Capstone Project

A Comparative Literature Survey of Psilocybin and LSD-25 Metabolism

By Ian Joyce

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 an extensive history and have been used by humans for centuries in a variety of rituals and religious ceremonies.[1] These substances exert powerful effects on an individual's attitude, thoughts, cognition, and behaviour without leading to the addiction or the habit formation often caused by the use of other legal and illicit drugs, see **Figure 1**.[1–4]

The term "psychedelic" (*i.e.* mind-manifesting) is used to classify a group of substances that possess the ability to alter human perception and transcend established personal and cultural conditioning.[5] Depending on the user's state of mind and location, known as the set and setting, these substances can evoke profound "mystical" of

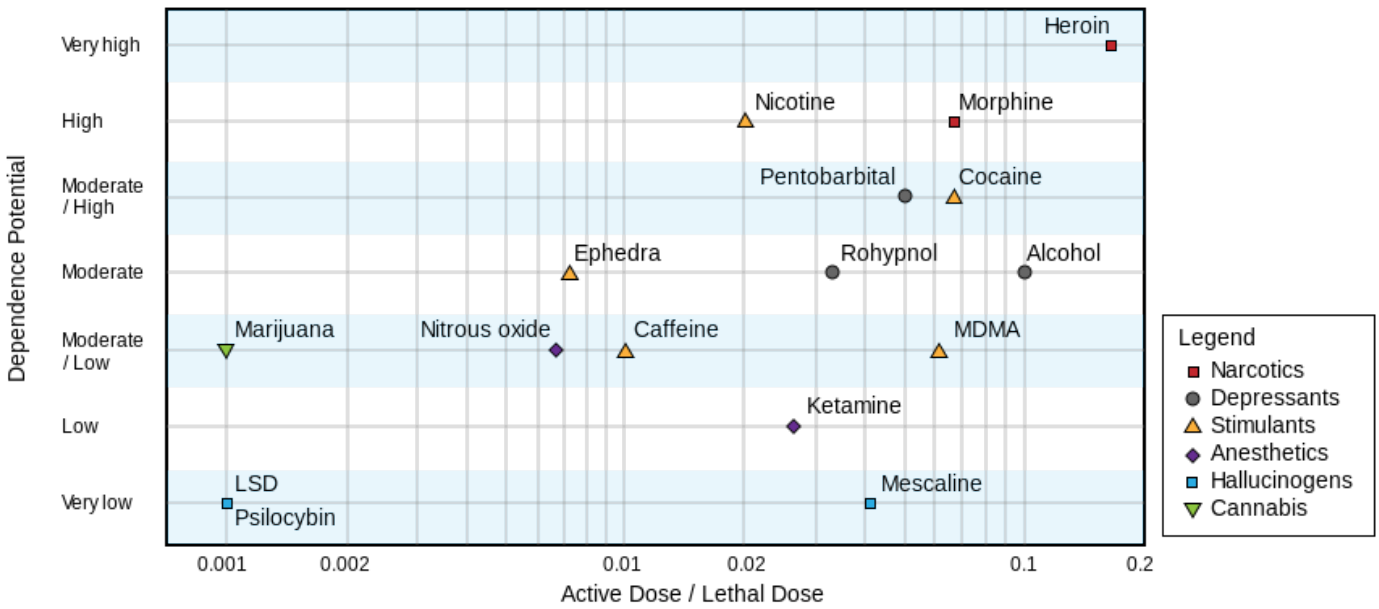


Figure 1: Gable, R. S. In *Drugs and Society: U.S. Public Policy*; Fish, J. M., Ed.; Rowman and Littlefield Publishers, Inc.: Lanham, 2006; pp 149–162.

"religious-like" experiences.[6,7] Although the terms are similar, it is important to note the distinction between a 'psychedelic' and 'hallucinogen'. A hallucinogen is defined as "a substance that causes a person to see or sense things that are not real".[8] Psychedelics rarely cause hallucinations; instead, they cause the user to experience altered perceptions or illusory distortions based on real and existing stimuli.[5,9]

One of the most appealing aspects of psychedelic compounds is their ability to be applied therapeutically or in a medical setting. Psychedelic compounds tend to stimulate neural receptors in an abnormal fashion, which can result in novel synergistic or discordant effects.[5,10] This altered neural state changes the flow of sensory information and cognition and allows the user to develop unique and novel perceptions toward pre-existing ideas or beliefs. [10,11] For these reasons, there has been a renewed effort in recent years to utilize these psychedelic compounds in tandem with psychotherapy to treat a myriad of mental ailments including depression, anxiety, post-traumatic stress disorder and others.[10–12] Additionally, neurochemical studies on these compounds are likely to provide new insights into neural function and may contribute to the development new medicines and strategies for the treatment of psychiatric disorders.

Psychedelic compounds can occur naturally in both plants and fungus, while others may be derived synthetically. One example is N,N-dimethyltryptamine (DMT), which is present in the hallucinogenic beverage Ayahuasca. This sacred tea is traditionally brewed using the bark of *Banisteriopsis caapi* along with various other plants and tends to produce an intense dream-like state in the user.[13] The Peyote cactus is another example of a naturally occurring psychedelic compound. Native Americans have utilized the Peyote cactus, which contains the mind-altering compound known as mescaline, in religious rituals and ceremonies for thousands of years.[9] Other popular psychedelics compounds and their forms of delivery are illustrated in **Figure 2**.

Although there are many psychedelic substances that produce profound altered states of consciousness, the primary focus of this study will be on two of the most common and well known psychedelic compounds: psilocybin and LSD-25, see **Figure 3**.

	Ayahuasca	DMT	LSD	Peyote	Psilocybin
Swallowing as tablets or pills		✓	✓		
Swallowing as liquid		✓	✓	✓	
Consuming raw or dried	✓			✓	✓
Brewing into tea	✓			✓	✓
Snorting					
Injecting					
Inhaling, vaporizing, or smoking		✓			
Absorbing through the lining in the mouth using drug-soaked paper pieces			✓		

Figure 2: Common psychedelic drugs and their primary forms of administration.[89]

Psilocybin occurs naturally and is one the main psychedelic ingredients found in "magic" mushrooms.[14] The first recorded use of these mushrooms dates back to about 3000 years ago to the northern region of Mexico.[15]

The compound was originally introduced to the scientific community in 1957 by Robert G. Wasson and then successfully isolated by Dr. Albert Hofmann in 1958.[16] There are over 100 species of psychedelic mushrooms in the world with varying degrees of psilocybin content ranging from about 0.2%-1.0% by dry weight.[17,18] Today, psilocybin

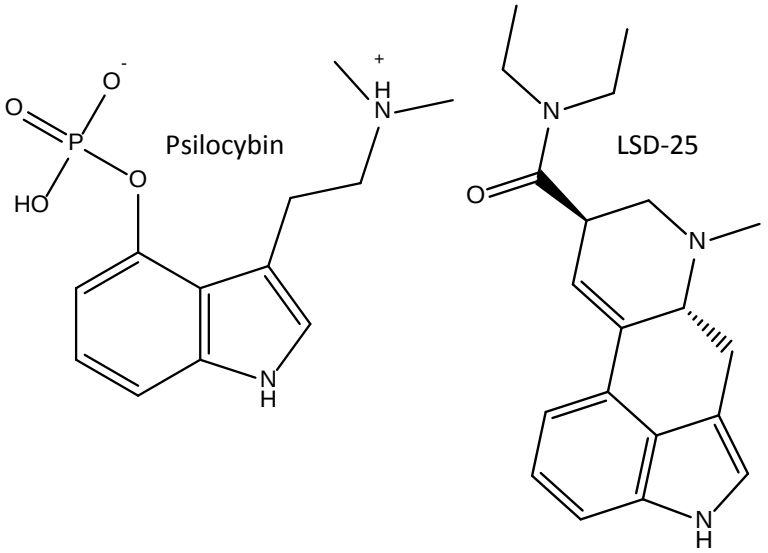


Figure 3: Psilocybin (left) and LSD-25 (right) are two of the most commonly known psychedelics compounds.

mushrooms are used both recreationally and in a psychiatric setting for the treatment of various mental ailments and neurosis.[11]

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.[16] Ergot alkaloids are generally utilized for the treatment of childbirth bleeding as well as migraines.[19] Although these ergot alkaloids are used as medicines today, during the Middle Ages, this fungus is suspected to have been accidently baked into breads and caused it's consumers to experience vivid and often hellish hallucinations, known at the time as "St Anthony's fire".[19]

LSD-25 was originally synthesized by Dr. Albert Hofmann at the Sandoz lab in 1938 as the twenty-fifth compound in a series of chemicals intended to act as a breathing and circulatory stimulant used during childbirth.[20] The substance was first tested on laboratory animals and found to be an effective uterotonic, but not as effective as the popular uterotonic, ergobasine, and was therefore abandoned as a possible medicinal choice.[20] It was not until five years later in 1943 that Dr. Hofmann re-synthesized the compound on a hunch that it had "other effective qualities than those found in the first test".[20] 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.[20]

Following its discovery, Sandoz labs distributed the substance to physicians, psychiatrists, and research laboratories to have its effects investigated further.[16] This popularized the drug and evidently led to its recreational use and abuse by the general population.[16] The reputation of LSD along with the counter cultural movement surrounding it peaked from 1964 to 1966. [16] Today, research is currently being conducted regarding the effectiveness of LSD-25 in the treatment of various neurological ailments, especially for anxiety caused by life threatening illnesses.[11,21]

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.[22]

After almost fifty years of prohibition, there is a renewed interest in the study of these compounds.[7] Understanding how these compounds affect the brain and interact with different cellular processes may potentially lead to new forms of treatment for mental illnesses.[7] The primary focus of this study will be to survey and assess the major differences in metabolism, biochemical pathways, receptor activity, biological signalling, physiological effects and behavioural effects between psilocybin and LSD-25 in humans.

