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Review

The behavioral pharmacology of hallucinogens

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ABSTRACT

Until very recently, comparatively few scientists were studying hallucinogenic drugs. Nevertheless, selective antagonists are available for relevant serotonergic receptors, the majority of which have now been cloned, allowing for reasonably thorough pharmacological investigation. Animal models sensitive to the behavioral effects of the hallucinogens have been established and exploited. Sophisticated genetic techniques have enabled the development of mutant mice, which have proven useful in the study of hallucinogens. The capacity to study post-receptor signaling events has led to the proposal of a plausible mechanism of action for these compounds. The tools currently available to study the hallucinogens are thus more plentiful and scientifically advanced than were those accessible to earlier researchers studying the opioids, benzodiazepines, cholinergics, or other centrally active compounds. The behavioral pharmacology of phenethylamine, tryptamine, and ergoline hallucinogens are described in this review, paying particular attention to important structure activity relationships which have emerged, receptors involved in their various actions, effects on conditioned and unconditioned behaviors, and in some cases, human psychopharmacology. As clinical interest in the therapeutic potential of these compounds is once again beginning to emerge, it is important to recognize the wealth of data derived from controlled preclinical studies on these compounds.

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1. Introduction

Although drugs producing sensory distortions have been used by man for several millennia, many consider the modern era of psychedelics to have begun when the psychotropic effects of lysergic acid diethylamide (LSD, Fig. 1C) were discovered by Albert Hofmann in 1943 [1]. This discovery ushered in an era of intense LSD research, with nearly 1000 articles appearing in the medical literature by 1961 [2]. Most of this early research was based upon the drug's capacity to produce a "model psychosis" [3] although there are significant differences between LSD-induced and endogenously occurring psychotic behaviors [4]. By the mid-1960s, LSD and other related drugs had become associated with various counterculture movements, depicted as dangerous, and widely popularized as drugs of abuse. Accordingly, scientific interest in these drugs faded by the late 1960s, but human research with related psychedelics has recently experienced a slight renaissance [5-13].

The term "hallucinogen" has come to describe LSD and related compounds based on the supposition that these drugs elicit hallucinations, but it has been argued that, at the doses commonly taken recreationally, frank hallucinations are produced only rarely [14]. Nevertheless, other designations for this class of drugs (for example, *psychedelics*, *psychotomimetics*, *entheogens*, etc.) have not necessarily caught on, and so we will use the term hallucinogen to refer to these compounds, despite the controversy surrounding the appropriateness of this appellation. As a drug category, hallucinogens are typically accepted to encompass an enormous range of pharmacological substances, with mechanisms of action ranging from cannabinoid agonism (i.e., Δ^9 -tetrahydrocannabinol), *N*-methyl-D-aspartate (NMDA) antagonism (i.e., phencyclidine), muscarinic receptor antagonism (i.e., scopolamine), κ opioid agonism (i.e., salvinorin A), mixed action monoamine release (i.e., 3,4-methylenedioxymethamphetamine [MDMA]), and more. Thus, within the confines of this review, we will use the term hallucinogen to denote

compounds with pharmacological effects similar to three prototypical drugs: 3,4,5-trimethoxy-phenethylamine (mescaline, Fig. 1A), *N,N*-dimethyl-4-phosphoryloxytryptamine (psilocybin, Fig. 1B) and LSD (Fig. 1C). All of these drugs function as agonists at 5-HT_{2A} receptors, and much work has culminated in the widespread acceptance that this particular receptor initiates the molecular mechanisms responsible for the unique effects of these compounds. Much of that work will be reviewed herein.

The aim of this review is to mark the sea change which seems to be occurring within the field of hallucinogen research. Until very recently, comparatively few scientists were studying these particular compounds, perhaps due to their unfortunate association with somewhat less than rigorous research techniques. In Nichols' recent review [14], for example, prominent clinicians are quoted as stating that the effects of hallucinogens transcend pharmacology, are unpredictable, and border on the mystical. Nevertheless, the state of hallucinogen research is now approaching something of a high water mark. Selective antagonists are available for relevant serotonergic receptors, the majority of which have now been cloned, allowing for reasonably thorough pharmacological investigation. Animal models sensitive to hallucinogen-like effects have been established and exploited to yield a wealth of largely concordant data. Along similar lines, sophisticated genetic techniques have enabled the development of mutant mice, which have proven useful in the study of hallucinogens. Finally, the capacity to study post-receptor signaling events has led to the proposal of a plausible mechanism of action for these compounds. The tools currently available to study the hallucinogens are thus more plentiful and scientifically advanced than were those accessible to earlier researchers studying the opioids, benzodiazepines, cholinergics, or other centrally active compounds. Those interested in hallucinogen research should thus be encouraged by all of these recent developments, and it is hoped that the perceived "scientific respectability" of the field will continue to increase.

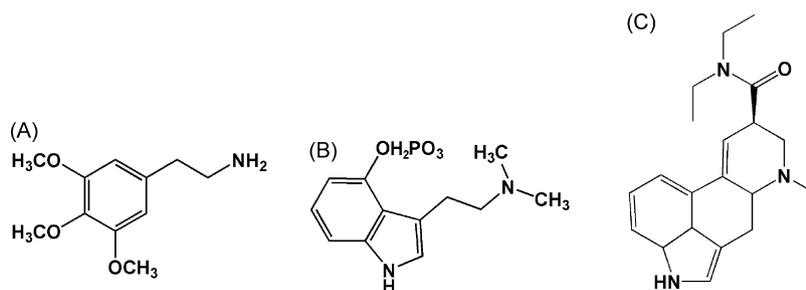


Fig. 1 – Chemical structures of the prototypical phenethylamine hallucinogen 3,4,5-trimethoxy-phenethylamine (mescaline, A), the representative tryptamine hallucinogen *N,N*-dimethyl-4-phosphoryloxytryptamine (psilocybin, B), and the archetypal ergoline hallucinogen lysergic acid diethylamide (LSD, C).

2. Animal models of hallucinogen-like action

2.1. Drug discrimination

Given the profound effects of hallucinogens on perception and other subjective variables, an animal model capable of assessing mechanisms of action of these drugs that informs their subjective effects in man would be especially useful. The main methodology presently employed in this regard is drug discrimination. In a typical discrimination task, an animal is trained to emit one response during experimental sessions initiated by the administration of a particular drug (the “training drug”), and a different response during sessions that follow administration of the drug vehicle. During the development of this assay, a diverse array of responses were typically engendered [15], but the majority of such research now involves discriminative responding on one of two operant devices (levers, nose-poke apertures, etc.) maintained by either appetitive reinforcement or shock avoidance. Under these contingencies, the injection condition (training drug versus saline, for example) serves as an interoceptive discriminative stimulus to cue the animal as to which response will be reinforced during a given session, in much the same way as the operant behavior of an animal may be guided by exteroceptive stimuli, such as colored lights or tones of certain frequencies. The drug discrimination assay is thus essentially a drug detection procedure whereby animals are trained to recognize the stimulus effects of a given dose of a particular training drug. During tests, well-trained animals may be administered different doses of the same training drug, or different doses of a novel compound suspected to have similar subjective effects to the training drug. Results of such tests generate asymptotic dose-effect curves where administration of a test compound with stimulus properties similar to those of the training drug dose-dependently increases responding on the drug lever. Similarly, prior treatment with a competitive antagonist tends to produce parallel rightward shifts in these discrimination dose-effect curves. A secondary measure of this assay is response rate. This measure is critical as it provides a built in positive control which ensures that behaviorally active doses of test compounds are reached. As drug dose increases, operant performance is disrupted, thus, if a test drug fails to elicit any drug-appropriate responding up to doses that suppress response rate, it can be safely concluded that the stimulus properties of the test drug do not overlap with those of the training drug. Theoretical data in this regard are presented in Fig. 2.

