A Comparative Literature Survey of Psilocybin and LSD-25 Metabolism

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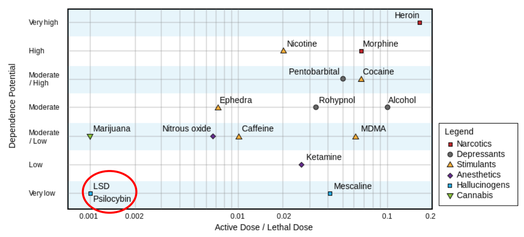
Abstract

Psilocybin and lysergic acid diethylamide (LSD-25) are two of the most popular and well known psychedelic drugs. Although both of the compounds are currently illegal in the United States, a renewed interest has begun in recent years to examine and analyze these drugs for therapeutic use. This review analyzes the current research pertaining to the metabolism, biochemical pathways, receptor activity, biological signaling, physiological effects and the behavioral effects associated with both of these compounds. For psychedelic compounds to be used in future therapeutic settings, it is important to understand how each compound affects the body and which psychedelic could provide more effective treatment for a particular ailment. Accordingly, this review addresses the chemical biology of psilocybin and LSD-25 and provides an initial comparative framework for assessing the effectiveness of each drug under certain circumstances.

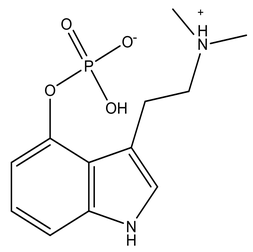
Introduction

Psychedelic and hallucinogenic drugs have been used by humans for thousands of years in rituals and religious ceremonies. These compounds possess the ability to alter human perception and transcend previously established personal and cultural conditioning. The current legal status of both psilocybin and LSD-25 compounds are Schedule I in the United States, meaning that they currently have no accepted medical use and possess a high potential for abuse.



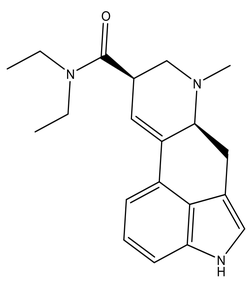
Psilocybin

Psilocybin occurs naturally and is one the main psychedelic ingredients found in "magic" mushrooms. The first recorded use dates back to about 3000 years ago. The compound was originally introduced to the scientific community in 1957 by Robert G. Wasson and then isolated by Dr. Albert Hofmann in 1958. There are over 100 species of psychedelic mushrooms in the world with varying degrees of psilocybin content.



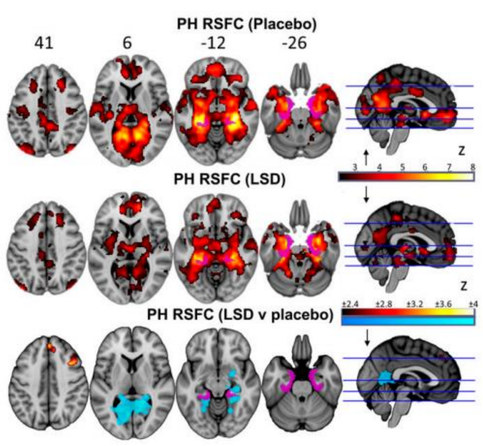
Lysergic Acid Diethylamide - 25

The compound LSD-25 is a semi-synthetic variation of an ergot alkaloid produced by the fungus Claviceps purpurea, which naturally grows on rye wheat. LSD-25 was originally synthesized by Dr. Albert Hofmann at the Sandoz lab in 1938. It was not until 1943 that Dr. Hofmann re-synthesized the compound on a hunch that it had "other effective qualities than those found in the first test". During the final step of the synthesis, Dr. Hofmann was interrupted by feelings of "unusual sensations" and decided to go home where he proceeded to embark on the world's first LSD trip.