Bioactive Forms and Metabolism

Psilocybin

The effective oral dose of psilocybin is around 0.045 mg/kg.[23] Depending on the mass of the individual and the species of psychedelic mushroom, this can translate to anywhere between 0.25-1.5 grams of dry mushroom to obtain an effective dose.[23] Once consumed, psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) is quickly dephosphorylated to the psychoactive compound psilocin (N,N-dimetyltryptamine) in the gastrointestinal tract by alkaline phosphatase and a nonspecific esterase.[3,17,24]

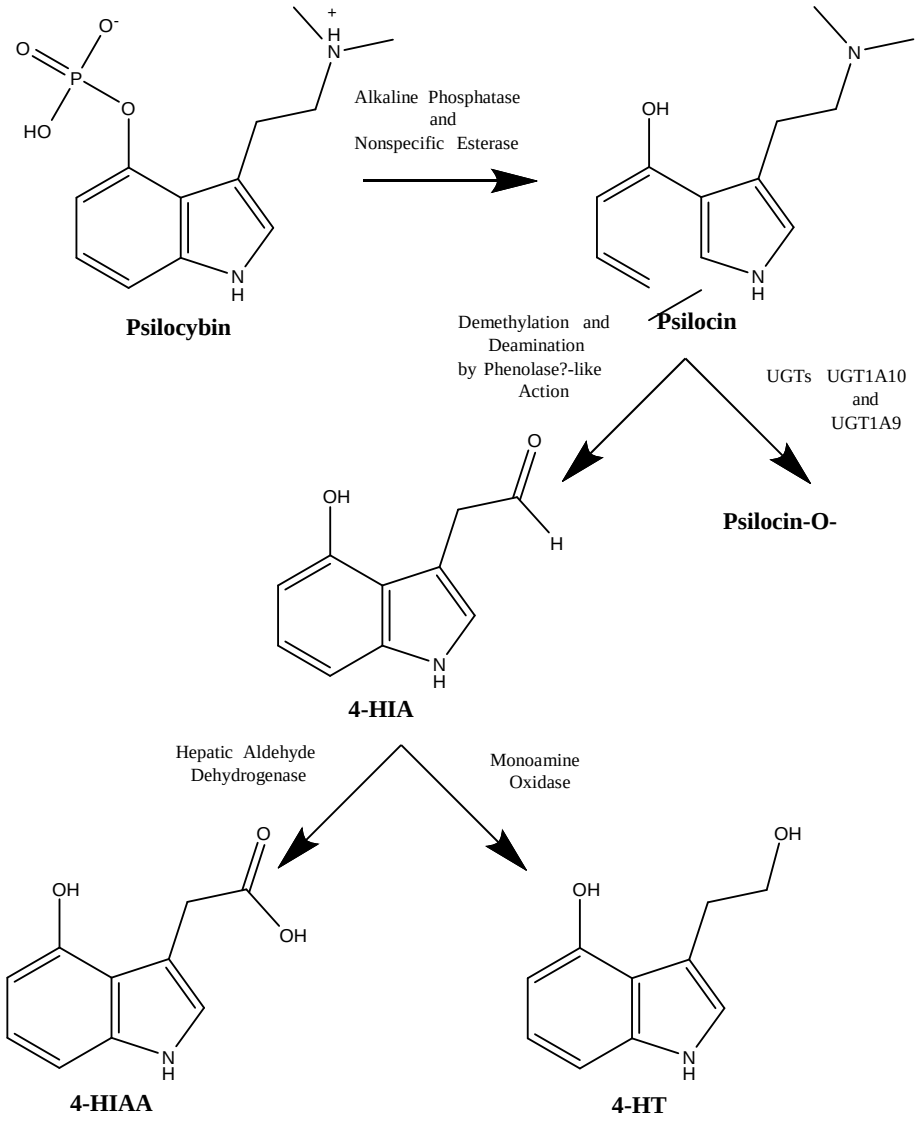


Figure 4: *The metabolic breakdown of psilocybin.*[3]

Both psilocybin and psilocin compounds belong to a group of hallucinogenic tryptamines that are structurally similar to the neurotransmitter serotonin.[3,17] Psychedelic mushrooms naturally contain varying amounts of both psychotropically inactive psilocybin and the psychoactive psilocin. [25]

The metabolic pathway of psilocybin after ingestion is shown in **Figure 4**.[3] In experiments using rats, only about 50% of the total volume of orally administered psilocybin was found to be absorbed within the digestive tract, while the rest is excreted through the urine.[17]

After dephosphorylation, the psychoactive compound psilocin undergoes either glucuronidation or oxidation and deamination.[3,26]

About 80% of the absorbed psilocin is converted to psilocin-O-glucuronide (see **Figure 5**) and excreted from the body through urination.[27] Typically, the glucuronidation process is carried out *via* 19 endoplasmic enzymes classified as UDP-glucuronosyltransferases (UGTs).[28] In the case of psilocin, a study conducted by Manevski *et al.* suggested that the molecule may undergo extensive glucuronidation by the UGT1A10 enzyme within the small intestine.[28] Their findings also found that UGT1A9 exhibited the most glucuronidation once psilocin was absorbed into the body's blood stream.[28]

The process of glucuronidation involves using a glycosidic bond to link glucuronic acid with another compound.[29] The mechanism is well studied for its ability to be applied to drug delivery, as well as its ability to be utilized by the body to make toxic compounds less harmful.[29] It is hypothesized that psilocin is converted to psilocin-O-glucuronide by employing the same metabolic pathway that serotonin utilizes in the in the formation of 5-hydroxytryptamine-O-glucuronide.[17,30–32]

As for the remaining 20% of absorbed psilocin, it is metabolized via oxidation, where the compound undergoes demethylation and deamination to form 4-hydroxyin-dol-3-yl-acetaldehyde (4-HIA). [33] The enzyme responsible for this step is not well-known and the mechanism is also not fully understood, however, research conducted on pig and rabbit

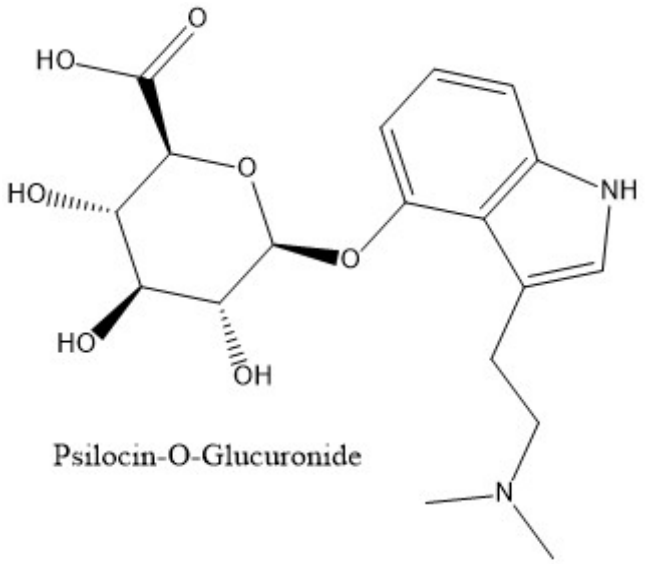


Figure 5: The process of glucuronidation allows some organic molecules to become more water soluble thereby making the molecule easier to metabolize in the cell.[90]

