6-1988

The Discriminative Stimulus Properties of Ethosuximide in the Pigeon

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THE DISCRIMINATIVE STIMULUS PROPERTIES OF ETHOSUXIMIDE IN THE PIGEON

by

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A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Arts
Department of Psychology

Western Michigan University
Kalamazoo, Michigan
June 1988

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Western Michigan University, 1988

After initial exposure to 80 mg/kg ethosuximide, pigeons trained in a two-key drug discrimination procedure rapidly learned to discriminate 120 mg/kg ethosuximide from saline. When 40 to 160 mg/kg doses of ethosuximide were administered during generalization tests, the percentage of the responses directed to the ethosuximide-appropriate key varied directly with dose. Time-effect determinations revealed that the discriminable properties of ethosuximide were evident as early as 15 min after, and as late as 2 hr after, intramuscular injection. The discriminative stimulus properties of ethosuximide failed to generalize to the anticonvulsant compounds clonazepam (0.5-4 mg/kg), methsuximide (25-200 mg/kg), and phenytoin (5-15 mg/kg). Generalization was apparent with certain doses of primidone (250, 300 mg/kg) and mepheytoin (80, 160, 240 mg/kg). The concomittant administration of pentylenetetrazol (5, 10, 20 mg/kg) partially blocked the discriminable properties of the training dose of the ethosuximide.

ACKNOWLEDGEMENTS

I would like to express my thanks to God, family, friends and colleagues without whose support this work would not have been possible.

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Order Number 1334664

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INTRODUCTION

The experimental analysis of behavior rests on a set of assumptions concerning the relationship between the environment and the behavior of an organism. One important assumption is that behavior rarely, if ever, occurs indiscriminantly. Instead, behavior almost always covaries with some change in the organism's internal or external environment (Reynolds, 1975). Environmental events often come to control responding through operant conditioning. In operant conditioning, in the presence of some specific stimulus--generally termed the discriminative stimulus or SD--a response produces a change in the environment. Consequently, the future probability of occurrence of the response under similar conditions is altered. If the probability of the response is increased, the process is called reinforcement. If, on the other hand, the probability of the response is decreased, the process is called punishment or extinction. Given the momentary effectiveness of a reinforcer, whether or not a response occurs following conditioning depends, to a large extent, on whether a discriminative stimulus for that response is present.

Catania (1968) defines the discriminative stimulus as any stimulus having a discriminative function in the control of behavior. In other words, the discriminative stimulus is an environmental event in the presence of which a specified bit of behavior is most likely to be reinforced. More clearly, Michael (1982) defines a discriminative stimulus as a stimulus condition which:

> (1) given the momentary effectiveness of some particular type of reinforcement (2) increases the frequency of a particular type of response (3) because that stimulus condition has been correlated with an increase in the frequency with which that type of response has been followed by that type of reinforcement. (p. 149)

A particular response is said to be under stimulus control if that response occurs primarily in the presence of the designated stimulus. Stimulus control and the discriminative stimulus function of an environmental event cannot be determined a priori but must be determined empirically.

Drugs as Discriminative Stimuli

Both interoceptive and exteroceptive stimuli can come to control behavior. The notion of interoceptive stimulation in the control of behavior was first experimentally demonstrated by Bykov and Ivanova in 1928 (Schuster & Brady, 1971). With the use of classical conditioning procedures, they demonstrated that an interoceptive stimulus could come to control behavior. The sequence of studies they conducted resulted in the discovery of interoceptors in many organs of the body. Subsequent experiments by Sluci, Gyorgi, and Porter (1965) demonstrated unequivocally that interoceptive stimulation could come to control operant behavior. Sluci and his associates surgically implanted inflatable balloon like devices in the gastrointestinal tracts of rhesus monkeys. The monkeys were differentially reinforced when they made one response in the presence of the inflated balloon and another response when the balloon was deflated. This procedure resulted in clear stimulus control exerted over operant behavior by the balloon-like device.

The discriminative stimulus properties of scores of drugs have been studied extensively over the past twenty years (Harris & Balster, 1971; Overton, 1964, 1966; Seiden & Dykstra, 1977). Landmark studies in this area were conducted by Overton (1964, 1966), who used a T-maze in which entering one arm was reinforced following drug administration and entering the other arm was reinforced following vehicle administration. Differential stimulus-controlled responding developed rapidly with several drugs (e.g., pentobarbital, ethanol, chloridiazepoxide, and atropine) when this procedure was employed. This drug discrimination procedure, like those devised after it, entails differentially reinforcing a specific response in the presence of a specific dose of a given drug and reinforcing another response in the presence of another dose of that drug, a different drug, or vehicle.

