



# Serotonin and Hallucinogens

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*This brief review traces the serotonin (5-HT) hypothesis of the action of hallucinogenic drugs from the early 1950s to the present day. There is now converging evidence from biochemical, electrophysiological, and behavioral studies that the two major classes of psychedelic hallucinogens, the indoleamines (e.g., LSD) and the phenethylamines (e.g., mescaline), have a common site of action as partial agonists at 5-HT<sub>2A</sub> and other 5-HT<sub>2</sub> receptors in the central nervous system. The noradrenergic locus coeruleus and the cerebral cortex are among the regions where hallucinogens have prominent effects through their actions upon a 5-HT<sub>2A</sub> receptors. Recently, we have observed a novel effect of*

*hallucinogens—a 5-HT<sub>2A</sub> receptor-mediated enhancement of nonsynchronous, late components of glutamatergic excitatory postsynaptic potentials at apical dendrites of layer V cortical pyramidal cells. We propose that an effect of hallucinogens upon glutamatergic transmission in the cerebral cortex may be responsible for the higher-level cognitive, perceptual, and affective distortions produced by these drugs. [Neuropsychopharmacology 21:16S–23S, 1999] © 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

**KEY WORDS:** Serotonin; LSD; Hallucinogens; 5-HT<sub>2A</sub> receptors; Glutamatergic; Excitatory postsynaptic potentials; Cerebral cortex; Locus coeruleus

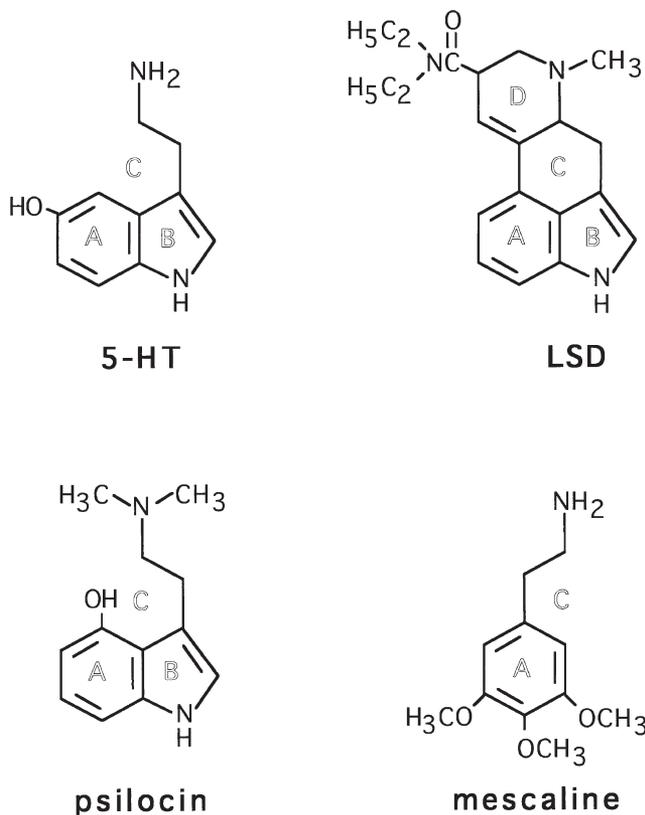
The accidental discovery in 1943 of the hallucinogenic properties of the synthetic ergoline compound LSD (d-lysergic acid diethylamide) by the chemist Albert Hoffman is well known. Five years later, in 1948, serotonin (later determined to be 5-hydroxytryptamine or 5-HT) was found in bovine blood serum (Rapport et al. 1948). Then, in 1953, during a routine survey of various tissues, relatively high concentrations of 5-HT were found in brain (Twarog and Page 1953). Shortly thereafter, based on the observation that LSD could antagonize 5-HT in peripheral tissues—plus the structural similarity between these two indole-containing structures (Figure 1)—it was proposed independently by Gaddum

