*EFFECTS OF BARBITURATES AND OTHER SEDATIVE
HYPNOTICS IN PIGEONS TRAINED TO
DISCRIMINATE PHENCYCLIDINE FROM SALINE*

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Pigeons were trained to peck the center key (lighted white) of three response keys to turn off the center keylight and to light one of the side keys with a red keylight and the other side key with a green keylight. Five responses (fixed-ratio component) on either side key relighted the center key. Food was delivered following 10 fixed-ratio components on the red key if 1.5 mg/kg phencyclidine had been given before the session, or 10 fixed-ratio components on the green key if saline had been given before the session. The position of the red and green keylights on the side keys varied randomly each time they were lighted by a peck on the center key. Subsequently, increasing doses of phencyclidine, barbital, amobarbital, phenobarbital, methaqualone, methyprylon, diazepam, oxazepam, and *d*-amphetamine were substituted for the training dose of phencyclidine, using a cumulative dosing procedure. At low doses of the sedative hypnotics, birds pecked the keylight color associated with saline. At higher doses, birds pecked both key colors. At the highest doses of pentobarbital and amobarbital, some birds responded almost exclusively on the color associated with phencyclidine. When responding on keys of both colors occurred following administration of phencyclidine or other sedative hypnotics, this responding was controlled by key position rather than by key color.

Key words: drug discrimination, phencyclidine, barbiturates, sedative hypnotics, color tracking, position responses, pigeons

Since the demonstration by Girden and Culler (1937) that drugs can function as discriminative stimuli to control responding, study of the stimulus properties of drugs has become a very active area of research in behavioral pharmacology (see Schuster & Balster, 1977; Winter, 1978, for reviews). The discriminative stimulus effects of a drug are frequently shared by other drugs that produce similar pharmacological effects, or have similar chemical structures, and some investigators have suggested that these discriminative stimulus effects may be used to define drug classes (Weissman, Milne, & Melvin, 1982). The basic assumption underlying such drug classification systems is that a drug that controls responding in a man-

ner analogous to the drug under which stimulus control was established (the training drug) produces a stimulus complex that overlaps that produced by the training drug.

Phencyclidine (PCP) has been shown to function as a discriminative stimulus in rats (Holtzman, 1980; Järbe, Johansson, & Henriksen, 1975; Overton, 1975) and pigeons (McMillan, Cole-Fullenwider, Hardwick, & Wenger, 1982). Recently, it has been suggested that the stimulus properties of PCP and its structural analog, ketamine, overlap with the stimulus properties of narcotics with mixed agonist and antagonist properties (Herling, Coale, Hein, Winger, & Woods, 1981; McMillan, 1982a; Teal and Holtzman, 1980). Using our three-key second-order schedule for studying drug discrimination in the pigeon, which requires that the bird peck a key of a designated color rather than a key at a designated position (McMillan et al., 1982), we observed that pigeons trained to discriminate between PCP and saline frequently pecked the key color associated with PCP when given pentobarbital (McMillan, 1982a). The purpose of the present experiments was to determine if this apparent stimu-

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lus generalization from PCP to pentobarbital occurred also to other barbiturates and to other classes of sedative-hypnotic drugs.

METHOD

Subjects

Five male White Carneaux pigeons, approximately four years of age at the beginning of these experiments and weighing 589 to 703 g with free access to food and water, were used in these experiments. These were the same birds used in previous experiments on phencyclidine discrimination (McMillan, 1982a; McMillan et al., 1982). The birds had been food deprived to 80% of their free-feeding weights and were maintained at these weights throughout the experiments.

Apparatus

The experimental chamber was a Gerbrands Model G7313 pigeon test cage equipped with a Gerbrands feeder and three response keys, each of which could be transilluminated with several colors by a Gerbrands 28-V dc keylight assembly containing two .04-W bulbs for each key color. The chamber was enclosed inside a Gerbrands Model G7211 sound and light attenuating enclosure. The minimum force required to operate the keys was .50 N. A relay mounted inside the chamber operated whenever the key contacts were opened on a side key, to provide auditory feedback for responses. Two 28-V dc houselights (Gerbrands) illuminated the experimental chamber during the session except during a feed cycle. Electro-mechanical programming and recording equipment for the experiments was located in a separate room adjacent to the room containing the experimental chamber.