Drug discrimination techniques have proven to be of considerable utility in psychopharmacological research. For example, drug discrimination procedures are an excellent method for classifying newly-synthesized compounds according to their "subjective effects" and physiological actions. Several structurally dissimilar compounds have been grouped together on the basis of their subjective effects (i.e., discriminative stimulus properties). Moreover, several drugs with similar chemical structures have been shown not to share discriminative stimulus properties (Barry, 1974; Woods, Young, & Herling, 1982).

As a research tool, drug discrimination procedures have become invaluable in the mapping of brain neurotransmitter systems (Woods,

Hein, Herling, Young, & Valen 1979). For example, drug discrimination techniques have played an important role in the discovery and subsequent characterization of several endogenous opioids (Hein, Young, Herling, & Woods, 1981; Woods et al., 1979). These techniques are well suited in the systematic investigation of drugs that may alter central nervous system (CNS) function. Finally, as Henningfield, Lucas, and Bigelow (1986) note, "From a theoretical perspective, the functional properties of drugs serving as discriminative stimuli are the mechanisms by which ingested substances control behavior" (p. 69). Understanding the behavioral effects of a drug requires knowledge of its potential stimulus properties.

Epilepsy and its Management

There are several forms of chronic central nervous system dysfunctions that are commonly designated as epilepsy (Rall & Schleifer, 1985). This group of dysfunctions can be characterized by the sudden onset of seizures and convulsions that are frequently associated with excessive EEG discharges. The exact mechanism by which epileptic episodes occur has not yet been completely delineated.

Drugs represent the most used and most effective means available of treating epilepsy (Rall & Schleifer, 1985). Therapeutic agents used in the clinical management of epileptic disorders appear to exert their effects in two fundamental ways (Rall & Schleifer, 1985). First, they may have "effects on pathologically altered neurones of seizure foci to prevent or reduce their excessive discharge," and second, they may have "effects that would reduce the spread of

excitation from seizure foci and prevent detonation and disruption of function of normal aggrogates of neurones" (p. 469).

Relatively little is known about the behavioral effects of anticonvulsant drugs, including their potential stimulus properties. In recent years, a series of investigations by Poling and his associates, summarized by Poling and Picker (1987), have begun to clarify the behavioral effects of several anticonvulsant drugs. These studies and others have examined phenytoin (Krafft, Cleary, & Poling, 1983), valproic acid (Picker, Wallace, Hancock, & Poling, 1985), and pentobarbital (Herling, Valintino, & Wenger, 1980) as discriminative stimuli. Some commonly used anticonvulsants, however, have not yet been studied as discriminative stimuli. Ethosuximide (EMS) is one such drug.

Ethosuximide is one of several succinimide compounds that are commonly used in the treatment of petit mal (absence) and myoclonic seizures (Rall & Schleifer, 1985). The drug has been called an ideal therapeutic agent for use with small children suffering from absence seizures (Sherwin, 1982). Preclinical observations of ESM by Pirredda, Woodhead, & Swinyard, 1985) indicate that EMS generally increases the seizure threshold and, when used in non-toxic doses, is basically inadequate in the prevention of supramaximal seizures. In addition, Pirredda et al. (1985) report that ESM will block minimal clonic threshold seizures and avert the occurrence of "tonic extension in maximal tonic extension threshold seizures" (p. 745). These data were obtained with nonhumans in which seizures were induced electrically or chemically. The neuropharmacological actions

of ESM are poorly understood. However, the drug is known to affect dopaminergic (DA) systems (Ferrendelli & Klunk, 1982). Ethosuximide is highly successful in protecting against seizures induced by gama-hydroxybutyrate, a substance that blocks impulse flow in DA-ergic pathways in the brain. Moreover, the anticonvulsant activity of ESM in experimentally-induced seizure models has been reversed by DA receptor agonist (Fluphenazine) and inhibitors of DA synthesis (d-methylparatyrocine). Ethosiximide may also affect gamma amino butyric acid (GABA) systems. This speculation is based upon similarities between ESM and drugs with known GABA-ergic effects (e.g., valproic acid and some benzodiazepines) with respect to their anticonvulsant activity. The evidence linking ESM with the GABA-ergic system is, however, inconclusive.

