CENTRAL VERSUS PERIPHERAL MECHANISMS IN DISCRIMINATIVE RESPONSE CONTROL BY d-AMPHETAMINE AND RELATED COMPOUNDS

A Thesis

Presented to

The Faculty of the Department of Psychology

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

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by

Catherine Nelson Jones

December, 1972

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ABSTRACT

To investigate the role of central vs. peripheral mechanisms in discriminative response control by pharmacological agents, the present study compared acquisition of a two-lever choice discrimination by three groups of albino rats required to discriminate either d-amphetamine sulfate (0.8 mg/kg), l-amphetamine sulfate (0.8 mg/kg) or para-hydroxyamphetamine hydrobromide (1.01 mg/kg) from saline. The drug condition was paired with reinforcement on one lever and the nondrug condition with the opposite lever for Ss in each group during training. The measure of response control was the proportion of cue appropriate responses during ten-minute extinction tests interspersed at four-day intervals during acquisition. Following acquisition, the administration of phentolamine hydrochloride (10 mg/kg) prior to drug injections was investigated to determine the relative importance of peripheral cues in these drug controlled discriminations.

The results of acquisition data clearly indicate the importance of central activity in the control of responding by drugs. Superior control was exhibited by the d-amphetamine vs. saline group, intermediate performance was displayed by the l-amphetamine vs. saline group and the para-hydroxy-amphetamine vs. saline group failed to acquire the discrimination. Pretreatment with phentolamine failed to produce meaningful results due to nonspecific behavioral effects of this agent.

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CHAPTER I

INTRODUCTION

Although drug-behavior interactions have been observed through the centuries, a formal discipline devoted to their study has only recently developed. The rapid expansion of the pharmaceutical industry since 1950 and the subsequent availability of numerous therapeutic agents for legal and illegal consumption created a need for research to analyze the effects of drugs on behavior. Early research in behavioral pharmacology was largely confined to observing the effects of drugs on behavioral baselines. The prevailing attitude toward such research is reflected in a statement by Kety (1961): "We cannot expect drugs to introduce anything new into the mind or into behavior, but merely to accentuate or to suppress functions in behavior which are already present" (p. 179). In this sense, drugs were considered primarily as unconditioned stimuli capable only of improving or disrupting some baseline performance.

This point of view is somewhat surprising since investigators in the 1800's had successfully employed drugs as unconditioned stimuli (US) in classical conditioning paradigms. Bykov (1957) reports conditioning of the cardiovascular reflex induced by nitroglycerin to auditory stimuli (Petrova). Delov conditioned a similar reflex induced by the injection of morphine (US) to environmental

conditions (conditioned stimulus - CS). Similarly, the salivary reflex induced by morphine (US) has been brought under the control of a CS (Collins and Tatum, 1925; Kleitman and Crisler, 1927).

The role of drugs in conditioning behavior has received renewed attention in more recent years. In a comprehensive review of this area (Thompson and Pickens, 1971) the physiological alterations produced by drugs are conceptualized as "stimuli" having three important functions--eliciting, reinforcing and discriminative (Hunt,1971, p. 73). With the recognition of these three functions, the analysis of drug-behavior interactions has taken new directions and drug states, i.e., the characteristic physiological changes produced by a drug, have been incorporated into experimental designs as organizers of behavior. Many drugs appear to be functionally equivalent to other internal and external stimuli in their ability to control behavior. The following is one investigator's reaction to studies in which such stimuli have been compared:

> ....what has impressed me perhaps the most is the high degree of orderliness in the data. It seems to me that they contain few surprises in that the results are congruent with what we know about the dynamics of behavioral control. For example, once it is established that a drug is a discriminative stimulus, the discriminative behavior that it controls is perfectly familiar and orderly; you would know it anywhere. It has its own parameter values of course, but that is also predictable (MacCorquodale, 1971, p. 215).

The elucidation of these functions has also had an impact on theories of drug abuse and drug therapy. The possible role of drugs

as stimuli in the genesis and relapse of drug abuse has been discussed by several authors (Harris and Balster, 1970; Thompson, 1968; Wikler, 1968; Storm and Smart, 1965; and Overton, 1972). One of these (Overton, 1972) has also proposed a direct correlation between abuse potential and discriminability. Such conclusions are tentative, however, since the role of drugs as stimuli, particularly in the control of discriminated behaviors, has not been confirmed in human subjects. Although such functions are suggested by clinical and experimental reports of partially dissociated learning or amnesia between drug and nondrug states, these effects may not be due simply to stimulus properties of drugs.

While drugs may be analogous to other stimuli at the behavioral level, it remains to be seen whether their underlying mechanisms are qualitatively similar. Little research has been devoted to this question but certain evidence suggests that factors other than simple stimulus properties of drugs may be operative. Attempts to correlate pharmacological activity with the stimulus functions of drugs may make it possible to strengthen the analogies between drugs and other stimuli or to distinguish them on this basis. The present study is concerned with revealing the underlying mechanisms of drugs as discriminative stimuli in choice situations. A limited problem within this area has been investigated in order to provide a first approximation of the mechanisms in question. The results should be meaningful in suggesting directions for further research.

CHAPTER II

REVIEW OF THE LITERATURE

Drugs as Discriminative Stimuli

Although drugs may serve eliciting, reinforcing and discriminative functions, the present review will only consider the role of drugs as discriminative stimuli capable of controlling the choice between two or more operant responses. Behavioral control evolves when one response has been reinforced in the presence of one drug while an alternative response has been reinforced in the absence of that drug or in the presence of another drug. Each drug state becomes the occasion for the response previously reinforced in that state. Differential responding in the absence of reinforcement feedback is used as the index of stimulus control relative to the performance of a control group or to random behavior.

A variety of behaviors maintained on diverse reinforcers have been brought under stimulus control by drugs. This type of control was first demonstrated when rats learned to approach the goal box of a straight alley for food in one drug state and passively avoid shock in the goal box in another state (Conger, 1951). A multiple approach-avoidance paradigm has since been adapted to the two lever Skinner box (Kubena and Barry, 1969-a; Morrison and Stephenson, 1969). Lever-A was reinforced under one drug condition and responses on lever-B were punished.

Conditions of reward and punishment were reversed for the opposing drug state. Similarly, simple choice between levers in the absence of aversive stimulation has been brought under the control of drugs (Kubena and Barry, 1969-a; Harris and Balster, 1971; Kilbey et al., 1971). In a more complex modification of the two-lever choice discrimination, different schedules of reinforcement were programmed on the two levers and each lever was reinforced only in a given drug state. Not only lever choice but also response patterning could be brought under stimulus control during extinction (Harris and Balster, 1971). Rats have also learned to choose the level of illumination previously paired with reinforcement in a given drug state (Barry, 1968). This design differs from response choice paradigms since response patterning was identical in both drug conditions and only the S_D and S_Δ changed across drug states. Position habits based on the presence or absence of particular drugs have been established in the T-maze and three alley maze motivated by shock (Overton, 1961, 1964, et alia). Stewart (1962) trained rats to escape to either the light or dark end of a box with an electrified grid floor on the basis of drug cues and Brown et al. (1968) employed a brightness discrimination task in a Lashley jumping stand apparatus.

When a drug state is to be defined as a discriminative stimulus, several important parameters must be considered. Identification of the drug itself is the first and most obvious consideration. Drugs which have been tested and found capable of controlling discriminated

behavior are summarized in Table I. In most cases, saline served as the alternative drug state. Other drugs alternated with saline showed only weak control or failed to produce discriminations after prolonged training. Among these agents are tetraethylammonium (Overton, 1964), gallamine (Flaxedil) (Overton, 1961, 1964), ACTH, atropine methyl nitrate and phenoxybenzamine (Overton, 1971).

