A BEHAVIORAL ANALYSIS OF HALLUCINOGENIC DRUGS

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ABSTRACT

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By

William James Marquis

The results from these studies indicate that operant conditioning paradigms can be a useful tool for characterizing hallucinogenic properties of psychoactive drugs as well as for differentiating agents within the hallucinogenic drug class. Furthermore, these schedules provided a practical means for assessing tolerance phenomena and cross-tolerance relationships between hallucinogenic drugs since the results derived from these experiments with rats as experimental subjects correlated well with data derived from human studies. Finally, the utilization of these schedules for drug interaction experiments provided data that may well be useful for ascertaining the mechanisms of action of hallucinogenic drugs. Since these techniques yielded unique behavioral profiles for hallucinogens they should prove useful in psychiatric research for testing endogenous compounds that are potentially instrumental in initiating naturally occurring psychosis.

The results from Section I indicate that DOM, a catecholamine-like hallucinogenic agent could be differentiated behaviorally from the indoleamine type hallucinogens, LSD and psilocybin. The behavioral profiles induced by DOM on

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DRL, FI and Sidman-Avoidance paradigms resembled those seen following d-amphetamine over a wide dose range. At the highest dose tested in DRL and FI paradigms, DOM resembled LSD and psilocybin. Additional behavioral similarities between DOM and d-amphetamine were noted in Section II. The development of a unidirectional cross-tolerance between these agents on both FR and DRL paradigms further confirmed the likelihood that they shared to some extent common mechanisms of action in the central nervous system. Finally, it was demonstrated in Section III that the stimulation of Sidman-Avoidance responding induced by either DOM or d-amphetamine was identically attenuated by AMPT pretreatment. These findings and the fact that AMPT pretreatment failed to attenuate the pause induced by DOM on an FR, whereas cinanserin (a 5-HT receptor blocking agent) did, indicated that the amphetamine-like stimulation induced by DOM was probably mediated by catecholamines, whereas the hallucinogenic behavioral depression is more likely due to an interaction with a serotonergic mechanism.

Studies investigating the effects of repeated administration of hallucinogens revealed that LSD and mescaline produced a rapid and complete tolerance formation on an FR-40 schedule, whereas psilocybin, DOM, DMT and d-amphetamine produced varying degrees of tolerance development and only over a longer period of daily injections. Drug dosage proved to be an important variable as larger doses of hallucinogenic agents consistently

prolonged tolerance development. In addition, the utilization of different schedules in tolerance assessment confirmed a previously reported finding that an animal will only develop tolerance if this development enhances the likelihood of meeting reinforcement requirements. Thus, in these studies, tolerance development to drug-induced disruptions was evident on DRL and FR paradigms, whereas tolerance was not manifested for drug-induced stimulation on the shock avoidance schedule.

The tolerance and cross-tolerance data suggest that the disruption of operant behavior induced by various hallucinogenic agents has a common basis in acting upon some central discriminatory function. There are likely to be several points of attack on this overall system, however, since a complete cross-tolerance was not demonstrable for all combinations tested. The assumption that the hallucinogenic action is exerted through some common pathway, regardless of the specific agent examined, was fortified by the finding that cinanserin is an effective antagonist of mescaline, DMT, LSD, DOM and psilocybin for the hallucinogenic pause in FR performance. Since cinanserin is a specific blocker of 5-HT receptors, it follows that the common factor for the hallucinatory effects would relate to increased activity at central serotonergic receptors. The one-way cross-tolerance relationships for DOM when tested with other agents, however, indicates that perhaps this agent has a wider spectrum of action in the central

nervous system than other hallucinogens and probably involves catecholamine mechanisms as well.

A working hypothesis of the mechanism of hallucinogenic drug action was developed based on the drug interaction studies (Section III): The drugs induce, directly or indirectly, an excessive activation of 5-HT receptors on the seretonergic raphe neurons projecting to the limbic forebrain and thereby markedly suppress the firing rate of the raphe cells. Theories purporting a 5-HT receptor antagonist role for hallucinogenic drug action were not supported by these studies.

The tolerance development to the FR impairment induced by hallucinogens (LSD and mescaline in this study) was not dependent upon contiguous presentation of the drug action and the specific behavioral measurement. Presumably, the tolerance development progresses independently of experiential interactions. If LSD and like agents result in marked and prolonged activation of receptors on raphe neuronal cell bodies, a desensitization may come about which would result in the reduction of the drug effect and subsequent tolerance formation.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GENERAL INTRODUCTION

A consciousness revolution has permeated our society. People utilizing such diverse techniques as meditation, hypnosis, yoga, ingestion of psychoactive drugs, sensory deprivation, biofeedback, etc., are discovering and exploring new states of awareness quite different and apparently infinitely more exciting and meaningful than those experienced during normal, everyday activity. Although this revelation is a fairly recent phenomenon in our society, primitive cultures have long recognized the significance of altered states of consciousness for spiritual development as well as physical and mental healing. Advocates hold out hope that, at a time when so much seems wrong in our world, a change of consciousness might help to reduce the problems, prejudices and inhumanities which prevail and provide an environment for the development and realization of man's true potentials.

It is important to appreciate the evolution of the <u>limited</u> awareness state which dominates our ordinary consciousness. It is both biologically and culturally conditioned for the purpose of selecting only those stimuli in our environment that have biological and psychological survival value. The central nervous system expends a

large amount of energy screening out irrevelant stimuli. Thus, from the plethora of potential sensory data, both external and internal, only a small proportion reaches consciousness. Our perception of reality is thus constricted under normal circumstances through a very limited sampling of our environment.

One can readily appreciate the significance of efficient and selective sensory screening in biological evolution, for one would be overwhelmed, confused and diverted from survival tasks if exposed to a total onslaught on the senses. This would certainly be disastrous for an animal whose very existence depended on its ability to detect predators. However, humans in their comparatively safe environment can probably afford to let down their "perceptual screens" and sample the wide spectrum of sensory data previously unknown. In this manner, human consciousness may progress beyond its present limitation to reveal the intimate nature of the mind and its vast potentialities. Of course, more conservative views emphasize the possible dangers of an "open" psyche to the emotional stability of the individual and to the maintenance of established social and cultural systems.

Because of the current widespread experimentation with altered states of consciousness by so many members

of our society and because of the potential usefulness of these states, it is imperative that multidisciplinary scientific research efforts be carried out in order to understand their biological mechanisms, psychological consequences and possible medical applications. Hopefully, objective scientific scrutiny and reporting will dissipate some of the mystery, uncertainty and emotionalism that seems to exist concerning the subject. William James, the eminent psychologist and pioneer of the consciousness movement, recognized the need for the scientific exploration of consciousness as early as 1902. In an often quoted passage he stated:

..... "Our normal waking consciousness is but one special type of consciousness, whilst all about it, parted from it by the filmiest of screens, there lie potential forms of consciousness entirely different. We may go through life without suspecting their existence; but apply the requisite stimulus, and at a touch they are all there in all their completeness, definite types of mentality which probably somewhere have their field of application and adaptation. No account of the universe in its totality can be final which leaves these other forms of consciousness quite disregarded. How to regard them is the question, for they are so discontinuous with ordinary consciousness. Yet they may determine attitudes though they cannot furnish formulas, and open a region though they fail to give a map. At any rate, they forbid a premature closing of our accounts with reality."

The class of drugs known as hallucinogens provide an excellent tool to explore and attempt to understand many aspects of altered states of consciousness, as many of the major effects induced by these drugs are characteristic

features of other altered states (Ludwig, 1969). The hallucinogenic drug-induced state in humans encompasses pronounced changes in physiological, sensory and psychological functions. Physiological changes involve the sympathetic nervous system and include tachycardia, increased blood pressure, mydriasis, hyperreflexia, increased muscle tone and hyperglycemia. Sensory alterations include perceptual distortions in all the sensory modalities usually attributed to a disinhibition of incoming sensory stimuli. The stimulus flooding may lead to hallucinations and synesthesias (colors heard, sounds seen, etc.). Psychological changes include extreme variations in mood ranging from deep anxiety and depression to intense euphoria, feelings of unreality, distortions of space and time sense, disintegration of ego function, upsurge of unconscious material, cognitive disturbances and hypersuggestibility. These are not the only effects induced by hallucinogenic drugs, but the listing should suffice to convey some idea of the range of experiences they afford. It should be stressed that the drug itself makes certain types of experiences probable but does not in any sense determine a particular experience. The drug experience is in many significant ways very individual, and depends for its structure and content principally upon two non-drug factors:

The individual's personal history and the expectancies referred to as the set (who he is at that time); and the physical and psychological environment, including other persons present during the trip, referred to as the setting. The significance of these non-drug variables is often not adequately considered in human drug experimentation, either in the laboratory or on the street. A thorough evaluation of one's set as well as a serious effort to provide a physically and psychologically comfortable environment certainly appears to enhance the likelihood of a beneficial drug experience. John Lilly stresses the importance of "programming your trip" with some dramatic examples in Programming and Metaprogramming in the Human Biocomputer (1971).

Classification of the Hallucinogens

Attempts to classify hallucinogenic drugs into meaningful categories have resulted in several varied schemes. In the literature one finds different nomenclatures for the general class which reflects the diversity of the experiences afforded as well as the author's bias. Thus, such terminology as hallucinogenic (emphasizing the perceptual alterations), psychotomimetic (mimicking psychosis) and psychedelic (mind manifesting) are some of the general class names employed. These designations serve to portray the particular attitude and proclivity of the author, so that

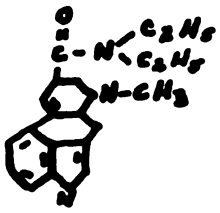
one can often predict where he stands on the moral, social and ethical ramifications of this controversial class of drugs. I feel that all these appelations appropriately convey some aspect and/or potential of the drug experience, but none of the terms are comprehensive enough to include the vast spectrum of psychological transformations that may eventualize. Contributing to the ambiguity in nomenclature is the often reported fact that the nature and essence of the drug experience is difficult to comprehend and communicate. This sense of the ineffable results from the uniqueness of the subjective experience as well as the limitations of our language system to describe these states. Recently a new branch of psycholinguistics has developed for the purpose of establishing more descriptive and meaningful terms to express the dimensions of human consciousness (Authur Hastings, personal communication). For the purpose of this paper, I will use the term hallucinogenic drugs, it being the least controversial designation in current usage. A hallucinogenic drug will be generally defined as a chemical which in non-toxic doses produces changes in perception, thought and mood without memory loss, mental confusion, or profound disorientation for the sense of self, place or time. This distinguishes this class from a group of anticholinergic compounds (deliriants),

such as atropine, scopolamine and ditran, which induce unpleasant hallucinations accompanied by a delirious state including memory loss, mental confusion and dysphoria.

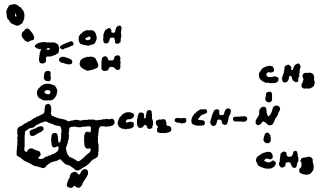
Attempts to subdivide agents within the hallucinogenic drug class have generally been based on chemical structure and resemblance to biogenic amines purported to be neurotransmitters in the central nervous system.. Thus, two broad categories would include hallucinogens with an indole structure (resembling serotonin) and those with a phenethylamine structure (resembling the catecholamines, norepinephrine and dopamine). In addition, the tetrahydrocannabinols (THC's), the active ingredients of Cannabis, are sometimes regarded as a third subclass of hallucinogens, although some difference of opinion still exists as to whether Cannabis is truly an hallucinogen (Jones, 1972). Hallucinogenic agents with a basic indole structure include lysergic acid diethylamide (LSD-25), Psilocybin, N,N-dimethyltryptamine (DMT), N,N-diethyltryptamine (DET), and 5-OH DMT (Bufotenin). Examples of catecholamine-like agents include mescaline (3,4,5-trimethoxy-phenethylamine) and several amphetamine derivatives including 2,5-dimethoxy-4-methylamphetamine (DOM). The chemical structures of these hallucinogens are illustrated in Figure 1, along with d-amphetamine, a potent central nervous system stimulant.

Figure 1: Chemical structures of some hallucinogenic drugs

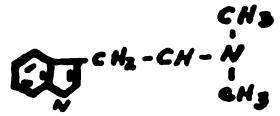
INDOLEAMINES



LSD

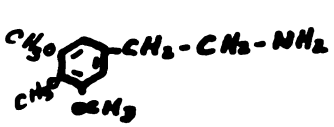


PSILOCYBIN

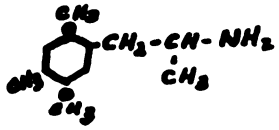


DMT

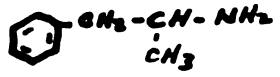
PHENETHYLAMINES



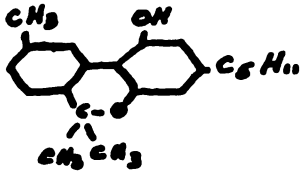
MESCALINE



DOM



D-AMPHETAMINE



THC

Although not typically classed as an hallucinogen, it will be included in these present investigations for comparison purposes.

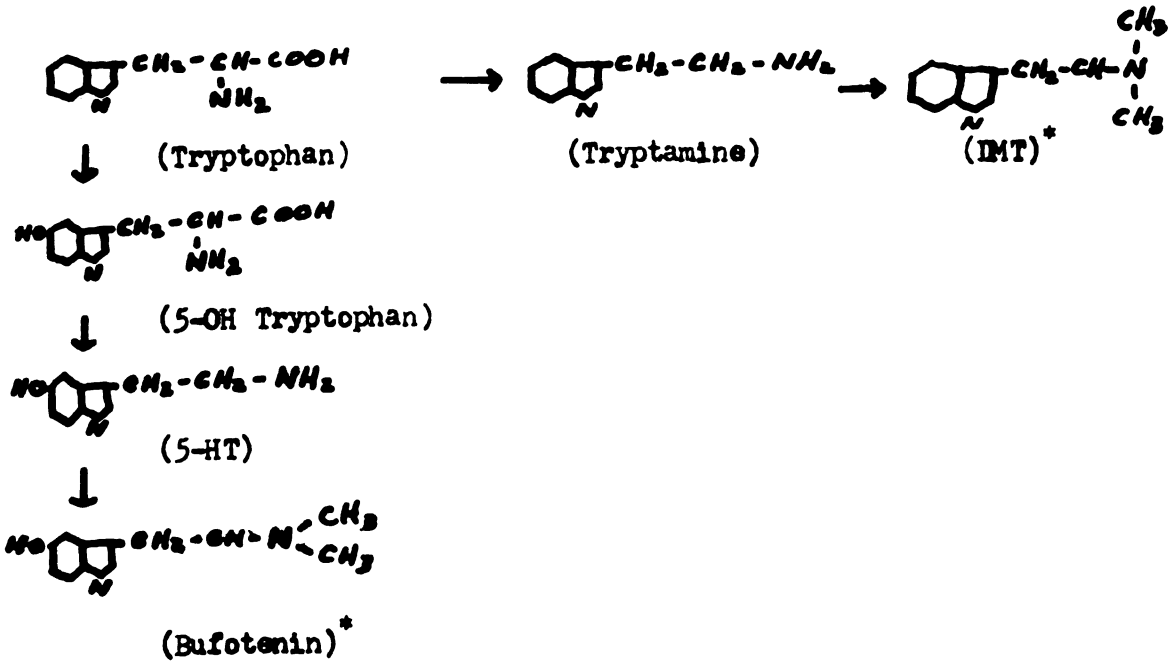
History and Importance of Hallucinogenic Drug Research

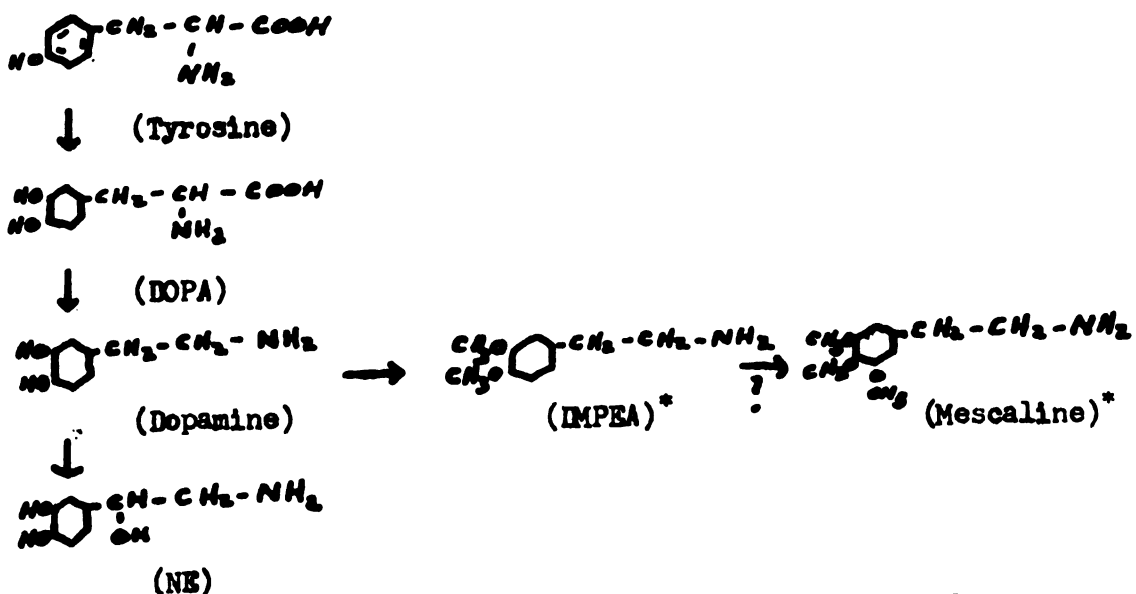
Hallucinogenic plants have been known for milleninums and have been utilized in primitive societies for divination, curing and as a facilitator for communion with supernatural powers. However, it has only been since the serendipitous discovery of the powerful hallucinogenic effect of LSD-25 by Albert Hoffmann in 1943 that interest was generated among scientific researchers. Hoffmann had been synthesizing various amides of lysergic acid in an attempt to develop a potent analeptic agent. On the way home from work after having handled the resultant compound, he was seized by a bizarre mental state which he correctly attributed to the accidental ingestion of the material he had synthesized. He subsequently took what he thought to be a modest dose (250 ug) and shortly thereafter was overwhelmed by the full impact of the hallucinogenic experience. Later investigations revealed that he had ingested 8 to 10 times the minimal effective dose. The fact that a small amount of a chemical (30 to 50 ug) could trigger such profound psychological changes led investigators to believe that similar endogenous mechanisms were operating to produce naturally occurring psychosis. Thus, the state induced

by hallucinogens was postulated to be a drug model of schizophrenia, and the search was on to elucidate the biochemical mechanisms occurring in the brain of a schizophrenic which resulted in the production of a hallucinogenic-like compound.

As the structures of more hallucinogenic drugs were elucidated, it was evident that they all resembled putative central nervous system neurotransmitters. Thus, the hypothesis was advanced that faulty metabolism of one of these neurotransmitters yielded endogenous hallucinogenic compounds. Figure 2 shows the biosynthetic pathways in neurotransmitter production as well as potential pathways leading to hallucinogenic metabolites. Since that time several enthusiastic reports have periodically appeared claiming to have isolated hallucinogenic-like substances in psychotic patients. In 1952, the adenochrome hypothesis of schizophrenia was suggested by Hoffer, Osmond and Smythies. It was postulated that epinephrine and norepinephrine may not be matabolized properly under stress and instead of following the usual route of metabolism, might be transformed into a cyclized indole-like quinone (adenochrome) with psychotomimetic effects. This compound was reported to be found in the blood and urine of psychotics. The enthusiasm generated by this finding was soon dissipated by the failure of other research groups to replicate these findings.

Figure 2: Biosynthetic pathways involved in neurotransmitter production; potential pathways leading to hallucinogenic compounds.





* indicates hallucinogenic compound.

Another interesting study implicating an endogenous psychotomimetic metabolite of an amine was carried out by Friedhoff and Van Winkle (1962). Engaged in an investigation of the matabolism of catecholamines, these workers discovered the presence in the urine of schizophrenic patients of a metabolite identified as 3,4-dimethoxy-phenylethylamine (DMPEA) which is closely related to mescaline and probably derived from abnormal methylation of dopamine (see Figure 2). This finding, along with the observation that methionine (a methyl donor) caused deterioration in the mental states of schizophrenics (Brune and Himwich, 1962; Pollin et al., 1961), stimulated extensive investigation of abnormal methylation of central amines as the cause of psychosis. Some subsequent reports failed to replicate these early findings and attributed the abnormal metabolite to dietary factors and conflicting methodologies (Perry et al., 1964). Nevertheless, intensive interest in this approach has continued to this date and additional methylation hypotheses have appeared. For example, melatonin, a pineal gland hormone, is an o-methylated derivitive of serotonin and, although without psychotomimetic activity in man, has been demonstrated by McIsaac (1964) to form a metabolite, 10-methoxy-harmalin, that is structurally related to harmine and harmaline (potent hallucinogens). It is conceivable that psychotomimetic metabolites of this

type result as a consequence of a shift in the normal metabolism of serotonin toward these pathways.

Another intriguing hypothesis currently attracting much attention states that excessive methylation of endogenous tryptamines, yielding psychotomimetic products, may be responsible for the onset of schizophrenia. Saavedra and Axelrod (1973) recently demonstrated that the human brain contains enzymes that will convert endogenous tryptamines to DMT and bufotenin. This significant finding clearly demonstrates, for the first time, that the human brain is capable of synthesizing hallucinogenic compounds. The tryptamine-methylation hypothesis of schizophrenia is further supported by the following evidence: DMT and bufotenin have been reported to be present in the urine of schizophrenic subjects; and, the administration of L-tryptophan, the amino acid precursor of tryptamine and serotonin, along with methionine, to schizophrenic patients resulted in intensification of their symptomatology (Hoffer and Osmond, 1967). Further studies, of course, are necessary to validate and extend these findings. Hopefully a rigorous research effort will be made, as the outcome of these studies has tremendous implications for psychiatry. One area of investigation that should be pursued in the evaluation of this hypothesis is the phenomenon of tolerance. An endogenous psychotogen should be one for which tolerance

does not develop. Most of the known psychotomimetic substances have been shown to evoke tolerance quite rapidly. Surprisingly, DMT has been little investigated in this regard.

Another important aspect of research with the hallucinogenic drugs is the evaluation of their therapeutic efficacy for certain mental and physical disorders. As mentioned earlier, primitive tribes for centuries have effectively utilized hallucinogenic plants for healing purposes. This is understandable, since they believed that health and disease hinged on their contact and relationship with supernatural and spiritual powers. Indeed, the witch doctor often became the most exalted and revered member of the tribe as a result of his frequent use of hallucinogenic plants to commune with the spirits and derive his assumed healing powers. In our society, however, the enthusiastic claims for therapeutic usefulness of hallucinogens has encountered staunch resistance from the medical "establishment". This opposition arose primarily from fear of the intensity of the responses these drugs evoke, as well as their presumed potential to induce emotional lability and personality changes. It has been far easier to view this power with alarm and repression than to try to find ways of controlling and utilizing it. Establishment attitudes and influence are clearly reflected by the

widespread publicity given to studies which purportedly show that hallucinogenic drugs are in some respects harmful, whereas contrary evidence is often ignored. Despite these impediments, encouraging reports have emerged in several therapeutic areas. Psychiatrists throughout the world have enthusiastically reported on the efficacy of hallucinogenic drugs in the treatment of several types of mental disorders. In many of these reports, therapists stated that the incidence of recovery or significant improvement was substantially greater than with other therapies used by them in the past. In addition, the treatment typically required much less time and was accordingly less costly for the patient.

The types of conditions stated to respond favorably to treatment with hallucinogens include the psychoneuroses, such as obsessive, compulsive, anxiety and phobic conditions; depressive states (exclusive of endogenous depression); sexual deviations; criminal psychopathy; psychosomatic disorders; and autism in schizophrenic children. The value of hallucinogens in the therapeutic process may derive from several factors in the drug experience. LSD and related hallucinogens serve as powerful tools to uncover and reveal repressed material and thus provide the patient and therapist with insights into the history of the maladaptive behavior. In addition, the patient under the drug

may relive some crucial early experience with the re-expression of the emotions attendant to it. The cathartic effect of releasing pent-up emotions has been proposed to be effective for resolving neurotic behaviors. Another symptom-complex often expressed by psychiatric patients involves a loss of meaning in life, an absence of purpose and a failure of faith. LSD and similar agents in high doses often induce religious and mystical experiences accompanied by deep ecstasy which are claimed to inspire a major reorganization of one's beliefs and life outlook. The ability of these agents to induce mystical-religious experiences not only has therapeutic potential for the psychiatric patient, but also may provide those with a spiritual bent the opportunity to probe the wonders of mystical consciousness. Peyote, whose chief active ingredient is mescaline, is currently being employed by over 50,000 Indians of the North American Native Church as a vital part of their religious ceremonies.

It has also been shown experimentally that hallucinogenic drugs taken in a religious context can elicit profound mystical experiences. The "Good Friday" experiment conducted by Walter Panthke as part of his Ph.D. dissertation employed a double-blind technique whereby one-half of the participants received 30 mg. psilocybin and one-half received placebo. The subjects were divinity students and the setting was a Good Friday service in a Boston chapel.

A nine-category typology of the mystical state of consciousness was defined as a basis for measurement of the phenomena of the drug experience. In all categories the experimental group achieved a statistically significantly higher score, and in most cases the significance was overwhelming. According to the criteria used, follow-up studies six months later showed that the impact and significance of the drug experience had persisted to enrich their spiritual lives in many dimensions. It is hoped that more experiments of this nature will be undertaken. By judicious manipulation of set and setting, the effects of these agents in combination with various environmental stimuli on human experience may be evaluated for their propensities to enrich and extend the intellectual and emotional impact of the experience.

Another area where hallucinogenic drugs have been purported to be efficacious is in the treatment and rehabilitation of alcoholics. The rationale behind this approach initially derived from the frequent statements of alcoholics that rehabilitation practices were usually undertaken only when they had "hit bottom" and experienced delirium tremens (dt's). Since dt's are a toxic hallucinatory state, it was reasoned that LSD would perhaps simulate some aspect of this phenomenon. Canadian research groups (Osmond, 1952) employing high doses of LSD found that 50% of their patients

were substantially rehabilitated. They reported, however, that the drug was not simulating dt's but rather inducing a "psychedelic" experience (Osmond, 1957) during which patients gained insights into the nature of the factors responsible for their drinking. Subsequent reports, however, have refuted these earlier findings so the area is controversial. Nevertheless, since no other medical cure has been developed for alcoholism, this treatment technique, though in doubt, deserves further investigation and trial.

Another potential use for hallucinogenic drugs is in the treatment of painful, terminal stages of serious diseases such as cancer. Hallucinogens serve two useful functions in this regard. They act as potent analgesics (Kast, 1963) as well as attenuating the anxiety associated with anticipation of imminent death. These effects probably derive from several factors. The rich, expanded sensory experience induced by the drug compels the patient to divert his attention from his immediate pain and thus serves as an escape hatch through which his tension can be dissipated. In addition, hallucinogenic agents diminish the cortical control of thoughts, concepts and associations (Silverman, 1969) so as to reduce the significance of the pain and the associated affect. Finally, hallucinogenic drugs purportedly obliterate ego bounderies so as to promote a geographic separation of the self and the ailing part (Kast, 1964).

Another useful effect of these drugs in this regard is their ability to induce religious-mystical experiences which seem to alter the terminal patient's spiritual and philosophic attitudes about death. A study done by Kast (1964) in which 80 cancer patients were each given 100ug. LSD showed that 90% responded favorably as evidenced by a brightening of mood, lessening of pain intensity, improved attitude toward death and improvement of sleep patterns. These effects persisted in most cases for at least 10 days following the drug. Certainly in our society, which provides little to ease the inevitability of dying, the study of techniques such as these should be extended. Some other fields in which hallucinogenic drugs have been examined for potential applicability include: enhancement of creativity (Harman et al., 1966); training of workers in psychiatry (Hyde, 1968) in order to provide them insights into the nature of psychotic thinking, mood, and perception; and facilitation of the manifestations of psychic phenomena (Roll, 1972).

