

Interactive report

# Serotonin model of schizophrenia: emerging role of glutamate mechanisms<sup>1</sup>

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## Abstract

The serotonin (5-HT) hypothesis of schizophrenia arose from early studies on interactions between the hallucinogenic drug LSD (D-lysergic acid diethylamide) and 5-HT in peripheral systems. More recent studies have shown that the two major classes of psychedelic hallucinogens, the indoleamines (e.g., LSD) and phenethylamines (e.g., mescaline), produce their central effects through a common action upon 5-HT<sub>2</sub> receptors. This review focuses on two brain regions, the locus coeruleus and the cerebral cortex, where the actions of indoleamine and the phenethylamine hallucinogens have been shown to be mediated by 5-HT<sub>2A</sub> receptors; in each case, the hallucinogens (via 5-HT<sub>2A</sub> receptors) have been found to enhance glutamatergic transmission. In the prefrontal cortex, 5-HT<sub>2A</sub>-receptors stimulation increases the release of glutamate, as indicated by a marked increase in the frequency of excitatory postsynaptic potentials/currents (EPSPs/EPSCs) in the apical dendritic region of layer V pyramidal cells; this effect is blocked by inhibitory group II/III metabotropic glutamate agonists acting presynaptically and by an AMPA/kainate glutamate antagonist, acting postsynaptically at non-NMDA glutamate receptors. A major alternative drug model of schizophrenia, previously believed to be entirely distinct from that of the psychedelic hallucinogens, is based on the psychotomimetic properties of antagonists of the NMDA subtype of glutamate receptor (e.g., phencyclidine and ketamine). However, recently it has been found that many of the effects of the NMDA antagonists may also (1) involve 5-HT<sub>2A</sub> receptors and (2) be mediated through excess activity at non-NMDA (i.e., AMPA/kainate) glutamate receptors. Moreover, pharmacological manipulations of glutamate transmission (e.g., by inhibitory metabotropic glutamate agonists) provide unexpected parallels between the actions of these two classes of drugs. Given an emerging recognition of the importance of alterations in glutamatergic transmission in the actions of both psychedelic hallucinogens and NMDA antagonists, this review concludes with implications for the pathophysiology and therapy of schizophrenia. © 2000 Elsevier Science B.V. All rights reserved.

*Keywords:* Hallucinogen; 5-HT<sub>2A</sub> receptor; Ketamine; Locus coeruleus; LSD; Metabotropic receptor; NMDA receptor; Phencyclidine; Prefrontal cortex

## Contents

1. Introduction: LSD and the origins of the serotonin hypothesis . . . . .	303
2. Hallucinogens and the brain 5-HT system . . . . .	303
2.1. Early studies on the effects of hallucinogens on 5-HT neurons . . . . .	303
2.2. Affinity for 5-HT <sub>2</sub> receptors and hallucinogenic potency . . . . .	304
2.3. Hallucinogens (via 5-HT <sub>2A</sub> receptors) enhance glutamate-mediated sensory responses in the locus coeruleus. . . . .	304
2.4. 5-HT <sub>2A</sub> receptors enhance glutamate release in neo-cortex . . . . .	304
2.5. 5-HT <sub>2A</sub> receptors induce focal glutamate release at apical dendrites of layer V pyramidal cells . . . . .	305
2.5. 5-HT <sub>2A</sub> receptors and asynchronous transmission in the cerebral cortex . . . . .	306
3. Hallucinogens and the 'thalamic filter' hypothesis. . . . .	307
4. A convergence of the psychedelic hallucinogen and NMDA antagonist models of schizophrenia? . . . . .	307

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5. Hallucinogens and NMDA antagonists: brain imaging studies . . . . .	308
6. Drug models of schizophrenia: implications for pathophysiology and therapeutics. . . . .	308
6.1. New targets for pathophysiological studies . . . . .	308
6.2. New treatment approaches . . . . .	309
Acknowledgements. . . . .	309
References . . . . .	309

## 1. Introduction: LSD and the origins of the serotonin hypothesis

Norepinephrine (NE) was the first neurotransmitter implicated in the pathophysiology of schizophrenia. In 1952, Osmond and Smythies proposed that endogenous NE might be methylated to form mescaline-like hallucinogens in the body, the so-called transmethylation hypothesis [68]. Shortly thereafter, based on the antagonism by LSD (D-lysergic acid diethylamide) of the effects of serotonin (5-HT) in smooth muscle preparations and a similarity their in chemical structure (i.e., a common indoleamine moiety), it was proposed by Gaddum [34] and by Woolley and Shaw [89] that the hallucinogenic effects of LSD (D-lysergic acid) might result from an antagonism of 5-HT in the central nervous system. Because 5-HT antagonistic effects of LSD were observed initially, the 5-HT hypothesis of schizophrenia was first couched in terms of a possible 5-HT deficiency [88]. The 5-HT hypothesis was soon modified to include the possibility of an excess of 5-HT in schizophrenia since it was found that LSD could *mimic* as well as antagonize certain actions of 5-HT [77]. The 5-HT hypothesis grew to include the idea that simple indoleamine hallucinogens such as *N,N*-dimethyltryptamine [79] might act as endogenous psychotogens since the enzymatic machinery for their formation, through transmethylation of endogenous indoleamines, was demonstrated to be present in the body [16]. However, despite many years of effort, no generally accepted evidence has accumulated that an endogenous psychotogen, indoleamine or phenethylamine, is involved in the pathophysiology of schizophrenia.

