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Psilocybin: from ancient magic to modern medicine

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Abstract

Psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine) is an indole-based secondary metabolite produced by numerous species of mushrooms. South American Aztec Indians referred to them as *teonanacatl*, meaning "god's flesh," and they were used in religious and healing rituals. Spanish missionaries in the 1500s attempted to destroy all records and evidence of the use of these mushrooms. Nevertheless, a 16th century Spanish Franciscan friar and historian mentioned *teonanacatl* in his extensive writings, intriguing 20th century ethnopharmacologists and leading to a decades-long search for the identity of *teonanacatl*. Their search ultimately led to a 1957 photo-essay in a popular magazine, describing for the Western world the use of these mushrooms. Specimens were ultimately obtained, and their active principle identified and chemically synthesized. In the past 10–15 years several FDA-approved clinical studies have indicated potential medical value for psilocybin-assisted psychotherapy in treating depression, anxiety, and certain addictions. At present, assuming that the early clinical studies can be validated by larger studies, psilocybin is poised to make a significant impact on treatments available to psychiatric medicine.

Introduction

Secondary metabolites from plants, fungi, and bacteria over the years have proven to be a rich and valuable source of novel therapeutics. Most notably, they have been recognized and exploited for their anti-infective and anticancer properties. In many cases, they have served as prototypes, or lead compounds, which they have been modified through chemical synthesis to afford therapeutic agents with improved potency, stability, or superior drug-like properties.

A less common use for secondary metabolites is for treating diseases of the central nervous system (CNS). This short review will focus on a fungal secondary metabolite that has recently received rapidly increasing attention for its potential ability to treat a host of CNS disorders, including depression, anxiety, and various addictions. Indeed, at the present time it appears that it may revolutionize certain aspects of psychiatric medicine [1]. This metabolite, psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine; Fig. 1), is produced by more than 200 species of basidiomycetes, collectively known as psilocybin mushrooms. These mushrooms grow worldwide and have been strictly controlled legally due to their popularity as recreational drugs.

History and discovery of psilocybin

The story of psilocybin begins with Spanish Franciscan friar Bernardino de Sahagún who journeyed to Mexico ("New Spain") in 1529 and carried out ethnographic research studies. He learned Nahuatl, the Aztec language, and spent more than 50 years in the study of Aztec beliefs, culture, and history. Sahagún is perhaps best known for compiling the *Historia general de las cosas de la Nueva España*—in English, General History of the Things of New Spain. The most famous existing manuscript of the Historia General is the *Florentine Codex*, consisting of 2400 pages organized into 12 books, with ~2500 illustrations. In the Codex Sahagún repeatedly refers to *teonanacatl*, "God's Flesh," the sacred mushrooms of Mesoamerica.

The existence of these mushrooms was very controversial, was even denied by some, and was debated until 1936, when Roberto Weitlaner was able to obtain specimens. They ultimately arrived at Harvard University, but had decomposed so badly they could not be identified [2]. Two years later his daughter, her fiancé, and two others were able to attend a mushroom ceremony in Huautla (Mexico) and provide details

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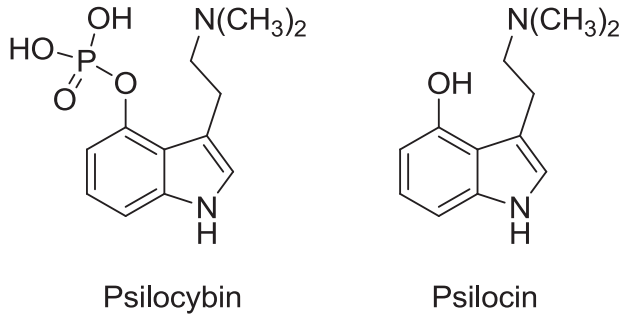


Fig. 1 Structures of psilocybin and psilocin

of the event. Later that year Harvard botanist Richard Evans Schultes, who also was then in Huautla, obtained specimens of three species of sacred mushrooms that were ultimately identified as *Psilocybe caerulescens*, *Panacolus campanulatus*, and *Stropharia cubensis*. Further investigations were then unfortunately interrupted by World War II.