A second consideration is dosage regulation. In general, the efficiency of a drug state as a discriminative cue increases with higher doses up to the point of behavioral toxicity (Overton, 1966, 1969; Morrison and Stephenson, 1969; Schechter and Rosecrans, 1971; Hill et al., 1971). Changes which occur along this dimension also allow subjects to learn discriminations based upon different dose levels of the same drug. Waters et al. (1972) trained rats to discriminate two dose levels of dl-amphetamine sulfate (0.3 vs. 2.5 mg/kg) which could be independently discriminated from saline. Generalization tests also indicated that dose levels of the same drug could be distinguished, since performance decrements occurred when subjects were tested with dose levels sufficiently different from the training dose (Waters et al., 1972; Overton, 1969, 1972; Schechter and Rosecrans, 1971).

The cue state is also time-locked to the injection-training interval. When this interval is varied during testing generalization decrements may occur (Overton, 1972; Schechter and Rosecrans, 1971). Such deficits are probably related to the time course of drug absorption and elimination from the body (Schechter and Rosecrans, 1971).

TABLE I

DRUGS EXHIBITING DISCRIMINATIVE RESPONSE CONTROL

Classification	Drugs	References
Anesthetics	Sodium Pentobarbital	Balster, 1970; Harris and Balster, 1971; Hill et al., 1971; Overton, 1961, 1964, 1966, 1967, 1968, 1969
	Ethyl Alcohol	Barry, 1968; Barry and Kubena, 1972; Conger, 1951; Harris and Balster, 1971; Kubena and Barry, 1969-a, 1969-b; Overton, 1966
Minor Tranquilizers	Chlordiazepoxide (Librium)	Brown et al., 1968; Harris and Balster, 1971; Overton, 1966
	Meprobamate	Overton, 1966
Muscarinic Drugs	Arecoline	Schechter and Rosecrans, 1972
Antimuscarinic Drugs	Atropine	Barry and Kubena, 1972; Harris and Balster, 1971; Kubena and Barry, 1969-b; Overton, 1966, 1967, 1969
	Benactyzine	Overton, 1969
	Scopolamine	Overton, 1966, 1969
	Ditran	Overton, 1969
Nicotinic Drugs	Nicotine	Morrison and Stephenson, 1969; Overton, 1969; Schechter and Rosecrans, 1971
Narcotics	Morphine	Hill et al., 1971
Antidepressants	Imipramine	Stewart, 1962

Table I (cont'd.)

Classification	Drugs	References
Hallucinogens	Lysergic acid diethylamide	Hirschhorn and Winter, 1972
	Mescaline	Hirschhorn and Winter, 1972
	Psilocybin	Harris and Balster, 1971
Phenothiazines	Chlorpromazine	Harris and Balster, 1971; Overton, 1966; Stewart, 1962
Other Drugs	dl-Amphetamine	Balster, 1970; Harris and Balster, 1968; Kilbey et al., 1971; Waters et al., 1972
	delta-9-Tetra-hydrocannabinol	Barry and Kubena, 1972; Kubena and Barry, 1972; Henrikksson and Järbe, 1972
	Epinephrine	Schuster and Brady, 1971
	Dextrose	Schuster and Brady, 1971
	Carbamate	Overton, 1966

Although characteristic cue states can be induced by given drugs, transfer of control may occur between drugs with similar pharmacological effects when dose levels and injection intervals are suitably adjusted. Drugs which do not show transfer to one another can usually be used as opposing cues to control discriminative behavior. Transfer is not always predictable a priori but drugs seem more likely to show transfer to other durgs within the same pharmacological classification (Stewart, 1962; Kubena and Barry, 1969-a, 1972; Overton, 1966, 1967, 1968; Barry and Kubena, 1972). For example, rats trained to discriminate alcohol (1200 mg/kg, ip) from saline showed transfer of the alcohol correct response to other general depressants including sodium pentobarbital (10-20 mg/kg, ip), chlordiazepoxide hydrochloride (10-15 mg/kg, ip) and chloral hydrate (90-120 mg/kg, orally), but not to a CNS stimulant, d-amphetamine (1 mg/kg, ip), or to a major tranquilizer, chlorpromazine hydrochloride (2 mg/kg, ip), (Kubena and Barry, 1969-b).

Mechanisms of Response Control by Drugs

The mechanisms which underlie the functioning of drugs as stimuli are far from clear. There is no direct evidence for an independent sensory system which allows the organism to identify and respond discriminatively to the presence of a drug per se. Although this is an interesting possibility, detection of drug induced changes in the internal milieu seems a more likely explanation. First, drugs might affect sensory processes at the central level or produce alterations in periph-

eral sensory receptors, thereby changing sensory input to the central nervous system (CNS). Pharmacological effects detected via internal sensory mechanisms might also serve as appropriate cues. Second, alteration of sensory function may not be involved, but undetermined effects upon the CNS might result in dissociation of learning between different drug states. These hypotheses derive from the divergent interests which initially motivated the use of drugs as discriminative stimuli.

The first investigator to employ drugs in this capacity was primarily concerned with analyzing the effects of alcohol on conflict behavior. Conger (1951) hypothesized that impaired passive avoidance under the influence of alcohol might be due to changes in internal stimulus conditions between training and testing. Deficits due to changes in the external environment had previously been reported (Miller, 1948) and the data suggested similar effects produced by alcohol. In order to differentiate possible stimulus change effects from the direct effects of this drug on fear, rats were trained to perform a discriminated approach-avoidance task in a straight alley. Half of the subjects learned to approach the goal box under alcohol and avoid under saline. Remaining subjects received opposite pairings of drug condition and required response. Both groups learned the discrimination indicating that drug states could serve as discriminative stimuli. In addition, the fear reducing effects of alcohol were still detected in the poorer performance of the group required to avoid under alcohol and approach under normal conditions.

The use of drug states as internal stimuli was also influenced by an interest in discriminative response control by other physiological states. "Drive discrimination" studies had demonstrated that differential responding could be based on physiological stimuli produced by hunger or thirst when food or water served as reinforcers (Hull, 1933; Leeper, 1935). Subjects could also avoid shock in a T-maze by going to one arm when food deprived and to the other when deprived of water (Amsel, 1949). Internal stimuli produced by deprivation were difficult to control, however, and their physiological basis was complex. Drugs were thought to provide a "...direct and relatively rapid means of altering internal stimuli..." (p. 95) and to make possible a "...more precise evaluation of their role in the formation of stimulus-response-reinforcement relationships" (p. 95) (Belleville, 1964). In these cases, drugs were thought to produce stimuli which could be processed through traditional sensory pathways.

Other investigators do not agree with the concept that drugs act as stimuli. Overton (1972) has stated that

> Although it is convenient to speak of the "stimulus properties of drugs", there is little evidence to suggest that when rats learn a discrimination they are actually discriminating the sensory consequences of drug action (p. 199).

Furthermore, Overton (1972) suggests that discriminative behavior based on drugs actually results from "...a sort of temporary 'fugue' state separated from the nondrug state by a partial or complete amnesic barrier" which allows for the dissociation of habits across states (p. 193).