The preceding discussion of the known and potential therapeutic uses of hallucinogenic drugs illustrates the wide spectrum of possible applications for these agents. Although medical science has been slow to evaluate their efficacy, it is hoped that in the future this resistance will be mitigated. One means, perhaps, of overcoming this anti-intellectualism is to provide a sound theoretical

foundation for the therapeutic utility of hallucinogens based on animal research studies. By integrating data derived from neurophysiological, biochemical and behavioral investigations of hallucinogenic drugs in animals, a better understanding of the fundamental effects of these agents on brain functions will undoubtedly promote greater application to clinical problems as well as aid in the elucidation of basic neurophysiological and psychological processes.

Extrapolation of data derived from animal studies to humans is often criticized on the basis of evolutionary differences in brain function, social conditioning factors, etc. However, in regard to hallucinogenic drugs, I believe that some extrapolation is justified. Hallucinogenic drugs purportedly interact primarily with phylogenetically primitive brain structures subserving basic perceptual, emotional and vegetative functions. These neural systems are practically identical (neurophysiologically and biochemically) throughout the mammalian animal kingdom, up to and including man. Another criticism often expressed in regard to extrapolation is that much higher doses of drugs are necessary in animals to elicit comparable effects seen in humans. I believe this might be understood if one realizes that humans have developed a highly active and sensitive inhibitory system that screens out the majority of internal and external sensory cues, whereas lower animal

species passively assimilate more of their environment. The active inhibitory system in humans would consequently be more easily disrupted by hallucinogenic drugs requiring a comparitively low dose. A more meaningful evaluation of the extrapolation would be based on comparison of potency ratios for various hallucinogens across species. In this regard, there is a remarkable similarity. For example, LSD for both man and rat is the most potent of the agents, followed by DOM, psilocybin, DMT and mescaline. This observation strengthens the assumption that similar brain mechanisms are involved across species in generating the hallucinogenic state.

There have been many attempts to form a general theory of hallucinogenesis: unfortunately, none can account for more than a small portion of the available data. The following discussion will involve a review of some of the pertinent studies which have evaluated the effects of hallucinogenic drugs in animals. Current theories of the mechanism of action of hallucinogenic drugs will be discussed in relationship to these findings. In order to judiciously formulate any theories regarding the complex nature of the hallucinogenic drug state, one must integrate data from many scientific disciplines. Emphasis in this review will be directed toward biochemical, neurophysiological and behavioral findings. It should be stated

that most of the early studies involved LSD as the prototype hallucinogenic agent, since it was traditionally assumed that all agents within the hallucinogenic class produced similar subjective and pharmacological effects by sharing common mechanisms of action (Snyder and Richelson, 1968; Kang and Green, 1970). This similarity of action was based on the finding that members of the class showed cross-tolerance in humans (Wolbach et al., 1962), interpreted by most to mean that they all acted on a common receptor site in the central nervous system. It has only been in the last few years that other members of the drug class have been evaluated. Unexpectedly, several studies have revealed significant differences in the action of these agents on several systems. These disparities will have to be considered in any attempt to formulate a unifying hypothesis for the mechanism of action of the hallucinogenic drug class.

Research on the biochemical correlates of the hallucinogenic drug state has focused on drug interactions with the endogenous central neurotransmitter, serotonin, 5-hydroxytryptamine (5-HT). This grew out of an early finding that LSD antagonized the action of 5-HT at certain neuromuscular effector sites, such as in the gut or uterus (Gaddum, 1957; Woolley and Shaw, 1954). The use of histofluorescent mapping techniques in recent years has revealed that the majority of central nervous system 5-HT neurons

are located in the brain stem raphe nuclei (Dahlstrom and Fuxe, 1965). The studies of Freedman et al. (1961) revealed that LSD had an influence on the metabolism of 5-HT in the brain, causing an elevation in its concentration. It was later seen that this increase was accompanied by a fall in the concentration of 5-hydroxyindoleacetic acid (5-HIAA), the principle metabolite of 5-HT (Rosecrans et al., 1967). Since the converse was seen after stimulation of the raphe, it was suggested that perhaps LSD had specific inhibitory effects on the raphe cell bodies to account for the reduced 5-HT turnover. In an experiment designed to test this hypothesis, it was found that LSD in minute parenteral doses (10-20 ug/kg) caused a complete inhibition of the spontaneous firing of single neuronal units in the midbrain raphe nuclei of the rat (Aghajanian et al., 1968). The entire population of raphe units was uniformly inhibited by LSD. The specificity of the effect for raphe neurons was demonstrated, as surrounding non-raphe neurons were unaffected or increased their firing rates. In addition, many other drugs were tested for this effect and it was shown that only hallucinogenic drugs and agents that elevated 5-HT (monoamine oxidase inhibitors, 5-hydroxytryptophan) demonstrated this dramatic inhibition. DMT and psilocybin both completely inhibited all raphe units when the agents were tested in doses approximating their behavioral potencies in rats.

On the other hand, catecholamine-like hallucinogens, mescaline and DOM, induced a selective depression of raphe units; only those in the ventral portion of the dorsal raphe nucleus were inhibited, whereas other units tested with these latter agents were unchanged or increased their firing rates. It is interesting to note that those units that increased their rates following DOM and mescaline also demonstrated an increased firing following d-amphetamine (Foote et al., 1969). This differential action on raphe units by hallucinogens will be further discussed in relationship to behavioral findings in the Discussion Section of Section III.

Little is known of the functions of the serotonergic raphe system and its afferent and efferent connections. Recent studies have implicated that it is somehow involved in sleep mechanisms (Jouvet, 1968), temperature regulation (Feldberg et al., 1966), sensory perception (Stevens et al., 1967), stimulus reactivity (Tenen, 1967), habituation (Sheard and Aghajanian, 1968), aggression (Koella et al., 1968), neurosecretion (Bloom et al., 1968) and pain perception (Tenen, 1967). Interestingly, most of these functions are also altered by hallucinogenic drugs. Efferents from the raphe have been traced to the hypothalamus and limbic forebrain (Fuxe, 1964; Anden et al., 1966) as well as the basolateral amygdala, ventrolateral geniculate, subiculum

and optic tectum (Haigler and Aghajanian, 1974). These areas are known to influence mood, perception and autonomic functions. Thus, the raphe neurons and their projections may well be intimately involved in the major effects of hallucinogenic drugs.

Two hypotheses have evolved attempting to elucidate the interaction of hallucinogens with serotonin and the raphe system. One theory proposes that hallucinogens antagonize 5-HT mediated functions in the central nervous system in a manner similar to their effects in the peripheral nervous system. Boakes et al. (1970) demonstrated that LSD antagonized 5-HT excitation of single brainstem neurons when applied iontophoretically or intravenously. In addition, Roberts and Straughan (1967), in a study of cortical neurons in cats, also found that iontophoretically applied LSD blocked the effects of 5-HT. Furthermore, Couch (1970) has demonstrated that particular raphe units are excited or inhibited by iontophoretically applied 5-HT and that iontophoretically applied LSD simultaneously blocked raphe excitations caused both by 5-HT and by stimulation of the midbrain reticular formation. This hypothesis was also favored by Brawley and Duffield in a recent review article (1972) on the pharmacology of hallucinogens. In contrast, another theory proposes that LSD and other hallucinogenic agents mimic the effect of 5-HT at post-synaptic receptor sites (see references below). This theory postulates a

negative feedback circuit at the end of which an excess of 5-HT at a receptor on the raphe cell body may inhibit the firing of these cells. This would account for the decreased turnover of 5-HT in the forebrain seen following hallucinogens, if the drugs acted like excess 5-HT at the raphe cell bodies. Several studies support a 5-HT receptor stimulation action by hallucinogens. Anden et al. (1971) in experiments on rat hindlimb reflexes showed that LSD, psilocybin and DMT caused changes similar to those seen after treatment with 5-hydroxytryptophan (5-HT precursor). Aghajanian (1972; 1973) has demonstrated that postsynaptic serotonergic raphe receptors respond to very low doses of i.v. LSD (10 ug/kg) and markedly accelerate their firing rate. LSD concomitantly depresses raphe neurons (cell bodies) at this same low dose. Thus, one requirement of a feedback loop is fulfilled, that of a reciprocal effect at a similar dose range. Other supporting evidence for this agonist hypothesis includes studies which demonstrate the similar actions of elevated 5-HT and hallucinogens. By stimulating the raphe nuclei electrically, Aghajanian et al. (1967) demonstrated that endogenous 5-HT is released in the forebrain. The most prominent behavioral concomitant was a failure of habituation to repetitive sensory stimuli. A similar loss of habituation was noted by Bradley and Key (1958) following administration of LSD. These two hypotheses

attempting to define hallucinogen interaction with the serotonin system both presume that these agents act at 5-HT receptor sites. Other studies have indicated that the interaction may be at a presynaptic locus. In this regard, Chase et al. (1967) suggested that hallucinogens may inhibit the release of 5-HT, while Freedman (1961) postulated that LSD may enhance 5-HT binding.

From the foregoing discussion, it appears evident that hallucinogens interact with 5-HT neural mechanisms but the details of the interaction are not settled by any means. Regarding norepinephrine (NE) and hallucinogens, Anden et al. (1968; 1971) have shown that LSD, psilocybin and DMT increase NE turnover. It was noted, however, that the doses were much higher than those needed for an effect on 5-HT. Some of the hallucinogen-NE interactions proposed include: direct action on the NE receptors (Bradshaw et al., 1971); increased intraneuronal release of NE (Leonard and Tonge, 1969); and increased extraneuronal release of NE (Menon et al., 1967; Vrbanac et al., 1973).

Surprisingly, few investigations have examined the effect of hallucinogens on dopaminergic systems in the brain. Recent theories regarding the neurochemical correlates of schizophrenia have postulated that excessive dopamine receptor activation may be responsible for the mental aberrations (Snyder, 1973; Matthyssee, 1974).

The recent finding that major antipsychotic drugs, i.e., chlorpromazine and haloperidol, are potent dopamine receptor blockers lends support to this hypothesis. In this regard, if one assumes that the hallucinogenic agents serve as a drug model for psychosis (i.e., psychotomimetic), it would be reasonable to assume that they interact with dopamine functions. In the only biochemical investigation of this correlation, Daiz (1968) found that dopamine levels decreased in the brain following the administration of LSD, implying increased utilization of this amine. Certainly, further study of hallucinogen-dopamine interactions is warranted.

In reviewing the literature describing the neurophysiological correlates of hallucinogenic drug action, one finds much conflicting data due to different methodologies, doses employed, species investigated, etc. However, I will attempt to integrate such material so as to present a few general statements which may contribute to a better understanding of hallucinogenic drug action. Studies investigating drug effects on spontaneous cerebral electrical activity have revealed that low doses of hallucinogens induce EEG activating effects as manifested by a desynchronized (fast, low voltage) "beta" activity (Rinaldi and Himwich, 1955). Higher doses generally result in intermittent, hypersychronous bursts superimposed on the "beta" activity, and in some cases continuous hypersynchrony.

Differences between various hallucinogenic agents on EEG manifestations have been noted and will be discussed in a later section.

In attempting to integrate and interpret the EEG activities, it is useful to observe the ongoing behavior manifested during a particular EEG state. In cats, Winters (1968) has observed that a "beta" activity reflected an alert, excitable behavioral state. d-Amphetamine will induce this state in animals and humans. The next level of CNS excitation (intermittent hypersynchrony) is accompanied by inappropriate behavior characterized by abnormal postures and movements, such as swatting at non-existent objects, and is postulated to represent an hallucinatory state. The next discernable EEG state constitutes a continuous hypersynchrony and is also indicative of hallucinatory phenomena. The behavioral concomitant of this state is described as a catatonic immobilization. The upper ranges of the continuum include anesthetic agents which induce a very slow, hypersynchronous EEG with a loss of consciousness, and finally convulsants with their characteristic epileptoid spiking EEG. It is important to note that this is a progressive excitation continuum so that a behavioral state of seizures would be preceded by alertness and hallucinatory manifestations followed by loss of consciousness. This progression of CNS excitatory states is

characteristically manifested during an epileptic seizure episode. Typically, excitation followed by an hallucinatory aura and loss of consciousness precedes the seizures. In an attempt to further characterize neurophysiologically the hallucinatory state, Winters examined modulation of sensory input during various excitatory states. By measuring sensory evoked potentials induced by visual and auditory stimulus cues during the various excitatory states, he derived a theory of hallucinosis based on a breakdown of sensory modulation. He postulated that a subcortical modulating system responsive to activity in the reticular activating system undergoes a progressive functional disorganization during progressive excitatory states so that it exerts reduced control over incoming sensory information. Thus, in the alert, activated state ("beta activity") the auditory evoked response (AER) is decreased as compared to the awake but resting control, due to an increased modulation of its input. During the intermediate stages of excitation (hallucinatory) the breakdown of modulation results in an enhancement of the AER which progresses to a maximum in seizure states. The visual system, he found, takes a high priority during arousal states and appears to resist modulatory control as evidenced by a progressive increase in the visual evoked response during arousal states (this would confer an adaptive advantage). The excessive activation

of the visual system as one progresses along the excitation continuum induces disruption of the modulating system at a time prior to the breakdown of auditory modulation. In this way, visual hallucinations occur prior to (i.e., at a lower state of excitation) the onset of multisensory aberrations (auditory, tactile, proprioceptive, etc.). Although Winters does not speculate on the neural substrate responsible for this sensory modulation, it seems possible that the raphe nuclei may be mediating this function. As previously noted, d-amphetamine increases the firing of raphe units (i.e., increased modulation), whereas hallucinogens inhibit their activity (breakdown of modulation). The biochemical data also support this idea; d-amphetamine induces an increased utilization (turnover) of 5-HT (Diaz and Huttenen, 1972) while hallucinogens decrease turnover.

In an attempt to locate the central site of action responsible for EEG effects of hallucinogenic drugs, Fuginori and Himwich (1969) performed brain transection experiments in the cat and determined that d-amphetamine induced typical EEG desynchronization at a midbrain site, whereas hallucinogenic amphetamines (DOM, TMA, MDA, etc.) induced their EEG effects (arousal progressing to hypersynchrony) in the medulla. A later study revealed that the hallucinogenic agents LSD, psilocybin and mescaline also exerted their EEG effect in the medulla. These authors

thus postulated that hallucinogenic agents act by inhibiting a medullary center, releasing from its restraint the midbrain activating system. These data thus imply a lower brainstem serotonergic feedback system which is activated during states of arousal and is sensitive to disruption by hallucinogenic drugs. Data from other studies support this hypothesis. Couch (1970) reported that LSD blocked the facilitation of raphe units induced by iontophoretically applied 5-HT or stimulation of the midbrain reticular formation. Koella and Czicman (1966) showed that administration of 5-HT via the vertebral artery in cats resulted in EEG synchrony, as does topical application of 5-HT to the area postrema, where some raphe units appear to terminate (Fuxe, 1965). Topical application of LSD to the area postrema blocked both of these effects. A study by Branzano (1971) demonstrated that evoked responses elicited in medullary sites (anterior portions of the nucleus of the solitary tract-NTS) by stimulation of the midbrain reticular formation were potentiated by topical application of 5-HT to this area. 5-HT cell bodies have been identified in NTS and the area postrema (Fuxe, 1965). That there may be a hallucinogen-sensitive feedback circuit involving the area postrema, NTS and the raphe nuclei, is further supported by the report of Morest (1960), who has demonstrated anatomical connections between these areas. Additional

evidence for the interaction of hallucinogens with this feedback system is indicated by reports demonstrating that the subjective effects and amount of EEG activation induced by hallucinogenic drugs depend on the level of environmental stimulation (Cohen et al., 1963; Pollard et al., 1965). Subjective effects of LSD are attenuated under conditions of sensory restirction and accentuated by increasing stimulation. Perhaps this can be interpreted neurophysiologically as follows: Increased sensory stimulation enhances the "tone" in the serotonergic feedback circuit, providing an active neural substrate for disruption by antagonists. When the environment supplies little input, this pathway would be relatively inactive and therefore not critically disrupted by hallucinogens. It should be noted that this hypothesis assumes that hallucinogens antagonize 5-HT mediated functions, which, as mentioned previously, is controversial.

Another neural circuit that would be expected to be influenced by hallucinogenic drugs is the visual pathway. Several findings have demonstrated a depressant action of LSD as well as 5-HT on lateral geniculate neurons (Curtis and Davis, 1961; Phillis et al., 1967; Evarts, 1957). These nuclei serve as relay stations for visual sensory pathways to the striate cortex. These findings and the observation that visual evoked potentials are potentiated

following hallucinogens (Winters, 1970; Purpura, 1956) imply that visual stimuli are less subject to modulation and consequently may flood into consciousness, resulting in hallucinations. Studies investigating the action of hallucinogens on retinal ganglion cells have yielded conflicting results. Schwartz and Cheney (1965) reported that both spontaneous and light-induced discharge rates of these units were stimulated by LSD. Heiss et al. (1973) found that DMT depressed the spontaneous activity of retinal ganglion cells. It has also been shown that 5-HT similarly has a depressing effect on these units (Straschill, 1968). Heiss postulated that the DMT-induced alteration of spontaneous activity might be of some relevance for the origin of visual hallucinations; maintained illumination was found to decrease the discharge rate of retinal ganglion cells; thus, the depression of the spontaneous activity caused by DMT might be interpreted by the brain as "light" and this might contribute to the origin of abnormal reactions in the visual pathways of the brain. In this regard, it has recently been demonstrated that environmental lighting information is conveyed to many brain structures via the inferior accessory optic tracts. These nerve bundles separate from the primary optic tracts just behind the optic chiasma, enter the hypothalamus, traversing the medial forebrain bundle to synapse in the midbrain. From this

site they pass through the medulla to synapse in the thoracic cord. Preganglionic fibers go to the superior cervical ganglion from which postganglionic fibers project to the pineal gland. The pineal gland thus serves as a neuroendocrine transducer sensitive to light influences. The synthesis and release of melatonin, the principle hormone of the gland, is regulated by environmental lighting and is very sensitive to small changes in light spectra and intensity (Wurtmann, 1969). Melatonin exerts profound effects on brain function, probably acting as a modulator of other CNS neurotransmitters. Prominent elevations of 5-HT occur in midbrain sites following i.p. injections of melatonin (Anton-Tay, 1970). Thus, the alterations of the spontaneous activity of retinal ganglion cells induced by hallucinogens are likely to be sensed by neural circuits involving the pineal and may play a prominent effect in inducing the visual distortions of hallucinations. The perception of a brilliant "white light" often reported at the peak of drug and mystical experiences (Tart, 1972) may result as a consequence of these mechanisms.

Another indication that hallucinogens may be interacting with pineal gland function was demonstrated by Snyder and Reivich (1966). Studying the distribution of LSD, they found the highest concentration of the drug in the pineal, which contained eight times the amount found in cerebral

cortex and four times that found in any other subcortical structure. The authors argued that this cannot be explained by regional differences in blood flow or lipid solubility and suggested that the selective concentration of LSD might be related to the perceptual and emotional effects of this drug. The high concentrations of 5-HT in the pineal also suggest a likely site for hallucinogenic interactions.

Visual discrimination and gereralization studies have revealed additional perceptual alterations induced by hallucinogens. In humans (Hollister, 1962) and animals (Bradley and Key, 1958) it has been shown that hallucinogenic drugs facilitate the subject's responding to irrevelant stimulus cues (stimulus generalization). Discrimination studies investigating accuracy of perception, however, have revealed that hallucinogens have an enhancing effect (Blough, 1957; Beeker, 1967). Thus, ever though more visual sensory data is impinging on cortical interpretative areas, the discrimination capabilities are not impaired. Perhaps selective attention mechanisms are facilitated by hallucinogens to allow enhanced perception of task-relevant inputs. Another phenomenon associated with hallucinogen interaction with visual systems is the occurrence of persisting after-images. This has been demonstrated in humans with psilocybin (Keeler, 1965) and in monkeys under LSD (Peterson, 1966). This may be related to effects on

habituation mechanisms. As previously noted, hallucinogenic drugs impair the normally limiting and inhibiting effect of the process of habituation. An important aspect of habituation is that it occurs only if the stimulus is without significance to the subject. In this manner, irrevelant cues are screened from awareness. In the hallucinogenic state, however, visual stimuli acquire a uniqueness so as to compel central interpretive mechanisms to retain the novel image for maximal evaluation. This loss of habituation coupled with the enhanced sensitivity to discrimination of stimuli may account for the often stated reports of the increased significance and meaning attributed to objects and events during the drug state.

While it is generally acknowledged that hallucinogens interact with lower brainstem mechanisms, little is known regarding their involvement with forebrain limbic structures. Since hallucinogenic drugs induce affective, attentional and perceptual changes and since the temporal lobe, hippocampus, amygdala, hypothalamus, septal area and their connecting pathways are implicated in such functions, it would be logical to assume that these drugs might exert some effects on these structures. The fact that 5-HT terminals have been traced to these structures (Fuxe, 1965) and that raphe stimulation facilitates 5-HT turnover in these areas further implicates their interaction with hallucinogens.

Indeed, it has been reported that the behavioral effects of LSD are not seen after temporal lobectomy in monkeys (Baldwin et al., 1957). The advance of stereotaxic techniques have made it possible to record the electrical activity of deep structures in the human brain. LSD in doses of 50 to 200 ug. administered to schizophrenics induced paroxysmal, hypersynchronous bursts in many subcortical structures (Adey, 1962; Eidelberg, 1965). These abnormal brain wave activities were correlated with overt psychotic behavior in these patients. Animal studies have also revealed widespread hypersynchrony in many subcortical structures following hallucinogenic agents (Schwartz, 1956; Fairchild, 1967; Adey, 1962). It was suggested by Killam and Killam (1956) that paroxysmal electrophysiological abnormalities induced by hallucinogens might be specific for limbic structures. They reported that LSD exerted little effect on the diffuse thalamocortical or reticular activation system. The widespread hypersynchrony noted in many limbic structures may represent a reverberating circuit that has functional significance in the control of behavior. In 1937, Papez proposed the existence of a limbic circuit interconnecting several of the above mentioned structures that was operational in controlling emotional behavior. Since that time many studies have appeared regarding Papez's circuit and its significance for a variety of

brain functions (Leaton, 1971).

Iontophoretic studies in which 5-HT has been applied to limbic structures have revealed a depression of the spontaneous activity in amygdala (Legge, 1966), septum (Herz and Gogalak, 1965), hippocampus (Salmoiraghi and Stefans, 1968), and hypothalamus (Bloom et al., 1972). These findings, based on microelectrode recording and iontophoretic drug application, would imply that the raphe based serotonergic system normally functions to inhibit the activity of limbic structures. Bloom (1973) investigated the suprachiasmatic nucleus in the hypothalamus in an attempt to develop a model system for the study of drugs which specifically interact with 5-HT mediated synapses. Histochemical fluorescence had revealed a high concentration of 5-HT containing nerve terminals at this site (Dahlstrom and Fuxe, 1965). In addition, raphe lesions are known to result in terminal degeneration in this nucleus. Microiontophoretic 5-HT depressed the spontaneous or glutamate-induced activity of these neurons. Furthermore, electrical stimulation of the median raphe mimicked this effect of depression. It was then found that LSD in large parenteral doses (200 ug/kg) would not block the effect of raphe stimulation; that is, the neurons continued to respond to the inhibitory effects of raphe stimulation. Utilizing a similar model, Haigler and Aghajanian (1974) likewise

demonstrated that the inhibition of postsynaptic terminals of raphe neurons induced by 5-HT was not blocked by LSD. This was demonstrated in the amygdala as well as non-limbic structures receiving raphe 5-HT terminals, including the lateral geniculate, tectum and subiculum. These studies would thus refute the 5-HT antagonist theory of hallucinogenic drug action held by many researchers in the field.

Since the normal physiological functions of limbic structures are obscure, it is difficult to ascertain the significance of their interaction with hallucinogenic drugs. In general, however, it is presumed that portions of the limbic system are associated with inhibitory functions (McCleary, 1966; Leaton, 1971), both in a physiological and a behavioral sense. The hippocampus and septum may serve to selectively filter from consciousness those stimuli which have no biological significance and rewarding consequences (Carlton, 1963). Animals with hippocampal lesions perform poorly on behavioral tasks that require the inhibition of responses (Douglas, 1967). It appears as if hippocampectomy renders an animal ineffective in withholding inappropriate responses. In addition, habituation mechanisms are disrupted following hippocampal ablation. Carlton (1963; 1969) has compiled considerable evidence which suggests that a component of this system involved in response inhibition is cholinergic. Anticholinergic drugs (atropine and scopolamine) produce similar behavioral deficits as those seen

following hippocampal lesions. An interaction of 5-HT with this cholinergic inhibitory system was suggested by Swonger and Reeh (1972). They postulated that 5-HT neurons originating in the raphe nuclei and projecting to limbic regions modulate some cholinergic inhibitory mechanisms. The 5-HT neurons act to monitor the amplitude setting of the reticular activating system and then exert a gain-controlling function on certain limbic pathways representing a discriminatory process. According to the level of signals passing through the reticular formation and to past experience, the 5-HT pathways increase the gain of particular cholinergic tracts to enhance the inhibitory control on certain sensory and motor systems, i.e., those representing non-adaptive response patterns. The total effect would be a filtering mechanism, with only the relevant signals being transmitted to higher centers and exerting a large control over behavior. Other inappropriate signals would be processed only to the extent of recognizing their unimportance, and further projection throughout the brain would be curtailed by an increased inhibitory tone in related limbic tracts. This theory assumes that in moderate or low arousal states, the cholinergic inhibitory system would function adequately and independently in discriminatory functions, whereas high arousal levels necessitate mediation by the 5-HT system to enhance selective inhibition. Hallucinatory phenomena,

they propose, would result from the dual change of increased arousal and reduced 5-HT modulation. This theory nicely accounts for the previously mentioned finding that the subjective and behavioral effects of hallucinogenic drugs are attenuated in a sensory-poor environment. In this situation, according to their theory, 5-HT mechanisms (which are disrupted by hallucinogens) would not be essential for the maintenance of homeostasis.

Turning now to a discussion of hallucinogenic drug effect on neocortical structures, it is difficult to assess and differentiate direct from indirect drug effects. Thus, a facilitation or inhibition of cortical neurons might reflect indirect mechanisms deriving from the drug interaction with subcortical mechanisms. In an attempt to circumvent this, Marrazzi (1957) utilized the transcallosal response (intercortical transmission) and reported that LSD directly inhibits cortical cells at axodendritic synapses. However, latencies between stimulus and response were quite long and variable to have been true transcallosal responses; the potentials may in fact have been related to impulses traversing subcortical or even spinal tracts. In addition, Krnjevic and Phillis (1963), employing single unit studies, demonstrated that several hallucinogenic drugs injected microiontophoretically had short latency, depressant actions on cortical cells.

Roberts and Straughan (1967) found that iontophoretically applied LSD tended to depress firing rates and amplitudes of cortical cells and in addition antagonized 5-HT mediated excitations of these units. 5-HT induced inhibition of these cells was unaffected by LSD. Purpura (1956), working with cats, observed decreased electrical activity from the primary sensory cortex to cortical association areas following LSD, concomitant with an increased activity in the discrete sensory pathways to the cortex. Silverman (1971) interpreted these findings to represent a homeostatic, compensatory adjustment by the organism: The inhibition is an automatic attempt by the sensory control apparatus to reduce the intensity of overloading stimulation.

This inhibition in association pathways following LSD should result in disturbances of integration of sensory and perceptual information into organized and meaningful configurations, with the end result that previously learned response patterns may no longer be accessible to consciousness; or, alternatively, that previous experiences that are inappropriate to the present stimulus input are recalled from memory in an uncontrollable manner. Since the associational mechanisms are disrupted in the drug state, the organism would be compelled (stimulus-bound) to attend to the multitude of stimulus cues in attempting to make sense out of his environment; irrevelant and innocuous events

now would demand as much attention as biologically or psychologically relevant cues. Stimulus flooding thus would ensue without a corresponding increase in rate of data processing, leading eventually to hallucinations. This hypothesis is similar to other "arousal" theories for hallucinogenic drug action, but differs in terms of the importance attributed to cortical association areas in the genesis of hallucinations.

