Chapter 73

Neurobiology of the Effects of Psilocybin in Relation to Its Potential Therapeutic Targets

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INTRODUCTION

Characteristics of Psilocybin and Its Position Among Other Hallucinogens

Psilocybin is the main psychoactive substance contained in many species of hallucinogenic mushrooms (Figure 1) (genera *Psilocybe, Conocybe, Copelandia, Panaeolus, Indocybe,* etc.) (Tyls, Palenicek, & Horacek, 2014). Due to the wide distribution of psilocybin-containing mushrooms around the world, it is probably the most widely used natural hallucinogen in the world (Stafford, 1992).

Ritual use of *teonanácatl* (indigenous name for psilocybin mushrooms) by some indigenous tribes of Latin America is a conventional practice even today (Metzner, 2005). The main purposes for using sacred mushrooms in these cultures have been to gain knowledge (spiritual development) and to heal (Stafford, 1992). Ancient shamans used divine mushrooms for the induction of visions and trance states, which enabled individuals to transform their thoughts and to get a new view of the disease (Metzner, 2005). The ceremonies are examples of a long tradition of using so-called altered state of consciousness in therapy and can be inspirational for modern approaches. Trance states induced during shamanistic rituals resemble dream states or acute psychosis.

The increasing number of research papers on psilocybin published within the last decade (Figure 2) (Tyls et al., 2014) reflects the interest of the scientific community in understanding the neurobiology of psychedelic effects as well as the therapeutic value of psilocybin (Halberstadt, 2015). The methodology of psychedelic research has improved greatly, including the drafting of guidelines for hallucinogen use in human studies (Johnson, Richards, & Griffiths, 2008). New double-blind controlled studies have emerged, suggesting long-term positive subjective effects of psilocybin and thus proving earlier, methodically weaker, observations (Tyls et al., 2014).

Chemically, psilocybin is one of the indolalkylamine hallucinogens with high affinity to serotonin 5-hydroxytryptamine (5-HT) receptors (Halberstadt, 2015). When administered to humans, psilocybin has moderate effects on physiological functions (mild sympathomimetic effect, alterations in blood hormone levels, hyperreflexia) (Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004; Tyls et al., 2014). The most notable sign of psilocybin intoxication are marked psychological changes—the so-called altered state of consciousness (ASC). The degree of psychological alteration is dose-dependent (for dose–symptoms correlation see (Stebelska, 2013; Tyls et al., 2014)). It is characterized by changes of perception (both of the self and of the external world), thought, and mood (increased range of intense emotions). An intermediate dose of psilocybin (0.2 mg/kg) also induced increases in the experience of unity, spiritual experience, blissful state, insightfulness, disembodiment, elementary and complex imagery, audio-visual synesthesia, and changed meaning of percepts (Halberstadt, 2015).

Psilocybin itself has a very low toxicity; complications associated with its use have been reported only rarely. One recent review showed psilocybin-induced cardiovascular and cerebral damage (Stebelska, 2013); however, all cited case reports in this review were linked to the use of mushrooms, where commutation with other fungi containing possibly more toxic substances might be a confounding factor. In a commentary to this article, dos Santos (2014) concluded that the adverse effects of psilocybin were

FIGURE 1 **Psilocybe cubensis—Thai.** The figure shows hallucinogenic mushrooms *Psilocybe cubensis* (Thai type) artificially cultivated indoors. *Photograph from author's collection.*

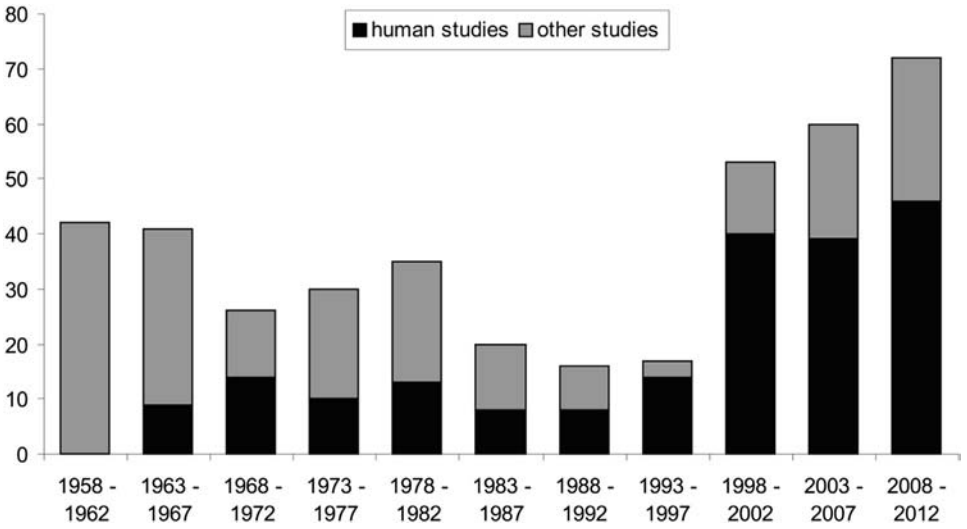

FIGURE 2 **Publications dealing with psilocybin.** The graph shows the number of publications dealing with psilocybin/psilocin (y axis) in 5-year intervals (x axis) from the year of its synthesis. Human studies are indicated in black, and other studies in gray. *Data obtained from PubMed dated 06/02/2013; advanced search criteria were "psilocybin" [Title/Abstract] OR "psilocin" [Title/Abstract] and Date "YYYY–YYYY" [Date—Publication]; for human studies, the relevant selection box was checked). Diagram reproduced from Tyls et al. (2014) with the permission of European Neuropsychopharmacology.*

overrated. In addition, psilocybin reportedly does not induce long-term memory impairment, delirium, or addiction (Halberstadt, 2015; Tyls et al., 2014)—on the contrary, it has actually been reported to have beneficial effects on human well-being (Griffiths, Richards, McCann, & Jesse, 2006). Finally, the ratio of lethal dose to psychoactive dose for psilocybin was estimated to be 1000:1 (Gable, 2006).

