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REVIEW

Early preclinical studies of discriminable sedative and hallucinogenic drug effects

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Abstract
Rationale One important technique in behavioral pharmacology is to train laboratory animals to discriminate between a psychoactive drug effect and a nondrug condition. Tests with different drugs have identified several categories of drugs that have different discriminable effects.
Objectives The two authors describe and discuss the early research on discriminable effects of sedative and hallucinogenic drugs and their acquaintance with each other at Yale University prior to their early and frequent publications on discriminable drug effects. Herb Barry studied sedative drugs primarily and Jim Appel studied hallucinogenic drugs.
Results Sedative drugs include ethyl alcohol, barbiturates, and benzodiazepines. Their discriminable effects are largely attributable to the activation of an inhibitory neurotransmitter, γ-amino butyric acid. Alcohol has the most pervasive effect in accordance with the high dose required to alter behavior. Hallucinogenic drugs include lysergic acid diethylamide and mescaline. They increase the activity of the neurotransmitter 5-hydroxytryptamine and, perhaps, dopamine in the central nervous system (CNS). In spite of their relatively low concentrations in the brain, both of these neurotransmitters have many important behavioral effects.
Conclusions Various sedative drugs cause a discriminable decrease in the function of the CNS. Different types of sedatives can be discriminated from each other. Indole and phenylethylamine hallucinogens have potent discriminative stimulus properties, which are related to the actions of biogenic amine neurotransmitters in the CNS.

Keywords Discriminative stimulus · Sedatives · Hallucinogens · GABA · Serotonin · Dopamine · Laboratory animals · History · Operant · Alcohol

A drug that changes the action of the central nervous system (CNS) can be a strong discriminative stimulus that alters behavior such as the choice between different responses. The most prominent type of discriminative stimulus is a sensory signal. Examples are a traffic light received by the eyes and a warning siren received by the ears. A drug effect that alters the action of the CNS is a discriminable change in physiological state or in "consciousness." An individual can, therefore, learn different responses depending on whether or not the drug is acting on the CNS.

Research on discriminable drug effects constitutes a portion of the interdisciplinary field of preclinical psychopharmacology. Potentially therapeutic or nontherapeutic drugs that alter behavior are tested in laboratory animals. An alternative term for this research field is behavioral pharmacology.

After a discriminable drug effect is trained, "substitution" or "generalization" tests determine whether the effect of another drug or of a different condition resembles the effect of the initial drug. Different conditions can include the initial drug after a lower or higher dose ("dose–response" test), after a shorter or longer time interval ("time–response" test), or after a different route of

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administration. The test can also combine the initial drug with a different drug ("combination," "potentiation," or "antagonism" test).

Table 1 lists the earliest publications on the discriminable effects of sedative and hallucinogenic drugs. Herb Barry was an early and frequent, although not the first, contributor to the knowledge about the discriminable effects of sedatives. Jim Appel was an early and frequent, although not the first, contributor to the knowledge about the discriminable effects of hallucinogens.

Barry and Appel were acquainted with each other when they were both at Yale University (1960–1961). Barry began research on discriminative sedative effects at the University of Pittsburgh in 1964. Appel's research on discriminable hallucinogenic drug effects, begun at the University of Chicago in 1967, expanded at the University of South Carolina beginning in 1972. Barry and Appel renewed acquaintance when the Society for the Stimulus Properties of Drugs was founded in 1978 (Overton et al. 1999). Barry was the third president and Appel was the fourth president of that organization.

Neuropharmacological effects of sedative drugs

Barry began preclinical psychopharmacology research as a postdoctoral research fellow, sponsored by Neal E. Miller in the Yale University Psychology Department. The research was financed by a grant from the National Institute of Mental Health to Miller. The effects of sedative drugs were tested on the behavior of albino rats. The sedatives were inferred to decrease fear because they decreased avoidance of electric shocks.

