Chapter 76

Hallucinogens: Circuits, Behavior, and Translational Models

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Abbreviations

2C-C 2,5-dimethoxy-4-chlorophenethylamine
2C-D 2,5-dimethoxy-4-methylphenethylamine
2C-I 2,5-dimethoxy-4-iodophenethylamine
5-HT 5-hydroxytryptamine (serotonin)
5-HTP 5-hydroxytryptophan
AA Arachidonic acid
CNS Central nervous system
DAG Diacylglycerol
DMT Dimethyltryptamine
DOB 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane
DOC 2,5-dimethoxy-4-chloroamphetamine
DOI (*R*)-(−)-DOI; (−)-2,5-dimethoxy-4-iodoamphetamine hydrochloride
DOM 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane
FISH Fluorescent in situ hybridization
GPCR G-protein-coupled receptor
HSV Herpes simplex virus
IP Inositol phosphate
LSD Lysergic acid diethylamide
LY379268 (1*R*,4*R*,5*S*,6*R*)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid
LY341495 (2*S*)-2-amino-2-[(1*S*,2*S*)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid
M100907 MDL-100,907,volinanserin,(*R*)-(+)-*a*-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-pipidinemethanol
MAO Monoamine oxidase
MDMA 3,4-methylenedioxy-*N*-methylamphetamine
MK801 (+)-MK801; dizocilpine hydrogen maleate; (5*S*,10*R*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate
NMDA *N*-methyl-D-aspartic acid
OCD Obsessive–compulsive disorder
PCP Phencyclidine
PIP_2 Phosphatidylinositol-4,5-bisphosphate
PLC Phospholipase C
SER-082 (+)-*cis*-4,5,7*a*,8,9,10,11,11*a*-octahydro-7*H*-10-methylindolo[1,7-*bc*][2,6]-naphthyridine
SSRI Selective serotonin reuptake inhibitor
TM Transmembrane domain

NEURONAL CIRCUITS

5-HT_{2A} receptors are found in multiple areas of the brain and are most strongly expressed in areas that have previously been involved in psychosis and psychotic symptoms, such as prefrontal cortex, striatum, ventral tegmental area, and thalamus (Pazos & Palacios, 1985). Original findings suggested that brain regions such as the dorsal raphe and locus ceruleus might play a key role in the electrophysiological properties of lysergic acid diethylamide (LSD). The neocortex expresses one of the highest densities of 5-HT_{2A} receptors throughout the brain, where they are particularly enriched in pyramidal and certain subpopulations of γ-aminobutyric acidergic interneurons. Studies have specifically addressed the neuronal population responsible for hallucinogen receptor function. Fiber-sparing chemical lesions of the medial thalamus, but not bilateral lesions of the amygdala, decreased the frequency of serotonin-induced excitatory postsynaptic currents via activation of 5-HT_{2A} receptors measured from layer V pyramidal neurons in the medial prefrontal cortex (Marek, Wright, Gewirtz, & Schoepp, 2001). These data suggest that hallucinogens activate 5-HT_{2A} receptors on thalamocortical neurons, a hypothesis that was further supported by the effects of *N*-methyl-D-aspartic acid lesions of the thalamic ventrobasal complex on the ability of (−)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) to induce Fos-like immunoreactivity in cortical neurons (Scruggs, Patel, Bubser, & Deutch, 2000), with the thalamic lesion attenuating the ability of DOI to increase the number of Fos-like immunoreactive neurons. Together with previous findings suggesting a presynaptic influence of 5-HT_{2A} receptors in the neocortex (see previously mentioned), these findings implicate thalamocortical transmission in the effects of hallucinogens targeting 5-HT_{2A} receptors.

An alternative, although not mutually exclusive, explanation for the psychoactive effects of hallucinogens is related to the effect of 5-HT_{2A} receptor-regulated signaling pathways on cortical pyramidal neurons. Using an elegant experimental approach to record signaling from a cortical pyramidal neuron that expressed 5-HT_{2A} receptors but that was surrounded by neurons devoid of 5-HT_{2A} receptors, Rodrigo Andrade and his collaborators used a biolistic transfection to rescue expression of 5-HT_{2A} receptors in prefrontal cortical neurons derived from 5-HT_{2A}-knockout mice (Beique,