Procedure

The training of these pigeons has been discussed in detail (McMillan et al., 1982). Under the schedule of reinforcement in effect for these experiments, a session began when the center key was illuminated with white light and the houselights were turned on. A single peck on the white center key extinguished it and lighted the two side keys, one with a red light and one with a green light. Five responses on either side key (FR 5 component) extinguished both side keylights, reset the ratio requirement on the side key to 5, and relighted the center

key to reinstate the original condition. Food (6-sec access to mixed grain) was presented only after ten FR 5 components had been completed on the correct key. Pecks on the red key were defined as correct if 1.5 mg/kg phencyclidine had been administered before the session, and pecks on the green key were defined as correct if saline had been administered before the session. Position of the red and green colors on the side keys varied randomly after each center-key response. The session terminated after food presentation had occurred six times or when no response had been made on any key for 2400 consecutive seconds. Sessions were conducted Monday through Friday.

During the first 4 days of the week, the pigeons were injected with 1.5 mg/kg PCP or saline 15 min before the session. Injections were given in a mixed order and each substance was injected twice during the 4-day period. The second injection of each substance (saline or 1.5 mg/kg PCP) each week was used as a measure of baseline stimulus control by presence or absence of the drug stimulus. On Friday, cumulative dose-effect curves (McMillan et al., 1982) were determined for phencyclidine and other drugs substituted for phencyclidine. Briefly, the bird was injected with drug and placed into the chamber. Fifteen minutes later, the session was initiated. Food was delivered after the bird completed 10 fixed-ratio components to either key color. Immediately after food delivery, the bird was removed from the test chamber and injected with a second dose. The bird was then placed in the chamber again and 15 min later the session resumed. The procedure was repeated until a dose was reached that suppressed responding for 40 min. On some occasions, a session was terminated at doses below those that suppressed responding for 40 min because of concerns that a higher dose might kill the bird. All doses shown in the figures are cumulative doses (sum of all doses given to the bird). Drugs were administered and doses were calculated in the following forms: phencyclidine hydrochloride, methaqualone hydrochloride, sodium pentobarbital, sodium barbital, *d*-amphetamine sulfate, diazepam hydrochloride, phenobarbital USP, sodium amobarbital, oxazepam free base, and methyprylon free base. All drugs were dissolved or suspended in .9% saline, except diazepam, which was given in its commercial solvent (Hoffman LaRoche, Inc.).

Discrimination data were plotted as percentage of responses to the key with the red key-light, hereafter referred to as the PCP key. In some experiments, the number of ratio components completed on each side key (left vs. right) was recorded. The average latency to respond on the center key and the average rate of responding on side keys were also determined. Only those responses prior to the first delivery of food were considered in the baseline calculations.

RESULTS

Figure 1 shows the percentage of total responses on the PCP key (red key color) for all drugs studied in these experiments. All birds averaged more than 90% of their responses on the PCP key when given PCP before the session, and only Bird 62 made any response on the PCP key when given saline before the session (see brackets in Figure 1). When a cumulative dose-effect curve was determined for PCP, all birds responded primarily on the PCP

key at a dose of 1.0 or 1.7 mg/kg. At doses of .3 mg/kg PCP (Birds 62 and 60) and at 1.0 mg/kg PCP (Bird 59), three birds responded on both keys with 27 to 60% of the responses on the PCP key. When four consecutive saline injections were given, birds responded almost entirely on the saline key (green key color; see Figure 4).

The top row of Figure 1 shows cumulative dose-effect curves for several barbiturates. Responding after barbiturates was characterized by responding on both keys for all birds. In fact, every bird at some dose of every barbiturate responded more frequently on the PCP key after barbiturate than it ever did after saline. Although the birds often responded on the PCP key more often than 50% of the time after receiving a barbiturate, in only a few instances did responding after a barbiturate fall within two standard deviations of the mean for PCP responding during control sessions. These instances included Birds 61 and 58 after 17.5 mg/kg amobarbital and Bird 61 after 17.5 mg/kg pentobarbital.

Fig. 1. Cumulative dose-effect curves for response generalization from 1.5 mg/kg phencyclidine (PCP) to saline, to other doses of PCP, and to other drugs. Abscissa: mg/kg dose. Ordinate: percentage of total responses on PCP key. Brackets at control show ± 2 standard deviations around the control mean with the upper brackets showing the values after 1.5 mg/kg PCP administration and the lower brackets showing the values after saline injections for percentage of total responses on the PCP key. Each point is a single observation in one pigeon.

