Review Article

Historical overview of psychoactive mushrooms

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Humans have used psychoactive mushrooms for medical, recreational, religious and ritual purposes since pre-history. Previous studies have clarified that psychoactive mushrooms produce psychoactive agents such as psilocybin, psilocin, ibotenic acid, and muscimol. However, the status of psychoactive mushrooms in most countries as illegal hallucinogens has prevented full investigation of their biochemical properties. Recent studies have shown that many psychoactive agents pass through the blood-brain barrier and act on neurotransmitter receptors. Psilocybin and psilocin are 5-HT_{1A} and 5-$HT_{2A/C}$ receptor agonists, respectively, while ibotenic acid is a glutamic acid receptor agonist and muscimol is a $GABA_A$ receptor agonist. A new psychoactive agent, aeruginascin, has also been isolated from psychoactive mushrooms, and it is expected that more useful compounds will be discovered as the technology of component analysis advances. In addition, it has been shown that psilocybin and psilocin have high therapeutic efficiency for obsessive-compulsive disorder, which is a difficult-to-treat nervous disease. The increase of nervous diseases in modern society has thus given new importance to psychoactive mushrooms. In this review, we summarize the history of the use of psychoactive mushrooms, from pre-history to the modern age, describe their classification and distribution, survey previous studies, and discuss their therapeutic effects for difficult-to-treat nervous disease. The utilization and distribution of psychoactive mushrooms in Japan is given special attention, as there are few articles on this subject.

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Introduction

Recently, the increasing number of people suffering from mental disease has become a serious social problem. Additionally, not only the number but also the range of disorders has been increasing; obsessive-compulsive disorder (OCD), for example, has earned recognition as mental disease only recently. As this phenomenon is likely to continue for the foreseeable future, it is likely that psychiatric studies will grow in importance, as further investigation of the link between the mind and body will be needed.

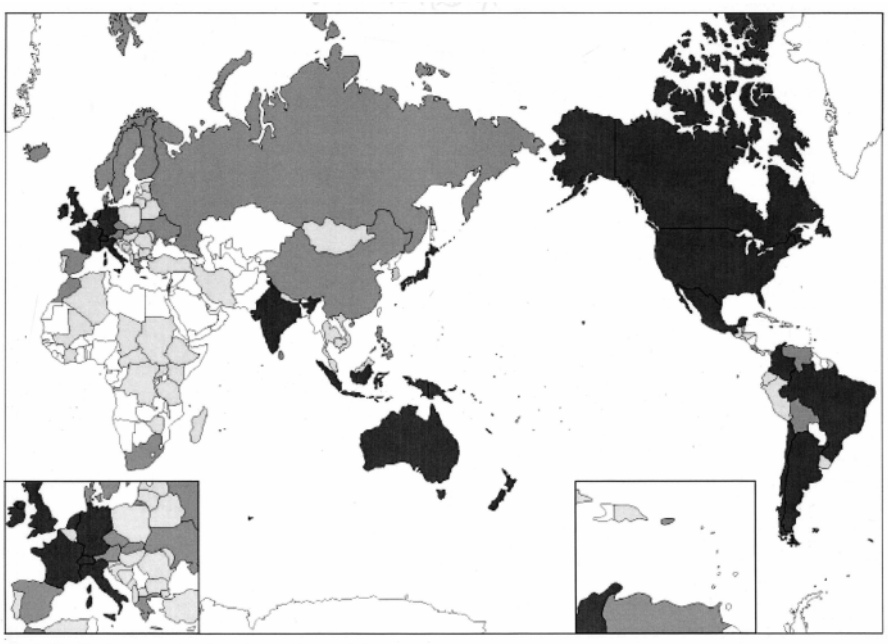


Fig.1 Distribution map of psychoactive mushrooms habitants

Light gray countries: 1-5 reports of psychoactive, Gray countries: 6-15 reports of psychoactive mushrooms, Black countries: more than 15 reports of psychoactive mushrooms

Humans have used psychoactive mushrooms for medical (physical and mental), recreational, religious and ritual uses (as tool for conversations with the inner self or God) since pre-history. Similar to alcoholic beverages, psychoactive mushrooms have had a long and generally positive relationship with humans.

Previous research has demonstrated that certain substances passing through the blood-brain barrier affect the central nervous system and cause hallucinogenic effects. Natural products that have the ability to pass through the blood-brain barrier are very valuable, and research on these substances is considered increasingly important. Moreover, recent studies have shown that substances produced by psychoactive mushrooms are highly effective for the treatment of intractable nervous diseases. Thus, these mushrooms have potential value as a novel pharmacotherapy' or something similar.

However, the number of comprehensive papers on psychoactive mushrooms is limited. In particular, for Japanese psychoactive mushrooms, there has been no comprehensive report on the classification, history and previous studies of these mushrooms. Hence, this article focuses on the history of the use of psychoactive mushrooms to comprehensively summarize their classification, distribution and active components, with an emphasis on Japanese psychoactive mushrooms.

Classification and distribution

Psychoactive mushrooms are generally classified as poisonous mushrooms. Lincoff and Michell developed a classification method for mushroom poisonings in 1977 which is still in wide use today[1,2]. Mushroom poisonings are roughly grouped into the following four categories: protoplast poisoning, autonomic nerve poisoning, central nerve poisoning, and stomach and intestine poisoning. Psychoactive mushrooms poisonings belong in the category of central nerve poisoning. When ingested, the mushrooms cause central nervous symptoms, including hallucinations, auditory hallucinations and mental alterations, as well as physical symptoms including spasm, numbness, and intoxication. These symptoms are expressed for 20 minutes to two hours after ingestion and are usually transient.

Guzman *et al.*(1998)[3] divided psychoactive mushrooms into four groups.

The first group comprises mushrooms that produce psilocybin, psilocin, and their derivatives. Psilocybin and psilocin are similar in structure to serotonin, an intracerebral neurotransmitter, and act on serotonin receptors in the brain to cause hallucinations. Many of the so-called called "magic mushrooms" used for recreational purposes belong to this group of psychoactive mushrooms. The main genera include *Psilocybe*, represented by *Psilocybe cubensis* and *Psilocybe cyanescens* Wakefield, and *Panaeolus*, represented by *Panaeolus papilionaceus* and *Panaeolus sphinctrinus, Gymnopilus, Copelandia, Hyboloma, Pluteus, Inocybe, Conocybe,* and *Panaeolina.*

The second group comprises mushrooms that produce ibotenic acid and muscimol. Ibotenic acid is a non-protein amino acid with an isoxazole skeleton and acts as an agonist to glutamic acid. Ibotenic acid is decarboxylated to muscimol, which acts as an agonist to GABA (gamma-aminobutyric acid). Mushrooms