Complete characterization of a novel compound is no more possible with drug discrimination than it would be with any other single pharmacological procedure, but the strength of the drug discrimination assay lies in its capacity to gauge a range of pharmacological variables relating to the stimulus properties of a drug, including those related to time course (speed of onset, duration of action, etc.), receptor mechanisms important to pharmacological action, similarity of subjective effects to other drugs, structure-activity relationships for a group of chemically related compounds, and identification and development of antagonists. Another advantage of this procedure is its high degree of pharmacologic specificity. In this regard, well-trained animal will respond on the drug lever

when injected with a novel drug that has actions in common with the training drug, in which case the test compound is said to “substitute” for the training drug. Importantly, novel compounds that are active, but pharmacologically dissimilar to the training drug, typically occasion responding on the lever reinforced following administration of the drug vehicle during training sessions. The discriminative stimulus effects of various hallucinogens will be described below.

2.2. Drug-elicited head twitch behavior

The drug-elicited head twitch response (HTR) [16,17] is a selective behavioral model for 5-HT_{2A} agonist activity in the rodent. The topography of this behavior is similar to a “wet dog shake” and is operationally defined as a rapid, rotational jerk of the head which can be distinguished from species-appropriate grooming or scratching behaviors. Several previous studies have established that direct and indirect 5-HT agonists induce this effect [18–25], and that 5-HT₂ receptor antagonists selectively block the HTR [26–29]. Importantly, the potency with which antagonists attenuate the HTR is highly correlated with the antagonist’s affinity for 5-HT_{2A} receptors [18,30].

The observation of drug-elicited behaviors can be immensely helpful in the initial characterization of the pharmacological actions of new compounds *in vivo*. For instance, the Straub tail reaction in rodents (contraction of the sacrococcygeus muscle, resulting in erection of the tail) is readily observed following administration of μ opioids, and it has been suggested that observation of this behavior is a sufficient determinant of opioid activity in mice [31]. However, the effects most characteristic of the hallucinogens (such as distortions, intensifications and mixing of the senses, alterations in the perception of the passage of time, etc.) are largely unobservable, even in the human. Nevertheless, the induction of a head twitch response in rodents seems to be a common property of the hallucinogenic drugs, and there is now general agreement that this behavior is mediated by 5-HT_{2A} receptors [32,33]. This is not to suggest that all drugs inducing the head twitch response are hallucinogenic. Indeed, head twitches are induced by various serotonergic, but not necessarily hallucinogenic, agents [20,34]. Thus, the induction of a head twitch response should not be taken as *prima facie* evidence for hallucinogenic effects without further study. Nevertheless, the establishment of this assay requires little more than a video camera and a steady eye, which may be attractive to researchers wishing to get involved with hallucinogen research. Results of such tests generate biphasic dose-effect curves where administration of an active test compound dose-dependently increases HTR up to some peak amount, and then decreases twitch behavior at higher doses. Prior administration of an antagonist will produce a parallel rightward shift in the dose-effect curves. Theoretical data in this regard are presented in Fig. 3. Given the biphasic nature of HTR dose-effect curves, single dose experiments involving the HTR are not particularly informative, particularly when pharmacological challenges are administered and shown to attenuate twitch behavior. In the absence of a full dose-effect curve determination, such attenuation could be due to either true antagonism (the test dose mimics the effects of a lower dose in

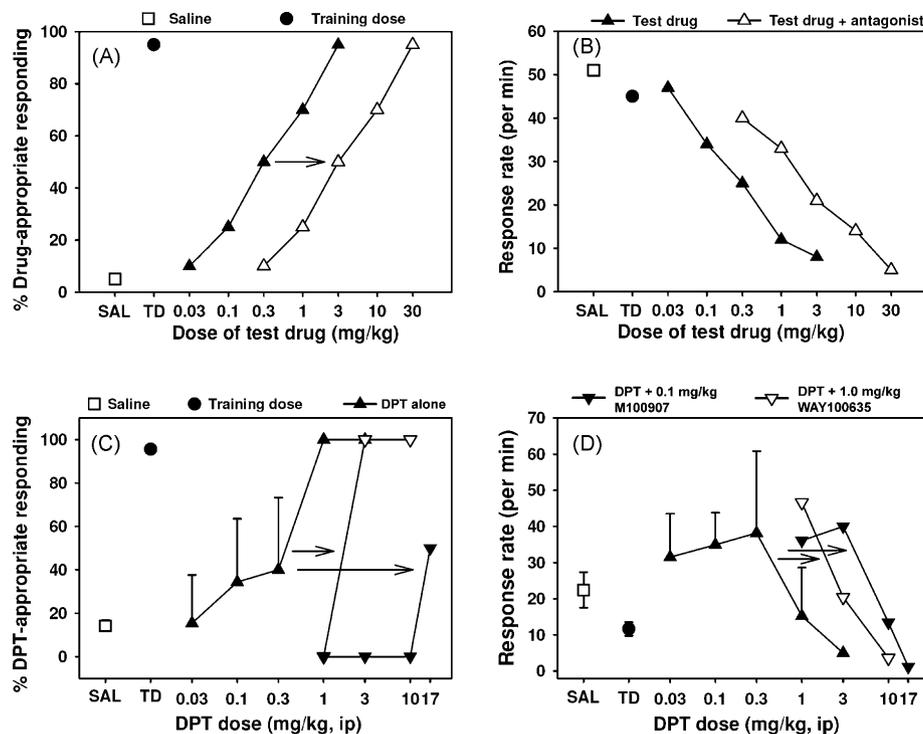


Fig. 2 - (A and B) Theoretical drug discrimination data illustrating discriminative control by saline (open square) or the training dose of the training drug (filled circle), dose-dependent substitution of the test drug for the training dose (filled triangles), and a parallel rightward shift in this dose-effect curve produced by prior treatment with a competitive antagonist (open triangles). The low percentage of drug-appropriate responding elicited by saline injection (A), coupled with the high response rate (B), demonstrates that the subjects are selecting the saline lever, while the near exclusive high rate responding on the drug lever following injection of the training dose indicates that the subjects have come under stimulus control. Note that increasing doses of the test drug asymptotically increase drug-appropriate responding while decreasing overall response rate. In this illustrative data, antagonist pretreatment attenuates both the discriminative stimulus and rate-decreasing effects of the test drug, but a dissociation of these two effects can be observed under some circumstances. **(C and D)** Empirical drug discrimination data from mice trained to discriminate 3.0 mg/kg DPT (filled circle) from saline (open square). Panel (C) illustrates dose-dependent substitution of DPT for its training dose (filled triangles), and parallel rightward shifts in this dose-effect curve produced by prior treatment with the selective 5-HT_{1A} antagonist WAY100635 or the selective 5-HT_{2A} antagonist M100907 (open triangles). Higher doses of WAY100635 produced no further shift in the discrimination curve and reduced response rates, suggesting that while some component of the discriminative cue induced by DPT is 5-HT_{1A}-mediated, the more salient component is attributable to 5-HT_{2A} receptor stimulation. Panel (D) shows that both antagonists reduced the rate-decreasing effects of DPT. These data previously unpublished (Murnane and Fantegrossi).

the presence of the antagonist) or could be due to potentiation (the test dose mimics the effects of a higher dose, which is incompatible with theories of antagonism). The effects of chemically diverse hallucinogens on head twitch behavior will be discussed below.