Detailed chemical, structural, pharmacokinetic, and pharmacodynamic characteristics were reviewed elsewhere (Stebelska, 2013). Phenomenology of intoxication is similar for all serotonergic hallucinogens; however, it is clearly distinguishable from intoxication with other psychedelics, e.g., dissociative anesthetics (ketamine), entactogens (MDMA), or phytocanabinoids (Halberstadt, 2015). During the 1960s, most of the clinical studies with psilocybin were performed using synthetic Indocybin® manufactured by Sandoz (Passie, Seifert, Schneider, & Emrich, 2002) (Figure 3).

Applications to Other Addictions and Substance Misuse

Psychedelic mushrooms became a popular recreational drug during the hippie cultural revolution of the late 1960s, due to their "natural" origin (unlike the synthetic LSD). As the abundant distribution of psilocybin-containing mushrooms was largely unknown at this time, users as well as researchers made successful attempts to cultivate them artificially (e.g., (Oss & Oeric, 1991), Figure 1). Even though psychedelic mushroom harvesting is popular in many countries worldwide these days, cultivation is still popular as well. Today it is also easy to obtain many kinds of hallucinogenic mushroom spores over the Internet. Psilocybin and psilocin belong to a group of Schedule I drugs in most countries around the world. They were classified as such during the hippie era despite the fact that psilocybin does not induce any signs of severe toxicity and addiction (either in animals or in humans). On the contrary, promising results from recent studies show that psilocybin could be beneficial in the treatment of addiction (detailed information in

FIGURE 3 **Synthetic psilocybin Indocybin®.** The figure shows an original phial with psilocybin pills from Sandoz, which was used during the initial psilocybin experiments. *Source: http://www.herbmuseum.ca/content/sandoz-indocybin-psilocybin.*

"Therapeutic targets"). The relative risks associated with the use of psilocybin as well as with other hallucinogens can be divided into two subgroups. First, the drug induces profound changes in perception, including hallucinations, and affects normal cognitive

processing, thereby increasing the risk of injury/accidents linked to inappropriate/inadequate behaviors. Even though cases of death or severe injuries have been described, these are extremely rare. Another risk is a toxic psychotic reaction (for the risk of persisting psychosis, see "Pro-psychotic potential of psilocybin"), and, finally, flashbacks or hallucinogen persisting perception disorder (HPPD). Again, these symptoms were reported only rarely and can be easily managed by psychotherapeutic and pharmacological (anxiolytics, atypical antipsychotics) interventions.

Pro-Psychotic Potential of Psilocybin

Extensive exploration has been conducted in order to estimate the potential of 5-HT hallucinogens to induce persisting psychotic symptoms. In thousands of individuals, the prevalence was estimated to be 0.1–0.2% (Tyls et al., 2014). The risk after a single dose of psilocybin is very low and is usually associated with a personal predisposition (Johnson et al., 2008). The main psychological side effects of psilocybin are anxiety, paranoia, derealization and depersonalization, psychotic reaction (toxic psychosis), and HPPD (Tyls et al., 2014). The causality between HPPD and the use of hallucinogens is criticized (Johansen & Krebs, 2015). It is essential to realize that the risk of all of these side effects can be decreased by subject education (the "set") and administration in a safe, comfortable environment (the "setting") (Johnson et al., 2008). Two Norwegian population studies (n = 130,000) did not find an increased risk of psychological disorders in hallucinogen users (lifetime use of LSD/psilocybin/mescaline was reported by 13.4% or 13.6% of respondents). Psilocybin use was actually associated with a lower rate of mental health problems (Johansen & Krebs, 2015; Krebs & Johansen, 2013).

NEUROBIOLOGY OF PSILOCYBIN'S ACTION

The Mechanism of Action of Psilocybin in the Brain

Psilocybin is an agonist at several serotonin receptors, especially 5-HT_{1A} and 5-$H_{2A/C}$; however, some other activities have been also reported (Table 1) (Tyls et al., 2014). It has been also shown to induce the release of dopamine in the human striatum (Vollenweider, Vontobel, Hell, & Leenders, 1999) and recently in the rat nucleus accumbens (Sakashita et al., 2015), an effect most likely mediated indirectly via activity at serotonin receptors. 5-HT_{2A} agonist activity has been postulated to be crucial for the hallucinogenic effects of classical hallucinogens. The similar phenomenology of intoxication in comparison with other serotonergic hallucinogens and the occurrence of cross-tolerance between these compounds (Halberstadt, 2015) suggest a common mechanism of action linked predominantly to $5HT_{2A}$ receptor agonism (Glennon, Titeler, & McKenney, 1984; Halberstadt, 2015). Because some 5-HT_{2A} agonists, e.g., lisuride, do not exert hallucinogenic effects, several recent hypotheses trying to explain this discrepancy related to the 5-HT_{2A} receptor–mediated intracellular signaling have emerged (e.g., activation of specific protein kinase, agonist trafficking of receptor signaling) (Gonzalez-Maeso et al., 2003, 2007; Páleníček & Horáček, 2008). The most recent theory reports protein kinase C (PKC)–dependent phosphorylation of serin on position 280 of the intracellular loop of the $5HT_{2A}$ receptor activated specifically by hallucinogens (Karaki et al., 2014). The authors suggest that this phosphorylation decreases desensitation/facilitates re-sensitization of the 5-HT_{2A} receptor and therefore strongly potentiates the effect of the agonist.

Psilocybin and other hallucinogenic tryptamines as well as LSD directly inhibit the dorsal raphe nucleus (DRN) by binding to presynaptic inhibitory 5-HT_{1A} receptors. Neurons of this nucleus send serotonergic projections to all forebrain structures, particularly to the frontal cortex. DRN is also inhibited indirectly by the stimulation of 5-HT_{2A} receptors on GABAergic interneurons in the periaqueductal gray (Liu, Jolas, & Aghajanian, 2000; Nichols, 2004; Páleníček & Horáček, 2008). Both mechanisms cause a decrease in overall serotonergic tone, thereby leading to a prevalence of the effects of hallucinogens on $5HT_{2A}$ receptors at the level of the cortex (due to lower competition with serotonin) (Nichols, 2004). In addition, 5-HT_{2A}-mediated disinhibition of the noradrenergic nucleus locus coeruleus (LC) and of the dopaminergic neurons in the ventral tegmental area (VTA) (Horacek et al., 2006) results in an increased release of norepinephrine and dopamine to the neocortex. It is assumed that although a suppression of activity of the DRN could theoretically be responsible for the relaxing (anxiolytic) and intoxicating effects of psychedelics, the increased activity of the LC accounts for the experience of novelty and surprise (King, 2012). Further on, electrophysiological studies have shown that hallucinogens enhance the response of LC to sensory stimuli (phasic activation) but simultaneously depress the spontaneous firing of LC neurons (tonic activation) (Halberstadt, 2015). The activity of hallucinogens at other receptors (5-HT_{1A}, 5-HT_{2C}, D_1, D_2) most likely modulates the effects and can be responsible for the small specific differences within the class of 5-HT hallucinogens (Tyls et al., 2014).