As interest waned in the idea that there were hallucinogen-like endogenous psychotogens involved in the pathogenesis of schizophrenia, attention turned increasingly to uncovering basic neuronal mechanisms underlying the actions of hallucinogenic drugs. Early on it was observed that the phenethylamine hallucinogen mescaline displayed similar clinical effects and cross tolerance when tested alongside LSD in human studies [17]; these similarities suggested that the indoleamine and phenethylamine classes of psychedelic hallucinogens might share a common mechanism of action or common final pathway. In the mid-1980's, the search for such a common action led to the demonstration that the psychotomimetic potency of in-

doleamine and phenethylamine hallucinogens correlated with their shared affinity for a subset of 5-HT receptors, the 5-HT<sub>2</sub> receptors [35,36,82]. As reviewed below, this discovery has directed basic studies toward exploring the common actions of indoleamine and phenethylamine hallucinogens upon 5-HT<sub>2</sub> receptor-mediated mechanisms. Recently, electrophysiological studies have shown that the activation of 5-HT<sub>2A</sub> receptors in the cerebral cortex, a region where these receptors are enriched, produces a dramatic increase in glutamatergic excitatory postsynaptic potentials (EPSPs) in the apical dendritic region of layer V pyramidal cells [7]. Given an emerging recognition of the importance of alterations in glutamatergic transmission in the action of psychedelic hallucinogens, this review concludes with a consideration of how the psychedelic hallucinogen model may be integrated with a major alternative drug model of schizophrenia based on antagonists of the NMDA subtype of glutamate receptor (e.g., phencyclidine and ketamine).

## 2. Hallucinogens and the brain 5-HT system

### 2.1. Early studies on the effects of hallucinogens on 5-HT neurons

Following upon the discovery and mapping of central monoaminergic neurons [30], LSD was found to have a potent inhibitory effect upon the tonically firing 5-HT neurons of the dorsal raphe nucleus [4]. Microiontophoretic studies indicated that this inhibition was through a direct action of LSD on the somatodendritic region of 5-HT neurons [6]. The reduction in 5-HT cell firing rate by LSD (along with the earlier biochemical finding of reduced 5-HT turnover in brain after LSD [33]) was consistent with the initial 5-HT-deficiency hypothesis of schizophrenia. Simple indoleamine hallucinogens such as DMT (*N,N*-dimethyltryptamine) and psilocin were also shown to directly inhibit 5-HT neurons in the raphe nuclei [5]. However, unlike LSD and the simple indoleamines, mescaline and various other substituted phenethylamine hallucinogens did not prove to have direct inhibitory effect on 5-HT neurons [40]. In subsequent years, the delineation of multiple 5-HT receptor subtypes by radiolabeled ligand binding and molecular methods (for reviews see Hoyer et al. and Kroeze and Roth [45,48]) provided a basis for explaining the difference between the effects of the indoleamine and

phenethylamine hallucinogens on 5-HT neurons. Serotonergic raphe neurons have a high density of somatodendritic 5-HT<sub>1A</sub> autoreceptors which function in a negative-feedback capacity [6]. The direct inhibitory effect of LSD on raphe neurons could then be explained by its potent agonist action at 5-HT<sub>1A</sub> autoreceptors [3]. However, an agonist action at 5-HT<sub>1A</sub> somatodendritic autoreceptors is shared by a number of selective 5-HT<sub>1A</sub> agonists such as buspirone which are known from clinical studies to have anxiolytic rather than hallucinogenic effects. In contrast, mescaline and other phenethylamines have negligible affinity for 5-HT<sub>1A</sub> receptors (see below), explaining their lack of a similar direct inhibitory effect on 5-HT raphe neurons. Thus, there is an overall lack of correlation between hallucinogenic properties and 5-HT<sub>1A</sub>-mediated inhibition of 5-HT cell firing.

## 2.2. Affinity for 5-HT<sub>2</sub> receptors and hallucinogenic potency

In contrast, an excellent correlation has been shown to exist between the affinity of hallucinogenic drugs for 5-HT<sub>2</sub> receptors and hallucinogenic potency in humans [36,82]. Indeed, among all the known 5-HT receptor subtypes, affinity for 5-HT<sub>2</sub> receptors is the only one shared by both the indoleamine and phenethylamine classes of hallucinogens. There is now abundant evidence from biochemical [75], electrophysiological [54], and behavioral [35] studies that the effects of hallucinogens involve a partial agonist action at 5-HT<sub>2</sub> receptors, particularly of the 5-HT<sub>2A</sub> subtype. Autoradiographic studies show the presence of 5-HT<sub>2A</sub> receptors in many regions of the brain, including the olfactory bulb, claustrum, nucleus accumbens, olfactory tubercle, facial motor nucleus (and other motor nuclei), the n. tractus solitarius, and the cerebral cortex [53,70]; a high density of 5-HT<sub>2A</sub> receptor mRNA has been demonstrated by *in situ* hybridization in similar locations [63]. Recent immunocytochemical studies have demonstrated a particularly high density of 5-HT<sub>2A</sub> receptors within the apical dendrites of cortical pyramidal cells [41,47,87]. At an electron microscopic level, one study reported 5-HT<sub>2A</sub> immunoreactivity associated with the postsynaptic density of asymmetric (excitatory) synapses in the neocortex [41] (but see Jakob and Goldman-Rakic [46]).