Table 1 Early reports on the discriminable effects of sedatives and hallucinogens (1951–1979)

Sedatives	Hallucinogens
Conger (1951)	Hirschhorn and Winter (1971)
Overton (1962)	Schechter and Rosecrans (1972)
Overton (1964)	Cameron and Appel (1973)
Overton (1966)	Winter (1973)
Barry et al. (1965b)	Winter (1974a)
Barry (1968)	Winter (1974b)
Brown et al. (1968)	Hirschhorn and Rosecrans (1974)
Kubena and Barry (1969a)	Greenberg et al. (1975a)
Kubena and Barry (1969b)	Greenberg et al. (1975b)
Schechter (1973)	Kuhn et al. (1976)
Winter (1975)	Joseph and Appel (1976)
Krimmer and Barry (1976)	Kuhn et al. (1977)
Barry and Krimmer (1977)	Joseph and Appel (1977)
Overton (1977)	Appel et al. (1977)
Barry and Krimmer (1979)	Kuhn et al. (1978)
Overton (1979)	Appel et al. (1978)

Ethyl alcohol was one of the drugs tested because of an article by John J. Conger (1951), which reported on his Ph.D. dissertation in Psychology at Yale. Neal E. Miller was his principal advisor. In common with alcohol, barbiturates are sedative drugs that cause anesthesia at a high dose and death at a higher dose. Instead of pentobarbital, the most frequently used barbiturate, Barry chose amobarbital because Nicholas Giarman, of the Pharmacology Department at Yale, advised him that its effects have a more gradual onset and a larger difference between the effective and anesthetic dose. The benzodiazepine chlordiazepoxide was also tested because benzodiazepines are sedatives that do not cause anesthesia and death at the doses used.

A frequent technique in the experiments was the use of a control group that tested the effects of change in the drug or control condition. Animals trained after placebo injections and tested after drug injections were compared with animals trained after drug injections and tested after placebo injections. The effects of a change in pharmacological state, whether from placebo to amobarbital or from amobarbital to placebo, were reported in articles published subsequently (Barry et al. 1962a, b, 1965a). The change in pharmacological state, regardless of the direction of change, was a state-dependent effect of the drug.

Barry remembers that he suggested to Miller an experiment with the principal purpose of training rats to discriminate between a drug effect and the placebo condition. Miller did not agree to undertake that project.

The early research on discriminable effects of sedative drugs is divided into five phases.

(1) The first publication was by Conger (1951), listed in Table 1. Rats were trained to run in a straight alley to food. The sessions were preceded by injection of alcohol or a placebo. Electric shock was delivered at the food cup to one group only after the injection of alcohol and to another group only after the injection of placebo.

The hypothesis was that alcohol diminishes the strength of the avoidance response to shock. Accordingly, avoidance was learned more rapidly by the group with shock in the placebo condition than by the group with shock in the alcohol condition. The discriminable effect of alcohol was also demonstrated because both groups of rats learned to avoid the food cup after the drug or placebo condition that was followed by shock and to approach and eat the food after the drug or placebo injection that was not followed by shock. Table 1 identifies Conger's article as the first publication on the discriminable effects of sedative drugs.

(2) Donald A. Overton's Ph.D. dissertation (1962) was designed to demonstrate and test the discriminative effects of several drugs. Portions of the results were

published in two journal articles (Overton 1964, 1966). Rats were trained to escape electric shock by turning in opposite directions in a T-shaped maze, depending on whether or not they had been injected with a drug. After approximately 30 training sessions, equally divided between drug and nondrug conditions, animals consistently chose the direction that escaped the shock.

Overton (1964) demonstrated a discriminable effect of a high dose of pentobarbital (25 mg/kg) after recovery from its anesthetic effect. Overton (1966) reported that the rats chose the same direction after sufficient doses of phenobarbital (80 mg/kg), ethyl alcohol (2.4 g/kg), carbamate (750 mg/kg), and meprobamate (200 mg/kg). All of these drugs, in common with pentobarbital, depress the activity of the CNS.

