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A review of psilocybin: chemistry, clinical uses and future research directions

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ABSTRACT

Classic psychedelics such as psilocybin, ketamine and lysergic acid diethylamide (LSD) are $5HT_{2A}$ serotonin receptor agonists that produce individualised subjective affects. Today, public interest in psychedelic medicine has reached a fervour but the evidence for clinical benefit still lags. Psilocybin and psilocin are tryptophan based alkaloids found worldwide in mushrooms of the genera *Psilocybe, Panaeolus, Conocybe, Gymnopilus, Stropharia, Pluteus* and *Panaeolina.* This review addresses the current evidence base for psilocybin as a clinical medicine, the general chemistry and proposed mechanism of its therapeutic effect and future research directions for psilocybin based therapies.

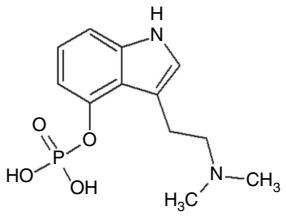
Keywords: addiction, altered protein expression, anxiety, brain-derived neurotrophic factor release, depression, executive network inhibition, network reorganisation, psilocybin as clinical medicine, $5HT_{2A}$ receptor agonism, sodium dependent serotonin transporter inhibition.

Introduction

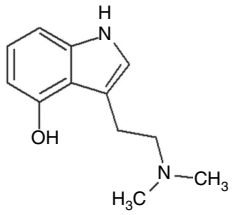
Classic psychedelics such as psilocybin, ketamine and lysergic acid diethylamide (LSD) are $5HT_{2A}$ serotonin receptor agonists that produce individualised subjective affects.[1–3] In 1799 the English *Medical and Physical Journal* reported the case of a well-meaning father who served his unsuspecting family *Psilocybe semilanceata* for dinner, this is the earliest official report of the species' hallucinogenic potential. It wasn't until 1958 that Albert Hofmann first isolated the active substances in psychoactive fungi. Today, public interest in psychedelic medicine has reached a fervour but the evidence for clinical benefit still lags behind.

Psilocybin and psilocin are tryptophan indole-based alkaloids found worldwide in mushrooms of the genera *Psilocybe, Panaeolus, Conocybe, Gymnopilus, Stropharia, Pluteus* and *Panaeolina.* Post ingestion, psilocybin is dephosphorylated via alkaline phosphatase in the gastrointestinal tract to the active compound psilocin 5′-diphospho-glucuronosyltransferase.[4,5] Psilocybin is not the active substance but rather the prodrug of psilocin, which can cross the blood brain barrier and is responsible for the drug's observed effects. An extended elimination phase in some subjects suggests hydrolysis of the psilocin glucuronide metabolite psilocin-O-glucuronide to reform psilocin, thus the multiple organ sites that have beta-glucuronidase activity can cleave glucuronide to reform active psilocin. Both psilocybin and psilocin are tryptamines; an indole with two carbon side chains at the 3-position terminated by an amino group. Naturally occurring tryptamines are known to affect intracellular signalling. Psilocin is structurally like the human neurotransmitter serotonin and undergoes similar metabolism.[6]

Psilocybin is rarely lethal but transient adverse effects are common with intoxication. These range from mild, such as headache, relative hypertension and tachycardia and anxiety, to potentially severe including panic attacks, derealisation, seizures, confusion and renal injury. Environmental factors such as emotional state and sensory environment (set and setting) are widely recognised as moderating the effects of psilocybin.[7] Psilocin may also have pro-arrhythmic potential. Concentrations higher than 31.1 ng mL^{-1} (dose of 0.3–0.6 mg kg^{-1}) show a QT prolongation on screening electrocardiogram 10 ms.[4]



Psilocybin
(3-[2-(dimethylamino)ethyl]-1*H*-indol-4-yl dihydrogen phosphate)



Psilocin
(3-[2-(dimethylamino)ethyl]-1*H*-indol-4-ol)

Fig. 1. Chemical structures of psilocybin and psilocin.