On the functional level, psilocybin and other hallucinogens are thought to disrupt the cortico-striato-thalamo-cortical (CSTC) circuits (Figure 4), most likely via 5-HT_{2A} agonism. On one hand, they attenuate the function of thalamus as a sensory filter, which in turn leads to an information overload in the cortex; on the other hand, they induce the hyperexcitability of the cortex. These two mechanisms in turn yield a reduction of the signal/noise ratio which is thought to be a characteristic underlying mechanism for the psychedelic/hallucinogenic effects (Geyer & Vollenweider, 2008; Nichols, 2004). The disruption of thalamic filtering is most likely caused by 5-HT_{2A}-mediated activation of GABAergic interneurons in the reticular nucleus and subsequent inhibition of other thalamic nuclei (Nichols, 2004). Increased cortical excitability is mediated via 5-HT_{2A} receptors on glutamatergic pyramidal neurons of the layer V (Artaloytia et al., 2006). These neurons are normally activated by axons from the mediodorsal nucleus of the thalamus in response to stimuli from the external environment. The excitability of pyramidal neurons in the cortex also increases due to the inhibition of the thalamic filter and the joint action of the activated dopaminergic (VTA) and noradrenergic systems (LC) (Nichols, 2004) and deactivated serotonergic systems (DRN) (King, 2012). Disrupted function of the thalamus in the limbic CSTC circuit with subsequent hyperfrontality can be the potential mechanism of the production of hallucinations (Behrendt & Young, 2004; Halberstadt, 2015).

TABLE 1 Affinity of Psilocin to Serotonin Receptors

Study	Method	Constant	Subtypes of Serotonin Receptors													
			$5HT_{1A}$	$5HT_{1B}$	$5HT_{1D}$	$5HT_{1E}$	$5HT_{1F}$	$5HT_{2A}$	$5HT_{2B}$	$5HT_{2C}$	$5HT_{3}$	$5HT_{4}$	$5HT_{5A}$	$5HT_{5B}$	$5HT_{6}$	$5HT_{7}$
Blair et al. (2000)	Radioligand competition, rat brain	K_i (nM)	49nM, [3H] 8-OH-DPAT	x	x	x	x	25nM, [1251] DOI	x	10nM, [1251] DOI	x	x	x	x	x	x
McKenna, Repke, Lo, and Peroutka (1990)	Radioligand competition, rat/bovine brain	K_i (nM)	190nM, [3H] 8-OH-DPAT	x	x	x	x	6nM, [1251] DOI	410 nM, [3H] ketanserin	x	x	x	x	x	x	x
Ray (2010)	http://pdsp.med.unc.edu/pdspw/binding.php	npK_i*	2,88	2,19	3,4	3,03	x	2,14	4	2,52	x	x	2,83	x	2,82	2,82

x, missing data.
*npK_i is the logarithm of the normalized value of K_i. It is calculated as follows: $npK_i = 4 + pK_i - pK_{imax}$, where $pK_i = -\log_{10}(K_i)$.
Table reproduced from Tyls et al. (2014) with the permission of European Neuropsychopharmacology.

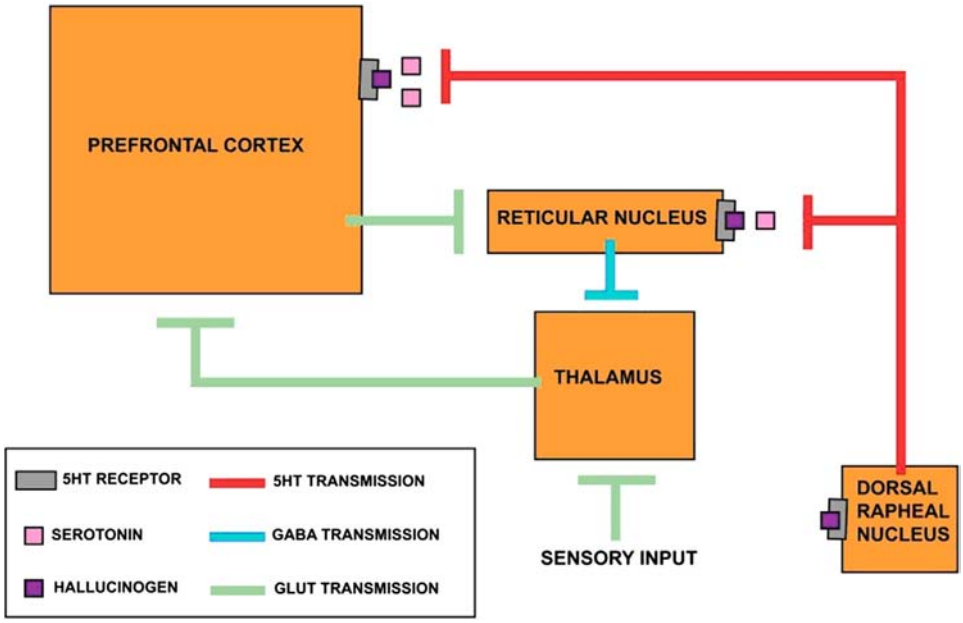

FIGURE 4 **The mechanism of hallucinogenic action.** Brain structures are depicted in orange, serotonin receptors as gray rectangles, and receptor agonists in rose (serotonin) and violet (hallucinogen). The main neurotransmission pathways are depicted in red (5-HT, serotonin), blue (GABA, γ-aminobutyric acid), green (GLUT, glutamate). *Modified, according to Baumeister et al. (2014).*

Psilocybin as a Model of Psychosis

Models of psychosis are crucial for understanding the neurobiology, neuropathology, and etiology of psychosis as well as for the development of novel treatment strategies. Various approaches have different levels of constructive, face, and predictive validity. Intoxication by serotonergic hallucinogens, which shows high face validity with positive symptoms of psychosis, resulted in a postulation of the serotonergic hypothesis of schizophrenia. Psilocybin is currently one of the main serotonergic models used in animal as well as human experiments (Tyls et al., 2014). The main animal behavioral models evaluate parameters such as startle habituation, prepulse inhibition, head twitch response, and interval timing (Halberstadt, Powell, & Geyer, 2013). In contrast to animals, human models give us the possibility of exploring the higher brain functions and unconscious processes. Furthermore, as mentioned above, the experience with hallucinogen intoxication can be a valuable tool for psychiatrists, providing insight into the mental states and experiences of their patients (Halberstadt et al., 2013).