2.3. Self-administration

Behaviorism proposes that the actions of an organism are governed by their consequences according to principles of operant conditioning [35,36], and the term *reinforcement* is used to describe the relationship between a behavior and its consequences. Drug self-administration is a technique which allows for the study of drug reinforcement, as the operant response directly produces administration of the pharmacological substance. Such experiments assess the reinforcing

effects of a drug by quantifying an increase in the frequency of the behavior which produces drug administration. One critical factor in establishing and maintaining behavior under a given set of contingencies is immediacy of reinforcer delivery, and when studying drugs as reinforcers, this can sometimes pose problems. Essentially, experimenters ask laboratory animals to associate their behavior (for example, the depression of a response lever) with some change in interoceptive state induced by drug administration. Ideally, this change in interoceptive state should occur as rapidly after drug administration as possible in order to facilitate such an association. To the extent that different routes of drug administration can influence onset of drug action, a majority of researchers using drug self-administration procedures have chosen to use intravenous preparations in order to maximize the speed with which drug effects are induced, although it should be

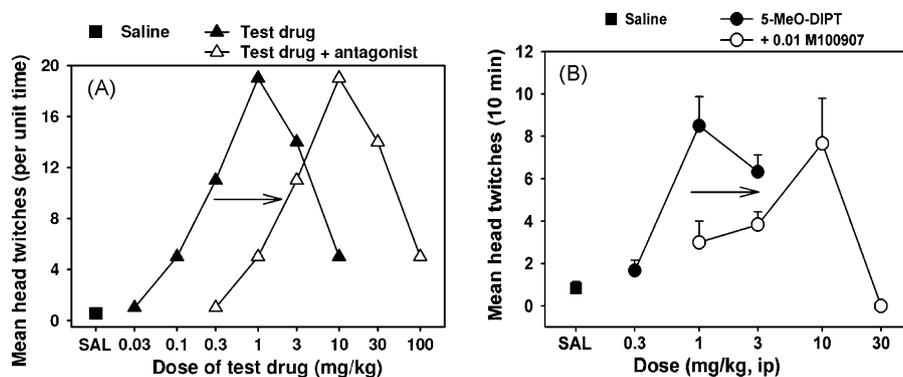


Fig. 3 – . (A) Theoretical head twitch data illustrating low levels of this behavior following injection of saline (filled square), dose-dependent and biphasic effects of a test drug on this behavior (filled triangles), and a parallel rightward shift in this dose-effect curve produced by prior treatment with an antagonist (open triangles). Note that pretreatment with either an additive agonist or an antagonist would decrease the HTR induced by the peak dose of the test drug by functionally increasing or decreasing, respectively, the drug dose. These data emphasize the importance of full dose-effect curve determinations using this assay. **(B)** Empirical head twitch data from mice injected with the tryptamine hallucinogen 5-MeO-DIPT, with or without prior treatment with the selective 5-HT_{2A} antagonist M100907. The antagonist produces a parallel rightward shift in the dose effect curve. Figure replotted and modified slightly from data previously published in [29]; used with permission.

noted that delivery of some compounds via intramuscular [37], inhalation [38] and oral [39] routes also maintain behavior. In laboratory animals, intravenous preparations involve the surgical insertion of an indwelling venous catheter (typically into a jugular vein) that is then routed subcutaneously to the mid-scapular region. From here, the catheter either exits the animal and passes through a “tether” system [40,41] or connects to a subcutaneously implanted vascular access port [42,43]. In either case, the catheter can then be attached to a drug supply via an electronic infusion pump, the operation of which is controlled by the behavior of the animal according to experimenter-determined schedule contingencies.

Despite the reasonably constant recreational use of hallucinogens since at least the early 1970s [44], the reinforcing effects of hallucinogens have not been widely investigated in laboratory animals. Indeed, one of the earliest studies on the reinforcing effects of drugs using the intravenous self-administration procedure in rhesus monkeys found that no animal initiated self-injection of mescaline either spontaneously or after 1 month of programmed administration [45]. Likewise, the phenethylamine hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) was not effective in maintaining self-administration in rhesus monkeys [46]. Nevertheless, the hallucinogen-like phenethylamine 3,4-methylenedioxy-methamphetamine (MDMA) has been shown to act as a reinforcer in intravenous self-administration paradigms in baboons [47], rhesus monkeys [48–50], rats [51] and mice [52]. Several structural analogues of MDMA, most notably *N*-ethyl-3,4-methylenedioxyamphetamine [53] and 3,4-methylenedioxyamphetamine [54], have also been shown to maintain self-administration behavior in baboons.

This is an important point to consider, as the traditional serotonergic hallucinogens of phenethylamine and tryptamine structures have long been distinguished as drugs that are abused by humans but fail to engender reliable self-administration behavior in laboratory animals [55]. These

methylenedioxy phenethylamines thus stand in contrast to more traditional hallucinogens such as DOM or mescaline in this regard. Nevertheless, in rhesus monkeys previously trained to self-administer MDMA, several monkeys periodically responded at high rates and earned a majority of all available infusions of mescaline, psilocybin and *N,N*-dimethyltryptamine (DMT), but did so with no discernible pattern or regularity [56]. This pattern of sporadic self-administration may indicate that these traditional hallucinogens have weak reinforcing effects, or, alternatively, mixed reinforcing and aversive effects. The effects of drug exposure history on initiation of subsequent self-injection and propensity to self-administer specific compounds has been reviewed previously [57], and it seems reasonable to suppose that a behavioral history which includes experience with the reinforcing effects of serotonergic drugs might predispose an organism to self-administer hallucinogenic compounds that have not previously been shown to maintain behavior. A more extensive manipulation of drug history in further studies may greatly improve our understanding of the reinforcing effects of hallucinogens, such as they may be.

Interestingly, hallucinogen-like compounds with antagonist affinity at glutamatergic *N*-methyl-*D*-aspartate (NMDA) receptors do maintain self-administration behavior in laboratory animals, as reinforcing effects have been previously demonstrated with phencyclidine (PCP) [58], ketamine [59], and memantine [60]. Furthermore, self-administration of cannabinoid agonists, though slow to be accepted, is now regarded as a robust phenomenon after the convincing demonstrations of the reinforcing effects of Δ 9-tetrahydrocannabinol in squirrel monkeys [61,62]. These findings may suggest that the appropriate schedules of reinforcement necessary to maintain regular self-administration of phenethylamine and tryptamine hallucinogens have not yet been identified. One of the fundamental tenets of behavioral pharmacology is that the reinforcing effects of drugs are

influenced, sometimes profoundly so, by the schedules that govern their contingent delivery [63,64]. As data regarding the self-administration of hallucinogens are sparse, there will be little mention of hallucinogen reinforcement for the remainder of this review. However, more work in this regard should be encouraged, as it might ultimately prove helpful in identifying the important behavioral and pharmacological variables which might be relevant to the self-administration of hallucinogens by laboratory animals, and perhaps also to the factors involved in hallucinogen use in humans.

3. Serotonin receptors and hallucinogen neuropharmacology

Pharmacologists currently recognize seven different serotonin (5-HT) receptors and 14 different subtypes. The current classification scheme was derived from the explosion of knowledge acquired during the molecular biology revolution of the 1980s and 1990s, as newly developed techniques allowed for the determination of sequence homology, leading to a more accurate characterization of new receptor subtypes and the re-classification of some previously known receptors. Although this work was incredibly important to the study of hallucinogens, the receptor and behavioral pharmacology of such drugs could not be conducted without ligands that specifically bind to those newly distinguished receptors. Only recently has the pharmacology of the serotonin system begun to catch up with the molecular biology. Therefore, the pharmacology of the serotonin system has been largely focused on a subpopulation of the serotonin receptors for which selective ligands have been available.

