Agonist-Trafficking and Hallucinogens

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Abstract: Seven transmembrane domain receptors, also termed G protein-coupled receptors (GPCRs), represent the most common molecular target for therapeutic drugs. The generally accepted pharmacological model for GPCR activation is the ternary complex model, in which GPCRs exist in a dynamic equilibrium between the active and inactive conformational states. However, the demonstration that different agonists sometimes elicit a different relative activation of two signaling pathways downstream of the same receptor has led to a revision of the ternary complex model. According to this agonist- trafficking model, agonists stabilize distinct activated receptor conformations that preferentially activate specific signaling pathways. Hallucinogenic drugs and non-hallucinogenic drugs represent an attractive experimental system with which to study agonist-trafficking of receptor signaling. Thus many of the behavioral responses induced by hallucinogenic drugs, such as lysergic acid diethylamide (LSD), psilocybin or mescaline, depend on activation of serotonin 5-HT_{2A} receptors (5-HT2ARs). In contrast, this neuropsychological state in humans is not induced by closely related chemicals, such as lisuride or ergotamine, despite their similar *in vitro* activity at the 5-HT2AR. In this review, we summarize the current knowledge, as well as unresolved questions, regarding agonist-trafficking and the mechanism of action of hallucinogenic drugs.

INTRODUCTION

Receptors can be classified according to their signaling mechanisms. This functional classification describes at least three types of cell surface receptors: ion-channel receptors, enzyme-associated receptors, and G protein-coupled receptors (GPCRs) [1]. GPCRs share a characteristic topology consisting of seven α-helical transmembrane spans [2-6], and owe their name to their signal transduction *via* heterotrimeric G proteins [7-10]. The utility of this structural template is evident from its wide evolutionary conservation [11, 12]. Members of the largest rhodopsin-like GPCR family can be found in slime mold [13], yeast [14], vascular plants [15], protozoa and ancestral metazoa [16, 17]. Although bacteriorhodopsin has no detectable sequence identity to the GPCR family, its structure of seven transmembrane domains suggests that the ancestor of GPCRs may reside in archebacteria [18]. In vertebrates, this class of surface receptors represents one of the largest families (1-3% of mammalians genome), and up to 1-5% of the total cell proteins [19, 20]. Moreover, GPCRs are the target of more than half of currently approved therapeutic agents, including a quarter of the 100 top-selling drugs [5, 21]. A better understanding of the mechanisms underlying GPCR signaling may lead to both a better knowledge of cellular communication and the design of new and more effective therapeutic drugs.

Serotonin (5-HT) receptors represent, with the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel [22], one of the largest evolutionarily conserved families of GPCRs [23-27]. The function of many 5-HT receptors in brain has been associated with specific physiological responses, ranging from modulation of neuronal activity and transmitter release to behavioral change. Hallucinogens such as psilocybin, mescaline or lysergic acid diethylamide (LSD) have been noted to be 5-HT_{2A} receptor (5-HT2AR) ligands [28-32], and many of the behavioral responses induced by these hallucinogenic drugs have been linked to the activation of 5-HT2ARs [33-36]. In contrast, this psychotic-like state in humans is not induced by closely related chemicals, such as lisuride or ergotamine [37, 38], which have similar functional activity at the 5-HT2AR *in vitro* [39-41].

Recent publications demonstrate how agonists, acting at the same GPCR target, can vary in the patterns of cellular signaling they elicit. Some terms to describe this pharmacological concept include agonist-trafficking of receptor signaling, functional selectivity, and biased agonism. Recent results suggest that agonist-directed trafficking at the 5-HT2AR explains the different neuropsychological effects of hallucinogens in comparison with closely related non-hallucinogens. The primary focus of this review will be to summarize recent advances in the mechanism of action of hallucinogenic drugs. The most relevant research topics about agonist-trafficking as a neuropharmacological model to explain how hallucinogenic drugs and closely related non-hallucinogenic drugs induce divergent behavioral responses will be discussed.

HALLUCINOGENIC DRUGS: A HISTORICAL PERSPECTIVE

In some cultures, natural hallucinogens have played a significant spiritual and religious role for millennia [29, 42, 43]. In 1897, Arthur Heffter discovered that mescaline was the centrally active compound in the peyote cactus [44] and, in 1938, LSD was first synthesized by Albert Hofmann [45], who also identified many natural hallucinogens such as psilocin and psilocybin. Since then many laboratories have investigated the molecular target and neuronal circuits involved in the hallucinogenic effects on perception and cognition.

