

Serotonin and the Action of LSD in the Brain

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In 1943, the chemist Albert Hoffman accidentally discovered the remarkably potent hallucinogenic properties of LSD (d-lysergic acid diethylamide). Within the next decade, serotonin (5-hydroxytryptamine; 5-HT), an endogenous indoleamine compound structurally related to LSD (Figure 1), was found in various tissues of the body including the brain. Based on this structural similarity and the finding that LSD could antagonize 5-HT in peripheral tissues, it was proposed independently by Gaddum and Woolley that the hallucinogenic effects of LSD might result from an antagonism of 5-HT in the brain. This hypothesis was soon expanded to include the possibility that LSD could *mimic* as well as antagonize the actions of 5-HT.¹

The first direct demonstration that LSD interacts with *brain* 5-HT came in 1961 from the biochemical studies of Freedman who showed that this drug could produce a small, dose-dependent increase in the concentration of endogenous 5-HT.² However, the significance of this change was unclear since the cellular location and function of 5-HT in the brain was unknown at the time. Nevertheless,

by the early 1960s the 5-HT hypothesis of the action of LSD had become firmly established in the field.

THE ACTION OF LSD ON SEROTONERGIC NEURONS LSD Inhibits Serotonergic Neurons of the Raphe Nuclei

The modern era of research on the actions of LSD in the central nervous system began in the mid-1960s following the discovery and mapping by histochemical fluorescence methods of serotonergic and other monoaminergic neuronal pathways in the brain.³ The maps revealed that serotonergic neuronal cell bodies were clustered in the raphe nuclei of the brain stem. In 1968, based on this new information, the first single-cell electrophysiological recordings from identified serotonergic neurons were performed.⁴

These experiments, conducted in anesthetized rats, showed that systemically administered LSD has a potent inhibitory effect on the tonically firing serotonergic neurons of the dorsal raphe nucleus. The local application of LSD by microiontophoresis indicated that the inhibition was through a direct action on the somatodendritic region of serotonergic neurons.^{5,6} The resulting reduction in impulse flow provided an explanation for the previously observed increase in brain 5-HT levels that had been detected by biochemical methods.

Other indoleamine hallucinogens such as DMT (N,N-dimethyltryptamine and psilocybin) were also shown to inhibit serotonergic neurons in the raphe nucleus. However, mescaline (Figure 1) and various other substituted phenethylamine hallucinogens did not share with the indoleamines the ability to inhibit

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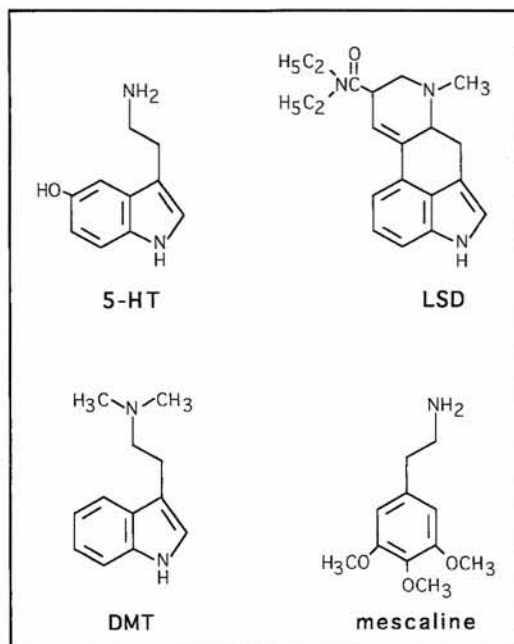


Figure 1. Structural formulae for serotonin (5-HT), LSD, mescaline, and the simple indoleamine hallucinogen DMT (N,N-dimethyltryptamine). The chemical structures are drawn so as to emphasize common structural features such as the indole/phenethylamine nucleus of 5-HT, LSD, and DMT and the phenethylamine nucleus shared by LSD and mescaline.

raphe neurons.⁷ Thus, inhibition of serotonergic neurons did not appear to represent a unitary mechanism for the action of indoleamine and phenethylamine hallucinogens.

LSD Inhibits Raphe Neurons Through 5-HT₁ Receptors

The recent delineation of multiple 5-HT receptor subtypes by radiolabeled ligand binding and molecular methods (eg, 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄)⁸ now provides a basis for explaining the difference between the effects of the indoleamine and phenethylamine hallucinogens on serotonergic neurons. Serotonergic raphe neurons have a high density of 5-HT_{1A} but not other subtypes of 5-HT receptors. Since they mediate responses of serotonergic neurons to their own transmitter, these receptors have been termed *somatodendritic autoreceptors*.