A lethal dose in animal studies is around 293 mg kg^{-1}, but absorbing enough psilocybin in raw mushroom product to cause death is unlikely given the large amounts of emetogenic chitin in wild mushroom species (Fig. 1).[8]

Current evidence for clinical benefit of psilocybin/psilocin

Clinical trial data is limited but preliminary studies of the therapeutic potential of psilocybin (and other psychedelics) are promising. There are several theories as to how benefit is achieved but improvement in conditions such as depression, anxiety and addiction seem to be linked to neuroplasticity, leading some researchers to rename psychedelics 'psychoplastogens' defined as 'compounds with the ability to rewire neural circuitry by engaging plasticity mechanisms'.[9] Studies of psilocybin in healthy volunteers have shown increases in positive or prosocial personality traits such as openness and extraversion and mindfulness, with these changes potentially persisting for months after ingestion.[10–12]

Studies of the effect of psilocybin on depression and other stress related neuropsychiatric disorders have seen positive results. A phase II randomised control trial (RCT) compared psilocybin with escitalopram. In this small study of 59 patients, psilocybin improved reported depression symptoms slightly more effectively than escitalopram with an improvement of 2.0 on a depression rating scale with a confidence interval of −0.5 to 0.9 and had a range of benefits over selective serotonin reuptake inhibitors (SSRIs) in secondary analysis (although the study was underpowered to draw conclusions on secondary variables).[13] This study represents the first adequately powered head-to-head RCT comparing psilocybin to traditional depression therapy. More recently another phase II double blind placebo-controlled trial randomised 233 individuals to receive 25 mg, 10 mg or 1 mg of psilocybin (control group). The investigators found a statistically significant improvement in depression assessment tool scores for the 25 mg group in comparison to the 1 mg group. However, adverse event incidence approached 77%, with headache, nausea and dizziness most reported. Other studies, including an 8 week open label trial of psilocybin versus control, have shown similar results but were underpowered.[13–15] A meta-analysis demonstrated clinical benefit of psilocybin for major depression and found large reductions of reported anxiety and depressive symptoms. Additionally, the authors of the meta-analysis did not discover evidence of publication bias, suggesting the benefits of psilocybin are not being overstated.[15]

Regardless, these studies have been limited by small cohort sizes and lack of placebo control, important as much of the antidepressant literature shows minimal benefit over placebo. Psychedelic studies are almost impossible to blind. Although placebos such as dexamphetamine or high dose niacin are given to suggest an active substance, it is quite easy to tell if a participant has received a full dose of psilocybin (for both the participant and the researcher). Additionally, social and cultural pressure to interpret positive outcomes may be a factor. Most of the trials to date can only be interpreted as pilot or Phase I data, although there is more than enough evidence to support the need for larger clinical trials as soon as possible.

Addiction is often a concern in the repurposing of illegal or 'recreational' drugs but notably psilocybin has not been noted to induce either dependence or addiction and prolonged use is empirically uncommon. Nevertheless, consistent use can induce tolerance.[5] Tachyphylaxis is seen with most hallucinogens due to $5HT_{2A}$ receptor down regulation, which returns to baseline levels within 1–4 weeks post cessation. Although this is not an issue in two-dose protocols it may be an issue for microdosing; a controversial practice in which low-dose psychedelic substances are taken daily for the treatment of various mental health conditions.[8,16] There is also a question as to whether chronic use of psilocybin could increase risk of valvular heart disease as has been shown with other serotonergic agents.[17]

Issues with language in research methodology

Studies to date have frequently used subjective terms such as 'religious' or 'spiritual' in the description of psilocybin's effect.[3,10] However, psychological and cognitive changes are divorced from any specific religion, meditation practice or culture. A better characterisation may be 'insight experience' to describe a state in which unhelpful psychological narratives or limiting conceptions of personal identity can be dispelled. It may be found that other drugs or

interventions such as meditation practices or 12-step programs are similarly capable of engendering a psychologically helpful insight experience.