THERAPEUTIC TARGETS

The main advantageous properties of psilocybin for human clinical research and treatment are its intermediate duration of action (3 h) and good oral absorption (Hasler et al., 2004). The four promising targets for psilocybin treatment seem to be anxiety/depression, addiction, obsessive-compulsive disorder, and cluster headache.

From a neurobiological point of view, psilocybin directly acts on receptors, neurotransmitters, and structures that are involved in the pathophysiology of the disorder. Another point of view is well represented by Abraham Maslow, who presented a psychological perspective on psilocybin action, stating that "ASCs are key to realizing one's psychological well-being" (Dutta, 2012). In accordance with that, it was hypothesized that the persisting effects (that is, the effects that outlast the acute pharmacological effects) of hallucinogens are related to the acute psychological effects during the intoxication (Bogenschutz, 2013). These biological and psychological aspects will be discussed in the subchapters focusing on the treatment of specific disorders.

Anxiolytic and Antidepressant Potential

A potential future use of psilocybin in the treatment of anxiety-depressive disorder is emerging (Carhart-Harris, Leech, et al., 2012; Vollenweider & Kometer, 2010). Baumeister et al. concluded their review of antidepressant potential of hallucinogens as follows: "Depression causes a profound burden on society. These drugs [hallucinogens] offer at least the potential of better understanding the neurobiology of depression, and of providing novel therapeutic agents." (Baumeister, Barnes, Giaroli, & Tracy, 2014).

The idea of using a psychedelic drug to alleviate the suffering of patients with terminal illness first surfaced in 1963 in the work of Dr. Eric Kast (Phifer, 1977). This early research focused on the pain-relieving effects of LSD, but later Dr. Kast recognized and described the transcendental experience that can help patients overcome the fear of death (Dutta, 2012). Dr. Walter Phanke explained this phenomenon as follows: "Once the patient is able to release all the psychic energy which he has tied to the fear of death and worry about the future, he seems able to live more meaningfully in the present." (Phifer, 1977). Dr. Stanislav Grof went further and performed a psychedelic peak therapy with high doses of LSD (350–400 μg) at the Maryland Psychiatric Research Center. Sixty terminal cancer patients received LSD as an adjunct for psychotherapy, with each patient receiving at least 20 h of psychotherapy prior to LSD administration. LSD-induced psychedelic experience increased the sense of unity, insight, and positive mood, and it

decreased fear of death, anxiety, and depression. One-third of the patients reported no significant improvement, one-third reported a certain extent of improvement, and one-third noticed dramatic improvement (Phifer, 1977).

The need to develop new strategies for depression treatment has gained importance in light of a recent metaanalysis that showed low efficacy of standard antidepressant drugs (Andrews, Thomson, Amstadter, & Neale, 2012). A recent paper reviewed the results of studies with a single application of the psychedelics ketamine and psilocybin (Young, 2013), showing high efficacy after a single dose. Further evidence comes from double-blind controlled studies with healthy volunteers, which showed long-term positive subjective effects of psilocybin, proving earlier, methodically weaker, observations (Tyls et al., 2014). Similarly, in animal models of depression, a reduction of anxiety-like behavior was observed after psilocybin treatment (Catlow, Song, Paredes, Kirstein, & Sanchez-Ramos, 2013).

The first recent placebo-controlled study (n = 12) in patients with low-dose psilocybin (0.2 mg/kg) was performed by Dr. Charlres Grob at the Harbor-UCLA Medical Center; it confirmed anxiolytic and antidepressant effects of this drug while discovering no side effects (Grob et al., 2011). During the intoxication, patients underwent an autobiographic reevaluation that allowed them to gain new insights into the meaning of their lives (Macready, 2012). The cancer study is currently being replicated by Dr. Stephan Ross at New York University with a similar design (n = 32), except that it uses a medium dose of psilocybin (0.3 mg/kg). Although the study has not yet been completed, the initial data (n = 12) indicate a rapid clinical improvement (decreased anxiety and depression). Patients reported that psilocybin transformed their perspective on life and death (Macready, 2012). Another study with cancer patients focused on the anxiolytic/antidepressant effect of psilocybin is currently ongoing at Johns Hopkins University since 2008 (Nichols, 2014). Psychedelic therapy of dying patients undermines the modern cultural paradigm of repressing the issue of death (Dutta, 2012). Psilocybin treatment of terminal cancer can thus be viewed as a shift in treatment strategy from delaying death to improving the quality of the remaining days of life. The celebration of death rather than repression (preparing for the death, planning the death, accepting the idea of assisted death) is something that we can learn a lot about from the indigenous nonwestern cultures (Sessa, 2008). It is very likely that the psychedelic experience itself is important for the antidepressant effects of psilocybin, similar to LSD and ketamine: it has been reported that the stronger the psychedelic/psychotic experience after LSD/ketamine, the better the antidepressant effect (Phifer, 1977; Sos et al., 2013).

The serotonergic system, which has a crucial role in the neurobiology of affective states, is a target for conventional antidepressants as well as psilocybin. The most striking difference between them is that psilocybin is effective after a single dose (Baumeister et al., 2014). The long-term effect of classical antidepressants is related to receptor upregulation/downregulation and induction of neuroplasticity. Contrary to classical antidepressants, the primary action of psilocybin is related to its activity on 5-HT receptors and not on the 5-HT transporter (SERT). The role of 5-HT_{1A} activity is supported by the facts that: (1) depressed patients have lower postsynaptic 5-HT_{1A} binding potential in the amygdala, hippocampus, and medial PFC; and (2) 5-HT_{1A} agonists show anxiolytic/antidepressant effects (e.g., buspirone) (Baumeister et al., 2014).