In common with many uses of a new technique, the procedures of Overton's initial studies had deficiencies. The choice response required rapid running to escape electric shock. The drug doses were very high. A disadvantage of requiring the rat to turn in opposite directions in the T-shaped maze was the experimenter's knowledge of the direction of escape from shock. An involuntary directional response by the experimenter might have been perceived by the rat. It was also undesirable for the experimenter to handle the rat on each trial.

In 1963, Barry joined the faculty of the University of Pittsburgh, School of Pharmacy. Ina Braden, a graduate student in the Psychology Department at the same university, told him about Overton's Ph.D. dissertation at McGill University in Montreal, Canada. She had been informed about it by Donald Posluns, another graduate student in her department who had graduated from McGill University. Barry felt greatly encouraged by Overton's demonstration that a drug effect can function as discriminable stimulus. Overton was subsequently the principal organizer and first president of the Society for the Stimulus Properties of Drugs founded in 1968 (Overton et al. 1999).

In 1964, Barry began research on the discriminable effect of alcohol. He guided two high school students in a research project. A T-shaped maze and several albino rats were placed in the separate homes of the students who trained the rats to obtain food by turning in one direction after alcohol injection and in the opposite direction after placebo injection. Their successful training was reported by Barry et al. (1965b).

(3) Most of the subsequent research by Barry and others used an operant lever-pressing response in a chamber. The experimenter's physical contact was limited to the initial placement of the animal in the chamber and removal of the animal at the end of the session.

In an initial experiment that used a chamber containing two levers, a food cup between them, and a light bulb near the ceiling, Barry (1968) demonstrated that rats learned to select the visual condition, darkness or illumination, associated with delivery of food after drug or placebo injection. Pressing either lever reversed the visual condition. Food was delivered after 20 s in one visual condition preceded by injection of alcohol (1.2 g/kg) and in the other visual condition preceded by injection of placebo. The rats learned to press the lever to obtain the visual condition that delivered food after the drug or placebo injection. This procedure prevented the possibility that, in a choice between two levers, the experimenter might involuntarily orient the animal toward the reinforced lever.

Barry was the principal advisor for Robert K. Kubena who conducted a series of experiments reported in his M.S. thesis. Kubena and Barry (1969a) demonstrated a discriminable effect of alcohol injection (1.2 g/kg). Each rat was trained with one of two procedures, conflict or choice.

In the conflict procedure, Conger's (1951) electric shock at the food cup in a straight alley was adapted to electric shock after pressing a lever in a chamber. Every fifth press of a lever delivered a pellet of food in one condition (drug or placebo) and an electric shock in the alternative condition. In the choice procedure, food after turning in one direction in a T-maze (Barry et al. 1965b) was adapted to food after pressing one of two levers. The lever that delivered a pellet of food depended on the drug or placebo condition. After an initial interval without food, to record the choices, presses on one lever delivered food on an intermittent time schedule (variable interval). The other lever recorded the number of presses but had no other effect.

Kubena and Barry (1969b), using both the conflict and choice procedures, reported tests with other drugs after the rats had acquired the discriminable response to the initial drug. The discriminable response to alcohol (1.2 g/kg) was made after sufficient doses of pentobarbital (10 mg/kg), chlordiazepoxide (10 mg/kg), and chloral hydrate (90 mg/kg).

Other early reports on the discriminable effects of sedative drugs were by Brown et al. (1968), Schechter (1973), and Winter (1975). Krimmer and Barry (1976) trained and tested the discriminable pentobarbital effect immediately after intravenous administration.

(4) In most of the studies, discrimination from the placebo condition was trained with a single dose of a drug, followed by tests with different doses of the same drug. The minimal discriminable dose is usually somewhat less than half of the dose used in the training sessions. Overton (1979) scheduled a gradual decrease of the drug dose after the discriminative choice had been established. Discrimination from the placebo condition was maintained at doses far below the level that causes other observable changes in behavior for three sedatives

(phenobarbital, chlordiazepoxide, and cyclazocine) and for an opioid (fentanyl). Smaller deceases in the minimal discriminable doses were found for amphetamine, scopolamine, and nicotine.