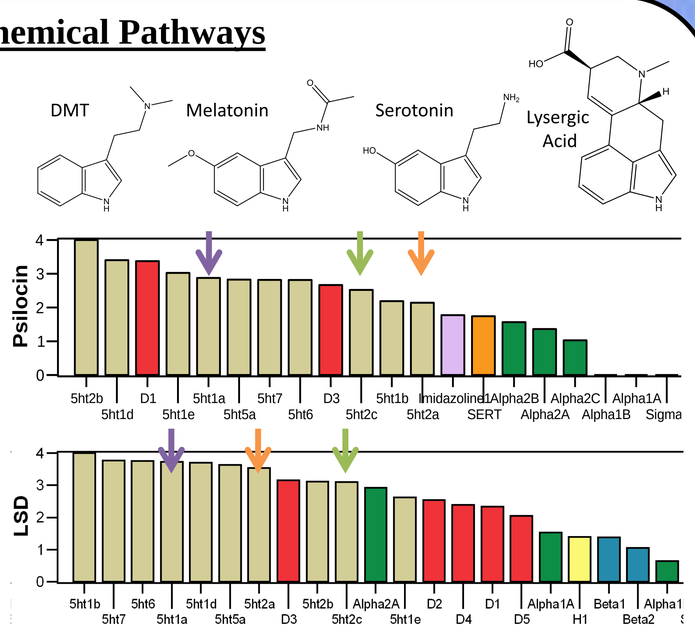


Biochemical Pathways

Many of the physical and psychological effects of psychedelic compounds are due to the interruption of normal serotonergic neurotransmission. Psychedelics modulate the excitatory (glutamate) and inhibitory (serotonin) neurotransmitters in the brain simultaneously. This modulation, in conjunction with early gene activation, alters the flow of sensory information and allows the user to develop unique and novel perceptions toward pre-existing ideas or beliefs.

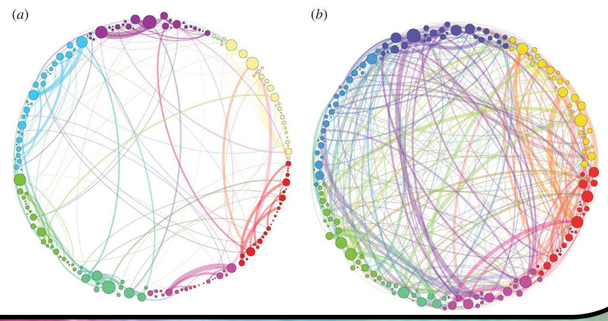


The figure above illustrates how modern neuroimaging techniques such as arterial spin labeling, blood oxygen level dependent measurements, and magneto-encephalography have helped to determine that the Default Mode Network in the brain shows significantly less activity in the presence of LSD-25. Top row: Placebo, Middle row: LSD-25, Bottom row: comparative difference (orange = increase, blue = decrease).



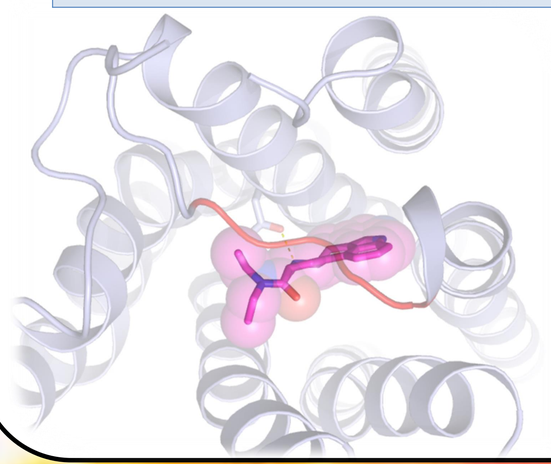
The binding affinities of psilocin and LSD-25 to various neural receptors. The y-axis is in units of npK_i (with the highest npK_i being the least selective i.e. highest affinity). The different colors represent different families of receptors.

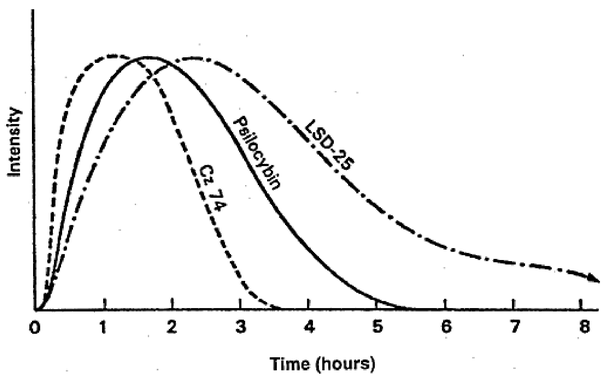
The figure below shows a persistence homological scaffold, or a simplified representation of the complex neurological connectivity network in the brain both on a placebo a) and on psilocybin b). It is important to note that in the presence of psilocybin, new connections are made and some pre-existing connections are also strengthened.