Although it has traditionally been assumed that hallucinogenic drugs induce a rather unique physiological state, it is interesting to note the similarities between this state and the condition that prevails during REM (dreaming) sleep. The subjective effects (where REM states are recalled) are quite similar and include the production of endogenously-generated imagery, loosening of associations, distortions of time and space, emergence of repressed memories and unconscious elements, etc. The hallucinatory state occurring spontaneously and precipitantly in subjects drprived of REM sleep for a number of days may show even more elements in common. The likelihood that hallucinogenic drugs shift the activity pattern of brain structures in the direction of that manifested during REM sleep is supported by the following findings. In both states, cortical EEG recordings have revealed a low-voltage, fast activity ("beta" pattern) indicative of an activated cortex. Depth recordings of

electrical activity in subcortical structures have also disclosed a remarkably similar pattern of activity. As mentioned previously, hallucinogens induce hypersynchronous spiking in these areas. The parallelism to the REM state is the occurrence of "PGO" spikes obtained from the pons, lateral geniculate and occipatal cortex (Jouvet, 1967). These hypersynchronous bursts are observed only during REM episodes under normal physiological conditions. REM deprivation, however, will result in the emergence of PGO spikes into the waking state, at which time hallucinatory experiences are often reported (Dement, 1967). Furthermore, LSD will shift PGO spiking from REM into the waking state (Stern et al., 1972). A possible mechanism to account for this effect may be related to the activity of the raphe neurons. It has recently been demonstrated by McGinity (1973) that anterior raphe units projecting to the forebrain cease to fire during REM sleep. Hallucinogens, as mentioned earlier, also induce a dramatic cessation of firing of these units. McGinity recorded the electrical activity of several subcortical structures and noted that, during the waking state, raphe units displayed a very stabile rhythm (0.5 to 2.0 cps) which was not disrupted by environmental stimuli introduced during the recording session. It was only immediately preceding and during REM that these units deviated from their normal rhythm, at which time they

periodically stopped firing. He determined that PGO spiking was reciprocally related to raphe firing and only occurred when raphe neurons were quiescent. When raphe cells did fire, PGO activity was completely suppressed. Thus, it appears that in both REM sleep and during the state induced by hallucinogens, raphe activity periodically ceases and allows the emergence of PGO spiking, which may be the electrical sign marking the brain trigger site of hallucinatory phenomena. Other parallelisms include: LSD produces in the dorsal hippocampus (Adey, 1962) hypersynchronous 4-5 cps waves (theta rhythm), a pattern whcih according to Jouvet (1963) is also observed during REM states in the cat; ablation of the raphe abolishes the effect of hallucinogenic drugs (Rosecrans, personal communication) as well as REM sleep (Jouvet, 1967). The similarity of these states might suggest that an endogenous hallucinogen-like dream transmitter may be responsible for the onset and maintenance of REM sleep. In this regard, the recent <u>in vivo</u> demonstration of DMT synthesis in human brain (Saavedra and Axelrod, 1973) has implications for elucidating dream mechanisms. It was found that the methylation enzyme in the DMT synthetic pathway was inhibited by normally occurring compounds in the brain. It is conceivable that the restraints on this enzyme are removed during REM episodes to facilitate the production and utilization of DMT.

Having reviewed some of the biochemical and neurophysiological correlates of hallucinogenic drug action, I would now like to focus on the behavioral concomitants of the hallucinogenic state. The earliest behavioral studies of hallucinogenic drugs involved crude measurements of such ambiguously labeled, naturally occurring behaviors as general excitation, aggression and emotionality during stressful situations. It is not surprising to find discrepancies in reported findings, as the definitions of the measured behavior, species investigated, doses employed, etc., have varied considerably in different laboratories. Thus, for example, Brown (1957) reported that LSD increased spontaneous motor activity, whereas Szara and Hearst (1963) found that most hallucinogens suppressed motor activity and exploratory behavior. Furthermore, Elder and Dille (1962) found that LSD increased aggression in the cat, but Chen and Watson (1960) reported increased docility in monkeys following LSD.

The next level of complexity in behavioral design to assess drug effects consisted of simple conditioning techniques such as the conditioned-avoidance response. These techniques can provide useful data, but their unstabile baselines and lack of specificity severely curtail their predictive or interpretive power (Smythies, 1969). In general, results from these types of investigations show

that an animal under the influence of hallucinogenic drugs will react to the conditioned stimulus (bell, light, etc.) as if it were the unconditioned stimulus (shock; Bridger and Mandel, 1967; Bridger and Gnatt, 1956). Thus, the conditioning stimulus comes to act as if it were the shock itself, eliciting emotional and autonomic disturbances so as to disrupt avoidance responding.

A further sophistication and increased specificity of behavioral paradigms followed the introduction of operant conditioning techniques as tools to measure drug-induced behavioral effects. The methods are based upon a simple principle: The characteristics of behavior are, to a large extent, determined by the environmental events that have been consequent upon past occurrences of the behavior. The behavior operates on the environment (operant behavior) and the process of manipulating such behavior by means of its environmental consequences is termed "operant conditioning" (Skinner, 1938). Utilizing operant paradigms, one is able to investigate a sample of behavior under rigid experimental controls and ascertain the influence of drugs on this particular well-established behavior. In this manner, drug-induced changes in behavior can often be related to programmed events in the animal's environment as well as to pharmacological variables. Thus, operant conditioning offers the most precise, sensitive and reproducible

technique for controlling the behavior of a subject. Operant conditioning schedules were employed in these studies primarily as a means of comparing and contrasting various agents within the hallucinogenic drug class and elucidating their possible mechanisms of action. Less emphasis will be directed toward interpreting the particular behavioral manifestations during the drug states, as the author feels that behavior generated in an artificial, well controlled, sterile environment (i.e., operant chamber) may not reflect natural behavioral functions that would be displayed in the animals' "home ground".

Since operant behavioral patterns are controlled by a delicate balance between facilitatory and inhibitory systems, they are susceptible to differential disruption by a variety of drugs. Although much research utilizing operant techniques has been carried out on tranquilizers, barbiturates, and stimulants, few investigations have explored the effects of hallucinogens on these paradigms. Consequently, Section I of my research project will involve the investigation of dose-response relationships of several hallucinogenic drugs on a wide variety of operant behavioral paradigms. This effort was directed at ascertaining similarities and differences within the hallucinogenic drug class, as well as establishing behavioral profiles for these agents which may be utilizable in drug-screening programs. Section II will

include an evaluation of the effects of long term, repeated hallucinogenic drug administration on the performance of rats in operant paradigms. Those agents that induce tolerance will be utilized for cross-tolerance studies in an attempt to determine similar mechanisms of action within the drug class. In addition, the mechanisms involved in tolerance development will be explored. Section III will involve drug-interaction studies to determine whether alterations of neurotransmitters and their receptors will influence the behavioral effects of hallucinogenic drugs. Using these data, possible mechanisms of action of hallucinogens will be presented.

SECTION I

INTRODUCTION

The hallucinogenic drug class includes a large number of compounds with varied chemical structures. Attempts to categorize these agents on the basis of biochemical, psychological, and pharmacological activity have generally resulted in three classes (Brawley and Duffield, 1972). The anticholinergics such as atropine or ditran and the tetrahydrocannabinols appear to differ from a third class which include indoleamine and catecholamine-containing hallucinogens. Drugs in this latter category comprise the better-known hallucinogens such as lysergic acid diethylamine-25 (LSD), mescaline, psilocybin, and 2,5-dimethoxy-4-methylamphetamine (DOM). These drugs produce similar subjective and pharmacological effects in man (Wolbach et al., 1962; Rosenberg et al., 1963; Hollister et al., 1969) and it has been frequently proposed that they share some common mechanism or act on the same common receptor or site (Wolbach et al., 1962; Snyder and Richelson, 1968; Kang and Green, 1970; Barker et al., 1973). However, Brawley and Duffield (1972) recently concluded that there may be no single underlying mechanism for the agents of this class of hallucinogens. This conclusion is supported by recent electrophysiological (Aghajanian et al., 1970; Haigler and

Aghajanian, 1973) and neurochemical (Freedman et al., 1970; Tilson and Sparber, 1972; Stolk et al., 1974) data indicating major differences among representative hallucinogenic substances.

The behavioral effects of the hallucinogens in rodents have been described extensively by Smythies and his colleagues (Smythies et al., 1969), particularly in regard to the effects of these drugs on signalled continuous avoidance responding. However, few if any dose-response comparisons of representative hallucinogens have been reported for other types of behavioral contingencies, although individual compounds such as LSD have been studied (Jarrard, 1963; Freedman et al., 1964; Appel, 1971; Tilson and Sparber, 1973). The purpose of the present investigation was to compare indolealkylamine-type hallucinogens such as LSD-25 and psilocybin with an hallucinogenic amphetamine derivative, DOM, using three different schedules of operantly reinforced responding. Behavioral comparisons with d-amphetamine were also included, since this drug is a potent central nervous stimulant not usually considered to be hallucinogenic.

METHODS

Subjects: Albino rats of the Sprague-Dawley and Fisher strains were used as subjects in these investigations. Animals were housed in groups of 2-4 in controlled quarters under a 12-hour light-dark cycle. Food and water were freely available in the home cages of animals trained on an avoidance schedule, whereas only water was freely available to animals trained to respond for food reinforcement.

Apparatus: Daily behavioral sessions were conducted in operant chambers enclosed within a ventilated, sound- and light-attenuated outer chamber. Control of schedule events in the chamber and recording of response data were accomplished by means of appropriate electromechanical components.

Drug injections and data analysis: The behavioral effects of various doses of d-amphetamine sulfate (K and K Labs, Plainview, N.Y.), lysergic acid diethylamide-25 (LSD) tartrate, psilocybin, and 2,5-dimethoxy-4-methylamphetamine (DOM) hydrochloride on three schedules of reinforced behavior were studied. The hallucinogens were obtained from the FDA/NIMH Psychotomimetic Agents Advisory Committee. All drugs except psilocybin were dissolved in isotonic saline solutions and were injected i.p. immediately before placing the animal into the operant chamber. Psilocybin was dissolved in 0.01 N HCl solution. Each rat served as his own control and received each drug at 4-5 dose levels twice

in an ascending-descending order. Drug sessions were separated by at least two daily control sessions in which the vehicle was injected. Group means were established for the baseline behavioral measures obtained from each schedule of reinforcement investigated. In most cases, drug-induced alteration in these measures were compared to upper and lower limits of control responding (NaCl injection). A significant drug effect is defined as an average behavioral measurement that is equal to or greater than $\pm$ 2 standard deviations from group NaCl control means (Tilson and Sparber, 1973). The drugs were studied randomly one at a time until completion of a dose-response evaluation. Two weeks separated the end of one series of dose-response studies for one drug and the beginning of the next series.

Schedule 1- drl-18 responding: A rat on a drl schedule receives reinforcement only if it does not make the designated response (bar-press) for a predetermined length of time since the last response. Responses occurring before the end of the interval reinstate the entire interval and postpone reinforcement. This schedule promotes low response rates and is a good measure of timing behavior. Several reports in the literature indicate that hallucinogenic drugs alter "time sense" in humans (Hollister, 1968; Aronson et al., 1959) and thus one might expect these agents to affect drl performance.

Four female Sprague-Dawley rats weighing approximately 250 grams at the beginning of the experiment were food-deprived to 80% of their free-feeding body weight. The rats were trained to lever press for food reinforcement (Noyes food pellets, 45 mg.) initially and the requirement for reinforcement was increased gradually to a drl-18 second schedule of reinforcement (Ferster and Skinner, 1957). Daily training for 10 weeks was required to produce stabile control rates of responding (3.2-3.4 responses/min.). Dose-response effects of the drugs were studied as described previously. The response measures analyzed were mean number of responses emitted and number of reinforcers received during 60-min. sessions. In addition, the average time between unreinforced responses (IRT's) was obtained by dividing the time lapsed between unreinforced responses into 2-sec. categories.

Schedule 2-Sidman (Continuous) Avoidance: Eight male Sprague-Dawley rats (300-400 gm.) were trained over a period of two months to avoid electric foot shock on an unsignalled continuous avoidance schedule. In this paradigm, behavior is controlled by negative reinforcement. The subject must bar-press to avoid an electric shock (2 ma.-0.5 sec. duration) delivered every 5 sec. (shock-shock interval). A bar-press will delay the shock for 30 sec. (response-shock interval). The mean number of responses

emitted, number of shocks received and IRT's (based on 2 sec. class intervals) were measured during 60 min. sessions. Four of the animals were used to study the effects of d-amphetamine and LSD, while the remaining four were used to study psilocybin and DOM.

Schedule 3-Fixed-Interval: Four male Fisher strain rats weighing approximately 150-175 grams at the beginning of the experiment were food-deprived to 80% of their free-feeding body weight. The subjects were trained gradually to lever press for food reinforcement on a fixed interval 60 sec. (FI-60 sec.) schedule of reinforcement. On this paradigm, a food-deprived rat receives food reinforcement (45 mg. Noyes pellet) for the first response following a fixed time interval (60 sec.) from the last reinforcer. Sessions were terminated following 50 reinforcers. Responses occurring during consecutive 15 sec. segments of each 60 sec. interval were measured. Average response rates during each 15 sec. segment and the overall response rate were determined (Tilson and Sparber, 1973). The rate-dependent effects of the drugs were analyzed by comparing average vehicle control response rates during each of the four 15 sec. segments and drug-induced changes in rate (McMillan, 1973). In the present study, each group's average control rate during each 15 sec. segment is plotted on the abscissa and the drug rates as a percentage of the average

control rate on the ordinate. The values were plotted on a log-log scale and the slopes of the resulting regression lines were determined by the method of least squares. In addition, the percent change in rate following drug (Y-variable) was extrapolated from the regression line for a control rate of 0.1 responses/sec. (X-variable; see Table 5).

RESULTS

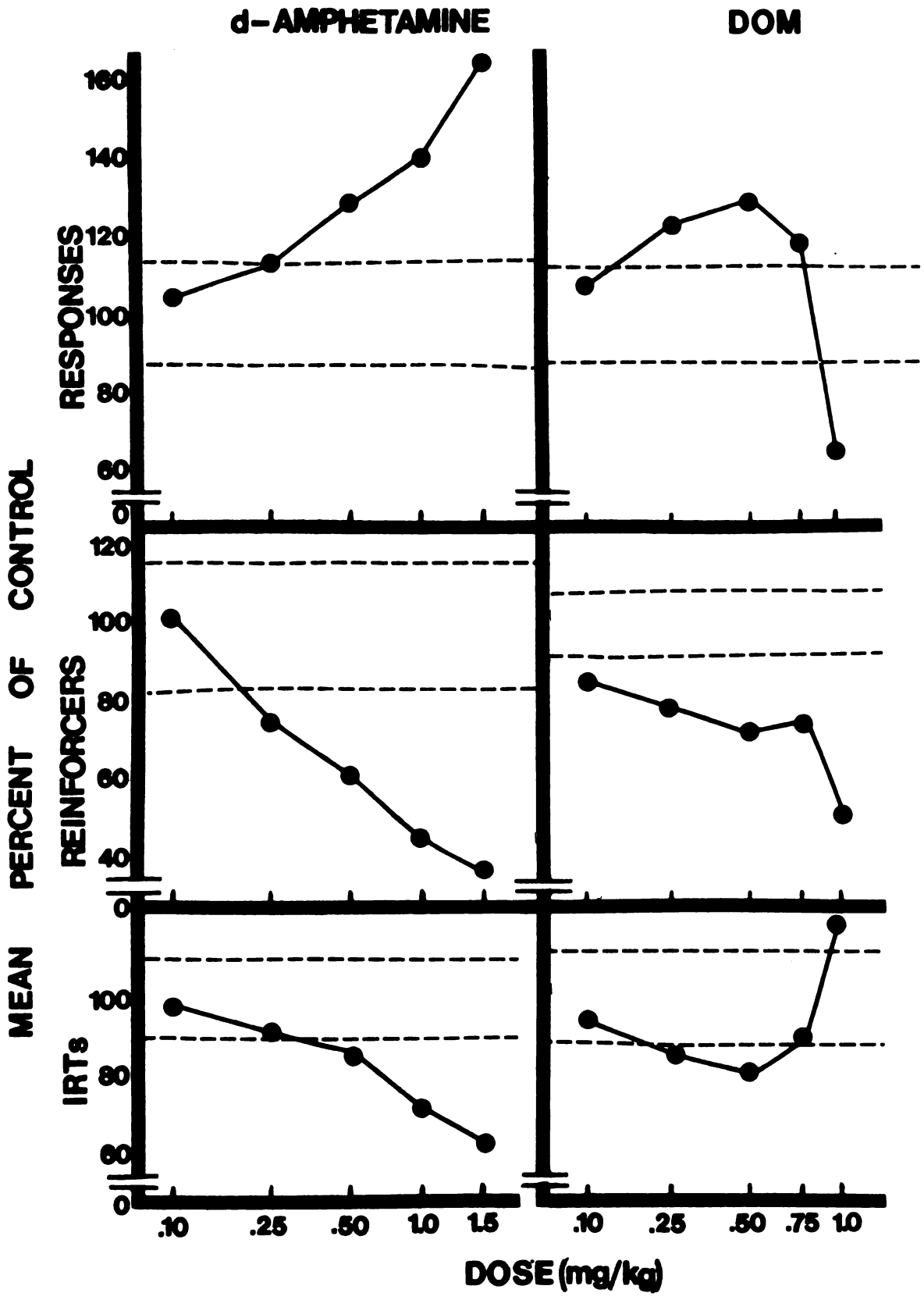
Effects of drugs on drl responding: Under vehicle-control conditions, the drl-18 sec. schedule of reinforcement generated stabile responding with an average rate of 3.28 responses/min. An analysis of the average rates of responding, number of reinforcers received and mean unreinforced IRT's for controls during each of the four experiments indicates little shift in responding occurred during the 5 month course of the experiment (Table 1). As reported by numerous investigators (Zimmerman and Schuster, 1962; Schuster *et al.*, 1966), d-amphetamine increased markedly the rate of drl responding. This behavioral stimulation was associated with a decrease in the number of reinforcers received and a decrease in the average time between unreinforced responses (shorter IRT's; Fig 1). Significant alterations in responding (above or below 2 S.D. from the mean) were observed for each of the 3 behavioral measures at 0.5 to 1.5 mg/kg of d-amphetamine. Higher doses up to 3.0 mg/kg (not shown in Fig.1) also increased the rate of drl responding, but the change in behavior was not as prominent as observed with 1.5 mg/kg of d-amphetamine. The hallucinogenic amphetamine derivitive, DOM, significantly decreased the number of reinforcers received at 0.10 mg/kg in a manner similar to 0.25 mg/kg of d-amphetamine. In addition, 0.25 mg/kg and 0.50 mg/kg of DOM significantly increased response rates

Table 1. Control drl responding during various phases of the experiment.

	Average behavioral measure during control drl responding		
Drug	Responses/min.	Reinforcers	Non-reinforced IRT's
d-Amphetamine	3.28±0.44[a]	114±19	16.3±1.6
DOM	3.25±0.40	118±10	16.3±2.0
LSD	3.20±0.30	117±13	16.6±1.8
Psilocybin	3.37±0.50	112±15	16.0±2.0

[a] Each value is the mean of four animals, each receiving 12-14 NaCl control sessions. Variability is expressed as 2 standard deviations since upper and lower limits of control responding correspond to ±2 S.D. of control responding.

Figure 1: The dose-response effects of d-amphetamine and DOM on drl-1d response patterns. Drug dosages are represented on the abscissas. The behavioral measures are represented on the ordinates. Drug effects are expressed as a mean percent of control. Each point represents the mean of eight observations (4 rats; 2 observations/rat at each dose of each drug). The dotted lines represent the upper and lower limits (2 standard deviations) of the mean group control measures. Significant drug effects therefore are represented as points outside of the 2 standard deviation boundry. IRTs= mean interresponse times.


d-AMPHETAMINE
DOM
MEAN PERCENT OF CONTROL
RESPONSES
REINFORCERS
IRTs
160
140
120
100
80
60
120
100
80
60
40
0
100
80
60
0
.10
.25
.50
1.0
1.5
.10
.25
.50
.75
1.0
DOSE (mg/kg)

and decreased reinforcers received and IRT's. The next higher dose of DOM (0.75 mg/kg) significantly increased responding and decreased the number of reinforcers received, but the average IRT was within the 2 S.D. lower limit of control responding. The behavioral effects of DOM up to this point resembled those produced by d-amphetamine, but the next dose of DOM studied (1.0 mg/kg) produced pausing in drl responding and was associated with a significant loss of reinforcers along with an increase in the mean IRT. Figures 2 and 3 show the cumulative records for one animal depicting response patterns to varying doses of d-amphetamine (Fig. 2) and psilocybin (Figure 3).

The two indolealkylamine-containing hallucinogens, LSD and psilocybin, had different effects on drl responding as compared to DOM and d-amphetamine. LSD tended to increase the response rate at 0.08 to 0.20 mg/kg, but the effect was not significant (Figure 4). A significant decline in responding was noted at 0.24 mg/kg. These results are similar to those of Appel (1971) who reported that low doses of LSD (0.01 to 0.08 mg/kg) increased drl responding, while higher doses (0.16 mg/kg) decreased it. However, we found that LSD markedly decreased reinforcers and that this effect was associated with a tendency toward shorted IRT's. Analysis of the IRT distributions indicated that LSD in doses of 0.08 to 0.20 mg/kg appeared to decrease the time between responses enough to result in a loss of reinforcement, but

Figure 2: Sample cumulative records depicting response patterns of Rat B-2 on drl-18 induced by various doses of d-amphetamine. Panel A shows the control response record for a 60 minute session. Panels B-F depict the responding characteristics following 0.1, 0.25, 0.50, 1.0 and 1.5 mg/kg d-amphetamine, respectively. Each downward deflection of the event pen represents a food reinforcement. The slope of the responding record gives an indication of the responding rates (i.e., steeper slope=faster rate and loss of reinforcement).

Figure 3: Sample cumulative records depicting response patterns of Rat B-2 on drl-18 induced by various doses of psilocybin. Panel A shows the control response record for a 60 minute session. Panels B-F depict the responding characteristics following 0.1, 0.25, 0.50, 0.75 and 1.0 mg/kg psilocybin. See Figure 2 for further detail. The typical hallucinogenic "pause" is evident in Panel F.

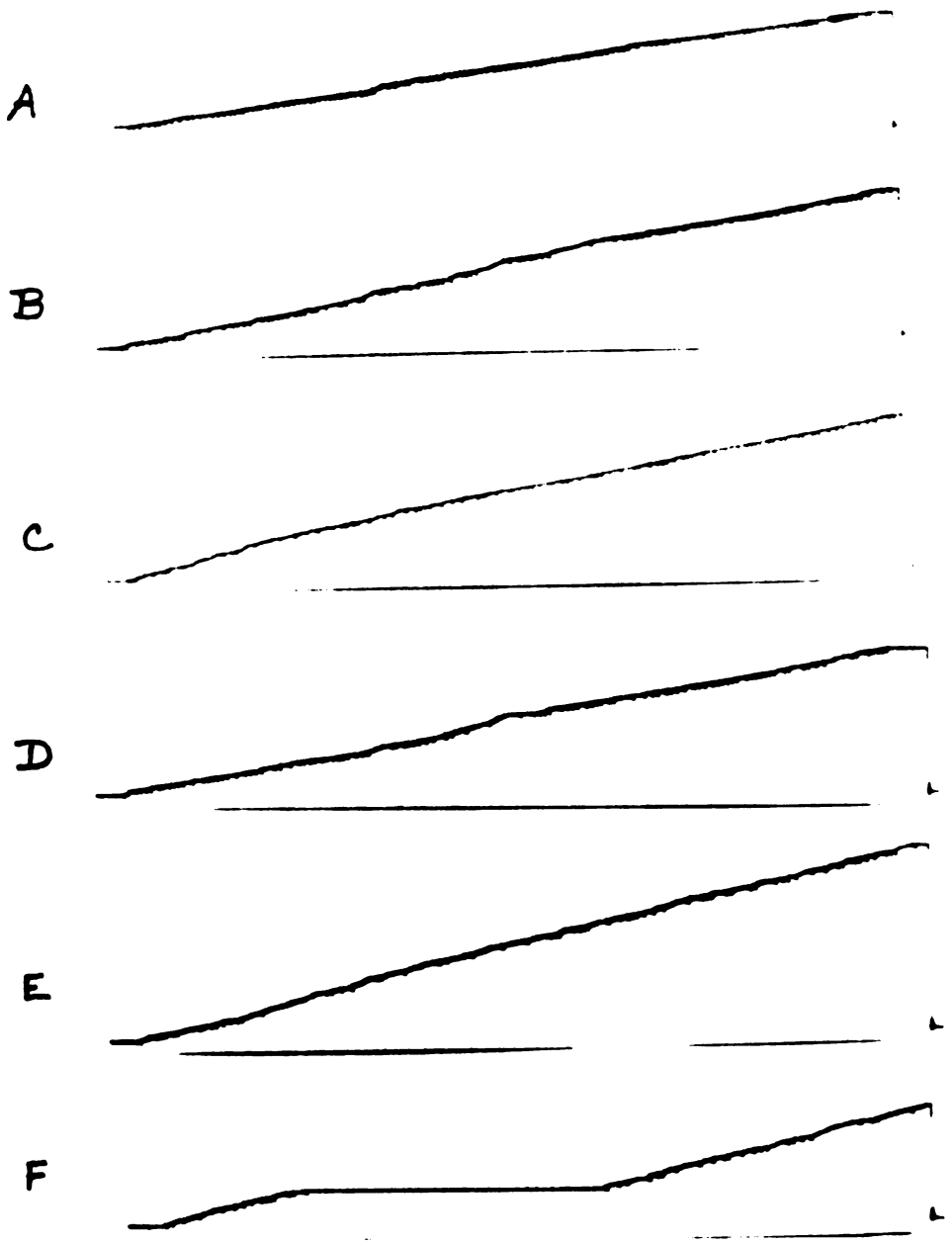
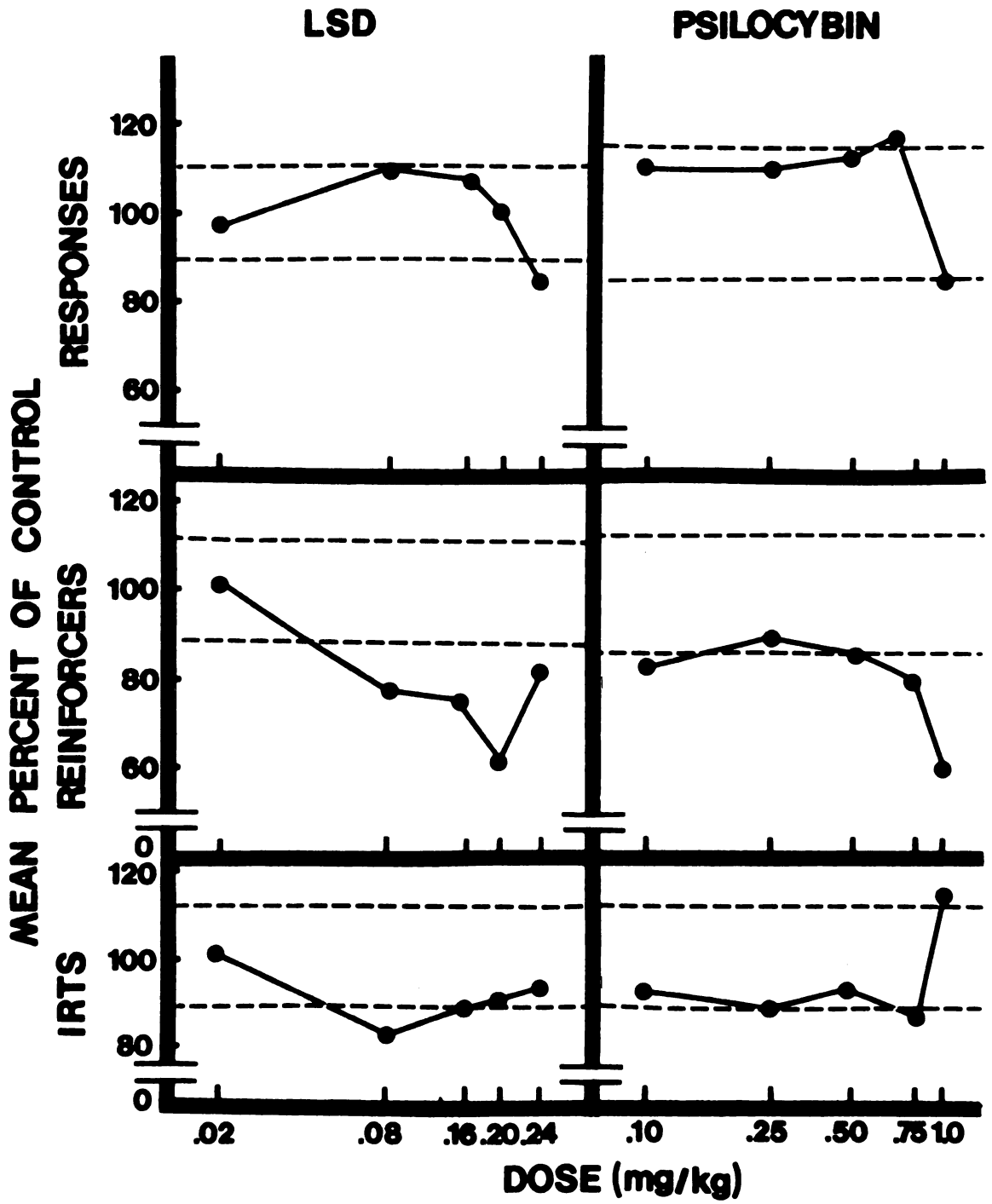

A
B
C
D
E
F

Figure 4: The dose-response effects of LSD and psilocybin on drl-18 response patterns. Each point represents the mean of eight observations. See Figure 1 for details.


