ANIMAL MODELS OF DRUG-INDUCED HALLUCINATIONS

by

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Introduction

For practical and ethical reasons we often study the effects of drugs on animals when our real interest is the drug's effect on humans. In this effort when we deal with drugs which alter complex mental states we are presented with obvious difficulties. Here we examine some of these difficulties and approaches to their solution using studies presented at this conference.

Problems in Developing Animal Models of Drug-Induced Hallucinations

The scientific study of drug-induced hallucinations (and of other private experiences) meets methodological difficulties at the outset because the phenomena of hallucinations are not directly accessible to the outside observer. Such phenomena can be verified, with the most certainty, after the experience and through the words of the experiencing self. Thus, we may find lively debates regarding what are and what are not hallucinations and how to quantify them. Attempts toward developing animal models of hallucinations must take into account that the phenomena being modelled are only conveyed verbally, and, at that, often poorly defined.

For some, studies of animal behavior are regarded as interesting but thought to be of little direct scientific relevance to the human experience. As Levy (1952) said, "We have accepted our kinship with the animal world structurally and biochemically, but we remain isolationists psychologically." It is indeed true that devices and methods used in some animal laboratories are often poor analogues to human clinical phenomena, and clinicians have often been unaccepting of animal models of human behavioral problems. Clinical psychiatry is still having enough trouble using terms such as "hallucination," "psychosis," depression," "despair," and "phobia" in describing clinical phenomena without using these same words to describe various behavioral states in animals.

To date, it cannot be determined if an animal hallucinates and there is no reliable biological predictor of the waking hallucinating experience (like the correlates of rapid eye movements during dreaming). We can only study behavioral, chemical and physiological end points.

The experimental production of hallucinations in animals would allow the investigation of biological variables (and individual or social factors) while the animal is "hallucinating." Since social factors, the processing of verbal/symbolic information are important in understanding hallucinations, it is probably more fruitful to couch animal models in nonverbal terms, and utilize hallucinogenic drug effects in animals as a conceptual tool--pointing to variables that might be looked for in man, generating hypotheses that can be tested, revealing information about mechanism of action. Although there may be some lack of homology among species, a comparative approach can identify new and significant problems for research in man, help to formulate theories about human behavior and provide a system for investigating and clarifying concepts by allowing them to be tested on an observational and experimental level in animals.

Animal Models of Human Psychological States

To a large extent, the development of animal models of drug-induced hallucinations is related to the proposition that naturally-occurring psychotic states can be modelled by drug-induced hallucinations in humans or hallucinogenic drug effects in animals. These models of psychotic states are beyond the scope of this paper.

There is no intrinsic or *a priori* reason which precludes the creation of animal models for subjective experiences or psychopathological disorders. In fact, animal models have already been proposed for depression (McKinney and Bunney, 1969), aggression (Eichelman and Thoa, 1973) and alcoholism (Lester and Freed, 1973). Animal models of hallucinations must be viewed in the larger context of animal models for psychopathological states, as a whole. The development of animal models of psychological phenomena has largely imitated the research strategy used in experimental medicine in that the major approach has been through *experimental induction*; in this case, induction of abnormal behaviors via biological or environmental manipulation. We lack *spontaneous* models, "experiments in nature."

Having mentioned some problems in developing an animal model of hallucinations we now discuss the following: (1) The use of models as *analogues* or *assays* of drug-induced hallucinations in humans; (2) criteria which may serve as guidelines in developing animal models of hallucinations; and (3) "The Early State of the Art" in terms of the extent to which these criteria have been satisfied and/or tested by the animal models already proposed.

Analogue or Assay Models

Analogue Model

An *analogue* model of drug-induced hallucinations in man refers to behavior in animals which is faithful to some features of (drug-induced) hallucinations in man. The use of animal models as an analogue to the behavior being modelled (i.e., hallucinations) rests on some intrinsic similarity in behavior

between animals and man. The value of the analogue model can be arrived at by looking at the content validity of the animal behavior; the more the substance of the animal behavior is representative of the content of what is being modelled, the better the analogue model is thought to be. Investigators who have interpreted their model behaviors as analogues have referred to drug-induced behaviors in animals as "a veritable hallucinatory crisis" (Courvoisier, 1956) or "stereotypy" (Ellinwood et al., 1973), recognizing that hallucinogenic drugs produce similar behaviors in humans. An analogue model runs the risk of analogizing animal and human behaviors on the basis of "face validity" and making either anthropomorphic or ratomorphic comparisons.