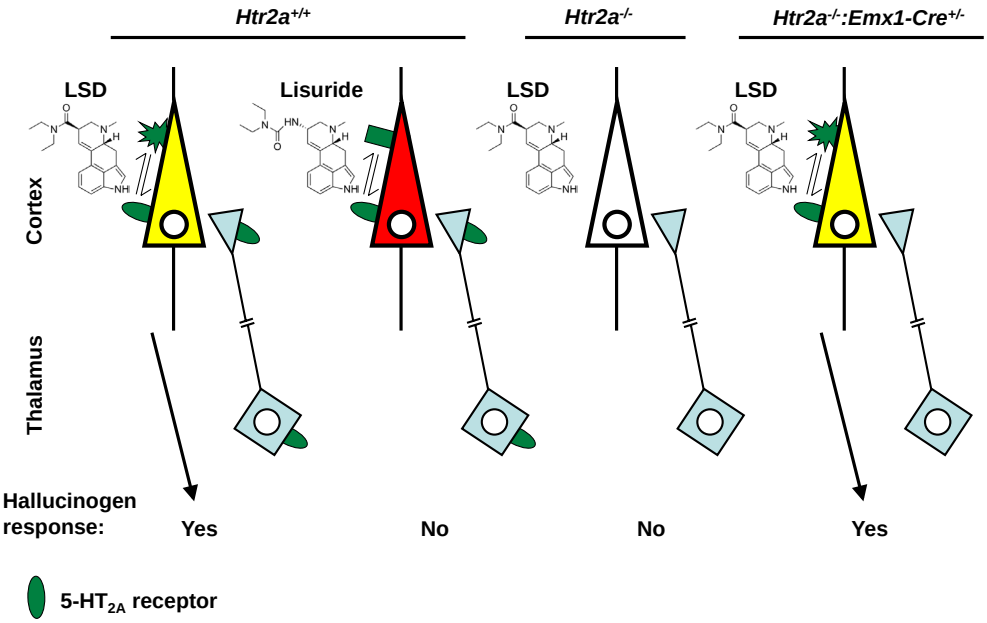

FIGURE 1 Model of the molecular mechanisms and neuronal circuits underlying the behavioral responses induced by hallucinogens. Both LSD and the closely related nonhallucinogen 5-HT_{2A} receptor agonist lisuride activate the same population of 5-HT_{2A} receptors expressed in cortical pyramidal neurons. LSD stabilizes a distinct receptor conformation that has been proposed to be responsible for the cellular signaling events that lead to the neurobehavioral responses observed. This does not occur with lisuride. The cellular and behavioral responses to LSD are absent in 5-HT_{2A}-knockout mice (*Htr2a*$^{-/-}$). Restoration of 5-HT_{2A} receptor signaling capacity in cortical pyramidal neurons of 5-HT_{2A}-knockout mice (*Htr2a*$^{-/-}$:*Emx1-Cre*$^{+/-}$) rescues the cellular and behavioral effects of LSD (see Gonzalez-Maeso et al., 2007).

Imad, Mladenovic, Gingrich, & Andrade, 2007). Based on these findings, the authors suggested a discrete subpopulation of cortical pyramidal neurons that are strongly excited by 5-HT_{2A} activation. The effect of DOI to increase activity of the prefrontal cortex by an action on postsynaptic 5-HT_{2A} receptors unrelated to thalamocortical neurons is also supported by previous findings based upon electrophysiological and microdialysis procedures after thalamic lesions performed by passing 1.5-mA pulses at three different locations (Puig, Celada, Diaz-Mataix, & Artigas, 2003). Additionally, the use of a genetic approach to express 5-HT_{2A} only in cortex further supports the important role of cortical 5-HT_{2A} receptor-mediated signaling pathways to affect behavior (Gonzalez-Maeso et al., 2007). The authors used 5-HT_{2A}-knockout mice that contain a transcriptional termination sequence ("neo-stop") inserted into the 5′ untranslated region of the 5-HT_{2A} gene (*Htr2a*) (Figure 1). This neo-stop cassette is flanked by lox-P sequences, allowing it to be excised by the bacteriophage P1 recombinase (Cre). To restore 5-HT_{2A} receptor-dependent signaling to the cortex, the authors crossed 5-HT_{2A} receptor-knockout mice with a second line of mice expressing Cre under the control of the *Emx1* promoter. *Emx1* is expressed in the forebrain during early brain maturation, and therefore Emx1–Cre restores 5-HT_{2A} receptor expression only to the forebrain while leaving other sites of 5-HT_{2A} receptor expression blocked. It was observed that genetic restoration of 5-HT_{2A} receptor signaling capacity to cortical pyramidal neurons of 5-HT_{2A}-knockout mice (*Htr2a*$^{-/-}$:*Emx1-Cre*$^{+/-}$) was sufficient to rescue the hallucinogen-specific signaling events and head-twitch behavioral response (Gonzalez-Maeso et al., 2007). They also found a predictive signaling response based on induction of expression of immediately early genes such as *c-Fos*, *Egr-1*, and *Egr-2* in cortical neurons that predicts hallucinogenic potential from effects in mice (Gonzalez-Maeso et al., 2007). Thus, whereas the possibility of a role for the 5-HT_{2A} receptor in subcortical regions such as thalamus (Marek et al., 2001) and nucleus accumbens (Goda, Piasecka, Olszewski, Kasicki, & Hunt, 2013) is not excluded, several lines of evidence indicate that cortical pyramidal neurons expressing 5-HT_{2A} receptors are the cellular targets responsible for hallucinogen effects (Figure 1).