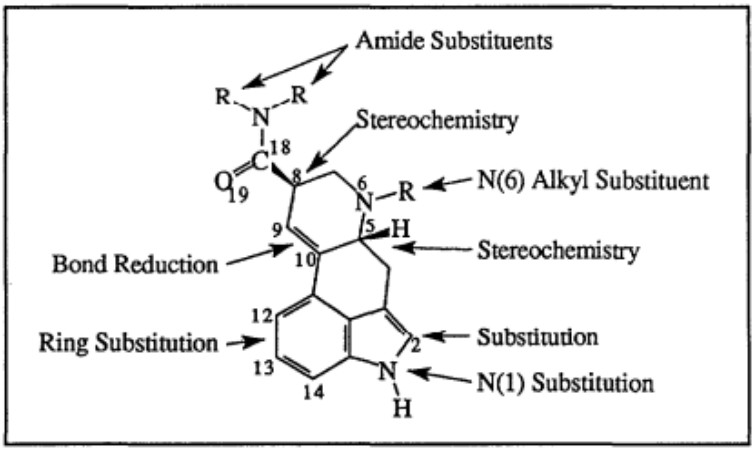
tissues by Horita and Weber suggests that a phenolase-like action may be involved in the oxidation process.[24] The group also hypothesized that the enzyme monoamine oxidase, which is abundant in the liver and responsible for many similar processes, may not be heavily involved in the metabolism due to its minimal activity in the presence of psilocin.[24]

After its initial oxidation to 4-HIA, it is at this point that the metabolite may be oxidized further by hepatic aldehyde dehydrogenase or monoamine oxidase to form 4-hydroxy-indole-3-acetic acid (4-HIAA) or 4-hydroxytryptophole (4-HT).[3,17,33] The 4-HIA, 4-HIAA, and 4-HT metabolites are fully excreted from the body after about twenty-four hours.[31]

In humans, psilocybin and psilocin can be detected in the blood about 20-40 minutes after ingestion.[33] Psilocin concentration in the blood peaks around 80 to 105 minutes after administration and is generally detectable in the bloods for up to six hours after oral administration. [3,17,33] Generally speaking, a typical psilocybin-induced psychoactive experience can last anywhere from three to six hours, depending on the dosage and the individual.[3] In addition, it was determined through urinary analysis that psilocin has a half-life of about 50 minutes.[3]

LSD-25

Lysergic acid diethylamide (LSD-25) is widely considered to be one of the most potent pharmacological substances.[19] It has an effective dose of 1 µg/kg of body weight, which is almost 45 times less than the effective dose of psilocybin.[17,23] For an average individual, the threshold dose that induces a measurable effect is around 20-30 µg.[19] A typical LSD-25 experience lasts approximately 9-12 hours with the half-life of orally administered LSD-25 being about 3.6 hours.[34,35]



R_1	R_2	Relative Potency
H	H (lysergamide, ergine)	3
H	CH_2CH_3	10
H	$CH(CH_2OH)CH_3$ (ergonovine)	3
CH_3	CH_3	10
CH_3	CH_2CH_3	3
CH_3	$CH_2CH_2CH_3$	3
CH_2CH_3	CH_2CH_3 (LSD)	100
CH_2CH_3	$CH_2CH_2CH_3$	32
$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	10
C_4H_8	(Cyclic pyrrolidide)	32
C_4H_8O	(Cyclic morpholide)	32

Figure 6: The locations of each constituent (top), as well as the modifications performed on the amide substituents of lysergamides and their relative potency compared to LSD-25.[38]

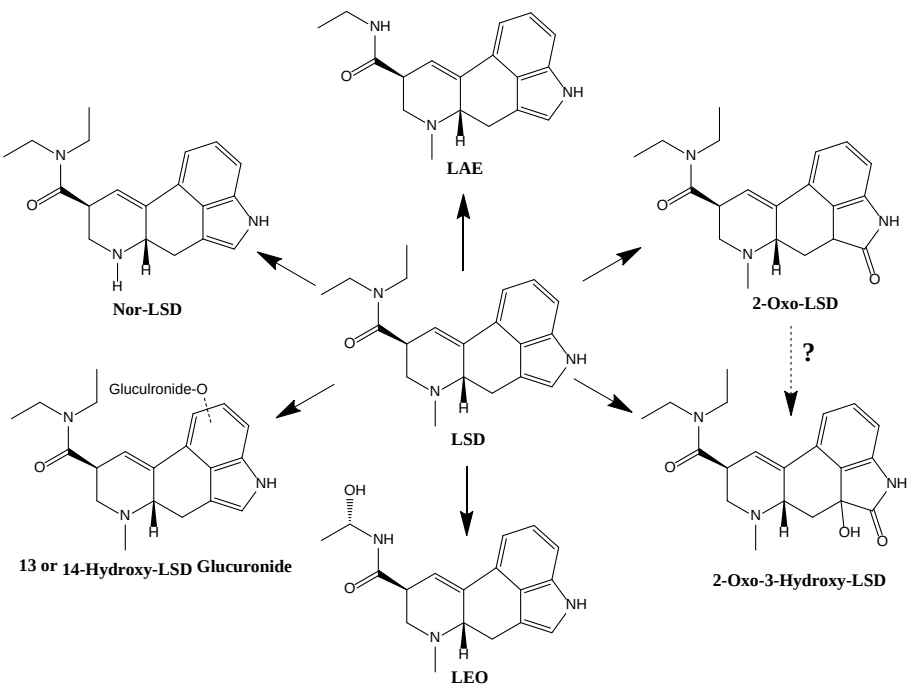


Figure 7: Known metabolites of LSD-25. [19]

In contrast to psilocybin, LSD-25 possesses two chiral centers, which result in the possibility of four stereoisomers.[19] Interestingly, only the dextro-LSD (5R, 8R) stereoisomer is pharmacologically active.[36] In addition to chirality playing a role in pharmacological effectiveness, small changes in the chemical constituents on the molecule can lead to drastic changes in overall effects.[37] For example, 2-Bromo-lysergic acid diethylamide (BOL-148) is one of the most investigated derivatives of d-LSD-25 because it yields almost no psychotropic effects on the user.[37] The only structural difference between d-LSD and BOL-148 is the presence of a Bromine atom attached to carbon number two, which can be depicted using **Figure 6**. Additionally, many of the d-LSD-25 derivatives can exhibit far more serotonin antagonism, but they do not display comparable psychotomimetic effects to that of d-LSD-25.[19,37] **Figure 6** displays some possible lysergamides modifications that have been synthesized and researched, and their potency relative to d-LSD-25.[38]

Because of the structural complexities, miniscule amounts, and the delicate nature of LSD-25, a consistent and viable metabolic pathway has not yet been established in its entirety.[19,39] Although the pathway is still not fully understood, many of the metabolites of LSD-25 have been identified and are shown in **Figure 7**.[19,40]

Once consumed, LSD-25 is quickly converted to its structural metabolites.[19,41] In rat livers, the metabolism of LSD-25 drops by fifty percent after a few minutes and stops almost completely after about 100-120 minutes, indicating a rapid metabolism of the drug.[42] Only about one percent of the LSD-25 consumed is excreted without chemical modification.[43]

A chromatographic analysis of human bile acid conducted in 1959 by E. Boyd determined about 60% of the LSD administered to the subjects was converted to either lysergic acid amide (2-Oxo-LSD) or lysergic acid (LAE).[44] In 1957, Axelrod *et* al. proposed that LSD can only be oxidized to 2-Oxo-3-LSD by the liver's NADH dependent microsomal enzymes.[45] These studies utilized rudimentary

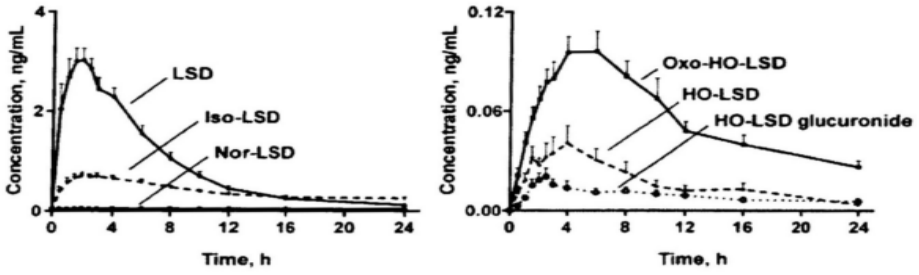


Figure 8: Concentration-time profiles of various LSD-25 metabolites in plasma (ng/mL). On the left, LSD and major metabolites present iso-LSD*, nor-LSD. On the right, Oxo-HO-LSD (2-oxo-3-hydroxy-LSD), HO-LSD (2-Oxo-LSD), HO-LSD glucuronide (13 or 14-hydroxy-LSD glucuronide).[46]

methods for analysing metabolites compared to today's modern techniques. There are relatively few studies on the metabolites of LSD-25 to date, and due to the uncertainty surrounding these older studies, a new effort is underway to identify the metabolites and metabolic pathways LSD-25 undergoes upon consumption.[40,46,47]

One particular study conducted in 2016 by Steuer *et al*. utilized sensitive micro-flow liquid chromatography (MFLC) in tandem with mass spectrometry to identify and quantify the metabolites of LSD-25.[46] The group determined that 2-oxo-3-hydroxy-LSD and nor-LSD are the major metabolites that are excreted through the urine, thereby disproving previous metabolite excretion theories.[46] The other metabolites displayed in **Figure 7** are generally present in small amounts relative to 2-oxo-3-hydroxy-LSD and nor-LSD and are much more difficult to detect.[46] **Figure 8** shows the concentration-time profiles of several LSD-25 metabolites.[46] The iso-LSD* compound in the left graph is not psychoactive and is generally synthesized during the drug manufacturing process.[46,48] Because of this fact, it is debateable as to whether LSD-25 is actually metabolized to iso-LSD *in vivo*.[46,48] However, in terms of forensic analysis and drug testing, toxicologists generally agree that the presence of iso-LSD is a good indicator of LSD-25 drug use.[46]