(5) The neurotransmitter γ-amino butyric acid (GABA) appears to be the principal mediator of the discriminable sedative effects of alcohol, barbiturates, and benzodiazepines (Meyer and Quenzer 2005). GABA inhibits the activity of neurons in the CNS. Sedative drugs increase the inhibitory activity. Pentylenetetrazol (Metrazol) and picrotoxin, which cause convulsant seizures, have the opposite effect of decreasing the inhibitory activity of GABA. Accordingly, Emmett-Oglesby et al. (1983) reported opposite discriminable effects of the benzodiazepine diazepam and the convulsant pentylenetetrazol.

Sedative drugs also differ from each other in some actions. Ethyl alcohol is a small molecule that has a weak physiological effect. A high alcohol dose is, therefore, required for a discriminable effect. Meyer and Quenzer (2005) describe various pervasive and generalized effects of alcohol in addition to increasing the inhibitory GABA activity. Overton (1966, 1977) and Barry and Krimmer (1977) reported evidence that the discriminable effect of alcohol differs from the discriminable effect of a barbiturate. Barry (1991) summarized findings that animals trained to discriminate alcohol from placebo choose the drug response in tests with sufficient doses of a barbiturate or a benzodiazepine. Contrary to this similarity, animals trained to discriminate a barbiturate or a benzodiazepine from placebo do not consistently choose the drug response in tests with alcohol. The discriminable drug effect transfers more easily from the generalized sedation caused by alcohol to the specific sedation caused by barbiturates and especially benzodiazepines than in the opposite direction.

The discriminable effects of barbiturates and benzodiazepines generally resemble each other. Nevertheless, differential effects might be mediated by different activities at the $GABA_A$ receptor. Barry and Krimmer (1979) and Barry et al. (1982) trained a discriminable choice between the effects of pentobarbital and chlordiazepoxide. Henteleff and Barry (1989) trained a discriminable choice between the effects of orally intubated amobarbital and diazepam. Barbiturates and benzodiazepines also showed evidence for different discriminable effects in baboons (Ator 2002) and in rats (Kohut and Ator 2008).

Neuropharmacological effects of hallucinogenic drugs

It is well-known that drugs such as lysergic acid diethylamide (LSD) cause perceptual and cognitive alterations that have been said to resemble hallucinations and other positive symptoms of schizophrenia in humans at doses that are not otherwise toxic (the "LSD trip"). For this reason, they are called "hallucinogens" and were once considered to be "psychotomimetic" even though drug-induced effects are primarily visual, while endogenous perceptual disturbances are usually auditory. The LSD trip was described in 1943 by Albert Hofmann, the Swiss chemist who first synthesized the drug (in 1938) and deliberately ingested a relatively high dose himself shortly thereafter (Hofmann 1968).

The description by Hofmann suggested that LSD has strong stimulus properties, which can be readily discriminated from nondrug or other drug-induced states. Table 1 shows that such effects were first reported in publications by Hirschhorn and Winter (1971), Schechter and Rosecrans (1972), Winter (1973, 1974a, b), and Hirschhorn and Rosecrans (1974). All of these authors were at The Medical College of Virginia (Virginia Commonwealth University).