and Hammeed (1954) and Woolley and Shaw (1954) that the hallucinogenic effects of LSD might result from an antagonism of 5-HT in the central nervous system. This hypothesis was soon modified to include the possibility that LSD could *mimic* as well as antagonize the actions of 5-HT (Shaw and Woolley 1956). The 5-HT hypothesis was later extended to include such simple indoleamine hallucinogens as psilocin, which are close structural analogs of 5-HT (Figure 1) and the phenethylamine hallucinogens, such as mescaline. Mescaline, despite differences in chemical structure (Figure 1), displayed similar clinical effects and cross tolerance with LSD in human studies (Balestrieri and Fontanari 1959), suggesting that the indoleamine (including ergoline) and phenethylamine classes of hallucinogens may share a common mechanism of action or final common pathway. By the end of the 1950s, three classical questions about the relationship between 5-HT and the hallucinogens had been set into place. First, do the hallucinogens produce their effects through an action upon the central 5-HT system? Second, are hallucinogens agonists or antagonists at 5-HT receptors? Third, do indoleamine and phenethylamine hallucinogens share a common site of action?

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**Figure 1.** Structural formulae for serotonin (5-HT), LSD, mescaline, and the simple indoleamine hallucinogen psilocin. The chemical structures are drawn in relation to the A, B, C, and D rings of LSD to emphasize common structural features such as the indolethylamine nucleus of 5-HT and psilocin and the phenethylamine nucleus shared by LSD and mescaline.

## NEURONAL ACTIONS OF HALLUCINOGENIC DRUGS

### Effects of Hallucinogens on 5-HT Neurons of the Raphe Nuclei

The identification of 5-HT as a neurotransmitter was not achieved until the mid-1960s, when monoaminergic neuronal pathways in the brain were discovered and mapped by histochemical fluorescence methods (Dahlstrom and Fuxe 1964). These maps, which revealed that 5-HT neuronal cell bodies were clustered in the raphe nuclei of the brainstem, provided the basis for single-cell electrophysiological recordings from identified 5-HT neurons. LSD was found to have a potent inhibitory effect upon the tonically firing 5-HT neurons of the dorsal raphe nucleus (Aghajanian et al. 1968); the local application of LSD by microiontophoresis indicated that the inhibition was through a direct action on the somatodendritic region of 5-HT neurons (Aghajanian et al. 1972). A reduction in 5-HT cell firing rate was consistent with earlier biochemical findings of reduced 5-HT

turnover in brain after LSD (Freedman 1961). Simple indoleamine hallucinogens such as DMT (N,N-dimethyltryptamine) and psilocin were also shown to inhibit 5-HT neurons in the raphe nuclei (Aghajanian and Haigler 1975). However, although systemically administered mescaline and various other substituted phenethylamine hallucinogens were able to suppress the firing of a subset of 5-HT neurons (Aghajanian et al. 1970), they were unlike the indoleamines in that they worked through an indirect mechanism rather than through a direct inhibition raphe neurons (Haigler and Aghajanian 1973). Thus, a direct, postsynaptic inhibition of 5-HT neurons did not seem to represent a unitary cellular mechanism for the action of indoleamine and phenethylamine hallucinogens.

In subsequent years, the delineation of multiple 5-HT receptor subtypes by radiolabeled ligand binding and molecular methods (see Hoyer et al. 1994) 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 5-HT<sub>1A</sub> but not other subtypes of 5-HT receptors. LSD is a potent agonist at 5-HT<sub>1A</sub> somatodendritic autoreceptors, thus accounting for its direct inhibitory effect on raphe neurons (see Aghajanian 1995). On the other hand, mescaline and other phenethylamines have negligible affinity for 5-HT<sub>1A</sub> receptors, explaining their inability to inhibit directly 5-HT raphe neurons. The action of LSD at 5-HT<sub>1A</sub> 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. Thus, no correlation exists between the activity of various drugs at 5-HT<sub>1A</sub> receptors and the presence or absence of hallucinogenic properties.