In regards to the enzymes and the mechanism by which LSD-25 is converted into its major metabolites, **Figure 9** hypothesizes two possible metabolic routes.[40,47] Mechanism A) is one of two possible mechanisms* that utilizes Cytochrome P450 complex liver enzymes, as well as an epoxide intermediate (see *Appendix 1).[40,47] This route is also suspected to utilize an unidentified dehydrogenase in order to oxidize the alcohol on carbon two, thus yielding 2-Oxo-3-hydroxy-LSD.[40] Mechanism B), proposed by Gomes *et al*., suggests that horseradish peroxidase or myeloperoxidase (MPO) could possibly use LSD as a substrate and obtain the same metabolites as mechanism A).[47] The method proposed by Gomes *et al*. yielded both of the major metabolites as well a new metabolite: FOMBK (N,N-Diethyl-7-formamido-

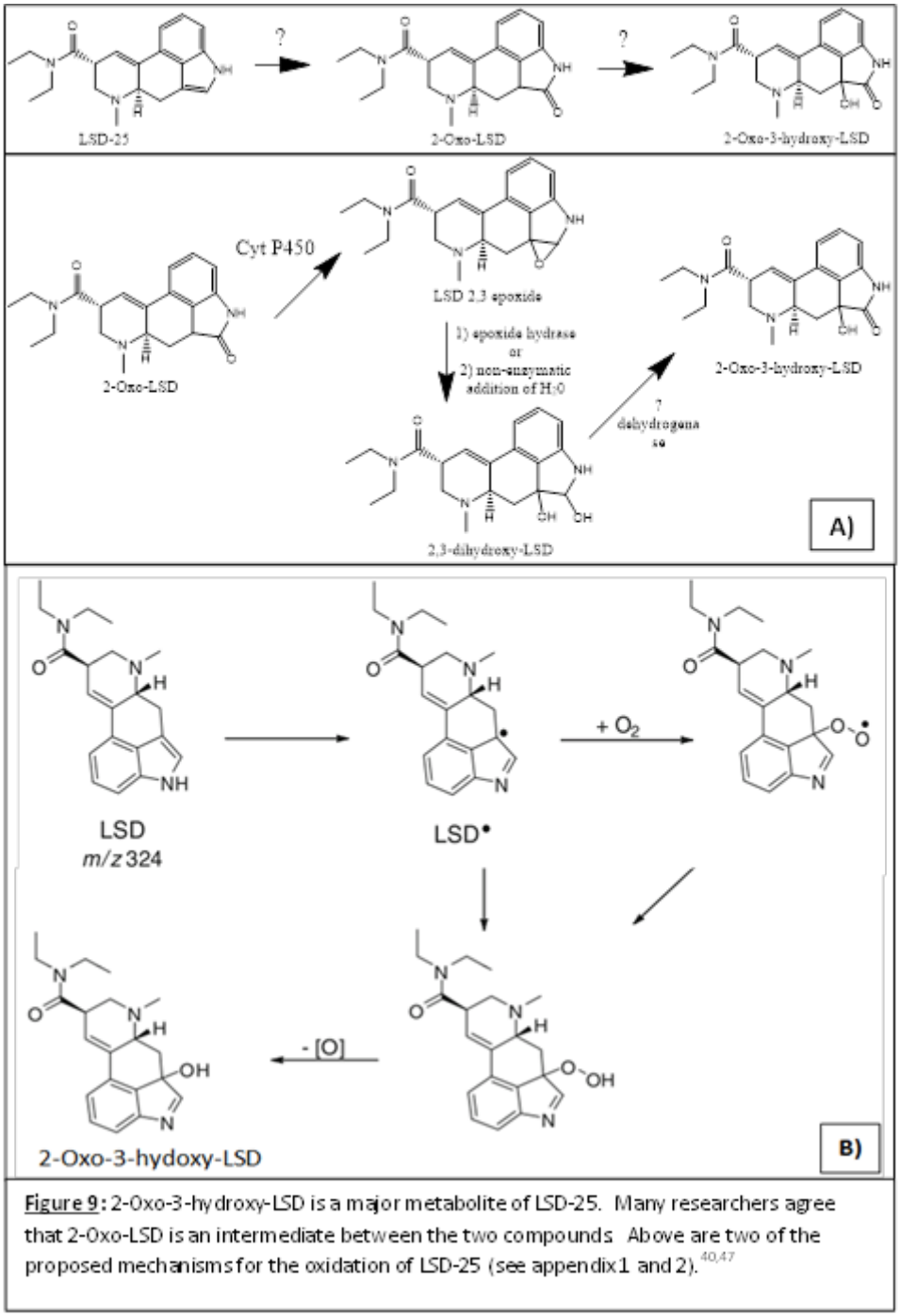


Figure 9: 2-Oxo-3-hydroxy-LSD is a major metabolite of LSD-25. Many researchers agree that 2-Oxo-LSD is an intermediate between the two compounds Above are two of the proposed mechanisms for the oxidation of LSD-25 (see appendix1 and 2).[40,47]

4-methyl-6-oxo2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxamide), suggesting the presence of additional metabolic steps.[47] Their study proposes that there may be an alternate pathway to A) that occurs alongside with the reaction catalysed by the cytochrome P450 complex.[47]

Biochemical Pathways

The neuropharmacology of both psilocybin and LSD-25 are particularly complex and the mechanisms by which they affect the brain, and ultimately human behaviour, are far from completely understood.[19] Since their entrance into the realm of modern science, the neural receptor activity of both of these compounds has been widely researched and the results are still somewhat unclear. Additionally, many of the earlier studies were conducted with rudimentary equipment and primitive methods when compared to today's modern technology. Nonetheless, the following is an attempt to describe what scientists and researchers have discovered thus far.

Serotonin

Serotonin is a key element in psychedelic research because many of the physical and psychological effects of psychedelic compounds are due to the interruption of normal serotonergic neurotransmission.[3,49–51]

Serotonin is located in many tissues throughout the body with neurons only possessing about one percent of the body's total supply.[19,52,53] It is estimated that there are about 100 billion neurons in the human brain, however, serotonin is only synthesized by a relatively small amount of neurons (on the order of 10^3), and each of these neurons interact with as many as 500,000 other neurons.[19,53] Interestingly, in the absence of a hallucinogen, an increase in the concentration of serotonin in the brain does not produce a hallucinogenic response, indicating that psychedelic compounds possess the ability to affect alternate cell-signalling pathways in the brain relative to serotonin.[54]

In addition, serotonin itself is not capable of permeating the blood-brain barrier and must therefore be transported to the brain in the form of the common amino acid, tryptophan.[52] Once tryptophan enters a neuron capable of serotonergic transmission, it is hydroxylated and decarboxylated by tryptophan hydroxylase and L-aromatic amino acid decarboxylase, respectively, to form serotonin (5-HT).[52]

Research suggests that serotonin and the 14 different types of 5-HT receptors in the brain play an important role in the regulation of mood, sleep, learning and memory.[51,52]

Psilocybin

Early studies on the effects of psilocybin in humans found that the psychedelic state induced by the compound closely resembled a schizophrenic episode.[55,56] Researchers at the time had hypothesized that schizophrenia was a result of abnormal serotonin activity within the brain.[55,56] Although some schizophrenic behaviours can parallel some behaviours observed during a psilocybin experience, the two states differ drastically on the receptor level.