The focus of this review will be on two brain regions, the locus coeruleus and the cerebral cortex, where the actions of indoleamine and the phenethylamine hallucinogens have been shown to be mediated by 5-HT<sub>2A</sub> receptors. In each of these examples, the hallucinogens have been shown to express their effects through a modulation of glutamatergic transmission.

## 2.3. Hallucinogens (via 5-HT<sub>2A</sub> receptors) enhance glutamate-mediated sensory responses in the locus coeruleus

The systemic administration of LSD, mescaline, or other psychedelic hallucinogens in anesthetized rats, while

decreasing spontaneous activity, produces a paradoxical facilitation of the activation of locus coeruleus neurons by sensory stimuli [2,72]; this effect is not through a direct action on LC cell bodies since it cannot be mimicked by the local, microiontophoretic application of the drugs. The effects of hallucinogens on locus coeruleus neurons can be reversed by low intravenous doses of selective 5-HT<sub>2</sub> antagonists such as ritanserin [72]. Antipsychotic drugs are also able to reverse the actions of hallucinogens in the locus coeruleus at doses correlating with their affinity for 5-HT<sub>2A</sub> but not other receptors [73]. The enhancement of phasic sensory responses by the 5-HT<sub>2</sub> agonist DOI (1-{2,5-dimethoxy-4-iodophenyl}-2-aminopropane) has been shown to be via activation of excitatory inputs acting upon glutamate receptors of the NMDA (*N*-methyl-D-aspartate) subtype [28]. This enhancement of glutamatergic transmission appears to be through an activation of afferent inputs rather than through a direct action upon locus coeruleus cell bodies which are lacking in 5-HT<sub>2A</sub> receptors [53]. Thus, the locus coeruleus itself cannot be used as a model for studying the direct receptor actions of hallucinogens. Nevertheless, effects on the locus coeruleus are of interest in relation to the expression of hallucinogenic effects because this nucleus receives such an extraordinarily widespread convergence of sensory information, both somatosensory and visceral, relaying this information to virtually all other parts of the neuraxis including the cerebral cortex [15,26].

## 2.4. 5-HT<sub>2A</sub> receptors enhance glutamate release in neocortex

The effects of hallucinogens on complex processes such as cognition, perception and mood suggest the involvement of the cerebral cortex in their action. The direct, postsynaptic effect of 5-HT in the cortex are variable: depolarization, hyperpolarization, or no change, depending on the balance of excitatory 5-HT<sub>2</sub> receptors and inhibitory 5-HT<sub>1A</sub> receptors that may be co-expressed to differing degrees in different layer V pyramidal cell [7,12,81]. However, the most striking effect of 5-HT in cortical regions is to increase postsynaptic potentials (PSPs). Synaptic potentials induced by 5-HT receptor activation in layer V pyramidal cells of neocortex are mostly blocked by the AMPA/kainate glutamatergic receptor antagonist LY293558, indicating that they represent largely excitatory postsynaptic potentials (EPSPs) [7]; this contrasts with piriform cortex, a paleocortical region, where 5-HT induces mostly inhibitory postsynaptic potential (IPSPs) [78]. The EPSCs induced by 5-HT in neocortex are blocked by low concentrations of the highly selective 5-HT<sub>2A</sub> antagonist MDL 100,907, indicating that they are mediated by 5-HT<sub>2A</sub> receptors [7,57]. While a 5-HT-induced increase in EPSCs occurs throughout the neocortex, this effect is most pronounced in frontal areas such as the medial prefrontal cortex [7] where there is an increased density of 5-HT<sub>2A</sub> receptors as compared to more posterior regions. NE, via

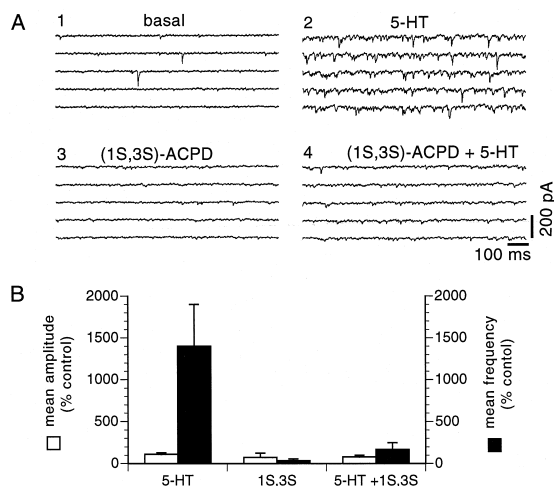


Fig. 1. The effect of the group II/III metabotropic glutamate agonist (1S, 3S)-ACPD on 5-HT-induced EPSCs. (A) shows a whole-cell voltage clamp recording from a layer V cell in medial prefrontal cortex in which the prior (4 min) and concurrent application of (1S, 3S)-ACPD (200  $\mu$ M) largely blocks the increase in EPSCs induced by a near maximal concentration of 5-HT (100  $\mu$ M); the effect of (1S, 3S)-ACPD reversed rapidly during 4–5 min of washout (not shown). (B) gives normalized mean EPSC amplitude and frequency data for 5 cells; basal amplitude was  $31 \pm 4$  pA and basal frequency was  $2 \pm 0.7$  Hz; (1S, 3S)-ACPD reduced both the 5-HT-induced increase EPSC frequency and amplitude. Adapted from Aghajanian and Marek [7].