Assay Model

An assay model of drug-induced hallucinations in man refers to behavior in animals as being independent of the behavior associated with hallucinations but dependent on the response of the animal behavior to pharmacological manipulations. The criterion we apply to an assay model of hallucinations amounts to a requirement of pharmacological isomorphism--at least one formal characteristic in one system (i.e., assay behavior) is required to have a counterpart in another (i.e., hallucinations) although the objects contained in the two systems may differ. The formal characteristics that are required to be preserved in going from the animal assay to hallucinations are parallel responses to pharmacological intervention (e.g., chlorpromazine may block a specific hallucinogenic drug-induced behavior in animals as well as hallucinations in man). The value of the assay model can be determined by testing the predictive validity of the animal behavior and the more predictive the animal behavior is of what is being modelled, the better the assay model is thought to be. Irrespective of the kind of behavior produced by the drug in the animal, the assay behavior is worthy to the degree to which is serves as an outside independent criterion against which we can check or predict hallucinations; it is simply a screening device.

Animal analogues or assays of hallucinations are not necessarily mutually exclusive. In fact, one might conceive of these two kinds of models not as dichotomies, but as extremes along a continuum with one extreme representing behaviors which have no apparent similarity (i.e., assay) and the other extreme representing behaviors which appear similar (analogue).

In Table 1 we summarized some salient findings of the models proposed in this conference along a spectrum from assay to analogue.

There are other behavioral procedures sensitive to hallucinogenic drug activity which were not represented in this conference. Among these are head twitching (Corne and Pickering, 1967), ambulation and defecation in the open field (Brimblecombe, 1963), "hallucinogenic pause" or suppression of bar pressing on fixed ratio operant behavior (Appel and Freedman, 1965) or DRL (differential reinforcement for low rates of responding) (Smythies et al., 1969), disruption of maze performance (Uyeno, 1969) and hallucinogenic drug states of discriminability from the no drug or saline state (Cameron and Appel, 1973; Hirschorn and Winter, 1971).

The analogue behaviors consist of excitatory behavioral syndromes with sympathomimetic stimulation, "hallucinatory-like" behaviors and disturbances in attention. Such behavioral changes are common after hallucinogenic drug administration to humans and various models of attentional defects in schizophrenia have been proposed (see Matthysse, 1977).

TABLE 1. Assay/Analogue Animal Behavior Models of Hallucinogenic Drug Effects

Assay	In Between	Analogue
Beaton et al.: MESC, LSD, DMT, 5-MeO-DMT have Bovet Gatti profile on discriminated Sidman avoidance (i.e., increased inefficient and premature responses, decreased efficient responses)	Davis: MESC, PMA, DOM have self administration properties	Domino: PCP caused locomotor sympathomimetic stimulation (stereotypic head turning, tremors, seizures, convulsions in the rat; more anesthetic and catatonic in monkeys)
Bridger et al.: MESC, LSD increased shuttlebox performance of low avoidance responders; MESC, LSD, DMT decreased performance of high avoidance	Geyer and Mandell: MESC, DOM, DOET, DOPR increased acoustic startle response	Jacobs and Trulson: LSD caused "hallucinatory-like" behaviors
Davis: MESC, PMA, MDA have biphasic effect on activity and well established shuttlebox avoidance (disruption, then facilitation)	Jacobs and Trulson: LSD, psilocybin elicit limb flicking and abortive grooming	Loh and Tseng: High doses of dl-PMA and dl-MMA caused locomotor stimulation (MMA was admphetamine-like but periodic while PMA was not amphetamine-like with slow, crawling movements, tremors, piloerection but no stereotypy)
Geyer and Mandell: LSD, DMT, psilocybin decreased holeboard exploration		Marquardt et al.: LSD, MESC, ℓ-MDA produced apparent hallucinations, increased reactivity to external stimuli, convulsions, ataxia
Gormezano and Harvey: Low dose of LSD facilitates acquisition of nictitating membrane classically conditioned response; high doses impair acquisition		Martin et al.: LSD, DOB, TMA, DMA produced autonomic and somatomotor stimulation, arousal, restlessness, whining, tracking or staring
Otis et al.: MESC, DOM, DET, PMA, MDA, MMDA-2 DMA-2,5, LSD, DMT decreased rat activity and increased rabbit body temperature		Siegel: LSD, DMT, PCP, THC impaired discrimination between real and apparent stimuli
		Winters: LSD, MESC produced "hallucinatory" movements, bizarre postures, visual tracking, fixating in space