This type of dissociation was described in the literature as early as 1917 by Lashley and was more extensively investigated by Girden and Culler (1937) and Girden (1940, 1942-a, 1942-b). Dissociative or "state-dependent" effects are most frequently investigated in studies using a 2 x 2 factorial design. Subjects are trained either in the drugged (D) or nondrugged (N) state. Half are tested for retention in the training state (D-D; N-N) and half in the opposite state (D-N; N-D). If poorer retention is shown by N-D and D-N groups relative to D-D and N-N then dissociation is said to occur. This phenomenon has also been produced by manipulations other than drug administration (Spear et al., 1971; McIntyre and Reichert, 1971; DeVietti and Larson, 1971). Ironically enough, the 2 x 2 design has also been proposed as a means of evaluating "stimulus change" effects between drug and nondrug states (Grossman and Miller, 1961).

Behavioral Analysis of Drugs as Discriminative Stimuli

The role of dissociative vs. stimulus properties of drugs in the control of discriminative behavior remains unresolved. Confusion arises since the manifestations of these properties should be similar in many cases as indicated by the examples above. Nevertheless, differentiation of these properties at the behavioral level has been attempted.

Overton (1964) trained rats to perform a position habit response in a T-maze under pentobarbital (25 mg/kg) or saline. Speed of relearning in the opposite state from training was identical to acquisi-

tion rates of naive control groups under the same drugs. Absence of transfer between these states indicated that dissociation of learning was essentially complete. Other subjects were then trained to perform a discrimination in a T-maze based on pentobarbital (25 mg/kg) vs. saline. Interference across drug states should have resulted in increased errors on both halves of the discrimination problem relative to errors committed by groups learning the simple position habit response. No interference was detected using this measure, further supporting the initial indication of dissociation between saline and 25 mg/kg pentobarbital.

Using similar testing procedures, Brown et al. (1968) presented evidence that drugs may serve as stimuli without producing dissociation. Chloridiazepoxide (CDP) (15 mg/kg) vs. saline were the cues for a brightness discrimination in a Lashley jumping stand. Simple brightness discriminations were learned by other groups under saline or CDP (15 mg/kg). Simple discriminations were acquired faster than either half of the CDP vs. saline problem, indicating interference between drug states. Nevertheless, a high degree of discriminative control was acquired on the basis of drug cues. In addition, the simple discrimination group underwent reversal training with the drug which they had not received during training. Both groups showed minimal disruption in performance during reversal indicating a strong degree of transfer from the initial drug state.

Furthermore, dose levels of other drugs which fail to produce dissociation in a 2 x 2 design have provided ample stimulus control over discriminated responding in a choice situation. Morrison and Stephenson (1969) established discriminated responding on right vs. left lever in a two lever Skinner box by using doses as low as 0.2 mg/kg nicotine vs. saline as the appropriate cue conditions. A previous study, however, had failed to demonstrate dissociation with a dose of 0.5 mg/kg nicotine (Oliverio, 1968). This comparison may be criticized on the basis of species differences, however, since rats were used in the discrimination task and mice in the test for dissociation between drug states.

Incidental evidence against the dissociation hypothesis is provided in a report by Harris and Balster (1971). Rats could be trained to discriminate right vs. left lever under dl-amphetamine (1 mg/kg) vs. saline with differential reinforcement of low rate (DRL-15) or fixed ratio (FR-50) schedules of reinforcement but not with continuous reinforcement (CRF). If discrimination resulted from the dissociation of habits learned in different drug states, then dissociation should have occurred regardless of the schedule of reinforcement employed. Alternatively, there is the argument that dissociation may be selective for different types of behavior (Bindra and Reichert, 1966), but there is no experimental evidence relevant to the particular case of reinforcement schedule effects.

Another approach to differentiating dissociative vs. stimulus effects is to compare the strength of response control exhibited by drug cues and other types of stimuli. Overton (1964) hypothesized that pentobarbital (15 mg/kg) might be distinguished from saline on the basis of distortion in several sensory modalities, distortion in a single modality, muscle flaccidity, or peripheral autonomic blockade. To test these possibilities the following stimulus pairs were compared for ability to control position responses in a T-maze motivated by shock: "stimulus cocktails" composed of different intensities of light, tone and shock; high vs. low levels of illumination; gallamine (a peripheral muscle relaxant) vs. saline; tetraethylammonium (a quaternary compound which blocks peripheral autonomic activity) vs. saline. In all cases, acquisition was faster under pentobarbital vs. saline cues. Only the stimulus cocktail group reached the same asymptotic level. Overton (1964) concluded that "...a mechanism of control different from the one that allows discriminative cues to control responses..." (p. 10) might be responsible for discriminative control by pentobarbital. Similar results were obtained when different intensity levels of shock were used as cues to test the possible role of drug induced analgesia (Overton, 1968). In the same study a group of blinded rats trained to discriminate pentobarbital (15 mg/kg) from saline showed only a small deficit in comparison to normals, demonstrating the irrelevance of visual cues in this particular discrimination (Overton, 1968). In addition, two-lever discriminations based on dl-amphetamine sulfate

(1 mg/kg) vs. saline or sodium pentobarbital (10 mg/kg) vs. saline have been compared to those based on high vs. low illumination or a 100 hz tone vs. no tone (Balster, 1970). In all cases, discriminations based on drugs were superior to those based on external cues.

Despite these differences, more recent evidence suggests that external and internal stimuli may be similar in their ability to control discriminative behavior (Kilbey et al., 1971). Lever choice based on dl-amphetamine sulfate (1 mg/kg) vs. saline was compared to that produced by tactile stimuli, i.e., a patterned plexiglass floor vs. the grid floor of the operant chamber. Rates of acquisition and reversal were comparable for both types of stimuli. The authors concluded "...that it is possible to select external stimuli which are comparable to internal stimuli in terms of effectiveness..." and that lever discriminations based upon these stimuli could be "...expected to vary in the same way as a function of experimental manipulation" (p. 768).

Pharmacological Analysis of Drugs as Discriminative Stimuli

An alternative approach to resolving the issue of dissociative vs. sensory mechanisms is to analyze response control by drugs at the pharmacological level. A large number of alternatives must be considered, however, since any drug produces multiple pharmacological effects. The number of possible mechanisms may be decreased by determining whether the relevant locus of action is in the periphery or CNS. Resolution in favor of peripheral mechanisms would essentially

eliminate the possibility of dissociation of learning. Validation of a central mechanism would not directly implicate either sensory or dissociative functions, but would at least narrow the number of possibilities. Information regarding the locus of action may be obtained a) by comparing a drug which fails to cross the blood-brain barrier with its centrally active counterpart or b) by comparing pharmacologically related drugs which affect the CNS in varying degrees but have similar peripheral effects. In both types of comparisons equivalent behavioral control is indicative of peripheral mechanisms while superior control by drugs with greater CNS efficacy indicates central mechanisms.

Evidence to date suggests a central locus of action in control of discriminative behavior by drugs. Agents such as dl-amphetamine (Overton, 1971; Harris and Balster, 1971), sodium pentobarbital (Overton, 1964) chlordiazepoxide (Harris and Balster, 1971) and others which exhibit central activity acquire response control much more rapidly than drugs which do not cross the blood-brain barrier (e.g., atropine methyl nitrate, gallamine, etc.). Some of the latter drugs acquire response control with extensive training, but their effectiveness is considerably diminished in comparison to centrally active drugs.