### Affinity for 5-HT<sub>2</sub> Receptors Correlates with Hallucinogenic Potency

Glennon, Titeler, and their colleagues showed that there is an excellent correlation between the affinity of both indoleamine and phenethylamine hallucinogens for 5-HT<sub>2</sub> receptors and hallucinogenic potency in humans (Glennon et al. 1984; Titeler et al. 1988). Indeed, among all the known 5-HT receptor subtypes, affinity for 5-HT<sub>2</sub> receptors is the only one shared by these two major classes of hallucinogens (Table 1). Based on this seminal work, subsequent research on hallucinogens has focused on interactions with 5-HT<sub>2</sub> receptors, particularly the 5-HT<sub>2A</sub> receptor. Unlike 5-HT<sub>1A</sub> receptors, 5-HT<sub>2A</sub> receptors are not located presynaptically on 5-HT cell bodies but rather are found upon subpopulations of neurons in postsynaptic regions. Although quantitative autoradiographic studies show the presence of 5-HT<sub>2A</sub> receptors in multiple regions of the brain, including the olfactory bulb, claustrum, nucleus accumbens, olfactory tubercle, facial nucleus, and the

n. tractus solitarius, the preponderance of these receptors are located in the cerebral cortex (Lopez-Gimenez et al. 1997; Pazos and Palacios 1985); a high density of 5-HT<sub>2A</sub> receptor mRNA has been demonstrated by *in situ* hybridization in similar locations (Mengod et al. 1990). Recent immunocytochemical studies have demonstrated a particularly high density of 5-HT<sub>2A</sub> receptors in the apical dendrites of cortical pyramidal cells (Jakab and Goldman-Rakic 1998; Willins et al. 1997).

Actions at 5-HT<sub>2C</sub> receptors, which have been associated with anxiogenic responses (Kennett et al. 1997), could also contribute to the effects of hallucinogens. However, for purposes of illustration, the focus of this review is on two brain regions, the locus coeruleus and the cerebral cortex, where the physiological actions of both LSD and the phenethylamine hallucinogens have been shown to be mediated primarily by 5-HT<sub>2A</sub> receptors.

### Hallucinogens Enhance Sensory Responses in the Locus Coeruleus via 5-HT<sub>2A</sub> Receptors

The locus coeruleus (LC) consists of two dense clusters of noradrenergic neurons located bilaterally in the upper pons at the lateral border of the 4th ventricle. The LC, which projects diffusely to virtually all regions of the neuraxis, receives an extraordinary convergence of somatic, visceral, and other sensory inputs from all regions of the body, has been likened to a novelty detector for salient external stimuli (Aston-Jones and Bloom 1981; Cedarbaum and Aghajanian 1978). In this context, it is of interest that the systemic administration of LSD, mescaline, or other psychedelic hallucinogens in anesthetized rats, although decreasing spontaneous activity, produces a paradoxical facilitation of the activation of LC neurons by sensory stimuli (Aghajanian 1980; Rasmussen and Aghajanian 1986); this effect is not through a direct action on LC cell bodies, because it cannot be mimicked by the local, microiontophoretic application of the drugs. The effects of hallucinogens on LC neurons can be reversed by low intravenous doses of selective 5-HT<sub>2</sub> antagonists, such as ritanserin (Rasmussen and Aghajanian 1986). 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 dopamine and adrenergic receptors (Rasmussen and Aghajanian 1988). Studies on the mechanism by which hallucinogens produce their effects on LC neurons have shown that the decrease in spontaneous firing caused by the 5-HT<sub>2</sub> agonist DOI (1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane) is via activation of inhibitory inputs acting upon GABA<sub>A</sub> receptors; whereas, the enhancement of phasic sensory responses is via activation of excitatory inputs acting upon NMDA (N-methyl-D-aspartate) receptors (Chiang and Aston-Jones 1993).

Because the effects of systemically administered hallucinogens are through an activation of afferent inputs rather than through a direct action upon LC cell bodies, the LC itself cannot be used as a model for studying the direct cellular actions of hallucinogens. Nevertheless, the effects of the hallucinogens upon the LC are of interest, 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.