LSD
PSILOCYBIN
MEAN PERCENT OF CONTROL
RESPONSES
REINFORCERS
IRTS
120
100
80
60
0
.02
.08
.16
.20
.24
.10
.25
.50
.75
1.0
DOSE (mg/kg)

without significant effects on overall rate of responding or on mean IRT's. A similar type of effect was observed with psilocybin (Figure 4) in which the rate of responding was not affected significantly by most doses. Significant decreases in the unreinforced IRT's were observed at 0.25 and 0.75 mg/kg. Shifts in the IRT's were generally associated with a loss of reinforcers. The highest dose of psilocybin studied (1.0 mg/kg) produced a significant decrease in responding (pausing) which was associated with decreases in the number of reinforcers and an increase in the IRT's.

Effects of drugs on continuous avoidance: As in the experiment with the drl responding, a behavioral differentiation between the hallucinogens was noted. In the first group of animals in which LSD and d-amphetamine were investigated, the average rate of responding was 3.26 responses/min. during 60 min. behavioral sessions. d-Amphetamine produced significant dose-dependent increases in responding at doses of 0.25 to 2.0 mg/kg, which were associated with decreases in the number of shocks received and a decrease in IRT's, (Table 2). Similar effects with d-amphetamine have been noted previously (Sidman, 1953; 1956). On the other hand, LSD increased response rates significantly at 0.20 mg/kg, while tending to decrease them at the highest dose studied (0.4 mg/kg). As in the case of the drl schedule, LSD tended to decrease the number of reinforcers (shocks) received

Table 2: The Effects of Various Doses of LSD and d-Amphetamine on Continuous Avoidance Responding.

TREATMENT	AVERAGE BEHAVIORAL MEASURE [a]		
	Responses/min.	Shocks	Interresponse Times
NaCl-Upper [b]	3.85	146	17.7
Mean [b]	3.25	127	15.6
Lower	2.65	108	13.5
LSD (mg/kg)			
0.02	3.63	117	15.6
0.05	3.78	84*	14.7
0.10	3.77	107	14.7
0.20	3.95*	130	14.9
0.40	3.12	154*	18.7*
NaCl-Upper	4.05	179	16.5
Mean	3.27	139	14.8
Lower	2.48	99	13.1
d-Amphetamine mg/kg			
0.10	3.52	141	16.3
0.25	4.63*	109	12.0*
0.50	5.77*	99*	11.7*
1.00	5.83*	90*	9.1*
2.00	6.33*	114	9.1*

[a] Each drug value is the mean of four animals, 2 observations per subject.

[b] NaCl control values were obtained from 10 observations per animal. Upper and lower limits are ±2 S.D. of NaCl control responding.

* Asterisk indicates that the value is above or below 2 S.D. limit.

at low doses (0.05-1.0 mg/kg) without pronounced effects on IRT's or on the response rate. Depression in responding at 0.40 mg/kg was associated with significant increases in the number of shocks received and increases in IRT's. Similar effects of LSD on rates of Sidman-type operant responding of rats have been reported previously (Jarrard, 1963).

The remaining animals trained to respond on the continuous avoidance schedule were given various doses of psilocybin and DOM (Table 3). The rats used in this study had a slightly higher mean rate of responding for the course of the entire study (4.87 responses/min.) than the previous avoidance responders (3.26 responses/min., Table 2). Psilocybin at doses of 0.10 to 1.0 mg/kg had no significant effect on avoidance responding and significantly decreased the rate of responding at 1.5 mg/kg. Significant increases in the number of shocks delivered and the mean IRT were also noted after this dose of psilocybin. On the other hand, DOM (0.50 to 1.0 mg/kg) increased significantly the rate of responding. Significant decreases in the mean IRT were also observed at 0.25 to 1.5 mg/kg. DOM tended to decrease the number of shocks received at all doses, but the effect was significant at 0.50 mg/kg only. These effects are similar to those produced by lower doses of d-amphetamine (0.25 to 1.0 mg/kg) in the previous group of animals.

Table 3: The Effects of Various Doses of Psilocybin and DOM on Continuous Avoidance Responding.

TREATMENT	BEHAVIORAL MEASURE [a]		
	Responses/min.	Shocks	Interresponse Times
NaCl-Upper [b]	5.73	115	13.4
Mean	4.92	90	11.5
Lower	4.10	65	9.6
Psilocybin (mg/kg)			
0.10	4.80	85	12.2
0.25	4.27	80	11.6
0.50	5.52	75	10.9
0.75	4.60	94	12.1
1.00	5.50*	75	11.4
1.50	3.92	124*	15.7*
NaCl-Upper	5.87	110	14.1
Mean	4.82	88	12.4
Lower	3.77	66	10.7
DOM (mg/kg)			
0.10	4.92	75	11.2
0.25	5.02	72	10.7*
0.50	5.90*	63*	10.1*
0.75	5.90*	71	9.8*
1.00	6.00*	72	10.1*
1.50	5.83	75	10.7*

[a] Each drug value is the mean of four rats, 2 observations per subject.

[b] NaCl control values were obtained from 12 control sessions per animal. Upper and lower limits are ±2 S.D. from NaCl control mean.

* Asterisk indicates that the value is above or below 2 S.D. of NaCl control value.

Effects of drugs on Fixed Interval responding: Responding under vehicle control conditions on the FI 60 sec. schedule resembled the typical "scalloped" performance (Ferster and Skinner, 1957) whereby low rates are seen during the early part of the interval and high rates are generated toward the end of the interval prior to reinforcement. Average control rates of responding in the first and second consecutive 15 sec. segments were 0.27 and 0.34 responses/15 sec., respectively, while responding in the third and fourth segments averaged 0.87 and 4.58 responses/15 sec. respectively (Table 4). Control responding of the animals appeared to remain relatively constant during the course of the four experiments. Figure 5 shows the rate-dependent effects of various doses of DOM on FI 60 sec. performance. Injections of isotonic saline (0 mg/kg) on a designated control session produced little percentage change in responding, as compared to the rates observed in two other NaCl control sessions. Thus, the slope of the regression line was low. The administration of 0.10 to 0.75 mg/kg of DOM procuced marked rate-dependent changes in FI responding. That is, DOM increased lower rates of responding and increased higher rates of responding less or even decreased them. At the highest dose of DOM (1.0 mg/kg) all FI responding was decreased. A very similar rate-dependent effect was observed with d-amphetamine (Figure 6) when studied in doses of

0.10 to 1.0 mg/kg. On the other hand, intermediate doses of psilocybin (0.25 and 0.50 mg/kg) tended to increase all rates of responding equally (Figure 7) while decreasing all responding at 0.75 and 1.0 mg/kg. Similar effects were observed with LSD (Figure 8) at 0.01 and 0.05 mg/kg (increase in responding) and 0.10 mg/kg (decreases in responding).

Table 5 shows the average slope of the regression line for the group following administration of various doses of each drug. When control rates were 0.1 responses/sec. d-amphetamine and DOM increased response rates, and the increase was associated with more negative slopes for the regression lines. At higher doses of the two drugs (0.75 and 1.0 mg/kg) which tended to decrease responding from control, the slope of the regression lines approached zero. Although some doses of psilocybin and LSD produced increases in response rates that were above control, the slope of the regression lines were not changed markedly. Higher doses of the two drugs (0.75 and 1.0 mg/kg for psilocybin and 0.10 mg/kg for LSD) decreased responding with little effect on the slope of the regression line.

Table 4: Responses rates during consecutive 15 second segments of FI 60 seconds responding under NaCl control conditions.

	Mean Responses per 15 second ± 2 S.D. [a]				
	Consecutive 15 second segments				
Drug	1	2	3	4	Average Overall
d-Amphetamine	0.31±0.14	0.28±0.25	0.60±0.50	5.13±0.62	1.58±0.77
DOM	0.26±0.10	0.45±0.15	1.09±0.52	4.07±0.83	1.46±0.32
LSD	0.24±0.12	0.28±0.17	1.00±0.56	4.26±1.83	1.45±0.64
Psilocybin	0.25±0.09	0.34±0.35	0.79±0.60	4.85±0.80	1.54±0.52

[a] The data are mean responses/15 seconds occurring during consecutive 15 second segments of FI 60 second responding. Mean values are derived from 4 animals during NaCl control sessions for each drug experiment (10-14 observations per animal). Variability of responding is expressed as 2 S.D. to show upper and lower limits of control responding.

Table 5: Dose-related effects on the slope of the regression line.

Drug	Dose (mg/kg)	Slope [a] (degrees)	Y as % of X when X = 0.1 Responses/second
d-amphetamine	0.00	-4	95%
	0.10	-6	122%
	0.30	-27	205%
	0.50	-15	102%
	0.75	-9	88%
	1.00	+2	72%
Psilocybin	0.00	-1	101%
	0.10	+1	100%
	0.25	-5	142%
	0.50	-5	143%
	0.75	+4	62%
	1.00	+3	58%
DOM	0.00	+2	106%
	0.10	-9	121%
	0.25	-13	156%
	0.50	-29	160%
	0.75	-16	98%
	1.00	-1	62%
LSD	0.00	+1	102%
	0.01	-1	112%
	0.02	-9	124%
	0.05	-5	120%
	0.075	-1	116%
	0.10	-4	85%

[a] Data are derived from four rats, two observations per rat.

Figure 5: The rate-dependent effects of various doses of DOM on FI-60 responding. The group's average control rates (4 subjects) during each 15 second segment are plotted on the abscissas and the drug rates as percentages of the average control rates on the ordinates. The values are plotted on a log-log scale. Each point is the mean rate of responding (log scale) during one of four successive 15-second segments of the fixed interval, and is compared to drug induced change in the rate. The doses of DOM analyzed for rate-dependent effects are listed at the top of each plot. 0 mg/kg represents a saline control injection compared to rates observed in 2 other control sessions. See text for details.

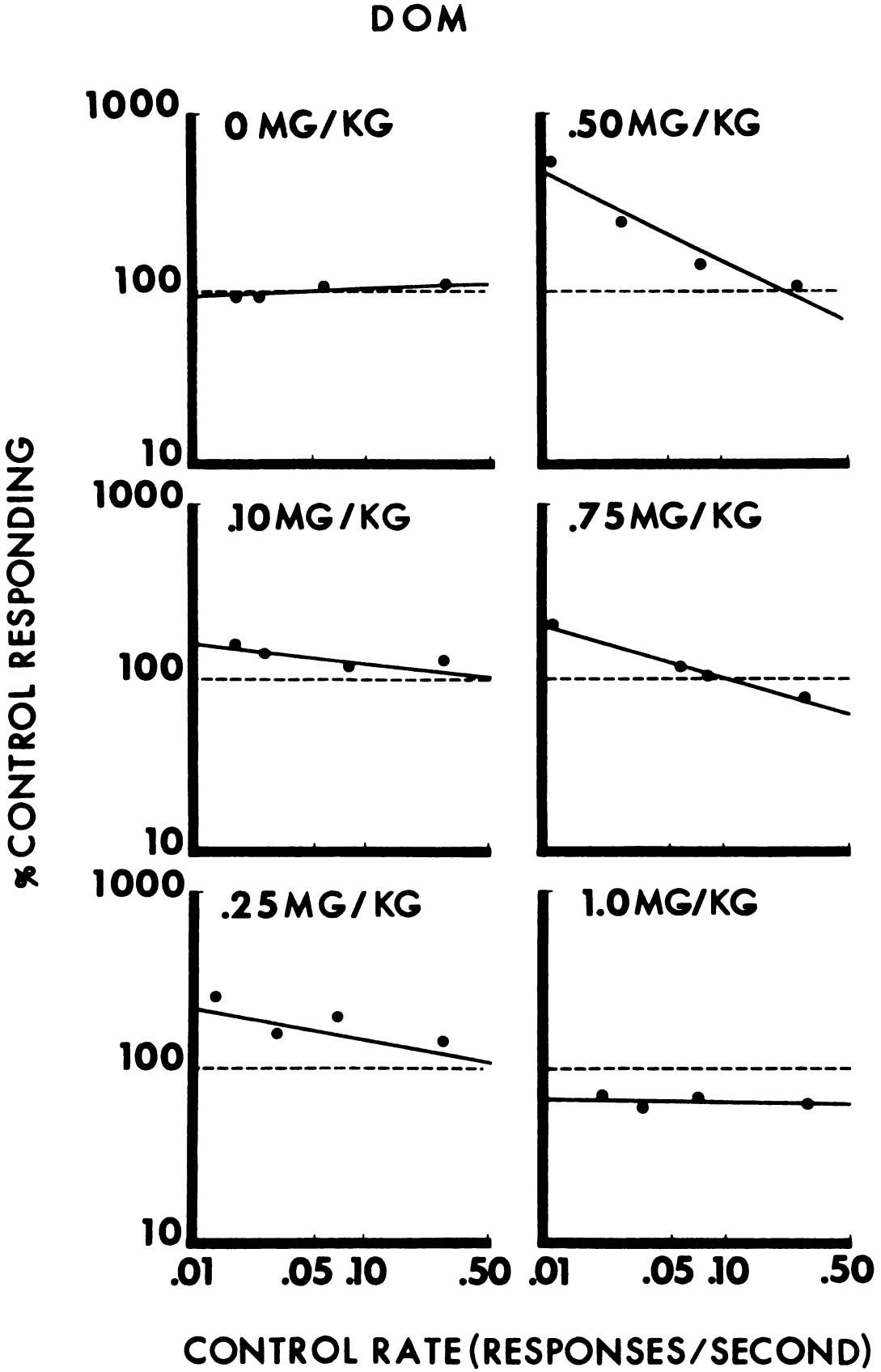

DOM
0 MG/KG
.50MG/KG
.10MG/KG
.75MG/KG
.25MG/KG
1.0MG/KG
1000
100
10
% CONTROL RESPONDING
.01
.05
.10
.50
CONTROL RATE (RESPONSES/SECOND)

Figure 6: The rate-dependent effects of various doses of d-amphetamine on FI-60 responding. See Figure 5 for details.

d-AMPHETAMINE

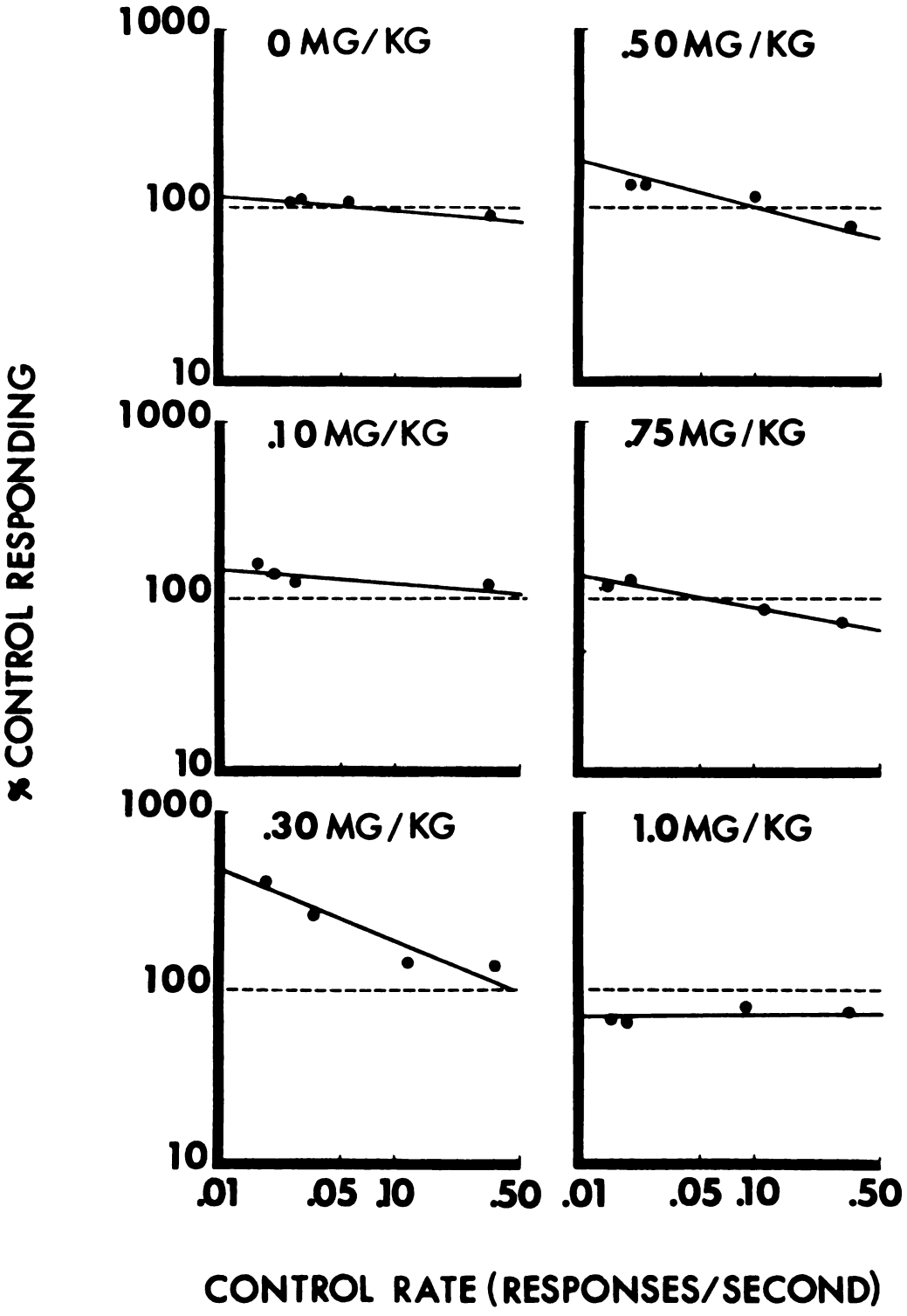


Figure 7: The rate-dependent effects of various doses of psilocybin on FI-60 responding. See Figure 5 for details.

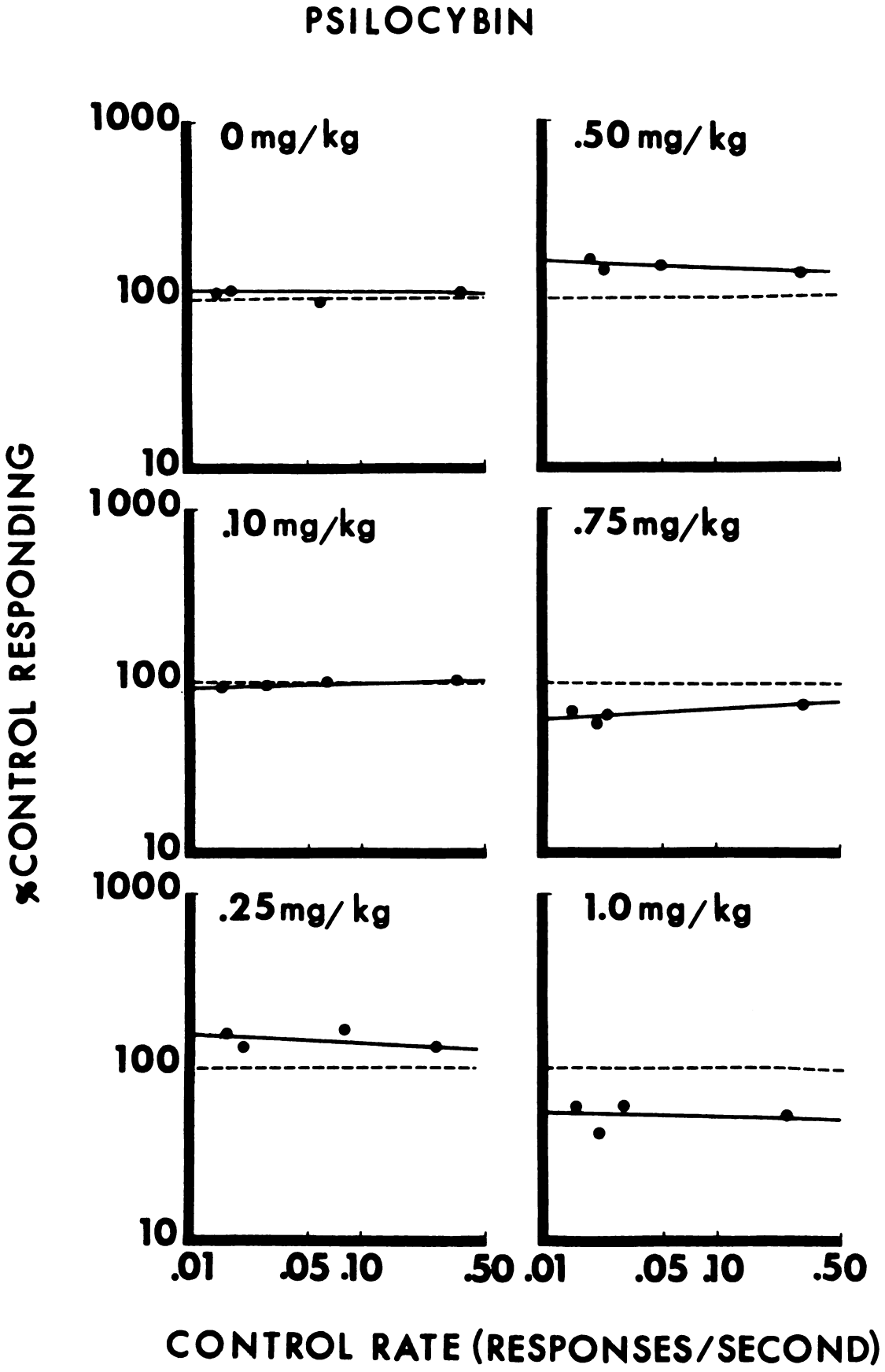
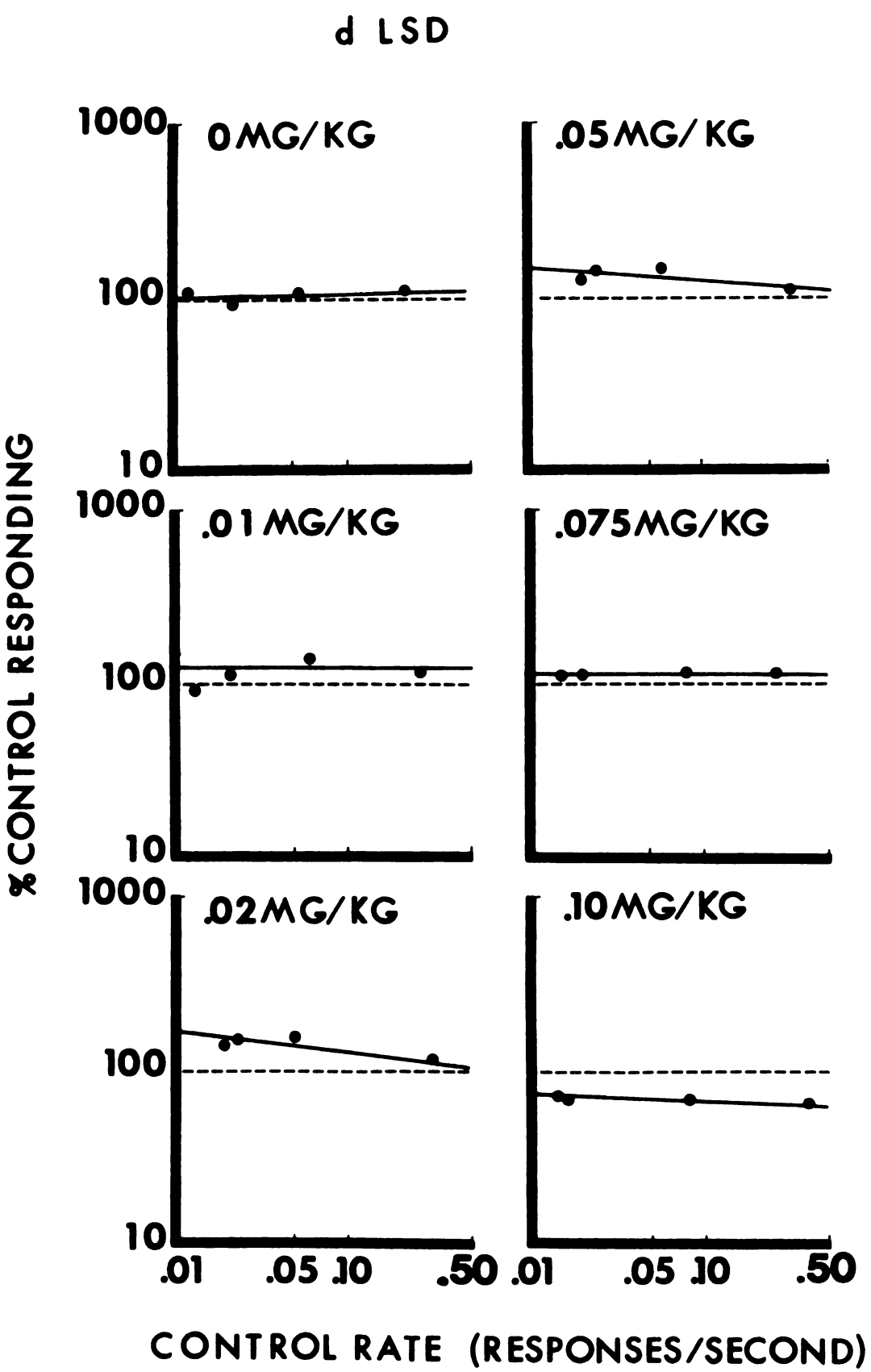

PSILOCYBIN
0 mg/kg
.50 mg/kg
.10 mg/kg
.75 mg/kg
.25 mg/kg
1.0 mg/kg
1000
100
10
% CONTROL RESPONDING
.01
.05
.10
.50
CONTROL RATE (RESPONSES/SECOND)

Figure 8: The rate-dependent effects of various doses of LSD on FI-60 responding. See Figure 5 for details.


d LSD
0MG/KG
.05MG/KG
.01MG/KG
.075MG/KG
.02MG/KG
.10MG/KG
1000
100
10
% CONTROL RESPONDING
.01
.05
.10
.50
CONTROL RATE (RESPONSES/SECOND)

DISCUSSION

The results of these experiments support the contention that hallucinogenic agents within the subclass investigated may be differentiated behaviorally. Thus, the hypothesis that they are all acting via a common receptor or site is not supported by this study. These data are in agreement with recent evidence which indicates that indolealkylamine-containing hallucinogens differ in their mechanisms of action from catecholamine-like hallucinogens. Freedman *et al.* (1970) reported that the catecholamine-like hallucinogens could be differentiated from indoleamine hallucinogens in their action on central 5-HT. Whereas all hallucinogens investigated increased 5-HT levels, it was demonstrated that indoleamines decreased 5-HIAA, the major metabolite. On the other hand, mescaline and DOM increased 5-HIAA, implying an increased turnover of 5-HT induced by these agents. Further neurochemical differences were shown by Tilson and Sparber (1972) who utilized a cerebral lateral ventricular perfusion technique to demonstrate that LSD and mescaline differed in their action on 5-HT mechanisms. Mescaline increased and LSD decreased the release of C^{14}-5-HT into the ventricular perfusate from pulse-labeled stores. There is also neurophysiological evidence that hallucinogens may differ in their action on 5-HT mediated

functions. Aghajanian et al. (1970) showed that intravenous administration of small doses of LSD and DMT completely inhibited the spontaneous firing of all midbrain raphe units in his test system. Mescaline and DOM, on the other hand, only inhibited a small proportion of the raphe units tested, those in the ventral portion of the dorsal raphe nucleus, and increased the firing rate or had no effect on units at other sites in the raphe area. Those units which responded with increased firing following mescaline and DOM have also been reported to increase their rates after d-amphetamine (Foote et al., 1969). A more recent study utilizing microiontophoretic application of hallucinogens to raphe units demonstrated that LSD had a direct effect to inhibit these cells, whereas mescaline's inhibition was indirect (Haigler and Aghajanian, 1973). An additional neurophysiological differentiation is demonstrated by EEG manifestations induced by hallucinogenic agents. Winters (1968) showed that LSD and mescaline differed in their effects on brain electrical activity of cats. Both drugs induced a hypersynchrony; however, the hypersynchrony associated with LSD was intermittent, whereas that induced by mescaline was continuous.