The story picks up again in 1952, when banker and amateur mycologist R. Gordon Wasson and his wife Valentina Pavlovna Wasson received a letter with a journal article enclosed that quoted Richard Evans Schultes discussing the ritual use of mushrooms by Mesoamericans in the 16th century. Intrigued, Wasson then made several trips to Mexico in search of the mushrooms. On a trip to the town of Huautla de Jiménez in Oaxaca, Mexico, in June and July 1955, Wasson and New York society photographer Allan Richardson were allowed to participate in a mushroom ritual with Mazatec curandera Maria Sabina. Their trip was chronicled in a May 13, 1957 photo-essay in Life Magazine, "Seeking the Magic Mushroom." This article introduced psychoactive mushrooms to a wide audience for the first time. Later in 1957 the Wassons were accompanied on a follow-up expedition by French mycologist Roger Heim who identified several of the mushrooms as species of *Psilocybe*. Heim was able to cultivate the mushrooms in France and sent a 100 g sample of dried *Psilocybe mexicana* mushrooms for analysis to Albert Hofmann, the natural products chemist at Sandoz Pharmaceuticals who had discovered the effects of LSD in 1943. Animal bioassays were not useful because extracts of the mushrooms had no dramatic effect on the behavior of mice or dogs. Indeed, a subtle head twitch of mice in response to low dose hallucinogens was not characterized until 1967 [3]. Therefore, Hofmann ingested 2.4 g of the dried mushrooms to convince himself that the mushrooms were indeed active. Subsequently, whole extracts of the mushrooms were subjected to preparative paper chromatography to separate the various components. The paper chromatogram was cut into distinct bands that several colleagues volunteered to ingest, and in that way the active fraction was identified.

Having identified the active component, Hofmann proceeded to isolate a sufficient amount of material for chemical characterization, which he crystallized and named psilocybin [4]. Proof for the structure of psilocybin came with the total synthesis of the molecule [5]. Psilocybin (3-[2-(dimethylamino)-ethyl]-1H-indol-4-ol dihydrogen phosphate) MW 248.248, mp 224 °C, is a relatively stable, white crystalline, water soluble material [6], and actually can be recrystallized from boiling water. Baker et al. [7] later reported the x-ray crystal structure of psilocybin.

Hofmann also identified a minor component in the mushroom extract, dephosphorylated psilocybin, which Hofmann named psilocin ((3-[2-(dimethylamino)ethyl]-1H-indol-4-ol) MW 204.268, mp 174.5 °C; Fig. 1) In contrast to psilocybin, psilocin is not water soluble and slowly decomposes at room temperature.

Bioactive dose and molecular target

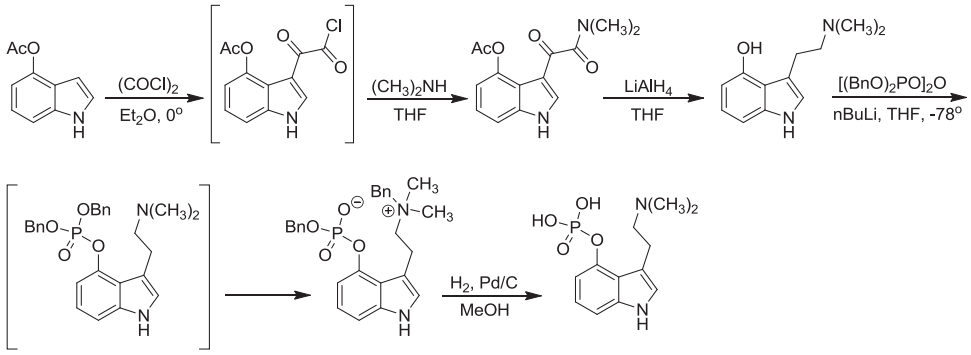
HPLC analysis of 20 species from seven genera of Pacific Northwest mushrooms found psilocybin in seven species from three genera. Total psilocybin and psilocin levels in species known to be used recreationally varied from 0.1% to nearly 2% by dry weight [8]. The medium oral dose of psilocybin is 4–8 mg, which elicits the same symptoms as the consumption of about 2 g of dried *Psilocybe Mexicana* [9]. The effects of psilocybin typically last from 2 to 6 h.