Rates of acquisition have been compared for discriminations based on atropine sulfate (25 mg/kg) vs. saline and atropine methyl nitrate (40 mg/kg) vs. no drug (Overton, 1971). Atropine methyl nitrate, a quaternary derivative of atropine, exhibits comparable antimuscarinic effects in the periphery but is relatively inactive in the CNS when

administered intraperitoneally (Innes and Nickerson, 1970-b). The atropine vs. saline group began criterion performance after a mean of 9.5 training sessions. The atropine methyl nitrate vs. no drug group required a mean of 41 training sessions. A comparable number of sessions was required by another group which received atropine sulfate (2.5 mg/kg) vs. saline as cues. These results have been confirmed by other investigators who report strong response control by atropine sulfate (10 mg/kg) vs saline in a two-lever choice discrimination, but no control by atropine methyl nitrate (10 mg/kg) vs. saline in the same number of trials (Harris and Balster, 1971).

More cogent evidence has been presented for a central locus of action in discriminations based on nicotine (0.2, 1.0, 1.5 and 2.0 mg/kg) vs. saline. Following acquisition of a two-lever approach-avoidance discrimination, generalization tests were conducted with the training drugs after pretreatment with anti-nicotinic blocking agents. Chlorisondamine which does not cross the blood-brain barrier failed to affect performance based on nicotine or saline. Mecamylamine, a blocking agent with central as well as peripheral effects, selectively disrupted performance based on nicotine (Morrison and Stephenson, 1969). Mecamylamine produced similar disruption of a T-maze position discrimination based on nicotine (0.4 mg/kg) vs. saline while hexamethonium, a quaternary anti-nicotinic agent, did not alter performance (Schechter and Rosecrans, 1971).

CHAPTER III

STATEMENT OF THE PROBLEM

The present study was conducted to determine whether a central or peripheral locus of control could be implicated in behavioral discriminations based on amphetamine vs. saline. Rats in three treatment groups were trained to discriminate d-amphetamine sulfate (0.8 mg/kg, ip), l-amphetamine sulfate (0.8 mg/kg, ip) or para-hydroxyamphetamine hydrobromide (1.01 mg/kg, ip) from saline in a modification of the two-lever choice paradigm reported by Harris and Balster (1971).

In the periphery, d- and l-amphetamine are equipotent with the exception that l-amphetamine produces slightly greater cardiovascular effects (Innes and Nickerson, 1970-a). In the CNS, however, d-ampnetamine is consistently more potent than l-amphetamine. d-Amphetamine is three to four times as potent as the l- isomer in eliciting CNS excitatory effects (Innes and Nickerson, 1970-a), up to ten times as potent in blocking norepinephrine (NE) reuptake (Taylor and Snyder, 1970) and three to five times as potent in its ability to deplete NE in the CNS (Moore, 1963; Lewander, 1971-b; Clay et al., 1971). d-Amphetamine also accelerates turnover rates of dopamine (DA) while l-amphetamine is without effect at doses three times greater than the threshold for the d-antipode (Costa et al., 1971). With regard to centrally mediated behaviors, d-amphetamine is ten times more potent in enhancing loco-

motor activity and twice as effective in producing stereotypies (Taylor and Snyder, 1970).

Para-hydroxy-amphetamine is equipotent with d-amphetamine in the periphery (Brodie, et al., 1970), but lacks CNS activity almost entirely when administered systemically (Innes and Nickerson-a, 1970). Hydroxylation of the ring causes a large reduction in lipid solubility (Vree et al., 1970) thereby preventing para-hydroxy-amphetamine from crossing the blood-brain barrier. According to Lewander (1971-a) a maximum of 0.012% of injected radioactivity was found per gram of brain tissue at 4/hours after administration of para-hydroxy-amphetamine, i.p. In comparison, a peak level of about 0.7% of the dose was found per gram of brain at 30 minutes after an amphetamine injection at the same dose level (Lewander, 1971-b). The inability of systemically administered para-hydroxy-amphetamine (up to 100 mg/kg) to produce stereotypies in the rat which can be reliably produced by its intracerebral injection (Fog and Pakkenberg, 1971) or by 10 mg/kg d-amphetamine, i.p. (Randrup and Munkvad, 1970) is further evidence for its inability to cross the blood-brain barrier.

Based on the pharmacological differences between these drugs, the following hypotheses were suggested: a) operation of a peripheral mechanism in response control should result in equivalent acquisition rates and asymptotic levels for all groups; b) central mechanisms should produce different acquisition rates and/or different asymptotic levels with superior control by d-amphetamine vs. saline and minimal control by p-hydroxyamphetamine vs. saline.

In the interest of observing acquisition of a d-amphetamine vs. saline discrimination under conditions of minimal peripheral stimulation, an additional group was originally proposed which would have received pretreatment with phentolamine hydrochloride on all training days. d-Amphetamine acts in the periphery as a sympathomimetic agent by facilitating the release of norepinephrine (NE) from postganglionic sympathetic nerve terminals. The resultant effects are due to the interaction of NE with alpha- and beta-adrenergic receptors. Phentolamine selectively blocks alpha-adrenergic receptors (Nickerson, 1970), and is therefore capable of reducing the peripheral effects of d-amphetamine when administered in suitable doses prior to the administration of amphetamine.

In the present study a subcutaneous route of administration for phentolamine was chosen since other investigators had reported successful blocking of amphetamine effects and no adverse side effects with single injections by this route (Cahn and Herold, 1970). Nevertheless, daily injections resulted in the delayed appearance of gross lesions of the skin and a general deterioration of physical condition. Therefore, six subjects were dropped from the experiment.

In order to compensate for the loss of this group in the overall design, an additional experimental phase followed acquisition for the remaining groups. Generalization tests similar to those reported by Morrison and Stephenson (1969) and Schechter and Rosecrans (1971) were

conducted to test for control by the training drugs and saline after pretreatment with an effective adrenolytic dose of phentolamine hydrochloride (10 mg/kg, iv) (Barnes and Eltherington, 1966).

CHAPTER IV

METHODS

Subjects

Eighteen naive male Sprague-Dawley rats (300-400 gm) obtained from Texas Inbred Mice Co. served as Ss. Throughout the study Ss were individually housed and ad lib water was available in the home cage. Purina Rat Chow was fed after daily experimental sessions in quantities adjusted to maintain individual Ss between 80-85% of normal ad lib body weight. Subjects were weighed daily immediately prior to experimental sessions.

Apparatus

Five operant chambers (Scientific Prototype, Model A-100) enclosed in sound attenuating chambers (Scientific Prototype, Model SPC-300) equipped with fans to circulate fresh air were used for behavioral training and testing. Two operant levers (Scientific Prototype, Model PLS-100) separated by three inches were mounted on the manipulandum panel approximately one inch above the grid floor of the operant chamber. A brass food tray located on the panel between the levers was connected to a pellet dispenser (Foringer, Model PDC) situated behind the panel. Reinforcement consisted of single 45 mg Noyes pellets (Standard Formula). A 7-watt house light provided illumination. All behavioral contingencies and data collection were con-

trolled by solid state programming equipment (Grason-Stadler 1200 Series) located in the same room. Cumulative recorders (Gerbrans, Model G3) were used during extinction test sessions.

Drug Preparation

Injection solutions of d- and l-amphetamine sulfate and para-hydroxy-amphetamine hydrobromide (Smith, Kline and French Laboratories) were made by dissolving the salt crystals in physiological saline (Sodium Chloride Injection USP, Travenol Laboratories) at a concentration of 0.8 mg/ml for d- and l-amphetamine sulfate and 1.01 mg/ml for para-hydroxy-amphetamine hydrobromide. Drug and control injections (physiological saline) were given intraperitoneally in volumes of 1 ml/kg resulting in appropriate doses of d- and l-amphetamine sulfate (0.8 mg/kg) and para-hydroxy-amphetamine hydrobromide (1.01 mg/kg). Such doses are equimolar across drugs and equivalent in ml/kg for all drugs and saline.