In the present study it was readily apparent that DOM (a catecholamine-like hallucinogen) could be differentiated behaviorally from the indoleamine-type agents

psilocybin and LSD. The behavioral profiles induced by DOM resembled those seen following d-amphetamine over a wide dose range. At the highest dose tested in drl and FI paradigms, DOM resembled LSD and psilocybin by inducing a significant depression of responding. Thus, it appears that DOM produces "sympathomimetic" effects over a low to moderate dose range similar to those seen following d-amphetamine and hallucinogenic effects at high doses. Perhaps the sensory distortions by the agents may underlie similarities in effects whereas the behavioral and biochemical differences may be associated with more subtle psychological phenomena.

SECTION II

INTRODUCTION

Experiments carried out in this section were designed to answer three questions:

1) What are the effects of repeated administration of hallucinogenic drugs? Will the animal develop tolerance to the initial behaviorally disruptive effects of these agents or will repeated administration result in an enhanced susceptibility to the behavioral effects?

2) Will hallucinogenic agents that induce a tolerance manifest a cross-tolerance when tested with other agents from this drug class? These data have relevance for determining similarities in mechanism of action within the hallucinogenic drug class.

3) What are the mechanisms involved in tolerance development? Do they involve cellular adaptations (direct tolerance) unrelated to experiental influences, or are they consistent with "behavioral tolerance" involving conditioned or learned phenomena?

Several investigators have reported that hallucinogens alter patterns of operant behavior and that repeated administration, in some cases, results in tolerance development to the behavioral effects (Freedman et al., 1964; Appel and Freedman, 1968; Winter, 1971; Sparber and Tilson,

1972). Since only a few drugs have been evaluated in this regard, I extended these studies to include many agents within the hallucinogenic drug class. In addition, the effects of varied doses of an agent will be investigated, as one previous report (Freedman et al., 1964) had indicated that the rate and extent of tolerance development may vary according to the dosage used. The time course for tolerance development will also be evaluated for each of the agents. Since many subjects, drugs, and doses will be utilized in these studies, I have chosen to utilize a fixed-ratio (FR) operant paradigm, it requiring the shortest training time to establish stabile responding rates for the subjects. In addition, drl and Sidman-Avoidance schedules will be employed to characterize long-term effects as well as cross-tolerance relationships. The importance of schedule differences has been noted by Schuster et al., 1965, to be an important variable in studies involving tolerance development. They postulated that behavioral tolerance will develop in those aspects of the organism's behavioral repertoire where the action of the drug is such that it disrupts the organism's behavior in meeting the environmental requirement for reinforcements. Conversely, where the actions of the drug enhance or do not affect the organism's behavior in meeting reinforcement requirements, one does not expect the development of behavioral tolerance.

According to this theory, one might expect tolerance development to drug-induced disruptions on drl and FR operant paradigms as the subject is initially losing reinforcements during a drug-induced pause or a rate increase on drl. However, one might not expect tolerance to develop to the rate increases following hallucinogens on a shock avoidance paradigm because this behavior serves to enhance the subject's adaptation to the negative reinforcement contingencies of the schedule. Thus, the utilization of three schedules will provide the opportunity for a more meaningful evaluation of tolerance and cross-tolerance phenomena.

Past studies utilizing an FR schedule have indicated that tolerance develops to the disruptive effects of LSD, mescaline and psilocybin (Freedman et al., 1964; Appel and Freedman, 1968). Tolerance is indicated by a decrement of effect contingent upon repeated administrations (daily) of the same amount of the compound. The decrement seen following these agents on an FR schedule is a dramatic cessation of responding occurring abruptly within a 40 minute behavioral session. Responding rates prior to and following the "pause" are similar to control rates so that it constitutes an "all or none" effect (i.e., no intermediate response rates are seen).

Enhanced susceptibility to a drug effect may also occur during chronic administration. Thus, Rech et al. (1974), showed that chronic, daily administration of d-amphetamine

to rats resulted in a progressive increase in motor activity, demonstrating that tolerance to the stimulant effects of the drug did not occur but rather an increased sensitivity ensued. In addition, these authors revealed that avoidance responding in the rat continued to increase following six consecutive daily sessions of d-amphetamine and that tolerance did not appear until the tenth session. Another pattern of response to repeated drug exposure was shown by Koella et al.,(1964). Measuring activity in goats, they recognized a cyclicity in the patterns of tolerance to repeated doses of LSD. It appeared that tolerance mechanisms periodically broke down during the course of drug administrations.

Those hallucinogenic agents that induce tolerance will be utilized for cross-tolerance investigations. Cross-tolerance generally suggests that two drugs act on the same receptor, or they exert their action through physiological or biochemical mechanisms on some common final pathway (Snyder and Richelson, 1968). Studies of the hallucinogens with regard to this phenomenon have not yielded cross-tolerance in every instance, suggesting that these compounds may be acting by different mechanisms. In human studies, cross-tolerance to the subjective and physiological effects of LSD, mescaline and psilocybin have been reported (Isbell et al., 1961; Rosenberg et al., 1963; Wolbach et al., 1962). It was found, however, that d-amphetamine and DMT did not

interact with the other hallucinogens to yield cross-tolerance (Isbell, 1962; Rosenberg, 1964). Animal studies have also yielded equivocal results. Appel and Freedman (1968) reported that rats tolerant to the disruptive effects of LSD on FR responding show cross-tolerance to psilocybin and a lower dose of mescaline, but not to d-amphetamine or a higher dose of mescaline. The cross-tolerance was reported to be complete (two-way), since rats tolerant to psilocybin and the lower dose of mescaline reportedly showed cross-tolerance to LSD. However, Freedman and Aghajanian (1959) have reported that rats tolerant to the effects of LSD on rope-climbing behavior were cross-tolerant to mescaline, but mescaline tolerant rats showed an enhanced response to LSD (i.e., one-way cross-tolerance). Tilson and Sparber (1972) showed partial cross-tolerance to the effects of LSD and mescaline on fixed-interval behavior and no cross-tolerance between LSD and d-amphetamine. It thus appears that the behavioral measures utilized, dosage, and experimental design are important variables that must be considered in a study of cross-tolerance.

Experiments in the last part of this section will involve an inquiry into the possible mechanisms responsible for tolerance formation. Tolerance development to the behaviorally disruptive effects of drugs may derive from one or more of the following mechanisms: (a) increased

rate of metabolism of the agent following prolonged exposure via an enzyme induction (metabolic tolerance); (b) decreased sensitivity of brain neuronal constituents initially affected by the drug (direct or cellular tolerance); and/or (c) psychological, homeostatic, adaptive adjustments that relate to conditioning or learning phenomena (behavioral tolerance). Winters (1971) assessed the potential contribution of metabolic tolerance to repeated LSD and found that there were no significant differences in concentration of LSD in brain and liver between rats which received LSD for the first time and those that had been pretreated for several days with LSD. Thus, no increase in metabolic disposition of LSD was occurring following prolonged administration. In order to ascertain the contribution and significance of the latter two mechanisms (cellular vs. behavioral tolerance), subjects in this study have received identical daily doses of an hallucinogenic agent, one group prior to and the other group following exposure to the behavioral paradigm. Once tolerance was evident for the group receiving drug before the behavioral task, both groups received drug prior to being tested in the behavioral procedure. In this manner the importance of conditioning phenomena should be revealed.

METHODS

Subjects: Sprague-Dawley, male rats were used as subjects throughout these investigations. The subjects used on drl and FR schedules were food-deprived to 80% of their free-feeding weight and maintained at this weight by intermittent feedings. Water was freely available for these subjects in their home cages. The rats utilized in the Sidman-Avoidance paradigm had continual access to food and water, except for the time they occupied the operant chamber.

Apparatus: Standard operant chambers were utilized throughout these investigations as previously described in Section I.

Drugs: The drugs employed in these studies included d-amphetamine, LSD, psilocybin, mescaline, DOM and DMT. Doses were calculated on the basis of previous findings in Section I. The drugs were all injected i.p. immediately prior to behavioral testing.

FR Schedule: A food-deprived rat is required to make 40 bar presses to obtain food reinforcement (FR-40). Training was accomplished by initially establishing bar pressing via a CRF paradigm (continuous reinforcement). The ratio of bar presses to reinforcement was gradually increased during subsequent sessions until steady rates were evident at FR-40. This procedure takes about 10 consecutive sessions. Responding rates were very stabile throughout the duration of behavioral testing. Since some hallucinogenic drugs have

been reported to induce a pause in a subject's responding during behavioral sessions on a FR paradigm, the duration of this pause will be utilized as a quantitative measure of tolerance formation. By employing an analysis of variance and a least significant difference test (lsd), drug treatment means can be compared to group control means to determine when tolerance development is evident.

Repeated Drug Administration: Following training to establish steady baseline rates of responding in drl, Sidman-Avoidance and FR operant schedules, chronic drug experiments were initiated. Each rat received a daily injection of drug just prior to being placed into the operant chamber. Identical doses of drug were administered daily for 10-14 days. Response measures analyzed were: drl:number of responses, number of reinforcers, and IRT's; Sidman-Avoidance: number of responses, number of shocks, and IRT's; FR: number of bar presses and duration of pause. These values were expressed as a percentage of the animal's control rate (based on the mean of three NaCl sessions preceding the initiation of drug injections).

Cross-Tolerance Studies: The FR schedule was extensively utilized in these investigations as the hallucinogenic drug-induced pause provided a quantitative measure for behavioral effects. In addition, the drl was employed to ascertain the potential for cross-tolerance between DOM and d-amphetamine,

since results from Section I suggested that over a low dose range these agents exhibited similar behavioral profiles. The general format of cross-tolerance investigations was as follows: Each experiment began with three consecutive NaCl control sessions followed the next day by a drug control session (Drug A). Two NaCl control sessions followed and the next day the other drug (Drug B) would be tested as a control. If the behavioral disruptions induced by these agents were approximately equal, consecutive daily drug sessions followed with one drug (A) until tolerance was evident (80% or more of the control rate). The day following tolerance to drug A, the subject was given a challenge dose of drug B to determine whether cross-tolerance had developed. By comparing the magnitude of behavioral disruption for drug B before (drug control) and after tolerance development to A, one can determine the extent of cross-tolerance between the agents. These determinations are expressed in tables depicting the average effect of a number of compounds on responding before ($\bar{X}$ %C pre) and after ($\bar{X}$ %C post) tolerance is induced. $\bar{X}$ %C post must be greater than $\bar{X}$ %C pre to demonstrate some degree of cross-tolerance. In addition, cross-tolerance relationships were determined by comparing the mean of the duration of the challenge drug-induced pause prior to tolerance formation to the mean length of pausing induced by the agent following presumed tolerance development

to the pretreatment drug. A paired Student's *t* test was employed for these comparisons.

Mechanisms of tolerance development: Utilizing an FR schedule, 4 rats (Group A) received 10.0 mg/kg mescaline prior to being placed into the operant chamber and run daily at this dose until tolerance developed to the pause in responding. Four other subjects (Group B) were treated daily with an identical dose of mescaline except that injections followed their exposure to the FR paradigm. On the day following tolerance development in Group A (day 4), both groups received the drug before being tested in the operant chamber. This provided the first occasion for simultaneous exposure to the drug influences and the behavior for Group B. If conditioning factors (adaptive learning) were instrumental for tolerance formation, then one may expect a drug-induced disruption at this time. On the other hand, if neuronal mechanisms (direct tolerance, cellular tolerance) were responsible for tolerance, independent of experiential or learning factors, one would expect tolerance to the hallucinogenic pause, since Group B received an equal amount of drug during the experimental session. Utilizing a similar design, LSD was also evaluated in this manner.

RESULTS

Since the FR paradigm had not been utilized in Section I, it was necessary to run pilot studies to establish dose-response relationships for the various hallucinogens on this schedule. Table 1 lists the threshold doses for these agents that induce a "pause" in FR responding. Doses larger than threshold generally induce the same pattern of disruption except that the period of cessation of responding is prolonged. d-Amphetamine, on the other hand, typically reduced the slope of responding during most of the 40 minute session, the decrease graduated in a dose-related manner. Pausing was rarely seen following d-amphetamine, only in a few subjects at very high doses. Figure 1 shows cumulative records of response patterns typically seen with LSD and d-amphetamine. Other drugs tested on the FR paradigm (chlorpromazine, barbiturates, etc.) produced similar effects as d-amphetamine by decreasing the slope of response rate without inducing a pause.

The effects of repeated, daily administration of various doses of hallucinogens on FR-40 responding are summarized in Table 2. It is readily apparent that the time course for tolerance development varies considerably for different drugs tested. Also, drug dosage is an important factor; lower doses of most agents induced a more rapid tolerance development. Table 3 shows in more detail the patterns and

Table 1: The minimum effective dose of various hallucinogenic drugs that will induce a pause in FR-40 responding.

DRUG	THRESHOLD DOSE TO INDUCE PAUSE [a]
LSD	0.08 mg/kg
PSILOCYBIN	0.80 mg/kg
MESCALINE	10.0 mg/kg
DOM	0.70 mg/kg
DMT	3.0 mg/kg

a Pause duration is greater than 5 minutes.

Figure 1: Representative response patterns (cumulative records) for LSD (0.10 mg/kg) and d-amphetamine (1.5 mg/kg) on FR-40. Control records are depicted on the top half and drug records on the bottom. The pips on the record indicate the delivery of a food pellet. The pen automatically resets following 550 responses. The legend on the right indicates the various response rates as a function of the slope of the responding record. Sessions ran 40 min.

Table 2: The time-course of tolerance formation for various hallucinogenic drugs on FR-40.

DRUG	DOSE (mg/kg)	DAYS TO TOLERANCE
LSD	0.1	2-3
LSD	0.195	14
Mescaline	10.0	2-4
Psilocybin	1.0	7-9
d-Amphetamine	0.5	8-10
d-Amphetamine	1.0	None by 14
DOM	0.7	9-11
DOM	1.0	11, but lost subsequently
DMT	3.0	None by 10 (2/3) ; 1/3 day 8

time-course of tolerance development following daily, consecutive drug injections. Each numerical entry designates in minutes the duration of the drug-induced period of no responding. An asterisk above a group designates that the pause duration on that particular day did not differ significantly from the group control mean (lsd test of group means) and thus, tolerance is indicated. From these data it appears that a rapid tolerance develops to the drug-induced pause following repeated injections of mescaline and a low dose (0.1 mg/kg) of LSD. Tolerance to repeated administration of a high dose of LSD (0.195 mg/kg) on the other hand is not evident until day 14. The results seen following repeated administration of a threshold dose of psilocybin (1.0 mg/kg) indicate that tolerance developed by day 7-9. A threshold dose of DOM (0.7 mg/kg) induced tolerance by day 9-11 which persisted during subsequent daily drug sessions (not shown), whereas a higher dose of this agent (1.0 mg/kg) produced a cyclicity of tolerance development. Tolerance was demonstrated on day 11; however, subsequent drug sessions resulted in a loss of tolerance (day 14). This pattern of cycling persisted over extended drug sessions (not shown) and resembled the periodic breakdown of tolerance reported by Koella in goats following chronic LSD administration. In 2 out of 3 subjects, no tolerance was evident following 10 daily injections of 3.0 mg/kg DMT.

Table 3: The effects of chronic, daily drug administration on the hallucinogenic pause.

Each numerical entry designates the duration in minutes of pausing (no responding) by a rat on a FR-40 paradigm. The drugs and dosages utilized are listed in the left column. Days are listed across the top of the table. C=control NaCl injection. The results of three subjects are listed for each drug.

An analysis of variance (random design) was performed for each drug treatment and a least significant differences (lsd) test was utilized to ascertain tolerance formation. Utilizing these criteria, an asterisk indicates that the group mean for a particular drug on a particular day is not significantly different from the group control mean and thus, tolerance is indicated.

Table 3 : The effects of chronic, daily drug administration on the hallucinogenic pause

DRUG AND DOSAGE	C	1	2	3	4	5	6	7	8	9	10	11	12	13	14
LSD 0.1 mg/kg	0.7	8.0	2.4*	2.5*	2.3*	0.8*									
	0.4	7.5	1.7	1.0	0.6	0.6									
	0.6	16.0	2.0	0.5	12.0	4.2									
LSD 0.195 mg/kg	0.6	33.1	23.2			20.1			18.1			13.3			1.5*
	0.3	31.0	20.1			24.6			21.4			23.1			1.3
	0.6	32.1	25.5			17.0			22.1			14.2			7.8
MESCALINE 10.0 mg/kg	0.4	7.6	0.5*	0.6	0.4*	0.5*									
	0.7	19.1	0.8	14.8	6.8	0.8									
	0.5	18.6	11.8	13.6	9.8	7.6									
PSILOCYBIN 1.0 mg/kg	1.0	35.6	29.6	34.8	27.6	26.3	20.3	11.8*	2.3*	0.7*					
	0.7	34.1	28.4	18.2	15.1	20.1	11.4	1.4	0.9	1.1					
	0.4	36.2	26.3	19.1	21.3	23.4	9.8	0.7	0.9	0.5					
d-AMPHETAMINE 0.5 mg/kg	1.2	1.2	1.5	2.3	1.9	1.6	1.9	1.7	1.4	1.9	1.7				
	0.6	2.8	2.4	1.8	1.6	1.2	1.4	1.0	0.9	1.1	0.7				
	0.9	1.2	1.8	1.9	2.3	1.7	1.5	1.9	0.9	1.1	0.8				
d-AMPHETAMINE 1.5 mg/kg	0.8	1.8	1.3	1.2	1.4	1.2	1.2	1.1	0.7	0.6	0.4				
	0.7	1.1	0.7	0.9	0.7	0.8	0.7	0.5	0.9	1.1	0.9				
	0.9	2.1	2.4	1.7	1.2	0.9	1.1	1.4	0.7	0.9	1.4				
DOM 1.0 mg/kg	1.4	29.1			35.1				30.3			6.9*			36.7
	0.6	30.2			31.7				16.9			16.8			16.0
	0.9	31.6			28.7				14.2			7.0			14.8
DOM 0.7 mg/kg	0.6	31.8	29.7	28.4	24.3	23.1	26.7	21.2	13.7	11.5*	7.7*	6.2*			
	1.2	26.2	14.3	11.1	16.2	8.4	3.2	0.7	0.9	0.8	1.7	0.6			
	0.9	28.1	24.6	21.3	16.4	29.1	13.1	7.9	13.9	6.2	0.9	0.6			
DMT 3.0 mg/kg	1.2	15.4	11.8	10.6	2.1	13.7	7.7	13.9	9.7	11.3	14.6				
	1.0	12.6	15.8	14.3	15.0	2.0	13.1	12.5	13.6	12.2	11.7				
	0.7	13.8	11.9	12.6	9.3	8.7	6.2	7.4	4.3	0.7	0.4				

Inspection of the pause duration data following chronic administration of 0.5 and 1.5 mg/kg d-amphetamine clearly indicates that no appreciable period of pausing occurs during 10 consecutive drug treatments. As previously stated, the disruption induced by this agent on an FR paradigm consists of a reduction in the slope of responding (see Figure 1) rather than a cessation of responding. Thus, tolerance formation cannot be deduced utilizing pause duration as a criterion. Figures 2 and 3 depict the effects of repeated administration of d-amphetamine utilizing the mean percentage of control responding as a measure to characterize tolerance development to this agent. Tolerance to drug-induced disruption was defined as a return of responding rates to at least 80% of control rates (Sparber and Tilson, 1972). Utilizing this criterion it appears that tolerance develops to 0.5 mg/kg d-amphetamine (Figure 2) by days 8-10, whereas no tolerance is evident following 14 consecutive injections of 1.5 mg/kg d-amphetamine (Figure 3).

Figure 4 shows the effect of repeated, daily injections of DOM (0.5 mg/kg) on drl behavior. The upper portion of the figure shows the mean (% of C) responses for three animals averaged over three consecutive daily sessions for 18 days. The bottom half of the figure depicts the mean number of reinforcers (% of C) received over these time intervals. It is apparent that tolerance develops to the

Figure 2: The effects of repeated, daily injections of d-amphetamine (0.5 mg/kg) on FR-30 responding. Each bar represents the mean and standard error of responding for three subjects following daily d-amphetamine administrations. Days are listed on the abscissa. Percentages are depicted on the ordinant.

Figure 2: The effects of repeated, daily injections of d-amphetamine (0.5 mg/kg) on FR-30 responding.

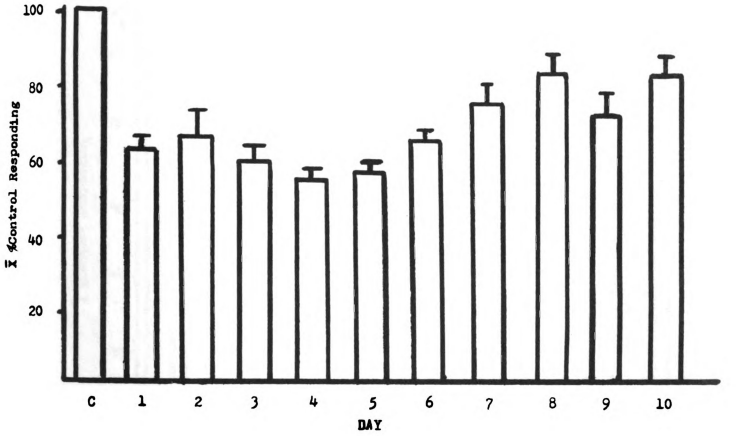


Figure 3: The effects of repeated, daily injections of d-amphetamine (1.5 mg/kg) on FR-40 responding. The consecutive days of treatment are listed on the abscissa. The mean percentage of control responding and the standard errors are depicted by the bars. Three subjects were tested.

Figure 3: The effects of repeated, daily injections of d-amphetamine on FR responding.

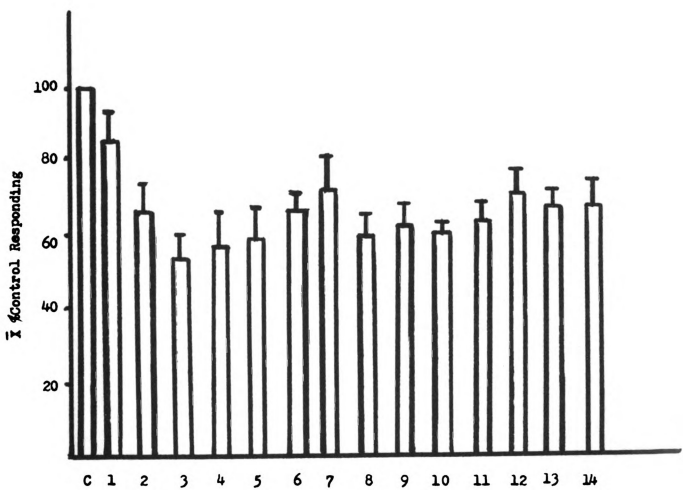


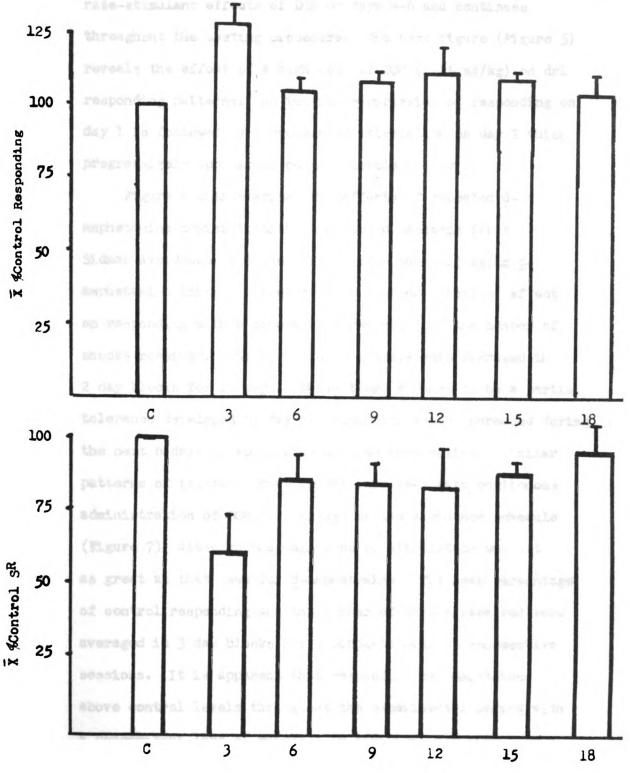
Figure 4: The effects of repeated, daily injections of DOM (0.5 mg/kg) on DRL-18 behavior. The top half represents responding patterns expressed as a percentage of the mean control, and the bottom half indicates reinforcers (S^R). Each bar depicts the mean behavioral measure averaged for 3 consecutive daily drug sessions. Thus, 3 indicates the mean drug effect for days 1,2, and 3; 6 indicates days 4,5, and 6, etc.
C=control NaCl injections
N=3

Mean Interresponse Times

Control	17.25
Days 1-3	14.51*
Days 4-6	16.59
Days 7-9	16.35
Days 10-12	15.58*
Days 13-15	15.79*
Days 16-18	16.38
Control	17.38

* denotes significant change

Figure 4: The effects of repeated, daily injections of DOM on DRL-18.



rate-stimulant effects of DOM by days 4-6 and continues throughout the testing procedure. The next figure (Figure 5) reveals the effect of a high dose of DOM (1.25 mg/kg) on drl responding patterns. An initial suppression of responding on day 1 is followed by a pronounced stimulation on day 2 which progressively approaches control levels by day 7.

Figure 6 characterizes the effects of repeated d-amphetamine administration on response patterns for a Sidman-Avoidance schedule. It is seen that 0.5 mg/kg d-amphetamine initially induced a pronounced stimulant effect on responding with a concomitant reduction in the number of shocks received. The means for 2 animals were averaged in 2 day blocks for 10 days. While there appears to be a partial tolerance developed by day 4, responding again increased during the next 6 days of continuous drug administration. Similar patterns of tolerance development were seen with continuous administration of DOM (1.0 mg/kg) on the avoidance schedule (Figure 7), although the magnitude of stimulation was not as great as that seen for d-amphetamine. The mean percentage of control responding and the number of shocks received were averaged in 3 day blocks for 3 subjects over 15 consecutive sessions. It is apparent that responding was maintained above control levels throughout the experimental period with a concomitant loss of shocks. In addition, the mean inter-response times were averaged over these time periods and are

Figure 5: The effects of repeated, daily injections of a depressing dose of DOM (1.25 mg/kg) on drl-18 response patterns. The points on the top line indicate the magnitude of responding (R) as a percentage of control on consecutive days of 1.25 mg/kg DOM injections for one rat. Points on the curve marked (S^R) represent the percent of control reinforcers received over the 16 day experimental session.