The purpose of the present study was to examine the discriminative stimulus properties of ESM in the pigeon by employing a two-key operant discrimination procedure. In addition, time-course data were obtained in order to determine the temporal parameters of the drug-cue. Generalization and antabonism tests were conducted to evaluate (a) the extent to which other entiepileptic compounds are similar to ESM, and (b) the extent to which the detectable effects of ESM can be blocked by pretreatment with pentylentetrazol, a convulsant with actions that are blocked by ESM.

METHODS

Subjects

Six experimentally-naive White Carneaux pigeons maintained at 80% of free-feeding body weights, served as subjects. Each bird was individually housed with unlimited access to grit and water.

Apparatus

Three operant conditioning chambers, each 38 cm high, 30 cm wide, and 40 cm long, were used as test environments. A 5 cm by 5 cm opening, horizontally centered in the front wall 8 cm above the floor, allowed access to a hopper filled with mixed grain when the hopper was raised. When raised, the hopper was illuminated by a 7-W white bulb. Two response keys, 2.5 cm in diameter, were located symetrically on the front wall, 12 cm from the adjacent wall and 24 cm above the floor. Ambient chamber illumination was provided by a clear 7-W bulb located on the chamber ceiling. An exhaust fan provided masking noise and ventilation. Scheduling of experimental events and data collection were accomplished through the use of a Digital Equipment Corp. (Maynard, MA) PDP/BA minicomputer using interfacing and software (SUPERSKED) provided by State Systems Inc. (Kalamazoo, MI).

Discrimination Training

Subjects were initially trained to peck each key by using a forward pairing autoshaping procedure (Brown & Jenkins, 1968) in

which 6-s key illuminations (white) were followed by 4-s access to mixed grain regardless of the pigeon's behavior. When reliable pecking was established, during each session one of the two keys was continuously lighted in white and food delivery (3-s) was made dependent upon completion of a fixed-ratio 1 (FR 1) schedule. Under this schedule, each peck of the lighted key produced food delivery. The key that was illuminated alternated irregularly across sessions; the probability of left-key and right-key illumination was equal. Through all phases of the study, sessions were conducted 6 days per week at about the same time each day, and training sessions were 20 min in duration.

Over sessions (ranging from 3 to 8 across birds) the number of responses required to produce food was gradually increased until an FR 20 schedule was in effect. When all birds responded reliably under this schedule, discrimination training was begun. During initial discrimination training, both keys were lighted in white and the birds received intramuscular (IM) injections of either 1.0 ml/kg isotonic saline solution or 80 mg/kg ESM 30 min prior to the start of the session. After 30 sessions of discrimination training with 80 mg/kg ESM, no discrimination had developed. Therefore, the training dose was increased to 120 mg/kg for the remainder of the study. A random sequence was used to determine the order of injections, with the restriction that the same injection (i.e., drug or saline) was not given for more than two consecutive sessions and that the number of saline and ESM were approximately equal. When saline was administered, 20 responses on the other key (ESM-appropriate key) resulted

in food delivery. Responses that were not stimulus-appropriate had no programmed consequences although they were recorded. For three subjects, left-key responses were ESM-appropriate, whereas for the other three subjects right-key responses were ESM-appropriate. These conditions remained in effect until the percentage of stimulus-appropriate responses prior to the first food delivery for each bird was at or above a mean of 80% for 10 consecutive sessions. This measure was determined by dividing the number of stimulus-appropriate responses prior to the first food delivery by the total number of responses emitted in this period.

Dose- and Time-Effect Determinations

Once the discrimination criterion was met, a dose-effect determination was completed in which 40, 80, or 160 mg/kg ESM was substituted for the training dose. All doses of ESM were dissolved in isotonic saline solution and injected at a volume of 1 ml/kg. During test sessions, the completion of 20 responses on either key produced 3-s access to food, followed by immediate termination of the session. If a subject failed to emit 20 responses on one key, the session was terminated after 20 min. In this case, the same dose was administered during the next scheduled test session. No subject received more than two determinations at a single dose. With few exceptions, each bird received each dose of ESM once, in an irregular sequence.