Hallucinogens are divided into two chemical classes: Phenethylamines such as mescaline, and tryptamines such as psilocybin or LSD. Because of their structural complexity, tryptamines are sub-classified into two major types: simple tryptamines and ergolines (Fig. **1**). Mescaline is the only natural hallucinogenic phenethylamine known, but a number

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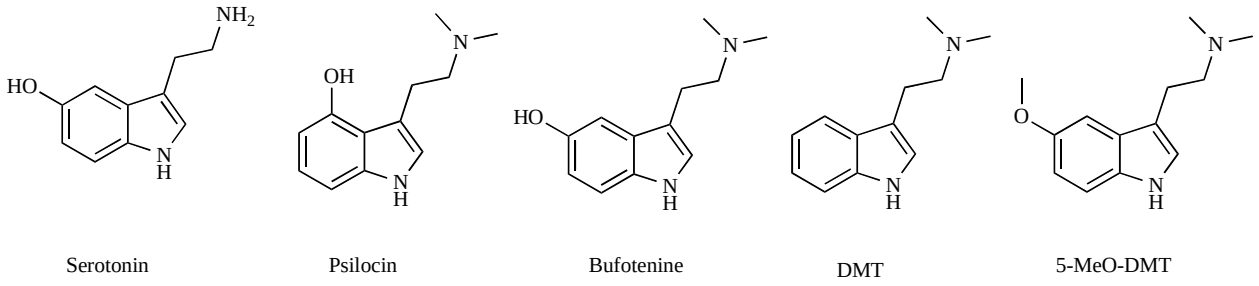
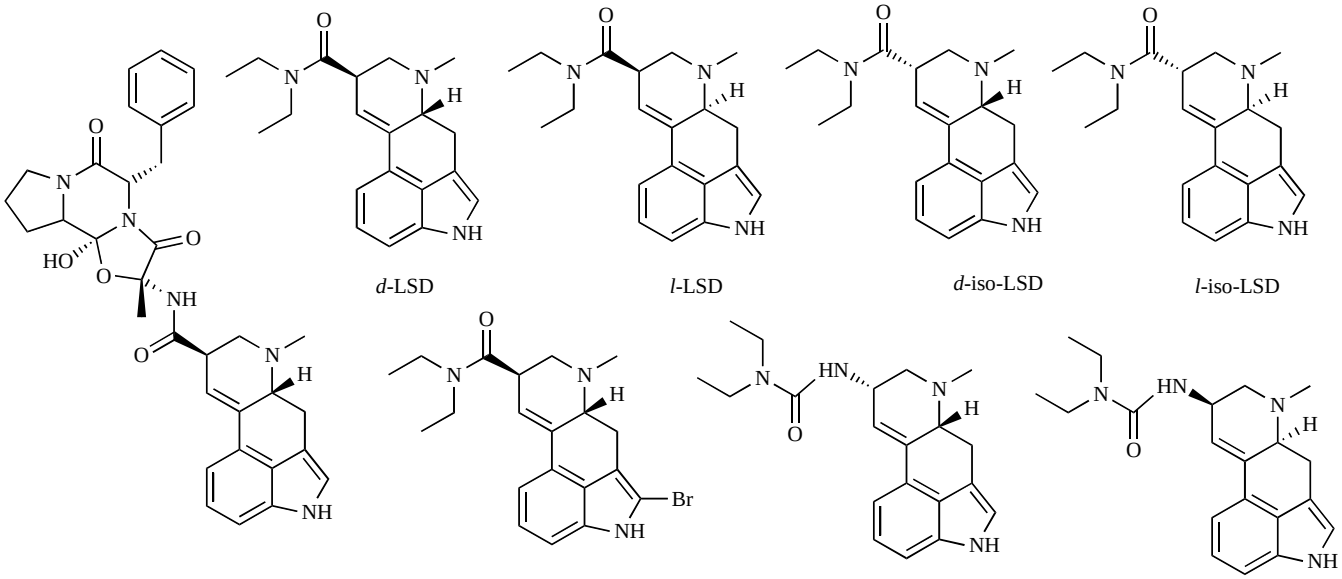
Tryptamines



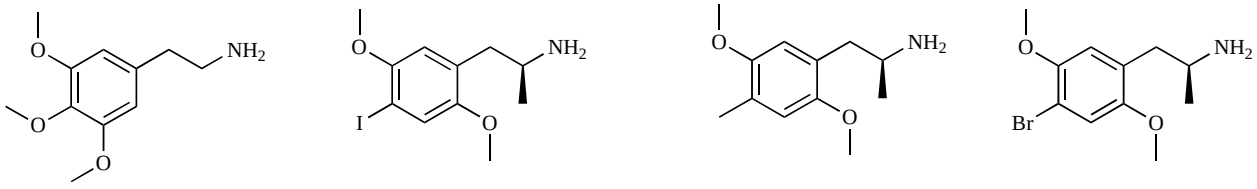
Serotonin Psilocin Bufotenine DMT 5-MeO-DMT

Ergolines



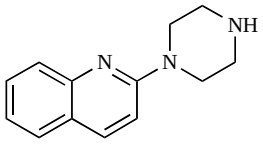
ergotamine *d*-LSD *l*-LSD *d*-iso-LSD *l*-iso-LSD 2-Br-LSD *R*-(+)-Lisuride *S*-(-)-Lisuride

