SACRED MUSHROOM OF VISIONS: TEONANÁCATL

A Sourcebook on the Psilocybin Mushroom

Edited by Ralph Metzner, Ph.D.
with Diane Conn Darling

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THIS BOOK IS DEDICATED TO

MARÍA SABINA (1894–1985), Mazatec Wise Woman and Healer who spoke the Holy Language of the *niños santos* and preserved their spiritual wisdom.

ROBERT GORDON WASSON (1898–1986), scholar, world traveler and ethnomycologist who rediscovered the *teonanácatl* cult of the indigenous people of Mexico and brought the gifts of this ancient religion to the modern world.

ALBERT HOFMANN (who celebrated his ninety-ninth birthday in 2005), scientist, alchemist and nature mystic who found the Stone of the Wise, identified the crystal essence—psilocybin—of the holy mushroom, and fathomed the secret of the Eleusinian Mysteries.

TIMOTHY LEARY (1920–1996), psychologist, visionary philosopher, and trickster, who ate the sacred mushroom and inspired a generation to "go out of your mind and come to your senses."

TERENCE MCKENNA (1946–2000), scholar, bardic seer, emissary from the mushroom world, who mapped the hidden landscape of hyperspace, communed with alien intelligence, and showed the way to join the cosmic community.

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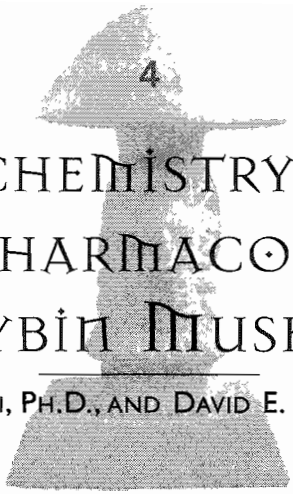

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Biochemistry and Neuropharmacology of Psilocybin Mushrooms

David E. Presti, Ph.D., and David E. Nichols, Ph.D.

This chapter will present a discussion of the chemistry of a particular type of psychoactive mushroom, of the genus *Psilocybe*, often known collectively as psilocybin mushrooms, and sometimes referred to as "magic mushrooms."

The history of the ritual use of these mushrooms spans millennia, from the contemporary Mazatec Indians of southern Mexico, to the Mayan and Aztec cultures of Mexico and central America six hundred years ago, to the cultures that came many centuries before them. In the sixteenth century the Spanish chronicler de Sahagún described teonanácatl, an Aztec word that can be translated as "sacred mushroom" or

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"God's flesh." We know from Sahagún's writings that teonanácatl was used for social occasions, festivals, and by the Aztec shamans (Hofmann 1971).

When used in a ritual context by the shaman, teonanácatl provided a bridge between everyday consensus reality and extraordinary states of consciousness that allowed perception of events and situations that were not ordinarily accessible: the weather was forecast, illness was diagnosed, aspects of the future might be seen, such as whether or not the harvest would be good. Thus, his ingestion of the "God's flesh" made the Aztec shaman seem like a god, able to transcend time and space.

Teonanácatl is classified as an entheogen, a substance that can manifest the god within. Certainly, for the Aztec shaman, the connection with the gods that arose in his mind through the ritual use of teonanácatl was the central purpose of the substance. Within this context, and for the purposes of the discussion, we shall use the term entheogenic to describe the effects produced by psilocybin fungi. This convention seems particularly appropriate because, of all the similar types of psychoactive substances of which we know today, these mushrooms have one of the clearest historical justifications for applying this term. Those readers who are more formally inclined should consider it to be synonymous with the terms psychedelic and hallucinogenic.

The chemical makeup of psychoactive mushrooms is extraordinarily complex, with hundreds of chemicals created by the organism's metabolic biochemistry. Though any number of these may have effects on human physiology, the psychoactive effects of various entheogenic fungi and plants are usually attributable to a small number of identified compounds. The psychoactive chemicals identified in entheogenic fungi are generally secondary metabolites of the organism's biosynthetic processes. That is, they are not believed to function as part of the mushroom's energy-generating or structural biochemistry, their primary metabolism, but are instead products of biochemical syntheses.