Throughout all phases of the experiment, testing occurred only when the percentage of stimulus-appropriate responses emitted prior to the first food delivery was at or above 80% across two consecutive

discrimination training sessions in which the training dose of ESM (120 mg/kg) or saline solution was administered. After dose-effect testing, a time-course determination was conducted in which the training dose of ESM was administered 15, 60, and 120 min prior to the test session. With the exception of presession injection interval, conditions of testing were identical to those just described.

Generalization and Antagonism Tests

Following completion of the time effect determination, generalization tests were conducted with clonazepam, mephenytoin, methsuximide, phenytoin, and primidone. Four doses of each drug were evaluated (Table 1, p. 14). All doses of clonazepam, methsuximide, and primidone were administered IM 30 min prior to experimental sessions. All doses of mephenytoin were administered 8 hr before behavioral testing because data from pilot studies indicate this presession injection interval to be more effective than shorter intervals. Methsuximide and clonazepam were dissolved in a vehicle containing 4 parts propylene glycol, 1 part ethyl alcohol, and 5 parts distilled water, prepared at an injection volume of 1 ml/kg. Mephenytoin and primidone were dissolved in dimethyl sulfoxide and injected at a volume of 1 to 2 ml/kg, depending dose. All test drugs were administered at an irregular order that varied across subjects. In instances where a subject failed to complete 20 responses on either key, the same does was administered during the next scheduled test session; no subject received more than two determinations at a single dose.

During antagonism tests, each of five doses (see Table 1) of

pentylenetetrazol (dissolved in isotonic saline solution and injected at a volume of 1 ml/kg) was administered in conjunction with the training dose (120 mg/kg) of ESM 30 min before testing. In these tests, the two drugs were injected on opposite sides of the breast muscle. Otherwise, all test conditions were identical to those described above. In the final phase of the study, 10 mg/kg pentylenetetrazol was administered alone and a generalization test was conducted as described above.

RESULTS

No descrimination developed with 80 mg/kg ESM. After the initial training with 80 mg/kg, however, all birds rapidly learned to discriminate 120 mg/kg ESM from saline. The mean number of sessions required to meet the training criterion was 14, the range across subjects was 10 to 16 sessions. Group performance for the dose-effect and time-effect determinations are shown in Figure 1. The left panel shows that the percentage of ESM-appropriate responses prior to the emission of 20 responses on either key was an increasing function of the ESM dose. The right panel shows that ESM (120 mg/kg) was an effective discriminative stimulus at all presession injection intervals examined, although percentage of ESM-appropriate responses decreased slightly as presession injection interval increased.

Table 1 shows group performance during generalization and antagonism tests. The discriminative stimulus properties of ESM did not generalize to any dose of clonazepam, methsuximide, or phenytoin. Some generalization did occur, however, to 80, 160, and 240 mg/kg doses of mephenytoin. Percent ESM-appropriate responding decreased across these doses of mephenytoin, ranging from 75% at 80 mg/kg mephenytoin to 52% at 240 mg/kg. Primidone at 300 mg/kg strongly generalized to the training dose of ESM; this dose of primidone produced 95% ESM-appropriate responding. The 240 mg/kg dose of primidone produced 50% ESM-appropriate responding, and lower primidone doses were associated with little ESM-appropriate responding. The