Phenethylamines



Mescaline DOI DOM DOB

Others



quipazine

Fig. (1). Chemical structures of hallucinogenic and non-hallucinogenic 5-HT2AR agonists. Hallucinogens are divided into two chemical classes: Tryptamines (sub-classified into simple tryptamines and ergolines) and phenethylamines. Hallucinogenic 5-HT2AR agonists include: Psilocin, bufotenin, DMT (*N*,*N*-dimethyltryptamine), 5-MeO-DMT (5-methoxy-DMT), *d*-LSD (lysergic acid diethyl amide, LSD), mescaline, DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane), DOM (1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane), and DOB (1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane). Non-hallucinogenic 5-HT2AR agonists include: Ergotamine, *l*-LSD, *d*-iso-LSD, *l*-iso-LSD, 2-Br-LSD, *R*-(+)-lisuride, *S*-(-)-lisuride, and quipazine.

of synthetic analogs with equivalent activities have been described [46]. The ergoline LSD has not been found in nature, but other lysergic acid amides with similar activity, but much lower potency, have been extracted from a parasitic fungus that grows on rye, *Claviceps purpurea*. The mushroom compounds, which include tryptamine derivatives such as psilocybin and psilocin, have been described in a wide variety of mycological species. It is likely that many other hallucinogens remain to be identified.

Hallucinogenic Drugs and Schizophrenia

The psychoactive effects of hallucinogens such as LSD or psilocybin share some features with the symptoms of schizophrenia, including perceptual disturbances, sensory processing, cognition, changes in brain metabolism, and in self-representation [47, 48]. The discovery of the behavioral effects of LSD and the observations that LSD and other hallucinogens are related in structure and pharmacology to the endogenous ligand serotonin, led to the suggestion that serotonin was involved in certain mental disorders such as schizophrenia [49]. Indeed, hallucinogenic drugs provided one of the earliest models of schizophrenia [48]. Because the entire spectrum of positive (*e.g*., hallucinations and delusions) and negative (*e.g*., alogia and avolition) symptoms is not elicited by hallucinogens, the relevance of the effects of these drugs to the pathophysiological brain processes of schizophrenia has been questioned. The behavioral effect induced by non-competitive NMDA antagonists, such as phencyclidine (PCP) and ketamine [50], is generally believed to be a more accurate model of schizophrenia than the effect elicited by LSD-like drugs. However, recent investigations reported that the PCP model of psychosis is not substantially superior when compared to the LSD model of psychosis, but they model different clinical symptoms of schizophrenia [34, 51-53]. Furthermore, the LSD-like model of schizophrenia has facilitated the identification of therapeutic drugs. The antipsychotic risperidone was discovered as a unique full antagonist of the interoceptive effects of LSD [54], and at least some of the extraordinary ability of clozapine to improve schizophrenic symptoms more effectively and with fewer CNS side effects than typical neuroleptics has been attributed to its antagonism at 5-HT2ARs [47, 55]. It has been recently reported that the 5-HT2AR is upregulated in *postmortem* human brain cortex from untreated schizophrenic subjects [56]. Although hallucinogens as a model of schizophrenia has limitations [57], these findings raise the possibility that understanding the mechanism of action of hallucinogenic drugs may help unravel the molecular basis of psychosis in schizophrenic patients.

