proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 198, December 2017

www.proteinspotlight.org

when the mind bends

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Science has its backlashes. Consider nuclear fission, or the drug thalidomide*. Psilocybin is also a discovery that brought trouble with it – though of a very different and milder kind. Psilocybin is none other than the magic referred to in "magic mushrooms". The compound was extracted from psilocybin mushrooms, and its chemical structure resolved in the late 1950s. The effects it had on the human mind were studied extensively by clinical psychiatrists in the 1960s; the intriguing results became known outside the laboratory, and readily adopted by the prevailing counterculture movements. It did take not long, however and understandably so, for magic mushrooms, like LSD, mescaline and other psychedelic drugs, to become illegal, making it very difficult for scientists to carry out research on them. Yet, they had been fast to recognise the beneficial effects psilocybin could have on patients suffering from psychiatric disorders, such as depression or schizophrenia for example. Since the turn of the millennium, and despite the administrative harassments, the interest in psilocybin has been rekindled. Recently, researchers discovered a set of four enzymes involved in the compound's synthesis: psiD, psiH, psiK and psiM.

artist and original source unknown

It all began in 1957 when Robert Gordon Wasson, an American banker and amateur ethnomycologist, described the magical twists of the mind he experienced after having ingested mushrooms he had been given during a traditional ceremony in Mexico. Roger Heim, a French botanist, had accompanied him on the expedition and, together, they collected a few of the mushrooms and sent them to the Swiss chemist Albert Hofmann – already well-known for his research on LSD in the late 1930s and 1940s. In 1959, Hofmann managed to extract the compound, psilocybin, from the mushroom *Psilocybe mexicana*, and resolved its chemical structure. Psilocybin was subsequently synthesized and sold by Sandoz, for whom Hofmann was working at the time, to be used in psychedelic psychotherapy. Meanwhile, in the 1960s, the American psychologist Timothy Leary was carrying out research on the use of psilocybin in clinical psychiatry.

The Beat poet Allen Ginsberg took a keen interest in Leary's project and asked to be part of it. The magic leaked out of the laboratory, and it didn't take long for the counterculture movements of the period to find in magic mushrooms, as in other psychedelics, a way of reaching unknown levels of consciousness, which some referred to as spiritual. Indeed, Albert Hofmann took small doses of LSD throughout his life, which he described as a "sacred drug" and believed in its mystical qualities. He also believed that LSD could be used in clinical psychiatry. During the 1960s and 1970s, psychedelic drugs were to inspire many an artist and intellectual – and gave rise to the wonderfully rich pastures of psychedelic visual arts, rock music and literature.

The term "psychedelic" was invented in 1957 by the British psychiatrist Humphry Osmond while corresponding with the British writer and philosopher Aldous Huxley, as they tried to find a word to designate the psychopharmacological group of substances such as LSD, mescaline and psilocybin. Huxley was already familiar with mescaline and LSD and their effects, which he recounts in his writings. The abuse of psychedelic drugs turned out to be dangerous, however, and by

the late 1970s, they had become illegal. This was unfortunate for research. Studies led by Leary had already shown that psilocybin alleviated certain psychiatric disorders. Following the drug ban, research on psilocybin – as on LSD – was dramatically hindered. Despite this, and the administrative hurdles, medical research on psychedelic drugs revived in the 2000s.

Hofmann resolved the chemical structure of psilocybin in 1959, and was thus able to synthesize it artificially. Psilocybin is a tryptamine compound, chemically related to the amino acid tryptophan. The order of molecular events that leads to the actual synthesis of psilocybin from tryptophan was only published in 1968, however. It took a further 60 years to bring to light the biosynthetic pathways which lead to psilocybin in mushrooms. The initial tryptophan undergoes four subsequent reactions: 1) decarboxylation, 2) methylation, 3) hydroxylation and 4) phosphorylation, carried out by four different enzymes, known as psiD, psiH, psiK and psiM, respectively.

Psilocybin is structurally similar to the neurotransmitter serotonin. Consequently, when ingested, it competes with serotonin to bind to serotonin receptors, or 5-HT receptors. Serotonin receptors are found in many parts of the brain where they are involved in mood regulation, motivation, learning and memory. It is hardly surprising then that when psilocybin beats serotonin to its 5-HT receptor, it will do something to our minds. The studies carried out by Leary had already demonstrated that psychedelic drugs could help anxiety disorders, aggressive behaviour and depression – besides opening our minds to other forms of spiritual consciousness.

Recent studies have shown that psilocybin can indeed lift severe depression for up to several months, and is safe as long as it is administered with care. Some treated patients had been suffering from depression for most of their lives. Other recent studies have found that patients suffering from obsessive compulsive disorder and addiction can also benefit from psilocybin administration, as can patients suffering from advanced cancer who, faced with the contemplation of death, go through experiences that are spiritually significant and produce positive changes in their life, mood and behaviour. An understanding of the molecular basis of psilocybin biosynthesis will help to find ways of bioengineering the drug, as it will help to understand the finer role of serotonin in the brain.

Two hundred different kinds of mushrooms found around the world are “magic”. That is to say, two hundred different kinds of mushroom synthesize psilocybin. The world of psychedelics may have begun in the late 1950s, but mushrooms had probably been chewed for their magic for millennia already. Mushrooms painted on prehistoric murals in Spain and Algeria date as far back as 9000 BC. In the 16th century, Spanish colonists had already documented the use of magic mushrooms in Mesoamerica during spiritual and divinatory ceremonies. The Mayas and Aztecs have symbols, statues and paintings that depict psilocybin mushrooms.

There is little chance, however, that magic mushrooms synthesize psilocybin for Aztec rituals. Psilocybin mushrooms live off rotting wood and dung. The four enzymes involved in digesting this mulch happen to be the four enzymes involved in psilocybin biosynthesis. This is why scientists think that the magic molecule is probably a mushroom’s answer to insects who feed off the same matter they do. When ingested by insects, there is a fair chance they will find the task of concentrating on dung and rotting wood a somewhat psychedelic affair.

*** Read “Short Story”, Protein Spotlight issue 117**

Cross-references to UniProt

L-tryptophan decarboxylase psiD, *Psilocybe cubensis* (Psychedelic mushroom): P0DPA6
Cytochrome P450 monooxygenase psiH, *Psilocybe cubensis* (Psychedelic mushroom): P0DPA7
4-hydroxytryptamine kinase psiK, *Psilocybe cubensis* (Psychedelic mushroom): P0DPA8
N-methyltransferase psiM, *Psilocybe cubensis* (Psychedelic mushroom): P0DPA9

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Angew. Chem. Int. Ed. 56:12352-12355(2017)
PMID: 28763571

Protein Spotlight (ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB).