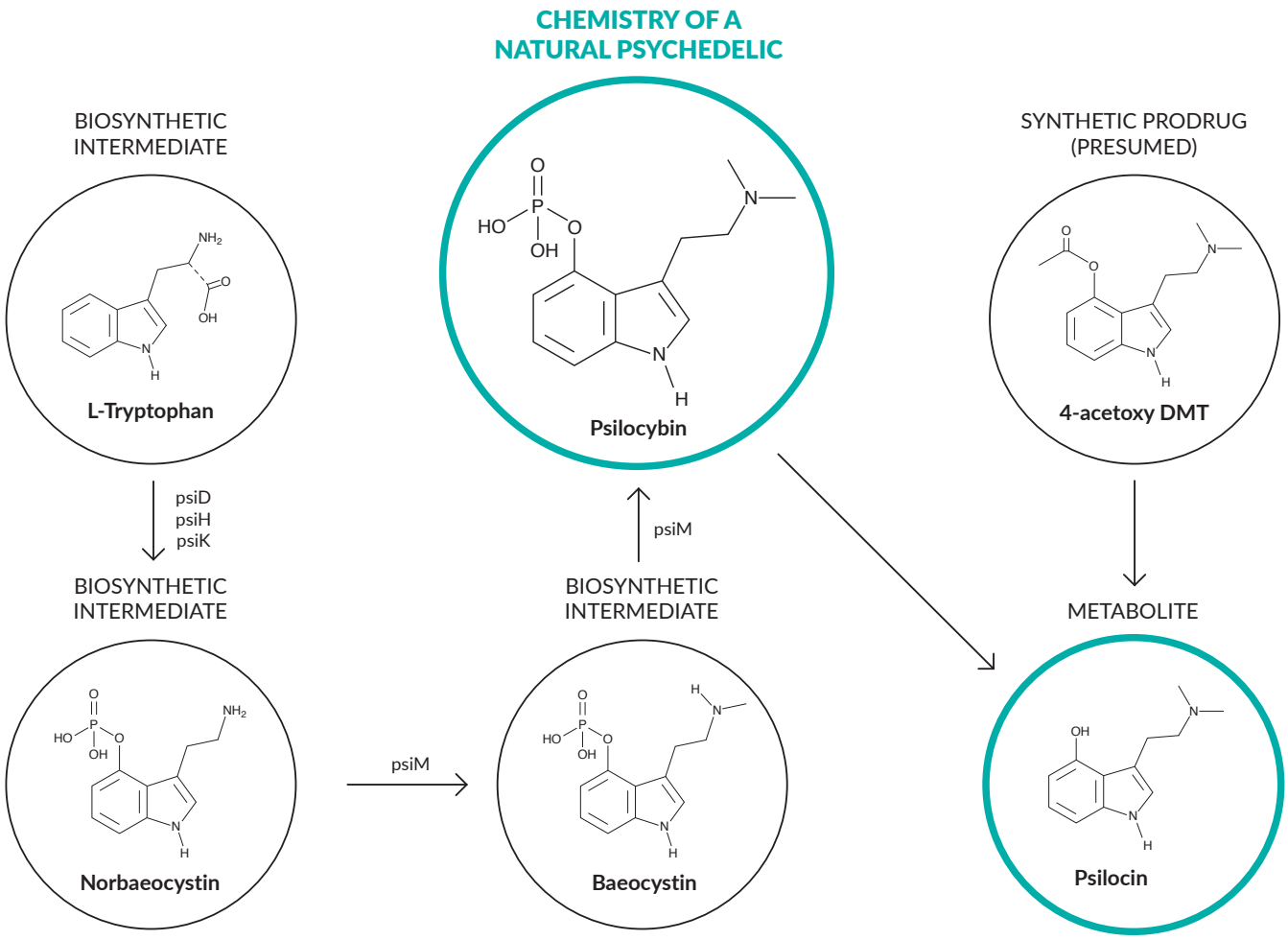
Rediscovering Psilocybin and Its Therapeutic Potential