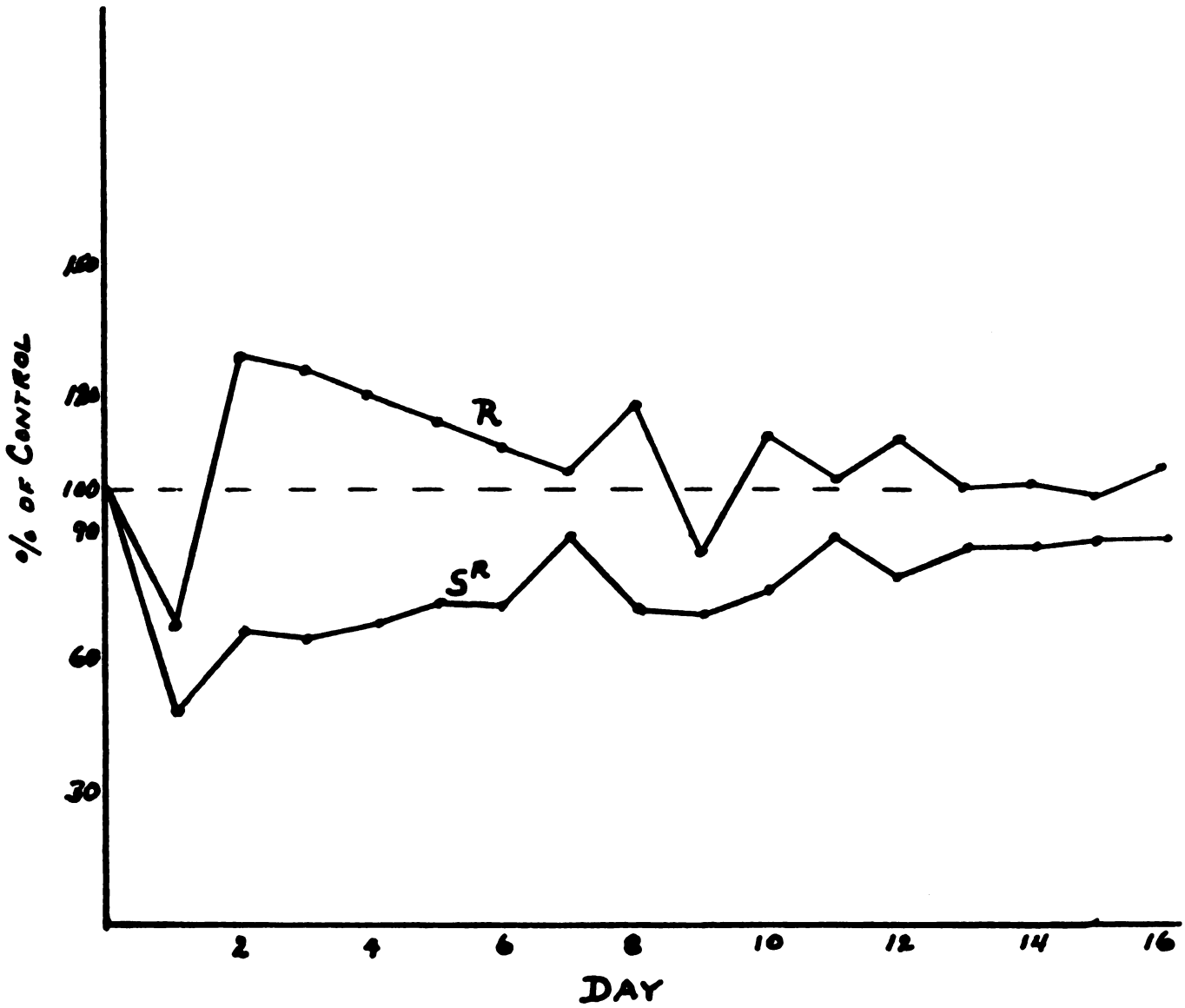

% of Control
120
100
90
60
30
R
S^R
2
4
6
8
10
12
14
16
DAY

Figure 6: The effects of repeated, daily injections of 0.5 mg/kg d-amphetamine on Sidman-Avoidance behavior. The bars on the upper graph represent the mean drug induced responding rates for two subjects averaged for 2 day periods and are expressed as a percentage of the mean control rates. The bottom graph depicts the mean number of shocks received for the 2 subjects over this time period. Days are represented on the abscissas.

Figure 6: The effects of repeated, daily injections of 0.5 mg/kg d-amphetamine on Sidman-Avoidance behavior.

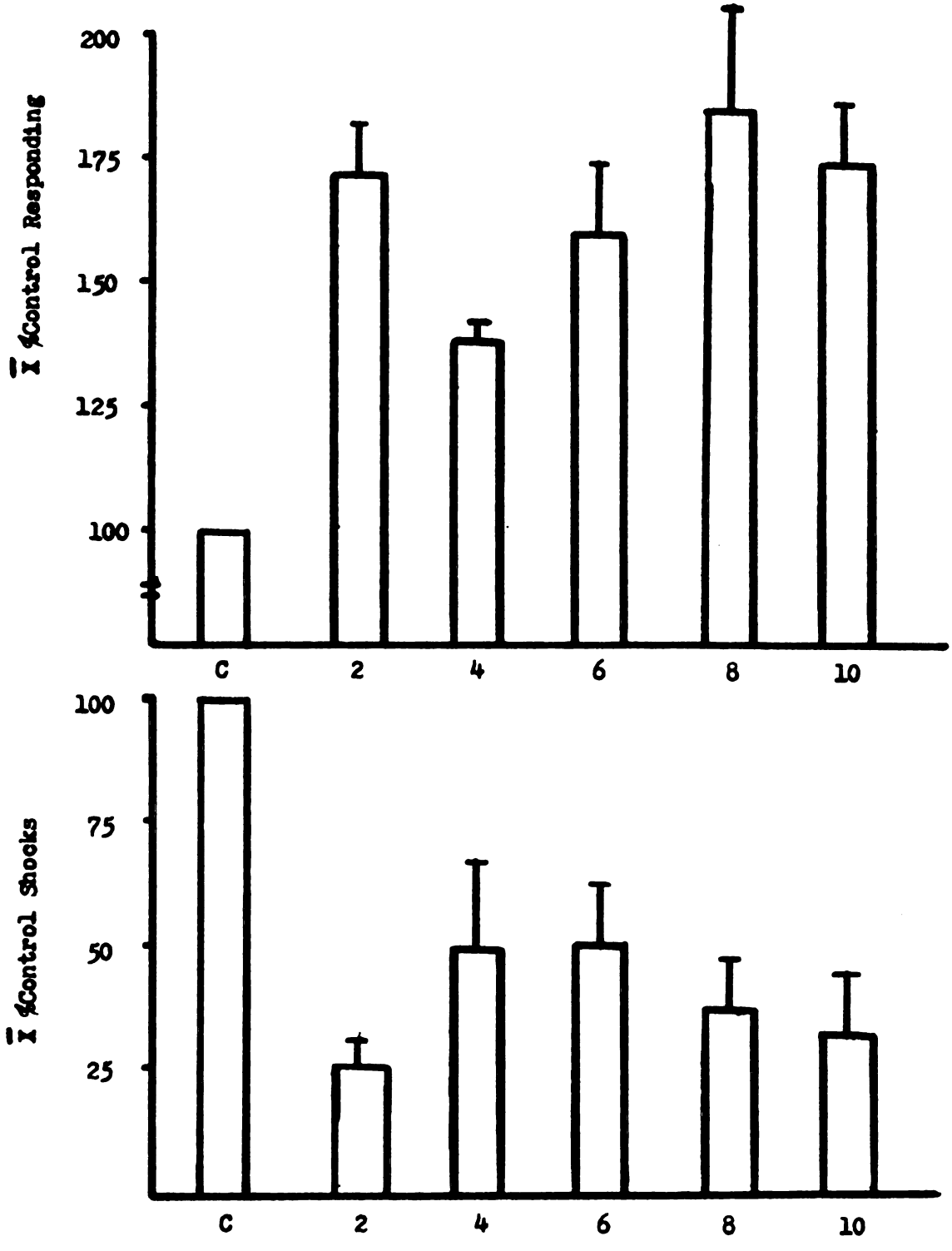
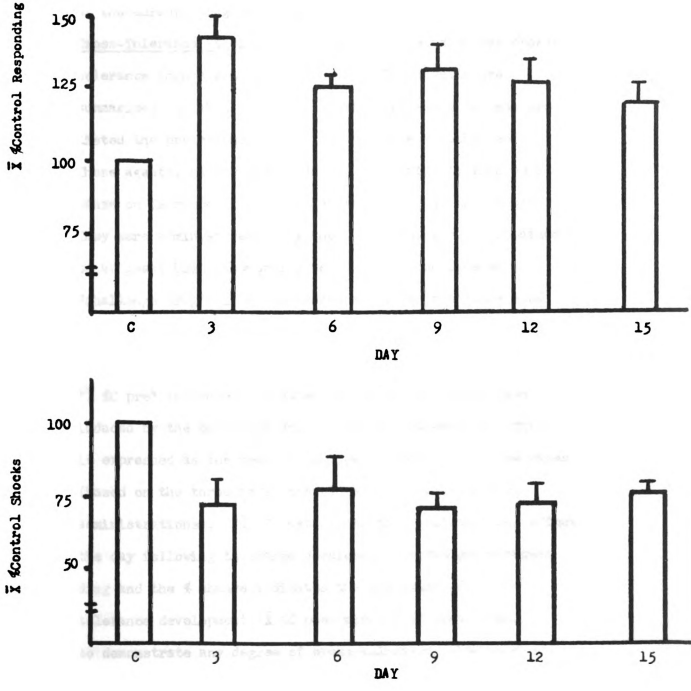


Figure 7: The effects of repeated, daily injections of DOM (1.0 mg/kg) on Sidman-Avoidance behavior. The bars on the upper graph represent the mean drug induced responding rates for 3 subjects averaged for consecutive 3 day periods and are expressed as a percentage of the mean control rates. The bottom graph depicts the mean number of shocks received for the 3 subjects over this time period.

Mean Interresponse Times

Control = 12.62±1.1
Day 1-3 = 10.30±1.5
Day 4-6 = 11.40±1.6
Day 7-9 = 11.50±1.3
Day10-12= 11.40±0.3
Day13-15= 11.80±0.4

Figure 7: The effects of repeated, daily injections of DOM on Sidman-Avoidance behavior.



indicated in the figure legend. It can be seen that the drug-induced shortening of the mean IRT persists during the course of the chronic drug sessions.

Cross-Tolerance Studies: The results of the extensive cross-tolerance investigations utilizing an FR schedule are summarized in Tables 4 and 5. In the left-hand columns are listed the pretreatment drugs and the dosages employed. These agents, as previously described, initially induced a pause on FR responding (d-amphetamine being an exception). They were administered daily until responding rates returned to at least 80% of control rates. The column labeled "Challenge Drug" lists the agents and doses that were subsequently tested in each case on the day following tolerance to the pretreatment drug. In Table 5, the column headed "$\bar{X}$ %C pre" indicates the extent of behavioral disruption induced by the challenge drug prior to pretreatment. This is expressed as the mean percentage of control response rates (based on the three NaCl control sessions prior to drug administrations). "$\bar{X}$ %C post" lists the challenge drug effect the day following tolerance development to the pretreatment drug and the % change indicates the magnitude of cross-tolerance development ($\bar{X}$ %C post minus $\bar{X}$ %C pre). Thus, to demonstrate any degree of cross-tolerance, $\bar{X}$ %C post must be greater than $\bar{X}$ %C pre so that the % change will be positive. Since the n numbers are small, it is difficult

to demonstrate cross-tolerance significance by statistical analysis utilizing responding as a criterion. Therefore, potential cross-tolerance relationships were assessed by comparing the challenge drug-induced pause duration prior to and following tolerance development to the pretreatment drug. Table 4 demonstrates these comparisons. The column headed "Pre, pause duration" lists the duration of pausing induced by the challenge drug for 3 subjects at each dose. The column labeled "Post, pause duration", lists the pause durations induced by the challenge drug the day following tolerance development to the pretreatment drug. The means for these behavioral measures (3 subjects) were compared by a paired Student's t test. The values of t.05 are listed in the right column and significant differences at the 5% level are indicated by an asterisk. Although a large amount of data is presented in these tables, which makes cross-tolerance relationships somewhat difficult to recognize immediately, close scrutiny discloses some consistent findings. It appears that cross-tolerance interrelationships are demonstrated for the indoleamine-containing hallucinogenic agents, as LSD-psilocybin, psilocybin-LSD, and DMT-LSD combinations suggest this phenomenon. It also appears that mescaline shares some common mechanisms with LSD, as pre-treatment with mescaline produces a significant cross-tolerance to LSD. When the drug order is reversed (i.e., pretreatment

Table 4: Cross-tolerance relationships between various hallucinogenic drugs based on pause durations.

a=drug and dosage utilized to induce tolerance following daily, consecutive administration. Tolerance is defined as a return of responding rates to at least 80% of control rates.

b=the drugs and doses tested prior to and following tolerance formation for the pretreatment drug.

c=pause durations induced by the challenge drug prior to tolerance to pretreatment drug.

d=pause durations induced by the challenge drug following tolerance to the pretreatment drug.

e=pause durations are expressed in minutes.

*=denotes significance at the 5% level utilizing a Student's paired t test.
t (tabular-2 degrees of freedom=4.303)

Table 4: Cross-tolerance relationships between various hallucinogenic drugs based on pause durations.

a Pretreat Drug	b Challenge Drug	c Pre, Pause duration	d Post, Pause duration	$t_{.05}$
LSD 0.1 mg/kg	Psilocybin 1.0 mg/kg	18.0	8.0	5.61*
		16.4	0.8	
		21.6	2.8	
	DOM 0.7 mg/kg	31.6	28.8	1.33
		30.0	27.2	
		33.6	32.1	
	DOM 1.0 mg/kg	22.6	23.1	0.98
		31.8	30.7	
		29.7	13.8	
	Mescaline 10.0 mg/kg	16.4	2.4	2.63
		31.7	16.3	
		23.6	2.0	
DOM 0.7 mg/kg	Mescaline 10.0 mg/kg	19.7	7.6	4.32*
		24.4	2.4	
		23.9	13.2	
	Psilocybin 1.0 mg/kg	31.6	32.4	0.68
		28.8	30.6	
		38.1	29.6	
	LSD 0.15 mg/kg	30.8	18.0	5.23*
		27.6	19.9	
		25.4	19.6	
Psilocybin 1.0 mg/kg	DOM 0.7 mg/kg	23.6	22.4	3.47
		26.0	21.2	
		25.6	19.2	
	LSD 0.15 mg/kg	22.8	13.2	4.26
		22.0	2.4	
		20.9	9.2	
Mescaline 10.0 mg/kg	DOM 0.7 mg/kg	19.6	19.2	0.92
		32.2	26.8	
		27.2	21.2	
	LSD 0.1 mg/kg	23.2	11.6	5.84*
		20.1	7.4	
		27.4	8.7	

Table 4 (cont'd)

Pretreat Drug	Challenge Drug	Pre, Pause duration	Post, Pause duration	t
d-Amphetamine 2.0 mg/kg	DOM 1.0 mg/kg	32.4 35.6 26.8	34.1 35.1 31.7	-0.73
DMT 3.0 mg/kg	LSD 0.15 mg/kg	24.2	1.6	

Table 5: Cross-tolerance relationships between various hallucinogenic drugs based on responding rates.

a=drug and dosage utilized to induce tolerance following daily, consecutive administrations. Tolerance is defined as a return of responding rates to at least 80% of control rates.

b=drug utilized prior to and after tolerance to the pretreatment drug to assess cross-tolerance relationship.

c=extent of behavioral disruption induced by the challenge drug prior to tolerance to the pretreatment drug. The behavioral disruption is expressed as the mean % and standard error of drug induced responding rates compared to control responding.

d=extent of behavioral disruption induced by the challenge drug following tolerance development to the pretreatment drug. This is expressed as the mean and S.E. and is compared to control responding rates.

e=indicates the magnitude of cross-tolerance development (X %C post minus X %C pre). A + indicates some degree of cross-tolerance.

Table 5: Cross-tolerance relationships between various hallucinogenic drugs.

Pretreat. Drug and Dose	Challenge Drug	Dose	N	$\bar{X}$ %C Pre	$\bar{X}$ %C Post	% Change
LSD 0.1 mg/kg	Psilocybin	1.0	(3)	53.3±3.3	89.7±4.9	+36.4
	DOM	0.7	(3)	20.7±2.6	26.6±3.5	+ 5.9
	DOM	1.0	(3)	32.7±5.4	47.6±14.0	+14.9
	Mescaline	10.0	(3)	39.7±11.5	78.6±15.8	+38.9
DOM 0.7 mg/kg	Mescaline	10.0	(3)	43.0±3.5	80.7±7.7	+37.7
	Psilocybin	1.0	(3)	17.3±7.4	23.0±6.8	+ 5.7
	LSD	0.15	(3)	29.3±2.4	51.6±1.7	+22.3
	d-Amphetamine	2.0	(3)	44.7±6.0	64.7±2.9	+20.0
Psilocybin 1.0 mg/kg	DOM	0.7	(3)	37.3±1.8	47.6±2.3	+10.3
	LSD	0.15	(3)	46.0±2.1	82.3±5.8	+36.3
	d-Amphetamine	2.0	(3)	37.8±2.8	38.8±4.7	+ 1.0
Mescaline 10.0 mg/kg	DOM	0.7	(3)	34.0±9.2	39.7±3.7	+ 5.7
	LSD	0.10	(3)	42.0±3.7	75.0±4.6	+33.0
d-Amphetamine 2.0 mg/kg	DOM	1.0	(3)	21.0±6.4	14.3±2.6	- 6.7
DMT 3.0 mg/kg	LSD	0.15	(1)	47	84	+37.0

with LSD and challenge with mescaline) 2 out of 3 subjects manifested a cross-tolerance relationship even though group significance was not attained. The relationships between DOM and other agents are somewhat equivocal. Whereas pretreatment with DOM generated significant cross-tolerance to LSD and mescaline, no cross-tolerance relationships are evident when DOM is the challenge drug. Thus, the cross-tolerance is termed "one-way" (Tilson and Sparber, 1973). For example, when rats were pretreated with DOM until tolerance became evident and then challenged with mescaline, a significant cross-tolerance was observed. However, rats tolerant to repeated doses of mescaline did not manifest cross-tolerance when challenged with DOM. Figures 8 and 9 are representative cumulative records which may more clearly demonstrate the cross-tolerance procedure and results. In Figure 8, the top panel depicts the typical mescaline induced pause. A control record follows. The next panel shows the the pause that was induced by 0.7 mg/kg DOM. Continued daily injections of 0.7 mg/kg DOM resulted in a shortening of the pause, as shown in the 4th panel. After 8 days of daily drug injections tolerance was evident, as shown in panel 5. The following day 10.0 mg/kg mescaline produced no pause, i.e., cross-tolerance was demonstrated. Figure 9 demonstrates in a similar manner the complete cross-tolerance relationship between LSD and DMT.

Figure 8: Cross-tolerance relationships between DOM and mescaline on FR-40. Panels A-F represent cumulative records of one subject and demonstrate complete cross-tolerance between 0.7 mg/kg DOM and 10.0 mg/kg mescaline. Panel A shows the typical pause in responding induced by 10.0 mg/kg mescaline. Panel B shows the control record (NaCl) obtained the following day. Panel C shows the pause induced by 0.7 mg/kg DOM. Continual daily injections of 0.7 mg/kg DOM resulted in a shortening of the pause by the third consecutive dose (Panel D). Panel E indicates that tolerance had developed to DOM (8th day of daily DOM injections). Panel F shows the record obtained the following day when 10.0 mg/kg mescaline was administered. Complete cross-tolerance was evident.

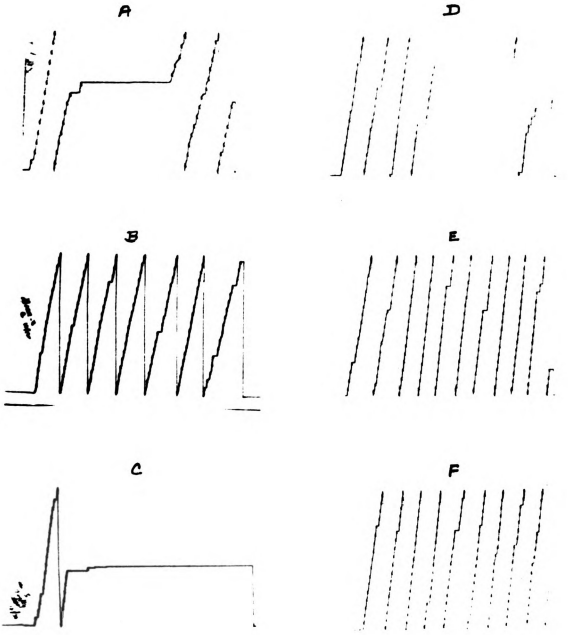

A
D
B
E
C
F

Figure 9: Cross-tolerance relationships between LSD and DMT on FR-40. Panels A-F represent cumulative records of one subject and demonstrate complete cross-tolerance between 0.15 mg/kg LSD and 3.0 mg/kg DMT. Panel A depicts the pause induced by 0.15 mg/kg LSD. A control record obtained the following day is shown in Panel B. Panel C illustrates the pause induced by 3.0 mg/kg DMT. Continual daily administration of this dose of DMT produced partial tolerance development (Panel D). Complete tolerance to 3.0 mg/kg DMT (Panel E) was evident by the 10th consecutive daily injection. A challenge dose of LSD the following day resulted in complete cross-tolerance as depicted in Panel F.

Since d-amphetamine and DOM at some doses appeared to produce similar behavioral profiles on several schedules (Section I) it was decided to assess cross-tolerance relationships between these agents on both FR and drl schedules. Table 5 shows that some degree of cross-tolerance was seen on the FR when DOM was used as a pretreating agent to induce tolerance and then subjects were challenged with d-amphetamine. However, when the drug order was reversed (Table 5) no degree of cross-tolerance was seen. Thus, indications of a one-way cross-tolerance were suggested. A similar one-way cross-tolerance was noted utilizing the drl schedule. Figure 10 clearly demonstrates a complete cross-tolerance between d-amphetamine and DOM when DOM was used to induce tolerance and d-amphetamine was the challenge drug. The top-half of the figure represents responding as a percentage of control and the bottom-half shows the number of reinforcers received. The drug treatments are represented on the abscissas. Drug control determinations reveal similar behavioral disruptions for comparable doses of d-amphetamine and DOM, seen as an increase in responding and loss of reinforcers. Tolerance to these effects was induced by repeated injections of DOM, demonstrated by the return of these parameters to control levels by the third day of daily drug administration. The challenge dose of d-amphetamine produced responding patterns almost identical to control, thus indicating complete cross

Figure 10: Cross-tolerance relationships between DOM and d-amphetamine on dr1-18. The top-half of the figure represents mean responding rates for 3 subjects as a percentage of control rates following various drug treatments (represented on the abscissas). The bottom-half shows the mean reinforcers (S^R) received for these treatments. Each treatment occurs on a consecutive day over the 10 day experimental period depicted on the abscissas. C = control (NaCl injection). d-A = d-amphetamine. It is evident that cross-tolerance is established. See text for more details. N = 3.

Mean Interresponse Times

Control = 17.53±0.08

0.5 DOM = 14.12±0.27

Control = 17.40±0.28

0.5 d-A = 14.95±0.87

Control = 17.78±0.15

0.5 DOM = 13.57±0.58

0.5 DOM = 15.17±0.19

0.5 DOM = 17.35±0.24

0.5 d-A = 16.41±0.83

Control = 17.60±0.15

Figure 10: Cross-tolerance relationships between DOM and d-Amphetamine on DRL-18.

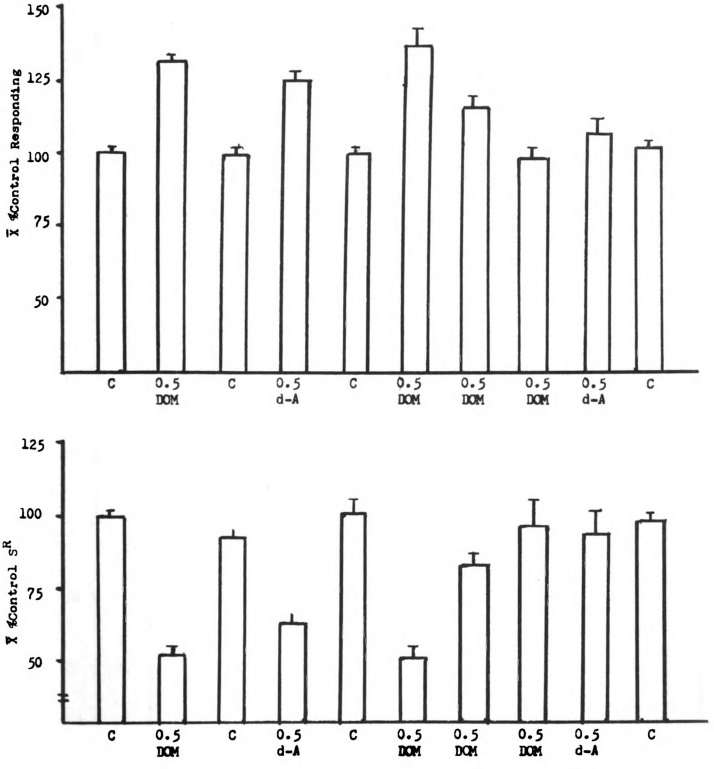
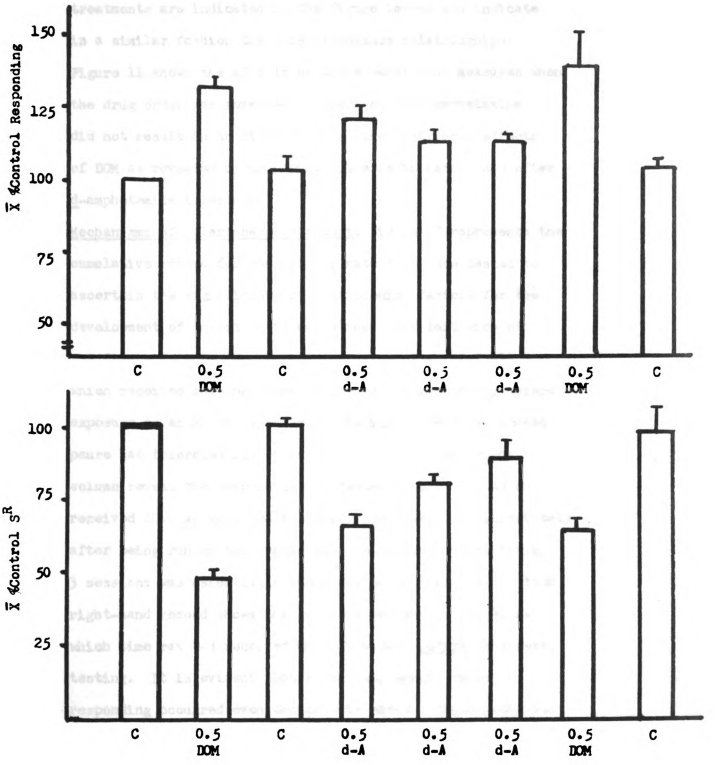


Figure 11: Cross-tolerance relationships between d-amphetamine and DOM on drl-18: Importance of drug order. The top-half of the figure represents mean responding rates for 2 subjects as a percentage of control rates following various drug treatments (represented on the abscissas). The bottom-half shows the mean reinforcers (S^R) received during these treatments. Each treatment occurs on a consecutive day over the 8 day experimental period depicted on the abscissas. A lack of cross-tolerance is demonstrated as opposed to the results illustrated in Figure 10 where the drug order is reversed. See text for more detail.