$\alpha_1$  adrenoceptors, also induces an increase in EPSPs in layer V pyramidal cells, but to only a fraction of that produced by 5-HT [57].

The most pronounced effect of 5-HT is to increase the frequency of EPSCs [7]. Changes in the frequency of synaptic currents or potentials are considered presumptive evidence for modulation of presynaptic function. Consistent with this model, the group II/III metabotropic glutamate receptor agonist (1S, 3S)-ACPD [7] (Fig. 1) or the selective group II metabotropic agonist LY354740 [56], which act upon presynaptic inhibitory autoreceptors on glutamatergic nerve terminals, suppress the 5-HT-induced increase in the frequency of EPSCs. In general, these findings suggest that activation of 5-HT<sub>2A</sub> receptors increases the release of glutamate onto layer V pyramidal cells through a presynaptic mechanism. However, the effect may be mediated indirectly by a retrograde messenger since 5-HT<sub>2A</sub> receptors appear to have predominantly a postsynaptic localization [41,46]. There is also a small but significant increase in the amplitude of spontaneous EPSCs produced by 5-HT, an effect which may involve a postsynaptic amplification mechanism [7]. Such a postsynaptic effect is consistent with the finding of a high density of 5-HT<sub>2A</sub> receptor immunoreactivity in the apical dendrites of cortical pyramidal cells [46,87].

### 2.5. 5-HT<sub>2A</sub> receptors induce focal glutamate release at apical dendrites of layer V pyramidal cells

Blockade of 5-HT-induced EPSCs by bath application of the fast sodium channel blocker tetrodotoxin (TTX) or

perfusion of the slice with a solution containing no added calcium ('0' calcium) would generally suggest that 5-HT had activated glutamatergic cells located within the slice, leading to an impulse-flow dependent release of glutamate. However, several lines of evidence argue against this conventional interpretation. First, rarely were there any neurons within the confines of the brain slices that were induced to fire by bath application of 5-HT. Second, none of the recorded pyramidal cells (a potential source of intracortical excitatory inputs) were depolarized sufficiently by 5-HT to reach threshold for firing. Third, EPSCs could be induced by the microiontophoresis of 5-HT onto the apical dendrites of layer V pyramidal cells (Fig. 2), but no cell firing was detected in the same location while recording extracellularly through the microiontophoretic electrode [7]. Together, these experiments suggest that

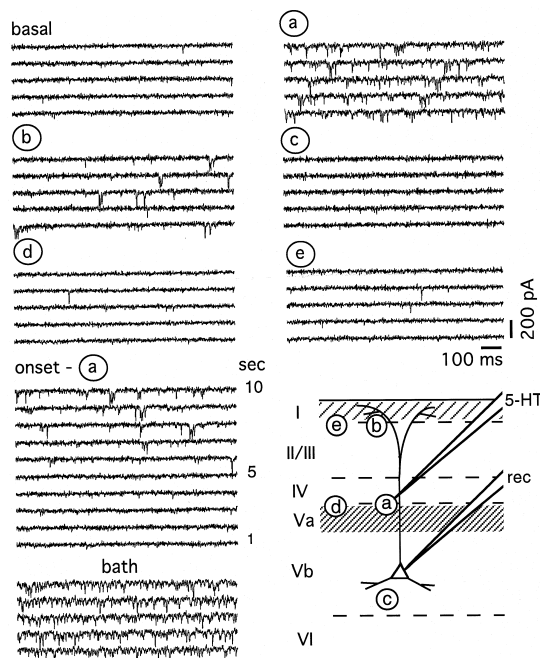


Fig. 2. The elicitation of EPSCs by microiontophoretically applied 5-HT to the apical dendritic field of a frontoparietal layer V pyramidal cell. In this cell, while recording from the soma (rec) there was a low level of basal EPSC activity prior to the application of 5-HT. At site *a*, near the border of layers IV/Va, there was a brisk response which began within 6 s of the onset of 5-HT iontophoresis (*onset-a*); 5-HT (20 mM) was ejected at +100 nA from a second patch pipette for 30 s. A gradual recovery occurred within 2–3 min following cessation of microiontophoresis. At site *b*, in the area of the apical tuft, there was also a clear but less pronounced response to 5-HT iontophoresis. However, at sites lateral (>100–200  $\mu$ m) to a radial corridor extending perpendicularly from the recording site to the pial surface (sites *e* and *d*), there were virtually no EPSCs elicited by 5-HT; microiontophoresis of 5-HT into the basilar dendritic field (site *c*) also was ineffective. At lower left, the response of this cell to bath applied 5-HT is shown. A schematic diagram indicating the relative positions of the recording (rec) and iontophoretic (5-HT) micropipettes are shown in relation to the cortical layers (I–VI); the shaded zones indicate bands of high-density 5-HT<sub>2A</sub>-receptor binding [19]. Intracellular recording, 1 M K-acetate pipette solution. Adapted from Aghajanian and Marek [7].

5-HT-induced EPSCs in neocortical cells via a focal action involving a novel  $\text{Ca}^{2+}$ -dependent mechanism that does not require impulse flow.