Recently it has become increasingly appreciated that so-called secondary metabolites may play any number of important roles for the organism. For some plants, certain secondary metabolites that have psychoactive effects in humans have been demonstrated to function as

chemical defenses against insect predators. This observation is usually hypothesized to be the reason why they are present, having been selected over the course of biological evolution for their defensive properties. Examples include noxious effects on insects from cocaine in coca plants, caffeine in coffee and tea plants, and nicotine in tobacco plants. Moreover, the psychoactive effects produced by these plants in humans have resulted in an additional evolutionary advantage for the plants in that they have been spread throughout the world by people who cultivate them to maintain ready availability.

The psychoactive chemicals synthesized by entheogenic fungi have not thus far been demonstrated to play chemical defensive roles for the organism. No experiments have been conducted, for example, to investigate whether entheogenic fungi avoid predation by invertebrates such as slugs and snails because of their peculiar chemical content. The notion that entheogenic substances are present in fungi and plants primarily to foster their consumption by humans is a speculative and interesting hypothesis (McKenna 1992), but one for which there is absolutely no scientific evidence.

PSILOCYBIN AND ITS CHEMICAL RELATIVES

The primary effects of the entheogenic psilocybin mushrooms on human physiology are due to several tryptamine alkaloids synthesized and accumulated by these fungi. The categorical name "tryptamine alkaloids" (or "tryptamines") designates molecules whose molecular structure contains 3-(2-aminoethyl)indole as a central feature (fig. 1).

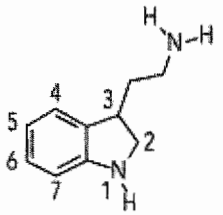

Figure 1. Tryptamine, showing numbering of the indole ring.

The identified psychoactive chemical components of psilocybin mushrooms are psilocybin, psilocin, baeocystin, and norbaeocystin (figs. 2–5).

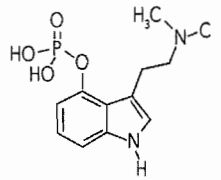

Figure 2. Psilocybin or 4-phosphoryloxy-N,N-dimethyltryptamine.

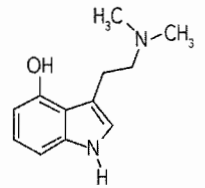

Figure 3. Psilocin or 4-hydroxy-N,N-dimethyltryptamine.

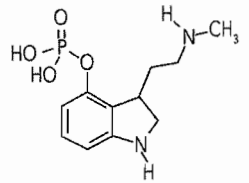

Figure 4. Baeocystin or 4-phosphoryloxy-N-methyltryptamine.

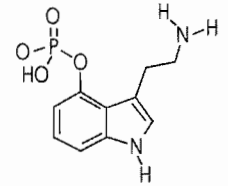

Figure 5. Norbaeocystin or 4-phosphoryloxytryptamine.

Psilocybin and psilocin were identified as the primary psychoactive components of *Psilocybe* mushrooms by the renowned Swiss chemist Albert Hofmann in 1958. Hofmann isolated and identified the compounds from samples of *Psilocybe mexicana* mushrooms collected in Mexico. To identify the compounds that produced the effects on consciousness, he and several of his coworkers ingested fractions obtained from the paper chromatographic separation of the fungal extracts (Hofmann et al. 1958, 1959).

Psilocybin can produce significant psychoactive effects in humans following oral doses of approximately 10 to 20 mg (Shulgin and Shulgin 1997). Taken orally, psilocybin and psilocin produce identical effects when given at equivalent molar doses. That is because following oral ingestion, the phosphoryl group of psilocybin is rapidly lost to generate psilocin, which is the actual active molecule. Alkaline phosphatases located in the digestive system, kidney, and perhaps in the blood probably carry out this enzymatic transformation (Horita and Weber 1961). Early animal studies showed that the behavioral effects of psilocybin paralleled the increase in brain level of psilocin (Horita 1963). After

administration of psilocybin, only psilocin is detectable in the blood (Hasler et al. 1997). These same workers found that following oral administration of 10–20 mg of pure psilocybin, peak levels of psilocin in the blood (about 8 ng/ml) occur approximately 105 minutes after ingestion. Effects on the psyche appear when a blood concentration of between 2–6 ng/ml is achieved, about 20–90 minutes after oral administration of pure psilocybin. After intravenous administration of 1 mg of pure psilocybin, the conversion to psilocin occurs rapidly, and peak blood concentrations of psilocin (about 13 ng/ml) are achieved within 2 minutes of injection (Hasler et al. 1997).