The second mechanism is related to the activity on 5-HT_{2A} receptors. Hallucinogens including psilocybin induce rapid 5-HT_{2A} downregulation after a single dose (Roth, Berry, Kroeze, Willins, & Kristiansen, 1998; Tyls et al., 2014), whereas increased cortical expression of 5-HT_{2A} receptors has been observed in depressed patients post mortem and in "learned helplessness," an animal model of depression (Baumeister et al., 2014). Therefore, 5-HT_{2A} downregulation is likely to be one of the key mechanisms (Baumeister et al. 2014; Roth et al., 1998; Tyls et al., 2014). Hallucinogens also increase neuroplasticity in a way similar to antidepressants, because the activation of 5-HT_{2A} receptors leads to increased expression of cellular brain-derived neurotropic factor (BDNF) (Baumeister et al., 2014; Vollenweider & Kometer, 2010) and it was also shown to reduce the inflammatory cytokines tumor necrosis factor-α and interleukin-6 (Baumeister et al., 2014). Some activity can be also related to psilocybin's activity at 5-HT_{2C} receptors: (1) opposite changes in expression have been associated with anxiety (increase) and depression (decrease); and (2) in animal models, 5-HT_{2C} antagonist showed an antidepressant effect (Baumeister et al., 2014). Finally, psilocybin also affects hippocampal neurogenesis; at a low dose (0.1 mg/kg i.p.), it tends to increase neurogenesis, whereas at high doses (1 mg/kg i.p.) it tends to be suppressed (Baumeister et al., 2014; Catlow et al., 2013).

Although the mechanism of acute psilocybin action has been well investigated, the prolonged duration of changes is still to be elucidated. Some investigators propose that these effects are secondary to the spiritual epiphany during ASC resulting in complex psychological changes (Macready, 2012; Young, 2013). It was shown that a structural correlate of psychologically induced ASC, namely mindfulness meditation, increased the volume of the gray matter of the brain (Holzel et al., 2011). Therefore psilocybin could induce similar structural changes due to the psychological effects during acute intoxication (ASC), which can be considered correlates of the long-term changes in the subjects' well-being (Young, 2013). Furthermore, psilocybin alters the brain's neural networks in a manner similar to selective serotonin reuptake inhibitors (SSRIs) and the form of psychotherapy known as cognitive-behavioral therapy (both of which reduce medial PFC activity) and meditation (which causes a decrease in default mode network [DMN] activity) (Baumeister et al., 2014).

Dependence Treatment

Psilocybin and possibly other hallucinogens are now studied as a potential adjunct in the treatment of addiction. In fact, substance dependence was the first indication for psychedelic therapy, a concept that pointed toward religion and mysticism (Carhart-Harris, Leech, et al., 2012). Most of the available evidence supports the high-dose, single-session model (Bogenschutz, 2013).

From the 1950s until the early 1970s, LSD was used in alcohol dependence treatment (Bogenschutz, 2013). The promising results initiated the use of psilocybin in studies on the treatment of substance dependence (Young, 2013). Dr. Bogenschutz at the University of New Mexico, Albuquerque, used psilocybin for alcohol dependence treatment in a small pilot study (n = 10), showing some promising outcomes in the recent follow-up (Nichols, 2014). Dr. Johnson at Johns Hopkins University examined the effect of three psilocybin sessions (20 or 30 mg) on tobacco smoking cessation using self-report measures and smoking-related biomarkers.

In this small pilot study (n = 15), he found that 80% of participants showed 7-day point prevalence abstinence in the 6-month follow-up. Such a smoking cessation rate is much higher compared to other behavioral/pharmacological approaches (<35%) (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014). The relevance of the study is limited by the absence of a control group. Dr. Ross (2012) at New York University is going to start a controlled trial of psilocybin-assisted psychotherapy in the treatment of alcohol dependence. Burdick et al. proposed a design of opioid dependence treatment study with psilocybin controlled by a nonpharmacological ASC induction (holotropic breathwork) and active placebo (niacin) (Burdick & Adinoff, 2013).

Dr. Johnson postulated that hallucinogen-mediated treatment of addiction involves higher psychological and/or biological mechanisms. This contrasts with conventional pharmacotherapy of dependence, in which the treatment aims at the same pharmacological system as the drug of abuse (Johnson et al., 2014). There are two main psychological components of the antiaddictive effect: psychological insight and mystical experience (Burdick & Adinoff, 2013). Similarly to the situation with depression, psilocybin-induced deepening of spirituality can have a significant positive impact, just like religiosity (Burdick & Adinoff, 2013; Cook, 2004). The sacramental use of hallucinogens in native communities, together with low rates of alcohol and drug consumption, suggests antiaddictive effects. This was shown in two religious groups in the United States that are allowed to use hallucinogens by the government: the Native American Church, with mescaline, and Uniao do Vegetal, with ayahuasca. There are considerable confounding factors such as social, spiritual, or communal aspects of religion (Ross, 2012); however, all of these can be potentially linked to or even directly potentiated by hallucinogens.

The biological components of psilocybin's antiaddictive effects remain unclear. Although the acute effects of psilocybin on the brain are relatively well understood, the long-lasting changes, which are more relevant for addiction treatment (Bogenschutz, 2013), are yet unexplored. It is a common feature of substances with dependence potential that they increase extracellular dopamine in the mesolimbic pathway (Ross, 2012). Although psilocybin lacks affinity for dopamine receptors, it can increase dopamine levels indirectly through 5-HT receptors. In humans, psilocybin increased dopamine in the striatum (in correlation with euphoria and depersonalization) (Vollenweider et al., 1999) but failed to activate the nucleus accumbens to any significant extent (Ross, 2012). Dr. Ross et al. suggested that a low-grade increase in dopaminergic transmission caused by 5-HT hallucinogens can lead to regeneration of D_2 receptors (i.e., normalization of their function), similarly to a substitution therapy of addiction (Ross, 2012).