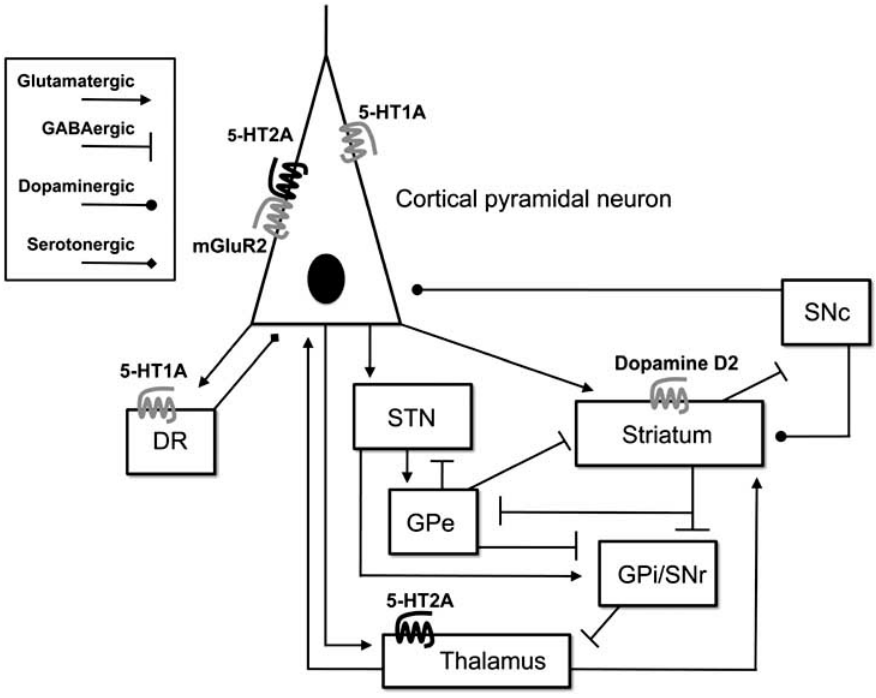


Fig. (2). Schematic representation of the GPCR subtypes and neuronal circuits implicated in the mechanism of action of hallucinogens. Several independent approaches including electrophysiological recordings in mouse cortical slices, electrolytic lesions in the thalamic nuclei, and mutant mice that express 5-HT2AR primarily in mouse cortical neurons suggest that cortical pyramidal 5-HT2ARs are necessary for the unique cellular and behavioral effects of hallucinogens. These data do not exclude the possibility that 5-HT2AR expressed by thalamocortical neurons may be responsible for some of the effects induced by LSD-like drugs. Also shown are other GPCR subtypes that may be involved both in cortex and in subcortical regions in the mechanism of action of hallucinogens. Dopamine D_2-like receptors, which are highly expressed in striatum, have been proposed to contribute to some of the effects of LSD. The prefrontal cortex contains a very large density of 5-HT_{1A} and 5-HT_{2A} receptors located on cortical pyramidal neurons, and 5-HT_{1A} may be responsible for some of the behavioral differences between LSD and the non-hallucinogenic lisuride. In addition, 5-HT_{2A} and mGluR2 form a receptor heterocomplex that affects the cellular responses induced by LSD-like drugs. Abbreviations: dorsal raphe (DR), external and internal segments of the globus pallidus (GPe and GPi, respectively), the pars compacta and pars reticulata of the substantia nigra (SNc and SNr, respectively), and the subthalamic nucleus (STN).

Receptor Target for Hallucinogenic Drugs

Evidence from pharmacological [58, 59], biochemical [39, 40, 60, 61], electrophysiological [30, 62], and behavioral studies in a variety of species including humans [33, 34, 63, 64] indicate that several effects of hallucinogens involve agonist activity at 5-$HT_{2A/2C}$ serotonin receptors. However, in the absence of highly specific hallucinogenic ligands activating a specific receptor subtype, the molecular target responsible for inducing the psychotic-like state has been questioned. It has been recently shown that 5-HT2AR knock-out mice are insensitive to the cellular, electrophysiological and behavioral effects of hallucinogens [35, 36]. These results correlate with the suppression of some of the cellular [65-72], physiological [62, 73-80] and behavioral [34, 71, 72, 81-86] effects of hallucinogens with the selective 5-HT2AR antagonist M100907. Thus it is now accepted that 5-HT2AR is necessary for the effects induced by hallucinogenic drugs. However, other receptor subtypes such as 5-HT_{1A} [30, 65, 87], 5-HT_{2C} [60, 84, 88, 89], 5-HT_{5A} [90], and dopamine D_2 [91, 92] receptors have been also involved in some of the cellular and behavioral effects mediated by hallucinogens (Fig. **2**). Thus, it is still possible that the activation and/or antagonism of other receptor subtypes, together with the activation of the 5-HT2AR, may contribute for some of the neuropsychological effects of hallucinogens.

All hallucinogenic drugs are 5-HT2AR agonists. Paradoxically, not all 5-HT2AR agonists are hallucinogens. Thus, some chemicals such as lisuride and ergotamine, which have similar agonist activity at 5-HT2ARs [39-41] are unable to induce psychosis-like states [37, 38]. In view of the promiscuous signaling capabilities of GPCRs [3, 93], these observations raise the possibility that hallucinogens may act at 5-HT2ARs on their target neurons to induce specific cellular responses that are qualitatively different from the responses generated by non-hallucinogens acting at the same molecular target (*i.e.*, the selective effects of hallucinogenic drugs may result from agonist-trafficking of receptor signals).

Agonist-Trafficking of Receptor Signals

The most widely accepted pharmacological model to explain GPCR activation is the ternary complex model (*i.e.*, agonist-receptor-G protein). Following this model, the basal activity of the receptor in the absence of agonists is determined by the equilibrium between the inactive (R) and the active (R*) conformational states [94-96]. The efficacy of different ligands is thought to be dependent on their ability to shift the equilibrium between R and R* [97, 98]. Thus agonists bind the active conformation of the receptor with higher affinity, shifting the equilibrium from the inactive to the active state (Fig. **3**). Inverse agonists are able to decrease the basal activity of the receptors, and bind R with higher affinity, shifting the equilibrium to the inactive state. A neutral antagonist presents equal affinity for both the active and inactive states of the receptor, and therefore occupies the receptor without any conformational change. The ternary complex model based on one single R* state is able to explain most of the functional responses induced by agonists, partial agonists, inverse agonists and antagonists, both *in vitro* in transfected cells as well as in native tissue preparations [97, 99, 100]. However, various experimental results and mathematical models support the hypothesis of agonist-trafficking of receptor signaling, in which different agonists may induce distinct conformations of the targeted receptor that preferentially activate specific signaling pathways (Fig. **3**; for reviews, see [93, 101-103] [98, 104-107]). Due to the consequences for receptors that bind different endogenous ligands, such as opioid [108, 109] and adrenergic [110, 111] receptors, as well as for the design of therapeutic drugs that could modulate the activity of specific cellular signaling pathways without unwanted side effects, finding an adequate experimental system in which to investigate agonist-trafficking represents an important challenge in molecular pharmacology.