In the mushroom, the phosphoryl group of psilocybin confers protection against oxidation. Indeed, crystalline samples of psilocybin have been stored at room temperature for decades with no appreciable degradation. Furthermore, psilocybin can even be recrystallized from boiling water, a treatment that would destroy psilocin itself (Nichols and Frescas 1999). Thus, psilocybin is a remarkably stable molecule, particularly when compared with other tryptamines. This stability provides the basis for the extraction of psilocybin mushrooms with hot water for the preparation of ritual teas.

Psilocin, by contrast, is a fairly unstable molecule. The pure material slowly darkens in air, whereas solutions, particularly at basic pH, decompose rapidly. Many psilocin-containing mushrooms turn a bluish color when bruised. This effect is believed to be due to degradation products of psilocin that have yet to be chemically identified (Stamets 1996). Hydroxyindoles in general are readily oxidized, leading to highly colored products, and it is likely that bruising the mushrooms releases psilocin from a protective matrix so that it is exposed to air oxidation or to the action of enzymes that use oxygen to oxidize aromatic substrates. Although the nature of these colored products has not been elucidated, no doubt some of them are quinoid-type species, which typically have dark colors. Although 5-hydroxytryptamines such as bufotenin also oxidize very readily, they do not generate the blue colors that occur with 4-hydroxytryptamines.

Baeocystin and norbaeocystin were first identified from *Psilocybe baeocystis* (Leung and Paul 1968). Baeocystin has since been found in at least twenty-six species of mushrooms and there is one report that it

is psychoactive in humans at doses of approximately 10 mg, ingested orally (Ott 1993). Unfortunately, sufficient data are not available for these two compounds to assess their clinical properties, but it is very likely that they produce qualitatively different psychopharmacological effects. Based on current neurochemical knowledge, one could reasonably speculate that these two compounds would have different affinities and abilities to activate the various brain receptors relevant to the actions of entheogens. Therefore, the relative proportions of psilocybin and baeocystin in a particular species of mushroom are probably relevant to its effects after ingestion. This idea would be consistent with anecdotal reports that some species of mushroom, for example *P. cubensis* and *P. azurescens*, can induce qualitatively different effects.

Several related psychoactive tryptamine molecules, which, although synthesized by a variety of plants, have not yet been detected in fungi, include: N,N-dimethyltryptamine or DMT (fig. 6); 5-hydroxy-N,N-dimethyltryptamine or bufotenin; and 5-methoxy-N,N-dimethyltryptamine or 5-MeO-DMT (fig. 7). Conversely, psilocin and psilocybin have not thus far been found in plants.

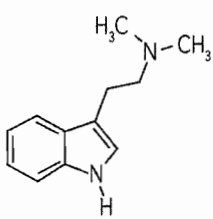

Figure 6. N,N-dimethyltryptamine or DMT.

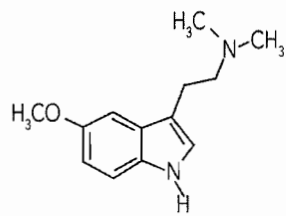

Figure 7. 5-methoxy-N,N-dimethyltryptamine or 5-MeO-DMT.

LEGAL STATUS

The legal status of several of these molecules has been specified by the Federal Controlled Substance Act, passed into law by the United States Congress in 1970. Psilocybin, psilocin, DMT, and bufotenin have been classified as Schedule 1 substances by the U.S. Controlled Substances Act. Psilocybin and psilocin are essentially nontoxic to body organs and do not cause physiological dependence or addictive behaviors (presumably the basis for the dangers of drugs of abuse as this term is used in the Controlled

Substances Act). The classification of psilocybin, psilocin, and many other entheogens as dangerous drugs is primarily based on socio-political reasons rather than clinical-scientific evidence. Psilocybin, psilocin, and DMT are also internationally classified as Schedule 1 substances by the 1971 United Nations Convention on Psychotropic Substances.

TRYPTAMINES IN THE HUMAN BODY

Some tryptamine molecules found naturally in the human body include *tryptophan, 5-hydroxytryptophan, serotonin, melatonin,* and *N,N-dimethyltryptamine.*

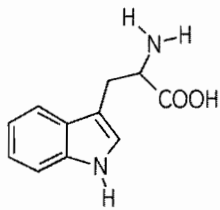

Figure 8. Tryptophan.