A study conducted in 1998 by Vollenweider *et al*. tested this hypothesis by treating test subjects with ketanserin, a known 5-HT_{2A} antagonist, prior to dosing the subjects with psilocybin.[55] The researchers found that the ketanserin effectively blocked the psychotropic effects of psilocybin, suggesting that over-activation of 5-HT receptors, particularly 5-HT_{2A} receptors, may play a role in the psychotic symptoms of schizophrenia as well as the psychotropic effects of psilocybin.[55,57]

Further studies confirmed that psilocin acts as an agonist on the 5-HT_{2A} receptor and also displays agonist activity on the 5-HT_{1A}, 5-HT_{1D}, and 5-HT_{2C} receptor subtypes.[3,17,58] It was initially suspected that psilocin had a much higher affinity for the $5HT_{2A}$ receptor than for the $5HT_{1A}$ receptor, however this theory was later proven false.[3,17,58] Additionally, early research proposed that psilocin has no affinity for dopamine receptors, which was also later found to be false.[3,17,58]

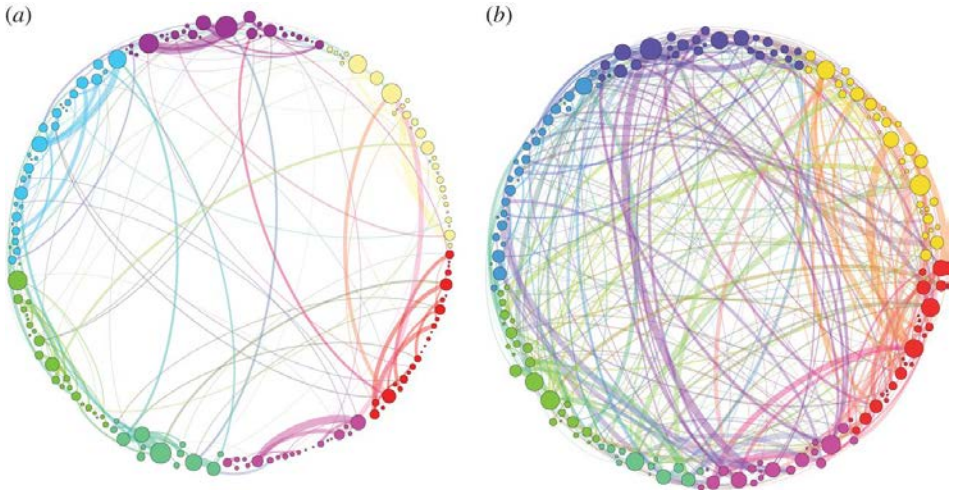


Figure 10: This figure shows a persistence homological scaffold, or a simplified representation of the complex neurological connectivity network in the brain both on a placebo **a)** and on psilocybin **b).** It is important to note that in the presence of psilocybin, new connections are made and some pre-existing connections are also strengthened.[74]

It is now known that psilocin interacts with many receptors in the brain, with decreasing affinity in the following order: 5-HT_{2B} > 5-HT_{1D} > D_1 > 5-HT_{1E} > **5-HT_{1A}** > 5-HT_{5A} > 5-HT_7 > 5-HT_6 > D_3 > **5-HT_{2C}** > 5-HT_{1B} > **5-HT_{2A}** (with weak binding to Imidazoline$_1$, $\alpha_{2A/B/C}$, and 5-HT transporters), see **Figure 11.**[17,59] Although many receptors are affected, the hallucinogenic effects of psilocin are a result of agonist activity primarily on the serotonin 5-$HT_{2A/C}$ and 5-HT_{1A} receptor subtypes.[3,17] These findings were confirmed in head-twitch behaviour experiments conducted on rodents using specific 5-$HT_{1A/2A}$ agonists and antagonists.[17,60,61] Head-twitch behaviour is often used in studies employing hallucinogens as it is useful as an indication of 5-HT_{2A} stimulation.[17,60,61] In addition, psilocin is able to bind to the sodium-dependent serotonin transporter (SERT) which is a type of transporter protein that helps shuttle serotonin from the synaptic cleft back into the pre-synaptic neuron.[59,62] During this process, the effects of serotonin are effectively stopped, but then shortly after able to be used once again.[63]

Additionally, it was determined that the presence of psilocin also increased the release of dopamine in the ventral striatum region of the brain, which led some users to experience a sense of ecstasy and euphoria.[64] Although the D_1 and D_3 receptors display some binding activity in this region, the D_2 receptor displays little to no binding affinity to the compound.[55,59,64] This is of particular interest to researchers because the D_2 receptor is thought to play a significant role in schizophrenic and psychotic episodes.[65] Although it is not well understood, it is suggested that the hyperdopaminergic state induced by psilocin may be due to both direct agonistic effects on the D_1 and D_3 receptors, as well as an indirect effect brought on by psilocin binding to the 5-HT_2 and 5-HT_1 receptors and evidently leading to the release of dopamine through an alternative biochemical route.[64]

Another notable study conducted by Vollenweider *et al*. analysed cerebral glucose metabolism in ten healthy volunteers, both before and after the administration of psilocybin.[3,66] The study determined that there was a significant increase in the rate of glucose metabolism within the prefrontal cortex, anterior cingulate gyrus, temporal gyrus and the basal ganglia.[3,66] Additionally, neural activity in the right hemisphere of the brain was shown to be significantly higher than the placebo, and neural activity in the thalamus was shown to drop considerably. [3,66] These trends are important because they parallel the gluco-metabolic effects observed in patients undergoing psychotic and schizophrenic episodes.[66]

In terms of gene regulation, it has also been shown that psilocybin increases the expression of the early genes *egr-1, egr-2, **c-fos**, jun-B, period-1, gpcr-26, fra-1, N-10, and I-κβα*, and decreases the expression of *sty-kinase.*[17,67,68] The *c-fos* gene is an important gene because it is a nuclear transcription factor responsible for converting extracellular signals into changes in gene expression by binding with promotor regions on specific segments of the DNA.[52,69,70] In addition, the *fra-1* early gene is a close

relative to the *fos* and *jun* family of genes and helps in regulating cell proliferation, differentiation, and transformation.[71] The *egr-1*, *egr-2* genes are responsible for early growth response proteins which are linked to cell proliferation, and the *jun-B* early gene is linked to regulating gene expression following primary growth factor responses.[72,73] It is thought that these genetic factors, along with abnormal receptor activity, are what lead to the hyper-connectivity of neurons observed during a psilocybin induced experience, see **Figure 10**.[74]

LSD-25

The majority of research concerning LSD pharmacodynamics points toward the hypothesis that LSD acts to inhibit serotonin synaptic firing and interfere with post-synaptic up-down regulation.[19] The mechanism by which this process occurs is still not fully understood, however, more recent studies have begun to uncover how LSD may work to affect the brain.

As stated earlier, serotonin is an important aspect of psychedelic mechanisms, with relatively few neurons actually synthesizing serotonin within the brain.[19,75] Due to minute quantity of LSD-25 needed to induce a psychotropic response, one of the predominant hypotheses is that LSD-25 affects the raphe nuclei of the brain where the majority of these serotonin synthesizing neurons are located.[19,75] The raphe nuclei are largely innervated with the locus coeruleus, which reaches out to affect a variety of cerebral regions including the thalamus, hypothalamus, hippocampus, cerebral cortex and cerebellum.[19,75] The locus coeruleus affects many regions of the brain and is largely responsible for regulation of the sympathetic nervous system, which dictates "fight-or-flight" response mechanisms.[52,76,77]

It should be noted, however, that the locus coeruleus is not directly responsible for hallucinogenic effects of psychedelic drugs because direct delivery of a hallucinogenic drug via iontophoresis does not increase excitation of locus coeruleus neurons.[78] This being said, the locus coeruleus is not particularly useful for studying direct effects of hallucinogens; however, because of its unique central role as a processing channel of sensory information, it is a useful tool for studying the indirect effects of hallucinogens.[78]

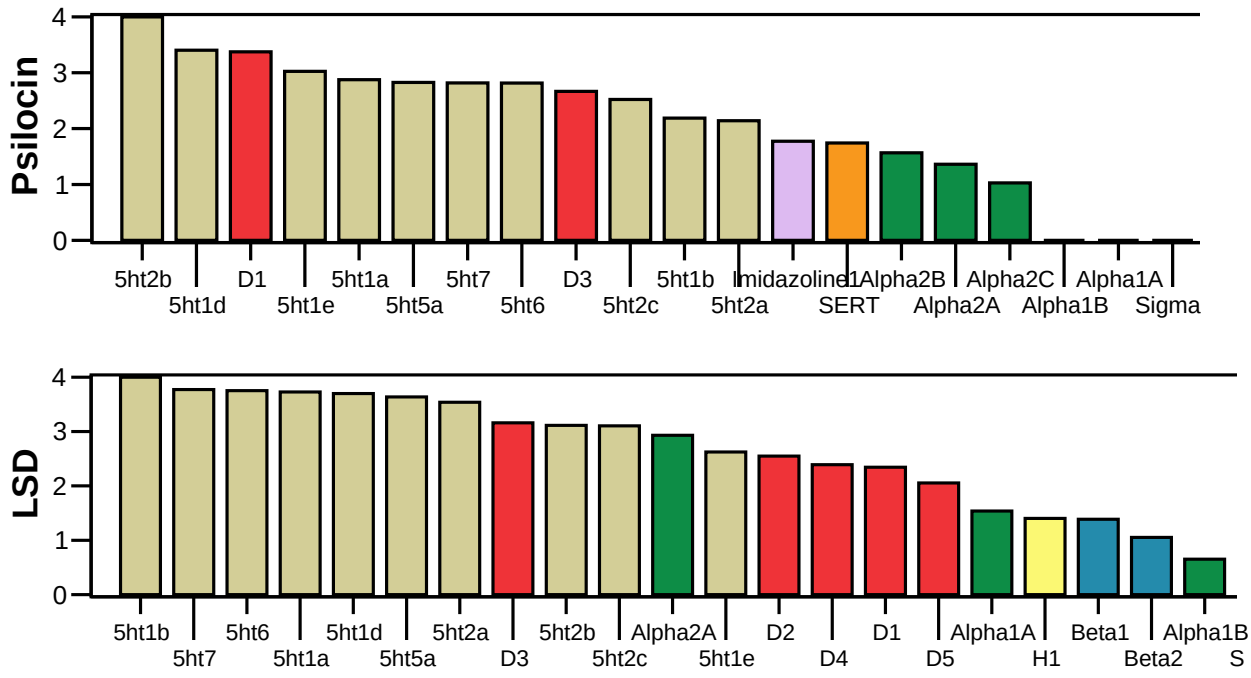


Figure 11: The binding affinities of psilocin and LSD-25 to various neural receptors. The y-axis is in units of npK_i (with the highest npK_i being the least selective i.e. highest affinity). The different colors represent different families of receptors.[59]