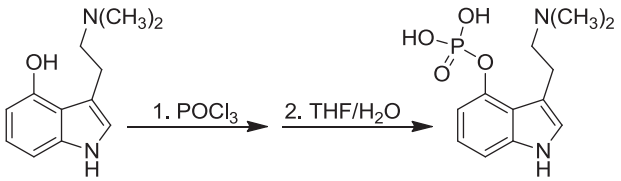
It is now known that after ingestion, psilocybin is rapidly dephosphorylated to psilocin. That is, psilocybin is essentially a prodrug for psilocin. Horita and Weber [10] first showed that dephosphorylation of psilocybin is readily accomplished by alkaline phosphatase, and proposed that psilocin is the actual active species in vivo. Horita [11] subsequently showed that behavioral effects of very large doses (100 mg/kg) of psilocybin in mice paralleled the increase in tissue concentrations of psilocin following psilocybin administration. Hasler et al. [12] later verified the rapid in vivo dephosphorylation of psilocybin to psilocin in humans. Psilocin, but not psilocybin, is an agonist at cortical serotonin 5-HT_{2A} receptors and it now is generally accepted that agonist activity at this receptor mediates the effect of psilocin and other psychedelics [13].

Chemical synthesis of psilocin and psilocybin

Hofmann's original synthesis [5] employed dibenzylphosphoryl chloride to introduce the phosphate group into psilocybin. This reagent, however, is hazardous and unstable and was replaced by tetrabenzylpyrophosphate [14]. This approach was subsequently improved and optimized [15, 16]. The synthetic method is outlined below in Scheme 1.

Scheme 1 Total chemical synthesis of psilocybin





Scheme 2 Modified synthesis of psilocybin from psilocin reported by Kargbo et al. [17] using phosphorous oxychloride as the phosphorylating agent

Subsequently, Kargbo et al. [17] developed an efficient synthesis utilizing a direct phosphorylation of psilocin with phosphorous oxychloride (Scheme 2). This facile method eliminates the need for tetrabenzylpyrophosphate as the phosphorylating reagent, as well as the subsequent hydrogenation step, and affords high yields of relatively pure psilocybin. This route was used to prepare 1.21 kg of cGMP material. Because of its simplicity and economy, this synthesis seems likely to become a route of choice for manufacture of psilocybin.

Biosynthesis of psilocybin

The biosynthetic events leading to psilocybin, with its unique 4-phosphoryloxy group at the indole 4-position, were first published in 1968, based on ^{14}C and ^{3}H radiotracer labeling [18, 19]. Recently, Fricke et al. [20] sequenced the genomes of *P. cubensis* and *P. cyanescens* and then used heterologously produced enzymes and 4-hydroxy-L-tryptophan as the substrate to reconstitute the biosynthetic pathway of psilocybin in vitro. They identified a new class of fungal L-tryptophan decarboxylases, and provided evidence that *N,N*-dimethylation is the final step in the biosynthesis. Their refined biosynthetic pathway for psilocybin is shown in Scheme 3 below.

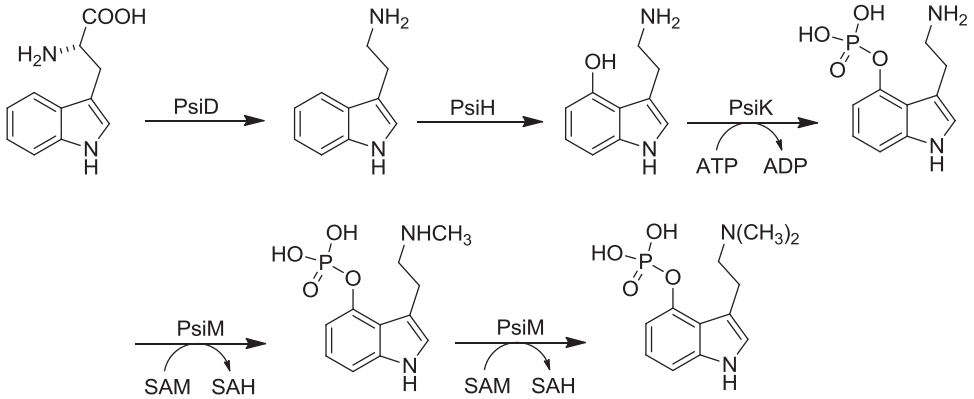
They characterized four psilocybin biosynthesis enzymes, namely PsiD, a new class of fungal L-tryptophan decarboxylase, PsiH, a monooxygenase, PsiK a kinase that catalyzes the phosphotransfer step, and the methyltransferase PsiM, catalyzing iterative N-methyl transfer as the terminal biosynthetic step. In a combined PsiD/PsiK/PsiM reaction, psilocybin was synthesized enzymatically in a step-economic route from 4-hydroxy-L-tryptophan. They indicate their results may lay the foundation for its biotechnological production.