LSD is a potent agonist at 5-HT_{1A} autoreceptors, thus accounting for its direct inhibitory effect on raphe neurons. On the other hand, mescaline and other phenethylamines have negligible affinity for 5-HT_{1A} receptors, explaining their inability to inhibit serotonergic raphe neurons. The action of LSD at 5-HT_{1A} autoreceptors is shared by a number of selective 5-HT_{1A} 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_{1A} receptors and

the presence or absence of hallucinogenic properties.

ACTIONS OF LSD AT POSTSYNAPTIC SITES Affinity for 5-HT₂ Receptors Correlates with Hallucinogenic Potency

In contrast to their disparate affinities for 5-HT_{1A} receptors, there is a very good correlation between the affinity of both indoleamine and phenethylamine hallucinogens for 5-HT₂ receptors and hallucinogenic potency in humans.^{9,10} Unlike 5-HT_{1A} receptors, 5-HT₂ receptors are not located presynaptically on serotonergic cell bodies but rather are found on subpopulations of neurons in postsynaptic regions. Quantitative autoradiographic studies show high concentrations of 5-HT₂ receptors in selected regions of the brain including the neocortex (layers IV/V), piriform cortex, claustrum, nucleus accumbens, olfactory tubercle, facial nucleus, and the n. tractus solitarius.¹¹ A high density of 5-HT₂ receptor mRNA has been demonstrated by *in situ* hybridization in the same locations.¹² Immunocytochemical studies also show the presence of 5-HT₂ receptors in some of the same regions.¹³

For purposes of illustration, this review will focus 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 by 5-HT₂ receptors.

Hallucinogens Enhance Sensory Responses in the Locus Coeruleus

The locus coeruleus (LC) consists of two dense clusters of noradrenergic neurons located bilaterally in the upper pons at the lateral border of the fourth 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 and has been likened to a novelty detector.^{14,15} Thus, the LC represents a nodal point for the detection of significant changes in both the internal and external environment and for relaying this information to the remainder of the central nervous system.

The systemic administration of LSD, mescaline, and other psychedelic hallucinogens in anesthetized rats results in a decrease in spontaneous activity and, paradoxically, a facilitation of the activation of LC neurons by sensory stimuli.¹⁶ The effects of hallucinogens on LC neurons can be reversed by low intravenous doses of selective 5-HT₂ antagonists such as ritanserin.¹⁷ Antipsychotic drugs are also able to reverse the actions of hallucinogens in the locus coeruleus at doses correlating with their affinity for 5-HT₂ but not dopamine and adrenergic receptors.¹⁸ Of particular note is the fact that spiperone, which has almost a 1,000-fold greater affinity for 5-HT₂ than for

the closely related 5-HT_{1C} receptors, completely blocks the effects of the hallucinogens at extremely low doses. Thus, the effects of hallucinogens on the LC appear to be mediated by 5-HT₂ rather than 5-HT_{1C} receptors.

The effects of systemically administered hallucinogens are not through a local action on LC cell bodies as they are not mimicked by the microiontophoretic application of the drugs. Moreover, the excitation of LC neurons by the local application of acetylcholine, glutamate, or substance P is not enhanced by the systemic administration of mescaline or LSD.¹⁶ These results imply that hallucinogens are acting indirectly, presumably via afferents to the LC. Consequently, the LC itself cannot be used as a model for studying the direct cellular actions of hallucinogens. Nevertheless, the effects of the hallucinogens on 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.

Hallucinogens Excite a Subpopulation of Interneurons in the Cerebral Cortex

The majority of 5-HT₂ receptors in the brain are located in the cerebral cortex. Accordingly, the effects of hallucinogens on perceptual and cognitive functions are likely to be mediated predominantly within this structure. In brain slices, pyramidal cells in various regions of the cerebral cortex have been found to respond to 5-HT by either a small hyperpolarization, depolarization, or no change in potential.¹⁹⁻²¹ It has been suggested that the depolarizations are mediated by 5-HT₂ receptors since they can be blocked by 5-HT₂ antagonists. However, the interpretation of this data is somewhat unclear since 5-HT₂ receptors do not seem to be expressed by pyramidal cells in the cortex.^{12,13}