Table 1 Species of Japanese psychoactive mushrooms

Groupe	Scientific name	Japanese name	References
I	*Aglocybe farinacea* Hongo	Tsubanashi-fumizukitake	[5-7]
II	*Amanita ibotengutake* T. Oda, C. Tanaka & Tsuda	Ibo-tengutake	[7,8]
II	*A. muscaria* (L.:Fr.) Pers	Beni-tengutake	[6,9]
II	*A. pantherina* (DC.:Fr.) Krombh	Tengutake	[6,9-11]
I	*Anellaria antillarum* (Fr.) Hongo	Tsuyamagusotake or Jingasatake-modoki	[6,7,12]
I	*A.* (Sow.:Fr.) Peason & Dennis	Jingasatake	[6,12]
I	*Copelandia cyanescens* (Berk. & Br.) Sing	Aizome-hikagetake	[6,13]
I	*C. tropicalis* Ola'h s. Hongo	Variant of Aizome-hikagetake	[3,6]
I	*Gerronema fibula* (Bull.:Fr.) Sing	Hinanohigasa	[6,7,9]
I	*Gymnopilus aeruginosus* (Peck) Sing	Midorisugitake	[5,6,9]
I	*G. liquiritiae* (Pers.:Fr.) Karst	Chatsumutake	[5-7,9]
I	*G. spectabilis* (Fr.) Sing	Oh-waraitake	[5,6,9]
I	*Hygrocybe psittacina* (Schaeff.:Fr.) Wunsche	Wakakusatake or Rokushougasa	[5-7,9,14]
I	*Panaeolina foenisecii* (Pers.:Fr.) Maire	Hime-shibafutake	[6,13]
I	*Panaeolus papilionaceus* (Bull.:Fr.) Quel	Waraitake	[12,13,16]
I	*P. semiovata* (Sow.:Fr.) Lund	Saigyougasa	[6,12]
I	*P. sphinctrinus* (Fr.) Quel	Hikagetake	[9,12,13]
I	*P. subbalteatus* (Berk. & Br.) Sacc	Sembon-saigyougasa	[9,12,13]
I	*Pluteus salicinus* (Pers.:Fr.) Kummer	Biroudo-benihidatake	[6,7]
I	*Psathyrella candolliana* (Fr.:Fr.) Maire	Itachitake	[7,12]
I	*Psilocybe argentipes* K.Yokoyama	Hikage-shibiretake	[12,16,17]
I	*P. coprophila* (Bull.:Fr.) Kummer	Tofuntake	[6,7,12]
I	*P. cubensis* (Earle) Singer	Minami-shibiretake	[4]
I	*P. fasciata* Hongo	Aisembontake	[6,9]
I	*P. subaeruginascens* Hohnel	Oh-shibiretake	[6,.7]
I	*P. subaeruginascens* Hohnel var. *septentrionalis* Guzman	Variant of Oh-shibiretake	[3,6]
I	*P. subaeruginascens* Hohnel var. *subaeruginascens*	Variant of Oh-shibiretake	[5-7,9]
I	*P. subcaerulipes* Hongo	Aizome-shibafutake	[12,16,18]
I	*P. venenata* (Imai) Imazeki & Hongo	Shibiretake	[9,16]
II	*Tricholoma muscarium* Kawamura	Haetori-shimeji	[6,9]

*Groupe I : "mainly produce psilocybin and psilocin groupe", Groupe II : "mainly produce ibotenic acid and muscimol groupe"

of the second group belong to genus *Amanita*, represented by *Amanita muscaria* and *Amanita pantherina*. However, *A. pantherina* and *A. muscaria* produce not only ibotenic acid and muscimol but also other poisons, often causing complex poisoning symptoms by several agents.

The third group is made up of the genus *Claviceps*, which produces ergot alkaloids and is represented by *Claviceps purpurea*, and the genus *Cordyceps*. The fourth group has been subjected to neither credible chemical research nor the identification of its active components. Several species of *Psilocybe* and *Russula* belong to this group, and some members (as well as many species of *Amanita*) produce serotonin, baeocystine, norbaeosystine and bufotenine, indole alkaloids derived from tryptophane, from which psilocybin and psilocin are also derived.

The figure below (Fig.1) is based on a report by Guzman *et al.* (1998)[3] and shows a distribution map of psychoactive mushrooms habitants. Psychoactive mushrooms are distributed nearly worldwide, with reports published in Canada, the U.S. (particularly the Northwest and Northeast), Mexico, South America, Europe, India, Japan, New Guinea, and Australia (particularly the eastern part). Indigenous peoples in these regions are said to have traditionally used psychoactive mushrooms.

Japanese psychoactive mushrooms

Numerous psychoactive mushrooms that inhabit Japan, including the 30 species listed below (Table 1), and this number is projected to increase further as research advances. In addition, *P. cubensis*, whose culture kits have widely been distributed, was confirmed to grow wild in Japan[4]. There is concern that the prevalence of ready-to-culture, exotic species of psychoactive mushrooms will affect the ecological status of indigenous species in Japan.

Most psychoactive mushrooms that have been non-purposely ingested in Japan are *A. pantherina* and *Psilocybe argentipes*[19]. However, the number of mushroom poisonings due to unintentional ingestion is relatively small compared with the total number of mushroom poisonings in Japan, with no confirmed cases of death[11,20].

Musha *et al.*(1986)[21], (1988)[22] reported detailed records of poisoning by *P. argentipes* which inhabit only in Japan, and classified the symptoms into the following three groups: physical symptoms alone, alterations mainly in visual sensation, and mental alterations. The physical symptoms observed include a feeling of drunkenness, heat and cold sensations, numbness, weakness, the feeling of floating, headache, and sleepiness. These are basic symptoms that appear regardless of dose. In addition, physical symptoms are often short-lived and mild. Observed alterations in visual sensation included oscillating vision, colored vision, changes in the perception of light intensity, and photoma. Changes in other senses, including auditory hallucination, were also reported. Mental symptoms, which indicate mental alterations, are roughly divided into the following two groups: a dreamy state and stupor without mental excitation, and confusion with mental excitation. These symptoms resemble poisoning symptoms caused by psychoactive mushrooms reported overseas.

History of psychoactive mushrooms usage

Humans have used psychoactive mushrooms, which cause changes in visual sensation, hallucination and mental alterations, for religious, medical and recreational purposes.

Pre-modern age

Because the relationship between psychoactive mushrooms and humankind is extremely old, records showing the relationship date back to so-called remains. The oldest record is believed to be wall paintings discovered in Tassili, located in the Sahara desert in the southern part of Algeria. Many of these are believed to be related to psychoactive mushrooms, among them a symbolic painting drawn around 3500 B.C. showing a shaman dancing with a mushroom in his hands. The mushroom and the head of the shaman, who is wearing mushroom-shaped hat, are connected with a broken line, suggesting a mental linkage. This painting is believed to show a psychoactive mushrooms being used in a religious rite[23].