### 2.6. 5-HT<sub>2A</sub> receptors and asynchronous transmission in the cerebral cortex

As 5-HT-induced EPSCs do not appear to result from an increase in impulse flow in excitatory afferents, it was necessary to a search for alternative mechanisms of transmitter release. Two distinct types of vesicular neurotransmitter release have been characterized in experiments analyzing electrically evoked synaptic potentials [37]. The first type of neurotransmitter release, termed *synchronous* release, is closely coupled to invasion of the nerve terminals by an action potential, with a subsequent flooding of  $\text{Ca}^{2+}$  into the terminal through voltage-gated  $\text{Ca}^{2+}$  channels. However, analysis of ‘synaptic noise’ shows that there is also a slow, *asynchronous* phase of transmitter release, characterized by the presence of small EPSCs with a slightly longer latency than the synchronous EPSC which can persist up to ~500–1000 ms following the evoked synchronous EPSC. This delayed form of release is sustained by low levels of residual  $\text{Ca}^{2+}$  remaining within the terminal following the initial wave of  $\text{Ca}^{2+}$  influx. One of several distinguishing characteristics for this alternative mechanism of transmitter release is that  $\text{Sr}^{2+}$  is able to substitute for  $\text{Ca}^{2+}$  for the asynchronous, but not synchronous release [37]. This feature appears to be a result of two different isoforms of the calcium sensing-protein synaptotagmin, being differentially involved in the two alternative release mechanisms [51]. Consistent with this idea that the 5-HT-induced EPSCs result from an activation of the asynchronous release pathway, we have found that  $\text{Sr}^{2+}$  is highly effective in enabling 5-HT to induce an increase in the frequency of EPSCs in the absence of  $\text{Ca}^{2+}$  [8].

Recently, we have found that LSD and other hallucinogenic drugs, while having low efficacy in inducing spontaneous EPSCs, promote a late component of EPSCs evoked by electrical stimulation of the subcortical white matter [8,9]. As illustrated in Fig. 3, LSD and DOI increase the probability of occurrence of late components of the EPSC which follow the short latency synchronous EPSC. We hypothesize that this late component, which can be distinguished from late EPSCs due to polysynaptic transmission, represents the asynchronous mode of transmitter release [8]. An enhancement of asynchronous evoked EPSCs via 5-HT<sub>2A</sub>-receptors would provide a possible synaptic mechanism for the hallucinogenic effects of these drugs. In contrast, 5-HT itself does not promote the late component of *electrically evoked* release except during the washout phase (Fig. 3), presumably due to opposing actions at 5-HT<sub>1</sub> or other non-5-HT<sub>2A</sub> receptors [8]. The opposition by non-5-HT<sub>2A</sub> receptors of 5-HT<sub>2A</sub>-mediated actions of

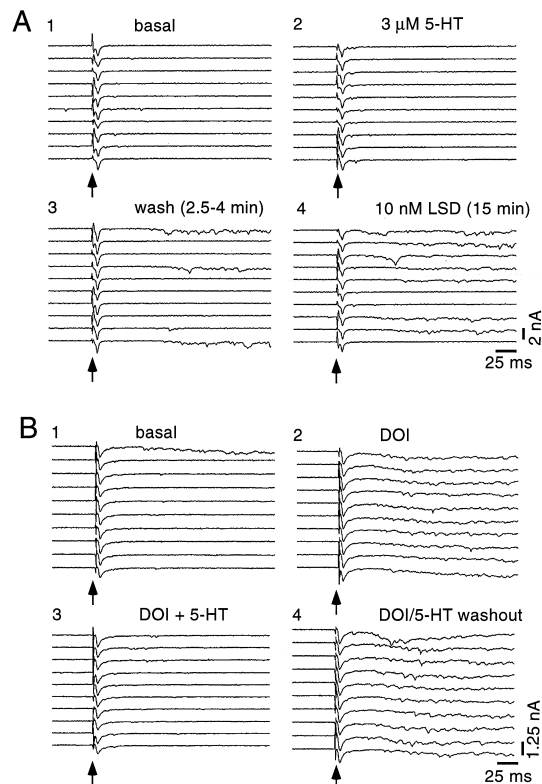


Fig. 3. Effects of 5-HT, LSD, and DOI on electrically evoked EPSCs (evEPSCs) in a layer V pyramidal cells of medial prefrontal cortex. (A) Effect of LSD: (1) responses to 10 consecutive stimuli (arrowheads) where only short latency synchronous EPSCs are evoked within ~3–4 ms following the stimulus (arrow); (2) after a 1–2.5 min application of a low concentration of 5-HT (3  $\mu\text{M}$ ) there was little change amplitude of the synchronous evoked EPSC and no increase in late components of the EPSC; (3) after a short washout of 5-HT (2.5–4 min), sustained late or asynchronous EPSCs appear after 3/10 stimuli; recovery to the basal state occurred after an additional 10 min of washout (not shown); (4) subsequent perfusion with a low concentration of LSD (10 nM) resulted in a marked increase in the occurrence of the late, asynchronous component of the EPSCs (7/10 sweeps). (B) Effect of DOI: (1) under basal conditions, there is an all-or-none sweep of a late component of the evEPSC only after the first in a series of 10 stimuli; (2) following DOI (3  $\mu\text{M}$ ) applied for 10–12 min there is a progressive increase in the proportion of sweeps with a persistent late component of EPSCs; at the time point shown (~10 min following the end of DOI application), all sweeps show a late component following the synchronous response; (3, 4) during the application of 5-HT (100  $\mu\text{M}$ ) for 1 min there is a suppression of this late component; the latter return after ~10 min of washout. Adapted from Aghajanian and Marek [7,8].