TRANSCRIPTOME FINGERPRINT AS HALLUCINOGEN PREDICTOR

As discussed previously, the regulation of individual signaling pathways, such as G protein coupling, β-arrestin-dependent signaling, or inositol phosphate accumulation, is a poor predictor of hallucinogen activity. Hallucinogenic and nonhallucinogenic 5-HT_{2A} receptor agonists are not distinguishable based on the signaling responses that they elicit in model systems, including heterologous expression in cell lines (Gonzalez-Maeso & Sealfon, 2009a). These observations suggest that any unique responses that hallucinogens generate may be dependent on the specific subcellular microenvironment of the 5-HT_{2A} receptors and the stoichiometry of the signaling mediators in the neurons responsible for these effects. Additionally, this response may result from the regulation by hallucinogens of more than one signaling pathway. To test the hypothesis that hallucinogens modulate unique signaling pathways compared to closely related nonhallucinogens, a tempting approach was to compare multiple signaling pathways affected by these two groups of drugs in whole animal models. Most signaling pathways ultimately regulate gene expression in response to extracellular stimuli. It has been

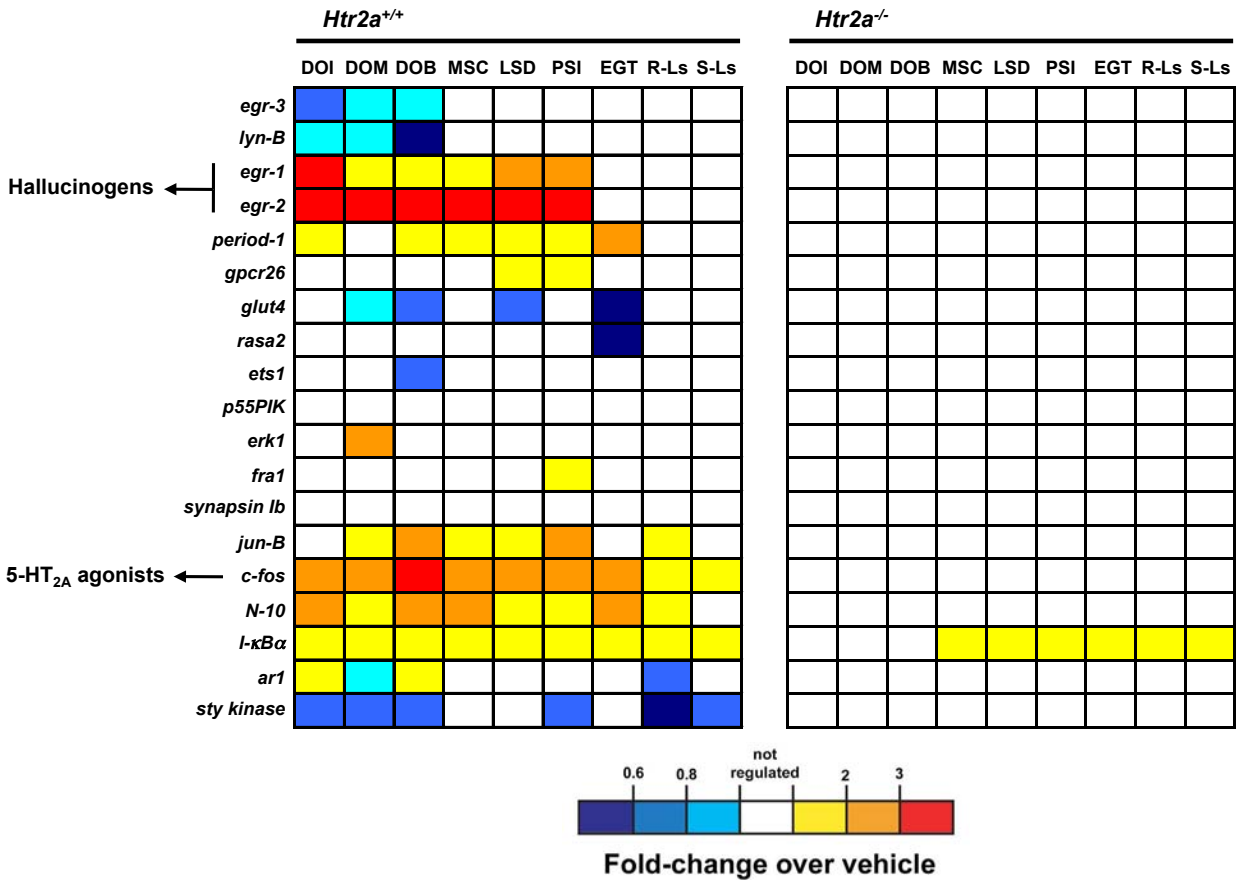

FIGURE 2 Transcriptome fingerprint induced by hallucinogens ((−)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI), 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB), mescaline, lysergic acid diethylamide (LSD), and psilocin) and nonhallucinogens (ergotamine, *R*-lisuride, and *S*-lisuride) in somatosensory cortex of wild-type (*Htr2a*$^{+/+}$) and 5-HT$_{2A}$-knockout (*Htr2a*$^{-/-}$) mice. Note that *c-Fos* is induced by all 5-HT$_{2A}$ receptor agonists (hallucinogens and nonhallucinogens), whereas *Egr-1* and *Egr-2* are induced only by hallucinogens (see Gonzalez-Maeso & Sealfon, 2009b; Gonzalez-Maeso et al., 2007). MSC, mescaline; PSI, psilocin; EGT, ergotamine; R-Ls, *R*-lisuride; S-Ls, *S*-lisuride.

shown that receptor activation can cause concentration-dependent changes in the level of expression of specific genes. Indeed, gene reporter constructs are widely used as monitors of the cellular responses induced by G-protein-coupled receptor activation. To test the hypothesis of hallucinogen-specific signaling specificity, we compared hallucinogen and nonhallucinogen regulation of multiple signaling pathways in vivo (Gonzalez-Maeso et al., 2007, 2003). The activity of many signaling pathways is difficult to quantify in brain tissue. We therefore relied on precise quantification of rapidly regulated genes as reporters of multidimensional neuronal signaling. As gene expression is regulated by signal transduction pathways, rapidly regulated endogenous transcripts can serve as intrinsic reporters of cellular signaling. High-throughput measurement of a panel of intrinsic reporters provides a comprehensive and quantitative assay of receptor-mediated changes in cellular responses. We used this approach to measure the cellular responses elicited by hallucinogen and nonhallucinogen 5-HT$_{2A}$ agonists in mouse somatosensory cortex, a region that has been implicated in the cellular and behavioral responses of hallucinogenic drugs.