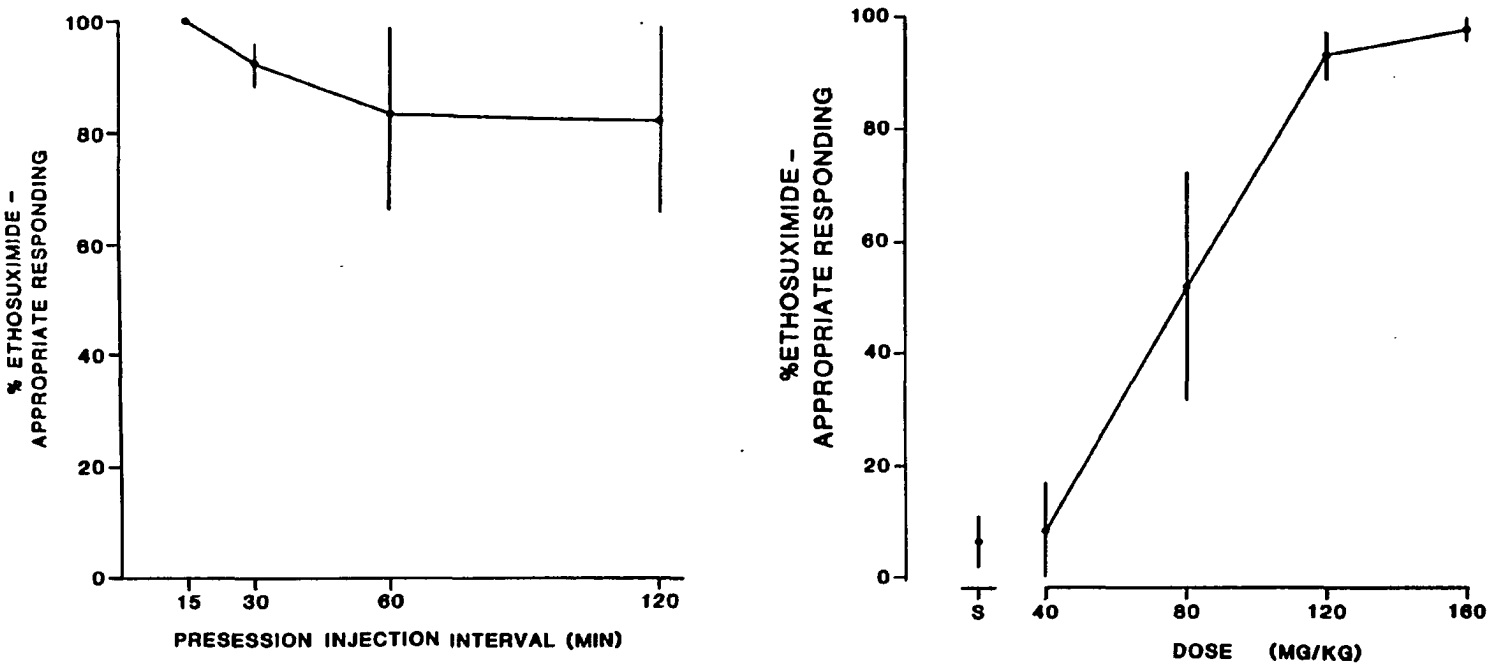

Figure 1. Dose- and Time-Effect Relations for Ethosuximide in Pigeons Trained to Discriminate 120.0 mg/kg Ethosuximide from Saline.

Table 1

Mean Percentage of Responses on the Ethosuximide-Appropriate Key During Test Sessions after Injection with Various Compounds

Drug	Dose (mg/kg)	% Ethosuximide-appropriate responses (+ 1 SE)	Rate as % of control (+ 1 SE)	Source
Saline[a]	--	6 (4)	100	--
Ethosuximide[a]	120.0	93 (4)	134 (22)	Warner-Lambert, Ann Arbor, MI
Clonazepam	0.5	36 (19)	99 (41)	Hoffman-La
	1.0	12 (12)	111 (22)	Roche,
	2.0	17 (17)	98 (31)	Nutley, NJ
	4.0	17 (17)	46 (26)	
Mephenytoin[b]	40.0	0 (0)	174 (28)	Sandoz,
	80.0	75 (25)	114 (19)	East Hanover,
	160.0	63 (23)	121 (28)	NJ
	240.0	52 (15)	65 (26)	
Methsuximide	25.0	2 (2)	152 (21)	Warner-Lambert,
	50.0	33 (21)	158 (23)	
	100.0	33 (21)	135 (15)	Ann Arbor, MI
	200.0	27 (18)	59 (24)	
Phenytoin	5.0	1 (1)	127 (28)	Parke-Davis,
	7.5	2 (2)	95 (22)	Morris Plains,
	10.0	0 (0)	100 (35)	NJ
	15.0	0 (0)	60 (29)	
Primidone	150.0[c]	1 (1)	139 (20)	Ayerst,
	200.0[c]	0 (0)	113 (43)	New York
	250.0[c]	50 (29)	137 (37)	
	300.0[c]	95 (5)	151 (27)	
Pentylenetrazol	10.0[c]	0 (0)	146 (19)	Sigma, St. Louis, MO
Ethosuximide + Pentylenetrazol	120.0[c] 1.0	74 (25)	173 (26)	

Table 1, Continued

Drug	Dose (mg/kg)	% Ethosuximide-appropriate responses (+ 1 SE)	Rate as % of control (+ 1 SE)	Source
Ethosuximide + Pentylenetrazol	120.0[c] 2.5	100 (0)	86 (18)	
Ethosuximide + Pentylenetrazol	120.0[c] 5.0	72 (24)	99 (34)	
Ethosuximide + Pentylenetrazol	120.0[c] 10.0	50 (29)	33 (31)	
Ethosuximide + Pentylenetrazol	120.0[c] 20.0	25 (20)	20 (20)	

[a]These values represent performance during the 10 sessions when the discrimination criterion was initially met; each separate value is the mean of 5 sessions.