LSD-25 affects a wide range of receptors with its affinity for these receptors listed in the following decreasing order: 5-HT_{1B} > 5-HT_7 > 5-HT_6 > **5-HT_{1A}** > 5-HT_{1D} > 5-HT_{5A} > **5-HT_{2A}** > D_3 > 5-HT_{2B} > **5-HT_{2C}** > α_{2A} > 5-HT_{1E} > D_2 > D_4 > D_1 > D_5, see **Figure 11**.[17,59] Although the compound affects a variety of receptors, many researchers agree it is best classified as a mixed 5-HT_2/5-HT_1 partial receptor agonist.[19,38,68,70,76]

At this point it is important to note that serotonin acts mainly as an inhibitory neurotransmitter, meaning that it decreases trans-membrane ion flow, thereby decreasing the probability of the cell reaching an action potential.[76,77] LSD-25 behaves as an agonist on the 5-HT_1 receptor thereby inhibiting serotonin release as well as axon firing.[19,34,38] When LSD-25 interferes with serotonin's inhibition, the cascading neurons down the chain are likely to increase in electrochemical and synaptic activity, potentially leading to some of the psychotropic effects associated with the compound.[19,76,77]

The 5-HT_{2A} receptor sites are abundant in neocortical pyramidal cells which are thought to play an important role in higher level cognitive processing.[76] LSD-25 activates the 5-HT_{2A} receptor thereby triggering the release of glutamate, one of the most abundant excitatory neurotransmitters within the brain.[19,79] When this increase in glutamate concentration occurs, it alters normal cellular communication between cortical and subcortical regions of the brain.[19,79]

The inhibitory effects of LSD on the 5-HT_1 and the excitatory effects on the 5-HT_{2A} receptors may be responsible for why LSD-25 appears to be both an agonist and antagonist within the brain.[19,53] The diverse interactions of this compound within the brain appear to allow LSD-25 to regulate and modulate its own activity.[19,53]

A recent experiment conducted by Wacker *et al*. suggests that one of the reasons LSD-25 seems to have such prolonged hallucinogenic effects (9-12h) is due to a conformational change that is undergone within the receptor site.[35,80] The group was able to crystalize the molecular structure of an LSD molecule bound to a 5-HT_{2B} receptor site and found that the presence of LSD-25 seemed to prompt the receptor site to fold over on itself, similar to a lid over a jar, effectively trapping the molecule in the receptor site, see **Figure 13**.[80] This evidence provides useful insight for the long lasting effects of LSD-25 as well as the importance of the LSD-25's diethylamide group and its interaction with the receptor site.[80]

In addition to serotonin receptor activity, evidence also suggests that LSD-25 possesses the ability to interact with dopaminergic receptors in the brain, particularly with the D_1 and D_2 receptors.[59,81] However, despite interacting with the dopaminergic system, LSD does not possess any relevant dependence Dopamine receptor activity, along with serotonergic activity, reinforce the notion that LSD-25 is extremely complex in its biochemical interactions and more research is necessary to determine its exact route of action.[59,81]

In terms of gene expression, the ingestion of LSD-25 appears to increase expression of the early genes *c-fos* and *arc*.[19,70] The *c-fos* gene was discussed earlier, but the *arc* gene plays a critical role in learning, memory and plastic changes within the brain.[52,69,70] Both of the genes show increased expression around 90 minutes after LSD is initially ingested.[19,69,70] *C-fos* expression increased two-fold in the hippocampus, prefrontal cortex and midbrain regions.[69,70] Interestingly, *arc* expression was unchanged in the hippocampus, undetectable in the midbrain region and increased five-fold in the prefrontal cortex, where there is a high concentration of 5-HT_{2A} receptors.[69,70]

Additionally, micro-assays performed by Nichols and Sanders-Bush determined that the genes known as gluco-corticoid kinase (*sgk*), *I-κβα*, *krox-20,* neuron-derived orphan receptor 1 (*NOR1*), and *ania3* also displayed modified expression in the presence of LSD-25.[70] Many of these genes are responsible for vital functions within the brain; however, *ania3* is of particular importance due to its upregulation of glutamate. Because glutamate acts as one of the primary excitatory neurotransmitters, this upregulation of glutamate in conjunction with 5-HT receptor activity, and down regulation of the other neural regions implies that the drug has the potential

to effectively modulate its own hallucinogenic effects.[70]

Physiology and Behaviour

At this juncture, it is important to note that psilocybin and LSD-25 are similar in their physiological and behavioural effects.[82] Although there has been significant research conducted on the physical and psychological effects of both individual drugs, there is very little comparative data available. This is due partly to the legal status of the drugs, but it may also be due to a lack of interest, a lack of resources, or a lack of time. However, this data is important because if these drugs are to be used in a psychiatric or medicinal setting, the physical and behavioural effects of these drugs should be identified and compared in order to provide patients with the best care possible. For example, psilocybin may be better geared towards treating those suffering from anxiety or depression than LSD-25. Additionally, LSD-25 may be better suited toward treating patients suffering from addiction or alcoholism than psilocybin. The point is that there is very little comparative data available to address this issue and doctors and psychiatrists should use the best drug to treat whatever ailment the patient is suffering from. That being said, the following is an overview of the currently known and scientifically reported physiological and behavioural effects of both psilocybin and LSD-25, which are largely similar across the board.

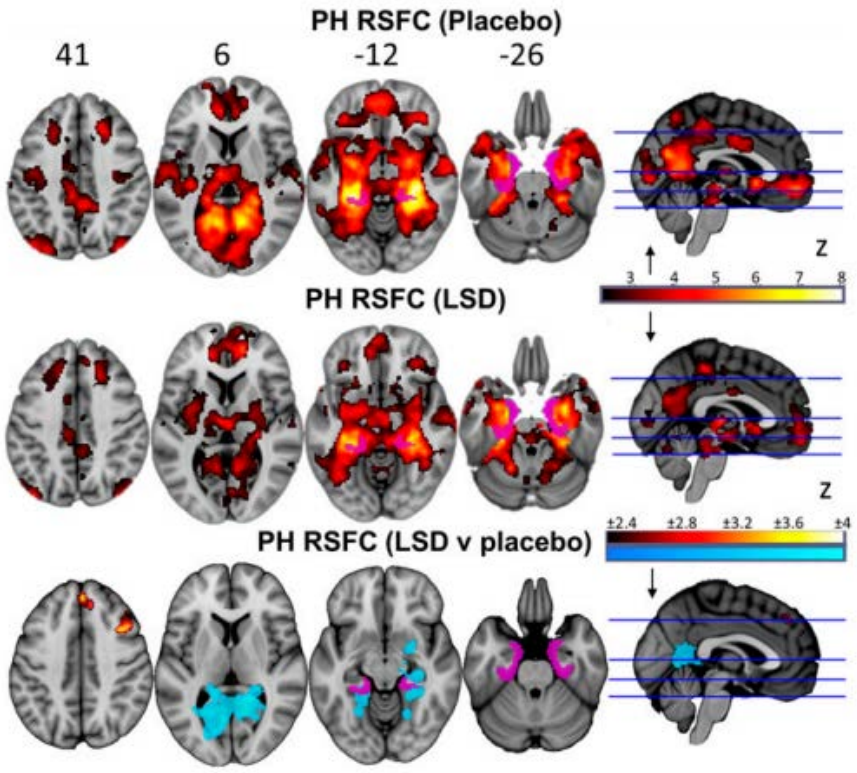


Figure 12: Modern neuroimaging techniques such as arterial spin labeling, blood oxygen level dependent measurements, and magnetoencephalography have helped to determine that the Default Mode Network in the brain shows significantly less activity in the presence of LSD-25. Top row: Placebo, Middle row: LSD-25, Bottom row: comparative difference (orange = increase, blue = decrease).[88]