Adams et al. [21] recently presented the development of a modular biosynthetic production platform in *Escherichia coli*. Efforts to optimize and improve pathway performance using multiple genetic optimization techniques were evaluated, resulting in a 32-fold improvement in psilocybin titer. Further enhancements to this genetically superior strain were achieved through fermentation optimization, ultimately resulting in a fed-batch fermentation study, with a production titer of 1.16 g/L of psilocybin, the highest psilocybin titer achieved to date from a recombinant organism and a significant step toward demonstrating the feasibility of industrial production of biologically-derived psilocybin.

Most recently, Fricke et al. [22] described the first combined chemical/biocatalytic synthesis of psilocybin. This "hybrid" synthesis of psilocybin involved treatment of chemically synthesized psilocin with heterologously produced *P. cubensis* PsiK. Their cell-free in vitro procedure combined the facile synthetic access to psilocin with side product-free quantitative conversion through PsiK-mediated biocatalysis in a final step; they produced one gram of psilocybin from psilocin within 20 min.

Clinical studies with psilocybin

Following the identification and synthesis of psilocybin, in 1960 Sandoz Pharmaceuticals began distributing tablets containing 2 mg of psilocybin under the trade name Indocybin™. Sandoz proposed it to be useful as a drug adjuvant to psychotherapy. From 1960 until 1980 there were more than 100 published literature reports about psilocybin that included anecdotal reports of human use, as well as analytical and biochemical studies. Unfortunately, there were no controlled clinical studies, and virtually nothing noteworthy of therapeutic value was reported.



Scheme 3 Biosynthesis of psilocybin as determined by Fricke et al. [20]

Since 1980, however, there have been about 200 published reports focused on various aspects of psilocybin pharmacology, chemistry, and biochemistry as well as careful studies in humans. Starting in 1996 and up to the present time, increasing numbers of reports have appeared of studies of the effects of psilocybin on human perception, emotion, and psychopharmacology. Among those are 112 reported studies of psilocybin in humans, including recent therapeutic trials in depression, anxiety, and substance use disorders. With the dramatic renewed interest in the therapeutic value of psilocybin, several randomized, placebo-controlled clinical studies meeting modern guidelines have been reported.

Moreno et al. [23] reported results of an open-label study administering psilocybin to nine subjects with obsessive-compulsive disorder (OCD). They found that psilocybin was safe in this population and was associated with acute reductions in core OCD symptoms in several subjects. A larger study with a better study design and more power is currently underway at Yale University.

Griffiths et al. [24] administered psilocybin to 30 healthy hallucinogen-naïve volunteers in a placebo-controlled randomized study. Psilocybin produced a range of acute perceptual changes, subjective experiences, and labile moods. Psilocybin also increased measures of mystical experience. At 2 months, the volunteers rated the psilocybin experience as having substantial personal meaning and spiritual significance and attributed to the experience sustained positive changes in attitudes and behavior consistent with changes rated by community observers. Participants also claimed they had increases in esthetic appreciation, imagination, and creativity. MacLean et al. [25] followed up this study with analysis of potential changes in personality and found significant increases in the personality trait of openness. Openness remained significantly higher than baseline for more than 1 year after the session. Their findings suggest a specific role for psilocybin and mystical-type experiences in adult personality change.

The first trial of psilocybin with clear evidence for a therapeutic effect was reported by Grob et al. [26]. This study enrolled 12 adults with advanced-stage cancer and anxiety in a placebo-controlled design and administered a moderate dose of (0.2 mg/kg) psilocybin. Follow-up data included results from the Beck Depression Inventory, Profile of Mood States, and State-Trait Anxiety Inventory, which were collected unblinded for 6 months after treatment. There were no clinically significant adverse events with psilocybin. The State-Trait Anxiety Inventory trait anxiety subscale demonstrated a significant reduction in anxiety at 1 and 3 months after treatment. The Beck Depression Inventory revealed an improvement of mood that reached significance at 6 months; the Profile of Mood States identified mood improvement after treatment with psilocybin that approached but did not reach significance. This study established the feasibility and safety of administering moderate doses of psilocybin to patients with advanced-stage cancer and anxiety.