[b]Administered 8 hr before behavioral testing.

[c]N = 4. Two birds died before these data were obtained.

Source:

highest dose of all drugs that did not generalize to control levels (Table 1), which indicates that behaviorally-active doses were evaluated.

Administering pentylenetrazol in combination with the training dose of ESM (120 mg/kg) reduced the percentage of ESM-appropriate responding at pentylenetrazol doses of 5, 10, and 20 mg/kg. When 20 mg/kg pentylenetrazol was combined with 120 mg/kg ESM, only 25% of the total responses were directed to the ESM-appropriate key. No

ESM-appropriate responding was apparent when 10 mg/kg pentylenetrazol was administered alone.

DISCUSSION

In the present study, pigeons learned to discriminate a dose of 120.0 mg/kg ESM from saline after only marginal success at a lower dose (80.0 mg/kg). This suggests that the 120.0 mg/kg dose, but not the 80.0 mg/kg dose, produces detectable interoceptive effects. Dose-response determinations revealed that doses above 120.0 mg/kg were similar to the 120.0 mg/kg dose in that they also engendered high levels of drug-appropriate responding. With 120.0 mg/kg ESM, time-course evaluations at various presession intervals demonstrated discriminative stimulus effects as soon as 15 min and as long as 2 hr after IM injection. Presession injection intervals longer than 2 hr were not evaluated, thus the present study does not reveal the duration of the discriminable effects of ESM. Only two of the five anticonvulsant compounds tested showed substantial generalization to ESM. All other drugs failed to generate appreciable ESM-appropriate responding. Of the drugs that did engender ESM-appropriate responding, only the anticonvulsant primidone (PRM) generalized completely. It should be noted that a major in vivo metabolite of PRM is the barbiturate, phenobarbital (Schafer, 1982, p. 396). This suggests that the discriminative effects of phenobarbital may be similar to ESM, but this possibility was not evaluated in the present study. A hydantoin, mephenytoin, produced partial generalization (a maximum of 75% ESM-appropriate responding). These data were obtained with an extended pretreatment time of 8 hrs. Methsuximide,

like ESM (a succinimide), as well as mephenytoin (a hydantoin) and clonazepam (a benzodiazepine) all failed to generalize to the training dose of ESM 120.0 mg/kg. Thus, structure-specificity may be among the requirements for common discriminative stimulus properties. That ESM appears to share some discriminative stimulus properties with a select few of the antiepileptic agents tested is indicative of differing sites of action. At the present time, however, the exact mechanism that may explain the apparent differences in the discriminable effects of antiepileptic drugs is unknown. Regardless of the mechanism responsible for the shared discriminative effects of anticonvulsant drugs, the present findings are in accordance with earlier observations (Herling et al., 1980, Krafft et al., 1983; Picker et al., 1985) indicating that not all antiepileptic compounds share discriminative characteristics.

The present study is limited in the sense that the two-key operant drug discrimination procedure provides a relatively crude analysis of the discriminative functions of drugs. That is, more sophisticated techniques are now available (France & Woods, 1985; McMillian, Cole-Fullenwider, Hardwick, & Wenger, 1982; White & Holtzman, 1981). Specifically, the three-key discrimination and the various "tracking" procedures provide a more finely tuned analysis of the discriminative functions of drugs. In a two-key procedure, if an animal responds on the saline-appropriate key during generalization tests with other drugs does not necessarily mean that drug is like saline. Furthermore, difficulties in interpretation arise when drugs only "partially" generalize. For example, if a test drug

produces 65% training drug-appropriate responding, does this reflect activity at a subset of a specific receptor population? Or at a different population of receptors with a similar endpoint? The two-key procedure is useful for an initial analysis of the interoceptive effects of drugs, but the procedure may be surpassed as the technique of choice for studying drug discrimination in the not-to-distant future.

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