Appel, while at the Yale University School of Medicine, participated in a project "Biogenic Amines and Brain Neurohumors" on LSD and other "hallucinogenic" or "psychotomimetic" drugs. The directors were Nicholas Giarman in the Pharmacology Department and Daniel X. Freedman in the Psychiatry Department. Appel worked primarily on the disruptive effects of LSD and related indoleamines and phenyethylamines on lever-pressing behavior in rats and monkeys controlled by various schedules of reinforcement. He believed that the effects of "psychotomimetic" drugs might resemble some of those seen in schizophrenia and related psychoses in humans and that a mechanism for the drug effects might be a change in the activity of biogenic amine neurotransmitters, such as serotonin (5-hydroxytryptamine [5-HT]) and dopamine (DA) in the CNS. When controlled by a fixed-ratio schedule of reinforcement, the disruptive effect of these compounds was later called the "hallucinogen-induced pause" (Rech et al. 1988). These studies resulted in several publications (Appel and Freedman 1964, 1965; Freedman et al. 1964). However, Appel realized that the drug effects reported in these articles were highly variable and depended largely on the schedule used to maintain the animal's behavior. He decided that instead of behavioral disruption, the discriminable drug effect might be a more robust, reliable, sensitive, and selective behavioral assay which, indeed, proved to be the case (Appel et al. 1978).

Appel shifted from schedule-controlled behavior with a single lever to more complex drug discriminations with two and sometimes three levers after he moved to the University of Chicago in 1966, along with his mentor and colleague at Yale, Dan Freedman. In Chicago, Appel attracted outstanding graduate and medical students in the Biopsychology program. One such student was Oliver G. Cameron who proposed a doctoral dissertation on the stimulus properties

of psychotomimetic drugs. Appel and Cameron began a series of studies in which they systematically studied both the unconditional ("unconditioned") and discriminative stimulus properties of LSD and functionally related substances (Cameron and Appel 1972a, b, 1973).

Appel's research in this area continued for almost three decades after he moved to South Carolina. The major findings have been reviewed in two articles (Appel et al. 1982, 2004) and are summarized, more briefly, in the following paragraphs. In general, the findings describe the discriminable stimulus effects of LSD more fully than previously reported and relate them to such pharmacological variables as training and test doses. Their mechanisms of action were analyzed by comparing them with those of other drugs that are more site-selective neurotransmitter receptor agonists (substitution tests) and by determining the extent to which putative antipsychotics and other transmitter antagonists might block or potentiate the LSD signal (Appel et al. 1982, 2004; White and Appel 1982c).

In addition to its perceptual, hallucinogenic, or "psychotomimetic" effects, LSD is interesting because of its extreme potency in humans and other animals (Hofmann 1968). For example, doses as low as 10 μg/kg inhibit the firing of neurons in the dorsal raphé nuclei of the midbrain (Aghajanian and Haigler 1974). Greenberg et al. (1975a) found that the discriminable effect of LSD can also occur at the same low dose in intact, behaving rats. The drug discrimination assay may, therefore, be as sensitive as other neuropharmacological, neurophysiological, and behavioral techniques. The minimal discriminable doses are much higher for sedative drugs, especially alcohol.

Another reason for the continued interest in LSD arose in the 1950s when structural similarities between hallucinogens and serotonin suggested that such drugs might act by altering the functional activity of serotonin receptors. Serotonin is a transmitter at neuromuscular junctions in many invertebrates. The clam heart was a useful bioassay of serotonergic activity for many years until it was replaced by more modern, less time-consuming chemical procedures. Brodie and Shore (1957) were among the first to speculate that serotonin acts as a neurotransmitter in the mammalian CNS.

Experiments at Yale, and later at the University of Chicago, showed that lowering the concentration of serotonin in the CNS by a variety of physiological and pharmacological methods increased sensitivity to the behaviorally disruptive effects of LSD and related indoleamines but not to other excitatory substances, such as the CNS stimulants D-amphetamine and cocaine, which act primarily through actions on other, nonserotonergic neuronal systems. These methods included lesioning the cell bodies of 5-HT-secreting neurons in the medial forebrain bundle or dorsal raphé nuclei of the midbrain (Sheard et al. 1967; Appel et al. 1968), inhibiting the synthesis of 5-HT from dietary tryptophan with the tyrosine hydroxylase inhibitor ρ-chlorophenylalanine (Appel et al. 1970) or blocking its storage (binding) in synaptic vesicles by pretreatment with drugs such as reserpine or tetrabenazine (Appel and Freedman 1964).