In the Scandinavian Peninsula in northern Europe, numerous pieces of bronzeware and wall paintings with a mushroom motif, believed to have been created during the Bronze Age (3000 B.C. to 500 A.D), have been found. Based on a tradition of use in Scandinavia, morphological similarity and the abundance of mycorrhiza-forming white birch and pine trees, Kaplan (1975)[24] proposed that the mushrooms depicted was A. muscaria, a psychoactive mushrooms.

Numerous Mayan artifacts known as "mushroom stones" have been discovered throughout modern Guatemala in Central and South America. These stones are mushroom-shaped icons approximately 30 cm high, with human and animal carvings in the grip, and are thought to date to the Pre-classic Period of Mayan civilization (500-200 B.C). Although there is a theory that these stones represent not mushrooms but the penis, the Mayan civilization is known to have considered psychoactive mushrooms sacred and an object of religious veneration[25,26].

Along with the Aztec civilization, the Mayans used psychoactive mushrooms mainly for religious rites, and some regions still retain these traditions. The Spanish conquistadors destroyed most artifacts from these civilizations, leaving little information on how mushrooms were used; however, two Spanish sources from this period have survived. The first, Fray Bernardino de Sahagun, was a Franciscan monk who worked as a missionary in Mexico for more than 60 years between 1529 and 1590[27,28]. While converting the local indigenous population, he began recording in detail the religion, history and culture of Aztec society, and their surrounding environment. Sahagun's "*Historai de las Cosas de Nueva Espana*" eventually spanned 12 volumes, half of which were written in the indigenous Nāhuatl language using the Latin alphabet. The book is an excellent record of the indigenous culture during the mid-1550s, and Sahagun left detailed descriptions of psychoactive mushrooms called *teonanācatl*, which means "god's flesh" in the Aztec language. According to Sahagun, *teonanācatl* was used mainly for rites, was harmless, and induced a feeling of drunkenness similar to that caused by wine. When ingested in large doses, it caused varied visual hallucinations and mental alterations.

The second record is attributed to Francisco Hernandez, a court physician for Phillip II, King of Spain, who was dispatched to Mexico in 1570 to conduct a botanical survey; he also studied the herbal treatments practiced by the indigenous peoples in Central America[27,28]. Hernandez was able to identify more than 3,000 plants unknown to Europe, and produced a 16-volume manuscript comprising 893 pages of description and 2071 pages of drawings before returning to Spain in 1577. However, this monograph was not made available to the public until its first publication in Mexico in 1615, after Hernandez's death, and was not published in Europe until 1651. In "*Nova plantarum historia Mexicana*", Hernandez described three psychoactive mush-

rooms considered sacred by the indigenous people of Mexico. According to his descriptions, the first mushroom caused uncontrollable laughter, while the second caused varied visual hallucinations, such as visions of warriors and devils. These two mushrooms were deep yellow and had a bitter taste. The third mushroom was difficult to obtain and thus very valuable, and was used for rites and pre-ritual preparations. When ingested, it was said to cause either wonderful or dire hallucinations throughout the night, depending on the mental condition of the person who took it. The third mushroom was described as yellowish brown, with a bitter taste. According to Hernandez, none of the three mushrooms was lethal. Hernandez's descriptions are significant in that they provide evidence that a number of psychoactive mushrooms were used in Mesoamerica. Although samples of these mushrooms were brought back to Spain, the psychoactive substances, which are unstable, apparently lost their activity during transport, and their presence was reputedly ignored upon arrival in Europe.

Berlant (2005)[29] proposed a theory that psychoactive mushrooms were associated with the Egyptian civilization; because of many psychoactive mushrooms-shaped remains and inscriptions in a tomb of Pharaoh. The Aryans, who invaded India at around 2000 B.C., were described using a psychoactive drink called "soma" to raise morale for religious rites and combat. Wasson *et al.* theorized that soma was actually *A. muscaria*[30]. Wohlberg (1990)[31] proposed that soma was eventually brought to ancient Greece. Wasson also suggested that psychoactive mushrooms were used in the "Eleusinian Mysteries", a secret ceremony practiced in Greece around 1400-1100 B.C. which later developed into a prototype for esoteric religions[32]. Hajicek-Dobberstein (1995)[33] postulated that psychoactive mushrooms may have been used to attain spiritual enlightenment for early Buddhism; because some contents of Buddhist manuscripts from the second to ninth centuries.

However, due to the age of these religions, information about the real origin of their rites are rarely shared with outsiders. Thus, many of these theories on relationships between the ancient religions and psychoactive mushrooms are based primarily on conjecture.

A. muscaria has been used worldwide as a psychoactive agent. Wasson (1979)[34] reported that the Objway and Algonkin tribes, indigenous North American tribes, have and continue to use psychoactive mushrooms, including *A. muscaria*, traditionally known as "Miskwedo". Wasson was given permission by Keeway-dinoquay, the leader of the Objway tribe, to participate in a rite using Miskwedo and listen to folklore passed down through generations by oral recitation[35]. Dunn (1973)[36] and Saar (1991)[37] described the traditional use of *A. muscaria* in Siberia and Northeast Asia, while Harkonen (1997)[38] reported the use of psychoactive mushrooms, mainly *A. muscaria*, for religious and medical purposes by Karelians in Finland, which is still practiced in some regions of the country.

Psychoactive mushrooms were used for a wide range of rites. Mushrooms were said to be used by shamans of Ugrian and Saami to reach a transcendental state in which they communicated with the spirits and gods, received divine messages, told fortunes, and searched for the souls of the diseased[39].

Modern age

While psychoactive mushrooms were long considered mythic in the modern age, several scholars began to study them in the early 1900s. In 1914, A.E. Merrill of Yale University published a detailed report of poisoning due to accidental ingestion of *P. papilionaceus* in Science[23]. A year later, W.E. Safford, an American botanist, attempted to identify *teonanācatl*, the psychoactive mushrooms traditionally used in religious rites in Mexico; he eventually concluded that no such mushrooms existed[23,40]. Many scholars accepted Safford's assertion, which remained an established theory for nearly 30 years, until R.G. Wasson provided conclusive evidence for the existence of *teonanācatl*.