Phentolamine hydrochloride (CIBA) was prepared by dissolving the salt in physiological saline at 10 mg/ml. The sealed vial in which the salt was dissolved was heated with running tap water to facilitate complete dissolution of the crystals. Solutions of phentolamine were prepared and used on the same day. Injections were given intravenously at 1 ml/kg resulting in a total dose of 10 mg/kg/injection.

Procedure

Pretraining: On the first day of pretraining Ss were allowed 30 minutes in the operant chamber with noncontingent delivery of food

pellets on a variable interval (VI) schedule of 60 seconds. Reinforcement on a continuous reinforcement (CRF) schedule was also available on one bar during this time. Following magazine training another 30-minute period was allowed with reinforcement available on CRF only. The same procedure was used on day two but the alternate bar was activated. Subjects failing to bar press were further deprived until the pressing response appeared. They were then allowed experience on both bars comparable to that received by the other Ss. Magazine training was discontinued and daily sessions limited to 30 minutes. Two additional days on each bar under CRF were allowed. A differential reinforcement of low rate (DRL) schedule was then introduced. Four days on each bar under DRL-10 seconds were followed by four days on each bar under DRL-15 seconds. In order to prevent chaining of responses between levers on DRL, responses on the incorrect lever reset the DRL interval timer. DRL-15 seconds (unlimited hold) served as the schedule of reinforcement throughout the remainder of the experiment. Due to a delay in drug shipment, the Ss received no further training during the following twelve days.

Training and Extinction Testing: Subjects were randomly assigned to three groups (N = 6) which received either d-amphetamine, l-amphetamine or para-hydroxy-amphetamine in opposition to saline as the appropriate drug cues. These will be designated as the "d-A", "l-A" and "p-OH-A" groups respectively.

An equal number of Ss in each group received daily injections of drug or saline fifteen minutes prior to placement in their assigned operant chambers. For a given S, one lever was reinforced exclusively under the drug (D) state and the other lever only in the nondrug (N) state. The same lever was reinforced for all Ss on a given day. Thirty-minute training sessions were given daily. On day one and every fourth day thereafter, a ten-minute extinction test preceded the regular training session. During all sessions total responses on each lever and total reinforcements were recorded on digital counters. Cumulative records were kept during extinction sessions.

The right (R) and left (L) levers were activated across four-day blocks in one of the following patterns: RLRL, LRLR, LRRL, RLLR. The semi-random lever sequence used during training (Table II) resulted in an equal number of extinction tests in which the drug state was the same or different from the one imposed on the previous day. In addition, each S received half of the eight extinction tests under D and half under N conditions.

Generalization Testing: Following completion of training, all groups demonstrating stimulus control were subjected to two extinction sessions preceded by phentolamine hydrochloride (10 mg/kg, iv) injections. Drug or saline injections were administered fifteen minutes after phentolamine and fifteen minutes prior to the beginning of the extinction session. No additional training occurred on these test days.

TABLE II

LEVER SEQUENCE DURING ACQUISITION

Day	Lever	Day	Lever
1	R*	15	L
1	R	16	R
2	L	17	L*
3	L	17	L
4	R	18	R
5	L*	19	L
5	L	20	R
6	R	21	R*
7	R	21	R
8	L	22	L
9	R*	23	L
9	R	24	R
10	L	25	R*
11	R	25	R
12	L	26	L
13	L*	27	L
13	L	28	R
14	R	29	L*

*Extinction Sessions

One normal training session on each bar preceded each test. The correct test bar was designated as the opposite bar from the previous day of training and the drug condition previously paired with that bar was imposed.

An additional extinction test with the training drugs was conducted to insure that control by the original drug cues had been maintained during this phase. The scores obtained on this test plus the eighth extinction test were compared to the phentolamine test scores. The sequence of session for this phase are presented in Table III.

TABLE III

LEVER SEQUENCE DURING GENERALIZATION TESTING

Day	Lever
1	L*
1	L
2	R
3	L**
4	R
5	L
6	R**
7	R
8	L
9	R*

*Extinction under training drugs with no pretreatment.

**Extinction under training drugs with phentolamine pretreatment.

CHAPTER V

RESULTS

Acquisition

A dose level of 2 mg/kg d-amphetamine calculated as the base was initially selected for use in this study. This dose, which is equivalent to 3.42 mg/kg d-amphetamine sulfate calculated as the salt, inhibited bar pressing in 4 subjects upon first administration. A lower dose, 1.71 mg/kg d-amphetamine sulfate, disrupted behavior in 2 subjects. Finally, 0.8 mg/kg d-amphetamine sulfate, a dose reported to accelerate bar pressing in rats on DRL-20 (Morrison, 1968) was administered. No disruption occurred and this dose was employed throughout the study. l-Amphetamine sulfate was administered at the same dosage (0.8 mg/kg) and para-hydroxy-amphetamine hydrobromide was equated on a molar basis at 1.01 mg/kg. Training sessions in which behavioral disruption occurred were repeated under the adjusted dosage. Due to this disruption, data from the first extinction test were not included in the statistical analysis.

Extinction test data for each S were converted into the proportion of cue-appropriate responses for each test. Data from seven tests were organized in a groups x trials design for analysis of variance. The cell means for this analysis are presented graphically in Figure I. Preliminary tests for homogeneity of variance were calculated