Each agonist studied elicited a reproducible and unique response in this signaling assay (Figure 2). Importantly, some of the individual signaling response components were common to all these 5-HT$_{2A}$-agonists studied, whereas others distinguished hallucinogenic and nonhallucinogenic drugs. Two regulated transcripts (*c-Fos* and *I-κBα*) showed a similar modulation by both hallucinogenic and nonhallucinogenic drugs. Notably, the genes *Egr-1* and *Egr-2* were activated by all hallucinogens (DOI, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB), mescaline, LSD, and psilocin), but were unaffected by nonhallucinogens (*R*-lisuride, *S*-lisuride, and ergotamine). Given that 5-HT$_{2A}$ receptor agonists have varying selectivity for this receptor subtype, the degree to which the signaling profiles obtained in wild type were dependent on the 5-HT$_{2A}$ receptor was determined by comparing them with responses obtained in 5-HT$_{2A}$-knockout mice. The signaling response profile in somatosensory cortex obtained by the structurally related phenethylamines DOI, DOM, and DOB was completely abolished in 5-HT$_{2A}$-knockout mice. Among the 19 gene reporters assayed, only a single response component, induction of *I-κBα*, was regulated by three of the hallucinogens and all the nonhallucinogens in 5-HT$_{2A}$-knockout mice, and therefore it could be attributed to activation of non-5-HT$_{2A}$ receptors (Figure 2). Thus,

with the exception of *I-κBα*, the entire signaling response and the hallucinogen-specific component depend on activation of the 5-HT_{2A} receptor (Gonzalez-Maeso et al., 2007).

It was also investigated whether these different 5-HT_{2A} receptor-mediated responses occurred in the same or different populations of cells (Gonzalez-Maeso et al., 2007). Using fluorescent in situ hybridization (FISH), it was tested whether *c-Fos* and *Egr-2* were induced in 5-HT_{2A} receptor-expressing neurons in vivo. Consonant with immunohistological studies of primate and rodent cortex, it was demonstrated that 5-HT_{2A} expression was most intense in layer V, but also observed in layers II and III. The 5-HT_{2A} agonist marker *c-Fos* was induced in layers II/III and V by both LSD and *R*-lisuride, and the c-Fos-positive cells were overwhelmingly 5-HT_{2A} positive. The hallucinogen-specific marker *Egr-2* was selectively induced by LSD in layer V 5-HT_{2A}-positive neurons, whereas induction of *Egr-2* was not detected in layers II/III. Confirming the biochemical assays, *Egr-2* was not induced by *R*-lisuride when assayed by FISH. No induction of *c-Fos* or *Egr-2* was observed in 5-HT_{2A}-knockout mice injected with LSD or *R*-lisuride.