In 1919, B.P. Reko published the results of a 25-year-long anthropological and botanical study of Mexico in which he described psychoactive mushrooms, including *teonanācatl*[23,28,41]. However, because of an error in an early part of the research, the report was considered invalid; Reko then submitted another report to the U.S. National Museum of Natural History in 1923 asserting that *teonanācatl*, as described by Sahagun, did in fact exist, and was still used under the same name by indigenous people in the Juarez tableland of Estado de Oaxaca, Mexico[23]. In 1936, the Australian anthropologist J. Weitlaner obtained *teonanācatl* in Estado de Oaxaca and sent it Reko, who in turn sent it to Harvard University. However, the university was unable to confirm the sample because it had not been kept in good condition[23,40]. That same year, V.A. Reko, brother of B.P. Reko, published "Magische Gifte". This book, which describes Mexican psychoactive plants, including *teonanācatl*, had a great influence on the academic community[42]; however, in the publication, V.A. Reko wrongly deduced that *teonanācatl* belonged to the genus *Amanita*.

I. Weitlaner *et al.* described participating in a rite in which psychoactive mushrooms was used in Huautla de Jimenez, Estado de Oaxaca, in 1938. Other anthropologists, such as J.B. Johnson,

also attended, making this the first documented case of participation in a rite involving a psychoactive mushrooms in the modern age[23,40]. In that same year, A. Hofmann, a chemist at Sandoz, a pharmaceutical firm based in Basel, Switzerland, synthesized LSD-25 (Lyserg-Säure-Diäthylamid) from lysergic acid, which is produced by the parasitizing rye *Claviceps purpurea*. However, because of animal experiments showed no marked action, LSD-25 was not taken up as a research subject for five years thereafter. In addition, R.E. Schultes, a botanist at Harvard University, obtained specimens of two psychoactive mushrooms in Estado de Oaxaca in 1938, confirmed that *teonanācatl* was a psychoactive mushrooms and was still used in rites, and brought the mushrooms back to Cambridge[23,27,40]. His field notes contained a description of *Psilocybe caerulescens* var. *Mazatecorum* Heim, which was later identified by R. Heim, a French mycologist. D. Linder, a Harvard mycologist, identified the two specimens Schultes brought back as *Panaeolus campanulatus* L Var. *sphinctrinus* and *Stropharia cubensis*[40].

Wasson, a physician, visited Mexico to confirm the religious use of mushrooms in 1953 and were guided to Huautla de Jimenez by Weitlaner[43]. Two years later, Wasson, joined by photographer A. Richardson, participated in a rite involving psychoactive mushrooms, which was subsequently described in an article eventually published in many well known magazines, including the popular American weekly *Life*. In the article, Wasson wrote that his fantastic experience of psychoactive mushrooms ingestion. The article elicited such a substantial response that psychoactive mushrooms gained worldwide recognition in only a few years. Wasson then invited R. Heim, a French mycologist, to Estado de Oaxaca, and asked him to survey the psychoactive mushrooms used in rites. Heim identified 14 genera, including *Psilocybe, Stropharia* and *Conocybe*, and a several subspecies, some of which were new fungal species[28]. Heim sent these fungal species to Hofmann in 1958. Hofmann isolated two active psychoactive substances from the *Psilocybe* genus, which he identified and named psilocybin and psilocin[27,28], and Sandoz, Hofmann's firm, started selling them as commercial products[23].

The psychoactive mushrooms discovered by Wasson soon became known worldwide as "magic mushrooms". Wasson also indexed ethnic mycological research papers to show that psychoactive mushrooms were used in various regions of the world[44]. "Hippies", individuals who denied conventional values and aimed to return to nature, used magic mushrooms for their psychotropic actions. However, because magic mushrooms were used as a narcotic, the public demanded their regulation. In 1966, the U.S. enacted a law prohibiting the production, trade or ingestion of hallucinogens such as mescaline and psilocybin, which were then traded underground[27]. Sandoz ceased the production and sale of LSD-25 and psilocybin in the same year[23]. Since then, psilocybin, psilocin and psychoactive mushrooms have increased in value as natural hallucinogens. However, malicious intentions, in which LSD was sold as psilocybin or psilocin or mixtures of LSD and a non-psychoactive mushrooms were sold, was in place for nearly a decade. L. Eneos published "A Key to the North American Psilocybin Mushroom" in 1970, which described sites and methods for amateurs to collect natural psychoactive mushrooms in detail and explained how to culture mycelia to mushrooms on agar media. Terence and Dennis McKenna discovered a new and efficient method for the private, home-based cultivation of *Psilocybe cubensis*, and published "Psilocybin: Magic Mushroom Growers Guide" in 1975 under the pseudonyms O.T. Oss and O.N. Oeric[23]. The guide sold very well, and was followed by similar publications that spread the home culture of psychoactive mushrooms worldwide in a short time. Today, law regulates psychoactive mushrooms in many countries; however a lot of adverse opinions following almost no dependent and less toxic.

Psychoactive mushrooms in Japan

Although psychoactive mushrooms have been used for religious and medical purposes worldwide since pre-history, there is no historical record of intentional use in Japan. The oldest record of poisoning by psychoactive mushrooms is reputedly "a story of nuns who climbed a mountain, ate a mushrooms, and danced" in "Konjaku Monogatari Shuu", a collection of stories compiled at the end of the Heian period in the 12th century. However, the collection contains no descriptions of hallucination[22]. Nonetheless, psychoactive mushrooms themselves were known to exist since ancient times, known as Odoritake (dance-inducing mushroom), Maitake (dance-inducing mushroom), or Waraitake (laugh-inducing mushroom). The name Maitake is the same as that for the edible maitake mushroom: It is said that joy of finding delicious mushrooms induced dance. Taxonomical differences between Maitake and the edible maitake were unclear for a long time.

The widespread use of the Internet facilitated the availability of culture kits for psychoactive mushrooms, rapidly spreading the recreational use of psychoactive mushrooms, since the end of the 1990s. The National Institute of Health Sciences reported that two mushroom species from culture kits sold in Europe, *Psilocybe cubensis* and *Psilocybe cyanescens*, comprised about 90% of all psychoactive mushrooms distributed for intentional

ingestion in Japan[22]. This fact shows that many psychoactive mushrooms used in Japan are cultured from kits imported from overseas. The number of inquiries to the Japan Poison Information Center received was one in 1997, but sharply increased to 10 in 1998, 19 in 1999, 32 in 2000, and 55 in 2001[45,46]. In addition, the danger of psychoactive mushrooms was illustrated by cases of users jumping out of windows, resulting in severe injury, or abusing psychoactive mushrooms as an illicit drug. These incidents were taken into consideration in the revision of the Japanese "Law for the Control of Narcotic Drugs, Psychotropic Substances, and their Raw Materials" in June 2002[47]. The revised law regulates psilocybin, psilocin and the mushrooms from which they are produced and prohibits their culture, possession, trade, and ingestion. The number of inquiries received by the Japan Poison Information Center before the law was enacted in 2000 was 33, which sharply decreased to three after the law was enacted in the same year, and further decreased to two the following year. It seems that psychoactive mushrooms use in Japan is currently very low.