The next therapeutic trial was reported by Johnson et al. [27]. These investigators conducted an open-label pilot study administering 20 mg/70 kg or 30 mg/70 kg oral doses of psilocybin within a structured 15-week smoking cessation treatment protocol. Participants were 15 psychiatrically healthy nicotine-dependent smokers with a mean of six previous lifetime quit attempts and smoking a mean of 19 cigarettes per day for a mean of 31 years at intake. In total, 12 of 15 participants (80%) showed 7-day point prevalence abstinence at 6-month follow-up. Their findings suggest psilocybin may be a potentially efficacious adjunct to current smoking cessation treatment models, and this study has been expanded and is currently underway at Johns Hopkins University.

Another addiction trial was subsequently reported by Bogenschutz et al. [28]. They examined the possibility that psilocybin-assisted psychotherapy could be beneficial in alcohol use disorder. Ten volunteers with DSM-IV alcohol dependence were administered oral psilocybin in one or two supervised sessions coupled with Motivational Enhancement Therapy. The study included a placebo control. Abstinence did not increase significantly in the first 4 weeks

of treatment (before participants had received psilocybin) but increased significantly following psilocybin administration. Gains were largely maintained at 36-week follow-up. The intensity of effects in the first psilocybin session strongly predicted change in drinking during weeks 5–8 and predicted decreases in craving and increases in abstinence self-efficacy during week 5. There were no significant treatment-related adverse events. These preliminary findings provided a strong rationale for controlled trials with larger samples to investigate efficacy and mechanisms; such an expanded trial is currently underway at New York University.

The most widely cited studies of psilocybin-assisted therapy were reported in December 2016 and involved psilocybin-assisted treatment of cancer patients. One of these, by Griffiths et al. [29], was a randomized, double-blind, crossover trial of the effects of psilocybin-assisted psychotherapy in 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. A very low (placebo-like) (1 or 3 mg/70 kg dose) vs. a high (22 or 30 mg/70 kg) dose of psilocybin was administered in counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up. Participants, staff, and community observers rated participant moods, attitudes, and behaviors throughout the study. The high-dose psilocybin produced large and significant decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety. At 6-month follow-up, these changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety. Mystical-type psilocybin experience on the session day appeared to mediate the effect of psilocybin on therapeutic outcomes.

The second study of cancer patients was reported by Ross et al. [30] and was a double-blind, placebo-controlled, crossover trial of 29 patients with cancer-related anxiety and depression. Patients were randomly assigned and received treatment with single-dose psilocybin (0.3 mg/kg) or niacin, both in conjunction with psychotherapy. The primary outcomes were anxiety and depression assessed between groups prior to the crossover at 7 weeks. Prior to the crossover, psilocybin produced rapid, robust, and enduring anxiolytic and antidepressant effects in patients with cancer-related psychological distress. Psilocybin led to decreases in cancer-related demoralization and hopelessness, improved spiritual wellbeing, and increased quality of life. At the 6.5-month follow-up, ~60–80% of participants continued with clinically significant reductions in depression or anxiety, sustained benefits in existential distress and quality of life, as well as improved attitudes toward death. The psilocybin-induced mystical experience mediated the therapeutic effect of psilocybin on anxiety and depression.

In late 2018, the FDA gave "breakthrough therapy" status to a psilocybin treatment developed by London-based Compass Pathways Ltd. for treatment-resistant depression, expediting the development process (https://compasspathways.com/our-research/#about-psilocybin-therapy). Subsequently, the FDA also approved breakthrough therapy status to psilocybin treatment for major depressive disorder (MDD) in trials sponsored by the Usona Institute (https://www.usonainstitute.org/research/).