If the cortical effects of hallucinogens result from their activity at 5-HT_{2A} expressed by neurons projecting to cerebral cortex, then cultured cortical neurons would be unlikely to recapitulate the characteristic signaling response signature of hallucinogens observed in vivo. However, results similar to those obtained in vivo in mouse somatosensory cortex were obtained in mouse cortical primary cultures (Gonzalez-Maeso et al., 2007). Thus, 5-HT_{2A} receptor-expressing cells showed induction of *c-Fos* after exposure to either LSD or *R*-lisuride. After exposure to LSD, 5-HT_{2A} receptor and Egr-2 colocalized in cultured cortical neurons. Taken together with the in vivo results, these observations indicate that the 5-HT_{2A} receptor is a key target in determining the divergent cellular and behavioral responses elicited by hallucinogens and nonhallucinogens.

Also explored were dose- and concentration-dependent responses in both mouse somatosensory cortex in vivo and mouse cortical primary cultures in vitro to ascertain whether the different responses obtained with hallucinogenic and nonhallucinogenic drugs resulted only from differences in their potencies or efficacies (Gonzalez-Maeso et al., 2007). Induction of the response marker for 5-HT_{2A} activation *c-Fos* was obtained by both LSD and *R*-lisuride in vivo and in cortical primary cultures. Activation of *Egr-1* and *Egr-2*, which are specific for the signaling of hallucinogens in vivo, did not occur at any dose or concentration of *R*-lisuride. Control experiments using 5-HT_{2A}-knockout animals for in vivo and primary cultures showed that in both systems LSD and *R*-lisuride can activate small responses, presumably owing to cross-reactivity with other receptor subtypes. The inability of *R*-lisuride to activate any components of the response to hallucinogens at any concentration tested and the observation that the gene for STY kinase is specifically modulated by *R*-lisuride strongly indicate that the differences observed are of kind and not of degree (Gonzalez-Maeso et al., 2007).

Interestingly, one intrinsic reporter gene activated by LSD in vivo, *Period-1*, was not regulated in primary culture (Gonzalez-Maeso et al., 2007). Although *Period-1* is a poor reporter for distinguishing hallucinogens and nonhallucinogens, these results suggest that the induction of *Period-1* by LSD requires a neuronal circuit not present in the primary culture system.

A goal of molecular neuroscience research is to understand the relationship between changes that occur at different scales: molecular, cellular, circuit, and behavior. These results based on the transcriptome fingerprint approach may help resolve the long-standing paradox of why only some 5-HT_{2A} receptor agonists are hallucinogens and demonstrate that, while both hallucinogens and nonhallucinogens show agonist activity at cortical 5-HT_{2A} receptors in vivo, the hallucinogens elicit a characteristic and predictive signaling signature (Gonzalez-Maeso et al., 2007, 2003). The demonstration of a transcriptome fingerprint that can predict the behavioral response of diverse 5-HT_{2A} agonists is highly relevant to the development of more specific therapeutic neuropharmacological drugs. This assay is now widely used to investigate signaling events induced by hallucinogenic 5-HT_{2A} agonists in rodents.

BEHAVIOR MODELS

The principal caveat with respect to studying hallucinogens in preclinical models is the inability of the currently available behavioral paradigms to demonstrate convincingly that rodents experience effects of hallucinogens that are noticeable to human users. There are several animal models that can effectively discriminate hallucinogen from nonhallucinogen serotonergic agonists (for review, see Hanks & Gonzalez-Maeso, 2013). However, there have not been any behaviors identified in rodents that are induced by the effects of both serotonergic (e.g., LSD and psilocybin) and nonserotonergic (e.g., phencyclidine (PCP) and scopolamine) hallucinogenic drugs, suggesting that the models that will be described in the following are not directly related to the phenomenon of hallucination.

The model that comes closest to providing face validity is that of two (or three)-drug discrimination. In this paradigm, rodents (rats) are given either a training drug (e.g., LSD) or vehicle prior to each training session, during which one of the levers (right or left) is rewarded depending on whether drug or vehicle was administered before that session. Once the training is completed, the rats discriminate the training drug from vehicle as shown by which lever they press. During the test session, animals are administered the test drug, after which responses on the training drug lever are taken to mean that the interoceptive cues induced by the test drug are similar to those induced by the training drug. As an example, tryptamine, ergoline, and phenethylamine hallucinogens generalize to one another almost completely, whereas other psychoactive drugs such as PCP and ketamine do not. Despite the fact that animals are apparently responding to sensations induced by the training and test drugs, it remains questionable as to whether those behavioral models parallel the sensations induced by the same hallucinogens in humans. Thus, these patterns of drug stimulus generalization might reflect that pharmacological target(s) of the drug in question, rather than their phenomenological effects as experienced by humans.