Previous studies on psychoactive mushrooms

Studies on psychoactive mushrooms have been mainly taxonomical verifications, surveys and analyses of their narcotic use, extraction and analyses of their psychoactive components, and historical verifications. In a previous survey and analysis of their narcotic use, psychoactive mushrooms were mainly identified by morphology[48]. In recent years, however, the original species of the psychoactive mushrooms have been classified by base sequence analysis, which improves precision and widens applicability[45,49]. Effect of psychoactive mushrooms to brain center nervous system have not studied much. Future studies examining the effect of psychoactive mushrooms on the cerebral nervous system are required.

Mycelium characteristics and cultivation

With regard to mycelium characteristics, psychoactive mushrooms, which are not expected to be edible, have not been studied as much as other mushrooms. Singer *et al.*(1958)[50] showed that *P. cubensis* had an optimum temperature of 30℃ and died at 40℃, and both *Psilocybe mexicana* Heim and *Psilocybe caerulescens* var *mazatecorum* had an optimum temperature of 27℃ and died at 35℃. Concerning the effects of carbon and nitrogen sources as required nutrients for mycelia, Leung *et al.* (1969)[51] reported that *Psilocybe baeocystis* showed no mycelial growth at all on a medium with lactose as the carbon source and inhibited mycelial growth on a sucrose and galactose medium. Leung *et al.* also reported that a medium with glucose and another medium with trehalose both supported good mycelial growth, with the latter producing more psilocybin. The addition of tryptophane, a psilocybin precursor, did not change the production amount of psilocybin or its analogues. Regarding the effect of plant hormones on mycelia, Gartz *et al.*(1990)[52] reported that the addition of brassinosteroid, a plant growth promoter, markedly increased the speed and tended to increase the frequency of the fruiting body development of *P. cubensis*.

Past studies clearly showed that psychoactive mushrooms form fruiting bodies mainly on a medium with cereal, straw, feces, or manure. High relative humidity around 95% and good aeration are also considered necessary. According to Badham (1980)[53], light irradiation was essential for fruiting body development, with visible light in the short wave region being particularly effective. Soil covering has also been shown to be a good stimulus for fruiting body development.

Kitamoto *et al.*(1975)[54], (1980)[55] studied nutritional requirements for the fruiting body development of *Psilocybe panaeoliformis*. According to their results, the optimal range for the fruiting body development was narrow; deficiency or excess of nutrients resulted in malformed fruiting bodies. Glucose, trehalose and fructose were found to be good carbon sources for fruiting body formation, while glycerin, xylose and sucrose increased the frequency of fruiting body malformation, and thiamin was clarified to be essential. Optimal addition levels of major nutrients were found to be as follows: glucose, 1-2%; casamino acid, 0.032%; KH_2PO_4, 0.03%; $MgSO_4 \cdot 7H_2O$, 0.01%; and $CaCl_2 \cdot 2H_2O$, 0.01%.

Extraction and analysis

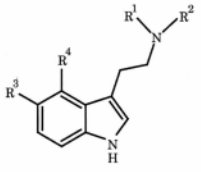
Over the nearly 40 years since the discovery of psilocybin and psilocin, numerous studies have investigated methods and conditions for extracting psychoactive components. Hofmann, who discovered psilocybin, found that both psilocybin and psilocin are soluble in methanol and aqueous ethanol solutions but insoluble in chloroform and petroleum[28]. Because Hofmann used mainly 100% methanol as an extraction solvent, most studies that followed adopted the same extraction method.

Wurst *et al.*(1992)[56] made the first significant discovery in research on extraction solvent, in which they showed that the largest yield of psilocybin was obtained with an aqueous 75% methanol solution saturated with potassium nitrate, and the largest yield of psilocin was obtained with an aqueous 75% ethanol solution. These data were significant in that optimal conditions

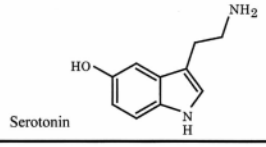
Table 2 Chemical structures of psychoactive agents

Tryptamine derivatives

Compound	R^1	R^2	R^3	R^4
Psilocybin	CH_3	CH_3	H	$OPO(OH)_2$
Psilocin	CH_3	CH_3	H	OH
Baeocystin	CH_3	H	H	$OPO(OH)_2$
Norbaeocystin	H	H	H	$OPO(OH)_2$
Bufotenin	CH_3	CH_3	OH	H



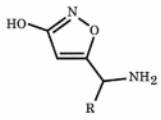
Similar neurotransmitter



Serotonin

Ibotenic acid derivatives

Compound	R
Ibotenic acid	COOH
Muscimol	H



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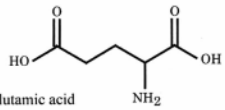
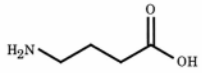


Glutamic acid



γ-aminobutyric acid

for extraction differed between psilocybin and psilocin. Gartz (1994)[57] also showed that amounts psilocybin and baeocystin by 100% methanol extraction lager than mixture of water and methanol; while amounts psilocin were lager by mixture of water and methanol. Based on these studies, Gartz showed that 100% methanol was the method of choice for measuring real contents of indole derivatives in mushrooms; heating an experimental condition, was responsible for the dephosphorylation of psilocybin to psilocin.

Jensen *et al.* recently (2006)[58] isolated aeruginascin (4-phosphoryloxy-*N,N,N*-trimethyltryptamine), a new hallucinogenic substance, from the mushroom *Inocybe aeruginascens* Babos, and identified its structure. They found that aeruginascin is similar in structure to bufotenidine, which is produced by frogs, and acts as an agonist on 5-HT_3 receptor. This discovery indicates possible new applications of hallucinogenic mushrooms.

Psilocybin and psilocin

Hofmann isolated and identified psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine) and psilocin (4-hydroxy-*N,N*-dimethyltryptamine) in 1958, which are the most important hallucinogens that mushrooms produce (Table 2)[27,28]. The structural similarity of psilocybin and psilocin to serotonin (5-hydroxytryptamine), a neurotransmitter also derived from tryptophane, is believed to be the cause for their action on the serotonin receptor in the brain and for hallucination.