Mechanism of action

It is now accepted that the brain target for psilocin is the serotonin 5-HT_{2A} receptor, which is densely expressed on apical dendrites of cortical pyramidal cells where psilocin is an agonist (see review by Nichols [13]). Modern brain imaging studies of brain states after administration of psilocybin have been particularly interesting and have revealed changes in brain dynamics induced by this and related drugs. Vollenweider et al. [31] investigated the effects of oral psilocybin on regional cerebral glucose metabolism in ten healthy volunteers using positron emission tomography (PET) and [^{18}F]-fluorodeoxyglucose (FDG) prior to and following a 15- or 20-mg dose of psilocybin. They found that psilocybin produced a global increase in cerebral metabolic rate of glucose (CMRglu) with significant and most marked increases in the frontomedial and frontolateral cortex, anterior cingulate, and temporomedial cortex. Somewhat smaller increases of CMRglu were found in the basal ganglia, and the smallest increases were found in the sensorimotor and occipital cortex. The increases of CMRglu in the prefrontal cortex, anterior cingulate, temporomedial cortex, and putamen correlated positively with hallucinatory "ego disintegration." Their data suggest that 5-HT_{2A} receptor activation results in a hyperfrontal metabolic pattern that parallels comparable metabolic findings associated with acute psychotic episodes in chronic schizophrenics.

Similarly, Gouzoulis-Mayfrank et al. [32] investigated the neurometabolic effects of orally-administered psilocybin (0.2 mg/kg), with a prefrontal activation task in a double-blind, placebo-controlled human FDG-positron emission tomographic PET study (each group: $n = 8$). Subjects underwent two scans (control: word repetition; activation word association) within 2–4 weeks. Psilocybin increased MRGlu in distinct right hemispheric frontotemporal cortical regions, particularly in the anterior cingulate and decreased MRGlu in the thalamus. Cognitive activation-related increases in left frontocortical regions were attenuated after psilocybin. Both of these studies indicate that psilocybin leads to a general cortical activation.

Analysis of human brain connectivity using modern imaging methods has identified sets of regions that are

essential for enabling efficient neuronal signaling and communication. These "brain hubs" are centrally embedded within anatomical networks and participate in functional roles across a range of cognitive and affective tasks with widespread dynamic coupling within and across functional networks. Data from numerous empirical and computational studies support the idea that brain hubs are crucial for integrating information that serves as the basis for various aspects of complex cognitive function.

A variety of imaging studies have now shown that psilocybin produces marked alterations in brain network connectivity during the time of drug action. Carhart-Harris et al. [33] used arterial spin labeling (ASL) perfusion and blood-oxygen level-dependent (BOLD) fMRI to map cerebral blood flow and changes in venous oxygenation before and after intravenous infusions of placebo and psilocybin. A total of 15 healthy volunteers were scanned with ASL and a separate cohort of 15 with BOLD. They were surprised to find only decreases in cerebral blood flow and BOLD signal, which were maximal in hub regions such as the thalamus and anterior and posterior cingulate cortex (ACC and PCC). Decreased activity in the ACC/medial prefrontal cortex (mPFC) was a consistent finding and the magnitude of this decrease predicted the intensity of the subjective effects. Based on these results, a seed-based pharmacophysiological interaction/functional connectivity analysis was performed using a medial prefrontal seed. Psilocybin caused a significant decrease in the positive coupling between the mPFC and PCC. Their results indicate that the subjective effects of psilocybin are caused by decreased activity and connectivity in the brain's key connector hubs, enabling a state of unconstrained cognition.

Although the earlier psilocybin PET research suggested regional increases in glucose metabolism in frontal cortex (hyperfrontality) the ASL study by Carhart-Harris et al. [33] suggested that psilocybin led to hypoperfusion in various brain regions. Lewis et al. [34], however, more recently reported on a placebo-controlled, double-blind study using pseudo-continuous ASL to measure perfusion changes, with and without adjustment for global brain perfusion, after two doses of oral psilocybin (low dose: 0.160 mg/kg; high dose: 0.215 mg/kg) in two groups of healthy controls ($n = 29$ in both groups, total $n = 58$) during rest. After adjusting for global brain perfusion, they found that psilocybin *increased* relative perfusion in distinct right hemispheric frontal and temporal regions and bilaterally in the anterior insula and decreased perfusion in left hemispheric parietal and temporal cortices and left subcortical regions. Psilocybin significantly reduced absolute perfusion in frontal, temporal, parietal, and occipital lobes, and bilateral amygdala, anterior cingulate, insula, striatal regions, and hippocampi. Their analyses were consistent with both the hyperfrontal hypothesis of psilocybin and the more recent study demonstrating decreased perfusion, depending on analysis method. Importantly, these data illustrate that relative changes in perfusion should be understood and interpreted in relation to absolute signal variations.