Psilocybin is a phosphorylated prodrug form of the psychedelic compound psilocin that has been found in fungi of the genus *Psilocybe*, as well as in fungi from other genera. Ingestion of psilocybin-containing mushrooms for their hallucinogenic effects has occurred for thousands of years. In the 1500s, Bernardino de Sahagún, a Spanish Franciscan friar, studied Aztec culture and *Psilocybe* mushrooms in Mexico. Sahagún called these mushrooms *teonanácatl*, meaning "God's flesh", and described their use for medical and religious purposes. Broader use of so-called "magic mushrooms" in the United States began after publication of a LIFE magazine article in 1957 written by the amateur mycologist R. Gordon Wasson. Wasson wrote about his experience participating in a spiritual ritual using the mushrooms for their curative powers conducted by the Mazatec curandera María Sabina in the village of Huautla de Jiménez, Mexico. This led to widespread cultivation and use of the mushrooms for recreation and research. In 1971, psilocybin was regulated as a Schedule I controlled substance and its use was drastically reduced. Psilocybin-based research increased in the late 1990s and now it is one of the most common psychedelics used in human studies. It has potential applications in the treatment of major depressive disorder, obsessive-compulsive disorder (OCD), substance use disorder, end-of-life anxiety and depression, and cluster headaches. A couple of US states are leading the way into this new exploration into psychedelic medicine. Currently, Colorado and Oregon have legalized psilocybin, and several other states are considering similar legislation to legalize psilocybin and/or psilocin.

Chemistry

Psilocybin was originally isolated from *Psilocybe mexicana* in 1958 by Albert Hofmann, the same chemist that synthesized lysergic acid diethylamide (LSD) in 1938. It is biosynthesized from tryptophan through norbaeocystin and baeocystin intermediates. Psilocybin and its active metabolite, psilocin, are categorized as tryptamines, with structures similar to that of the neurotransmitter serotonin (5-HT). Psilacetin, also known as 4-acetoxy DMT, is another presumed prodrug of psilocin that contains an acetoxy group at the four position of the indole ring in place of the phosphoryloxy group in psilocybin (**Figure 1**). Tryptamines substituted at the four position of the indole ring are closest in structure to psilocin, which contains a hydroxy group in that position. Some derivatives of psilocybin, such as 4-acetoxy MET or 4-methyl-α-ethyltryptamine, combine indole ring modifications and substitutions on the primary amine or the ethylamine chain.