With the discovery of serotonin as a biologically active substance it was immediately obvious to chemists that LSD and serotonin were structurally similar. However, it was not immediately clear whether LSD mimicked or blocked the effects of serotonin. In fact, initial experiments by John Gaddum and others argued for a mechanism of action wherein LSD blocked the effects of serotonin [65,66]. However, this early hypothesis of 5-HT antagonist activity was abandoned when drugs such as 2-bromo-LSD, which function as 5-HT antagonists in peripheral tissues were found to not only lack the subjective effects of LSD [67,68] but also to block the subjective effects of LSD itself [69]. These findings, among others, lead to general acceptance that the subjective effects of LSD were in fact mediated through 5-HT receptor agonist activity. The next prominent hypothesis of the mechanism of hallucinogenesis was based on observations by Aghajanian and colleagues that LSD, as well as the simple tryptamines psilocin, DMT, and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), suppressed firing of neurons in the dorsal raphe nucleus [70,72]. These researchers hypothesized that this mechanism might underlie the hallucinogenic effects of the tryptamines and the ergolines. However, this hypothesis was eventually abandoned because it was found that the putatively non-hallucinogenic ergoline lisuride also suppressed dorsal raphe firing [73], that the phenethylamines lacked this effect entirely [71,74], and that the suppression of firing lasted longer than the behavioral effects in cat models [75].

More recent work on the mechanisms of hallucinogenesis has focused on the 5-HT_{2A} receptor. This latest hypothesis emerged from work involving drug discrimination procedures which demonstrated that the discriminative stimulus properties of both phenethylamines and tryptamines could be blocked by 5-HT₂ receptor antagonists such as ketanserin and pirenperone [76,19]. This body of work was compelling because it provided a common mechanism of action between the phenethylamines and the tryptamines. Perhaps the most convincing demonstration of 5-HT₂-mediated hallucinogen effects was reported in a seminal paper published almost 20 years ago [77]. In these studies, an incredibly tight correlation ($r = 0.97$) between affinity at 5-HT₂ receptors and hallucinogenic potency in humans was established. This work provided a persuasive mechanism of action to be more thoroughly explored by future research.

It is important to note, however, that the apparent affinity of agonists for the 5-HT_{2A} receptor estimated from displacement experiments will depend critically on the intrinsic efficacy of the radioligand used to label the binding site. This was elegantly demonstrated by an experiment in which the human 5-HT_{2A} receptor was stably expressed in NIH3T3 cells, then radiolabeled with [³H]5-HT (a full agonist), [³H] 4-bromo-2,5-dimethoxyamphetamine (DOB, a partial agonist), and [³H]ketanserin (an antagonist) [78]. In this report, receptors labeled with [³H]5-HT displayed a K_d value of 1.3 nM and a B_{max} value of 3461 fmol/mg protein, and the radiolabeling was sensitive to the stable guanosine 5'-triphosphate (GTP) analogue guanylyl-imidodiphosphate (GMP-PNP). Ketanserin labeled significantly more receptors ($B_{max} = 27,684$ fmol/mg protein, $K_d = 1.1$ nM) than did [³H]DOB ($B_{max} = 8332$ fmol/mg protein, $K_d = 0.8$ nM), but both of these agents labeled significantly more receptors than did [³H]5-HT. Most germane to the present argument, agonists had a higher apparent affinity for [³H]-agonist-labeled receptors than for [³H]-antagonist-labeled receptors. Thus, comparisons of affinities for various hallucinogens across multiple sites of action must be regarded as tentative, particularly when distinct receptor populations have been labeled with ligands of varying efficacy.

4. Glutamatergic and dopaminergic involvement in hallucinogen neuropharmacology

Stimulation of 5-HT_{2A} receptors in brain regions relevant to hallucinogen action is typically associated with an increase in spontaneous glutamate-mediated synaptic activity [79-84]. These findings and others suggest that 5-HT_{2A} receptors may modulate the excitability of specific neural systems, but theories of 5-HT/glutamate (GLU) interactions remain incomplete due to the lack of a plausible mechanistic account for this effect. Multiple such mechanistic explanations have been proposed to account for 5-HT_{2A}-mediated stimulation of GLU activity, but the most widely accepted theory implicates an as yet unidentified retrograde messenger capable of triggering GLU release [81,83,85]. Although this theory fits a range of data, from cellular to whole animal preparations, the failure thus far to identify the retrograde messenger has precluded rigorous testing. Recently, however, a series of studies used molecular and cellular techniques to directly test different aspects of the

retrograde messenger hypothesis, and the resulting findings were inconsistent with this theory [86]. Instead, the authors argued that stimulation of 5-HT_{2A} receptors may lead to an increase in glutamatergic recurrent network activity via direct excitation of specific pyramidal cells in the deeper layers of the prefrontal cortex [86].

Similarly, dopamine D1/D5 receptor agonists may function as neuromodulators that decrease extracellular GLU in prefrontal cortex, an effect which would decrease recurrent network activity induced by hallucinogens [87]. In slices of prefrontal cortex harvested from the rat, it has been demonstrated that low concentrations of D1/D5 agonists suppressed recurrent activity, that their effects were opposite to the enhancement of such activity induced by hallucinogens, and that these dopamine-mediated actions could completely overcome network activity stimulated by 2,5-dimethoxy-4-iodoamphetamine (DOI) [87]. A larger discussion of these effects on neurophysiology is largely outside the scope of this review, but the interested reader is directed to the references cited above for a more thorough treatment of these topics.

5. Chemical classes of hallucinogens

There are two main chemical classes of hallucinogens, based upon either phenethylamine (mescaline-like) or tryptamine (psilocybin-like) backbones. LSD and a few interesting analogues represent elaborated, conformationally restrained tryptamines, and are commonly referred to as ergolines. Here we dedicate a separate section to LSD and its purportedly non-hallucinogenic analogue lisuride. The behavioral pharmacology of these drugs will be described in the sections below, paying particular attention to important structure activity relationships which have emerged, receptors involved in their behavioral actions, discriminative stimulus effects, capacity to elicit HTR, and in some cases, human psychopharmacology.

5.1. Phenethylamines

The chemical backbone for all of the hallucinogenic phenethylamines is based upon the amino acid phenylalanine. Enzymatic decarboxylation biotransforms phenylalanine to phenethylamine, which is a prevalent structure in a range of endogenous compounds, including neurotransmitters and hormones. With regard to drugs of abuse other than hallucinogens, substituted phenethylamines can function as stimulants (i.e., amphetamine), entactogens (i.e., MDMA), and even as opioids (i.e., the morphinans). Although we have grouped LSD with the tryptamines for purposes of this review, it is important to note that the phenethylamine structure can

be found as part of the more complex ring system of the ergolines as well. Substituted phenethylamines may be chemically modified along the phenyl ring, the sidechain, or the amino group. In this regard, substituted amphetamines are homologues of phenethylamines containing an α -CH₃ group (see Fig. 4A). Additions of OH groups at the 3- and 4-positions give rise to the catecholamines, which include dopamine, epinephrine, and norepinephrine. Shulgin's "2C" compounds (discussed below) lack an α -CH₃ group, but contain MeO groups attached to the 2- and 5-position carbons.