Studies of the role of serotonin and other neuronal systems in the mechanism of action of LSD continued in collaboration with graduate and undergraduate students in South Carolina. Drug discrimination experiments were implemented in a major way. The methods most often consisted of training groups of rats to discriminate intraperitoneal injections of 0.08 mg/kg of LSD from nondrug or, less frequently, other drugs. Interventions involving serotonin included electrolytic or more recently developed and more selective chemical lesioning of selected brain regions, for example, with the serotonin neurotoxins 5,6-dihydroxytryptamine or 5,7-dihydroxytryptamine (Appel et al. 1977; Joseph and Appel 1976, 1977; White et al. 1980). Another type of intervention was treatment with a range of doses of known or putative agonists and antagonists at various subtypes of serotonin and other receptor sites (Appel and Cunningham 1986; Appel et al. 1977, 1978, 1982, 1985; Cunningham and Appel 1987, 1988; Holohean et al. 1982; Kuhn et al. 1976, 1977, 1978; White and Appel 1982a; White et al. 1980; West et al. 1995). In the most recent type of intervention, microinjections of LSD and related substances were placed directly into different regions of the brain, including the ventricles, nucleus accumbens, dorsal raphé, and fimbria striatum (Appel et al. 2004; West et al. 1997).

The following five findings are identified as significant results of this research:

(1) Reducing the concentration of 5-HT in the CNS increases sensitivity to both the discriminable and behaviorally disruptive effects of LSD and related hallucinogenic drugs. Less 5-HT in the brain, therefore, causes the dose–response curve to shift so that lower doses have greater than normal effects. This change was attributed to a decrease in competition between endogenous 5-HT and an agonist such as LSD for postsynaptic 5-HT (probably 5-HT2_A) receptor sites (Appel et al. 1982).
(2) Other indoleamine and phenylethylamine hallucinogens substitute completely for LSD with an order of potency that parallels their hallucinogenic potency in humans (Cunningham and Appel 1987).
(3) Drugs such as pirenperone, ketanserin, and ritanserin completely antagonize the discriminative effects of LSD. Each of these compounds acts both at 5-HT and at other receptor sites, primarily DA_2 (Cunningham and Appel 1987). Another nonselective compound with similar effects and a similar mechanism of action

but with fewer side effects is risperidone (Risperdal), a widely used antipsychotic.

(4) Among putatively more site-selective drugs, 5-HT_2 antagonists block the LSD cue to a greater extent than either 5-HT_1 or 5-HT_3 antagonists but do not block it completely or even as well as the less selective antagonists (Appel et al. 2004). It is, therefore, likely that nonserotonergic neuronal systems contribute to the in vivo effects of LSD.

(5) Studies involving the administration of drugs directly into the brain suggest that brain areas containing terminal fields (rather than cell bodies) of serotonergic neurons might be involved in the discriminable effects of LSD. These include the prefrontal cortex, habenular nuclei, hippocampus, and paraventricular nuclei (Appel et al. 2004).

An important question is whether the discriminative LSD stimulus is specific to drugs with hallucinogenic effects in humans. Animals trained to discriminate LSD from the nondrug condition choose the drug response after a sufficient dose of a structural congener of LSD, lisuride hydrogen maleate (LHM). This drug is not known to be hallucinogenic and has been used to treat migraine headaches (in Europe). Under similar conditions, the drug response may also be chosen after a sufficient dose of quipazine, a 5-HT agonist (White et al. 1977), and in one study, the α2 NE agonist, yohimbine (Colpaert 1984). Both of these substances have no structural resemblance to LSD and are not classified as hallucinogens. This "false-positive" effect of LHM (and possibly, other drugs) contradicts a popular hypothesis that substitution for LSD in the rat is a good predictor of hallucinogenic potency in humans (Fiorella et al. 1995).