Pharmacology & Mechanism of Action

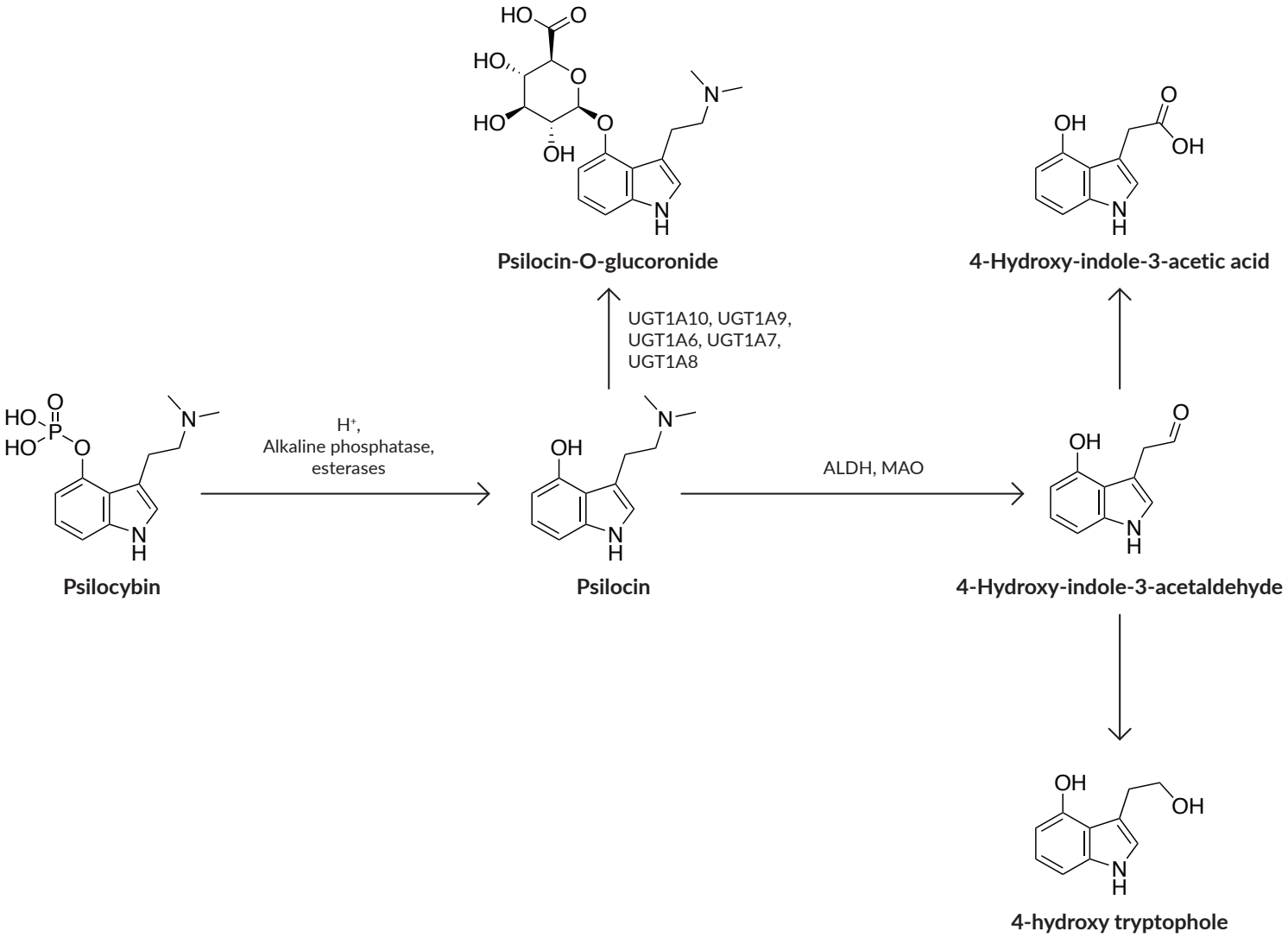
Psilocin, the active metabolite of the prodrug psilocybin, is a partial agonist at the 5-HT_{2A} receptor. It has moderate affinity for additional 5-HT receptors (5-HT_1, 5-HT_5, 5-HT_6, 5-HT_7), as well as lower affinity for dopamine D_3 receptors and α_2-adrenergic receptors (α_2-ARs). Psilocybin is not the only psychedelic whose ingestion and metabolism leads to 5-HT_{2A} receptor activity. Like psilocin, LSD and mescaline are also 5-HT_{2A} receptor agonists and share many of the same psychedelic effects as psilocybin.

Psilocybin ingestion induces visual and auditory hallucinations, time distortion, and synesthesia, as well as feelings of spirituality and interconnectedness. The occupancy of cerebral 5-HT_{2A} receptors by psilocin in human volunteers correlates with the intensity of their psychedelic experiences, and psilocybin-induced hallucinations can be blocked by 5-HT_{2A} receptor antagonists, indicating that 5-HT_{2A} receptor activation is responsible, at least in part, for its psychedelic effects. The visual cortex highly expresses postsynaptic 5-HT_{2A} receptors on serotonergic and glutamatergic neurons, and their activation may be sufficient to explain, at a cellular level, the mechanism of the visual hallucinations induced by psilocybin. However, recent research suggests the 5-HT_{1A} receptor may play a role in the effects of psilocybin as well. The 5-HT_{2A} receptor antagonist ketanserin does not block certain psilocybin-induced effects, such as attentional tracking, binocular rivalry, and reductions in arousal and vigilance. In addition, the euphoric feelings of psilocybin can be inhibited by the dopamine D_2 antagonist haloperidol, suggesting involvement with the dopaminergic system. Preclinical models have been used to help elucidate the mechanism of psilocybin's effects and to screen for CNS-active derivatives.