MESC: 3,4,5-trimethoxyphenylethylamine (Mescaline)
TMA: 3,4,5-trimethoxyamphetamine
MMDA: 2-methoxy-4,5-methylenedioxyamphetamine
MDA: 3,4-methylenedioxyamphetamine
MMA: meta-methoxyamphetamine
PMA: para-methoxyamphetamine
DMA-2,5: 2,5-dimethoxyphenylisopropylamine
DOM: 2,5-dimethoxy-4-methylamphetamine
DOET: 4-ethyl-2,5-dimethoxyamphetamine
DOPR: 4-propyl-2,5-dimethoxyamphetamine
DOB: 2,5-dimethoxy-4-bromoamphetamine
DMT: N,N-dimethyltryptamine
DET: N,N-diethyltryptamine
5-MeO-DMT: 5-methoxy-N,N-dimethyltryptamine
LSD: Lysergic acid diethylamide
PCP: Phencyclidine
THC: Tetrahydrocannabinol

It is interesting to note that some of the assay model behaviors could be interpreted as analogues to hallucinations, although they would at first seem to bear no intrinsic similarity. For example, Bridger et al. (this Volume) liken hallucinogen-induced facilitation of rat shuttlebox avoidance to "bad trip" or "psychotomimetic" effects and disruption of avoidance to "good trip" or "psychedelic" effects; Bridger (1967) postulates that the mescalinized rat "hallucinates" (a stimulus to-be-signalled) by reacting to a signal and the to-be-signalled stimulus in the same way. Alteration in startle responding (see Geyer and Mandell, this Volume), disruption of discriminated Sidman avoidance (see Beaton et al., this Volume) and head twitching (Corne and Pickering, 1967) may be thought of as analogues in that all may reflect defects in stimulus control. Disruption of attention and impairments in reality judgments are salient features in humans given hallucinogenic drugs: attention wanders from outer dimensions to inner private events shifting from relevant cues to irrelevant cues (Fischer, 1975), there is a shortened concentration span and distractibility (Hoffer and Osmond, 1967, p. 120). There is a growing body of evidence that the major deficit in schizophrenic patients is related to attention (Matthysse, 1977; Shakow, 1962; Zubin, 1975).

Criteria for an Animal Model of Hallucinations

The extent to which the behavior of an animal treated with hallucinogenic drugs represents (i.e., models) aspects of drug-induced hallucinations in man cannot be answered at present. Probably the greatest difficulty in evaluating the validity of such a model is the lack of specific ground rules or criteria, against which we can test the heuristic and clinical significance of the model. The following criteria may be useful as a guideline in developing an experimental animal model of hallucinations. The criteria may apply to an analogue or assay model and no single criterion is a requisite condition.

1. Methodological: Administration of hallucinogenic drugs should produce observable behavioral changes which are quantifiable, reliable and reproducible.

2. Drug specificity: The behavioral changes should be specific only to the class of hallucinogenic agents, defined psychologically, structurally or biochemically.

3. Behavioral specificity: Behavioral changes are observed as alterations in performance of an animal in a particular situation. Observed behavioral changes can be due to specific effects on learning (e.g., retention, retrieval) or nonlearing processes (e.g., perception, motivation, motor ability) or just nonspecific effects on all behaviors. Obviously, influencing only a limited number of behavioral systems, rather than multiple systems, make interpretations of drug effects on behavior easier and less confounding.

4. Chemical specificity: If a specific neurotransmitter system is implicated in the behavioral changes (not excluding others) then activation of that system through different mechanisms (e.g., receptor agonist, amine release) should yield similar effects in one direction while inhibition through different mechanisms (e.g., receptor blockade, synthesis inhibition) should yield similar effects in the opposite direction.

5. Anatomical specificity: If there is a specific anatomical site of action then the behavioral changes induced by hallucinogenic drugs should be

similar when the drug is applied directly into central nervous system tissue (e.g., intraventricular administration) and systemically, assuming the drug crosses the blood brain barrier.

6. Species generality: From an evolutionary point of view, assuming some degree of structural and behavioral uniformity along the phylogenetic scale, the behavioral changes, defined nonlinguistically, should be relatively general among different species.

7. Dose related: For a given drug, the effective dose for behavioral changes in animals should roughly parallel the effective dose for psychoactivity in humans in terms of mg/kg body weight.

8. Relative potency and duration: Among the drugs considered to be hallucinogenic in humans, the magnitude and time course of the behavioral changes (perhaps blood and brain concentrations as well) in animals should roughly parallel the relative psychological potency and duration of action of these drugs, in terms of mg/kg body weight.

9. Tolerance: Pharmacological tolerance to the behavioral changes should develop for those hallucinogenic agents which show tolerance in humans, using similar drug regimens (see Wyatt et al., 1976); if only partial tolerance or no tolerance occurs for some effects of hallucinogens in humans under particular environmental conditions (e.g., stress), then partial tolerance or no tolerance should occur to the behavioral changes in animals when similar conditions are maintained.

10. Blocking: Those drugs or other treatment modalities which are effective in antagonizing the drug-induced hallucinogenic state in humans should also be effective in decreasing the behavioral changes in animals (see Wyatt et al., 1976).