Neuronal Target for Hallucinogenic Drugs

The neuroanatomical location, and the population of the 5-HT2ARs responsible for the behavioral effects of hallucinogenic drugs have been the focus of several investigations over the last few years (Fig. **2**). Autoradiographic studies show the presence of 5-HT2AR in many regions of the brain [112-115], and a high density of *5-HT2AR* mRNA has been demonstrated by *in situ* hybridization in similar locations [116]. A particularly high density of 5-HT2AR has been reported in cerebral cortex [112, 116] and, whereas pyramidal neurons constitute the major 5-HT2AR-expresing cells in the cortex [35, 112], 5-HT2ARs are located both postsynaptically and presynaptically [112]. Both behavioral responses induced by local injection of the hallucinogen DOI in medial prefrontal cortex [81], and electrophysiological responses *in vitro* in cortical brain sections [62, 73, 117] suggest the involvement of cerebral cortex in the effects of hallucinogens. However, 5-HT2ARs on somatodendritic regions of thalamocortical neurons have also been proposed as a possible target for hallucinogens [68].

Electrophysiological and microdialysis approaches have reported that hallucinogenic drugs activate the 5-HT2ARs located on presynaptic terminals and increase the release of glutamate onto layer V pyramidal cells [62, 79]. Based on these and other studies with experimental thalamic lesions in rodents [68, 117], some researchers proposed that hallucinogens activate presynaptic cortical 5-HT2ARs expressed in thalamocortical terminals. Other investigations suggested postsynaptic cortical 5-HT2AR, unrelated to thalamocortical afferents, as the target of the hallucinogenic drugs [77, 78, 118-120]. Recently, the neuronal target for hallucinogens was investigated in a conditional rescue of the 5-HT2AR knock-out mouse such that 5-HT2AR function is restored only in cortical pyramidal neurons [35]. If presynaptic cortical 5-HT2ARs were the molecular target for hallucinogenic drugs, then restoring 5-HT2AR in cortical neurons would not restore the behavioral response. In contrast, if cortical neurons expressing 5-HT2AR were targeted by hallucinogens, then restoring 5-HT2AR in these cells would rescue the cellular and behavioral responses in animals injected with hallucinogens. Interestingly, mutant mice in which 5-HT2AR is only expressed by cortical pyramidal neurons show cellular, electrophysiological and behavioral responses indistinguishable from the ones induced in wild type animals [35]. While not excluding a role of 5-HT2ARs on subcortical neurons in modulating some of the responses to hallucino-