The naturally occurring compound mescaline, an alkaloid isolated from the dumpling peyote cactus, has served as the lead compound in the development of structure–activity relationships (SAR) for the phenethylamines [88–93]. A major finding of hallucinogenic phenethylamine SAR is that increasing the length of the alkyl group on the 4-position oxygen atom increases potency of the resultant compound (as compared to mescaline, the reference standard). An important result of these efforts has been the design of relatively selective and potent compounds such as DOI and DOB, which have been widely used *in vitro* and *in vivo* to probe hallucinogen mechanisms of action. Further information on phenethylamine SAR is largely beyond the scope of this review, but the interested reader is directed to the erudite reviews of this subject by Jacob and Shulgin [94] and by Nichols [95].

As seen in Table 1, the selective phenethylamines DOI, DOM and DOB possess low nanomolar affinities for 5-HT_{2A} receptors, and appreciably higher (on the order of 1000-fold) affinities for 5-HT_{1A} receptors. The selectivity of these compounds for 5-HT_{2A} over 5-HT_{2C} receptors is typically less than 10-fold, and some of the two carbon phenethylamine homologues of mescaline lacking the alpha-methyl group, such as 2,5-dimethoxy-4-(*n*)-propylthiophenethylamine (2C-T-7), actually display *higher* binding affinity for 5-HT_{2C} receptors. Thus, although these drugs may be accurately described as 5-HT₂-selective agents, there is generally reasonably promiscuous binding within the 5-HT₂ receptor family. The potency of these compounds (with the exception of mescaline) also tends to be quite high, and the duration of action of these agents can last more than a day.

The 5-HT_{2A} and 5-HT_{2C} receptors are extremely similar in terms of structure and function, and studies of the biochemical efficacies of a series of tryptamine and phenethylamine hallucinogens at these receptors indicated that all of these compounds tend to act as partial agonists at the 5-HT_{2C} receptor [96–97]. The majority of drug discrimination studies with these compounds have involved the training of DOI or DOM. Across multiple species, it has been shown that, in agreement with studies in humans, these hallucinogens generalize with one another [98,99]. Furthermore, antagonist

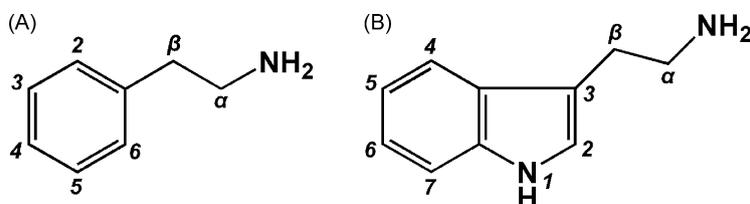


Fig. 4 – . Chemical structures, with position labels, for phenethylamine (A) and tryptamine (B). These two molecules form the chemical backbones for a range of hallucinogenic compounds discussed in this review.

Table 1 – Binding affinities (K_i , nM) of various hallucinogenic phenethylamines mentioned in the text at selected central serotonin sites, and estimated hallucinogenic potency and duration of action (following oral administration) in man

DRUG	5-HT _{1A}	5-HT _{2A}	5-HT _{2C}	Hallucinogenic potency in man (mg)	Duration of action in man (h)
Mescaline	–	20,000 [167]	–	200–400 [93]	10–12 [93]
DOI	3843 [168]	0.65 [168]	5.37 [173]	1.5–3.0 [93]	16–30 [93]
DOM	7267 [169]	21.00 [170]	41.68 [171]	3.0–10 [93]	14–20 [93]
DOB	3770 [172]	1.17 [168]	152.00 [170]	1.0–3.0 [93]	18–30 [93]
2C-T-7	1170* [28]	120.00* [28]	39.00* [28]	10–30 [93]	8–15 [93]

Where possible, affinities are listed as determined by competition binding vs. an agonist radioligand. Affinities for receptors in the inactive conformation (determined by saturation binding assays vs. an antagonist radioligand) are generally lower (higher K_i values) for all compounds, and are indicated in the table by an asterisk. Dashes in cells denote no data on affinity at that receptor. Full references to the source articles, denoted by numbers in square brackets, can be found in the References section.

correlation analysis has determined that the stimulus effects of phenethylamine hallucinogens are mediated by agonist activity at 5-HT_{2A} receptors and are modulated by agonist activity at 5-HT_{2C} receptors only rarely [100]. A specific example of this generalization is illustrated by the finding that the selective 5-HT_{2A} antagonist M100907, but not the selective 5-HT_{2C} antagonist SB 200,646, blocked the discriminative stimulus effects of DOI in the rat [101].

Head twitch studies involving injection of DOM and 2C-T-7 in the mouse have indicated pronounced antagonism of this effect by selective 5-HT_{2A} antagonists such as M100907 [28], and mutant mice lacking this receptor do not exhibit the HTR when administered DOI [102]. Similarly, repeated exposure to various stressors increases the density of 5-HT_{2A} receptors in the cortex [103–107], and such increases in receptor density have been shown to augment DOI-induced head twitches in rats and mice [108]. This implied relationship between stress, overexpression of 5-HT_{2A} receptors, and hypersensitivity to DOI-elicited HTR was explicitly demonstrated by exposure to repeated foot-shock and a consequent augmentation of DOI-stimulated twitch behavior in the mouse [109].

The phenethylamines are also noted for the rapid development of tolerance which develops upon their repeated administration. This hallucinogen-induced tachyphylaxis has primarily been studied in humans receiving LSD [110], but tolerance also develops to some behavioral effects of phenethylamine hallucinogens amenable to study in animals, such as DOM-elicited HTR [111], and mescaline- and DOM-induced limb jerks [112]. The mechanism underlying such tolerance appears to be downregulation of 5-HT_{2A} receptors, as decreases in 5-HT_{2A} receptor density have been demonstrated in rats receiving chronic administration of hallucinogenic drugs [111,113–115]. These changes in receptor expression have sometimes been correlated with changes in behavior. In this regard, repeated administration of DOM decreased both the HTR and 5-HT_{2A} receptor density [111]. The neuroendocrine response to DOB was attenuated over 1 week of repeated administration, and at the end of this drug regimen a significant decrement in 5-HT₂ receptor density was quantified [115]. Despite the high affinity of the phenethylamine hallucinogens for 5-HT_{2C} receptors, most reports indicate that behaviors mediated by these receptors are unaltered by chronic drug administration [116]. As might be expected, the discriminative stimulus effects of phenethylamine hallucinogens are also subject to tolerance development. In the first demonstration of this phenomenon, tolerance was

observed to the discriminative stimulus effects of DOI in animals treated with DOI for 8 days, although the discriminative performance of animals treated chronically with vehicle did not change significantly during the same time interval [117]. In these same studies, it was observed that repeated treatment with DOI decreased the density of 5-HT_{2A} receptors, which was interpreted as a mechanism for the development of tolerance to the discriminative stimulus effects of DOI [117]. In keeping with the literature described above, chronic DOI treatment did not cause a downregulation of 5-HT_{2C} receptors [117].

5.2. Tryptamines

The basic structure for all the hallucinogenic tryptamines is derived from tryptophan, which serves as an essential amino acid in some animals. The core structure is composed of a double indole ring system with an aminoethyl at the 3-position. Decarboxylation of the acid on the beta carbon converts tryptophan to tryptamine. The biosynthesis of various endogenous tryptamines proceeds through differential modification of the tryptophan structure. For example, serotonin biosynthesis commences with hydroxylation of the 5-position by tryptophan hydroxylase and then proceeds to decarboxylation of the β -carbon by amino acid decarboxylase. The biosynthesis of other endogenous tryptamines such as melatonin proceeds through a different metabolic sequence. Since all tryptamines contain the basic indole ring, they are all structurally similar to serotonin. This double ring system contains seven positions that are open to chemical modification (see Fig. 4B). However, the majority of medicinal chemistry efforts have thus far focused on modification of the 4- and 5-positions. One reason for this is because it has been shown that modification of either the 6- or 7-positions significantly reduce the psychoactive effects of the resulting compound [118]. Therefore, the hallucinogenic tryptamines can be largely divided into three broad categories based on modification to the 4- or 5-position on the indole ring, or a lack of modification to either position.