The bottom row of Figure 1 shows cumulative dose-effect curves for other sedative-hypnotic drugs. Following injections of these drugs, some birds responded on both keys, but not all birds did so, and the proportion of responding on the PCP key never reached the levels observed with PCP.

The effects of *d*-amphetamine, a drug that is not classified as a sedative hypnotic, were also studied in these birds. Following administration of *d*-amphetamine, responding was confined almost entirely to the saline key.

The data in Figure 1 suggest that there might be reliable individual differences among birds. These individual differences are summarized in Table 1, where for each of the sedative hypnotics studied, the highest percentage of responses made on the PCP key at any dose is listed. Bird 59 was the least likely of the five birds to respond on the PCP key after a barbiturate, whereas Birds 61, 58, and 60 made about three-quarters of their responses on the PCP key after optimal barbiturate doses.

Table 1 also shows that responding on the PCP key was less likely after nonbarbiturate sedative hypnotics than after barbiturates. Birds 60, 59, and 58 responded with a higher percentage of responses on the PCP key after all barbiturates than they did after any of the other sedative hypnotics. Birds 62 and 61 responded with a higher percentage of responses on the PCP key after three of the four barbiturates than they did after any of the sedative hypnotics. Across all birds and drug conditions, Bird 61 responded most frequently on the PCP key after sedative hypnotic drugs,

whereas Bird 59 was least likely to respond on the PCP key after sedative hypnotics.

Table 2 shows the effects of these drugs on average latency to respond on the center key and on average rate of responding on the side keys once a response had been made on the center key. During training sessions, the rate of responding and latency measures were similar for PCP and saline in Birds 62 and 61. For the other 3 birds, response latencies were longer and response rates were lower after PCP than after saline. The highest doses of the other drugs frequently eliminated responding completely.

Approximately midway through the study, it was discovered that one of the birds that was responding on both the PCP key and the saline key after administration of a barbiturate made all of its responses on the left side key. Thus, the bird responded at a particular location rather than continuing to respond under control of a key color. Therefore, in subsequent experiments, the total number of fixed-ratio components completed on each key was recorded during determination of cumulative dose-effect curves.

Figure 2 shows the percentage of ratios completed on the PCP key (red key) and on the preferred key (left key = 0, right key = Δ) after phenobarbital and pentobarbital. The preferred key was defined as the key position (left or right side key) at which more than 50% of the key pecks occurred. The figure shows clearly that after most doses that produced considerable responding on both key colors (e.g., percentage of responses on the PCP key was

Table 1

Highest percentage of responses on the PCP key for each bird during determination of cumulative dose-effect curves.

Drug	Bird					Mean
	62	61	58	60	59	
PCP	100	77	90	100	100	93 $\pm$ 10*
BARBITAL	44	22	77	90	9	48 $\pm$ 35
AMOBARBITAL	2	100	100	83	24	62 $\pm$ 46
PHENOBARBITAL	52	74	48	64	35	55 $\pm$ 15
PENTOBARBITAL	65	87	63	73	32	64 $\pm$ 18
BARBITURATE MEAN	41 $\pm$ 27*	71 $\pm$ 34	72 $\pm$ 22	78 $\pm$ 11	25 $\pm$ 12	—
METHAQUALONE	0	9	37	0	0	9 $\pm$ 16
METHYPRYLON	2	28	18	0	2	10 $\pm$ 12
DIAZEPAM	35	53	0	61	3	30 $\pm$ 28
OXAZEPAM	40	61	0	0	2	21 $\pm$ 28

*Standard deviation.

between 30 and 70%), there was a high percentage of responses at one of the two key locations (e.g., more than 80% of responses at one position). Although the left key seems to have been preferred more frequently, this was not always true. For example, for Bird 60, all responses were made on the right key after 30 mg/kg phenobarbital and all responses were made on the left key after 56 mg/kg phenobarbital.