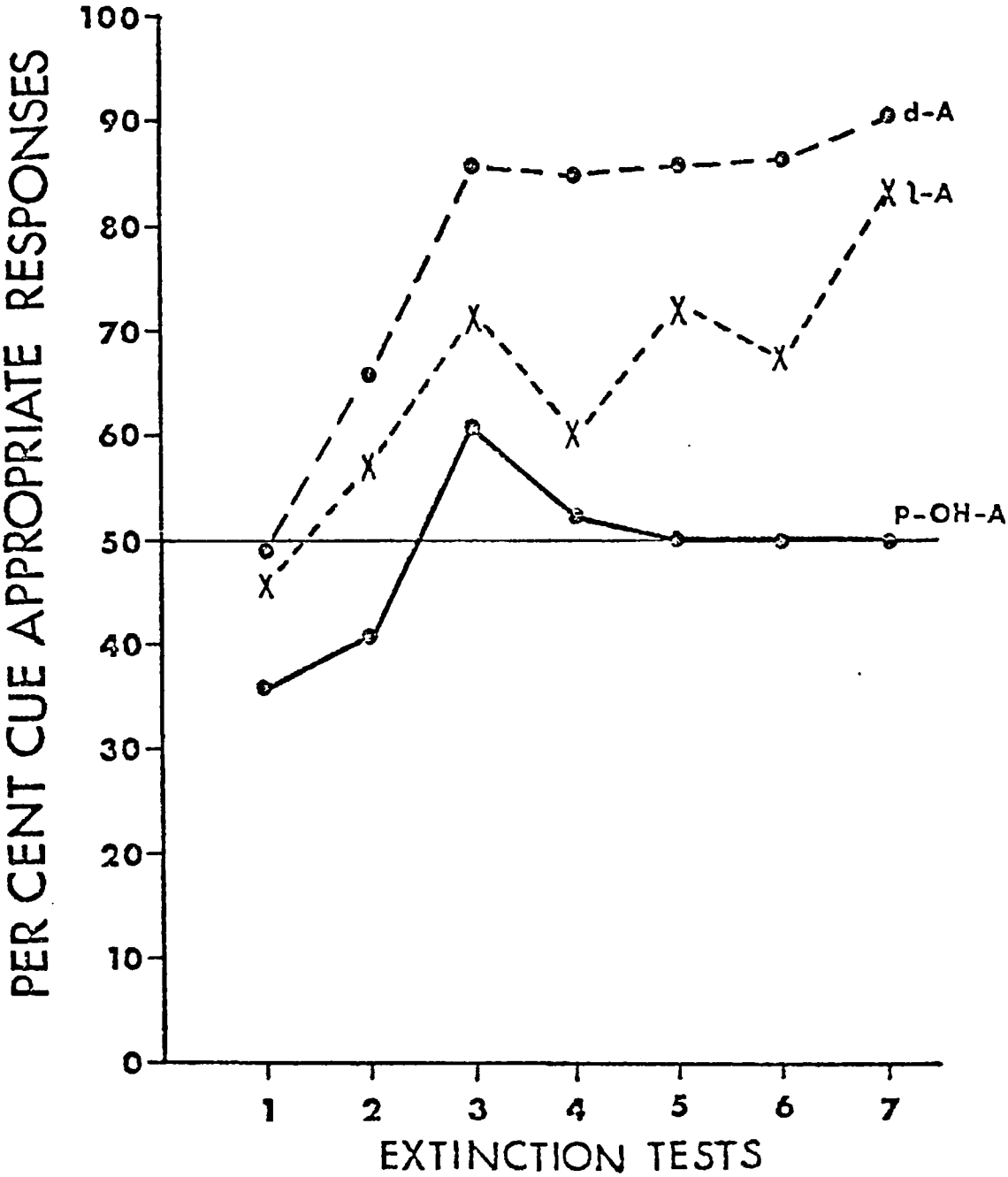

Figure 1

ACQUISITION OF RESPONSE CONTROL

for subjects within groups and trials x subjects within groups. Hartley's test (Winer, 1962) yielded nonsignificant results for both terms respectively ($F_{max\ (3,41)} = 2.14$, p .05 and $F_{max\ (21,5)} = 17.23$, p .05) supporting the assumption of homogeneity of variance. The results of the analysis of variance are presented in Table IV. Groups and trials factors were both highly significant; the groups x trials interaction was nonsignificant. In order to further analyze the relationship between groups, individual comparisons for treatment groups were calculated using the Newman-Keuls procedure (Winer, 1962). The results are presented in Table V. All groups were significantly different from one another with the d-A group exhibiting superior performance, the l-A group demonstrating performance at an intermediate level and the p-OH-A group showing no response control.

Generalization Tests

Results from generalization tests were expressed as proportion of responses appropriate to the training drug injected. Scores from tests under saline or drug alone were compared to scores from tests under saline or drug with phentolamine hydrochloride pretreatment. In some cases phentolamine disrupted behavior by reducing the total number of responses during extinction tests. When less than 10 responses occurred, data were discarded. A two-tailed t-test for correlated observations (Winer, 1962) was run on scores collected under pretreatment or no pretreatment for each group of Ss under its training drug and saline. Only one test reached the .05 level of

TABLE IV

SUMMARY TABLE FOR ANALYSIS OF VARIANCE

Source	SS	df	MS	F
Between Subjects	22,390.00	17		
A (groups)	18,492.42	2	9,246.21	35.58*
Subjects within groups	3,897.58	15	259.84	
Within Subjects	32,015.71	108		
B (trials)	13,618.04	6	2,269.67	13.06*
AB	2,755.58	12	229.63	1.32^{ns}

*$p < .01$

ns - nonsignificant

TABLE V

NEWMAN-KEULS TEST FOR

INDIVIDUAL COMPARISONS BETWEEN GROUPS

	p-OH-A	l-A	d-A
p-OH-A		*	*
l-A			*
d-A			

*p < .01

significance (saline vs. phentolamine + saline for the 1-A group). In order to test the possibility that disruption was produced by transfer of the drug-correct response to phentolamine, an additional comparison was made by converting the phentolamine + saline (1-A group) test scores to proportion of responses on the drug-correct bar and calculating a t-test between the 1-A and phentolamine + saline (1-A group) scores. This comparison was also significant at the .05 level. The results of all tests on generalization data are presented in Table VI.

TABLE VI

EFFECTS OF PHENTOLAMINE PRETREATMENT ON THE PROPORTION OF CUE-APPROPRIATE RESPONSES UNDER SALINE AND DRUG CONDITIONS

Groups	Conditions Compared	Means and SD	df	t_{obs}
p-OH-A	saline	43.80 ± 18.74		
	vs.		4	0.45^{ns}
	phentolamine + saline	53.00 ± 30.73		
p-OH-A	p-OH-A	49.75 ± 7.68		
	vs.		3	1.07^{ns}
	phentolamine + saline	34.25 ± 21.93		
l-A	saline	75.50 ± 16.25		
	vs.		5	2.63*
	phentolamine + saline	41.33 ± 23.54		
l-A	l-A	74.50 ± 16.22		
	vs.		3	-0.59^{ns}
	phentolamine + l-A	80.00 ± 13.95		
l-A	l-A	74.50 ± 16.22		
	vs.		5	3.45*
	phentolamine + saline (drug appropriate responses)	58.67 ± 23.54		
d-A	saline	88.83 ± 10.91		
	vs.		5	0.11^{ns}
	phentolamine + saline	88.50 ± 14.25		
d-A	d-A	96.25 ± 2.63		
	vs.		3	2.34^{ns}
	phentolamine + d-A	76.75 ± 14.17		

ns - nonsignificant

*$p \leq .05$

CHAPTER VI

DISCUSSION

The importance of amphetamine's central activity in response control is clearly indicated by two aspects of the acquisition data. First, response control exhibited by d- and l-amphetamine is totally lacking in the case of para-hydroxy-amphetamine, a chemical derivative with equivalent peripheral activity but scant central activity. Second, d-amphetamine exhibits control superior to that produced by l-amphetamine, an optical isomer with equivalent peripheral activity but less potency in the CNS. These two points present a strong case for the necessity of central activity in the development of response control by d-amphetamine and further support the conclusions of other investigators that central activity plays a crucial role in behavioral control by pharmacological agents in general.

The results of generalization tests with phentolamine are less conclusive but do not contradict the acquisition data. Disruption of behavioral discrimination by phentolamine was statistically significant in only one case. The ability of the l-A group to discriminate the saline condition was impaired with responding biased toward the drug appropriate lever. This bias, however, was not strong enough to justify the assumption that phentolamine was identified as l-amphetamine. Disruption also occurred to a lesser degree when

phentolamine preceded the administration of d-amphetamine, but the differences between the pretreated and nonpretreated conditions did not reach significance. It is not at all clear why phentolamine should disrupt saline performance for the l-A group but not for the d-A group. Possibly, the effects of phentolamine per se, without relation to the specific drugs involved in discriminative training, are responsible for the effects produced. Phentolamine produces an initial period of behavioral depression after administration by the intravenous route at the dose level employed (10 mg/kg). This depression results from the initial rapid decrease in blood pressure mediated by phentolamine in the periphery and is probably responsible for the lack of responding in some animals during extinction testing. Individual differences in sensitivity to the effects of phentolamine may also have contributed to the results of comparisons between pretreated and nonpretreated conditions. Since the behavioral depression caused by phentolamine is relatively transient whereas the blocking properties endure for approximately four hours (i) it might have been possible to clarify the results of these tests by repeated testing using a longer interval between phentolamine pretreatment and injection of the training drugs. This procedure could not be completed on the animals trained for this experiment since intravenous injections resulted in collapsed tail veins in most of the Ss. The possible significance of phentolamine produced disruption of discriminated

behavior under the control of d-amphetamine and its derivatives requires further investigation before any definitive statements can be made regarding the specificity of its actions.