Head-twitch (rapid lateral movement of the head) is a behavior model with less obvious relevance to hallucinogen action, but indeed it shows a highly significant predictive power, as does drug discrimination. All known serotonergic hallucinogens induce head-twitch, and very few nonhallucinogenic compounds induce this behavioral response, with cannabinoid antagonists and α_2-adrenergic receptor antagonists as notable exceptions. Additionally, head-twitch discriminates hallucinogens and nonhallucinogen 5-HT_{2A} receptor agonists, such as lisuride and ergotamine.

Head-twitch behavior also has advantages in terms of time and resources and shows a similar rate of false positives compared to drug discrimination. This method has been automated by experiments conducted to detect head-twitch behavior based on a head-mounted magnet and a magnetometer coil (Halberstadt & Geyer, 2013). The authors demonstrate that the use of magnetometer-based head-twitch detection provides a semiautomated assay for this behavior, which offers several advantages over traditional assessment methods.

Hallucinogens have also been shown to alter time and perception in both humans and rodents. In the so-called "peak interval tasks," which require animals to elicit responses based on the amount of time that has passed, the hallucinogen DOI causes rats to make errors that indicate an overestimation of time durations, and similar errors have been shown in humans under the effects of psilocybin. However, it also appears that the specific task can influence whether there is an over- or underestimation of time duration (for review, see Hanks & Gonzalez-Maeso, 2013).

CLINICAL POTENTIAL

There are numerous studies investigating the effects of hallucinogens in humans, the better designed of which provide useful information regarding their profound effects on cognition, sensorimotor gating, mood, perception, and self-control. These findings have been reviewed elsewhere and suggest a key role for the 5-HT_{2A} receptor in the psychological effects of hallucinogenic drug action in humans and its contributions to psychosis (Nichols, 2004). Many of these drugs are used recreationally, and hence elucidating the mechanisms by which hallucinogens induce their neuropsychological effects is an important objective of drug abuse research (Nutt, King, & Nichols, 2013). Owing to their persistence on the black market, the manufacture, importation, possession, use, and distribution of hallucinogens are carefully regulated by the Drug Enforcement Administration as well as other national and international conventions. However, clinical studies carried out in the 1950s and 1960s suggest that hallucinogens, particularly LSD, may serve as therapeutic drugs for the treatment of severe psychiatric and neurological disorders such as alcoholism, obsessive–compulsive disorder, and cluster headache. Although hallucinogen research faces major regulatory hurdles as a potential tool to treat these and perhaps other disorders (Nutt et al., 2013), here we review previous and more recent studies focused on the effects of serotonergic hallucinogens as therapeutic drugs.

Alcoholism

Among drug addictions, alcoholism is one of the most prevalent. In most Western countries, a significant proportion of the population (8–15%) will develop an addiction to alcohol. Clinical studies in the 1950s through the early 1970s tested the effects of LSD in the treatment of alcoholism. These studies suggested that LSD can help to prevent a relapse of alcohol misuse; a few trials included an arguable control group. It is, however, interesting that a meta-analysis study evaluated quantitatively the effectiveness of LSD for alcoholism (Krebs & Johansen, 2012). Of 4275 records identified through database searching, the authors identified six eligible trials that included a total of 536 adults. The authors found a statistically significant beneficial effect of LSD on alcohol misuse. The heterogeneity of the between-trial treatment outcome was negligible. These interesting findings highlight the need for better investigation in rodent models of the molecular and synaptic plasticity mechanisms through which LSD could serve as a psychopharmacological tool to treat alcoholism.

Obsessive–Compulsive Disorder

Obsessive–compulsive disorder (OCD) is a psychiatric condition that affects 1–3% of the population worldwide. The symptoms of OCD are characterized by repetitive ritualistic behaviors (compulsions), such as cleaning behaviors; persistent intrusive thoughts, such as obsessions about germs and contamination; and excessive anxiety. Currently, the first-line medications for OCDs are selective serotonin reuptake inhibitors, such as fluoxetine, together with the tricyclic antidepressant clomipramine. However, up to 60% of the patients do not respond to antidepressant treatment, and those who do are often partial responders. Based on case report data, there is evidence suggesting therapeutic effects of hallucinogens in some patients with OCD (Delgado & Moreno, 1998). The first case was described in 1962. After two doses of LSD, a 35-year-old man with depression and violent obsessive thoughts was described as having substantial and long-lasting improvement. Reductions in OCD symptoms while under the influence of psilocybin have also been shown (Moreno, Wiegand, Taitano, & Delgado, 2006). These and other case report studies support the hypothesis that a single administration of hallucinogen may lead to therapeutic effects in OCD patients. Further carefully controlled investigation is necessary to validate these findings and to characterize the time course and benefits, if any, from hallucinogen treatment, as well as how long any beneficial effect lasts. Further investigation in rodent models is also necessary to characterize its therapeutic-like mechanism of action.