Figure 3 shows a similar analysis for diazepam and *d*-amphetamine. In addition to the cumulative dose-effect curve for diazepam, a 3-mg/kg dose was studied twice and a 5.6-mg/kg dose was studied once, 30 min after injection. Again, following diazepam there was a high correlation between responding to both key colors and responding at a key position. Following *d*-amphetamine, however, pigeons pecked only the green key (saline key) and responding was approximately equally distributed between the left and the right key positions.

Since responding to both key colors was associated with the position of a key rather than with its color after administration of phenobarbital, pentobarbital, and diazepam, it was important to determine if a similar phenomenon occurred after lower doses of the training drug. Therefore, the cumulative dose-response curve for PCP was redetermined with the loca-

Fig. 2. Cumulative dose-effect curves for generalization from 1.5 mg/kg PCP to phenobarbital and pentobarbital. Abscissa: mg/kg dose. Ordinate: percentage of total responses on the PCP key (filled circles) or percentage of total responses on the preferred key (o, left; Δ , right key).

Fig. 3. Cumulative dose-effect curves for generalization from 1.5 mg/kg PCP to diazepam and *d*-amphetamine. Abscissa: mg/kg dose. Ordinate: percentage of total responses on the PCP key (filled circles) or percentage of total responses on the preferred key (o, left; Δ , right key).

tion of each response recorded. These data are shown in Figure 4.

Four of the five birds (all except Bird 58) responded on both key colors at doses ranging from .3 to 1.0 mg/kg PCP. In every instance more than 80% of the total responses were made at one key location, although in no instance did 100% of the responses occur at one location, as was seen frequently with the barbiturates and diazepam. At doses higher than those that produced responding to both colors,

Fig. 4. Cumulative dose-effect curves for generalization from 1.5 mg/kg PCP to phencyclidine and saline. Abscissa: mg/kg dose. Ordinate: percentage of total responses on the PCP key (filled circles) or percentage of total responses on the preferred key (o, left; Δ , right key).

Table 2

Effects of drugs on mean latency (in seconds) to respond on center key and rate (in responses/sec) of responding on the side keys. Control data show mean ± 2 standard deviations for training days. α = bird did not respond on the center key during the 40 min session. — = bird was not tested with this dose.

Mg/Kg		62		61		58		60		59	
Dose		Latency	Rate	Latency	Rate	Latency	Rate	Latency	Rate	Latency	Rate
Control	0	2.5 $\pm$ 2.7	1.3 $\pm$ 0.2	1.2 $\pm$ 0.2	1.6 $\pm$ 0.4	3.1 $\pm$ 2.0	1.6 $\pm$ 0.4	1.4 $\pm$ 0.4	1.4 $\pm$ 0.4	1.8 $\pm$ 0.5	1.8 $\pm$ 0.5
	1.5	2.2 $\pm$ 2.7	1.0 $\pm$ 0.5	1.8 $\pm$ 0.9	1.6 $\pm$ 0.5	6.0 $\pm$ 4.8	0.8 $\pm$ 0.3	4.0 $\pm$ 1.4	1.1 $\pm$ 0.4	55.8 $\pm$ 93.0	1.1 $\pm$ 0.7
PCP	0.1	1.0	1.1	1.0	1.5	6.9	2.0	1.3	1.0	1.3	1.9
	0.3	1.2	1.3	1.5	1.5	4.3	1.4	2.4	1.2	2.0	1.8
	1.0	289.2	0.6	1.2	1.6	144.0	0.7	16.6	1.1	2.5	0.7
	1.7	—	—	—	—	—	—	—	—	262.0	0.3
Barbital	10	1.6	1.1	0.9	1.7	0.8	2.2	2.0	1.1	1.1	2.0
	30	1.1	1.3	0.9	1.5	1.3	2.2	3.3	1.1	1.4	2.1
	100	1.5	1.1	1.6	1.3	11.4	1.1	24.7	0.4	20.2	0.4
	170	1.4	0.5	α	0	6.0	0.6	α	0	α	0
Amobarbital	3	1.2	1.5	0.8	1.6	1.1	1.9	1.6	1.5	1.1	2.0
	17.5	α	0	28.7	0.2	2.2	1.8	1.5	1.2	1.6	1.3
Phenobarbital	10	2.1	0.8	1.5	1.7	1.0	1.6	1.0	1.1	2.7	1.4
	30	8.8	1.0	2.8	1.5	2.2	2.0	2.2	1.8	13.0	1.0
	56	α	0	3.7	0.7	3.4	2.1	1.9	1.4	136.6	0.1
	100	—	—	α	0	α	0	α	0	—	—
Pentobarbital	3	0.9	0.8	0.8	1.6	0.9	2.0	1.5	1.7	1.0	2.5
	17.5	3.3	1.7	165.6	0.5	7.1	0.6	70.3	0.5	3.3	1.4
Methaqualone	3	1.2	1.3	—	—	—	—	—	—	—	—
	10	1.0	1.5	1.0	1.7	1.3	1.7	1.4	1.5	1.4	1.7
	30	2.3	1.3	1.1	1.3	32.8	0.4	α	0	1.8	1.4
	56	α	0	α	0	α	0	—	—	α	0
Methylprylon	10	0.8	1.7	1.0	1.6	1.5	2.1	0.8	1.8	2.0	0.2
	30	1.3	1.6	5.9	1.2	1.4	2.1	α	0	22.3	0.7
	56	α	0	α	0	α	0	—	—	α	0