The ingestion of psilocybin or LSD-25 can cause a variety of physical symptoms including stimulation of the sympathetic nervous system, which can be observed by mydriasis, increase in blood pressure, and an increased heart rate.[6,23] Some other physiological symptoms can include dizziness, nausea, weakness, tremors, tingling sensations, drowsiness and blurred vision.[6,23] Psilocybin and LSD-25 are reported to have no significant effect on normal body temperature or electrocardiograph readings.[23] Additionally, the compounds do not seem to affect blood glucose levels or ion concentrations in the blood.[17,23] In 1999, Goulzoulis-Mayfrank *et al*. discovered that psilocybin increased the expression of several hormones including prolactin, corticotropin, cortisol, and thyreotropin; however, the hormone levels dropped back to baseline after about five hours.[17,23,83]

The behavioural effects of psilocybin and LSD-25 are largely dependent on the dose administered to the test subject. At small doses, drowsiness is reported, as well as an emphasis on the user's current mood and state of mind.[23] Medium doses tend to elicit a noticeably altered state of consciousness.[23] At higher doses, the drugs cause the user to undergo a full psychedelic experience accompanied by profound changes in perception.[3,17,23,39]

Many users describe this profound altered state as "mystical" or "dream-like" and are accompanied with drastic alterations to their normal stream of conscious thought.[23,84,85] These alterations can take many forms, but some of the overarching themes reported by test subjects include: impaired perception of "self" or 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 focussing or paying attention, perceived pseudo-hallucinations or illusions, and audio-visual synaesthesia (hearing colours, seeing sounds, etc.).[6,11,17,23,84] In addition to these effects, reports of drastic shifts in mood, from euphoria to anxiety, were also recorded.[23]

It is also important to note that, unlike other drugs that affect the central nervous system in a straightforward and predictable manner, the feelings induced by psilocybin and LSD-25, are largely dependent on the user's mind-set and immediate environment (set and setting).[4] A user with a positive mind-set and a comfortable environment is far more likely to have a positive experience than a user in an unfamiliar or uncomfortable environment.[4,23] This being said, emergency responders and clinicians could benefit from being familiar with the importance of set and setting when treating users who are experiencing a "bad trip".[86]

Psilocybin mushrooms possess an LD-50 of 280 mg/kg, or 17 kg for a normal human, and are typically considered non-toxic.[86] LSD-25 has an LD-50 of 50-60 mg/kg in mice, 16.5 mg/kg for rats, and 0.3 mg/kg for rabbits.[16] Typically, the test subjects die from respiratory arrest, indicating the physiology of the animal in question plays a large role in the LD-50.[16] Most of the deaths associated with psilocybin mushrooms or LSD-25 have occurred while the user was under the influence of additional drugs, or because the user committed suicide.[86] Only two reported cases of death caused solely by overdose of psilocybin mushrooms are noted in the scientific literature.[86] In terms of deaths associated with the two drugs, the most common form of death, although very rare, is suicide either during or following the use of these psychedelics.[19]

Psilocybin and LSD-25 possesses the ability to affect the user in a variety of ways, effectively making the user's psychoactive experience very unpredictable.[86] Interestingly, when applied in a controlled setting, parallelisms between the state induced by a large dose of either drug and a deep meditative state are reported.[11,85,87,88] Both of these mental states involve modulation of the Default Mode Network (DMN), which is a series of highly correlated brain regions that are more active during rest and daydream states than they are during the execution of goal oriented tasks.[87,88] Additionally, there is a relationship between decreased neural activity within the Default Mode Network and dissolution of the ego or sense of self, see **Figure 12**.[88]

Discussion

Psilocybin and LSD-25 are two incredibly powerful mind altering substances. The two chemicals share a common indoleamine skeleton within their structures and they both illicit similar psychological responses. Although there are a variety of similarities amongst the drugs, the goal of this section is to address some of the major differences between the two.

The first difference, and most obvious, is that the two psychedelic compounds are noticeably dissimilar in both size and elemental composition. Psilocybin is a naturally occurring substance that shares a close resemblance to other naturally occurring biosynthetic double-ring compounds including tryptamine and serotonin. Psilocybin itself, in its phosphorylated form, is not as psychoactive as its derivative psilocin, and must therefore be chemically modified before it generates the desired psychotropic response. LSD-25, on the other hand, is a semisynthetic ergot alkaloid in a stereospecific four-ring system that is much larger than psilocin and does not need to be chemically modified prior to interacting with serotonin receptors in the brain.

Another notable difference between the two compounds is the minimum dosage that is required in order to provoke a psychological response. The effective dose for psilocybin is 0.045 mg/kg, while the

effective dose for LSD-25 is 0.001 mg/kg. Additionally, the longevity of the trips differ drastically with the typical psilocybin trip lasting between 3-6 hours with a half-life of 50 minutes and the typical LSD-25 trip lasting between 9-12 hours with a half-life of 3.6 hours. This indicates that LSD-25 is far more potent and lasts much longer than psilocybin. A potential reason for this difference was discussed earlier when it was noted that the 5-HT_{2B} receptor in the brain undergoes a conformational change when LSD-25 binds - which leads to a kind of amino acid chain seatbelt latching over the molecule, see **Figure 13**. Although the following is simply speculation and it has not yet been tested, it may be reasonable to assume a similar conformational change is generated upon psilocin binding. However, with psilocin being a smaller molecule, it is possible that if this were the case, the psilocin molecule could more easily slip out of the seatbelt and therefore be metabolized at a faster rate.

In terms of metabolism, it is apparent that the compounds will be broken down in different fashions by different enzymes. However, it is interesting to note that 50% of the psilocybin consumed is excreted unmodified while only 1% of LSD-25 consumed is excreted unmodified. This difference in the susceptibility for the molecules to interact and be broken down by the body may also be responsible for the difference in potency and trip longevity. Additionally, both substances have the potential to undergo glucuronidation, however, 80% of absorbed psilocybin is excreted in its glucuronidated form while the percentage of LSD-25 that was glucuronidated was much lower (as seen in **Figure 8**).

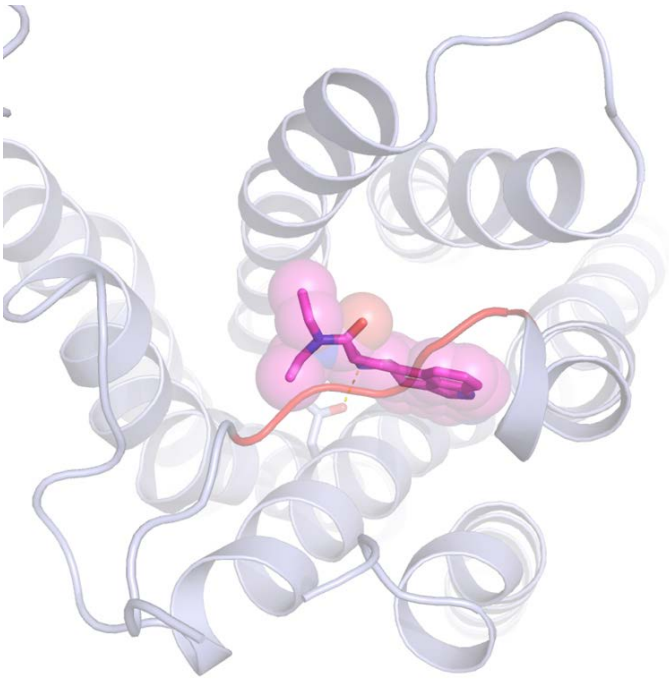


Figure 13: When LSD-25 binds to the 5-HT_{2B} receptor, the receptor site undergoes a conformational change, effectively locking the compound in the receptor, similar to a seatbelt.[80]

At this point, the difference is psychological effects should be addressed. As stated previously, there is an abundance of scientific research that details the similarities between psilocybin and LSD-25 trips, but very little scientific research in the way of differences. Traditionally, online websites, blogs and discussion forums are not considered reliable scientific sources; however, given the legal status of the compounds, the nature of psychological research, and the consistency of these drug experience reports, these resources should be examined further in order to frame and gain some understanding on how "experienced" users interpret differences in these drug trips.

Erowid.com and Reddit.com are two major sources of information that psychedelic participants utilize in order to conduct research on harm reduction and share drug experiences. All in all, the online forums suggest that each drug experience, regardless of the substance used, is highly subjective and also highly dependent on the set and setting of the person in question. That being said, there are some overarching themes that some users say differentiates the drug experience. Online users report that the feelings and visuals associated with psilocybin mushrooms are much more "natural" and "flowing", while LSD-25 users report a more "calculated" feelings and more "geometric" visuals. In addition, some users describe an LSD-25 trip as "flying a rocket ship" and a psilocybin trip as "being strapped to a rocket ship". This analogy, often used by online reporters indicates that some users have an easier time controlling their trip while on LSD-25 than while on psilocybin, indicating it may be easier to

suffer from a "bad trip" while on psilocybin than while on LSD-25.