Mechanism of antidepressant effect

Serotonergic effects

Psilocin is an agonist or partial agonist for almost a dozen neuronal receptors. Its overall effect has similar neurochemical properties to SSRI and serotonin and norepinephrine reuptake inhibitor (SNRI) medications.[18] Postulated antidepressant effects of psilocybin are summarised in Table 1. The serotonergic effect of psilocybin occurs via inhibition of the sodium-dependent serotonin transporter (SERT), which leads to decreased serotonin reuptake. However, hallucinogenic and euphoric serotonergic effects seem to be most related to $5HT_{2A}$ serotonin receptor agonism, which is associated with general neuronal excitation, enhanced memory and learning, bronchial and gastric smooth muscle contraction and release of oxytocin, prolactin, adrenocorticotropic hormones and renin.[2,8,18,19] Metabolic activity is altered in key regions of the brain implicated in the pathogenesis of depression and anxiety such as the amygdala, the hippocampus, the pre-frontal cortex and the default mode network. This altered metabolism seems to foster new neural pathways and unique neuronal 'cross-talk', which could also be described as increased neuroplasticity.[9,19,20] The therapeutic effect of conventional antidepressants is also thought to be at least partly due to restoration and enhancement of neuroplasticity.[19] There is persuasive evidence to suggest that modulation of the serotonergic system (including serotonin release and downstream gene expression alteration) mediated by $5HT_{2A}$ receptor agonism is significant to psilocybin's beneficial effects.[18] It is less clear what role interaction with lower affinity neuronal receptors (not $5HT_{2A}$) plays. Psilocin increases levels of glutamate in the pre-frontal cortex, which has been associated with negative experiences of ego-dissolution or deconstruction of personal conceptions of fixed identity.[21] Conversely decreased glutamate release in the hippocampus was associated with positive perceptions of ego-dissolution.[21] Studies have suggested that hallucinogenic or 'trip' intensity has a dose response relationship with the strength and longevity of clinical effect.[21] Notably, $5HT_{2A}$ receptor agonism also inhibits IL-6 and TNF-α.[18] Possibly significant as elevated markers or inflammation have been implicated in major depressive disorder, either with inflammation as a causative factor or as marker of disease state (Fig. 2).

Table 1. Postulated mechanisms of psilocybin's benefit for mental health diagnoses (depression/anxiety/substance misuse disorders).

$5HT_{2A}$ receptor agonism
• (serotonergic)
Sodium-dependent serotonin transporter inhibition
• (prevention of serotonin reuptake).
$5HT_{2A}$ mediated modification of downstream serotonin system gene expression
Acute inhibition of executive/default mode neural networks. Network reorganisation (neuroplasticity).
Stimulation of brain-derived neurotrophic factor release

Brain derived neurotrophic factor

Some researchers have suggested that the most important mechanism for the treatment of stress-related neuropsychiatric disorders such as depression is induction of brain-derived neurotrophic factor (BDNF). It has been suggested that BDNF serves as a 'transducer' acting as a link between the antidepressant drug and the downstream neurophysiological changes that manifest as an improvement in depressive symptoms.[22] It has been shown that infusion of BDNF into the ventricles or directly into the hippocampus is sufficient to induce a relatively rapid antidepressant-like effect. In mice who have had BDNF signalling genetically reduced, conventional antidepressants are less effective. The rapid effect of ketamine on depression is also postulated to be due to BDNF signalling.[22]

It has been theorised that psilocin binding to serotonin receptors may engender greater downstream BDNF expression.[18] This is supported by the knowledge that $5HT_{2A}$ receptor binding causes glutaminergic medication of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (*N*-methyl-D-aspartate) receptors, the consequence of which is increased BDNF. Glutaminergic NMDA receptor and BDNF expression is also the proposed antidepressant mechanism of ketamine, another psychedelic agent. This suggests the effect of psilocybin may be similar.

Network reorganisation

Even in a resting state the brain is organised into networks. The activity within these networks correlates with personality traits including perception of lived experience and the ego.[23]

During the psychedelic experience, psilocybin produces a reduction in the activity of the default-mode network.[20,21,23] Functional magnetic resonance imaging has shown that, 1 week after administration of psilocybin, resting-state functional connectivity (RSFC) is altered. However, RSFC changes in brain activity do not persist on repeat imaging at 3 months post-dose.[23] The altered activity was focally located in $5HT_{2A}$ receptors in the neocortex, pointing to dis-integration of the default mode network. Additionally, Carhart-Harris *et al.* reported that psilocybin decreased cerebral blood flow and venous oxygenation to