Due to the scheduling of psilocybin and LSD as controlled substances, human research using these compounds dwindled and the head-twitch response assay was widely adopted as a behavioral assessment to approximate hallucinogen-like effects in rodents. This paroxysmal side-to-side head movement is one of few behaviors that can distinguish between hallucinogenic and non-hallucinogenic 5-HT_{2A} receptor agonists. A variety of psilocin derivatives have been assessed using the head-twitch response assay, including 4-hydroxy MET, 4-acetoxy DMT (psilacetin), and 4-acetoxy DiPT, and have been found to elicit the response.

Metabolism

Psilocybin is dephosphorylated *in vivo* to psilocin by phosphatases in the intestine and other tissues. It is directly glucuronidated to form psilocin-O-glucuronide primarily by the UDP-glucuronosyltransferase (UGT) isoforms UGT1A10 and UGT1A9. A small amount of psilocin is oxidized to 4-hydroxyindole-3-acetaldehyde (4-HIA), then oxidized again to 4-hydroxyindole-3-acetic acid (4-HIAA) or reduced to 4-hydroxy tryptophole (4-HT). Psilocin is predominantly excreted as the glucuronidated product but approximately 25% is excreted as psilocin and a minor amount as 4-HIAA. Excretion of psilocin and its metabolites primarily occurs in the urine, with only 15-20% excreted in the bile and feces, within eight hours of an oral dose. However, they can be detected in the urine in lower amounts at least seven days after administration.



Therapeutic Potential

The field of psychedelic therapeutics is growing at a fast pace due to the benefits of these compounds over current treatments. Psilocybin is a rapid-acting antidepressant (RAAD), and the United States FDA has granted breakthrough therapy status for its use in treatment-resistant depression. This status is intended to fast-track drugs that have shown evidence of substantial improvement over current therapeutics in preliminary trials. Psilocybin also has potential applications in the treatment of OCD, substance use disorder, and cluster headaches.

The rapid-acting nature of psilocybin for depression is not the only improvement over current therapeutics. Its effects also persist long after administration, which would eliminate the need for daily dosing. In a double-blind placebo-controlled study involving patients with life-threatening cancer, psilocybin-assisted psychotherapy immediately reduced cancer-related feelings of hopelessness and anxiety and improved patients' quality of life. Remarkably, these effects persisted in the majority of patients for at least 6.5 months after the drug-assisted therapy session. Psilocybin, given two times three weeks apart, also reduced depression in patients with moderate-to-severe major depressive disorder at a level comparable with daily escitalopram.

Psilocybin has shown promise in open-label studies for use in drug-assisted psychotherapy for patients with OCD and for cessation of alcohol or nicotine use. Further research is warranted, and there is a need for double-blind placebo-controlled trials and trials that control for the effect of psychotherapy. Due to the potential for "bad trips"—negative experiences while under the influence of psilocybin—the administration of psychedelic compounds requires supervision in carefully controlled settings, such as a psychotherapy session.

If the psychedelic experience is not required for the therapeutic effects of psilocybin, it would make dosing more manageable by eliminating the need for psychotherapy at the time of dosing. It would also widen the field for finding tryptamine derivatives with improved efficacy in related therapeutic areas. Evidence from animal studies suggests that the hallucinogenic potential can be decoupled from the antidepressant-like effects. In a study using mice, Hesselgrave *et al.* found that the antidepressant-like effect was independent of 5-HT_{2A} receptor activation and the head-twitch response that indicates hallucinogenic potential in rodents.

Taken together, psychedelic therapies like psilocybin are growing rapidly and show great promise in treating several conditions not well-addressed by current treatments.