Although the psychological effects of the drugs are similar, the types of receptors affected and the binding affinity of these receptors differs amongst the two compounds. As an example, the 5-HT1A receptor displays high affinity for both compounds; however, LSD-25 displays a much higher selectivity for the 5-HT_{2C} receptor than the 5-HT_{2A} receptor, whereas with psilocin, the trend is reversed. Also, as mentioned before, the dopamine receptor activity may play a key role in the difference in psychological response between these two compounds. Psilocin does possess a propensity to bind with dopamine receptors, but only the D_1 and D_3 receptors. LSD-25 on the other hand displays binding affinity for D_1, D_2, D_3, D_4, and D_5 dopamine receptors, and as discussed earlier, it is suspected that certain characteristics of schizophrenia or psychosis are deeply intertwined with the D_2 receptor, which psilocin does not possess binding affinity for.

Also, it is interesting to note that psilocin possesses the ability to bind to sodium-dependent serotonin transport receptors and activate serotonin transporter proteins, and LSD-25 does not. This may be contribute to some of the overwhelming or uncontrollable feelings that psilocin evokes, when compared to LSD-25.

Additionally, early gene activation also differs amongst the two compounds. The *c-fos* gene is activated in the presence of both drugs, leading to increased gene expression prompted by extracellular signals; however, aside from this, the two compounds promote the activation of different early genes. Psilocybin tends to activate certain early genes such as *egr-1, egr-2* and *jun-B* which are responsible for cell proliferation, differentiation and transformation. While LSD-25, on the other hand, tends to promote early genes such as *arc* which promotes learning, memory and plastic changes in the brain, and *ania3* which is responsible for the upregulation of glutamate an important excitatory neurotransmitter. This difference in early gene activation and the roles that these genes play, may also contribute to some of the behavioural and psychological differences between the two compounds.

Currently, the research on these compounds is hindered by their legal status. The primary goal of future research on these drugs should be to provide ample and undeniable evidence that these compounds have therapeutic and medicinal benefits. Once this is accepted, research on these molecules will become much easier to conduct - which can lead to an abundance of scientific and psychiatric research. In the 1970's the drugs were classified as Schedule I narcotics because they were used carelessly without caution. If the drugs are to be used in future scientific exploration, the priority should be safety and security. In addition, educating the public on these drugs could remove some of the negative stereotypes associated with these compounds and allow society to approach the issue from a mental health perspective rather than a law enforcement perspective.

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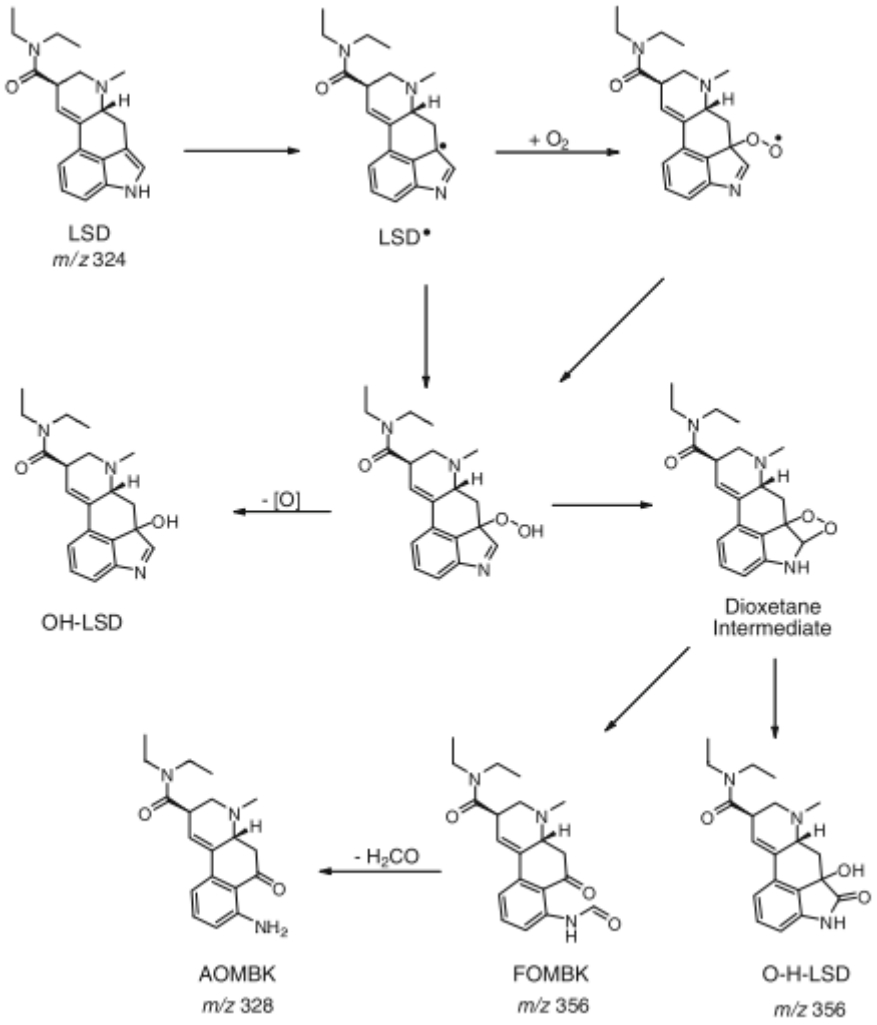
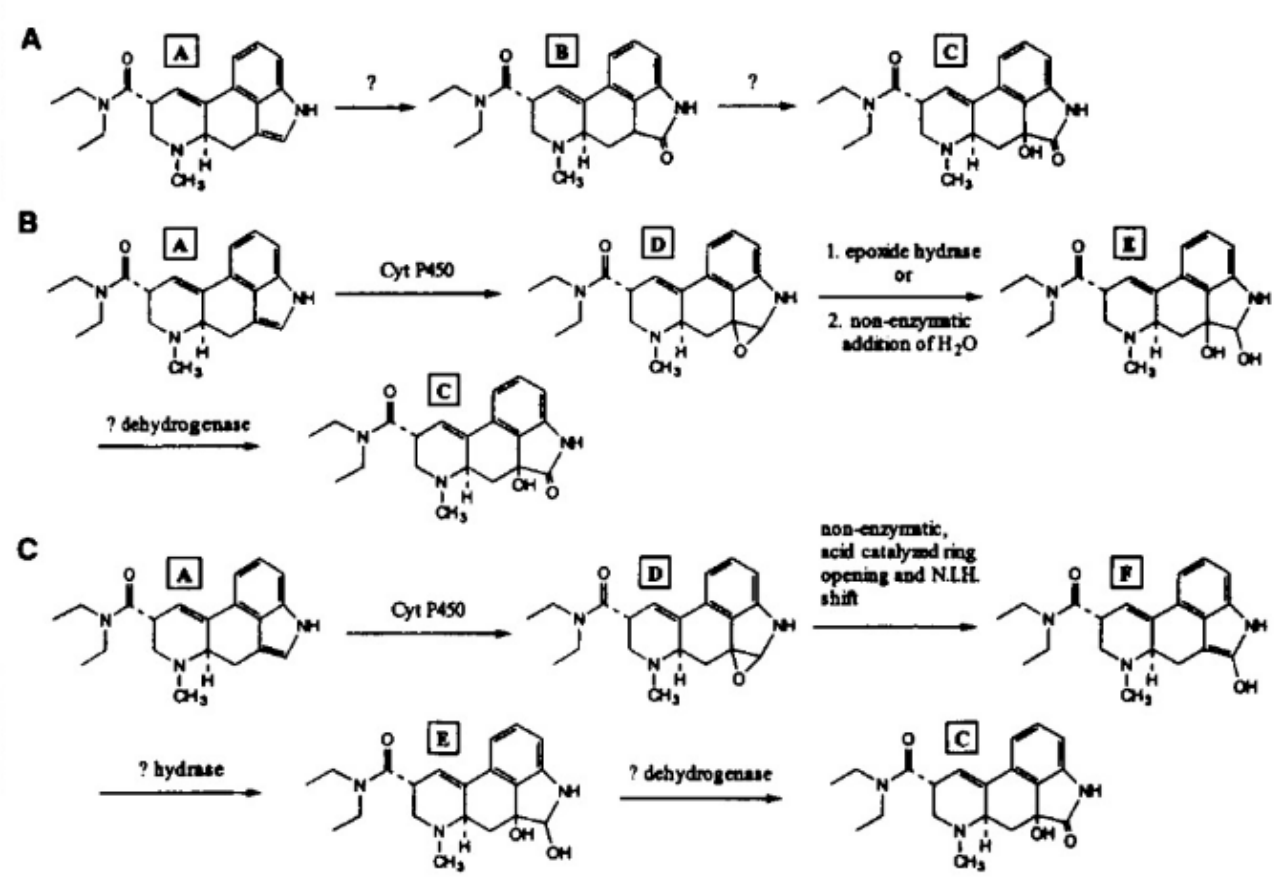
Appendix



Gomes, M. M.; Dörr, F. A.; Catalani, L. H.; Campa, A. *Forensic Toxicol.* **2012**, *30* (2), 87.



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