Tryptophan (fig. 8) is one of the twenty amino acids used by all of life on Earth to build proteins. Although plants, fungi, bacteria, and some other organisms can biosynthesize tryptophan from smaller carbon molecules, humans cannot and must ingest tryptophan as part of their diet. That is, tryptophan is one of the "essential" amino acids. In fungi and plants, tryptophan is the chemical precursor for the biosynthesis of tryptamines such as DMT and psilocybin. In humans and other animals, tryptophan is the precursor for the synthesis of the neurotransmitter serotonin, 5-hydroxytryptamine (5-HT; fig. 9).

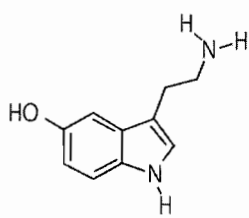

Figure 9. Serotonin or 5-hydroxytryptamine.

The synthesis of 5-HT from tryptophan in serotonergic neurons occurs in two steps. First, the enzyme tryptophan hydroxylase catalyzes the conversion of tryptophan to 5-hydroxytryptophan (5-HTP). Then, the enzyme aromatic amino acid decarboxylase catalyzes the conversion of 5-HTP to serotonin.

In the brain, serotonergic neurons are located in the brainstem in clusters of cells called the *raphe nuclei*, within which is the *reticular network*. These serotonergic neurons send their axonal projections throughout the entire brain. As a neurotransmitter, serotonin is involved in the regulation of numerous behavioral and physiological processes, including mood, appetite, sleep, sexual function, blood flow, body temperature, and more. The fact that both tryptophan and 5-HTP are chemical precursors for the synthesis of serotonin is presumably the reason for the claim of their efficacy in the treatment of problems related to mood, sleep, and appetite (Murray 1999).

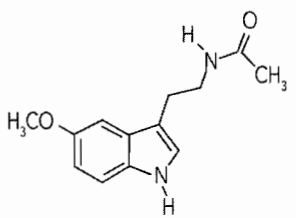

Figure 10. Melatonin.

Melatonin (fig. 10) is a hormone produced from serotonin in the pineal gland, which is embedded within the brain. It is released into the brain and general blood circulation and is involved in the regulation of the sleep-wake cycle and other circadian biological clock processes.

N,N-dimethyltryptamine (DMT) (fig. 6) has been found to occur endogenously at very low concentrations within the human brain, cerebrospinal fluid, and blood. Its function is unknown, but some have speculated that it plays neurotransmitter-like roles in psychotic mental states and dream-sleep imagery (Barker et al. 1981; Callaway 1988; Strassman 2001). Thus, all humans are, presumably at all times, in possession of a Schedule 1 substance and therefore in violation of United States and international law!

METABOLISM OF TRYPTAMINES BY MONOAMINE OXIDASE

Most tryptamine molecules are metabolized by the enzyme *monoamine oxidase* (MAO). MAO actually occurs in two different forms, MAO-A and MAO-B, which have preferences for different neurotransmitter molecules. MAO-A oxidizes the terminal amine of the tryptamines to an imine. This imine then undergoes nonenzymatic hydrolysis to an aldehyde that is subsequently converted to a carboxylic acid by a second enzyme, aldehyde dehydrogenase. The result is the conversion of the tryptamine into an acidic molecule, called an indole-3-acetic acid, which lacks psychoactivity. DMT is converted into indole acetic acid, whereas serotonin is converted into 5-hydroxyindole acetic acid (5-HIAA), and psilocin is converted into 4-hydroxyindole acetic acid.

The two forms of MAO are found throughout the body, including in the nervous system, where they function to inactivate monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine. MAO is also found in the liver, where it is involved in the metabolism of amines taken in through the digestive system. MAO in the liver will limit the bioavailability of some tryptamines that are orally ingested. For example, DMT lacks significant oral activity due to breakdown by MAO in the liver. However, psilocybin, psilocin, and baeocystin are orally active. Apparently the presence of the 4-oxygen substituent on these latter tryptamines confers resistance to MAO because tryptamines lacking this substituent, or those with the oxygen moved to the 5-indole position, are readily degraded by MAO.

There may be some unique chemical interaction between the tryptamine side chain and the 4-oxygen substituent. A study by Migliaccio et al. (1981) found that psilocin had much greater lipid solubility than bufotenin (5-hydroxy-DMT), and that the amino group of psilocin was also less basic. The decreased basicity of psilocin results in a larger fraction of this molecule being in an uncharged (unionized) form in the body, which leads to enhanced intestinal absorption and enhanced penetration into the brain, relative to a tryptamine such as bufotenin. Those workers speculated that hydrogen bonding could occur between the 4-hydroxy group and the amine side chain, as illustrated in figures 11A and 11B. It was noted that such a hydrogen bond, if it indeed

formed, need only be a weak one to explain their results on basicity and lipid solubility. Computer modeling shows that because of the particular geometry of the indole ring, the illustrated structure has almost ideal geometry for hydrogen bonding.