5-HT may explain why treatments that elevate endogenous 5-HT (e.g., monoamine oxidase inhibitors or selective serotonin uptake blockers) are not hallucinogenic and may in fact attenuate the subjective effects of hallucinogens in humans [20,74]. This concept is consistent with the report that the ‘antipsychotic’ effect of 5-HT<sub>2A</sub>-receptor antagonism in an animal model system (i.e., blockade of hyperlocomotion in rats induced by MK-801, an NMDA antagonist) depends on the unmasking of inhibitory effects of endogenous 5-HT at non-5-HT<sub>2A</sub>-receptors [59].

### 3. Hallucinogens and the ‘thalamic filter’ hypothesis

The ‘thalamic filter’ hypothesis of psychosis, advanced by Carlsson and his colleagues [23,24], proposes that the striatal complexes exert an inhibitory influence on the thalamus to maintain optimal transmission of sensory information to the cerebral cortex. Consequently, an impairment of thalamic filtering would result in excessive transmission of sensory information to the cortex, leading to a breakdown of integrative cortical functions. Recently, thalamocortical inputs to layer V pyramidal cells have been implicated in action of hallucinogens based on the observation that agonists acting at  $\mu$  opioid receptors, which are located presynaptically on thalamocortical inputs to layer V pyramidal cells, are able to suppress the EPSCs produced by 5-HT<sub>2A</sub> receptor stimulation [55]. Therefore, it would be of interest to consider how the intracortical effects of hallucinogens might interact with the thalamic filter model. The intracortical effects of hallucinogens could interact with thalamic inputs in two ways: (1) there could be an enhancement of glutamate release directly from the terminals thalamocortical inputs to layer V pyramidal cells by 5-HT<sub>2A</sub>-receptor stimulation and (2) by altering the activity of corticothalamic or corticostriatal projections, hallucinogens could indirectly affect thalamic filtering. In addition to these cortical actions, it is possible that effects of hallucinogens on 5-HT<sub>2</sub> receptors associated with striatal inputs to the thalamus could be involved in modulation thalamic filter function. Of interest in this regard is the fact that the psychomotor stimulant action of the NMDA antagonist MK-801, which is thought to disrupt thalamic filter function, is strongly potentiated by a 5-HT<sub>2A</sub>-receptor mediated action of LSD [25]. Finally, the enhancement by hallucinogens of the sensory responsivity of LC neurons could contribute, via extensive cortical projections, to the characteristic intensification of perceptual experience produced by these drugs. This would constitute an extra-thalamic pathway by which excesses in the transmission of sensory information relayed via thalamocortical pathways could be reinforced. These possibilities remain to be evaluated experimentally.

### 4. A convergence of the psychedelic hallucinogen and NMDA antagonist models of schizophrenia?

There has been much debate about whether the psychedelic hallucinogens or phencyclidine and ketamine more closely model naturally occurring schizophrenia (see Abi-Saab et al. [1] and Gouzoulis et al.[38] for reviews). Generally, it has been assumed that the two drug models are entirely distinct in their underlying mechanisms: the hallucinogens acting through 5-HT<sub>2</sub> receptors while phencyclidine or ketamine acting through a non-competitive

block of the NMDA subtype of glutamate receptor. However, there are a growing number of studies implicating 5-HT mechanisms, particularly involving 5-HT<sub>2A</sub> receptors, in the actions of the NMDA antagonists. It has been shown by microdialysis techniques that systemically administered NMDA antagonists elevate extracellular brain levels of 5-HT [58] as well as its metabolite 5-HIAA [52] in prefrontal cortex. Moreover, 5-HT<sub>2</sub> antagonists have been shown to block certain behavioral effects of NMDA antagonists (e.g., head twitch [90] and hyperlocomotion [25,61]). Thus, some of the behavioral effects NMDA antagonists and those of the psychedelic hallucinogens may be expressed through a common pathway since both can be blocked by 5-HT<sub>2</sub> antagonists.

Another commonality between the psychedelic hallucinogens and NMDA antagonists can be seen in relation to glutamatergic mechanisms. This review has described an enhancement by hallucinogens (via 5-HT<sub>2A</sub> receptors) of glutamatergic transmission in two regions of brain, the locus coeruleus and the cerebral cortex. In the prefrontal cortex, 5-HT<sub>2A</sub>-receptors stimulation increases the release of glutamate as indicated by a marked increase in the frequency of EPSCs; this effect is blocked by inhibitory group II/III metabotropic glutamateric agonists acting presynaptically and by an AMPA/kainate glutamate antagonist, acting postsynaptically at non-NMDA glutamate receptors [7,56]. It has recently been reported that many effects of the NMDA antagonists may also be mediated through excess activity at non-NMDA (i.e., AMPA/kainate) receptors. Subcortically, it has been shown that the local administration of CNQX, an AMPA/kainate antagonist, blocks the hyperlocomotion and increase in dopamine release seen in the ventral tegmental area after systemic administration of the NMDA antagonist dizocilpine (MK-801), suggesting that excess stimulation of non-NMDA receptors may mediate these effects [60]. In prefrontal cortex, it was shown directly by microdialysis methods that systemic administration of ketamine enhances the release of glutamate in prefrontal cortex [66]. Parallel behavioral studies have shown that the systemically active AMPA/kainate antagonist LY293558 ameliorates the cognitive deficits produced that ketamine, suggesting that NMDA antagonists may disrupt cognitive function by increasing the release of glutamate, thereby stimulating non-NMDA receptors. Based on this model, it was subsequently demonstrated that a group II metabotropic glutamate agonist, LY354740, prevented excessive release of glutamate and reduced the cognitive and motoric effects of phencyclidine [65]. The idea that NMDA antagonists may produce their psychotomimetic effects through glutamate hyperactivity contrasts with the traditional view that the effects of these drugs are primarily due to NMDA receptor hypofunction (see Olney and Farber [67]).

