Hallucinogen actions on human brain revealed

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With regard to hallucinogens like psilocybin—an ingredient of so-called "magic mushrooms" (e.g., *Psilocybe cubensis*)—it may be high time to reconsider long-standing hypotheses related to their actions in the human brain.

Although psilocin (the active metabolite of psilocybin) (Fig. 1*A*) and other classical hallucinogens like lysergic acid diethylamide (LSD) have complex pharmacologies with high affinities for multiple neurotransmitter receptors (1), it has long been appreciated that their psychedelic actions correlate best with 5-HT_{2A}–serotonin receptor agonism (2). Indeed, in 5-HT_{2A} knockout mice, classical hallucinogens are devoid of activity (3, 4). Importantly, the psychedelic actions of psilocybin in humans are abolished by pretreatment with relatively selective 5-HT_{2A} antagonists (5, 6). Taken together, these findings support the hypothesis that psilocybin and other classical hallucinogens exert their psychedelic actions in humans via activating 5-HT_{2A} serotonin receptors.

Although there is consensus regarding the pharmacological actions of classical hallucinogens, the neuronal mechanisms responsible for the psychedelic actions of hallucinogens remain controversial. Thus, some investigators have observed that LSD-like hallucinogens can enhance pyramidal neuron activity by activating 5-HT_{2A} serotonin receptor signaling (7, 8) (Fig. 1). These findings that hallucinogens activate glutamatergic neurotransmission are consistent with many other studies demonstrating that 5-HT_{2A} receptors were enriched on Layer V glutamatergic neurons (9) although we and others have noted that 5-HT_{2A} receptors are also found on GABA-ergic interneurons (10–12). Indeed, 5-HT_{2A} agonists can also augment inhibitory neuronal activity (13). Taken together, these previous findings have implied that the actions of hallucinogens such as psilocybin might be due to a mixture of actions on both excitatory (e.g., pyramidal) and inhibitory (e.g., GABA-ergic interneuronal) neuronal circuits (Fig. 1*C*). Conceivably, then, hallucinogens like psilocybin could induce their psychedelic effects via augmenting either excitatory or inhibitory neuronal activity in humans. Unfortunately, because of medical, legal, human use, and societal concerns, well-controlled studies of hallucinogen actions in humans have languished since the early 1960s.