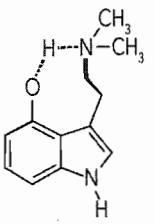

Figure 11A. Possible hydrogen bonding interaction in psilocin.

It is not unreasonable to speculate that the interaction between the 4-hydroxy and the side chain amino group also lies at the heart of the resistance of 4-oxygenated tryptamines to attack by MAO. Although still controversial, MAO catalysis is generally thought to proceed by what is called a single-electron-transfer pathway. According to this mechanism, the initial step of this catalytic process involves transfer of one electron from the nitrogen lone pair of the amine group to oxidized flavin adenine dinucleotide (FAD), a necessary cofactor for the reaction, to generate an aminyl radical cation and reduced FAD. The important point to be made here is that the type of intramolecular interaction illustrated between the 4-hydroxy and the side chain amine group (figs. 11A and 11B) would make the nitrogen lone pair of electrons less available for this initial step of the MAO degradation process. Hence, by making the first step of the MAO mechanism less efficient, the whole degradation process is blocked.

The oral activity of tryptamines that are degraded by MAO can be enhanced by chemicals called *monoamine oxidase inhibitors* (MAOI). This synergism serves as the basis for the Amazonian entheogenic brew, ayahuasca (which means "vine of the souls"), where DMT is rendered orally active by the presence of MAOI harmala alkaloids from the plant *Banisteriopsis caapi* (Metzner 1999). Another botanical source of the MAOI harmala alkaloids *harmaline* and *harmine* is the seed of the Syrian rue, *Peganum harmala*, a bush related to the creosote, native to Asia and Africa. There are anecdotal reports that the potency of psilocybin

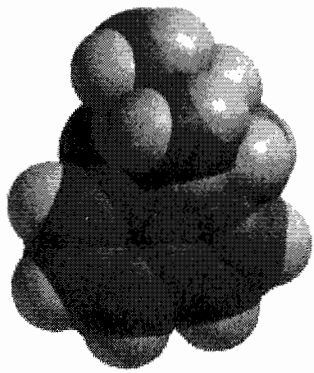

Figure 11B. A space-filling representation of the framework drawing of psilocin depicted in Figure 11A. The molecular structures depicted in the figures in this chapter are two-dimensional, line-drawing representations of the molecules that show how the atoms are connected and allow for ready comparison of similarity between molecules. Molecules actually have three-dimensional shapes in which each of the constituent atoms occupies a volume defined by its cloud of electrons. Linus Pauling and two of his colleagues, Robert Corey and Walter Koltun, first developed a form of molecular models to depict the 3-dimensional space-filling aspect of molecules in the way shown in this figure.

mushrooms can be increased by perhaps a factor of two by ingestion of 1 to 3 grams of ground *Peganum harmala* seeds 30 minutes prior to ingestion of the mushrooms (DeKorne 1994).

Note: MAO inhibitors can have a profound impact on the metabolism of the monoamine neurotransmitters, serotonin, dopamine, and norepinephrine. Phenethylamines such as amphetamine and MDMA (3,4-methylenedioxymethamphetamine, "ecstasy") cause the release from axon terminals of monoamine neurotransmitters. Normally these amines are rapidly degraded by MAO and have little physiological effect. In the presence of an MAOI, however, these transmitters can accumulate and lead to severe and potentially fatal consequences. Thus, it is essential to avoid using MAOIs together with any amine that might stress the cardiovascular system (such as amphetamine or MDMA). One must also avoid the ingestion of MAOIs if one is using any of the antidepressant medications that block the uptake of serotonin into neurons, such as SSRIs (like Prozac, Paxil, Zoloft, or celexa) and certain tricyclic antidepressants. Such a combination could result in toxic overactivity of serotonergic neurotransmission and produce what is called a serotonin

syndrome. This potentially life-threatening condition may include symptoms such as mental confusion, anxiety, hypomania, hallucinations, hyperthermia, tachycardia, muscle rigidity, and tremor. Your physician will counsel you that it is best (and sometimes essential) to avoid MAOIs whenever any antidepressant medications are being used.