With regard to mechanistic implications, the results of the present study can only suggest directions for future research. In the case of d-amphetamine, a drug whose pharmacological properties have been extensively investigated, further delineation of response control mechanisms might be profitably pursued at the pharmacological level. For example, comparisons between different dose levels of the d- and l- isomers may suggest possible mechanisms on the basis of information already available concerning their relative potencies. The use of blocking agents such as phenoxybenzamine, a centrally active alpha-adrenergic blocker, and propranol, a centrally active beta-adrenergic blocker, may also shed light on the mechanisms under consideration. Other means of analysis would include blocking the synthesis of dopamine (DA) and/or NE, blocking the activity of DA in the CNS and selective degeneration of dopaminergic and/or noradrenergic neurons in the CNS by intraventricular administration of 6-hydroxy-dopamine. Specification of pharmacological mechanisms might in turn suggest directions for investigations at the neuroanatomical level since the brain is heterogeneous in respect to many forms of pharmacological and biochemical reactivity.

BIBLIOGRAPHY

Amsel, A. Selective association and the anticipatory goal response mechanisms as explanatory concepts in learning theory. Journal of Experimental Psychology, 1949, 39, 785-789.

Balster, R. L. The effectiveness of external and drug produced internal stimuli in the discriminative control of operant behavior. Unpublished doctoral dissertation, University of Houston, 1970.

Barnes, C. D. and Eltherington, L. G. Drug doses in laboratory animals: a handbook. Los Angeles: University of California Press, 1966.

Barry, H. Prolonged measurements of discrimination between alcohol and nondrug states. Journal of Comparative and Physiological Psychology, 1968, 65, 349-352.

Barry, H. and Kubena, R. K. Discriminative stimulus characteristics of alcohol, marihuana and atropine. In J. M. Singh, L. H. Miller and H. Lal (Eds.) Drug addiction: experimental pharmacology: volume I. Mount Kosco, New York: Futura Publishing Company, 1972. Pp. 3-16.

Belleville, R. E. Control of behavior by drug-produced internal stimuli. Psychopharmacologia, 1964, 5, 95-105.

Bindra, D. and Reichert, H. Dissociation of movement initiation without dissociation of response choice. Psychonomic Science, 1966, 4, 95-96.

Brodie, B. B., Cho, A. K. and Gessa, G. L. Possible role of p-hydroxynorepinephrine in the depletion of norepinephrine induced by d-amphetamine and in tolerance to this drug. In E. Costa and S. Garattini (Eds.) International symposium on amphetamines and related compounds. New York: Raven Press, 1970, Pp. 217-230.

Brown, A., Feldman, R. S. and Moore, J. W. Conditional discrimination learning based upon chlordiazepoxide: dissociation of cue? Journal of Comparative and Physiological Psychology, 1968, 66, 211-215.

Bykov, K. M. (translated by W. H. Gantt) The cerebral cortex and the internal organs. New York: Chemical Publishing Company, 1957.

Cahn, J. and Herold,M. Effects of amphetamine in rats and rabbits injected with alpha- and beta-adrenergic blocking agents. In E. Costa and S. Garrattini (Eds.) International symposium on amphetamines and related compounds. New York: Raven Press, 1970. Pp. 493-510.

Clay, G. A., Cho, A. K. and Roberfroid, M. Effect of diethylaminoethyl diphenylpropylacetate hydrochloride (SKF-525A) on the norepinephrine-depleting actions of d-amphetamine. Biochemical Pharmacology, 1971, 20, 1821-1831.

Collins, K. H. and Tatum, A. L. A conditioned reflex established by chronic morphine poisoning. American Journal of Physiology, 1925, 74, 14-15.

Conger, J. J. The effects of alcohol on conflict behavior in the albino rat. Quarterly Journal of Studies on Alcohol, 1951, 12, 1-29.

Costa, E., Naimzada, M. K. and Revuelta, A. Pharmacological implications of the effects of amphetamine and its analogs on the turnover rate of tissue catecholamines. In B. T. Ho and W. M. McIsaac (Eds.) Brain chemistry and mental disease; advances in behavioral biology: volume I. New York: Plenum Press, 1971.

DeVietti, T. L. and Larson, R. C. ECS effects: evidence supporting state dependent learning in rats. Journal of Comparative and Physiological Psychology, 1971, 74, 407-415.

Fog, R. and Pakkenberg, H. Behavioral effects of dopamine and p-hydroxyamphetamine injected into corpus striatum of rats. Experimental Neurology, 1971, 31, 75-86.

Girden, E. Cerebral mechanisms in conditioning under curare. American Journal of Psychology, 1940, 53, 397-406.

Girden, E. The dissociation of blood pressure conditioned responses under erythroidine. Journal of Experimental Psychology, 1942-a, 31, 219-231.

Girden, E. The dissociation of pupillary conditioned responses under erythroidine. Journal of Experimental Psychology, 1942-b, 31, 322-332.

Girden, E. and Culler, E. Conditioned responses in curarized striate muscle in dogs. Journal of Comparative Psychology, 1937, 23, 261-274.

Grossman, S. P. and Miller, N. E. Control for stimulus-change in the evaluation of alcohol and chlorpromazine as fear-reducing drugs. Psychopharmacologia, 1961, 2, 342-351.

Harris, R. T. and Balster, R. L. Discriminative control by dl-amphetamine and saline of lever choice and response patterning. Psychonomic Science, 1968, 10, 105-106.

Harris, R. T. and Balster, R. L. An analysis of psychological dependence. In R. T. Harris, W. M. McIsaac and C. R. Schuster (Eds.) Advances in mental sciences: volume II: drug dependence. Austin: University of Texas Press, 1970. Pp. 214-226.

Harris, R. T. and Balster, R. L. An analysis of the function of drugs in the stimulus control of operant behavior. In T. Thompson and R. Pickens (Eds.) Stimulus properties of drugs. New York: Appleton-Century-Crofts, 1971. Pp. 111-132.

Henriksson, B. G. and Jarbe, T. Delta-9-tetrahydrocannabinol used as discriminative stimulus for rats in position learning in a T-shaped water maze. Psychonomic Science, 1972, 27, 25-26.

Hill, H. E., Jones, B. E. and Bell, E. C. State dependent control of discrimination by morphine and pentobarbital. Psychopharmacologia, 1971, 22, 305-313.

Hirschhorn, I. D. and Winter, J. C. Mescaline and Lysergic acid diethylamide (LSD) as discriminative stimuli. Psychopharmacologia, 1971, 22, 64-71.

Hull, C. L. Differential habituation to internal stimuli in the albino rat. Journal of Comparative Psychology, 1933, 16, 255-273.

Hunt, H. F. Unconditioned stimulus functions of drugs: interpretations: I. In T. Thompson and R. Pickens (Eds.) Stimulus properties of drugs. New York: Appleton-Century-Crofts, 1971. Pp. 73-78.

Innes, I. R. and Nickerson, M. Drugs acting on postganglionic adrenergic nerve endings and structures innervated by them (sympathomimetic drugs). In L. S. Goodman and A. Gilman (Eds.) The pharmacological basis of therapeutics, 4th edition. New York: The MacMillan Company. 1970-a. Pp. 478-523.

Innes, I. R. and Nickerson, M. Drugs inhibiting the action of acetylcholine on structures innervated by postganglionic parasympathetic nerves (antimuscarinic or atropinic drugs). In L. S. Goodman and A. Gilman (Eds.) The pharmacological basis of therapeutics, 4th edition. New York: The MacMillan Company, 1970-b. Pp. 524-548.