Mg/Kg Dose	62		61		58		60		59	
	Latency	Rate	Latency	Rate	Latency	Rate	Latency	Rate	Latency	Rate
Diazepam	0.3	1.3	1.3	1.5	7.5	1.4	1.2	1.5	14.8	2.0
	1.0	1.8	2.4	1.6	α	0	3.5	1.4	α	0
	3.0	35.2	9.8	0.5	—	—	α	0	—	—
	5.6	α	α	0	—	—	—	—	—	—
Oxazepam	10	1.2	1.1	1.7	1.5	1.3	2.4	1.3	1.7	2.0
	30	1.3	1.1	1.6	15.2	1.0	3.1	0.7	1.8	1.5
	56	1.6	4.6	1.4	92.0	1.5	α	0	6.0	1.2
	100	1.8	5.5	1.1	93.3	1.0	—	—	α	0
d-Amphetamine	0.3	1.5	0.8	1.3	2.5	1.3	2.3	1.4	1.9	1.3
	1	3.8	1.0	1.7	5.4	1.4	α	0	2.9	1.4
	3	α	1.2	1.2	1.6	0	—	—	α	0
	5.6	—	α	0	—	—	—	—	—	—

the pigeons distributed their responses more equally across positions (e.g., responded only on the PCP key that was red). When saline was given repeatedly, the birds responded on the green key. The highest percentage of fixed-ratio components that could be completed on one key when the bird was responding only to one color was 70%. Thus, after saline injections, the percentage of ratios completed on the preferred key varied from 50 to 70%.

DISCUSSION

Pigeons trained under the color-tracking procedure discriminated PCP from saline and responded on both key colors when barbiturates and benzodiazepines were given. Behavior under the latter drugs was characterized by responding at a particular location, that is, the birds tended to make almost all of their responses on either the left or right key rather than on the color associated with the drug or the nondrug state. The interpretation of the loss of control by the key color and the ensuing pattern of responding at one position is the fundamental question raised by these experiments.

At least three interpretations of these observations will be discussed. First, responding on both key colors may reflect a "third drug state" that is neither PCP-like nor saline-like (Winter, 1978). The pigeon had not been trained to respond to stimuli associated with a "third drug state" and so responded at one position. Arguing against this interpretation are the results obtained with *d*-amphetamine. *d*-Amphetamine was given at dose levels that have been shown to function as discriminative stimuli (Barry, 1974), yet when *d*-amphetamine was given, the pigeons responded only on the saline key. These birds also responded on the saline key when they were given a variety of other drugs in a previous experiment (McMillan, 1982a). Thus, production of a third drug state was not a sufficient condition for birds to respond at a position rather than to a color.

A second possibility is that although there was considerable similarity between the barbiturate stimulus and the PCP stimulus, the bird was unable to respond to the PCP color because the barbiturate affected performance (e.g., induced errors, or directly produced position responding). Perhaps the situation is analogous to our data on the effects of pento-

barbital on delayed-matching-to-sample performance (McMillan, 1982b). In this procedure, the bird pecks the middle key of three keys. The color of the middle key is red or green and the response on the middle key darkens it. After a short delay, the side keys come on, one of which is red and the other, green. The bird must respond on the key color that matches that previously occurring on the middle key. When pentobarbital is given to pigeons trained on delayed matching to sample, the birds respond largely at a side-key position, rather than matching the center key color. The color-tracking discrimination procedure has many elements similar to delayed matching to sample, the major difference being that the discriminative stimulus is the drug state rather than the stimulus produced by the color of the center key in the matching-to-sample procedure.