Animal experiments showed that 50% of ingested psilocybin was absorbed by the stomach and intestine, 65% of the absorbed psilocybin was excreted into urine within 24 hours, and 15-20% of the absorbed psilocybin was excreted into bile and feces within 24 hours[59]. In addition, the majority of psilocybin remaining in the body was excreted within eight hours; and a small amount of psilocybin remaining in the body was excreted into urine in about seven days. Malitz *et al.*(1960)[60] confirmed that a dose-dependent administration of psilocybin to a human expressed physical symptoms at a dose equal to or more than 14 mg and visual hallucination at a dose greater than or equal to 30 mg. They also reported that the effects were reported within 30-60 minutes of administration and peaked within 90-150 minutes, with a large variance among individuals. In Japan, Miyoshi (1964)[61] administered psilocybin to humans to compare its psychological and physical effects with those of LSD-25 and reported that their effects were very similar[62]. LSD-25 is often used as a control, as it has a structure similar to serotonin as psilocybin and psilocin.

Cross tolerance due to structural similarity has also been found between LSD-25 and psilocybin and psilocin. In addition, it was suggested that psilocin is the substance that actually causes hallucination, because psilocybin was rapidly dephosphorylated to psilocin by alkaline phosphatase in the body[59,63,64]. However, the subsequent metabolic pathway has not been elucidated.

Advanced techniques for the synthesis of serotonin receptor ligands and for molecular biological research are enabling the elucidation of the action mechanism of psilocybin and psilocybin. McKenna *et al.*(1990)[65] used a radioactive ligand for a competition test to show that psilocin strongly binds to 5-HT_{1A} and 5-HT_{2A} receptors. Buckholtz *et al.*(1990)[66] administered psilocybin to rats for eight days to run a competition test using a radioactive ligand and reported that the amount of 5-HT_{2A} receptor decreased. These experiments showed that indoleamines, such as psilocybin, psilocin and LSD-25, act as agonists mainly on 5-HT_{2A} receptor located among serotonin receptors to cause hallucination.

Vollenweider *et al.*(1998)[67], (1999)[68] reported that pretreatment with ketanserin, an agonist to 5-HT_{2A} receptor, suppressed hallucination by psilocybin. However, because haloperidol, an antagonist to dopamine-D_2 receptor, also suppressed hallucination by psilocybin, they considered that the involvement of a secondary dopamine receptor was indicated in hallucination by psilocybin.

Psilocybin and psilocin as therapeutic agents

Hallucinogens, such as psilocybin and psilocin, have been used for medical purposes since ancient times. However, there have also been reports of hallucinogen-induced illnesses. Fanciullacci *et al.*(1974)[69] reported that psilocybin and LSD-25 stimulated intracerebral receptors to induce headache. When hallucinogens were first discovered, many studies were conducted with the hypothesis that "mental illness is caused by conflicts in the mind, which are clarified under the influence of a hallucinogen"[70]. In addition, therapeutic studies focused on the use of hallucinogens to acquire new values and recover suppressed memories for the treatment of alcoholism, antisocial conditions, depression, schizophrenia, autism, and obsessive-compulsive disorder[71].

Experimental study led T. Leary, a Harvard psychologist, to consider using psilocybin and psilocin for psychotherapeutic treatment at Concord Prison in Massachusetts, U.S. The experiment involved the administration of psilocybin and psilocin to habitual criminal offenders as psychotherapy, followed by a survey of the ratio of repeated offenses of these subjects after release on parole. Although the recidivism rate initially dropped substantially, the duration of this effect was unclear[72].

In recent years, psilocybin and psilocin were found to be highly effective for treating obsessive-compulsive disorder (OCD), an intractable mental illness[73]. The clinical symptoms of OCD are "compulsive ideas", acute anxiety and distress resulting from repeated and sustained thinking, and "compulsive acts", repetitive actions prompted to alleviate anxiety and distress. Patients with severe OCD symptoms are also known to face difficulty in living an ordinary life. Serotonin reuptake inhibitors (SRI) and selective serotonin reuptake inhibitors (SSRI), which are drugs for depression, are currently the primary treatment for OCD; however, the effect is not satisfactory for many patients.

Brandrup *et al.*(1977)[74] first reported a case of OCD treatment with LSD-25. In recent years, Leonard *et al.*(1987)[75] and Moreno *et al.*(1997)[1] also reported similar cases, which showed the effect of hallucinogens on OCD. In the case of Leonard *et al.*, the subject was a 17-year-old Caucasian man who suffered OCD since the age of eight. The patient suffered OCD symptoms aggravated by cocaine and amphetamine. However, such hallucinogens as psychoactive mushrooms and mescaline alleviated OCD symptoms more than other drugs did. Moreno et al. reported a case of a 34-year-old Caucasian man who developed OCD at the age of six. The patient took psychoactive mushrooms containing psilocybin and its analogues for the first time at the age of 20 and found that the mushrooms alleviated his OCD symptoms. He continued to use psilocybin for nearly four years thereafter. The patient developed tolerance to hallucination during this period, but the mitigating effect of psilocybin on his OCD symptoms did not lessen.

Based on these case studies, hallucinogens showing treatment effects on OCD symptoms were reported to possess a common agonist action on 5-HT_{2A} and 5-HT_{2C} receptors.

After considering case reports on the treatment effects of hallucinogens on OCD, several U.S. hospitals, with permission from the U.S. Food and Drug Administration (FDA) began clinical tests on psilocybin in 2005[73]. Ichimaru *et al.*(1995)[77] and Matsushita *et al.*(2005)[78] also reported results of animal experiments in which agonistic action on 5-HT_{1A} receptor showed a suppressive effect on an OCD model. Sard *et al.*(2005)[73] also reported that agonistic action on 5-HT_{2C} receptor showed a suppressive effect.

Conclusion

Psychoactive mushrooms characteristically produce substances that influence the intracerebral nervous system, including psilocybin and psilocin. In addition, humans have been using psy-

choactive mushrooms since the age of the gods. These mushrooms, which are believed to be very safe and to incur no physical dependence, and which produce psilocybin and psilocin as natural substances, are considered extremely promising for the treatment of nervous disease, which require long-term treatment. Most previous studies on psychoactive mushrooms have been component analyses; however, as they are living organisms, such mushrooms produce diverse substances whose actions are not consistent. It is thus considered necessary to closely examine psychoactive mushrooms themselves, instead of isolated substances, to elucidate their influence on the nervous system in future studies.