CROSSING THE BLOOD-BRAIN BARRIER

The particular way in which the walls of the blood vessels in the central nervous system are constructed results in their being impermeable to many substances, thereby limiting the ability of molecules to pass from the blood into the brain. This phenomenon is called the "blood-brain barrier." Molecules may cross the blood-brain barrier by mechanisms of active transport, or by being sufficiently lipid soluble that they can diffuse through the hydrophobic core of the lipid membranes that form the boundaries of the cells composing the blood-brain barrier. Most psychoactive drugs are sufficiently lipid soluble that they can pass from the blood into the brain by passive diffusion.

It was noted earlier that psilocin is less basic than bufotenin by a factor of more than ten-fold. The consequence of this is that there is less of the protonated form of psilocin in the blood, and therefore more of the free base, which is the more lipid-soluble species that actually crosses the blood-brain barrier. In that earlier cited study (Migliaccio et al. 1981), it was shown that even after one considers the reduced ionization of psilocin, this molecule still has greater lipid solubility than would be predicted. Again, it appears that some interaction between the 4-hydroxy and the amino group of the side chain may be responsible, perhaps a hydrogen bond between the 4-hydroxy and the amine (fig. 11A). The same effects are not seen in bufotenin, 5-hydroxy-DMT, which has much lower lipid solubility than psilocin, and also is a substrate for MAO. The atomic distances would preclude such an intramolecular hydrogen bond in bufotenin. Thus, not only does the 4-oxygen substituent of psilocin appear to confer resistance to degradation by MAO, but it also enhances lipid solubility, making the molecule enter the brain more readily.

NEUROCHEMISTRY

Entheogens pharmacologically related to psilocin produce profound changes in thought, feeling, perception, and conscious awareness. They produce alterations in some very basic brain neurochemical processes and many entheogenic chemicals share at least some common neurochemical mechanisms. Interaction with brain circuitry employing the neurotransmitter serotonin is believed to be central to the brain mechanism of entheogens, including the tryptamine entheogens found in psilocybin mushrooms.

Serotonin has many different types of receptors, characterized by differences in the amino-acid sequences of the protein that folds across the nerve cell membrane to form the receptor. All known serotonin receptors except one belong to a large family of receptors called G-protein (GTP-binding protein) coupled receptors. (The exception is the 5-HT3 receptor, which is a cation channel.) G-protein coupled receptor proteins are thought to be comprised of seven alpha-helical segments that span the neuronal membrane, with external and internal connecting loops. Different types of G-protein coupled receptors have certain key amino acids that appear in all such receptors, but also have differences that give them their unique properties of recognizing a specific neurotransmitter and producing a particular type of intracellular signaling message (fig. 12).

Molecules that activate G-protein coupled receptors and cause an intracellular signal to be generated are called *agonists*. Other molecules can occupy the receptor binding site and prevent the neurotransmitter from gaining access and generating a signal. Those drugs are called *antagonists*. Interaction of the neurotransmitter with a specific extracellular binding site on the receptor causes a change in the shape of the receptor that leads to the binding and activation of a G-protein on the side of the receptor that is within the neuronal cell. The activated G-protein then goes on to initiate various intracellular biochemical processes that may result in alterations of the activities of various enzymes, changes in cyclic nucleotide levels, and cleavage of membrane phospholipids. Such processes may cause the opening or closing of ion channels, which will alter membrane electric potential with resulting excitation or inhibition of neuronal activity.