As discussed previously, although the serotonin 5-HT_{2A} receptor is necessary for most of the effects induced by hallucinogens in rodents and in healthy volunteers, monoaminergic receptors such as dopamine D_2 and serotonin 5-HT_{1A}, 5-HT_{2C}, and 5-HT_{5A} receptors are also implicated. Interestingly, it has been shown that 5-HT_{2C}-knockout mice show alterations that might model OCD-like behaviors (Chou-Green, Holscher, Dallman, & Akana, 2003). The authors placed small circular grid-style mats (conventionally used for needlepoint) into the cage. After 10 days, they found that 5-HT_{2C}-knockout mice chewed the circular mats more extensively and methodically, in a characteristic well-ordered route, compared to wild-type mice (Figure 3). Because no plastic fragments were observed in stomach and colon, together these findings suggest that mice were not chewing the plastic mats in an ingestive manner. Because it is currently believed that serotonin plays an important role in OCD, the role of 5-HT_{2C} and other monoaminergic receptors in the effects of hallucinogens on the treatment of OCD deserves much more intensive investigation. This and other promising behavioral models of OCD require further validation to better understand their translational relevance.

Cluster Headache

Cluster headache, which is often considered the most painful of all types of headache, affects men more frequently (0.4%) than

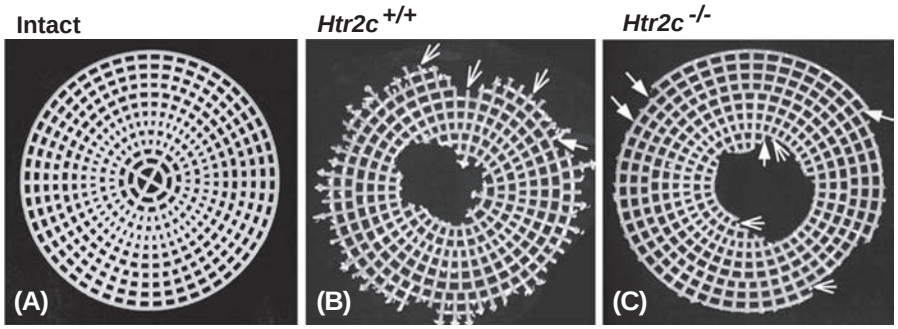

FIGURE 3 Compulsive behavior in 5-HT_{2C}-knockout mice. (A) Intact screen. (B) Screen chewed by wild-type (*Htr2c*$^{+/+}$) mouse. (C) Screen chewed by 5-HT_{2C}-knockout (*Htr2c*$^{-/-}$) mouse. Note that wild-type and 5-HT_{2C}-knockout mice differed in chewing pattern. The screen from the 5-HT_{2C}-knockout mice appears smoother, with fewer remaining spoke pieces. Spokes are labeled with open arrows. Radial pieces that are not categorized as spokes are labeled with filled arrows (see Chou-Green et al., 2003).

women (0.08%), and usually the first symptoms occur after the age of 20 years (Rapoport, 2012). Chronic cluster headache is often resistant to all attempts at treatment. Patients usually take opioids and other severe pain-reliever medications with little evidence of their efficacy. For many years, the sphenopalatine ganglion has been involved in cluster headache, and its removal or ablation leads to variable relief. Anecdotal reports and experiential film footage of patients with cluster headache suggest that psilocybin-containing mushrooms or LSD specifically treats their disorder (McGeeney, 2012). In a 2006 report, the authors interviewed 53 cluster headache patients who had used psilocybin or LSD to treat their disorder (Sewell, Halpern, & Pope, 2006). They found that psilocybin aborted cluster headache attacks in 22 of 26 psilocybin users. It was also reported that 25 of 48 psilocybin users and 7 of 8 LSD users showed cluster period termination and that 18 of 19 psilocybin users and 4 of 5 LSD users reported remission period extension. Further investigation is warranted to elucidate the precise mechanisms of hallucinogens in the treatment of cluster headache. However, given that normal circadian function and seasonal changes occurring in the suprachiasmatic nucleus and pineal gland are correlated with the clinical features and abnormalities of circadian rhythm seen in cluster headache (Pringsheim, 2002), it is tempting to speculate that the effects of hallucinogens on day–night cycles (Davies & Redfern, 1973), together with alteration in expression of genes involved in the circadian clockwork, such as *Period-1* (Gonzalez-Maeso et al., 2007), might be associated with the therapeutic effects of psilocybin and LSD on cluster headache.