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References

1) Moreno FA, Delgado PL: Hallucinogen-induced relief of obsessions and compulsions. Am J Psychiatry, 154: 1037-1038, 1997.
2) Kamimura H: Hallucinogenic mushroom poisoning. Ryoikibetsu Shokogun Shirizu, 27: 676-678, 1999.
3) Guzman G, Allen JW, Gartz J: A worldwide geographical distribution of the neurotropic fungi, an analysis and discussion. Ann Mus Civ Rovereto, 14: 189-280, 1998.
4) Yokoyama K, Kyodo K: Psilocybe cubensis: a hallucinogenic fungus, new to Japan. Proc Symp Mycol Soc Japan, 41: 27, 1997.
5) Koike Y, Wada K, Kusano G, Nozoe S, Yokoyama K, Isolation of psilocybin from Psilocybe argentipes and its determination in specimens of some mushrooms. J Natural Prod, 44: 362-365, 1981.
6) Imazeki R, Hongo T: Color Illustrations of Mushrooms of Japan I. Hoikusha, Osaka, Japan, pp24-285, 1987.
7) Nagasawa, E: Poisonous Fungi in Japan. Gakken, Tokyo, Japan, pp20-268, 2003.
8) Oda T, Yamazaki T, Tanaka C, Terashita T, Taniguchi N, Tsuda M: Amanita ibotengutake sp. nov., a poisonous fungus from Japan. Mycological Progress, 1: 1861-8952, 2002.
9) Imazek R, Hongo T, Ootani Y: Fungi of Japan. Tama-Kei Publishers, Tokyo, Japan, p623, 1988.
10) Mihara M, Yokoyama K: A Field Guide to Japanese Mushrooms. J.T.B, Tokyo, Japan, pp8-206, 1985.
11) Ushiyama H, Kan K, Shindo T, Yasuda K, Nishijima M: Interpretation of food poisoning by natural poisons and chemical substances (1980-1997). Shokuhin Eiseigaku Zasshi, 42: 324-330, 2001.
12) Kusano G, Koike Y, Inoue H, Nozoe S: The constituents of Gymnopilus spectabilis. Chem Pharm Bull (Tokyo), 34: 3465-3470, 1986.
13) Hongo T: Classification of Coprinaceae in Japan. Trans Mycol Soc Japan, 27: 211-219, 1986.
14) Tanaka M, Hashimoto K, Okuno T, Shirahama H: Neurotoxic oligoisoprenoids of the hallucinogenic mushroom, Gymnopilus spectabilis. Phytochemistry, 34: 661-664, 1993.
15) Hongo T: Materials for fungus flora of Japan. Trans Mycol Soc Japan, 19: 455-456, 1978.
16) Yamaura Y, Yokoyama K: The poisonous mushrooms in Japan. Korean J Toxicol, 1: 51-62, 1986.
17) Yokoyama K: A new hallucinogenic mushroom, Psilocybe argentipes K. Yokoyama sp. nov. from Japan. Trans Mycol Soc Japan, 17: 349-354, 1976.
18) Yokoyama K, Poisoning by a hallucinogenic mushroom, Psilocybe subcaerulipes Hongo. Trans Mycol Soc Japan, 14: 317-320, 1973.
19) Gonmori K, Yoshioka N: The examination of mushroom poisonings at Akita University. Leg Med (Tokyo), 5 (Suppl 1): S83-S86, 2003.
20) Endo Y, Hatano Y, Kinda S, Kuroki Y: Mushroom poisoning in Japan. Chudoku Kenkyu, 19: 77-82, 2006.
21) Musha M, Ishii A, Tanaka F, Kusano G: Poisoning by hallucinogenic mushroom hikageshibiretake (Psilocybe argentipes K. Yokoyama) indigenous to Japan. Tohoku J Exp Med, 148: 73-78, 1986.
22) Musha M, Kusano G, Tanaka F, Gotoh Y, Ishii A: Poisoning by the hallucinogenic mushroom hikageshibiretake (Psilocybe argentipes)--with special reference to subjective experiences during psilocybin poisoning. Seishin Shinkeigaku Zasshi, 90: 313-33, 1988.
23) Oss OT, Oeric ON: Psilocybin: Magic Mushroom Grower's Guide: A Handbook for Psilocybin Enthusiasts. Quick American Publishing Company, Oakland, USA, pp13-77, 1992.
24) Kaplan RW: The sacred mushroom in Scandinavia. Man, 10: 72-79, 1975.
25) Lowy B: New records of mushroom stones from Guatemala. Mycologia, 63: 983-993, 1971.
26) McGuire TM: Ancient Maya mushroom connections: a transcendental interaction model. J Psychoactive Drugs, 14: 221-238, 1982.
27) Badham ER, Ethnobotany of psilocybin mushrooms, espe-