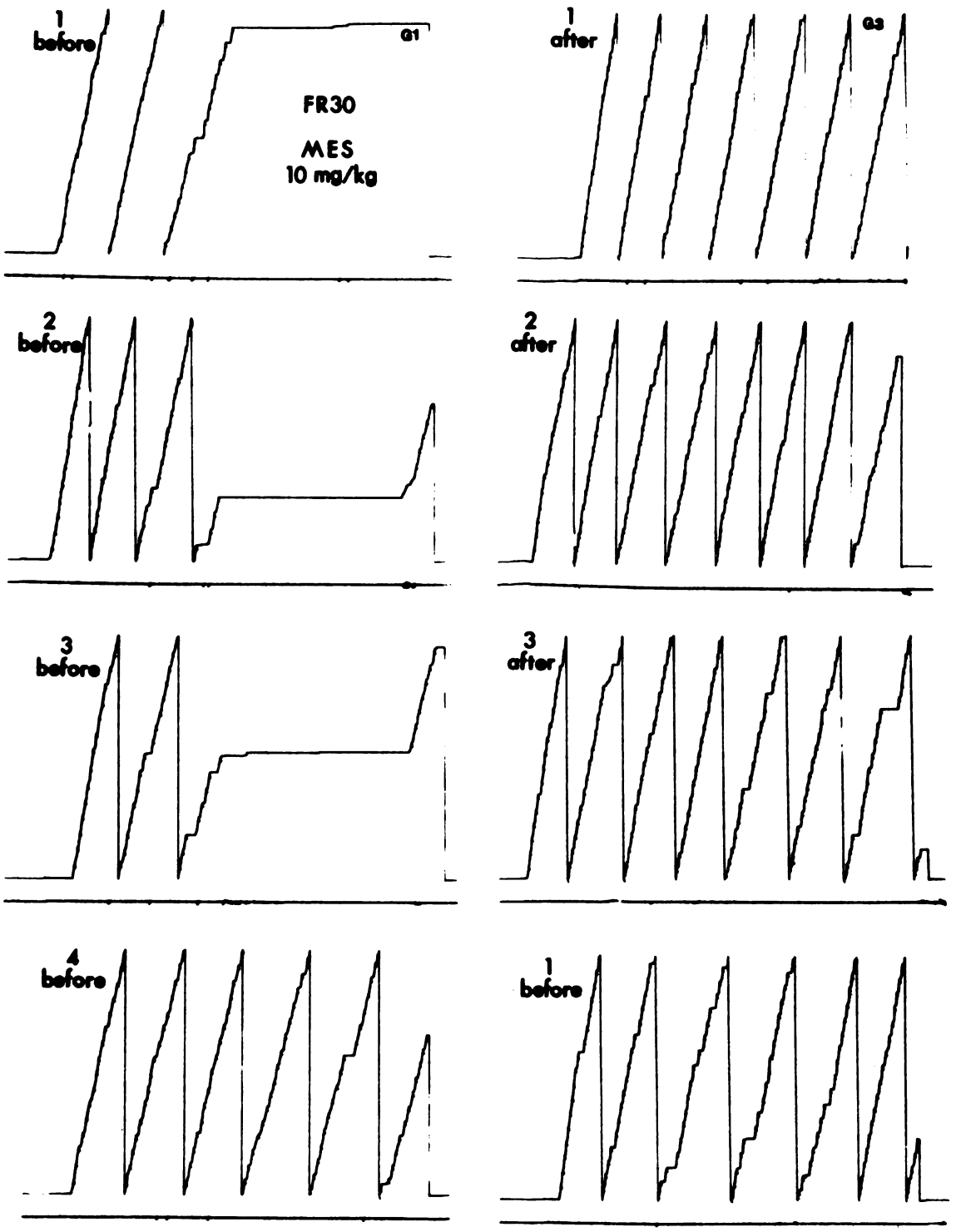
Figure 11: Cross-tolerance relationships between d-Amphetamine and DOM on DRL-18; Importance of drug order.



tolerance. The mean interresponse times following these treatments are indicated in the figure legend and indicate in a similar fashion the cross-tolerance relationships. Figure 11 shows the effects on these behavioral measures when the drug order was reversed. Tolerance to d-amphetamine did not result in an attenuation of the behavioral effects of DOM as revealed by comparing DOM effects before and after d-amphetamine tolerance.

Mechanisms of tolerance development: Figure 12 represents the cumulative record for one pair of rats that were tested to ascertain the significance of conditioning factors for the development of tolerance to mescaline. The left side of the figure depicts the response patterns of a rat (G-1) which received 10.0 mg/kg mescaline daily immediately before exposure to an FR-30 behavioral paradigm. The drug-induced pause had tolerated out by day 4. Records in the right column reveal the responding manifested by rat G-3, which received 10.0 mg/kg mescaline daily for 3 sessions immediately after being run on this paradigm. Responding during these 3 sessions was essentially identical to control. The bottom right-hand record shows the response pattern on day 4, at which time rat G-3 received mescaline just before behavioral testing. It is evident that no hallucinogenic pause in responding occurred even though this was the first occassion for rat G-3 to experience the drug influence at the time of

Figure 12: The lack of effect of conditioning factors in the development of tolerance to mescaline on FR-30. This figure represents sample cumulative records for a pair of rats that were tested to ascertain the significance of conditioning factors for the development of tolerance to 10.0 mg/kg mescaline. The responding patterns for rat G-1 are depicted on the left side of the figure. The notation "before" designates that this subject received drug before being tested on the FR behavioral paradigm. The numbers indicate the day of consecutive drug injection. Rat G-3 received drug after being run on the FR-30 schedule on days 1, 2, and 3. On day 4 (1 before) this subject received 10.0 mg/kg mescaline for the first time immediately before being tested on the FR behavioral task. See text for details.


1
before
a1
FR30
MES
10 mg/kg
1
after
a3
2
before
2
after
3
before
3
after
4
before
1
before

exposure to the specific behavioral procedure. Two additional pairs of animals exhibited essentially the same patterns. This design was also carried out with LSD and the FR-30 schedule. It required 7 daily repetitions of dosing with LSD (0.15 mg/kg), injected before the subjects entered the Skinner Box, to develop complete tolerance in the first group of 3 rats. The second group of 3 subjects received LSD for 6 days following the behavioral measurement. On the seventh day, this second group was injected with LSD before exposure to the FR-30 session and demonstrated complete tolerance to the hallucinogenic pause initially induced by a test dose of the drug.

DISCUSSION

These investigations indicate that the FR schedule is a useful behavioral paradigm for assessing hallucinogenic drug effects. The threshold doses of hallucinogens that induce a "pause" in responding behavior on FR parallel in their order of potency the effects found in humans. Since other classes of drugs at behaviorally effective doses appear to decrease the slope of the FR response rate rather than induce a pause, this manifestation (pause) may be specific for the hallucinogenic properties of psychoactive drugs.

The chronic drug studies revealed that differences exist between the various hallucinogenic agents in the patterns and extent of tolerance development. Thus, it was found that threshold doses of LSD and mescaline produced a rapid tolerance formation, whereas psilocybin, DOM, larger doses of LSD, and d-amphetamine induced varying degrees of tolerance only over a longer period of daily injections. Drug dosage proved to be an important variable for all agents, as higher doses consistently prolonged tolerance development.

Aghajanian (1973) has recently reported that some degree of tolerance occurs to the depression of raphe unit firing following 3 to 4 daily treatments of LSD. This correlates with the time course of tolerance development to the pause induced by LSD on FR-40. However, if the behavioral tolerance manifested in these studies derived exclusively from the

drug action on raphe neurons, one might expect the indoleamine agents (LSD, psilocybin and DMT), which presumably directly inhibit raphe units (Haigler and Aghajanian, 1973), to show a more similar time-course in their tolerance development patterns. The lack of tolerance seen following repeated, daily administration of 3.0 mg/kg DMT in two out of three subjects is difficult to interpret. Since this agent directly inhibits the firing of raphe units in a manner similar to LSD, one might expect more similar patterns of tolerance formation for these two drugs. One recent report (Kovacic and Domino, 1974), however, indicated that long-term and much more frequent injections of DMT (every 2 hours for 2-3 weeks) did result in tolerance to the behaviorally disruptive effects in rats, as well as partial cross-tolerance to LSD. Since DMT has a very short half-life compared to LSD, perhaps the daily injections utilized in these studies are spaced too far apart to promote this phenomenon. On the other hand, if tolerance actually does not develop to DMT, this would strengthen the likelihood that its endogenous production may be the biochemical trigger of schizophrenia and/or REM sleep. Certainly, further and more extensive investigation regarding these relationships is warranted.

The behavioral findings following repeated administration of 0.5 mg/kg DOM on drl-18 revealed that the initial disruption of timing behavior during the first 2-3 sessions showed

tolerance by days 4-6. This finding has also been reported for d-amphetamine (1.0 mg/kg) during chronic injections on drl-30 by Schuster et al. (1966). When a high dose of DOM (1.25 mg/kg), which initially induced a pause in drl responding, was continually administered, the depression reverted to a stimulation during days 2-7. Since DOM produces a biphasic dose-effect on drl (Section I), it is conceivable that a partial tolerance resulted by day 2, causing the subjects to interpret 1.25 mg/kg (depressing dose) as a stimulant dose (0.25 to 0.75 mg/kg). The stimulation induced on day 2 by the high dose of DOM gradually showed tolerance (days 2-7) with a similar time course as seen for 0.5 mg/kg DOM, described in Figure 8.

The response patterns (maintained high rates and loss of shocks) following repeated injections of d-amphetamine and DOM on continuous avoidance further demonstrate the similarity of these agents in their behavioral profiles. In addition, the lack of tolerance formation supports the theory of Schuster (1966); thus, stimulation of responding confers an adaptive advantage on a shock avoidance paradigm, so that tolerance development would not be expedient. Tolerance development to the stimulation on a drl schedule, on the other hand, would enhance the likelihood of meeting reinforcement contingencies and, therefore, would be expected in these investigations.

Results from the cross-tolerance investigations generally indicated that combinations of indoleamine-like hallucinogenic agents demonstrated cross-tolerance, implying that they share some common factors in their mechanisms of action. These data confirm and extend the findings of previous reports in animals (Appel and Freedman, 1968) and man (Isbell, 1961; Welbach et al., 1962). Mescaline also demonstrated cross-tolerance relationships when tested with LSD, even though these compounds differ markedly in chemical structure, effect on raphe unit firing (Aghajanian, 1970), 5-HT turnover (Freedman et al., 1970) and EEG manifestations (Winter, 1970). On the other hand, Schechter and Rosecrans (1972) showed that mescaline, LSD, and psilocybin produced qualitatively similar interoceptive cues in the rat. It is difficult to reconcile these findings. Perhaps the biochemical and neurophysiological differences between these agents may be associated with more subtle psychological phenomena and are not reflected in this behavioral measure. In this regard, Tilson and Sparber (1972), utilizing a discrete analysis of FI responding, showed that complete cross-tolerance did not occur for mescaline and LSD.

The cross-tolerance tests between DOM (a catecholamine-like hallucinogen) and the indoleamine agents revealed an interesting relationship. Generally when 0.7 mg/kg DOM was utilized as the pretreating agent to establish tolerance, some degree of cross-tolerance was evident with another challenge

drug (psilocybin was an exception). However, in all cases where the drug order of presentation was reversed (i.e., DOM was the challenge drug) no evidence of cross-tolerance was demonstrated. As previously stated, DOM appears to exhibit a one-way cross-tolerance with other hallucinogenic agents. Perhaps DOM has a wider spectrum of action in the central nervous system, interacting with several brain sites to produce its behavioral effects, whereas other hallucinogens are more restricted in their locus of action. Thus, the behavioral tolerance formation induced by LSD, mescaline, etc. may only involve the adaptation (biochemical, neurophysiological, ?) of one or a few brain mechanisms or sites, and the introduction of DOM with a more diversified spectrum of action would result in behavioral disruption (i.e., lack of cross-tolerance). If one reverses the order of drug presentation and establishes behavioral tolerance to DOM, one may speculate that cross-tolerance would result following a challenge with LSD or mescaline, since the adaptations induced by DOM tolerance overlap and protect against the mechanisms of behavioral disruption for the latter two agents. In this regard, DOM does appear to interact with several brain neuronal mechanisms compared to other hallucinogens, as evidenced by its biphasic action on operant schedules (Section I). Another factor that might account for a one-way cross-tolerance relationship between DOM and other

hallucinogens is the time factor involved in inducing tolerance. As previously shown, tolerance is evident following 2-4 daily administrations of LSD and mescaline, whereas 10 consecutive daily sessions are necessary to induce tolerance with DOM. Perhaps the extended exposure to drug effects facilitates the establishment of cross-tolerance. This could be tested by prolonging the daily administration of LSD or mescaline beyond the tolerance day (i.e., 10 sessions instead of 2-4) and then challenging with DOM.

The relationship between DOM and d-amphetamine in cross-tolerance studies also suggested a one-way cross-tolerance on both FR and drl paradigms, indicating some overlap in mechanisms of action. In previous investigations cross-tolerance has never been demonstrated in either direction between d-amphetamine and hallucinogenic agents (Appel and Freedman, 1968; Rosenberg et al., 1963; Sparber and Tilson, 1972). Thus, this is the first behavioral demonstration that suggests similarities between a stimulant and an hallucinogenic agent, and confirms the results obtained in Section I which demonstrated similarities following acute injections of these agents. Explanations of the one-way cross-tolerance might be derived in a similar manner as described above; that is, DOM may have a broader spectrum of action than d-amphetamine.

The results derived from studies investigating the

importance of conditioning and learning phenomena in tolerance development to hallucinogenic agents showed that these factors were probably not critical variables. It thus appears that the mechanisms involved in tolerance formation on this behavioral paradigm are more related to direct, neuronal adaptations indicative of cellular tolerance.

SECTION III

INTRODUCTION

Few reports in the literature have described the effects of brain amine alterations on hallucinogenic drug-induced behavioral disruptions or assessed the significance of receptor blocking agents on these drug effects. These types of investigations might help to elucidate the role and relative contribution of specific transmitter systems in their interaction with hallucinogenic drugs.

Appel and Freedman (1964) showed that pretreatment of rats with reserpine or tetrabenazine (which significantly deplete 5-HT and norepinephrine) prolonged the period of no responding induced by LSD on FR-30 behavior, while chlorpromazine attenuated the response to LSD. This study showed that non-specific monoamine depleters alter the sensitivity of rats to LSD on a behavioral task. In order to evaluate whcih amines may be involved in ahe LSD induced disruption of FR behavior, Appel et al. (1970)selectively depleted 5-HT with parachlorophenylalanine (PCPA) and norepinephrine with alpha-methyl-para-tyrosine (AMPT) and found an enhanced sensitivity to LSD following PCPA depletion of 5-HT. Sensitivity to LSD was unaffected by pretreatment with AMPT. On the other hand, Knoll and Vizi (1970) found that PCPA pretreatment markedly reduced the behavioral effects of LSD and mescaline in rats. They postulated that intact 5-HT stores were

necessary for hallucinogenic drug effects. AMPT in their hands failed to alter the behavioral effects of these agents. Menon et al. (1967), however, have reported that the central stimulant effect of high doses of mescaline (100 mg/kg) was attenuated by pretreatment with AMPT, implying that mescaline produces increases in motor activity in mice via norepinephrine or dopamine release. Thus, the few interaction studies which have been done are conflicting and limited to only a few drugs. By utilizing several agents known to alter neurotransmitter levels as well as blocking agents and evaluating their effects on the behavioral potency of several hallucinogens, the mechanisms by which hallucinogens interact with central neurotransmitter systems may be more clearly elucidated. Emphasis will be directed toward evaluating hallucinogen-5-HT interactions, as most theories of hallucinogenic drug action involve this system. Since recent reports have indicated that cinanserin (2'- (3-dimethylaminopropylthio)-cinnamanilide) is a potent, selective blocker of 5-HT receptors (Dyer and Gant, 1973; Chase and Murphy, 1973; Winter, 1969), this drug will be utilized extensively in these interaction studies.

METHODS

Subjects: Male, Sprague-Dawley rats were used throughout these investigations. Rats trained on an FR-30 behavioral paradigm were food deprived to 80% of their free-feeding body weight and maintained at that level throughout the investigations. Water was freely available in their home cages. Animals run on the Sidman-Avoidance achedule had ad libitum access to food and water.

Apparatus: The subjects were run in standard operant chambers as previously described in Section I.

Behavioral Procedures: Food deprived and drug naive rats were initially trained to bar press on a continual reinforcement schedule (CRF). The ratio of bar presses to reinforcement was gradually increased during subsequent training sessions until stabile rates were evident on FR-30. Sessions ran 40 minutes. Prior to the initiation of drug studies, three consecutive NaCl sessions were conducted to establish a mean control rate. Each animal served as his own control. On the Sidman-Avoidance paradigm the three rats that were used in this study had past exposure to drugs (Section I) but had been drug-free for two months prior to the initiation of this procedure.

Pharmacological Procedures: The experimental design of the interaction studies is summarized in the following table:

Experiment #	Schedule	Pretreatment Drug	Test Drug	N
1	FR-30	PCPA (100 mg/kg) x 3 days	DOM (0.70 mg/kg)	2
	FR-30	PCPA (100 mg/kg) x 3 days	Mescaline 10.0 mg/kg	2
2	Sidman-Avoidance	AMPT (40 mg/kg)	DOM (1.0 mg/kg)	3
	Sidman-Avoidance	AMPT (40 mg/kg)	d-A (0.5 mg/kg)	3
3	FR-30	AMPT (40 mg/kg)	DOM (0.7 mg/kg)	2
	FR-30	Chlorpromazine (CPZ) (0.5 mg/kg)	DOM (0.7 mg/kg)	1
	FR-30	Cinanserin (30 & 10 mg/kg)	DOM (0.7 mg/kg)	3
	FR-30	"	LSD (0.15 mg/kg)	2
	FR-30	"	LSD (0.195 mg/kg)	1
	FR-30	"	Psilocybin (1.0 mg/kg)	2
	FR-30	"	DMT (3.0 mg/kg)	3
	FR-30	"	Mescaline 10.0 mg/kg)	3
	FR-30	"	d-A (2.0 mg/kg)	2

In experiment 1, PCPA was administered on 3 consecutive days (100 mg/kg/day); two days following the last injection (when maximal depletion of 5-HT occurs; Koe and Weissman, 1966) the test drug was administered just prior to running the subjects on the FR paradigm. The extent of the behavioral disruption (pause) was compared with that seen with the same dose of

drug prior to PCPA administration. In Experiment 2, AMPT (40 mg/kg) was administered 1½ hours prior to DOM or d-amphetamine. Drug-induced stimulation of avoidance responding was compared before and after AMPT pretreatment by comparison of cumulative records. In Experiment 3, 0.5 mg/kg CPZ was administered ½ hour prior to testing the effects of DOM on FR-30. Cinanserin as a pretreatment drug was given 70 minutes prior to behavioral testing and the test drugs were administered immediately prior to placing the rat into the operant chamber. Drug effects were quantified by comparing them to control levels of responding (based on 3 NaCl sessions prior to drug testing). In addition, inspection of cumulative records revealed, in most cases, the effects of the drug interactions. These will be displayed.

RESULTS

Experiment 1: Figure 1 gives the results of experiments to determine the effect of lowering 5-HT on the behavioral response to 0.7 mg/kg DOM (top) and 10.0 mg/kg mescaline (bottom). The ordinates represent the percentage of control responding on FR-30; the abscissas list the daily treatments. Although PCPA does slightly decrease responding, the effects are minimal and no pause in responding was evident at any time. By comparing the magnitude of behavioral depression before and after PCPA, it is evident that lowering brain 5-HT levels does not attenuate the behavioral disruption induced by 0.7 mg/kg DOM or 10.0 mg/kg mescaline. In fact, some enhancement of sensitivity is apparent.

Experiment 2: Figures 2 and 3 show representative cumulative records demonstrating the effect of AMPT pretreatment on the stimulation induced by d-amphetamine (Figure 2) and DOM (Figure 3) on Sidman-Avoidance. The top records in each figure represent responding under control conditions. The middle records show the typical stimulation of avoidance responding induced by d-amphetamine or DOM. This is demonstrated by the increase in the slope of the responding rate. The bottom records reveal that responding returns to near control levels when AMPT is used as a pretreatment in combination with these drugs. AMPT alone did not alter avoidance responding (not shown);(see also Rech and Stolk, 1970).

Figure 1: The effects of lowering 5-HT on the behavioral response to DOM and mescaline on FR-30. The ordinates represent the mean percentage of control responding averaged for 2 subjects. On the abscissas are listed the treatments. The top graph depicts the extent of behavioral disruption on FR-30 induced by 0.7 mg/kg DOM before and after PCPA pretreatment. The lower graph shows the effects of 10.0 mg/kg mescaline before and after this pretreatment. PCPA (100 mg/kg) was administered i.p. on three consecutive days. Two days following the last PCPA injection, the drugs were tested. C = control NaCl injection.

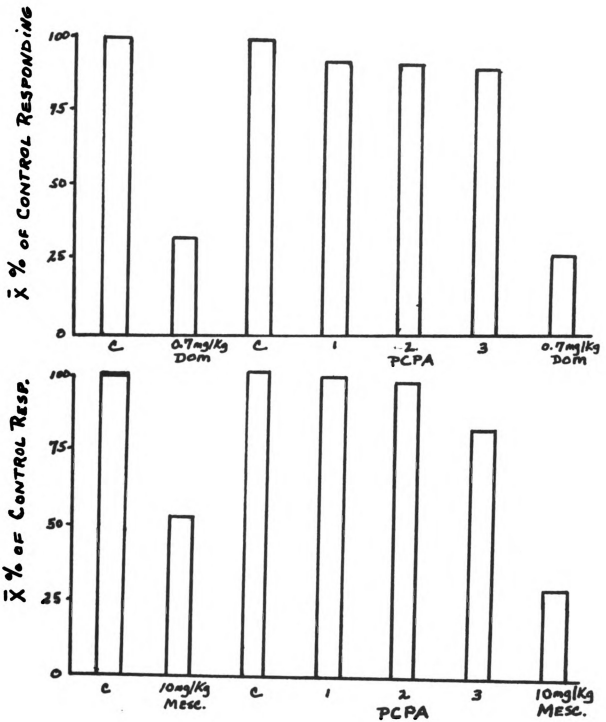
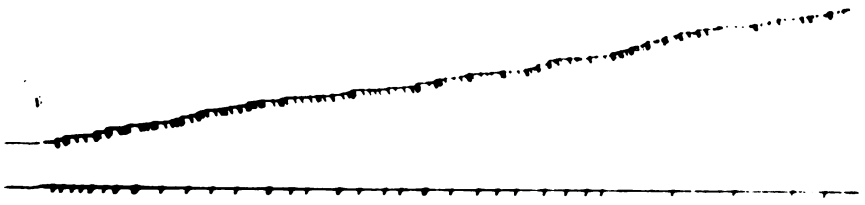

X̄ % of Control Responding
100
75
50
25
0
C
0.7mg/kg Dom
C
1
2
3
0.7mg/kg Dom
PCPA
X̄ % of Control Resp.
100
75
50
25
0
C
10mg/kg Mesc.
C
1
2
3
10mg/kg Mesc.
PCPA

Figure 2: The effect of lowering catecholamines on the behavioral response to d-amphetamine on Sidman-Avoidance. The cumulative record of one rat is depicted showing response characteristics following various treatments. In Panel A, a control record is presented. The slope of the diagonal line indicates the magnitude of responding during a 60 minute session. Each response is designated by a downward deflection on the event pen. Downward deflections of the baseline indicate shocks received during the session (2 ma. delivered to the grids of the operant chamber for 0.5 sec. duration). Panel B shows the responding patterns of this subject following 0.5 mg/kg d-amphetamine. It can be seen that responding is significantly increased with a concomitant loss of shocks received (only one shock delivered during the session). Panel C shows that responding patterns return to control level when AMPT (alpha-methyl-para-tyrosine ethyl ester-40 mg/kg) pretreatment (1½ hours before session) preceeds the d-amphetamine treatment.
R-S Interval = 30 sec.
S-S Interval = 5 sec.

A



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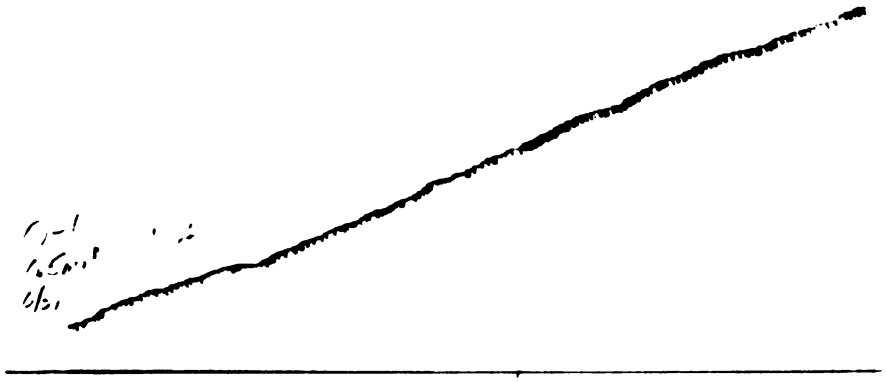


C.

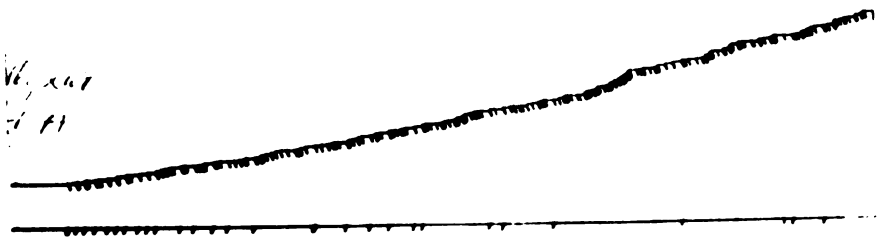
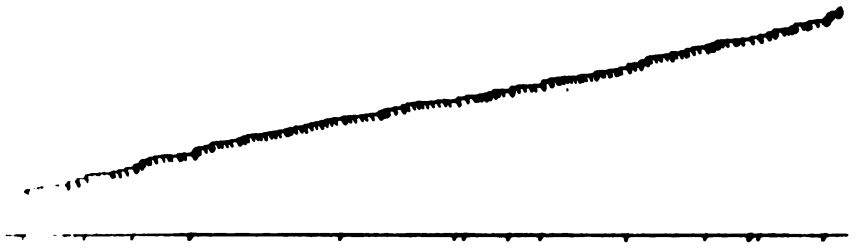


Figure 3: The effect of lowering catecholamines on the behavioral response to DOM on Sidman-Avoidance. See Figure 2 for details.
Panel A = control NaCl injection

Panel B = 1.0 mg/kg DOM i.p. immediately before session.

Panel C = pretreatment with 40 mg/kg AMPT 1½ hours prior to 1.0 mg/kg DOM.

A



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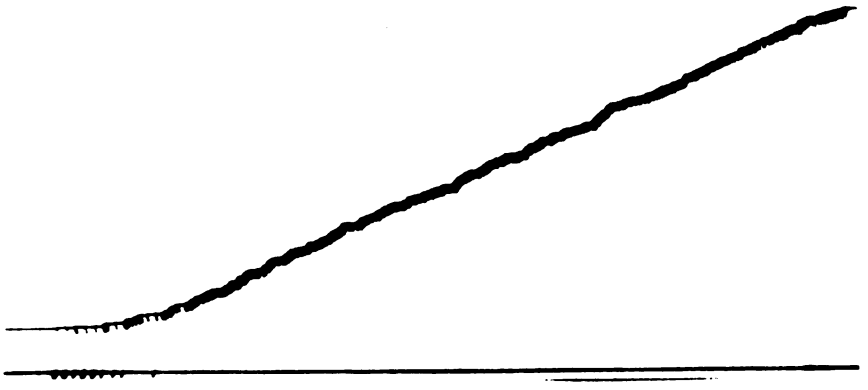

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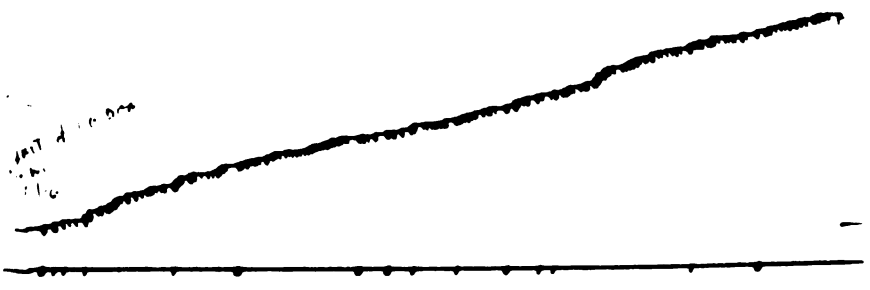


Experiment 3: Figure 4 shows cumulative records illustrating the FR responding patterns following 0.7 mg/kg DOM (top) and AMPT pretreatment and DOM (bottom). It is evident that AMPT pretreatment has little effect on the pause induced by DOM. The next figure (Figure 5) demonstrates the effect of two other pretreatment agents on DOM-induced responding patterns. Panel A shows control responding; Panel B, the typical pause induced by 0.7 mg/kg DOM; Panel C, demonstrates that CPZ (0.5 mg/kg) pretreatment has little effect on the pause induced by DOM; and Panel D illustrates that cinanserin (30 mg/kg) completely blocks the pause induced by DOM. CPZ and cinanserin when given alone in these doses had only slight effect on patterns of responding.