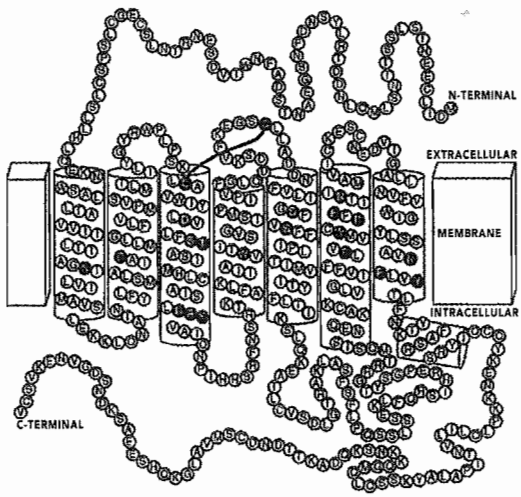

Figure 12. Schematic representation of the human serotonin 5-HT2A receptor. Each small circle represents one of the 471 amino acids that comprise the receptor and the alphabetic characters are the standard abbreviations for amino acids (e.g., alanine=A, glycine=G, tyrosine=Y, etc.). The protein structure is believed to be comprised of seven alpha-helices packed together and spanning the neuronal cell membrane; these are represented by the cylindrical segments. Although these helical segments are shown here arranged in a linear fashion for ease of visualization, in the actual receptor they adopt a more barrel-like packing arrangement, with a central cavity for binding serotonin. The connecting loops between the helical segments inside the cell membrane (at the bottom of the figure) also are arranged in specific shapes but are less well understood. Activating ligands (e.g., serotonin or psilocin) approach the receptor from the extracellular side of the receptor, which is at the top of the figure. After the agonist binds to the receptor, the bundle of helical segments rearranges, causing the connecting chains on the interior of the cell membrane (at the bottom in the figure) to change their 3-dimensional shape. This latter effect leads to the generation of a signal inside the cell by way of the association of the intracellular loops with the binding of a G-protein. When the intracellular loops change shape, a process is initiated within the associated G-protein that leads it to bind GTP (guanosine triphosphate), dissociate from the receptor, and become "activated." These activated G-proteins then interact with other enzymes within the cell that, in turn, increase or decrease in activity, leading to various changes in the cellular biochemistry that constitute the intracellular "signal" that ultimately derives from the agonist molecule. Amino acids of importance for maintaining structure/function are shown in black, and those thought necessary to recognize and interact with the agonist ligand are shown in gray. (Figure provided courtesy of Dr. James Chambers)

Still other changes may be induced by activating transcription factors within the cell nucleus, leading to alterations in gene expression and subsequent protein synthesis. In short, many things may happen following the activation of a G-protein coupled receptor by a neurotransmitter or other agonist, some things relatively quickly, and some over longer periods of time.

Although serotonin activates all subtypes of serotonin receptors, tryptamine entheogens interact predominantly with the type-2 serotonin receptors. In this subfamily, comprised of three members: 5-HT2A, 5-HT2B, and 5-HT2C, it is currently believed that the key receptor is the one designated as the 5-HT2A (Aghajanian and Marek 1999). Although other receptors could be involved, this is the one site that has been consistently implicated as most important. Antagonists that block this receptor appear to block the major psychoactive effects of psilocybin in humans (Vollenweider et al. 1998).

The 5-HT2A receptor has been the focus of increased interest in recent years for a variety of reasons. It has been implicated in a number of psychiatric disorders, consistent with its important role in the regulation of cognition and mood states. Furthermore, it is found in highest density throughout the cerebral cortex of the mammalian brain (Willins et al. 1997; Jakab and Goldman-Rakic 1998). This finding is significant because the cerebral cortex is the most recent and largest evolutionary addition to the brain. The frontal cortex of the human brain is very involved in judgment, planning, and complex reasoning (so-called "executive functions"), emotional processing, and language, while more posterior regions of the cortex (temporal, parietal, and occipital lobes) are responsible for the analysis and interpretation of sensory information. Jakab and Goldman-Rakic (1998) indicate that 5-HT2A receptors are highest in density in regions of the frontal cortex, temporal cortex, and occipital cortex, as well as the cingulate cortex of the limbic system. These workers also note that 5-HT2A receptors are often located on promixal dendritic regions rather than on more distal dendritic spines, the former location resulting in a greater impact on modulation of cell activity. More recently, Williams et al. (2002) have found that prefrontal cortical 5-HT2A receptors have a previously unrecognized role in the cognitive function of working memory.

These studies all indicate that the site that is believed to be essential to the action of entheogens, the serotonin 5-HT2A receptor, is located in key areas of the brain that are responsible for memory, sensory processing, and a variety of functions that make us uniquely human. There is great research interest today in the neuroscience community in these receptors. As they are studied further, we shall no doubt learn more about how they modulate our awareness, and how they are affected by entheogens. Indeed, one might suppose that continued study along these lines will result in increasing understanding of the cellular and molecular aspects of entheogenic experiences!

