

Hallucinogen actions on human brain revealed

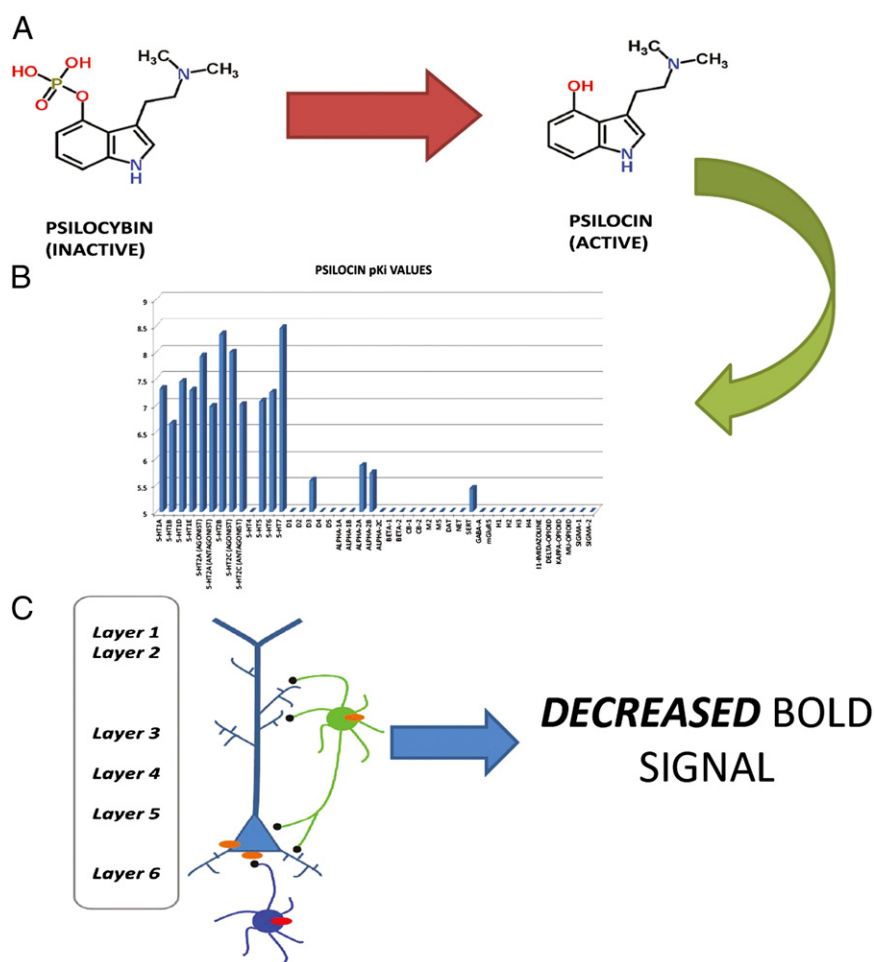
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With regard to hallucinogens like psilocybin—an ingredient of so-called “magic mushrooms” (e.g., *Psilocybe cubensis*)—it may be high time to reconsider long-standing hypotheses related to their actions in the human brain.

Although psilocin (the active metabolite of psilocybin) (Fig. 1A) 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. 1C). 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 hallu-



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

Psilocybin appears to decrease brain “connectivity” as measured by pharmaco- physiological interaction.

prefrontal cortex and other regions that they interpret to indicate an overall diminished connectivity.

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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