Classical hallucinogens are associated with tachyphylaxis (rapid induction of tolerance following repeated administration) that is hypothesized to be a result of 5-HT_{2A} receptor downregulation (Tyls et al., 2014). Dr. Bogenschutz (2013) pointed out that this can be relevant, because 5-HT_{2A} receptors are upregulated with chronic alcohol exposure in rats (Akash, Balarama, & Paulose, 2008). 5-HT_{2A} downregulation can also result in the prevention of stress-induced relapse of abuse, since higher 5-HT_{2A} density in the human brain correlates with an increase in anxiety and stress response activation (Ross, 2012). Another possible mechanism can be a decrease in dopamine activity precipitated by the activation of 5-HT_{2C} receptors by psilocybin, which results in inhibition of dopaminergic neurons in the ventral tegmental area (VTA) (Baumeister et al., 2014).

The antiaddictive effects of 5-HT hallucinogens can be also mediated by an increase in neurotrophic factor levels, leading to synaptic remodeling. Activation of BDNF signaling in the medial prefrontal cortex and dorsal striatum has antiaddictive effects; however, it has opposite effects in the nucleus accumbens (Ross, 2012). 2,5-Dimethoxy-4 iodoamphetamine (DOI) induced 5-HT_{2A}-mediated increase in BDNF mRNA in the neocortex but a decrease in the hippocampus (Bogenschutz, 2013; Vaidya, Marek, Aghajanian, & Duman, 1997) and an increase of dendritic spine remodeling in rat pyramidal cells (Bogenschutz, 2013; Jones et al., 2009).

On the level of brain networks, 5-HT hallucinogens increase activity in the prefrontal–limbic circuitry through an increase in glutamate levels. The normalization of functional connectivity in this network is associated with antiaddictive effects (Ross, 2012).

Obsessive-Compulsive Disorder (OCD)

OCD is a severe psychiatric disease with pathological changes in the 5-HT system. Specific treatment is yet to be developed. The most effective treatment for OCD, namely, SSRIs and clomipramine, reduces OCD symptoms only by 30–50% (Moreno, Wiegand, Taitano, & Delgado, 2006). Identifying new approaches in affecting the 5-HT system of OCD patients is therefore of high importance.

The first observations indicating the effectiveness of psilocybin in OCD treatment were made by OCD patients self-medicating with psychedelic mushrooms. One case report showed that obsessive thoughts completely disappeared after ingestion of psilocybin-containing mushrooms (Leonard & Rapoport, 1987). Based on these early observations, Dr. Moreno designed a double-blind study exploring the effects of up to four psilocybin sessions (doses of 25–300 μg/kg) in patients with OCD. This study found an acute alleviation of OCD symptoms in all (n = 9) subjects (23–100% decrease in Yale–Brown Obsessive Compulsive Scale [YBOCS]) during the session. The 25% and 50% reduction of OCD symptoms persisted after 24 h after psilocybin administration in 89% and 67% of subjects, respectively. Moreover, one patient achieved a complete 5-month remission (Moreno et al., 2006). Although these results are promising, the limitations of the study are the absence of a placebo group, small sample size, and no long-term follow-up (Baumeister et al., 2014). Especially the placebo effect should be taken into account, because Hallucinogen Rating Scale (HRS) scores after such a low dose of psilocybin were higher than the authors expected.

The study by Dr. Moreno et al. also explored the relationship between psychedelic effects (measured by the HRS) and the severity of obsessive and compulsive symptoms (measured by the YBOCS and visual analog scale [VAS]); however, he did not find any significant interaction (Moreno et al., 2006). This is supported by a case report that showed the reduction of OCD symptoms after repeated doses of psychedelic mushrooms despite the absence of psychedelic effects due to a development of tolerance (Moreno & Delgado, 1997). The observation that psilocybin is useful in OCD treatment irrespective of the depth of the psychedelic experience and of the dose administered

suggests that the contribution of psychological effects to the long-term clinical effects is only small.

Psilocybin-induced increase in extracellular 5-HT levels may underlie the acute alleviation of obsessions and compulsions in a way similar to SSRIs. On the other hand, Dr. Moreno et al. suggested that the long-lasting effect of psilocybin can be partially mediated by 5-HT_{2A} downregulation or early gene expression (Moreno et al., 2006). This means that repeated low doses and induction of tolerance are more beneficial for OCD patients than the psychedelic experience.

Cluster Headache

A promising effect was observed in patients with so-called cluster headaches—strong, disabling, periodically occurring headaches, which are often resistant to medication. One of the possible pharmacological treatments of these headaches are indole derivatives and antimigraine drugs, triptans, to which psilocybin is also structurally related (Johnson, Sewell, & Griffiths, 2012).

Based on a case report of a complete remission of cluster headache attacks after psychedelic mushroom ingestion, Dr. Sewell et al. performed an online survey in a group of individuals diagnosed with cluster headache, assessing psilocybin mushroom–induced alleviation of the symptoms of both episodic and chronic (i.e., no remission period) forms of the disease. They found that psilocybin is effective in aborting cluster headache attacks (85%) as well as in preventing future attacks (52% completely, 37% partially). Psilocybin is thus more effective than conventional medication in both acute and prophylactic treatment. Furthermore, psilocybin was the only treatment that was able to extend the remission period. The psychedelic effects seem not to be necessary for the reduction of cluster headache symptoms, considering the fact that the users reported only relatively low doses (Sewell, Halpern, & Pope, 2006). One cannot exclude the confounding factor of other substances contained in psychoactive mushrooms, but the superior effect of psilocybin is supported by the similar efficacy of LSD, which was also assessed in the survey (Sempere, Berenguer-Ruiz, & Almazan, 2006). A placebo-controlled clinical trial is needed to confirm these promising results.

However, recent human studies with psilocybin also showed an opposite effect, namely, that psilocybin can induce transient mild to moderate headaches. The incidence and duration of the headaches was dose-dependent (Johnson et al., 2012).