The mechanism by which NMDA antagonists induce an increase in glutamate appears to be distinct from that of 5-HT<sub>2A</sub> agonists since local application of phencyclidine to

brain slices does not result in an increase in EPSCs in layer V pyramidal cells of prefrontal cortex (Marek and Aghajanian, unpublished data). This lack of a direct effect suggests a requirement for the activation of intact afferent systems for NMDA antagonists to induce an increase in glutamate release. Thus, the precise mechanisms by which psychedelic hallucinogens and NMDA antagonists cause an increase in glutamate release are likely to differ. Nevertheless, as depicted in Fig. 4, the evidence for an increase in glutamate transmission for both the psychedelic hallucinogens and the NMDA antagonists raises the possibility that there is a convergence upon a common final glutamatergic pathway that may account for overlapping aspects of their psychotomimetic effects. However, it would not be expected that the effects of the two classes of drugs would be identical since in the case of the psychedelic hallucinogens NMDA receptors would not be blocked. Thus, blockade of NMDA receptors may account for the severe disorientation or delirium seen clinically with near-anesthetic doses of the phencyclidine/ketamine class of drugs [71]; such disorientation is not characteristic of the psychedelic hallucinogens.

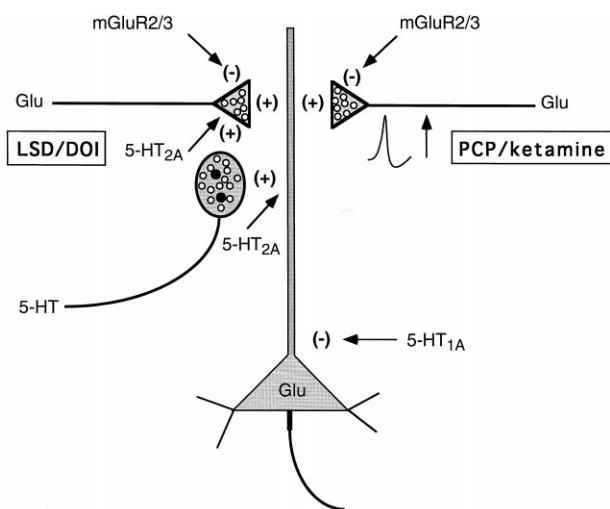


Fig. 4. Schematic diagram of a neocortical layer V pyramidal cell comparing the mechanisms by which hallucinogens (LSD and DOI) and NMDA antagonists (PCP and ketamine) may produce an increase in glutamate transmission in the cerebral cortex. In the left panel, LSD/DOI are shown, acting via 5-HT<sub>2A</sub> receptors to induce the release of glutamate (Glu) through a local action at excitatory nerve terminal (+). Also shown are presynaptic mGluR2/3 metabotropic glutamate receptors acting as inhibitory modulators of 5-HT<sub>2A</sub>-induced glutamate release. In the right panel, PCP/ketamine are shown as increasing glutamate transmission through activating impulse flow in excitatory afferent fiber rather than through a local effect upon the glutamate nerve terminals; group II/III metabotropic receptors are also shown here acting as presynaptic inhibitory modulators. Although the effects of LSD/DOI and PCP/ketamine are shown for different glutamatergic terminals, it is possible that some of the same terminals are involved in the effects of these two classes of drugs.

## 5. Hallucinogens and NMDA antagonists: brain imaging studies

Brain imaging studies in human subjects also reveal similarities in the effects of psychedelic hallucinogens and NMDA antagonists. Representatives of the two major classes of psychedelic hallucinogens, the indoleamine psilocybin [85] and the phenethylamine mescaline [44], have been shown to produce metabolic hyperfrontality in the anterior cingulate and other frontal regions. Interestingly, psychotomimetic doses of ketamine have been shown to produce a similar pattern of hyperfrontality both in healthy volunteers [21,84] and schizophrenic patients [49]. In rat studies, the metabolic activation produced by ketamine in prefrontal cortex and other regions is blocked by clozapine but not haloperidol, perhaps due to the 5-HT<sub>2A</sub> antagonist properties of clozapine which are not shared by haloperidol [31]. While the mechanisms for hyperfrontality seen with psychedelic hallucinogens and ketamine are not known, it is possible that one common element could be an increase in the release of glutamate produced by both classes of drugs. In contrast to the drug studies, the results from brain imaging in schizophrenic patients have been mixed. Some studies, particularly in acutely psychotic, unmedicated or drug-naive patients, have reported a hyperfrontal pattern similar to that produced by psychotomimetic drugs [29,32,69]. However, other studies, even in unmedicated or drug-naive schizophrenic patients [11,42], did not find a hyperfrontal pattern. At this time it is not clear what factors (e.g., patient subtype, stage of illness, etc.) may account for the apparent discrepancies between the various studies.