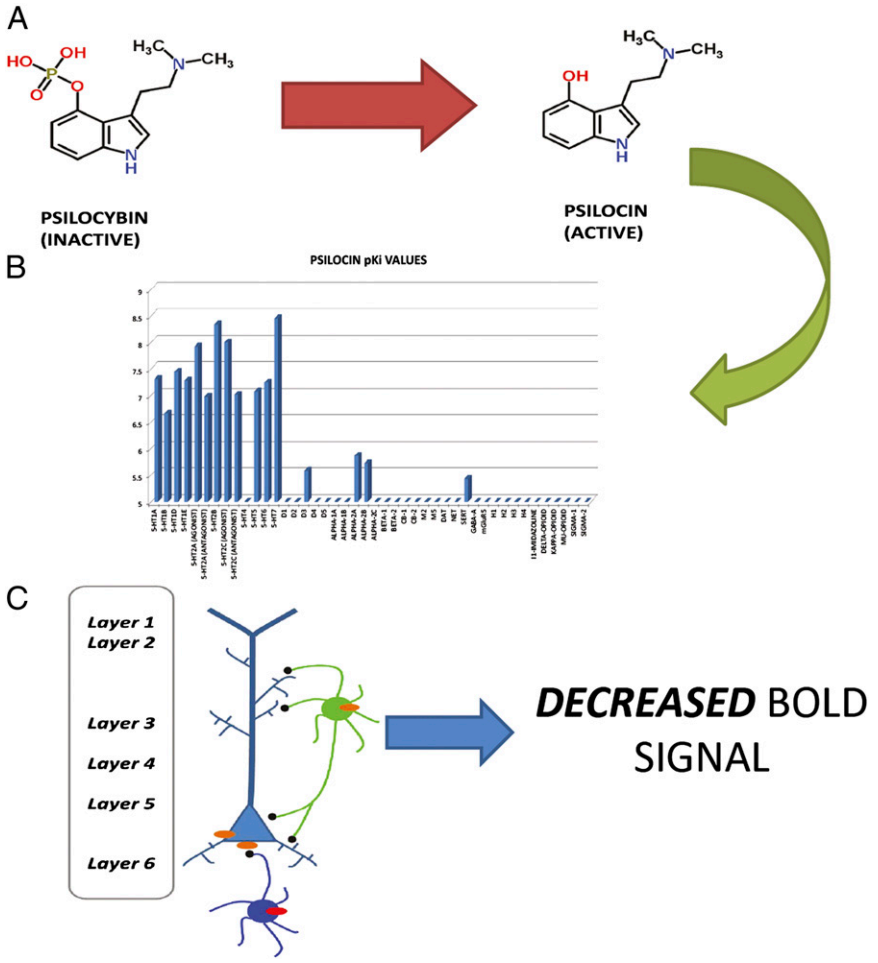

Fig. 1. Psilocybin diminishes brain activity and connectivity. (*A*) Psilocybin, which is inactive, is metabolized to the active ingredient psilocin. Psilocin then activates many neurotransmitter receptors (*B*) to modulate activity on excitatory pyramidal and inhibitory GABA-ergic neurons (*C*). (*B*) Affinity values for psilocin are expressed as –log in nanomoles (pK_i) and are from the National Institute of Mental Health Psychoactive Drug Screening Programs K_i Database (http://pdsp.med.unc.edu/kidb.php). (*C*) Psilocin interacts with various receptors on large excitatory pyramidal neurons and smaller inhibitory neurons. Psilocin may interact with excitatory (orange) or inhibitory (red) receptors to augment or inhibit neurotransmission. Psilocin's net effect is a decrease in neuronal activity and connectivity as measured by fMRI.

In PNAS, Carhart-Harris et al. (14) successfully execute an important study that begins to fill in our gaps regarding hallucinogen actions in humans. Surprisingly, they demonstrate that psilocybin decreases surrogate markers for neuronal activity [cerebral blood flow and blood oxygen level-dependent (BOLD) signals] in key brain regions implicated in psychedelic drug actions. They also report that psilocybin appears to decrease brain "connectivity" as measured by pharmacophysiological interaction.

To perform these studies, Carhart-Harris et al. (14) recruit 15 experienced hallucinogen users for arterial spin labeling (ASL) perfusion and BOLD fMRI studies. The individuals were

Author contributions: H.-M.L. and B.L.R. wrote the paper.

The authors declare no conflict of interest.

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scanned before and after receiving i.v. doses of placebo or psilocybin (2 mg). Individuals were also rated for the subjective effects of psilocybin or placebo. Not surprisingly, psilocybin exerted a robust psychedelic effect with individuals reporting alterations in consciousness, time perception, and visual perceptions within minutes of psilocybin administration.

Coincident with these profound perceptual alterations, decreases in cerebral blood flow were observed in key brain regions long implicated in psychedelic drug actions—the anterior and posterior cingulate cortices and thalamus. Intriguingly, the intensity of the psychedelic experience significantly correlated with decrements in blood flow in the thalamus and anterior cingulate cortex. Carhart-Harris et al. (14) also report what they refer to as decreases in "functional connectivity" between the ventral medial prefrontal cortex and other regions that they interpret to indicate an overall diminished connectivity.

Psilocybin appears to decrease brain "connectivity" as measured by pharmacophysiological interaction.

Overall, these findings are consistent with the hypothesis that psilocybin diminishes activity in key brain regions and networks implicated in hallucinogen actions. These provocative findings are important because they challenge many long-held models regarding hallucinogen actions that have focused mainly on their ability to enhance excitatory neurotransmission and overall brain activity.

The findings of Carhart-Harris et al. (14) are also important because they provide a nice proof that, provided appropriate safeguards are in place, psychedelic drug actions can once again be rigorously deconstructed in normal human volunteers. Psychedelic drugs are unique in their abilities to profoundly alter human awareness and perception, and these studies provide important hints regarding the neuronal substrates of human consciousness.

ACKNOWLEDGMENTS. Work in the authors' laboratory is supported by grants from the National Institutes of Health and the Michael Hooker Distinguished Chair of Pharmacology.

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