The potential of psilocybin to both induce and treat headaches can be better understood with a deeper insight into the complex role of the 5-HT system in the pathogenesis of headaches. One of the possible mechanisms of headache triggering is serotonin-mediated vasoconstriction. During the headache attacks, patients with migraines showed a strong increase in brain serotonin concentrations, with lower serotonin levels observed between attacks (Johnson et al., 2012). Psilocybin induced a decrease in 5-HT tone through DRN inhibition via $5HT_{1A}$ autoreceptors. Hypothetically, the agonist activity on these receptors can be responsible for the prevention of cluster headache episodes. Furthermore, animal studies showed that the activation of the 5-HT_{1A} receptor may have analgesic effects in relation to nociceptive pain (Colpaert, Deseure, Stinus, & Adriaensen, 2006). Another possible mechanism of headache reduction can be agonist activity on 5-$HT_{1B/1D}$ receptors, shared by both psilocybin and triptans (Tyls et al., 2014). The involvement of 5-HT_{2C} receptor is likely because many prophylactic anti-migraine drugs exhibit 5-HT_{2C} affinity. Other 5-HT receptors are also involved in the regulation of vascular lumen (Johnson et al., 2012).

Psilocybin can induce headache through many different mechanisms including NO release, increase in glutamate levels, inhibition of the DRN with consequent activation of LC, 5-HT_{2B} agonism, and induction of gene transcription. Acute administration of some 5-HT-releasing drugs (e.g., fenfluramine) can provoke migraine, but their repeated administration can also prevent migraine attacks. It is possible that related mechanisms can be involved in psilocybin-mediated induction and treatment of headaches due to the many rebound mechanisms at play (Johnson et al., 2012).

NEW INSIGHTS

New approaches such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), quantitative electroencephalography (QEEG), and magnetoencephalography (MEG) have been used to explore the neurobiology underlying the psychedelic state. The study of the phenomenology of psilocybin intoxication in combination with neuroimaging methods will help us to understand the ties between subjective consciousness and brain function (Nichols, 2014). The results of modern imaging studies with psychedelics can be interpreted in light of the theoretical framework of psychoanalysis but also the theory of chaos and complexity.

Brain Imaging Data from Recent Studies

Both animal and human studies have described nonspecific desynchronization of EEG activity after psilocybin administration. Recent animal data from our laboratory confirmed these initial findings. Psilocin induced a decrement of absolute spectral power (which can be explained by local network desynchronization) and a decrement of EEG coherences (a measure of functional connectivity of the long projections in the brain). Similar QEEG pattern was found with other serotonergic hallucinogens and the decrement of EEG coherences was shared with dissociative anesthetics, as reviewed elsewhere (Tyls et al., 2014). These findings are in accordance with the first MEG study in human volunteers intoxicated with psilocybin. It found decreased broadband spontaneous cortical oscillatory power during resting state with the most pronounced changes in the default mode network (DMN). Psilocybin reduced cortical synchrony by increasing the excitability of deep layer pyramidal neurons (Muthukumaraswamy et al., 2013).

PET studies using psilocybin (15–25 mg p.o.) documented increased metabolism in the prefrontal cortex (lateral, medial, and anterior cingulate cortex [ACC]), temporal cortex, and basal ganglia, and decreased metabolism in the thalamus (Gouzoulis-Mayfrank et al., 1999; Vollenweider et al., 1997), as reviewed elsewhere (Tyls et al., 2014). However, an fMRI study with psilocybin (2 mg i.v.) showed both blood-oxygen-level-dependent (BOLD) and arterial spin labeling (ASL) decrements in the frontal, temporal, and parietal cortical midline structures (ACC, PCC, precuneus) and the thalamus. This study also found decreased connectivity

between the medial PFC and PCC. The intensity of subjective effects correlated with decreased activity in the medial PFC and ACC. Another important finding is that two important brain networks, the DMN and task positive network (TPN), are both activated simultaneously under psilocybin intoxication, although under normal conditions they are always activated in mutual exclusion (Carhart-Harris, Erritzoe, et al., 2012; Carhart-Harris, Leech, et al., 2012). The discrepancy between these studies can be explained by several mechanisms, as recently reviewed (Tyls et al., 2014), but in light of the MEG study, both findings from fMRI and PET can be congruent. Psilocybin-induced increase in glutamatergic pyramidal neuron excitability can lead to desychronization, reflected by a decrease of fMRI signal, and to an increase in glutamate turnover and consequently increased glial metabolism, reflected by an increase in PET signal (Tyls et al., 2014).

Psilocybin and Brain Entropy

Looking at the findings from neuroimaging studies, we can hypothesize that disconnection might be one of the main mechanisms underlying the "psychedelic state." The coactivation of brain networks (DMN and TPN) may result from their disconnection from each other and may thus contribute to altered processing of information.

According to Dr. Carhart-Harris, the brain changes induced by psilocybin are characterized by an increase in entropy. He postulated the theory of the "entropic brain" (Carhart-Harris et al., 2014), which distinguishes a continuum of brain states based on the rate of entropy with two extreme states at each end of the spectrum. High-entropy states (called "primary consciousness") are unstable and characterized by creative thinking; they include altered states of consciousness such as drug-induced psychedelic state, moments of insight, dreaming during rapid eye movement (REM) sleep, near-death experiences, or sensory deprivation. Hypothetically, the disconnection of central connectivity hubs from the other brain areas can contribute to the increased entropy. There is, therefore, a link between the concept of acute psychosis as a state of pathologically increased entropy and the disconnection hypothesis (Friston & Frith, 1995). The main output of this link is lower regularity of the instrumentally measured biosignal. The observed coactivation of brain networks under psilocybin intoxication can be seen as a collapse of dualities, which is characteristic for primary consciousness (Carhart-Harris et al., 2014).

On the other hand, low-entropy states (called "secondary consciousness") are hyperstable and are characterized by rigid thinking with a low level of creativity (e.g., novelty of the worldview). These include sedation or deep sleep but also pathological conditions such as depression, OCD, and addiction (Carhart-Harris et al., 2014). The potential treatment of these states may include a transient increase in entropy. This explains the efficacy of psilocybin in clinical studies and implies that the induction of the psychedelic state is not a side effect but an integral part of the treatment.

CONCLUSIONS

Psilocybin is a substance that causes an altered state of consciousness, which is phenomenologically similar to acute psychosis, even though its potential for triggering acute psychosis is low. This state is induced by its effects of the 5-HT system, mostly by agonism of 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, which precipitates complex changes in the cortico-striato-thalamo-cortical circuitry and in different activations of neural networks. These changes result in aberrant processing of information (mostly visual hallucinations) and loss of ego boundaries, connected with positive as well as negative experiences. The complex effects of psilocybin, on the psychological as well as biological level, may yield promising results in the therapy of hyperstable pathological states such as depression, OCD, and addiction. There is also growing evidence for the efficacy of psilocybin in the therapy of cluster headaches.