Recently, we have found a novel effect of 5-HT in piriform cortex: the enhancement of spontaneous inhibitory postsynaptic potentials (IPSPs), which can be observed in pyramidal cells.²¹ A similar induction of IPSPs by 5-HT has also been seen in prefrontal cortex (Sheldon and Aghajanian, unpublished observation). The IPSPs in piriform cortex are blocked by the GABA antagonist bicuculline, suggesting that it is an excitation of GABAergic interneurons by 5-HT that gives rise to IPSPs in the pyramidal cells. In accord with this expectation, a subpopulation of cortical interneurons has been found that are excited directly by 5-HT. The 5-HT₂/5-HT_{1C} antagonist, ritanserin, blocks the 5-HT-induced activation of these interneurons. The hallucinogens LSD and DOM behave as partial agonists in this system, producing a modest activation by themselves but occluding the full effect of 5-HT.

A unitary mechanism—a shared action at 5-HT₂ but not 5-HT_{1A} receptors—holds for the two major classes of psychedelic hallucinogens.

The effects of antipsychotic drugs on 5-HT activations of cortical interneurons have also been examined. Two atypical antipsychotic drugs, risperidone and clozapine, in a concentration range corresponding to clinically efficacious blood levels, are able to block 5-HT₂ responses of interneurons in rat piriform cortex.²² In contrast, the conventional antipsychotic drugs chlorpromazine and haloperidol do not block 5-HT₂ responses, at least in a clinically relevant concentration range. These results indicate that certain atypical antipsychotic drugs could exert their antipsychotic effects, at least in part, by antagonizing 5-HT₂ receptors on cortical interneurons.

SUMMARY OF BASIC STUDIES

5-HT₂ Receptors Mediate the Physiological Actions of Hallucinogens

Physiological actions *shared* by LSD and the phenethylamine hallucinogens have been described in detail for two brain regions, the LC and the cerebral cortex. In these and other regions, there is pharmacological evidence that the neuronal effects of both classes of hallucinogens are mediated through 5-HT₂ receptors. Thus, a unitary mechanism—a shared action at 5-HT₂ but not 5-HT_{1A} receptors—holds for the two major classes of psychedelic hallucinogens (Figure 2). Thus, 50 years after the discovery of LSD, the 5-HT hypothesis can be reformulated in terms of a specific 5-HT receptor subtype, the 5-HT₂ receptor.

5-HT₂ Receptors Also Mediate the Behavioral Effects of Hallucinogens

The *shared* behavioral effects of indoleamine and phenethylamine hallucinogens are also mediated through 5-HT₂ receptors.^{9,23-25} What then is the relationship between the behavioral effects of hallucinogens and their actions on single neurons? We can now begin to provide neuronally and regionally specific answers to this question. For example, the enhancement of sensory responsivity of LC neurons may contribute to the characteristic intensification of certain kinds of perceptual

those that are lost. However, since there is a decrease in 5-HT₂ receptor binding, it is possible that the interneuronal abnormality in schizophrenia may involve 5-HT₂-expressing cells. Thus, studies on the anatomy, physiology, and pharmacology of cortical interneurons that express 5-HT₂ receptors are of interest in relation to a growing number of postmortem studies on the possible involvement of these receptors in the pathophysiology of schizophrenia.

Implications for the Treatment of "Bad Trips"

There is now ample evidence that 5-HT₂ antagonists are effective in blocking both the electrophysiological and behavioral effects of hallucinogenic drugs in animal model systems. Thus, 5-HT₂ antagonists offer great promise as potential treatments for the acute adverse reactions ("bad trips") that are experienced by some individuals with the use of LSD and other psychedelic hallucinogens.

As yet there are no FDA-approved selective 5-HT₂ antagonists available for use clinically. There are a few classical 5-HT antagonists (eg, cyproheptadine), approved for other indications that may have effectiveness against the hallucinogens since they have antagonist activity at 5-HT₂ receptors. However, side effects produced by actions at other receptors may limit their clinical utility.

Based on preclinical studies, clozapine should also be effective as a treatment, but its use is currently restricted to drug-resistant schizophrenia. Other prospective antidotes include recently developed "atypical" antipsychotic drugs such as risperidone which have a very high affinity for 5-HT₂ receptors. Obviously, as such drugs become available on the US market it would be of interest to test them as possible specific treatments for adverse reactions to the psychedelic hallucinogens.

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