The major argument against this interpretation is that after pentobarbital and amobarbital, some birds began to track the color associated with PCP at doses above those that caused responding on both key colors. If pentobarbital was simply inducing errors, it would not be expected that higher doses of pentobarbital would eliminate these errors, nor that the elimination of such errors would result in responding on the PCP key rather than on the saline key. Furthermore, when doses of PCP lower than the training dose were given, the birds responded on both key colors, and on the PCP key at higher doses. Thus, the PCP dose-effect curve was much like those of pentobarbital and amobarbital, except that the birds shifted more reliably to the PCP key after higher doses of PCP than after higher doses of amobarbital and pentobarbital.

A third possibility is that responding on both key colors represents generalization from the PCP stimulus to the stimulus produced by other drugs. Intermediate responding would thus reflect the degree to which the barbiturate discriminative stimulus overlaps that of PCP. This possibility is attractive because the dose-effect curve for PCP itself went through a similar orderly transition from responding on the saline key to responding at only one position to responding on the PCP key. Nevertheless, this interpretation does not explain why responding was confined to a particular side-key position at intermediate doses of PCP and the barbiturates.

A variation of this explanation would be that rather than there being a generalization gradient for the PCP stimulus, the stimulus complex produced by a barbiturate is either PCP-like, or not PCP-like, with a threshold dose level around which no stimulus control occurs. When stimulus control is lost at a threshold dose level, responding at a particular position eventually produces the reinforcer. This explanation assumes that below the drug stimulus threshold, the animal responds on the saline key. At doses close to the threshold value, stimulus control by the presence or absence of the drug is lost and therefore the bird responds at a side-key position that eventually results in reinforcement. At doses above threshold, stimulus control is again established and the bird responds to the color associated with PCP. Such a pattern of responding might also be seen if the generalization gradient was very steep.

Acceptance of responding to both key colors at a particular location as a reflection of stimulus similarity between PCP and the other drugs implies that the PCP stimulus does generalize to other drugs. For pentobarbital, the evidence for stimulus generalization is fairly strong because some birds did switch completely to the PCP key after high doses of these drugs and because there have been some reports of generalization between PCP and pentobarbital using other procedures (Herling, Valentino, & Winger, 1980; Overton, 1975). For phenobarbital and barbitol the case is less clear, inasmuch as no birds shifted completely to the PCP key after these drugs. A similar statement can be made for diazepam and oxazepam. Perhaps these drugs suppressed responding completely before doses sufficient to produce the full PCP stimulus could be reached. This possibility is difficult to eliminate for any drug.

It should be noted that some of these drugs are of slower onset and longer duration of action than PCP or the short-acting barbiturates. Barbitol has a relatively low lipid solubility that slows its onset of action and diazepam is converted to active metabolites. It seems unlikely that generalization of the PCP stimulus to the other drugs was limited by the slow onset of action caused by low lipid solubility or by a slow conversion to active metabolites, since the drugs eventually did totally eliminate responding and since responding to

both key colors did occur in most birds with all of these drugs. Attempts to maintain continued responding under the high doses of diazepam that eliminated responding during the cumulative-dosing procedure by administering some doses in a single injection also resulted in responding primarily at one key location.

Methaqualone and methyprylon generated responding to both key colors in only two birds and in both cases the amount of responding on the PCP key was less than 50%. If one accepts the idea that such responding represents stimulus generalization from PCP to other drugs, one might order the degree of generalization from PCP to sedative hypnotics as follows: amobarbital = pentobarbital > barbitol = phenobarbital = diazepam = or > oxazepam > methaqualone = methyprylon >>> *d*-amphetamine.

Other procedures do not always generate intermediate responding under a training drug. Our data offer a possible explanation for these failures. Under the color-tracking procedure, responding on both key colors was characterized as responding at a given location. Under other procedures, the expression of stimulus control by the drug is based on responding at a particular location. Thus, with such procedures it may not always be possible to separate the discriminative control by drug from the generation of a stereotyped position response during periods of weak stimulus control.

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