Contemporary scientific use of psilocybin can be seen as an extension of ancient rituals with psilocybin mushrooms. Clinicians have converted healing rituals into therapeutic sessions, and scientists have transformed the induction of trance states into the modeling of psychosis. The scientific community is divided in its view on psilocybin: some researchers remain extremely critical (Stebelska, 2013), especially with regard to the psychotomimetic effects of psilocybin. However, in light of a recent theoretical view on brain states, it seems that the psychotomimetic action and therapeutic value of psilocybin are two sides of the same coin, at least in the treatment of anxiety, depression, and addiction (Carhart-Harris et al., 2014). The impossibility of separating the psychedelic and therapeutic properties of psilocybin contributes to the aura of divinity surrounding *teonanácatl* and its unique position in society, which lasts to this day.

> *Psychedelics free people from their usual thinking patterns and show that thoughts and behaviour can be changed.*
>
> Dr. Carhart-Harris

DEFINITION OF TERMS

ASC Altered states of consciousness. ASC is any mental state induced by physiological, psychological, or pharmacological maneuvers or agents which deviates from the normal waking state of consciousness.

QEEG Quantitative electroencephalography. QEEG is a numerical analysis of electroencephalography data. Fourier analysis is often used for digital data processing to recognize shared activity between rhythms based on phase (phase lag, coherence) and magnitude synchrony (comodulation, asymmetry).

MEG Magnetoencephalography. MEG is a functional neuroimaging technique for mapping brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain, using very sensitive magnetometers.

fMRI Functional magnetic resonance imaging. fMRI is a functional neuroimaging procedure using MRI technology that measures brain activity by detecting associated changes in blood flow. This technique relies on the fact that cerebral blood flow and neuronal activation are coupled. When an area of the brain is in use, blood flow to that region also increases.

PET Positron emission tomography. PET is a functional imaging technique from the field of nuclear medicine that produces a three-dimensional image of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Three-dimensional images of tracer concentration within the body are then constructed by computer analysis.

KEY FACTS

Altered States of Consciousness

- ASCs are a diverse group of physiological and pathological brain states with some common features that can be induced in a variety of very different ways.
- Examples are drug-induced psychedelic states, acute psychosis, meditation, moments of insight, dreaming during REM sleep, holotropic breathing, near-death experiences, or sensory deprivation.
- All of these states have a dream-like phenomenology and other similarities such as certain patterns of brain activation.

Model of Psychosis

- Acute psychosis can be modeled in humans and, to a certain degree, in animals by using pharmacological agents such as amphetamines, serotonergic hallucinogens, dissociative anesthetics, and cannabinoids.
- The phenomenological validity of the models rests on the similarity of the phenomena induced by the model and symptoms of mental disorders (e.g., hallucinations, thought disorder, altered informational processing, self-awareness, empathy).
- The predictive validity of the models allows us to test new antipsychotics in animals. This makes them one of the most important tools in the research of psychosis.
- Construct validity is a degree to which a model actually mimics the pathophysiology of the disorder that is modeled.
- With modern imaging techniques, we can also study the role of brain structures and the networks affected or involved.

Terminal Depression

- Depression triggered by a serious somatic condition that cannot be cured and that is reasonably expected to result in the death of the patient within a short period of time (very often cancer).

Obsessive-Compulsive Disorder

- OCD is an anxiety disorder with intrusive thoughts and repetitive behaviors.
- Individuals with OCD experience uneasiness, apprehension, and worry (obsessions) that can be temporarily relieved by certain behaviors (compulsions).
- Symptoms of the disorder include excessive washing or cleaning, repeated checking, extreme hoarding, preoccupation with sexual, violent, or religious thoughts, relationship-related obsessions, aversion to particular numbers, and nervous rituals such as opening and closing a door a certain number of times before entering or leaving a room.
- These symptoms are time-consuming, may result in loss of relationships with others, and often cause severe emotional and financial distress.

Cluster Headache

- Cluster headache is a neurological disorder characterized by recurrent, severe headaches on one side of the head, typically around the eye. There are often accompanying autonomic symptoms (eye watering, nasal congestion, and swelling around the eye).
- A typical characteristic is grouping of headache attacks occurring in succession (cluster). Individuals typically experience repeated attacks of excruciatingly severe unilateral headache.
- Cluster headache attacks often occur periodically, and active periods of pain may be interrupted by spontaneous remissions, although about 10–15% of chronic cluster headaches never remit. The cause of cluster headache has not been identified.
- Although there is no known cure, cluster headaches can sometimes be prevented and acute attacks can be treated. Recommended treatments for acute attacks include oxygen or fast-acting triptans. Primary recommended prevention is verapamil. Steroids may be used as a transitional treatment and may prevent attack recurrence until preventive therapy takes effect.

SUMMARY POINTS

- Psilocybin is a serotonergic hallucinogen that is convenient for human research due to its relative safety and optimal pharmacokinetic profile.
- Psilocybin induces altered state of consciousness by agonist action at 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, precipitating complex changes in the cortico-striato-thalamo-cortical circuitry and in the activation of neural networks.
- These changes result in aberrant processing of information (mostly visual hallucinations) and loss of ego boundaries, connected with positive as well as negative experiences. This state is phenomenologically similar to acute psychosis.
- The complex effects of psilocybin (on the psychological as well as biological level) may yield promising results in the therapy of hyperstable pathological states such as depression, OCD, and addiction. There is also growing evidence for the effectiveness of psilocybin in the therapy of cluster headaches.
- Contemporary scientific use of psilocybin can be seen as an extension of ancient rituals with psilocybin mushrooms; clinicians have converted healing rituals into therapeutic sessions, and scientists have transformed the induction of trance states into the modeling of psychosis.
- The psychotomimetic action and therapeutic value of psilocybin are two sides of the same coin.

ACKNOWLEDGMENT

We would like to thank Jakub Korcak and Michaela Viktorinova for valuable feedback and Jan Tichy for language corrections. This study was supported by the projects IGA MHCR NT/13897, “National Institute of Mental Health (NIMH–CZ),” grant number ED2.1.00/03.0078, and by the European Regional Development Fund.

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