam produced selective reductions of lever pressing while at higher dosages both responses were reduced, a pattern of effects much like the third and last grouping of drugs, phenobarbital, alcohol and morphine. These compounds had the common effect of depressing both responses but differentially reducing lever pressing relative to biting. Phenobarbital had a small progressive decremental effect on bite responding while following low dose stimulation of lever pressing the drug produced dose dependent depression of this response. Across the dosage range tested, alcohol produced a gradual dose dependent depression of lever press responses while leaving biting relatively unaffected until depression was noted at the highest dosage. Morphine produced a dose dependent differential depression of lever pressing. Just as with phenobarbital and alcohol biting was elevated at a low dosage and less depressed than lever pressing at higher doses.

The highest drug dosage to be tested in this study was not arbitrarily chosen but rather was dictated by the responses and condition of the subjects. Since the testing procedure utilizes a partially restrained subject, high dosages of stimulant and depressant drugs were of concern regarding subject welfare. For example high dosages of caffeine and nicotine were not tested because of the extreme agitation of the subject at immediately lower dosages. Higher dosages of alcohol were not assessed even though the decrease in responding was only at 60% at 1200 mg/kg because of the concomitant ataxia produced at this dose.

Table 2 presents the results of the Wilcoxon Signed Ranks test applied to the data in Fig. 3. This analysis indicates the dosage range at which responding under the drug is significantly different from saline control and the direction of the difference from control.

Half of the subjects in the study were tested on more than

one compound. This was done to control for individual responses to specific drugs and to determine the replicability of drug effects within one subject. Although individual differences did occur in response to the drugs tested, each subject tested on each drug showed the characteristic drug effect across some portion of the dosage range. For all compounds, the dose response function was replicated for each subject, thus, establishing that the unique effect was reliable. Additionally, since most subjects were tested on several compounds, it was determined that characteristic drug effects of several drugs of several classes could be reliably produced in one subject and provide control for past history of drug exposure, age, sex, and experimental history.

DISCUSSION

The effects reported here agree with, complement, and extend previous observations of other investigators on these drugs and their classification. d-Amphetamine, cocaine and caffeine have generally been found to elevate behavior. d-Amphetamine produces increases in isolation-induced fighting [34,53] and foot shock-elicited fighting [9,47] at low dosages and decreases at high dosages. Additionally, amphetamine has been reported to increase avoidance responding [12,41]. The increases in biting and pre-shock lever pressing in the present study are congruent with these reports. Cocaine is also reported by others to elevate responding. Cocaine increases isolation-induced fighting [21] produces increases at low dosages and decreases at high dosages on isolation-induced fighting [34,53] and extinction-induced aggression [35] and increases avoidance and punished responding [23, 42, 54]. The present cocaine results parallel these findings. The elevation of responding produced by caffeine in the present study is in agreement with increases reported on foot shock-elicited fighting in the rat [15] and increases in avoidance [12,23] and punished responding [36].

Nicotine, chlorpromazine, chlordiazepoxide and diazepam here generally produced decreases in aggression and increases in other pre-shock behaviors. Other investigators report similar effects using several separate behavioral procedures. For example, nicotine produces decreases in muricide [52], footshock-elicited fighting [14,40] and other measures of aggression [1,45] as well as increases in avoidance [12] and punished responding [36]. Chlorpromazine has also been reported to produce decreases in shock-elicited biting [37], isolation-induced fighting [11, 29, 43, 46, 49, 56] and footshock-elicited fighting [6, 38, 48] in addition to producing selective increases in punished responding [13]. The present findings parallel these reports of chlorpromazine. Similarly, chlordiazepoxide produces decreases in aggression and increases in pre-shock lever press responding. These results are in agreement with "taming" effects [42] and decreases in shock-elicited fighting [7] and isolation-induced aggression [49] noted by other investigators and increases in avoidance [3], punished responding [4, 10, 36, 44, 55] and conflict responding [4,51] produced by chlordiazepoxide. Similarly previous reports that diazepam decreases aggression [7,49] and produces taming [42] and increases in avoidance [3], punished [5, 44, 55] and conflict responding [51] are congruent with effects of diazepam produced in the present experiment.