Leaving the indole ring unsubstituted, but adding two methyl groups on the terminal amine of the aminoethyl group, results in DMT which serves as a prototypical member of the ring-unmodified tryptamines. This hallucinogenic agent has been known for thousands of years to be naturally occurring in the *Banisteriopsis caapi* plant and has been extensively used in the form of a tea called *ayahuasca* that is consumed during

religious ceremonies of the indigenous people of the pan-Amazonian delta [119]. Double methylation and hydroxylation of the 4-position produces 4-hydroxy-*N,N*-dimethyltryptamine (4-OH-DMT, psilocin) which can serve as the prototypical agent of the 4-position modified tryptamines. Psilocin is the dephosphorylated active metabolite of the naturally occurring tryptamine psilocybin which is found in certain types of hallucinogenic mushrooms. It is thus important to recognize that, although psilocybin is the more commonly consumed agent, metabolic events within the body occur to biotransform this compound to psilocin, which mediates the majority of the drug effects *in vivo*. The prototypical compound chosen for the 5-position modified tryptamines is 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT). 5-MeO-DIPT or “Foxy Methoxy” is a synthetic designer drug which has largely come under scientific interest after its synthesis and description by Shulgin and Shulgin [118]. It is produced by the addition of two isopropyl groups to the terminal nitrogen of the aminoethyl group and methoxylation of the 5-position of the indole ring. The receptor and behavioral pharmacology of these different subclasses of the tryptamines will be discussed with principal comparisons made between these prototypical compounds.

Although the structural similarity of the tryptamines to serotonin engenders significant activity at serotonergic receptors across the chemical class, many tryptamines also bind and activate non-serotonergic receptors as well. Furthermore, the tryptamines have relatively lower affinity for the 5-HT_{2A} receptors than do either the phenethylamines or the ergolines. Even within the original paper [77] the tryptamines tested fell within a range of 207 nM (5-MeO-DMT) and 462 nM (DMT) affinity for the 5-HT_{2A} receptor, as compared to the hallucinogenic phenethylamines which largely fell within a range of 6 nM (DOI) to 162 nM (DOM). However, LSD did display the highest affinity for the 5-HT_{2A} receptor at 0.95 nM [77]. One limitation of this work was that the hallucinogens were tested in competition with the antagonist ketanserin, and, as described above, this may profoundly influence apparent affinity [78]. As Table 2 illustrates, more recent research has demonstrated that the tryptamines DMT, psilocin, and 5-MeO-DIPT have 230, 5620, and 25 nM affinity for the 5-HT_{2A} receptor, respectively. This compares to the phenethylamines DOI, DOM, DOB, and 2C-T-7 which have respective affinities for the

5-HT_{2A} receptor of 0.65, 21, 1.17, and 120 nM (Table 1). Thus, the tryptamines tend to have lower affinity for the 5-HT_{2A} receptor than do the phenethylamines.

In the original correlation [77], LSD had the highest affinity for the 5-HT_{2A} receptor and the highest potency for hallucinogenic effect in humans. It is still the case that LSD has the highest potency for hallucinogenic effects, however, as Tables 1 and 2 show, when the test compounds are placed in competition with agonists, the phenethylamines DOI and DOB have affinities for the 5-HT_{2A} receptor comparable to that of LSD. Furthermore, one of the main lines of evidence that discredited the idea that hallucinogenesis is mediated by suppression of dorsal raphe firing was that the putatively non-hallucinogenic compound lisuride also suppresses neuronal firing in this region [73]. As can be seen in Table 2, lisuride has comparable or in some cases considerably higher affinity for the 5-HT_{2A} receptor than some hallucinogenic tryptamines and phenethylamines. In addition, the phenethylamine hallucinogen mescaline showed very low affinity for the 5-HT_{2A} receptor, however, a full description of this work must come with the caveat that mescaline binding was measured against the bovine 5-HT_{2A} receptor. It is possible that mescaline's lack of affinity for the receptor is due to some species difference rather than a lack of affinity for the human 5-HT_{2A} receptor. Furthermore, while mescaline is hallucinogenic, it displays relatively low potency via the oral route.

Some of the evidence cited above may seem to challenge the role of 5-HT_{2A} receptors in hallucinogenesis, but the concept of agonist-specific signaling might have some explanatory power here. Agonist-specific signaling is a relatively novel concept in pharmacology that posits that while two drugs may be agonists at the same receptor, they may nonetheless selectively activate different functional effects. Recent work by Gonzales-Maeso and colleagues has shown that hallucinogenic and putatively non-hallucinogenic 5-HT_{2A} agonists activate a different set of genes [102,120]. Although these observed genetic changes are not proposed as the mechanism for the hallucinogen-like effects of the various agonists, they serve as markers for activation of a differential set of second messenger systems. Furthermore, these hallucinogenic agonists could be distinguished from purportedly non-hallucinogenic agonists *in vivo* by the mouse head twitch assay. Using a series of toxins [120], Gonzales-Maeso and

Table 2 – Binding affinities (K_i , nM) of various hallucinogenic tryptamines and ergolines mentioned in the text at selected central serotonin sites, and estimated hallucinogenic potency and duration of action (following oral administration) in man

DRUG	5-HT _{1A}	5-HT _{2A}	5-HT _{2C}	Hallucinogenic potency in man	Duration of action in man
Psilocin	49.00 [174]	25.00 [174]	10.00 [174]	10–20 mg [118]	3–6 h [118]
LSD	1.10 [175]	3.50 [175]	5.50 [175]	60–200 µg [118]	8–12 h [118]
Lisuride	0.15 [176]	1.40 [170]	5.30 [170]	N.A.	N.A.
DMT	119.51 [177]	230.27* [177]	–	>350 mg [118]	≤1 h [118]
5-MeO-DIPT	35.00* [29]	5620* [29]	1700* [29]	6–12 mg [118]	4–8 h [118]

Where possible, affinities are listed as determined by competition binding vs. an agonist radioligand. Affinities for receptors in the inactive conformation (determined by saturation binding assays vs. an antagonist radioligand) are generally lower (higher K_i values) for all compounds, and are indicated in the table by an asterisk. Dashes in cells denote no data on affinity at that receptor, while N.A. signifies a lack of hallucinogenic activity (but see text for more on this). Full references to the source articles, denoted by numbers in square brackets, can be found in the References section.

associates further demonstrated *in vitro* that hallucinogenic 5-HT_{2A} agonists may induce a conformation whereby the receptor can couple to a G_i protein in addition to the G_{q/11} protein that is classically considered to be coupled to the 5-HT_{2A} receptor. Additionally, a recent review article cited several publications pointing to the possibility of functional selectivity at the 5-HT_{2A} receptor [14]. This work is still in the early stages and thus it is unclear whether this will explain the effects of hallucinogenic versus purportedly non-hallucinogenic 5-HT_{2A} agonists. Therefore, given that hallucinogenic compounds display widely divergent affinities for the 5-HT_{2A} receptor, that some putative non-hallucinogens display high affinity for the receptor, that some hallucinogens display a lack of affinity for the receptor, and that a correlation can be drawn between hallucinogenic potency in man and affinity for serotonin receptor subtypes not known to have a role in hallucinogenesis, it seems plausible to speculate that the 5-HT_{2A} receptor may not be the sole mediator of hallucinogenic effects. However, this view contrasts with the overwhelming body of behavioral pharmacology that implicates a role for the 5-HT_{2A} receptor. Therefore, while the 5-HT_{2A} receptor is clearly a critical site of action for the hallucinogenic drugs, we may speculate that it is not the only important mediator of hallucinogenesis.