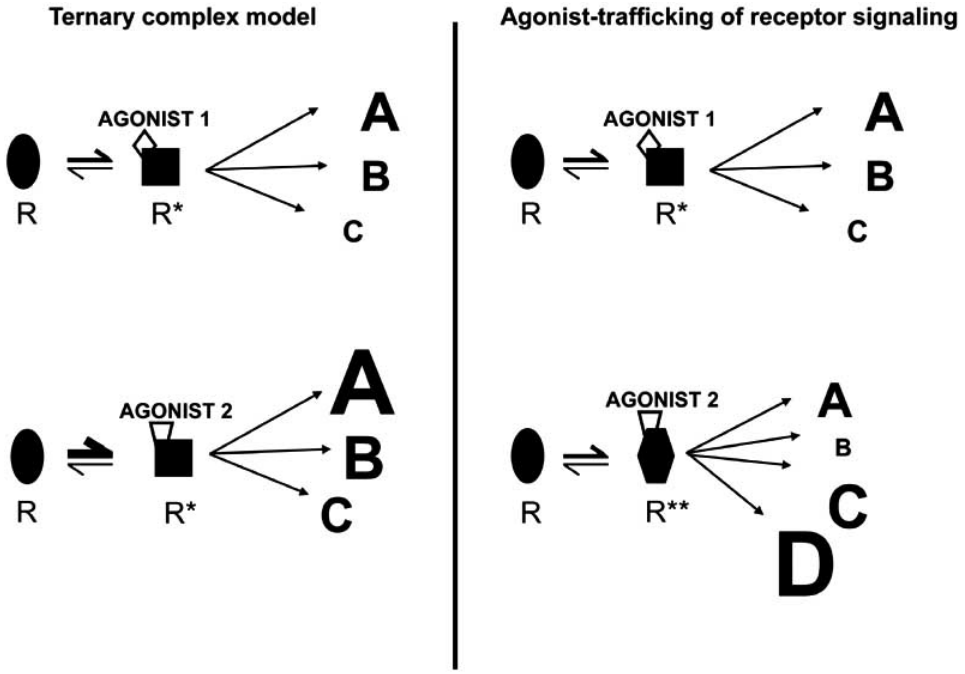


Fig. (3). Schematic representation of the pharmacological models to describe GPCR activation. Different cellular signaling pathways are shown as A, B, C, and D. The size of the text reflects the relative activity of the different signaling pathways. According to the ternary complex model (**left panel**), different agonists stabilize the same active conformational state of the receptor (R*). Based on the ternary complex model, the efficacies of the agonists may be different, but the rank order of the signaling pathways must be the same. According to the agonist-trafficking of receptor signaling model (**right panel**), agonists induce distinct active conformations of the receptor (R* and R**), which modulate the activity of different signaling pathways.

gens [68, 117, 121], these results suggest that the post-synaptic 5-HT2AR located on cortical pyramidal neurons is the primary target for hallucinogenic drugs [35, 77, 78, 80, 118-120].

Cellular Responses Induced by Hallucinogenic Drugs

Whereas a high correlation has been reported between the affinity of both tryptamine and phenethylamine hallucinogens for 5-HT2AR and their potency as psychedelics in humans, this psychotic-like state is not elicited by closely related chemicals with similar pharmacological profiles [37, 38]. The 5-HT2AR, in common with many other GPCR subtypes, has been found to activate a number of different signaling pathways (Fig. **4**). The best characterized effect of the 5-HT2AR is coupling to heterotrimeric $G_{q/11}$ protein and activation of phospholipase C (PLC), leading to formation of inositol phosphates (IP) and diacylglycerol (DAG) [23, 31, 122]. Recently, the agonist induced ERK1/2 phosphorylation by the hallucinogen DOI has been reported to be induced by 5-HT2AR activation through a PLC-dependent mechanism in mouse embryonic fibroblasts [71]. The 5-HT2AR-dependent formation of the endocannabinoid 2-arachidonylglycerol has also been shown to be PLC-dependent in NIH2T3 cells [123]. The induction of FOS-Li positive cells, and of *c-fos* gene expression in rodent cortex represents a reliable marker of 5-HT2AR activation [35, 36, 56, 67, 68, 72, 124-126]. It has been demonstrated that the 5-HT2AR dependent induction of FOS-Li positive cells is abolished in $G\alpha_q$ knock-out mice [72]. The induction of *c-fos* mRNA by hallucinogenic and non-hallucinogenic 5-HT2AR agonists is PLC-dependent in cortical primary neurons [35]. Furthermore, the efficacy of both hallucinogens and closely-related non-hallucinogens activating signaling pathways downstream of the 5-HT2AR-$G_{q/11}$ protein complex does not correlate with behavioral activity [35, 39, 40, 61, 127]. Head-twitch response is a 5-HT2AR-dependent behavior specifically induced in mouse by hallucinogenic drugs [35, 36]. Recent experiments reported that the head-twitch response was only partially attenuated in $G\alpha_q$ knock-out mice [72]. Concurrently, these results suggest that the 5-HT2AR-dependent behavioral responses induced by hallucinogens are not only $G\alpha_q$-associated but require the activation of additional G protein-dependent and/or G protein-independent signaling pathways.

Several laboratories have reported that a particular receptor subtype may activate different heterotrimeric G protein families [106]. Interestingly, some reports have recently implicated pertussis-toxin sensitive $G_{i/o}$ proteins in the cellular responses mediated by 5-HT2AR [25, 128]. Studies by Nichols and colleagues demonstrated that 5-HT2AR activates both PLC and phospholipase A_2 (PLA_2) in NIH3T3 cells [127]. They also demonstrated that the 5-HT2AR-dependent arachidonic acid (AA) release is PLA_2-coupled and PLC-independent [127]. Furthermore, they showed that the PLA_2-AA release is pertussis toxin-sensitive and $G_{i/o}$ protein-dependent in NIH3T3 cells, but not in CHO cells [128]. Different 5-HT2AR agonists present different preferential activations of PLC over PLA_2-AA signaling pathways, which strongly suggests agonist-trafficking of the 5-HT2AR-meditated signaling *in vitro* in CHO-K1 [122] and NIH3T3 [127] cells. However, this preferential activation does not