### 5-HT<sub>2A</sub> Receptors Enhance Glutamate Release in Neocortex

The ubiquitous effects of hallucinogens on such complex processes as cognition, perception, and mood suggest the involvement of the cerebral cortex. The direct, postsynaptic effect of 5-HT in the cortex are variable: depolarization, hyperpolarization, or no change, depending upon whether the effects of excitatory 5-HT<sub>2</sub> receptors or inhibitory 5-HT<sub>1A</sub> receptors are predominant in any given layer V pyramidal cell (Aghajanian and Marek 1997; Araneda and Andrade 1991; Tanaka and North 1993). However, the most striking effect of 5-HT in cortical regions is to increase postsynaptic potentials (PSPs). In earlier studies, we had found that 5-HT, via 5-HT<sub>2A</sub> receptors, induces inhibitory postsynaptic potentials (IPSPs) in layer II pyramidal cells of rat piriform cortex (a paleocortical region) through the direct excitation of a subset of GABAergic interneurons (Gellman and Aghajanian 1993; Sheldon and Aghajanian 1990); hallucinogens, acting as potent partial 5-HT<sub>2A</sub> agonists, have similar effects (Marek and Aghajanian 1996a). In contrast, we have found recently that synaptic potentials induced by 5-HT receptor activation in layer V pyramidal cells of the neocortex are predominantly excitatory rather than inhibitory (Aghajanian and Marek 1997), a finding that was surprising in view of the earlier work in piriform cortex. Thus, only ~15% of 5-HT-induced synaptic potentials in neocortex are blocked by the GABA<sub>A</sub> antagonist bicuculline; whereas, most synaptic potentials are blocked by the AMPA glutamatergic receptor antagonist LY293558, indicating

**Table 1.** Interaction of LSD and Phenethylamine Hallucinogens with 5-HT Receptor Subtypes (Glennon 1990; Marek and Aghajanian 1996a)

Receptor Subtype	LSD	Phenethylamines
5-HT <sub>1A</sub>	+	—
5-HT <sub>1D</sub>	+	—
5-HT <sub>2A/2C</sub>	+	+
5-HT <sub>3</sub>	—	—
5-HT <sub>4</sub>	—	?
5-HT <sub>5</sub>	+	—
5-HT <sub>6/7</sub>	+	—

that they represent largely excitatory postsynaptic potentials (EPSPs) rather than IPSPs. Nevertheless, as with IPSPs in the piriform cortex, the EPSCs induced by 5-HT in neocortex are mediated by 5-HT<sub>2A</sub> receptors as they are blocked by low concentrations of the highly selective 5-HT<sub>2A</sub> antagonist MDL100,907 (Aghajanian and Marek 1997). Although we have observed that 5-HT increases EPSCs throughout the neocortex, this effect is most pronounced in the medial prefrontal cortex, where there is an increased density of 5-HT<sub>2A</sub> receptors as compared to more posterior regions. NE also increases glutamatergic excitatory postsynaptic potentials in layer V pyramidal cells (Marek and Aghajanian 1996b), but to a much lesser extent than 5-HT. Nevertheless, because of the phasic quality of LC neuronal responses to sensory stimuli, sudden NE-induced increases in glutamate release could contribute to some of the distinctive effects of hallucinogenic drugs such as synesthesias.

Whole-cell patch clamp recordings have demonstrated that 5-HT induces a small, but significant, increase in the *amplitude* of spontaneous EPSCs, an effect that may involve a postsynaptic amplification mechanism (Aghajanian and Marek 1997). 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 (Jakab and Goldman-Rakic 1998; Willins et al. 1997). However, the most pronounced effect of 5-HT in neocortex is to increase the *frequency* of EPSCs (Aghajanian and Marek 1997). Classically, changes in the frequency of synaptic currents or potentials are considered presumptive evidence for modulation of presynaptic function. Consistent with this model, activation of  $\mu$ -opiate receptors (Marek and Aghajanian 1998a) and group II/III metabotropic glutamate receptors (Marek and Aghajanian 1998b) both suppress 5-HT-induced EPSCs through a presynaptic rather than postsynaptic action upon layer V pyramidal cells. 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.