cially Psilocybe cubensis. J Ethnopharmacol, 10: 249-254, 1984.
28) Wurst M, Kysilka R, Flieger M: Psychoactive tryptamines from basidiomycetes. Folia Microbiol (Praha), 47: 3-27, 2002.
29) Berlant SR: The entheomycological origin of Egyptian crowns and the esoteric underpinnings of Egyptian religion. J Ethnopharmacol, 102: 275-288, 2005.
30) Riedlinger TJ: Wasson's alternative candidates for soma. J Psychoactive Drugs, 25: 149-156, 1993.
31) Wohlberg J: Haoma-Soma in the world of ancient Greece. J Psychoactive Drugs, 22: 333-342, 1990.
32) Wasson RG, Hofmann A, Ruck CAP: The Road to Eleusis: Unveiling the Secret of the Mysteries. Harcourt, New York, USA, pp2-28, 1978.
33) Hajicek-Dobberstein S: Soma siddhas and alchemical enlightenment: psychedelic mushrooms in Buddhist tradition. J Ethnopharmacol, 48: 99-118, 1995.
34) Wasson RG: Traditional use in North America of Amanita muscaria for divinatory purposes. J Psychedelic Drugs, 11: 25-28, 1979.
35) Keewaydinoquay: The legend of Miskwedo. J Psychedelic Drugs, 11: 29-31, 1979.
36) Dunn E: Russian use of Amanita muscaria: a footnote to Wasson's soma. Current Anthropology, 14: 488-492, 1973.
37) Saar M: Ethnomyocological data from Siberia and North-East Asia on the effect of Amanita muscaria. J Ethnopharmacol, 31: 157-173, 1991.
38) Harkonen M: Uses of mushrooms by Finns and Karelians. Int J Circumpolar Health, 57: 40-55, 1998.
39) Mircea E: Shamanism: Archaic Techniques of Ecstasy. Bollingen Foundation. Princeton University Press, New Jersey, USA, pp220-403, 2004.
40) Wasson RG: Notes on the present status of Ololiuhqui and the other hallucinogens of Mexico. Bot Mus Lealf Harv Univ, 20: 161-212, 1963.
41) Kresanek J, Plackova S, Caganova B, Klobusicka Z: Drug abuse in Slovak Republic. Przegl Lek, 62: 357-360, 2005.
42) Tyler VE: The case for Victor A: Reko--an unrecognized pioneer writer on New World hallucinogens. J Nat Prod, 42: 489-495, 1979.
43) Wasson RG: The divine mushroom: primitive religion and hallucinatory agents. Proc Am Philos Soc, 102: 221-223, 1956.
44) Wasson RG: The hallucinogenic fungi of Mexico. Bot Mus Lealf Harv Univ, 19: 137-162, 1961.
45) Manabe K, Sakai Y, Hatano Y, Tamura M, Endou Y, Gotou K, Oohasi N, Yosioka T, Sugimoto K: Survey on accidental poisoning of magic mushroom in Japan. Chuudokukenkyuu, 12: 443-447, 1999.
46) Kuroki Y: Recent trend of using illegal drugs in Japana. Chuudokukenkyuu, 17: 241-243, 2004.
47) Maruyama T, Shirota O, Kawahara N, Yokoyama K, Makino Y, Goda Y: Discrimination of psychoactive fungi (commonly called "magic mushrooms") based on the DNA sequence of the internal transcribed spacer region. Shokuhin Eiseigaku Zasshi, 44: 44-48, 2003.
48) Tsujikawa K, Kanamori T, Iwata Y, Ohmae Y, Sugita R, Inoue H, Kishi T: Morphological and chemical analysis of magic mushrooms in Japan. Forensic Sci Int, 138: 85-90, 2003.
49) Maruyama T, Yokoyama K, Makino Y, Goda Y: Phylogenetic relationship of psychoactive fungi based on the rRNA gene for a large subunit and their identification using the TaqMan assay. Chem Pharm Bull (Tokyo), 51: 710-714, 2003.
50) Singer R, Stein SI, Ames RW, Smith AH: Observations on agarics causing cerebral mycetisms. Mycopathol Mycol Appl, 9: 261-284, 1958.
51) Leung AY, Paul AG: The relationship of carbon and nitrogen nutrition of Psilocybe baeocystis to the production of psilocybin and its analogs. Lloydia, 32: 66-71, 1969.
52) Gartz, J, Adam, G, Vorbrodt, HM: Growth-promoting effect of a brassinosteroid in mycelial cultures of the fungus Psilocybe cubensis. Naturwissenschaften, 77: 388-389, 1990.
53) Badham ER: The effect of light upon basidiocarp initiation in Psilocybe cubensis. Mycologia, 72: 136-143, 1980.
54) Kitamoto Y, Horikoshi T, Hosoi N, Ichikawa Y: Nutritional study of fruit-body formation in Psilocybe panaeoliformis. Trans Mycol Soc Japan, 16: 268-81, 1975.
55) Kitamoto Y, Ohshita K, Hosoi N, Ichikawa Y: Nutritional requirement for fruit-body development of Psilocybe panaeoliformis in replacement culture. Trans Mycol Soc Japan, 21: 369-380, 1980.
56) Wurst M, Kysilika R, Koza T: Analysis and isolation of indole alkaloids of fungi by high-performance liquid chromatography. J Chromatogr, 593: 201-208, 1992.
57) Gartz J: Extraction and analysis of indole derivatives from fungal biomass. J Basic Microbiol, 34: 17-22, 1994.
58) Jensen N, Gartz J, Laatsch H: Aeruginascin, a trimethylammonium analogue of psilocybin from the hallucinogenic

mushroom Inocybe aeruginascens. Planta Medica, 72: 665-666, 2006.
59) Aboul-Enein HY: Psilocybin: a pharmacological profile. Am J Pharm Sci Support Public Health, 146: 91-95, 1974.
60) Malitz S, Esecover H, Wilkens B, Hoch PH: Some observations on psilocybin, a new hallucinogen, in volunteer subjects. Compr Psychiatry, 1: 8-17, 1960.
61) Miyoshi A: A psychopathological study of the psilocybin psychosis; comparison with the LSD-25 psychosis. Seishin Shinkeigaku Zasshi, 66: 826-836, 1964.
62) Appel JB, Freedman DX: Tolerance and cross-tolerance among psychotomimetic drugs. Psychopharmacologia (Berl.), 13: 267-274, 1968.
63) Horita A: Some biochemical studies on psilocybin and psilocin. J Neuropsychiatr, 4: 270-273, 1963.
64) Horita A, Weber LJ: Dephosphorylation of psilocybin to psilocin by alkaline phosphatase. Proc Soc Exp Biol Med, 106: 32-34, 1961.
65) McKenna DJ, Repke DB, Lo L, Peroutka SJ: Differential interactions of indolealkylamines with 5-hydroxytryptamine receptor subtypes. Neuropharmacology, 29: 193-198, 1990.
66) Buckholtz NS, Zhou DF, Freedman DX, Potter WZ: Lysergic acid diethylamide (LSD) administration selectively downregulates serotonin2 receptors in rat brain. Neuropsychopharmacology, 3: 137-148, 1990.
67) Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D: Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport, 9: 3897-3902, 1999.
68) Vollenweider FX, Vontobel P, Hell D, Leenders KL: 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man--a PET study with [11C] raclopride. Neuropsychopharmacology, 20: 424-433, 1999.
69) Fanciullacci M, Franchi G, Sicuteri F: Hypersensitivity to lysergic acid diethylamide (LSD-25) and psilocybin in essential headache. Experientia, 30: 1441-1443, 1974.
70) Delgado PL, Moreno FA: Hallucinogens, serotonin and obsessive-compulsive disorder. J Psychoactive Drugs, 30: 359-366, 1998.
71) Henry DA, Andrew MA, Prashant G: The psychopharmacology of hallucinogens. Neuropsychopharmacology, 14: 285-298, 1996.
72) Doblin R: Dr. Leary's Concord Prison Experiment: a 34-year follow-up study. J Psychoactive Drugs, 30: 419-426, 1999.
73) Sard H, Kumaran G, Morency C, Roth BL, Toth BA, He P, Shuster L: SAR of psilocybin analogs: discovery of a selective 5-HT 2C agonist. Bioorg Med Chem Lett, 15: 4555-4559, 2005.
74) Brandrup E, Vanggaard T: LSD treatment in a severe case of compulsive neurosis. Acta Psychiatr Scand, 55: 127-141, 1977.
75) Leonard HL, Rapoport JL: Relief of obsessive-compulsive symptoms by LSD and psilocin. Am J Psychiatry, 144: 1239-1240, 1987.
76) Lin P-Y: Meta-analysis of the association of serotonin transporter gene polymorphism with obsessive compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry, 31: 683-689, 2007.
77) Ichimaru Y, Egawa T, Sawa A: 5-HT1A-receptor subtype mediates the effect of fluvoxamine, a selective serotonin reuptake inhibitor, on marble-burying behavior in mice. Jpn J Pharmacol, 68: 65-70, 1995.
78) Matsushita M, Egashira N, Harada S, Okuno R, Mishima K, Iwasaki K, Nishimura R, Fujiwara M: Perospirone, a novel antipsychotic drug, inhibits marble-burying behavior via 5-HT1A receptor in mice: implications for obsessive-compulsive disorder. J Pharmacol Sci, 99: 154-159, 2005.