NEW HALLUCINOGENS AND THEIR POTENTIAL RISK

A combination of enthusiasm for experiencing the effects of new compounds and the effort to evade legal sanctions on hallucinogens and their precursors has led to the popularity of novel tryptamines and phenethylamines. In general, these drugs are either hallucinogens or 3,4-methylenedioxy-*N*-methylamphetamine (MDMA)-like monoamine releasers, sometimes both. Several of these reported hallucinogens, such as 2C-I (2,5-dimethoxy-4-iodophenethylamine), 2C-C (dimethoxy-4-chlorophenethylamine), and 2C-D (2,5-dimethoxy--4-methylphenethylamine) (see also Figure 1), have been assayed using head-twitch behavior (Halberstadt & Geyer, 2014) and drug discrimination (Eshleman et al., 2014) models, in which they show a hallucinogen-like behavioral profile. Although they share pharmacological targets, and thus risks to the user, with their known chemical cousins (e.g., mescaline and DOI), there is an additional risk of potential off-target effects to cause adverse outcomes or pharmacokinetic interactions with other drugs. In addition, recent reports of seizures following 2C-I ingestions, fatal toxic leukoencephalopathy following 2C-E ingestions, and seizures and rhabdomyolysis following 2,5-dimethoxy-4-chloroamphetamine (DOC) and MDMA co-ingestion suggest that some of these compounds may have novel actions that lead to significant medical complications, neurotoxicity or unexpected drug–drug interactions.

CONCLUSIONS

Hallucinogens are most likely to result in adverse reactions that necessitate the intervention of health professionals and law enforcement when they are taken in uncontrolled environments. However, research suggests the therapeutic potential of hallucinogens when administered under clinical protocols that preserve hospitals' ethical and clinical responsibilities. Further basic and translational research on the efficacy of hallucinogens in the treatment of alcoholism, OCD, and cluster headache is warranted, as is their use as a tool for probing the molecular and neuronal circuit mechanisms of psychotic states.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

One of the main conclusions of this chapter focused on the neuronal circuits involved in the mechanism of action of hallucinogens such as LSD and mescaline is the recent demonstration that serotonin 5-HT_{2A} receptors expressed in cortical pyramidal neurons are the main molecular target responsible for the effects of these drugs. It is also described that preclinical and clinical findings suggest that hallucinogens may serve as potential therapeutic drugs in patients with neuropsychiatric disorders such as alcoholism, OCD, and cluster headache. Further preclinical findings will be needed to better understand the molecular basis of these clinical effects and provide the rationale for the therapeutic potential of hallucinogenic drugs of abuse when administered under clinical protocols that preserve ethical responsibilities.

DEFINITION OF TERMS

Preclinical model This is the stage of research in animal models that has the potential to be translated into clinical studies.

Pyramidal neuron Pyramidal neurons are abundant in the cerebral cortex and are characterized by their distinct apical and basal dendritic trees and the pyramidal shape of their soma. Although pyramidal neurons are not all identical, they share some functional domains such as distinct synaptic inputs and plasticity.

New hallucinogens These are novel tryptamines and phenethylamines such as 2C-I and 2C-C with potential risk, neurotoxicity, and medical complications.

Schizophrenia Schizophrenia is a severe and persistent psychiatric condition that affects more than 1% of the population throughout the world. Diagnostic features of schizophrenia include hallucinations and delusions. In addition to these "positive" symptoms, various negative symptoms occur, including inability to pay attention and social withdrawal. Eventually, cognitive impairment represents the prime driver of the significant disabilities in patients with schizophrenia.

Transcriptome The term transcriptome refers to the small percentage of the genetic code that is transcribed into RNA molecules. Findings suggest that the transcriptome fingerprint induced by hallucinogenic versus nonhallucinogenic drugs predicts their behavioral responses.

KEY FACTS OF HALLUCINOGEN ACTION

- Hallucinogens activate 5-HT_{2A} receptor-regulated signaling pathways on cortical pyramidal neurons.
- The demonstration of a transcriptome fingerprint that can predict the behavioral response of diverse 5-HT_{2A} agonists is highly relevant to the development of more specific therapeutic neuropharmacological drugs.
- The principal caveat with respect to studying hallucinogens in preclinical models is the inability of the currently available behavioral paradigms to demonstrate convincingly that rodents experience effects of hallucinogens that are noticeable to human users.
- Hallucinogens are used recreationally, and hence elucidating the mechanism by which these drugs induce their unique neuropsychological effects is an important objective of drug abuse research.
- Findings suggest, however, that hallucinogens may serve as therapeutic drugs for the treatment of severe psychiatric disorders such as alcoholism, OCD, and cluster headache.

SUMMARY POINTS

- This chapter focuses on the neuronal circuits responsible for the effects induced by hallucinogens.
- Cortical pyramidal 5-HT_{2A} receptor-mediated signaling pathways have been involved in the mechanism of action of hallucinogens.
- Head-twitch behavior represents a useful behavioral proxy of human hallucinogen action.
- A considerable number of case reports suggest the use of hallucinogens in the treatment of neurological and psychiatric disorders such as alcoholism, OCD, and cluster headache.
- Hallucinogen research may advance our understanding of neuropsychiatric disorders with treatment whose mechanistic effects are not yet fully understood.

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