Table 1 summarizes the results of the effects of cinanserin (30 and 10 mg/kg) on the disruption of FR-30 responding induced by various hallucinogens. The left columns list the drugs and dosages utilized to induce pausing on FR-30. Column 3 indicates the magnitude of disruption as a percentage of control responding. Columns 4 & 5 list responding as a percentage of control induced by these agents following pretreatment with cinanserin. It is evident that cinanserin pretreatment markedly attenuates the behavioral disruption induced by these hallucinogenic agents. Cinanserin alone (line 1) slightly reduced response rates, however, no prolonged pause of the hallucinogenic type of activity was seen. These

drug interaction effects are more clearly revealed on the cumulative records. Figures 6 through 9 depict the effects of 30 mg/kg cinanserin pretreatment on the pause induced by 10.0 mg/kg mescaline (Figure 6), 3.0 mg/kg DMT (Figure 6), 0.175 mg/kg LSD (Figure 7), 1.0 mg/kg psilocybin (Figure 8) and 2.0 mg/kg d-amphetamine (Figure 9).

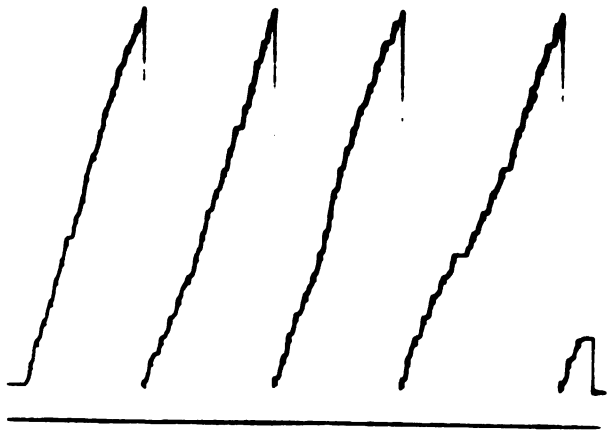
Figure 4: The effect of lowering catecholamines on the behavioral response to DOM on FR-40. In Panel A is depicted the typical pause induced by 0.7 mg/kg DOM. Panel B shows the record for the same animal when AMPT pretreatment (40 mg/kg-1½ hours prior to testing) preceeds the DOM injection. AMPT pretreatment alone induced little alteration of responding patterns (not shown).

Figure 5: The effects of pretreatment agents on the behavioral disruption induced by DOM on FR responding. Panel A shows a control record (NaCl injection). Panel B illustrates the pause induced by 0.7 mg/kg DOM. Panel C demonstrates that chlorpromazine pretreatment (0.5 mg/kg-½ hour prior to the session) had little effect on the responding pattern induced by DOM. Panel D shows the effect of cinanserin pretreatment (30 mg/kg-70 min. prior to testing) on the response patterns induced by 0.7 mg/kg DOM. It is seen that responding returns nearly to control levels following this drug interaction procedure.

Figure 6: The effects of cinanserin pretreatment on the behavioral disruption induced by DMT and mescaline on FR-30 responding. The left hand panels show the results of DMT (3.0 mg/kg) and cinanserin (30 mg/kg) interactions for rat B4. Panel A = control record; Panel B = responding pattern following 3.0 mg/kg DMT. Panel C = cinanserin (CIN) pretreatment (70 min. prior to behavioral testing) and DMT. The right hand panels show the interactions between 10.0 mg/kg mescaline and cinanserin for rat B1.

Figure 7: The effect of cinanserin pretreatment on the behavioral disruption induced by LSD on FR-30 responding. The cumulative records of one rat are depicted. Panel A = control responding manifested following the injection of NaCl. Panel B = responding induced by 0.175 mg/kg LSD administered immediately prior to behavioral testing. Panel C = response pattern following cinanserin pretreatment (30 mg/kg-70 min. prior to testing) and LSD.

A



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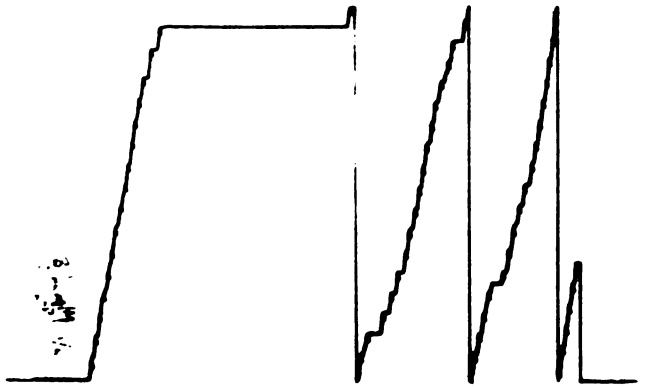

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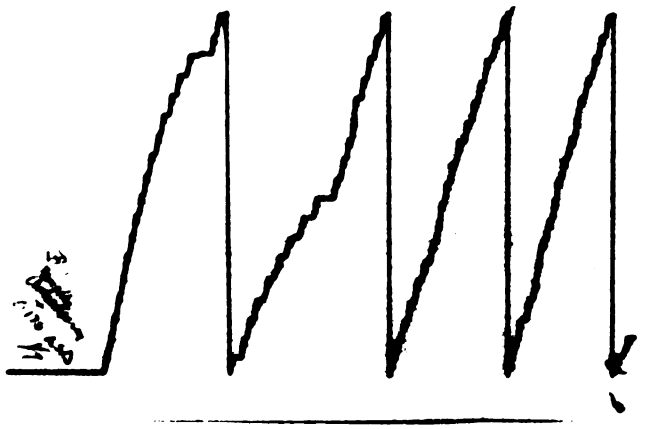
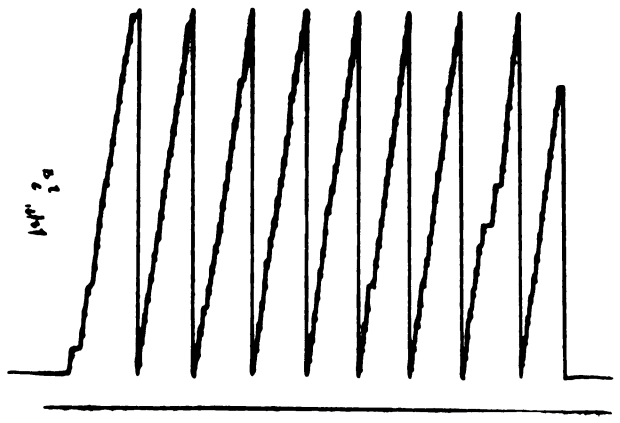


Figure 8: The effect of cinanserin pretreatment on the behavioral disruption induced by psilocybin on FR-30 responding. The cumulative records of one rat are depicted. Panel A = control responding. Panel B = responding pattern induced by 1.0 mg/kg psilocybin administered immediately prior to behavioral testing. Panel C = response pattern following cinanserin pretreatment (30 mg/kg-70 min. prior to testing) and psilocybin.

A



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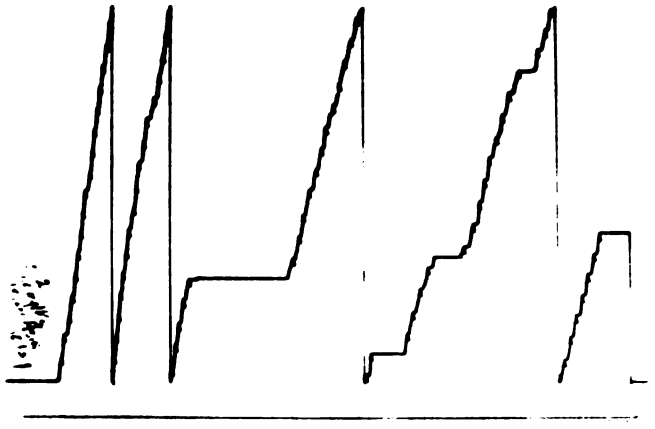

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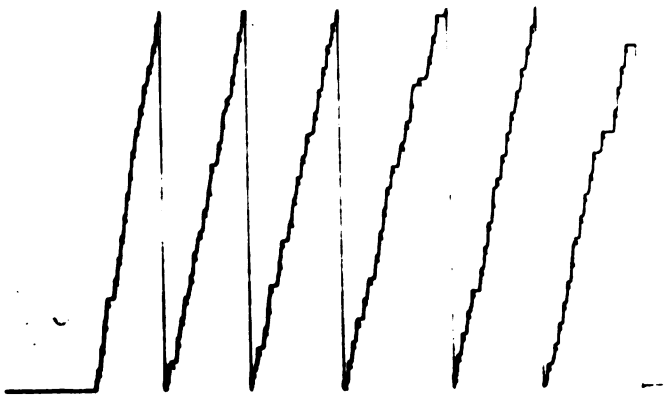


Figure 9: The effect of cinanserin pretreatment on the behavioral disruption induced by d-amphetamine on FR-30 responding. The cumulative records of one rat are depicted. Panel A = control responding. Panel B = responding pattern induced by 2.0 mg/kg d-amphetamine administered immediately prior to behavioral testing. Panel C = response pattern following cinanserin pretreatment (30 mg/kg-70 min. prior to testing) and d-amphetamine.

TABLE 1

EFFECT OF CINANSERIN ON THE DISRUPTION OF FR30 RESPONDING BY VARIOUS HALLUCINOGENS

Hallucinogenic Drug (H)[b]	N	% of Control Responding (Saline+Saline)[a]		
		H+Saline	H+Cin[c] 30 mg/kg	H+Cin 10 mg/kg
- (Saline)	2	-	89	96
Mes (10)	3	45	90	95
DMT (3)	3	30	92	98
LSD (0.15)	2	40	91	95
LSD (0.195)	1	20	88	76
DOM (0.7)	3	36	93	89
Psilo (1.0)	1	43	90	92
dA (2.0)	2	51	84	63
CPZ (2.0)	2	47	81	56

[a] Where N is more than one, values are the mean of the individual response rates.

[b] Mes=mescaline; DMT=dimethyltryptamine; LSD-lysergic acid diethylamide; DOM=2,5 dimethoxy-4-methylamphetamine; Psilo=psilocybin; dA=d-amphetamine; CPZ=chlorpromazine. Doses are listed in parentheses as mg/kg.

[c] Cin=cinanserin.

DISCUSSION

The results from these drug-interaction studies indicate that hallucinogens interact with 5-HT neural systems and that this interaction may be at the receptor sites in the hindbrain where they appear to exert a 5-HT agonistic effect. This interpretation is based on the following findings: PCPA, which markedly lowers 5-HT levels did not attenuate the behavioral disruption induced by DOM and mescaline but rather slightly potentiated the effects of these agents. This observation extends the findings of Appel et al. (1970), who demonstrated that PCPA enhanced the disruption of FR-40 responding induced by LSD. It thus appears that appreciable stores of 5-HT are not necessary for hallucinogenic behavioral effects. These findings would, thus, argue against theories purporting a presynaptic 5-HT action for hallucinogens (Chase, 1967; Knoll and Vizi, 1970) which would require intact 5-HT levels to support the drug effects. It is possible, however, that PCPA pretreatment may leave intact a releasable pool of 5-HT. In addition, these findings would also argue against an antagonistic action of hallucinogens at brain 5-HT receptor sites. One would expect an attenuation of hallucinogenic effect following PCPA if this mechanism of action were operative. The increased behavioral disruption induced by hallucinogens following PCPA may derive from an increased sensitivity of the 5-HT receptor to the action of agonists, as

has been reported for catecholamine receptors following amine depletion.

The results derived from hallucinogen-cinanserin interaction studies also favor a 5-HT receptor agonistic action for hallucinogens. Cinanserin has been reported to be a selective 5-HT receptor blocking agent in the periphery as well as in the central nervous system. It is also of interest that a vasoconstriction of umbilical vasculature induced by 5-HT, LSD, psilocybin and mescaline is potently and selectively blocked by cinanserin (Dyer and Gant, 1973). These findings would thus imply that the 5-HT receptor occupation by cinanserin prevents the accessibility of the receptor to hallucinogenic agents and thus the typical behavioral disruption is nullified. These data also argue against the hallucinogen-5-HT antagonist theory. One would predict that cinanserin alone would induce a "hallucinogenic pause" if this theory were valid. Responding was only slightly attenuated following cinanserin and no indication of a pause was evident in the doses employed. Nevertheless, other studies (Geller, 1973; Tilson, unpublished results) suggest that larger doses of cinanserin (60 mg/kg) do mimic the behavioral effects of hallucinogens.

Haigler and Aghajanian (1974) have recently demonstrated that 5-HT receptor sites on the raphe cell bodies are extremely sensitive to low doses of microiontophoretically

applied LSD, whereas 5-HT was as potent in its depression of these postsynaptic elements as it was for the raphe cell bodies. It appears that there may be a differential sensitivity of presynaptic (raphe cell bodies) and postsynaptic (raphe terminals) 5-HT receptor sites to the action of agonists and antagonists. The results derived from studies investigating the effect of systemic (i.v.) injection of low doses of LSD substantiate this interpretation. Injection of 20 ug/kg LSD completely inhibited the firing of raphe neurons, whereas acceleration of firing rates was recorded at post-synaptic cells receiving a 5-HT raphe input. These data suggest the possibility that at low doses LSD acts primarily by inhibiting the presynaptic raphe neurons and produces an acceleration of firing in the postsynaptic cells by releasing them from a tonic inhibitory raphe input. It thus appears that the raphe neuron has indoleamine receptors of two different types with different steric requirements. Perhaps cinanserin at low doses selectively blocks the 5-HT receptor sites on the raphe neuron, which as previously described, are exquisitely sensitive to LSD and other indole-hallucinogens.

It is thus postulated that LSD and other indole-containing hallucinogens exert their behavioral disruptive effects by acting as agonists at these 5-HT receptor sites on the raphe neuron that decrease their firing rate when activated, and that low doses of cinanserin attenuate these effects by competitively

occupying these sites and preventing hallucinogen interaction at this locus. The hallucinogenic effects seen following high doses of cinanserin may derive from its 5-HT receptor blocking action at both pre- and post-synaptic raphe 5-HT receptor sites with a net effect of interrupting the modulatory serotonergic tone projecting to the limbic forebrain and other sites.

The origin and physiological function of the 5-HT receptors on the raphe neurons are unknown. It has been suggested that they represent the terminals of a negative feedback circuit (Aghajanian and Freedman, 1968; Anden et al., 1968; Rech et al., 1974) which functions to modulate raphe neuron activity. The original conception of this circuit (Aghajanian and Freedman, 1968; Anden et al., 1968) involved a negative feedback from 5-HT raphe terminals in the forebrain to the raphe cell bodies. This mechanism was postulated in order to account for the inhibition of raphe neuronal cell body activity and decreased turnover of 5-HT induced by LSD and other hallucinogens. These investigators considered the primary site of action of hallucinogens to be at the post-synaptic raphe terminals where they mimicked the action of 5-HT and that, therefore, the drug effects on the raphe neurons were indirect. According to their theory the feedback circuit detected excess 5-HT at these receptors and relayed the message to the raphe cell bodies to inhibit their

activity. Recent reports, however, have generally not supported this mechanism. As described above, the primary mechanism of action of LSD and other indole hallucinogens appears to involve the raphe neurons and not the postsynaptic raphe terminals in the forebrain. In addition, the inhibition of raphe neuronal activity induced by LSD, DMT and psilocybin has been found to be a direct effect (Aghajanian et al., 1972; Bramwell and Conye, 1973) rather than an indirect inhibition mediated by a negative feedback circuit. Finally, Haigler and Aghajanian (1974) further ruled out the interaction of LSD with a neuronal feedback mechanism from the forebrain to the raphe by transecting the brain between the diencephalon and mesencephalon and testing the effect of LSD on the raphe cells. If the inhibitory effect of LSD on the raphe was dependent on a feedback inhibition emanating from the postsynaptic cells in the forebrain, then such a lesion should prevent or attenuate the inhibition of firing of raphe neurons produced by intravenous LSD. They reported no difference in the inhibition produced by i.v. LSD between a control animal and an animal with such a transection.

Rech et al. (1974) have proposed another type of feedback circuit involving the raphe system in its interaction with afferent reticular formation input and its modulation of limbic inhibitory functions (See General Introduction, pp 41-42, for discussion of this theory). Based on the findings

of Couch (1970) that neurons in the brainstem raphe contain postsynaptic receptors that are in some cases excitatory and in others inhibitory for 5-HT, they proposed the existence of a raphe interneuron in a 5-HT feedback loop. Couch found that raphe units with a low spontaneous frequency ("I" cells) were inhibited by microiontophoretically applied 5-HT as well as reticular formation stimulation, whereas raphe units with a higher spontaneous firing increased their frequency of discharge following 5-HT application ("D" cells). We interpreted these findings to indicate that perhaps the "D" cells represented serotonergic interneurons involved in a negative feedback loop that terminated on raphe cell neurons as inhibitory synapses ("I" cells). These speculations are represented schematically in Figure 10. The system proposes a collateral from the axon of the primary 5-HT raphe neurons which excites ("D" receptor) a 5-HT interneuron in the raphe that projects back onto the primary raphe neuron to inhibit its activity; or alternatively, the interneuron may be a part of a lower brainstem serotonergic feedback system involving NTS, the area postrema and the raphe (this system is discussed in the General Introduction, page 32-33). The primary raphe 5-HT neuron would probably receive other excitatory and inhibitory inputs, while the inhibitory interneuron may receive direct controlling inputs from several brain areas. LSD, DMT and other indoles presumably exert marked and long-lasting agonistic

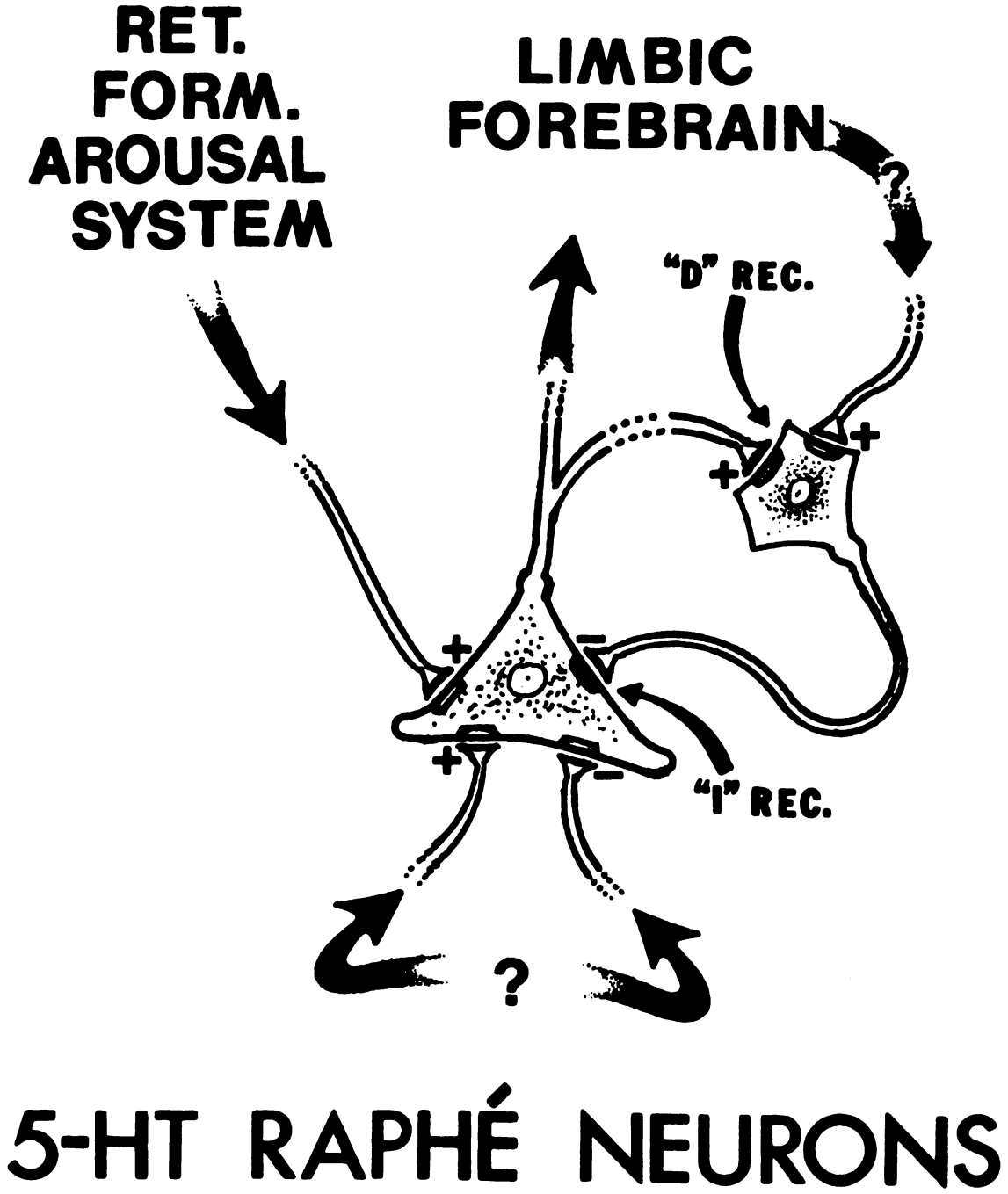
activity directly upon the "I" receptors. Other classes of hallucinogens (DOM and mescaline exert indirect effects on the raphe; Haigler and Aghajanian, 1973) may exert the same overall suppression of firing of the primary 5-HT raphe neurons by acting at other sites in the feedback pathway, perhaps on the cell body of the inhibitory interneuron.

On the basis of these studies the role of catecholamines in hallucinogenic drug action did not appear to be prominent. AMPT as well as CPZ pretreatment failed to attenuate the pause induced by DOM on FR-30, whereas cinanserin did block this effect. AMPT did, however, block the stimulation of responding induced by DOM on the Sidman-Avoidance paradigm to a degree similar to that seen when d-amphetamine was tested on this schedule. Thus, it appears that the amphetamine-like stimulation induced by DOM may be mediated by catecholamines, whereas the hallucinogenic behavioral depression (pause on FR) is a serotonergic function.

The decrease in response rate induced by d-amphetamine or CPZ was attenuated to a surprising degree by pretreating with 30 mg/kg cinanserin. However, after pretreatment with 10 mg/kg cinanserin the rate-decreasing effects of these agents were hardly changed from controls, whereas the effects of the hallucinogens were maximally attenuated at this dose. Therefore, the blocking action of cinanserin would appear to be somewhat specific to the hallucinogens. It is also

possible that a portion of the FR disruption induced by d-amphetamine or CPZ is mediated indirectly via an imbalance in 5-HT mechanisms.

Figure 10: SCHEMATIC REPRESENTATION OF HALLUCINOGEN-RAPHE INTERACTIONS.



SUMMARY AND GENERAL CONCLUSIONS

The results from these studies indicate that operant conditioning paradigms can be a useful tool for characterizing hallucinogenic properties of psychoactive drugs as well as differentiating agents within the hallucinogenic drug class. Furthermore, these schedules provided a practical means for assessing tolerance phenomena and cross-tolerance relationships between hallucinogenic drugs since the results derived from these experiments with rats correlated well with data derived from human studies. Finally, the utilization of these schedules for drug interaction experiments provided data that may well be useful for ascertaining the mechanisms of action of hallucinogenic drugs. Since these techniques yield unique behavioral profiles for hallucinogens, they should prove useful in psychiatric research for testing endogenous compounds that are potentially instrumental in initiating naturally occurring psychosis. In addition, these operant paradigms may prove useful for quantitative screening of street drugs in community drug analysis centers. The hallucinogenic pause seen on the FR and drl schedules was characteristically induced over a very narrow and predictable dose range for each agent that was tested. The threshold dose for this disruption was reliably reproducible over many trials. Thus, one could perform serial dilutions of an unknown street drug sample, test them on rats trained to perform on these schedules,

and extrapolate the dosage of the sample. Identity could be assessed by administering the unknown to other rats made tolerant to the known hallucinogen and determining cross-tolerance.

The results from Section I indicate that DOM, a catecholamine-like hallucinogenic agent, could be differentiated behaviorally from the indoleamine type hallucinogens, LSD and psilocybin. The behavioral profiles induced by DOM on drl, FI and Sidman-Avoidance paradigms resembled those seen following d-amphetamine over a wide dose range. At the highest dose tested in drl and FI paradigms, DOM resembled LSD and psilocybin. Additional behavioral similarities between DOM and d-amphetamine were noted in Section II. Both agents induced similar patterns of behavioral disruption following repeated, daily administration on an FR-40 procedure, inducing only a partial tolerance at low doses. The development of a unidirectional cross-tolerance between these agents on both FR and drl paradigms further confirmed the likelihood that they shared to some extent common mechanisms of action in the central nervous system. Finally, it was demonstrated in Section III that the stimulation of Sidman-Avoidance responding induced by either DOM or d-amphetamine was identically attenuated by AMPT pretreatment. These findings and the fact that AMPT pretreatment failed to attenuate the pause induced by DOM on an FR, whereas cinanserin did, indicated that the

amphetamine-like stimulation induced by DOM was probably mediated by catecholamines, whereas the hallucinogenic behavioral depression is most likely due to an interaction with a serotonergic mechanism.

Studies investigating the effects of repeated administration of hallucinogens revealed that LSD and mescaline produced a rapid and complete tolerance formation on an FR-40 schedule, whereas psilocybin, DOM, DMT and d-amphetamine produced varying degrees of tolerance development and only over a longer period of daily injections. Drug dosage proved to be an important variable as larger doses of hallucinogenic agents consistently prolonged tolerance development. In addition, the utilization of different schedules in tolerance assessment confirmed a previously reported finding that an animal will only develop tolerance if this development enhances the likelihood of meeting reinforcement requirements. Thus, in these studies, tolerance development to drug-induced disruptions was evident on drl and FR paradigms, whereas tolerance was not manifested for drug-induced stimulation on the shock avoidance schedule.

The tolerance and cross-tolerance data suggest that the disruption of operant behavior induced by various hallucinogenic agents has a common basis in acting upon some central discriminatory function. There are likely to be several points of attack on this overall system, however,

since a complete cross-tolerance was not demonstrable for all combinations tested. The assumption that the hallucinogenic action is exerted through some common pathway, regardless of the specific agent examined, was fortified by the finding that cinanserin is an effective antagonist of mescaline, DMT, LSD, DOM and psilocybin for the hallucinogenic pause in FR performance. Since cinanserin is a specific blocker of 5-HT receptors, it follows that the common factor for the hallucinatory effects would relate to increased activity at central serotonergic receptors. The one-way cross-tolerance relationships for DOM when tested with other agents, however, indicates that perhaps this agent has a wider spectrum of action in the central nervous system than other hallucinogens and probably involves catecholamine mechanisms as well.

A working hypothesis of the mechanism of hallucinogenic drug action was developed based on drug interaction studies (Section III): The drugs induce, directly or indirectly, an excessive activation of 5-HT receptors on the serotonergic raphe neurons projecting to the limbic forebrain and thereby markedly suppress the firing rate of the raphe cells. Theories purporting a 5-HT receptor antagonist role for hallucinogenic drug action were not supported by these studies.

The tolerance development to the FR impairment induced by hallucinogens (LSD and mescaline in this study) was not dependent upon contiguous presentation of the drug action

and the specific behavioral measurement. Presumably, the tolerance development progresses independently of experiential interactions. If LSD and like agents result in marked and prolonged activation of receptors on raphe neuronal cell bodies, a desensitization may come about which would result in the reduction of the drug effect and subsequent tolerance formation. Yet, such a tolerance mechanism would not be expected to lead to adaptive changes leading to physical dependence or withdrawal, usually equated with nerve terminal biochemical alterations such as enhancing synthesis of transmitters or with development of disuse supersensitivity of postsynaptic synapses.

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