#### **A Focal Mechanism for 5-HT<sub>2A</sub>-Induced Glutamate Release onto Apical Dendrites of Layer V Pyramidal Cells**

A novel mechanism, independent of impulse flow, seems to be involved in the increase in glutamate release induced by 5-HT<sub>2A</sub> receptor activation. 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 in the slice, leading to an impulse—flow-dependent release of glutamate. Several lines of evidence argue against this conventional

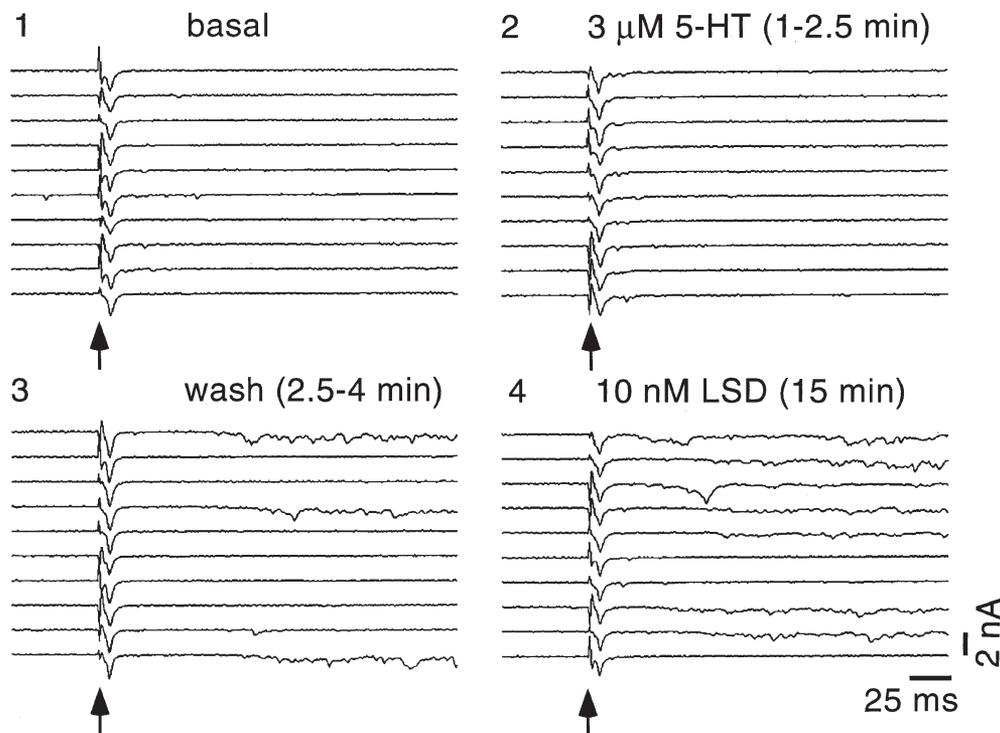
interpretation. First, we rarely found any neurons induced to fire by bath application of 5-HT (unlike our experience in the piriform cortex, where we readily found GABAergic interneurons excited by 5-HT). Second, none of the pyramidal cells (a potential source of intracortical excitatory inputs) in our sample were depolarized by 5-HT sufficiently 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, but no cell firing was detected while recording extracellularly through the *microiontophoretic electrode* (Aghajanian and Marek 1997). Together, these experiments suggest that 5-HT induces EPSCs in neocortical cells via a focal mechanism that does not require impulse flow.

#### **5-HT<sub>2A</sub> Receptors and Asynchronous Transmission in the Cerebral Cortex**

Because the microiontophoretic experiments indicate that 5-HT-induced EPSCs do not result from an increase in impulse flow in excitatory afferents, we were prompted to explore alternative mechanisms of transmitter release. Classically, two major types of vesicular neurotransmitter release have been characterized in experiments analyzing electrically evoked synaptic potentials (Goda and Stevens 1994). The first type of neurotransmitter release, termed *synchronous* release, is closely coupled in an almost immediate fashion to the action potential invasion of the nerve terminals with a subsequent flooding of Ca<sup>2+</sup> into the terminal through voltage-gated Ca<sup>2+</sup> channels. This is the form of neurotransmitter release that we typically envision. 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 (~50 ms) than the synchronous EPSC, which can persist for ~500–1,000 ms following the evoked synchronous EPSC. This form of release is sustained by low levels of residual Ca<sup>2+</sup> remaining within the terminal following the initial wave of Ca<sup>2+</sup> influx.