Phenobarbital, alcohol and morphine generally depress behavior. Phenobarbital has been reported to decrease isolation-induced [11,56] and footshock-elicited fighting [6,48] and to decrease avoidance and escape responding [8]. These effects are in agreement with the effects of phenobarbital observed in the present experiment. As noted also in the present study, alcohol has been reported to decrease fighting [32] or have biphasic dose dependent effect [31]. The decreases in lever pressing in the present experiment are in agreement with previous reports of decreases in avoidance responding [2]. Morphine also has been reported to decrease isolation-induced aggression [11,29] and to decrease avoidance [24,50] and to decrease both bite and lever press responding in the present experiment.

As discussed above, there is consistent broad agreement between drug effects on the present behavioral measures and drug effects on a variety of other procedures. The bite response used here is a sensitive and valid index of more naturalistic attack sequences [25]. The lever press response, a nonaggressive topography generated by shock, is similar both in "motivation" basis and temporal parameters of expression to lever responding observed in other procedures such as escape, avoidance, and conditioned suppression. The relevance of this measure to flight and escape-avoidance-suppression processes has been described elsewhere [26,28].

The broad categories of effect observed in the present studies parallel generally observed pharmacological effects and classifications of these drugs from other workers [20, 30, 39]. Those compounds which typically exert excitatory effects on the organism and produce general increases in behavioral responding are classified as stimulants [2]. Those compounds which produce selective sedation of attack or conditioned emotional responses [19] but in the absence of any generalized change in behavior are classified as tranquilizer type agents [39]. Those compounds which exert a general sedative effect on the organism and produce general decreases in behavioral responding are classified as depressants [30]. The extensive correspondence between the present results and the work of others on the same compounds extends the observed generality of each drug's pattern of performance influence, the utility of these general drug categorizations, and the suitability of the present method for such assessments.

The current procedure has special advantages for the pharmacologic testing of the antecedent influences on aggression and escape. Several different procedures have historically been employed for the study of effects of drugs on aggression. A recent review [33] of drug effects on "agonistic" responding reports considerable variation based on which methods have been used. With the shock-elicited attack in paired subjects and the isolation and resident-intruder paradigms, experimental findings are complex and may have many explanations because of the extended number of variables operating. Antecedent and consequent causal stimuli are not explicitly manipulated by the experimenter: rather, they are arranged by the history of the two animals. The resident-intruder model, for example, selects and develops histories in animals by manipulating contingent exposure to winning and reward accrual, or extinction, and punishment counterattack for fighting. By removing the second animal and its response propensities the present procedure has arranged explicit control over consequent stimuli. Alternatively, the paired-subject shock-elicitation paradigm does not control for counterattack as a punishment consequence of attack. The response-independent, fixed-time shock delivery procedure for studying aggression provides explicit manipulation by the experimenter over both antecedent and consequent stimuli surrounding attack. Additionally, the

multiple response baseline provides a control for general influences on activity and as an index of escape or flight, thereby, allowing the simultaneous assessment of several fundamental classes of behavior produced by noxious stimulation. The response-independent nature of the present test procedure has been discussed above. Since multiple effects of influential stimuli are controlled, multiple sources of confusion in the interpretation of the results are reduced.

The procedure used in the present experiment produces behavioral performances which are stable across repeated sessions. It is, therefore, possible to test several dosages of one compound, several compounds, or the same dosage of one compound several times without losing a common starting point. Each subject serves as his own control; all drug effects are determined as changes from previous or ensuing responding in the same organism, and a dose response function is determined for each individual. Although there is individual variability in absolute number of responses, the temporal pattern of responding and drug effects are similar. Therefore, grouped data may be used to illustrate an overall dose response function or drug effect without serious risk of distortion. Additionally, the squirrel monkey subject, a primate, is used and provides data on drug dosages which closely approximate human dose information. The present method provides explicit manipulation of antecedent and consequent stimuli; stimulus presentation is invariant and applied directly to the subject; complex response sequences are channeled and sensed by automatic apparatus and inaccuracy due to limitation of the human observer is thereby reduced. The fundamental advantage of the procedure is that it selectively measures two basic "emotion" related performances in a single organism in a single experimental session. Since the behaviors can be differentially altered by pharmacological compounds, they, therefore, provide a convenient control for the other, allowing assessment of drug action specificity. The described advantages of the current procedure coupled with the comparability of effects between this paradigm and traditional test procedures support its expanded use for assessment of other drugs.

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