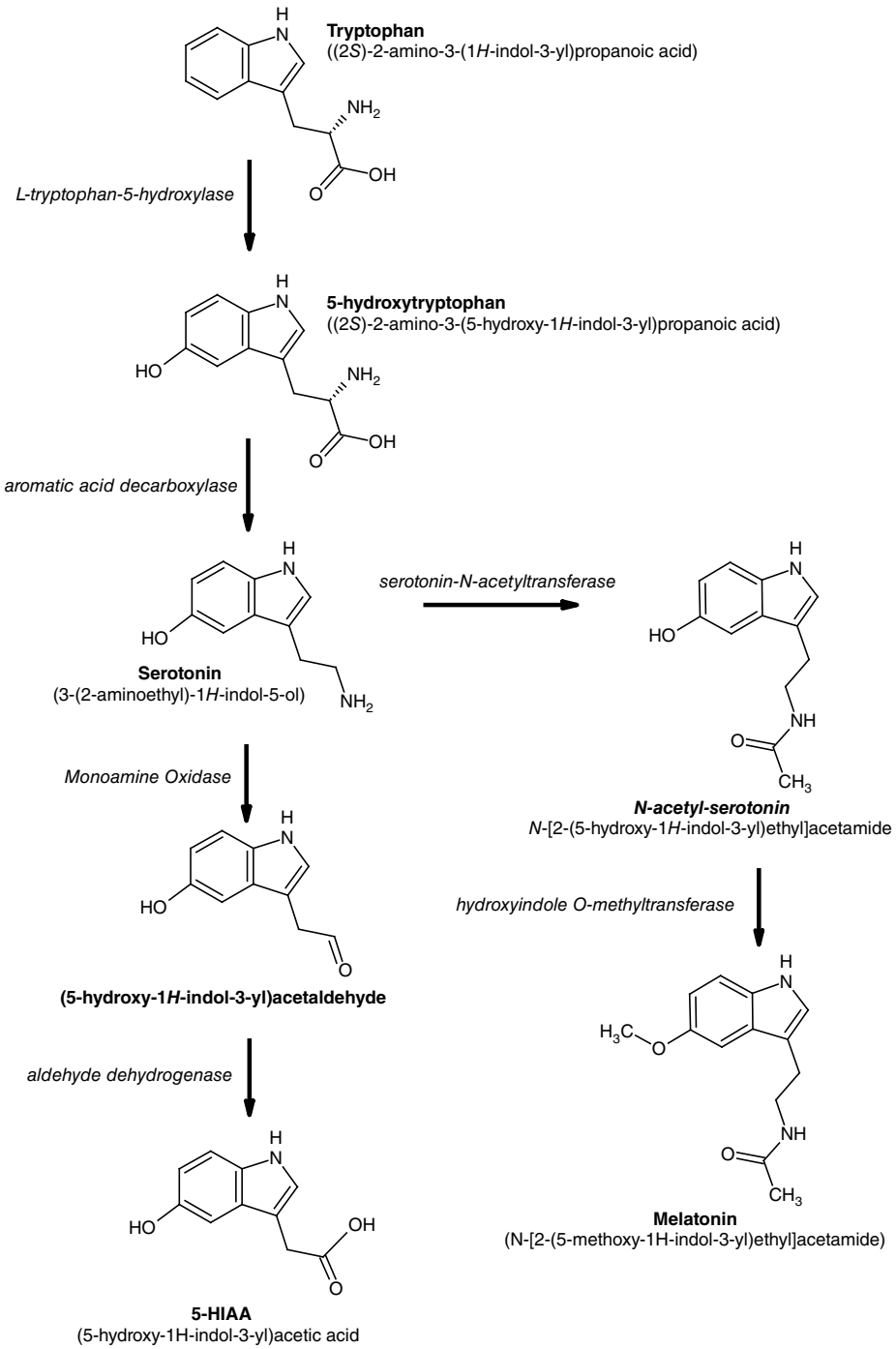


Fig. 2. Serotonin biochemical pathway.