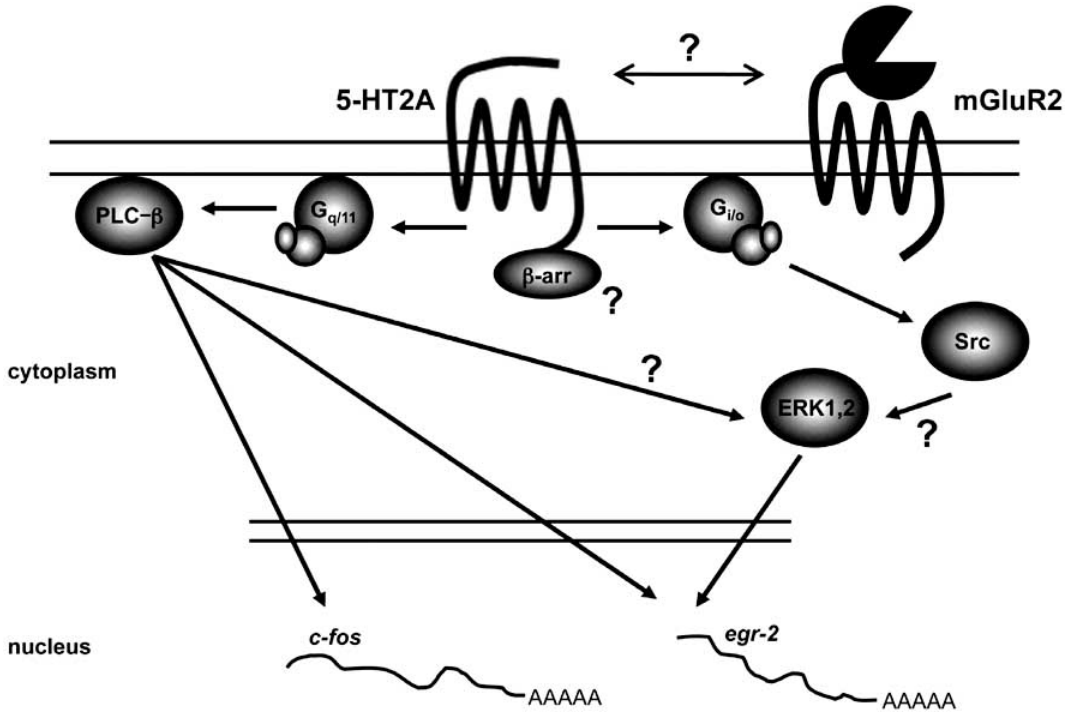


Fig. (4). Schematic representation of the hallucinogen-dependent 5-HT2AR signal transduction pathways. Hallucinogens and non-hallucinogens both activate a 5-HT2AR-dependent $G_{q/11}$ protein-PLC-β signaling pathway, and induce the expression of *c-fos* in mouse brain cortical pyramidal neurons. However, hallucinogens specifically activate a 5-HT2AR-dependent $G_{i/o}$ protein signaling pathway, and induce the expression of *egr-2* in mouse brain cortex. Several laboratories have implicated signaling proteins and neurotransmitter receptors such as β-arrestin, Src, ERK1/2, and mGluR2 in the mechanism of action of LSD-like drugs, but their specific role on hallucinogen responses remains unknown.

correlate with the hallucinogenic potential of the 5-HT2AR agonists.

Gene reporter constructs are widely used for monitoring receptor activation [129]. It has been recently validated that endogenous mRNA expression provides a global assay of changes in the signaling network that would be applicable to monitor ligand-specific intracellular signal processing [35, 36, 130-132]. Concentration-response curves by several 5-HT2AR agonists in HEK293 cells stably expressing 5-HT2AR showed that these agonists differed in their relative capacity to activate different genes [36]. However, similarly to the PLC over PLA_2-AA signaling pathways (see above), the gene expression patterns obtained in HEK293 cells do not correlate with the hallucinogenic potential of the 5-HT2AR agonists [36]. Therefore, further investigation is needed to recapitulate normal 5-HT2AR function in cell-line expression systems.

It was recently reported that the 5-HT2AR expressed by cortical pyramidal neurons appears to be necessary to induce the cellular, electrophysiological and behavioral responses induced by hallucinogenic drugs in mice [35]. Interestingly, the gene expression pattern induced in mouse somatosensory cortex, a region implicated in the neuropsychological activity of 5-HT2AR agonists [68, 112], is able to predict the presence or the absence of the head-twitch in mouse—a behavioral response induced only by hallucinogenic 5-HT2AR agonists [35, 36]. The signaling elicited by hallucinogenic and non-hallucinogenic 5-HT2AR agonists causes the induction of *c-fos*, and requires $G_{q/11}$-dependent activation of PLC in mouse brain cortical primary cultures. However, the signaling of hallucinogens induces *egr-2*, which is both $G_{q/11}$ and $G_{i/o}$ G protein-dependent. Thus, *c-fos* expression results for any 5-HT2AR signaling, and *egr-2* induction may be specific marker for hallucinogenic signaling through the 5-HT2AR. Concurrently, these results suggest that 5-HT2AR is able to activate both $G_{q/11}$ [35, 71, 72, 122, 128] and $G_{i/o}$ proteins [35, 128], that agonist-trafficking might affect the different 5-HT2AR-dependent cellular signaling patterns [35, 36, 71, 122, 128], and that the agonist-specific patterns of G protein activation depend on the cell-line expression system [36, 71, 122, 128]. Agonist-trafficking of 5-HT2AR signaling may underlie some of the behavioral differences between hallucinogenic and non-hallucinogenic drugs. An alternative hypothesis could be the activation by non-hallucinogens of other receptor subtypes, such as dopamine [133] and serotonin $5\text{-}HT_{1A}$ [134], that inhibits the hallucinogenic responses. Recent findings with dopamine ligands and $5\text{-}HT_{1A}$ knock-out mice suggest that this is not the case [35]. However, other GPCR subtypes may be responsible for some of the differences between hallucinogens and non-hallucinogens 5-HT2AR agonists.