But if the 5-HT_{2A} receptor is not the sole mediator of hallucinogenic effects, then what other receptors may be involved? The early hypothesis of suppression of dorsal raphe firing by Aghajanian and colleagues was based on work carried out primarily with tryptamines and the ergoline LSD [70–72]. Although this hypothesis was eventually abandoned, the evidence that the tryptamines suppress firing of the dorsal raphe neurons is still widely accepted. Indeed, it was ultimately discovered that this suppressive effect was mediated by pre-synaptic autoinhibitory feedback initiated by stimulation of somatodendritic 5-HT_{1A} receptors [121,122]. As can be seen in Table 1, the phenethylamines have essentially no biologically relevant affinity for the 5-HT_{1A} receptor, and it is therefore not surprising that they do not share this effect on raphe neurons.

Thus, if the hallucinogen-like effects of the tryptamines are mediated, at least in part, by 5-HT_{1A} receptors, then the behavioral and discriminative stimulus effects in animal models should also be mediated by the 5-HT_{1A} receptor. There is some evidence to support this hypothesis. It has been found that the rank order of potency for compounds which substitute in rats trained to discriminate 5-MeO-DMT from saline correlates more tightly with their affinity for the 5-HT_{1A} receptor than with their affinity for 5-HT₂ receptors [123]. Furthermore, of the antagonists tested, only the selective 5-HT_{1A} antagonist pindolol and the mixed 5-HT_{1A/2A} antagonist metitepine could fully block the 5-MeO-DMT cue [124]. Consistent with this finding, the 5-HT_{1A} selective antagonists pindolol and WAY100635 antagonized the discriminative stimulus effect of 5-MeO-DMT, whereas the 5-HT₂ receptor selective antagonist pirenperone did not [124]. Furthermore, the 5-HT_{1A} selective agonist 8-OH-DPAT fully substituted for 5-MeO-DMT, whereas, the phenethylamine DOM (which lacks relevant affinity at 5-HT_{1A}) only partially substituted [124]. The message of these studies seems to be that the discriminative stimulus properties of 5-MeO-DMT are primarily mediated through the 5-HT_{1A} receptor.

Furthermore, a recent study with rats trained to discriminate LSD found that 5-HT_{1A} agonists enhanced stimulus control by LSD and this effect could be blocked by specific 5-HT_{1A} receptor antagonists [125]. A recent study by Porter and colleagues [126] tested various hallucinogens in CHO-K1 cells transfected with human 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors, and reported that the tryptamines tested displayed a rank order of potency of 5-HT_{2B} > 5-HT_{2C} > 5-HT_{2A} whereas the phenethylamines tested displayed a rank order of potency of 5-HT_{2A} > 5-HT_{2B} > 5-HT_{2C}. This work further supports the existing evidence that, in contrast to the phenethylamines, tryptamines preferentially bind to receptors other than the 5-HT_{2A} receptor. Additionally, it has been shown that DMT is largely inactive in the mouse head twitch assay [29]. However, in the same study it was shown that despite at least a 100-fold selectivity in binding for the 5-HT_{1A} receptor over the 5-HT_{2A} or 5-HT_{2C} receptors, 5-MeO-DIPT elicited a robust HTR [29]. Furthermore, it was demonstrated that while the discriminative stimulus effects of 5-MeO-DIPT were partially but surmountably blocked by the 5-HT_{1A} receptor antagonist WAY100635, they were completely and insurmountably blocked by the 5-HT_{2A} receptor antagonist M100907 [29]. The strongest evidence that the 5-HT_{1A} receptor cannot by itself mediate hallucinogen-like effects is that there are no known agonists for the 5-HT_{1A} receptor that function as hallucinogens in man. Therefore, we suggest that while the 5-HT_{2A} receptor is likely to be the final common mechanism of hallucinogenic effects, the tryptamines and ergolines differ from the phenethylamines in that their subjective and behavioral effects are clearly modified by activity at the 5-HT_{1A} receptor.

The most convincing evidence of a role for the 5-HT_{1A} receptor in the actions of hallucinogenic tryptamines would be a clinical study in which human subjects were administered such compounds in the presence and absence of a 5-HT_{1A} antagonist. To our knowledge, no such studies have yet been undertaken. In fact, aside from the ethical difficulties inherent in such research, these experiments may turn out to be more difficult than anticipated. Previous authors have penned that the subjective effects of the hallucinogens in man, unlike other psychoactive compounds, are heavily modified by internal and external environmental variables such as mood, expectation, room lighting, and music [14,93,118]. Given the tightly controlled environment of laboratory animal testing, it may thus turn out to be the case that the animal models provide a more objective measure of the direct effects of these drugs. However, at least one recent study has been carried out in which the researchers tightly controlled the environment in which psilocybin was administered to human subjects [8]. This research points a way forward for appropriate design of future human research with hallucinogens, and may eventually allow for the assessment of the role 5-HT_{1A} receptors play in the subjective effects of the tryptamines in man.

More recently, a role for the newly discovered trace amine-associated receptors (TAAR) has been suggested by the relatively high affinity of tryptamine-containing hallucinogens such as LSD [127] and DMT [128,129] for these sites. More broadly, TAAR also bind substituted phenethylamines such as amphetamine, DOI and MDMA [127], perhaps suggesting a common pathway for the “hallucinogen-like” effects of all of

these agents (observed only at high doses with amphetamine and MDMA). Despite this promise, significant obstacles currently exist in the field of TAAR research. For example, three distinct families of TAAR, consisting of up to 21 individual receptors, have been identified and characterized in human, chimpanzee, rat, and mouse, and significant interspecies differences have been discovered [130]. The density of these sites in native tissue is extremely low, this TAAR must be cloned and expressed for *in vitro* assays, and thus far, few stable expression systems have been developed [130]. Until these and other technical issues are resolved, the role of TAAR in hallucinogen-induced effects must be regarded as unknown.

5.3. LSD

LSD is an extremely potent compound, with typical active human doses ranging between 0.05 and 0.20 mg. The subjective effects resulting from LSD ingestion can last up to 12 h and include alterations of mood, perceptual changes, and cognitive impairment [1,14,131,132]. Despite the capacity of LSD to induce profound perceptual changes, there is a lack of evidence demonstrating adverse physical consequences as a direct result of LSD administration. Indeed, there are no documented cases of death due to LSD overdose, however, one purported adverse consequence of LSD use is hallucinogen persisting perception disorder (HPPD), otherwise referred to as a “flashback”. This phenomena is defined (in part) as “the reexperiencing, following cessation of use of a hallucinogen, of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen” [133]. In a comprehensive review of 20 studies, Halpern and Pope [132] note that while some studies have reported the absence of “major complications” following LSD administration [132], other studies have reported rates of “spontaneous recurrences of LSD reactions” as high as 33% [134]. Polysubstance use, lack of dosage information, an inability to reliably trigger the phenomenon in the laboratory, and preexisting psychological disorders among the subjects examined make estimating the incidence of HPPD due to LSD use problematic, however, when considering the sheer number of people who have ingested LSD however, the incidence of HPPD would seem to be quite low [16].