Satisfaction of all these criteria is an "ideal state of affairs" and it is important to note that pharmacokinetic variables, interspecies differences and other relevant behavioral/pharmacological variables can influence the degree to which some of these criteria are satisfied for a given model.

The Early State of the Art

The state of the art in the development of animal models of hallucinations can be examined by determining whether the model behaviors presented in this conference satisfy the proposed criteria.

By and large the methodological criterion (criterion 1) has been met by the different models. However, in four of the models there are no reports of attempts toward reproducibility in laboratories other than the four mentioned here (see Geyer and Mandell; Gormezano and Harvey; Jacobs and Trulson; Siegel, this Volume).

Criterion 2 has been satisifed to a large extent by Beaton et al. Partial satisfaction of the drug specificity criterion exists for most of the other models: (1) although small qualitatively different hallucinatory experiences in humans occur among methoxylated amphetamines, anticholinergics, catechol or indole hallucinogens, the behavioral effects in animals among these drugs are virtually identical (see Marquardt et al.; Martin et al.; Otis et al.;

Siegel, this Volume); (2) other drugs (e.g., sedatives, antimuscarinics) share the behavioral effects produced by the prototypic hallucinogens (LSD, mescaline) (see Bridger et al., this Volume); (3) indole and catechol hallucinogens have opposite effects (see Geyer and Mandell, this Volume); (4) data for only catechol hallucinogens was documented (see Davis; Loh and Tseng, this Volume) or only indoles (see Gormezano and Harvey; Jacobs and Trulson, this Volume).

Some of the other behavioral procedures for hallucinogenic activity, not presented in this conference, also escape the criterion of drug specificity: (1) head twitches can be induced by the serotonin precursor, 5-hydroxytryptophan (Corne et al., 1963), and benzodiazepines (Nakamura and Fukushima, 1976) as well as by some hallucinogenic agents (Corne and Pickering, 1967); (2) nonhallucinogenic drugs, such as chlorpromazine and apomorphine produce similar effects on the open field test (Silva and Calil, 1975) as hallucinogens (Brimblecombe, 1963); (3) nonhallucinogenic drugs, such as morphine, apomorphine, clorpromazine and pentobarbital, produce the "hallucinogenic pause" on food reinforced operant behavior (Silva and Calil, 1975), like mescaline or LSD (Smythies et al., 1969).

Criterion 3 is met only by Gormezano and Harvey who showed that LSD's effects on classical conditioning are due specifically to associative processes, controlling for pseudoconditioning. In most cases, adequate behavioral controls have not been employed for nonspecific effects (e.g., generalized states of arousal, motivational or motor changes) and/or state dependency.

Species generality (criterion 6), anatomical specificity (criterion 5), and blocking (criterion 10) have not been tested in any of the models.

There have been a few tests of chemical specificity (criterion 5) implicating the action of hallucinogenic drugs (particularly the indoles) via tryptaminergic (see Martin et al., this Volume) or serotonergic mechanisms (see Geyer and Mandell; Jacobs and Trulson; Loh and Tseng, this Volume).

Every model satisfies the dose related and relative potency criteria (criterion 7 and 8) but only four of the models have tested for tolerance (criterion 9) (Beaton et al.; Bridger et al.; Jacobs and Trulson; Martin et al., this Volume). In general, tolerance has been found except for the demonstration by Bridger et al., that tolerance does not develop to excitatory effects of hallucinogens (although it does develop to inhibitory effects); Martin et al. failed to demonstrate complete cross tolerance among LSD and the methoxylated amphetamines.

Conclusion

This paper attempted to review the relationship between the effects of hallucinogenic drugs in animals and humans on a correlational (assay) or inferential (analogue) basis. The main value of animal screening procedures is to predict activity of potential hallucinogenic drugs and their potency. This goal neither requires nor precludes that an animal test be related in any logical or anthropomorphic way to the human mental state. Nevertheless, the premise that as a result of evolutionary processes the determinants of behavior are qualitatively similar among varied species has inspired numerous attempts at animal analogues of human behavior. The utility of such models is obvious; if validated, such models would allow direct inferences to be made about human behavior from observations of animals and would increase

confidence in making comparative statements about mechanisms of action. Unfortunately, to date, no model is entirely satisfactory, at least according to the criteria proposed.

If drugs that induced tail biting in rats were found to belong to the family of hallucinogenic drugs, then tail biting would become an important test to identify mechanisms of hallucinogenic activity. This may not be revealing about the phenomenology of subjective experiences; however, reliance on empirical correlations may be necessary since at present there is no exact and objectively identifiable animal counterpart of hallucinogenic drug states in humans or of human psychotic disturbances.

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