Kety, S. S. Chemical boundaries of psychopharmacology. In S. M. Farber and R. H. Wilson (Eds.) Control of the mind. New York: McGraw-Hill, 1961. Pp. 79-91.

Kilbey, M. M., Harris, R. T. and Aigner, T. G. Establishment of equivalent external and internal stimulus control of an operant behavior and its reversal. Proceedings, 79th Annual Convention, American Psychological Association, 1971, 767-768.

Kleitman, N. and Crisler, G. A quantitative study of a salivary conditioned reflex. American Journal of Physiology, 1927, 79, 571-614.

Kubena, R. K. and Barry, H. Two procedures for training differential responses in alcohol and nondrug conditions. Journal of Pharmaceutical Sciences, 1969-a, 58, 99-101.

Kubena, R. K. and Barry, H. Generalization by rats of alcohol and atropine stimulus characteristics to other drugs. Psychopharmacologia, 1969-b, 15, 196-206.

Kubena, R. K. and Barry, H. Stimulus characteristics of marihuana components. Nature, 1972, 235, 397-398.

Lashley, K. S. The effect of strychnine and caffeine upon rate of learning. Psychobiology, 1917, 1, 141-170.

Leeper, R. The role of motivation in learning: a study of the phenomenon of differential motivational control of the utilization of habits. Journal of Genetic Psychology, 1935, 46, 3-40.

Lewander, T. Displacement of brain and heart noradrenaline by p-hydroxynorephedrine after administration of p-hydroxyamphetamine. Acta Pharmacologica et Toxicologica, 1971-a, 29, 20-32.

Lewander, T. On the presence of p-hydroxynorephedrine in the rat brain and heart in relation to changes in catecholamine levels after administration of amphetamine. Acta Pharmacologica et Toxicologica, 1971-b, 29, 33-48.

MacCorquodale, K. Reinforcing stimulus functions of drugs: interpretations: II. In T. Thompson and R. Pickens (Eds.) Stimulus properties of drugs. Pp. 215-217. New York: Appleton-Century-Crofts, 1971.

McIntyre, D. C. and Reichert, H. State-dependent learning in rats induced by kindled convulsions. Physiology and Behavior, 1971, 7, 15-20.

Miller, N. E. Theory and experiment relating psychoanalytic displacement to stimulus-response generalization. J. Abnormal & Social Psychology 1948, 43, 155-178.

Moore, K. E. Toxicity and catecholamine releasing action of d- and l-amphetamine in isolated and aggregated mice. Journal of Pharmacology and Experimental Therapeutics, 1963, 142, 6-12.

Morrison, C. F. A comparison of the effects of nicotine and amphetamine on DRL performance in the rat. Psychopharmacologia, 1968, 12, 176-180.

Morrison, C. F. and Stephenson, J. A. Nicotine injections as the conditioned stimulus in discrimination learning. Psychopharmacologia, 1969, 15, 351-360.

Nickerson, M. Drugs inhibiting adrenergic nerves and structures innervated by them. In L. S. Goodman and A. Gilman (Eds.) The pharmacological basis of therapeutics, 4th edition. New York: The MacMillan Company, 1970. Pp. 549-584.

Oliverio, A. Effects of scopolamine on avoidance conditioning and habituation of mice. Psychopharmacologia, 1968, 12, 214-226.

Overton, D. A. Discriminative behavior based on the presence or absence of drug effects. American Psychologist, 1961, 16, 453-454.

Overton, D. A. State-dependent or "dissociated" learning produced with pentobarbital. Journal of Comparative and Physiological Psychology, 1964, 57, 3-12.

Overton, D. A. State-dependent learning produced by depressant and atropine-like drugs. Psychopharmacologia, 1966, 10, 6-31.

Overton, D. A. Differential responding in a three choice maze controlled by three drug states. Psychopharmacologia, 1967, 11, 376-378.

Overton, D. A. Visual cues and shock sensitivity in the control of T-maze choice by drug conditions. Journal of Comparative and Physiological Psychology, 1968, 66, 216-219.

Overton, D. A. Control of T-maze choice by nicotinic, antinicotinic, and antimuscarinic drugs. Proceedings, 77th Annual Convention, American Psychological Association, 1969.

Overton, D. A. Discriminative control by drug states. In T. Thompson and R. Pickens (Eds.) Stimulus properties of drugs. New York: Appleton-Century-Crofts, 1971. Pp. 87-110.

Overton, D. A. State-dependent learning produced by alcohol and its relevance to alcoholism. In B. Kossen and H. Begleiter (Eds.) The biology of alcoholism: volume II: physiology and behavior. New York: Plenum Press, 1972. Pp. 193-217.

Randrup, A. and Munkvad, I. Biochemical, anatomical and psychological investigations of stereotyped behavior induced by amphetamines. In E. Costa and S. Garrattini (Eds.) International symposium on amphetamines and related compounds. New York: Raven Press, 1970. Pp. 695-714.

Schechter, M. D. and Rosecrans, J. A. C.N.S. effect of nicotine as the discriminative stimulus for the rat in a T-maze. Life Sciences, 1971, 10, 821-832.

Schechter, M. D. and Rosecrans, J. A. Atropine antagonism of arecoline-cued behavior in the rat. Life Sciences, 1972, 11, 517-523.

Schuster, J. V. and Brady, C. R. The discriminate control of a food-reinforced operant by interoceptive stimulation. In T. Thompson and R. Pickens (Eds.) Stimulus properties of drugs. New York: Appleton-Century-Crofts, 1971. Pp. 133-148.

Spear, N. E., Klein, S. B. and Riley, E. P. The Kamin effect as "state-pendent learning": memory-retrieval failure in the rat. Journal of Comparative and Physiological Psychology, 1971, 74, 416-425.

Stewart, J. Differential responses based on the physiological consequences of pharmacological agents. Psychopharmacologia, 1962, 3, 132-138.

Storm, T. and Smart, R. G. Dissociation: a possible explanation of some features of alcoholism and implications for its treatment. Quarterly Journal of Studies on Alcohol, 1965, 26, 111-115.

Taylor, K. M. and Snyder, S. H. Amphetamine: differentiation by d- and l- isomers of behavior involving brain norepinephrine and dopamine. Science, 1970, 168, 1487-1489.

Thompson, T. Drugs as reinforcers: experimental addiction. International Journal of the Addictions, 1968, 3, 199-206.

Thompson, T. and Pickens, R. (Eds.) Stimulus properties of drugs. New York: Appleton-Century-Crofts, 1971.

Vree, T. B., Muskens, A. T. and Van Rossum, J. M. Some physiochemical properties of amphetamine and related drugs. Journal of Pharmacy and Pharmacology, 1969, 21, 774-775.

Waters, W. H., Richards, D. W. and Harris, R. T. Discriminative control and generalization of the stimulus properties of dl-amphetamine in the rat. In J. M. Singh, L. H. Miller and H. Lal (Eds.) Drug addiction: experimental pharmacology: volume I. Mount Kisco, New York: Futura Publishing Company, 1972. Pp. 3-16.

Wikler, A. Interaction of physical dependence and classical and operant conditioning in the genesis of relapse. Research Publication of the Association for Research in Nervous and Mental Disease, 1968, 46, 280-287.

Winer, B. J. Statistical principles in experimental design. New York: McGraw-Hill, 1962.

FOOTNOTES

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(i) Hill, H. H., Smith, Klein and French Laboratories, personal communication, August, 1972.