A systematic comparison of the effects of LHM and LSD was, therefore, conducted primarily by the late Francis J. White in Appel's laboratory. The results of this research were reported in White's Ph.D. dissertation and in several articles (White and Appel 1982a, b). While the two structural congeners do substitute or "cross-generalize" for each other in standard or typical two-lever drug discrimination procedures, animals could detect differences in their discriminable effects under appropriate conditions and, for this reason, LHM does not need to be considered a "false-positive." Such conditions included training the rats to discriminate between various drugs (rather than between a drug and the absence of the drug) in either two-lever, LSD–LHM, or three lever LSD–LHM–nondrug tasks (White and Appel 1982a, b; Cunningham et al. 1987). Lisuride can also be differentiated from LSD by animals that have been trained to discriminate LSD from a group of other treatments, consisting of cocaine, pentobarbital, and placebo (Appel et al. 1999).

These comparative experiments also strongly suggest that LSD and LHM have different mechanisms of action in vivo. In tests on intact, behaving animals, DA agonists substitute for and DA antagonists block the discriminable stimulus effects of LHM to a greater extent than those of LSD while 5-HT agonists substitute for and 5-HT antagonists block LSD to a greater extent than LHM (Cunningham et al. 1987; White and Appel 1982a, b). Under the conditions tested, LHM is, therefore, primarily dopaminergic (specifically, a D2 agonist) while LSD is primarily serotonergic.

Almost all the research at the Behavioral Pharmacology Laboratory was limited to the acute effects of LSD, occurring from about 15 min to less than 1 h following intraperitoneal injection. In humans and probably also in monkeys, the effects of LSD are biphasic (Freedman 1984; Peterson 1966). Most of the excitatory, hallucinogenic, and psychotomimetic effects (the "LSD trip") occur in the second phase, which begins after 1 h and has considerably longer duration. Recent pharmacological evidence suggests that the acute effects of LSD involve alterations in the activity of 5-HT neuronal systems and the subsequent effects are mediated by more dopaminergic mechanisms (Morona-Lewicka et al. 2005). Thus, altered serotonergic activity might be a necessary "trigger" that sets off a cascade of acute and more chronic perceptual and hallucinogenic effects, which involve more dopaminergic mechanisms. Such a change in DA activity is consistent with the still popular DA hypothesis of schizophrenia.

Conclusions

Sedatives and hallucinogens are two discriminable types of drug classes with contrasting characteristics. The discriminable effect of sedatives appears to be largely attributable to the increase in GABA, an inhibitory neurotransmitter. The discriminable effect of hallucinogens appears to be related to an increase in the action of biogenic amine neurotransmitters such as serotonin and DA.

The CNS activity normally varies greatly, such as between sleep and wakefulness or between strenuous activity and repose. The decrease caused by a sedative drug can, nevertheless, have a discriminable effect. The CNS continually contains opposing stimulant and inhibitory influences. A sedative drug can cause behavioral activation and feelings of exhilaration by depressing inhibitory influences more than excitatory influences.

Hallucinogens cause bizarre visual changes and emotional moods that are absent from normal behavior. The drug effect may, therefore, be expected to be highly discriminable. Very low doses of LSD, mescaline, and

other hallucinogens are sufficient to induce the extraordinary symptoms in humans and to enable a discriminable effect in laboratory animals.

In addition to sedatives and hallucinogens, several other categories of drugs appear to have different discriminable effects. Barry (1974) listed five other categories. They are antimuscarinics, nicotine, delta-9-tetrahydrocannabinol, opioids, and stimulants. Additional categories might be antipsychotic drugs, antihistamines, and the convulsants pentylenetetrazol (Metrazol) and bemegride.

Opposite effects are between antimuscarinics and muscarinic agonists and between the sedative diazepam and the convulsant pentylenetetrazol. Future research might reveal similar or opposite discriminable effects of other categories. Some categories of drugs probably constitute independent dimensions of change from the normal condition.

Ian Stolerman has contributed useful bibliographies of publications on the discriminable effects of all types of drugs (Stolerman et al. 1982, 1989a, b; Stolerman and Shine 1985). Several hundred publications report on a large number of different drugs and a great variety of research techniques.

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