It has been demonstrated that some GPCR can form dimers [135, 136], or potentially, higher-order complexes [137-139]. Although much biochemical and biophysical data are consistent with GPCR ability to bind and activate G proteins in a monomeric form [140-145], many recent studies support the hypothesis that G protein-coupling in cell membranes involves the formation of GPCR homo- and

heterodimers or oligomers [135, 146-154]. Several laboratories have shown that metabotropic glutamate receptor 2/3 (mGluR2/3) activation is able to affect the cellular [155-157], electrophysiological [78, 117, 158, 159] and behavioral [155, 160-164] responses induced by 5-HT2AR. It has been recently reported that 5-HT2AR forms a receptor complex with mGluR2 [56]. Interestingly, the 5-HT2AR/mGluR2 heterocomplex activates $G_{q/11}$ and $G_{i1,2,3}$ G proteins when targeted by hallucinogenic drugs. Experiments *in vitro* in NIH3T3 cells have demonstrated that 5-HT2AR can activate ERK1/2 though a signaling mechanism involving $G_{i/o}$ activation [128]. However, recent publications suggest that 5-HT2AR-dependent activation of ERK1/2 in mouse embryonic fibroblasts is primarily β-arrestin dependent when activated by serotonin, whereas DOI stimulates ERK1/2 predominantly thought a PLC-dependent pathway [71]. Furthermore, the cellular and behavioral responses induced by hallucinogenic drugs are affected by other GPCR subtypes such as μ-opioid [117, 165], α_1-adrenergic [166], α_2-adrenergic [167], serotonin 5-HT_{1A} [75, 80, 168], and adenosine A_1 [169] receptors. Further research is needed to fully unravel the complexity of the neuronal responses induced by hallucinogenic drugs.

FUTURE DIRECTIONS

The complexity of agonist-trafficking has been expanded with findings in which ligands may behave as neutral antagonists as well as agonists and/or inverse agonist [107]. Some cannabinoid CB_1 ligands behave as agonists, antagonists or inverse agonists activating the different subtypes of G_i proteins [170]. In unstimulated cells, the rate of GPCR endocytosis from the cell surface into endosomes is relatively slow. In the presence of an agonist, this endocytic rate is dramatically increased [171]. Paradoxically, atypical antypsychotics that are considered neutral 5-HT2AR antagonists, such as clozapine, induce 5-HT2AR endocytosis and down-regulation both *in vitro* and *in vivo* [56, 106]. Further investigation is necessary to better understand the structural and thermodynamic basis for the interactions between GPCRs and downstream signalling pathways.

Many GPCRs have been found to couple by G protein-independent mechanisms [172], and β-arrestin can function as an adaptor that associate to the signalling protein complex of the receptor [173, 174]. As an example, studies with the adenosine A_{1A} and the β_1-adrenergic receptors suggest that classical G protein signalling is unfavourable in heart failure, whereas β-arrestin-dependent signalling by these receptors is cardioprotective [175, 176]. Agonist functional specificity involving β-arrestin signalling has also been recently reported with β_2-adrenoceptors [177], angiotensin AT_{1A} receptors [178], and purinoreceptors P2Y [179] by fluorescence transference approaches in HEK293 cells. Thus, these data suggest that functionally specific receptor conformations can be translated to downstream effectors such as β-arrestin thereby governing their functional specificity. Several laboratories have suggested agonist-signalling trafficking as the starting point to understand the mechanism of action of hallucinogenic drugs (see above). Interestingly, recent publications have implicated β-arrestin-dependent signalling in the cellular and head-twitch behavioural responses induced by 5-HT2AR [71]. Many of the effects induced by the endogenous ligand serotonin *in vitro*, or the precursor of serotonin L-5-hydroxytryptophan (5-HTP) *in vivo* have been shown to be dependent on β-arrestin-2. However, the unique effects induced by the hallucinogen DOI *in vivo* were independent of β-arrestin-2 [71]. Therefore, other receptor subtypes and/or neuronal signalling pathways may be involved in the unique effects of hallucinogenic drugs.

Elucidating the mechanism by which hallucinogens induce their neuropsychological effects involves important implications for various human disorders in which the 5-HT2AR has been related, including drug abuse [29, 42], schizophrenia [56, 180, 181], depressive disorders [182, 183], and suicidal behaviour [184]. Decoding the molecular mechanism of action of hallucinogens may advance our understanding of other neuropsychiatric disorders with treatments whose effects are not yet fully understood.

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