As with the phenethylamine and tryptamine hallucinogens previously described, LSD can also function as a discriminative stimulus in the rat, and the stimulus effects of this ergoline can be blocked by prior administration of serotonergic antagonists [98,125]. Later, Glennon and colleagues implicated the 5-HT₂ receptor in the mechanism of action of LSD and hallucinogenesis based upon a correlation between the affinities of several hallucinogens for the 5-HT₂ receptor and hallucinogenic potency in man [135,136]. However, the subsequent discovery of a 5-HT_{2C} receptor [137,138] with a high level of structural homology and functional similarity to the 5-HT_{2A} receptor, and the demonstration that tryptamine and phenethylamine hallucinogens act as partial agonists at the 5-HT_{2C} receptor [96,97] demanded consideration of the potential role of this serotonin receptor subtype as well. To address this question, a series of antagonists with varying selectivity for 5-HT_{2A} and 5-HT_{2C} receptors were used. Results

of these experiments [100] determined that the *in vivo* potency of antagonists to block the stimulus cue of LSD is directly proportional to the *in vitro* affinity of those same antagonists for 5-HT_{2A} receptors. The role of the 5-HT_{2A} receptor in the stimulus effects of LSD is further buttressed by the complete blockade of the stimulus effects of LSD by the highly 5-HT_{2A}-selective antagonist M100907 [139]. Other drug discrimination studies have specifically implicated the anterior cingulate cortex (ACC) in the stimulus effects of LSD, as LSD locally infused into ACC dose-dependently substituted for rats trained to discriminate systemically administered LSD from saline [140]. Additional, indirect support for a role of 5-HT_{2A} receptors in LSD's mechanism of action stems from their anatomical location in the frontal cortex [141] an area containing a high density of 5-HT_{2A} receptors [138,142] and thought to play a significant role in hallucinogenesis and psychosis [143–146].

In one of the few studies where non-human primates were trained to discriminate a hallucinogen, the 5-HT₂ receptor antagonists ketanserin and pirenperone largely failed to block the interoceptive effects of LSD in vervet monkeys [147]. Furthermore, the purported 5-HT_{2A} specific agonist mescaline did not substitute for the LSD cue, whereas, the mixed 5-HT_{1A/2A} agonist 5-MeO-DMT did fully substitute [147]. However, the putatively non-hallucinogenic compound lisuride did fully substitute for LSD, raising the possibility that the LSD cue was unrelated to any hallucinogenic effects [147]. Nevertheless, these data may suggest that, like the tryptamines, the discriminative stimulus properties of LSD may also be mediated, at least partially, through the 5-HT_{1A} receptor.

With regard to lisuride, the designation of this compound as “non-hallucinogenic” is by no means well established. Animals trained to discriminate LSD generalize their responding to lisuride [148,149], which has led to the classification of this agent as a “false positive” under these procedures. Indeed, the substitution of lisuride for LSD has long been noted as a deficiency of the drug discrimination procedure, at least in terms of hallucinogen-induced stimulus control. But what is the evidence that lisuride is without hallucinogen action in man? Lisuride has been investigated as an anti-migraine medication, and as a therapeutic for Parkinson's disease. Several reports of the effects of lisuride in man thus appeared in the clinical literature in the early 1980s, and numerous such reports indicate that lisuride elicited toxic side effects including visual hallucination, reduced awareness, delusions, auditory hallucination, euphoria, morbid jealousy and paranoid ideation [150–155]. This side effect profile is not entirely inconsistent with the psychological effects of some hallucinogens. Nevertheless, the hallucinatory effects of lisuride, when present, are sometimes slow in onset, and at least one report explicitly states that no LSD-like effects have been observed in healthy volunteers [156]. Thus, the hallucinogenic status of this most interesting ergoline will likely remain controversial.

While it is well established that 5-HT_{2A} receptor stimulation is a necessary prerequisite for the effects of LSD [14,79,100,131] the biochemical and signaling pathways responsible for producing LSD's extraordinary effects remain largely unknown. The 5-HT₂ receptors (including the 5-HT_{2A} receptor) are G-protein coupled receptors. These membrane bound receptors have seven transmembrane spanning

domains and are classically linked to the activation of phospholipase C (PLC) via an activation of $G_{q/11}$. This activation results in the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) and the generation of 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). The activation of IP_3 and DAG lead to the release of intracellular Ca^{2+} , and the activation of protein kinase C, respectively [157]. Because 5-HT_{2A} activation activates PLC and phosphoinositide hydrolysis (PI) in most tissues, it has been assumed this is the relevant pathway for LSD signaling. However, there is no correlation between the capacity of a compound to substitute for LSD in the drug discrimination assay and PI hydrolysis [158] and LSD itself stimulates PI hydrolysis only weakly [96]. These results highlight the distinct differences between LSD and 5-HT with regard to activation of PLC and other signaling pathways. Indeed, different ligands for 5-HT_{2A} receptors have been shown to differentially activate 5-HT_{2A} signal transduction pathways, including other phospholipase subtypes [159,160].

Activation of 5-HT_{2A} receptors also leads to activation of the phospholipase A2 (PLA2) signaling pathway and subsequent arachidonic acid release (AA) [157]. Relative to the endogenous ligand 5-HT, in NIH3T3-5-HT_{2A} cells, LSD stimulates the PLA2 pathway to a greater extent than the PLC pathway. The significance of this finding with regards to LSD's mechanism of action is unclear though, as other hallucinogens (e.g. psilocin and 5-MeO-DMT) do not share this property (e.g. they stimulate PLC to a greater degree than PLA2) [159]. Lastly, 5-HT_{2A} receptors couple to the phospholipase D (PLD) signaling pathway [157]. This effect may be cell type specific [161] and has not been investigated with regards to LSD. Thus, the role of PLD signaling in LSD's mechanism of action remains unclear. Some of this uncertainty may be due to the previously discussed phenomenon of agonist-specific signaling via the 5-HT_{2A} receptor. Recent studies with LSD (among other hallucinogens) support this hypothesis [120]. Theoretical data from mathematical modeling of drug-receptor interactions and experimental observations suggest that G protein-coupled receptors (such as 5-HT_{2A}) may assume multiple conformations in response to agonist binding [102,162-164], which in turn preferentially activate specific signaling pathways [165,166].

6. Summary and conclusions

Current methods in behavioral pharmacology and neuroscience are finally beginning to chip away at the mystical façade that has defined the hallucinogens for too long. With the identification of exploitable SAR for these compounds, hypothesis-driven chemical syntheses have allowed the development of homologous compounds with specific binding at relevant 5-HT receptors. Study of the effects of these drugs on conditioned (drug discrimination) and unconditioned (HTR) behaviors have enabled scientists to bring these interesting compounds out of the counterculture and into the laboratory. The resulting data have indicated that the 5-HT_{2A} receptor is a critically important site of action for the hallucinogens, and have directed further attention towards understanding the modulatory roles of 5-HT_{2C} (for the phenethylamines) and 5-HT_{1A} receptors (for the tryptamines). Advanced genetic and molecular biological techniques have identified the possibility

that agonist-specific signaling is a factor in the mechanisms of action among these drugs, an idea which promises to capture research attention for years to come. All of these developments leave us on much firmer ground with regards to the study of hallucinogens than might have been imagined a generation before, and clinical interest in the therapeutic potential of these compounds is once again beginning to emerge. It is thus ironic to see that the hallucinogens – long claimed to be scientifically intractable – have yielded so much information in such a comparatively short time, and that the often desired resumption of human research with these agents might indeed be fit to commence thanks to controlled preclinical studies of these drugs.

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