Discussion

	Psilocybin	LSD-25
Naturally occurring compound		Semi-synthetic compound
Bicyclic aromatic structure with no stereo specificity		Larger four-ring system with two chiral carbon centers
Must be chemically modified to produce psychotropic response		Does not need to be chemically altered to produce psychotropic response
Effective Dose: 0.045 mg/kg		Effective Dose: 0.001 mg/kg
Effects last 3-6 hours		Effects last 9-12 hours
"Seatbelt" theory may not apply, or may not be as effective as LSD-25		"Seatbelt" theory - locks LSD-25 molecule in the receptor site
~50% excreted unmodified		~1% excreted unmodified
Glucuronidation rate: ~80%		Glucuronidation rate: <5%
Visuals described as "natural" and "flowing"		Visuals described as "geometric" and "calculated"
Described as "being tied to a rocket ship"		Described as "flying a rocket ship"
Higher affinity for 5-HT_{2A} receptor than the 5-HT_{2C} receptor		Higher affinity for the 5-HT_{2C} receptor than the 5-HT_{2A} receptor
Affinity only for the D_1 and D_3 receptors		Affinity for D_1, D_2, D_3, D_4, and D_5 receptors
Able to bind to sodium-dependent serotonin transport receptors		Unable to bind to sodium-dependent serotonin transport receptors
C-fos early gene activated (↑ gene expression from extracellular signals)		C-fos early gene activated (↑ gene expression from extracellular signals)
egr-1, egr-2 and jun-B (cell proliferation, differentiation and transformation)		Promotes arc (↑learning, memory and plastic changes in the brain)
		Promotes ania3 (upregulation of glutamate)



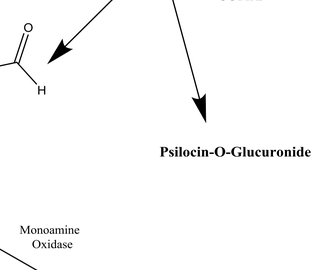


Physiology and Behavior

Many users report drastic shifts in their mood as well as a "mystical" or "dream-like" state of consciousness. Symptoms are largely dependent on the user's mind-set and immediate environment (set and setting).

Physiological symptoms include:

- Tingling sensations
- ↑ blood pressure
- Mydriasis
- Drowsiness
- ↑ heart rate
- Tremors
- Nausea
- Dizziness
- Weakness

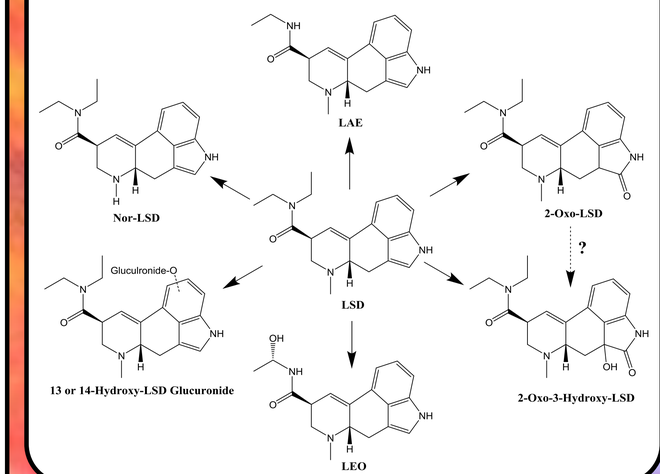


Psychological changes include:

- Impaired perception of "self"
- Separation form the ego
- Feelings of dissociation from a physical body
- Feelings of "unifying with a higher reality"
- Altered perceptions of time and space
- Difficulty focusing or paying attention
- Perceived pseudo-hallucinations or illusions
- Audio-visual synesthesia (hearing colors, seeing sounds, etc.).

Metabolic Breakdown of Psilocybin

Metabolites of LSD-25



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*Amended