## 6. Drug models of schizophrenia: implications for pathophysiology and therapeutics

### 6.1. New targets for pathophysiological studies

More than a decade ago, interest began in the possible role of 5-HT<sub>2A</sub> receptors in the therapeutic effect of atypical antipsychotic drugs such as clozapine and risperidone [10,27,62,73]. In this regard, it is of interest that an association has been reported between polymorphisms in the promoter and coding regions of the 5-HT<sub>2A</sub> receptor and clinical response to clozapine [14]. At present, a definitive assessment of the antipsychotic efficacy of 5-HT<sub>2A</sub> receptor-blockade still awaits results from clinical trials with highly selective 5-HT<sub>2A</sub> antagonists such as MDL 100,907. Nevertheless, interest in the possible role of 5-HT<sub>2A</sub> receptors in the action of atypical antipsychotic drugs has prompted research on whether 5-HT<sub>2A</sub> receptor abnormalities occur in schizophrenia. For example, an association has been reported between schizophrenia and T102C polymorphism of the 5-HT<sub>2A</sub> receptor gene [86]. Many postmortem studies have reported reductions in 5-

HT<sub>2A</sub> receptor levels in prefrontal cortex of schizophrenic patients [13,18,22,39,50,64]. However, a recent imaging study, using positron emission tomography in *young*, drug-free or drug-naïve schizophrenic patients, found no significant alteration in 5-HT<sub>2A</sub> receptor density [83]. To account for this discrepancy, the latter authors suggested that aging factors may have played a role in the post-mortem studies since most of those subjects in the latter studies were older, chronic schizophrenic patients with a long history of neuroleptic exposure. However, regardless of whether there are abnormalities of 5-HT<sub>2A</sub> receptors per se, it is possible that 5-HT<sub>2A</sub> neurotransmission could be altered by abnormalities in pathways that lie downstream from the receptor itself.

The mechanisms by which the hallucinogens or NMDA antagonists induce an increase in glutamate release are clearly different: the hallucinogens act through a focal action in the cortex while the NMDA antagonists appear to act more indirectly, perhaps through the activation of impulse flow in glutamatergic afferents (Fig. 4). Nevertheless, the shared ability of psychedelic hallucinogens and NMDA antagonists to increase the release of glutamate in the cerebral cortex suggests there may be a common final pathway responsible for some of the similarities between the psychotomimetic effects of these two classes of drugs. The elucidation of common mechanisms downstream from either 5-HT<sub>2A</sub> or NMDA receptors can provide new targets for investigating the pathophysiology of schizophrenia. Thus, hallucinogens could enhance the late, asynchronous component of glutamate release by elevating residual calcium levels in the nerve terminal to activate the high affinity calcium-sensing protein synaptotagmin III [8]. These post-5-HT<sub>2A</sub>-receptor intermediary mechanisms provide potential targets downstream from the 5-HT<sub>2A</sub> receptor for pathophysiological studies. Similarly, an elucidation of the mechanisms underlying the increase in glutamate release induced by NMDA antagonists should point to new targets for study.

## 6.2. New treatment approaches

There is need for new treatment approaches since even the best of therapeutic responses obtained with existing antipsychotic drugs, including the atypical drugs that act upon 5-HT<sub>2A</sub> receptors, are often delayed and not fully restorative [80]. As discussed above, a possible reason for this lack of full efficacy may be that the primary site of pathology in schizophrenia may lie downstream from the receptors (D<sub>2</sub>, 5-HT<sub>2A</sub> etc.) that are targeted by the drugs currently in use. This review has highlighted one example of such a downstream site, increased release of glutamate, which may represent a common final pathway for the psychedelic hallucinogens and NMDA antagonists. Studies on the effects of pharmacological manipulations of glutamate transmission provide unexpected parallels between these two classes of drugs. Thus, the group II/III

metabotropic agonist (1S, 3S)-ACPD and the preferential group II metabotropic agonist LY354740, which reduce the release of glutamate by acting upon presynaptic inhibitory autoreceptors, are able to block EPSCs induced by activation 5-HT<sub>2A</sub> receptors *in vitro* [7,56]. Similarly, LY354740 (which is active by the systemic route of administration [76]) has been shown to ameliorate certain cognitive deficits in rats produced by the NMDA antagonist phencyclidine *in vivo* [65]. Taken together, these results suggest that metabotropic agonists would be useful in normalizing excesses in glutamate release regardless of the cause. The availability of orally active metabotropic glutamate receptor agonists makes it feasible to test the hypothesis that excessive glutamate release, particularly in critical sites such as the prefrontal cortex, plays a role in the positive and/or negative symptoms of schizophrenia. LY354740 has been shown to be highly potent when injected systemically in producing anxiolytic effects in animal model systems and appears to lack many of the motor and cognitive side effects seen with other psychotropic drugs [43]. If metabotropic agonists prove to ameliorate core symptoms of schizophrenia, positive and/or negative, this would provide strong impetus to investigations on the role of altered glutamate transmission in this disorder.

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