OTHER PSYCHOACTIVE FUNGI, BRIEFLY NOTED

Although psilocybin-containing fungi are the most well understood, there are other fungi with psychoactive properties, although their neurochemistry is completely different. *Amanita muscaria* is found throughout the world and is known as a picturesque mushroom with a bright red cap. In the decade following his work with the *Psilocybe* mushrooms of Mexico, R. Gordon Wasson (1968, 1971) proposed that *Amanita muscaria* might be the sacred intoxicant "Soma" mentioned in the ancient Asian texts of the *Rig Veda*. Ott (1993) reviews many reports of psychoactive and entheogenic effects from ingestion of *Amanita muscaria*. Physiologically active chemicals in this mushroom include *muscarine*, isolated from *Amanita muscaria* in 1869 by German chemists. Muscarine affects the peripheral nervous system by activating muscarinic acetylcholine receptors in the parasympathetic branch of the autonomic nervous system. It is a quaternary amine carrying a fixed positive charge and, as such, does not cross the blood-brain barrier. Thus, there are no effects of muscarine on the brain. In addition, it is found only in small quantities in the mushroom.

The psychoactive effects of *Amanita muscaria* are believed to be due to the chemicals *ibotenic acid* (fig. 13) and *muscimol* (fig. 14). Ott (1993) summarizes reports that there are entheogenic (hallucinogenic) effects in humans following oral doses of 50–100 mg of ibotenic acid or 10–15 mg of muscimol. Once in the blood circulation, muscimol would cross the blood-brain barrier by inefficient diffusion. Ibotenic

acid would cross the blood-brain barrier using the transporter protein for certain amino acids. Ibotenic acid can be decarboxylated by the enzyme aromatic amino acid decarboxylase, found both within the brain and in the periphery, to form muscimol. Ibotenic acid is known to be an agonist at the NMDA-type glutamate receptor, one of the primary excitatory neurotransmitter receptors in the brain, and can lead to the so-called excitotoxic cell death of neurons. Muscimol is an agonist at the GABA-A receptor, the primary inhibitory neurotransmitter receptor in the brain. How these various receptor interactions may lead to hallucinogenic effects is unknown. What is clear, however, is that these effects are behaviorally and neurochemically very different from those of the tryptamine entheogens that occur in *Psilocybe* mushrooms.

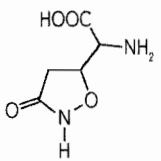

Figure 13. Ibotenic Acid.

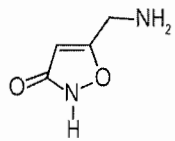

Figure 14. Muscimol.

It also should be noted that within the genus *Amanita* there exist several species of deadly mushrooms. They are among the small number of mushroom species the ingestion of which can prove fatal. These species include *Amanita phalloides* and *Amanita viA*, both of which contain small peptides called amanitins that inactivate RNA polymerase and cause irreversible damage to liver function.

A final example of a psychoactive fungus is the ergot *Claviceps purpurea*, which grows on grains such as rye and wheat, and from which Hofmann isolated the ergot-alkaloid precursor for his synthesis of LSD (lysergic acid diethylamide) (Hofmann 1980). Hofmann (in Wasson et al. 1998) has also established that the *Claviceps purpurea* fungus itself contains pharmacologically-active alkaloids in the form of ergonovine (lysergic acid propanolamide) and lysergic acid amide (fig. 15). The ergot alkaloids, in general, act at many different types of receptors, and the overall alkaloidal composition of ergot fungus makes it quite toxic. Nevertheless, there are a variety of strains of *Claviceps*, with differing

alkaloid content, some of which likely are more toxic than others. Wasson, Hofmann, and Ruck (1998) further proposed that ingestion of *Claviceps purpurea* or related fungi growing on cultivated grains or wild grasses may have been the basis for an entheogenic ritual of ancient Greece called the Eleusinian Mysteries. The neurochemistry of these molecules, closely related to LSD in structure, would largely be through serotonin-receptor mechanisms similar to those described above for psilocin.

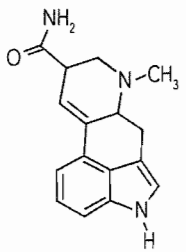

Figure 15. Lysergic Acid Amide.

CODA

The serotonergic neurons of the raphe nuclei in the brainstem innervate the entire brain and likely exert substantial modulatory effects on our perceptions, emotions, thought processes, and conscious awareness—the mental states that may collectively be called "the mind." Psilocybin and related tryptamines from *Psilocybe* fungi are believed to produce their profound effects on the brain and mind by way of interacting with 5-HT2A receptors in the cerebral cortex, limbic system, and elsewhere. As chemical probes that might lead to a better understanding of how the neural circuitry of the brain is related to the nature of mind, they offer unprecedented opportunities!

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