Muthukumaraswamy et al. [35] recorded spontaneous and induced oscillatory activity in healthy human participants with magnetoencephalography after intravenous infusion of psilocybin. Psilocybin reduced spontaneous cortical oscillatory power from 1 to 50 Hz in posterior association cortices, and from 8 to 100 Hz in frontal association cortices. Large decreases in oscillatory power were seen in areas of the default-mode network (DMN). Independent component analysis was used to identify a number of resting-state networks, and their activity was similarly decreased after psilocybin. Psilocybin had no effect on low-level visually induced and motor-induced gamma-band oscillations, suggesting that some basic elements of oscillatory brain activity are relatively preserved during the psychedelic experience. Dynamic causal modeling revealed that posterior cingulate cortex desynchronization can be explained by increased excitability of deep-layer pyramidal neurons, which are known to be rich in 5-HT_{2A} receptors. Their findings suggest that the subjective effects of psychedelics result from a desynchronization of ongoing oscillatory rhythms in the cortex, likely triggered by 5-HT_{2A} receptor-mediated excitation of deep pyramidal cells.

This mechanistic conclusion is buttressed by earlier results from a study by Beique et al. [36] who had identified a subset of deep pyramidal cells in layer V of the prefrontal cortex that was directly depolarized by 5-HT_{2A} receptor activation in rat brain slices. Martin and Nichols [37] recently used a novel fluorescence-activated cell sorting methodology to segregate and enrich specific cellular subtypes in the brain following treatment with a psychedelic phenethylamine. They also provided evidence that a small subset of 5-HT_{2A}-expressing excitatory neurons in deep pyramidal cells of the cortex is directly activated by psychedelics and subsequently recruits other select cell types including subpopulations of inhibitory somatostatin and parvalbumin GABAergic interneurons, as well as astrocytes, to produce distinct and regional responses.

In studies with psilocybin, Carhart-Harris et al. [33, 38] reported that psilocybin led to decreased connectivity within a key brain network known as the DMN. Using BOLD fMRI they observed decreased activity in the PCC, one of the key hubs of the DMN. Psilocybin also caused decreased activity in the mPFC, an interesting finding because increased activity and connectivity within this region of the DMN has been shown in individuals with depression. Hence, the ability of psilocybin to decrease activity in the DMN may be relevant to its antidepressant effects. They

conclude that psychedelics reduce the stability and integrity of well-established brain networks, and simultaneously reduce the degree of segregation between them. Psychedelic-induced alteration in brain connectivity is characterized by a synchronization of sensory functional networks and disintegration of associative networks. That is, psychedelics lead to a brain state where there is a greater repertoire of connectivity motifs that form and fragment over time. Psychedelics do not simply make the brain more random, but rather after the normal organization is disrupted, strong, topologically long-range functional connections emerge that are not present in the normal state [39].

There may be long-term changes in brain functioning after a single administration of psilocybin. For example, psilocybin leads to enduring changes in affect and neural correlates of affect. Barrett et al. [40] found that 1-week post-psilocybin, negative affect and amygdala response to facial affect stimuli were reduced, whereas positive affect and dorsal lateral prefrontal and medial orbitofrontal cortex responses to emotionally conflicting stimuli were increased. A 1-month post-psilocybin, negative affective and amygdala response to facial affect stimuli returned to baseline levels while positive affect remained elevated, and trait anxiety was reduced. Finally, the number of significant resting-state functional connections across the brain increased from baseline to one-week and one-month post-psilocybin.

Conclusions

In the past 10–15 years several FDA-approved clinical studies have indicated potential therapeutic value for psilocybin in treating end of life distress, depression, anxiety, and certain addictions. From its relatively unknown status up until the mid-1950s, it has become a major focus of research interest in what has been called a "renaissance in psychedelic research." Recently, the FDA has given psilocybin a Breakthrough Therapy Designation for treating MDD and treatment-resistant depression. Assuming that the early clinical work can be validated by larger studies, psilocybin is poised to make a significant impact on treatments available to psychiatric medicine. It seems possible that at some point in the future psilocybin will become a name as familiar as penicillin!

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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