One of several distinguishing characteristics for this alternative mechanism of transmitter release is that Sr<sup>2+</sup> is able to substitute for Ca<sup>2+</sup> for asynchronous, but not synchronous release (Goda and Stevens 1994). This feature seems to be a result of two different isoforms of synaptotagmin being differentially involved in the two alternative release mechanisms (Li et al. 1995). We are now investigating the possibility that the 5-HT-induced EPSCs result from an activation of the asynchronous release pathway. Consistent with this idea, in preliminary experiments, we have found that Sr<sup>2+</sup> is highly effective in enabling 5-HT to induce EPSCs in the absence of Ca<sup>2+</sup> (Aghajanian and Marek 1998).

Recently, we have found that LSD (Figure 2) and other hallucinogenic drugs, acting as partial agonists at



**Figure 2.** Effects of 5-HT, 5-HT washout, and LSD on electrically evoked EPSCs (evEPSCs) in a layer V pyramidal cell of medial prefrontal cortex. **(1)** shows responses to 10 consecutive stimuli (arrowheads), where only short latency synchronous EPSCs are evoked. **(2)** After a 1 to 2.5 min application of 5-HT ( $3 \mu\text{M}$ ), there is little change in 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 nonsynchronous 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 large increase in the occurrence of the late, nonsynchronous component of the EPSCs (7/10 sweeps) (Aghajanian and Marek 1998).

5-HT<sub>2A</sub> receptors, also promote a late component of electrically evoked EPSPs (Aghajanian and Marek 1998). We hypothesize that this late component, rather than representing conventional polysynaptic transmission, is mediated through the mechanism of asynchronous transmitter release, possibly involving a release of intraterminal Ca<sup>2+</sup> stores via the phospholipase C, inositol trisphosphate (IP<sub>3</sub>) pathway. An enhancement of asynchronous evoked EPSPs 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, presumably because of opposing actions at 5-HT<sub>1</sub> or other non-5-HT<sub>2A</sub> receptors (Aghajanian and Marek 1998).

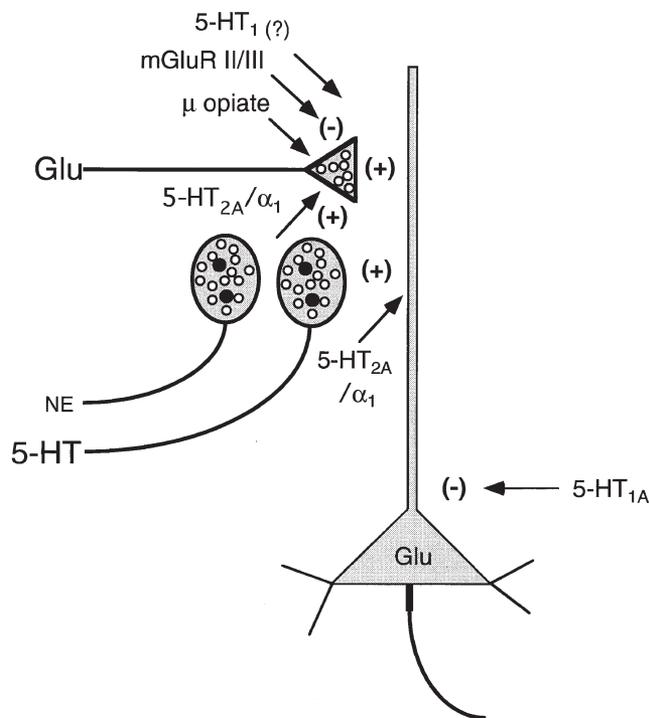
The opposition by non-5-HT<sub>2A</sub> receptors of 5-HT<sub>2A</sub>-mediated actions of 5-HT may explain why treatments that elevate 5-HT itself (e.g., monoamine oxidase inhibitors or selective serotonin uptake blockers) are not hallucinogenic and may, in fact, attenuate the subjective effects of hallucinogens in humans (Bonson et al. 1996; Resnick et al. 1964). Conversely, a reduction in serotonin levels or release could enhance the effects of hallucinogens (Isbell and Logan 1957; Resnick et al. 1965). By

decreasing 5-HT release, a direct inhibition of 5-HT cell firing in the raphe nuclei could contribute to the effects of LSD and other indoleamine hallucinogens. Although the phenethylamines suppress the firing of only a subset 5-HT neurons (an effect mediated through an indirect rather than direct postsynaptic mechanism, see above), this action could also contribute to the hallucinogenic effects of these drugs. Despite these interesting, but subtle, differences in mechanism, the over-all subjective effects of indoleamine and phenethylamine hallucinogens have been reported to be virtually identical in side-by-side comparisons in human subjects (Wolbach et al. 1962).