the ventral medial prefrontal cortex (vmPFC), thalamus, as well as anterior and posterior cingulate cortices (ACC) immediately following intravenous infusion.[20] Decreased blood flow in the aforementioned regions is correlated with decreased activity and as such implies decreased functional connectivity. In addition, cerebral blood flow to the thalamus and ACC was found to be positively correlated with the intensity of the psychedelic experience at a dose of 2 mg intravenously administered. Notably intensity of psychedelic experience is variable between individuals with standardised dosing. For comparison, doses used in most RCTs are 25 mg oral dose.[24]

Alterations in the executive control network connectivity are postulated to underpin the therapeutic effects of psilocybin.[23] This has been described as 'chemically induced cognitive behavioural therapy'. Reduced network activity is likely to be related to why psilocybin has been showing promising application in behaviour control disorders such as obsessive-compulsive disorder and substance dependence disorders.[25]

Bioassay and therapeutic drug monitoring

Bioassays of psilocybin have mostly been used in a forensic context to prosecute illegal use or verify if psychedelic use was a contributing factor in an accident or death.[26] With the legalisation of psilocybin in several countries and growing application of psychedelic-assisted psychotherapy, bioassays are now being developed for pharmacokinetic and other clinical research.

The presence of psilocin in body fluid can be verified by high performance liquid chromatography mass spectrometry (HPLC-MS) assay. The main metabolites of psilocybin in human plasma are psilocin and 4-hydroxyindole-3-acetic acid (4-HIAA). Kolaczynska *et al.* published a method for plasma bioassay using methanol precipitation and a C18 analytical column. The authors validated stability of the molecule to three thaw and refreezing cycles with a benchtop longevity of 8 h or 1 month at −20°C without degradation. L-Ascorbic acid is needed for stabilisation of the psilocin molecule in solution. All classic psychedelics carry a 58 Dalton *N*,*N*-dimethyltryptamine tail identifiable on HPLC-MS.[27]

Future clinical directions

Recent developments

A randomised control trial on the use of psychedelic assisted therapy (PAT) for generalised anxiety disorder is underway at Monash University Australia.[28] Microdosing is the practice of taking sub-hallucinogenic doses of psychedelic medicines on a sometimes daily basis, as with a traditional serotonergic antidepressant. Microdosing has some biological plausibility as a regular use antidepressant due to the serotonergic effects, BDNF modulation and SERT modification described above. A case report of psilocybin microdosing for depression resistant to traditional antidepressants and electroconvulsive therapy showed improvements on the Hamilton Depression Rating.[29] However, a double-blind placebo controlled trial showed no modulation compared to placebo in emotional symptoms. Qualitative questionnaires in this study only assessed participants after the second and seventh microdose. As SSRI/SNRIs take several weeks to work, this study may have been confounded by a short lead time in measure of effect.[30] Conversely, a survey of over 6000 people who regularly practice psilocybin or LSD microdosing reported enhanced 'mood, creativity and sociability'.[31] This contrasts with literature describing the therapeutic effect as correlated to intensity of psychedelic experience.[9,18]

Issues affecting interpretation of research findings

Although the early data on psilocybin and other psychedelics for the treatment of significant mental health disorders tends to show not much clinical difference from placebo or existing antidepressant therapies, controlled and randomised trials that systematise variables such as 'set and setting', dose, time points and administered psychological therapy are needed in larger cohort numbers to reach statistical significance and support interpretation of the data. Set and setting too, whilst being universally recognised as of the utmost importance in psychedelic work, are primarily based around conventions of comfort, music, lighting and interaction and have not yet found clear scientific foundation nor the consistency or rigour expected for clinical trial endpoints. Problematic terms like 'spiritual' are often used to discuss the subjectively positive outcomes of these conventional experiences. The authors suggest 'insight' or 'contemplation' experience would be better terms which would also be applicable to a broader context of psychedelic use.

Conclusion

The field of psychedelics is an interesting one, particularly for resistant depression, However significantly greater clinical research including dosing, comparison with placebo and current best practice is needed before a general clinical application can be established. Biological plausibility for antidepressant and anxiolytic effect exists given the described serotonergic and BDNF effects of psilocybin, however, caution is urged noting that such excitement was seen with the introduction of SSRIs and SNRIs. Larger and more rigorous clinical trials are likely to yield valuable data in the near future.

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