## OVERVIEW AND FUTURE DIRECTIONS

### The Classical Questions

Many of the original questions about the role of 5-HT in the action of hallucinogenic drugs can now be addressed in a highly specific manner. In the present review, neuronal actions *shared* by LSD and the phenethylamine hallucinogens have been described in detail for two brain regions, the LC and the cerebral cortex. In



**Figure 3.** Schematic diagram depicting 5-HT inputs (from the raphe nuclei) and nonadrenergic (NE) inputs (from the locus coeruleus) projecting to the vicinity of the apical dendrite of a layer V pyramidal cell in neocortex. 5-HT, acting via 5-HT<sub>2A</sub> receptors, is shown to induce the release of glutamate from an excitatory nerve terminal (+); to a lesser extent, NE, acting via  $\alpha_1$  receptors, also induces glutamate release. Also shown are inhibitory modulators of 5-HT<sub>2A</sub>-induced glutamate release:  $\mu$  opiate, group II and III metabotropic glutamate (mGluR II/III), and as yet an uncharacterized non-5-HT<sub>2A</sub> receptor (possibly a 5-HT<sub>1</sub> subtype). In addition, excitatory (5-HT<sub>2A</sub> and  $\alpha_1$ ) and inhibitory (5-HT<sub>1A</sub>) postsynaptic effects of 5-HT and NE are shown.

these and other regions, there is evidence that both classes of hallucinogens produce their electrophysiological effects through a partial agonist action at 5-HT<sub>2</sub> (particularly 5-HT<sub>2A</sub>) receptors. There is also evidence from biochemical (Sanders-Bush et al. 1988) and behavioral (Glennon 1990) studies that the effects of hallucinogens involve a partial agonist action at 5-HT<sub>2</sub> receptors. Thus, 50 years after the discovery of 5-HT, the 5-HT hypothesis of the action of both indoleamine and phenethylamine hallucinogenic drugs can be reformulated in terms of specific 5-HT receptor subtypes, with a primary focus on 5-HT<sub>2</sub> receptors.

#### Questions—1998

How do the discrete neuronal actions of hallucinogens, as described above, account for dramatic disruptions in cortical function produced by the hallucinogenic drugs? It is now possible to suggest regionally and neuronally specific answers to this question. For

example, enhancement of the sensory responsivity of LC neurons may contribute, perhaps through their extensive cortical projections, to the characteristic intensification of certain kinds of perceptual experience produced by hallucinogens. In the cerebral cortex, enhancement of the prolonged, late, asynchronous component of glutamatergic transmission by hallucinogens may underlie some of the cognitive and perceptual distortions produced by these drugs. Figure 3 depicts the enhancement of glutamatergic transmission by both 5-HT inputs from the raphe nuclei and NE inputs from the LC, acting via 5-HT<sub>2A</sub> and  $\alpha_1$  receptors, respectively. We hypothesize that hallucinogen-induced excesses in glutamatergic transmission are detrimental to cortical information processing; certain distinctive features of the effects of hallucinogens, such as distortions in perceptual and cognitive function, could fit into this framework. We suggest that an increase in asynchronous glutamatergic transmission could be responsible for the hallucinogen-induced hyperfrontal metabolic pattern that has been found recently in human brain-imaging studies (Vollenweider et al. 1997). A similar hyperfrontal pattern has also been found in acute, but not chronic, schizophrenic patients (Vollenweider et al. 1997). Ultimately, insight into how hallucinogens alter cortical information processing may provide clues about mechanisms underlying naturally occurring psychotic states.

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