LSD and the Brain: A Psychedelic Puzzle

Introduction and Brief History

For decades, lysergic acid diethylamide, or LSD, was dismissed as a relic of psychedelic excess, but modern research suggests it may be the key to unlocking the mysteries of consciousness. Lysergic acid diethylamide (LSD) is a powerful psychedelic first synthesized in 1938 by Swiss chemist Albert Hofmann at Sandoz Pharmaceuticals, while researching lysergic acid derivatives from the rye fungus *Claviceps purpurea* (Passie et al., 2008). Its psychoactive effects were discovered accidentally in 1943 when Hofmann unintentionally absorbed a small amount through his skin and experienced vivid perceptual distortions (Liester, 2015). By the 1950s, LSD gained traction in psychiatric research, where it was used as a model for psychosis and a psychotherapeutic tool for understanding alcoholism and mental disorders such as anxiety and depression (Liechti, 2017). Towards the end of the 1960s, it was distributed under the trade name Delysid and was widely used for recreational and spiritual purposes, becoming the face of counterculture and the psychedelic movement. This led to stringent legal restrictions and its classification as a Schedule I substance, effectively halting clinical research in the 1970s (Herian, 2022). Despite its criminalization, LSD remains one of the most fascinating and extensively studied psychedelics, with modern research reviving its potential applications in neuroscience and psychotherapy (Passie et al., 2008).

Pharmacokinetics

LSD is a remarkably potent substance, effective in microgram doses, and follows a well-defined pharmacokinetic pathway that explains its rapid onset and prolonged effects. It can be ingested in the form of a blotter, liquid, or tablet and is rapidly absorbed through the gastrointestinal tract, reaching peak plasma concentrations within 1-2 hours (Dolder et al., 2015). LSD has an approximate bioavailability of 71%, indicating efficient absorption (Dolder et al., 2015). Holze et al. (2020) illustrated a fairly straightforward dose-proportional increase in plasma concentrations of LSD; moreover, the study found a close relationship between plasma concentrations and the drug's dynamic effects, such as altered states of consciousness and sympathomimetic responses, underscoring the importance of understanding LSD's pharmacokinetics for clinical and forensic applications (Liechti, 2017; Carhart-Harris et al., 2016).

A study by Upshall and Wailling (1972) found that plasma concentrations of orally ingested LSD were highest on an empty stomach as compared to when a meal was consumed; this suggests that the amount of food as well as the pH of the stomach and duodenum might influence the absorption of LSD, although these observations were not highly significant. Due to its high lipid solubility, LSD readily crosses the blood-brain barrier, granting it access to serotonergic receptors in the central nervous system, where it exerts its profound psychoactive effects (Passie et al., 2008). LSD exhibits first-order kinetics, with an initial half-life of 3.6 hours up to 12 hours, after which it transitions into a slower elimination phase with a terminal half-life of 8.9 hours (Dolder et al., 2015). This could be ascribable to redistribution from tissues or even less precise measurement at low plasma levels of the drug. LSD undergoes extensive first-pass metabolism in the liver through CYP2D6 and CYP3A4 enzyme pathways, to produce the pharmacologically inactive

metabolite, 2-oxo-3-hydroxy-LSD (Holze et al., 2021). Dolder et al. (2015) demonstrated that only 1% of the ingested dose is excreted unchanged in urine, while 13% is eliminated as the metabolite. While LSD metabolism is not inherently unique and its metabolites do not produce individual effects, the drug's high potency despite rapid metabolism is notable.

Although LSD is completely eliminated from the body within 24 hours, its sustained psychoactive effects - lasting up to 12 hours - are attributed to its strong binding at 5-HT_{2A} receptors rather than its presence in the bloodstream. This unique pharmacokinetic and pharmacodynamic interplay contributes to LSD's long-lasting hallucinogenic experience, distinguishing it from shorter-acting psychedelics and making it a subject of renewed interest in psychiatric research.

Pharmacodynamics

LSD is a serotonergic psychedelic that primarily exerts its effects through the partial agonism of serotonin 5-HT_{2A} receptors, but its impact extends beyond serotonin signaling to influence dopamine, glutamate, and the default mode network (Herian, 2022). Activation of 5-HT_{2A} receptors leads to increased excitatory neurotransmission, particularly in the prefrontal cortex, which contributes to perceptual alterations and cognitive disruptions characteristic of LSD experiences (Liechti, 2017). However, the exact intracellular mechanisms remain incompletely understood. A study by Liester (2015) suggests that 5-HT_{2A} receptor activation initiates phospholipase C signaling cascades, leading to increased intracellular calcium release and thus neuron excitation; other studies indicate that alternative signaling pathways, such as phospholipase A2 activation, may play a more significant role (Herian, 2022).

LSD's pharmacodynamics are intriguing, not only because of its serotonergic activity but also due to its distinct receptor binding. It is established that LSD exhibits competitive binding to the 5-HT_{2A} receptor with high affinity, but unlike serotonin, it sustains receptor activation (Gobbi, 2024). LSD's "lid-like" trapping mechanism prevents the normal dissociation of the strong receptor-ligand complex, contributing to the drug's long-lasting effects even after it is no longer detectable in the bloodstream (Passie et al., 2008). This leads to activation of downstream signaling pathways, modulating brain networks involved in consciousness, sensory perception, and cognition. Additionally, LSD's interaction with other serotonin receptors, such as 5-HT_{1A} and 5-HT_{2C}, further complicates its pharmacodynamics. The functional consequences of LSD's actions at these receptors remain underexplored, with some evidence indicating that 5-HT_{1A} receptor activation may mitigate the intensity of hallucinogenic effects (Liester, 2015). In contrast, 5-HT_{2C} receptors, which contribute to the regulation of mood, have been thought to potentially add on to excitatory effects induced by LSD (Passie et al., 2008).

LSD-induced 5-HT_{2A} receptor activation in the prefrontal cortex also enhances glutamate neurotransmission, leading to increased excitatory signaling through NMDA and AMPA receptors (Liester, 2015). This glutamatergic hyperactivity has been hypothesized to underlie the perceptual distortions associated with LSD (Liechti, 2017). Metabotropic glutamate receptors (mGluRs), which regulate memory, anxiety, learning, and pain perception, have been studied as mediators of LSD's effects by activating neuronal excitability (Liester, 2015). These receptor interactions are crucial for the hallucinogenic effects of LSD, as evidenced by multiple studies showing that the administration of the 5-HT_{2A} receptor antagonist ketanserin can significantly block these effects (Holze et al., 2021; Kraehenmann et al., 2017).

Importantly, LSD's ability to influence glutamate transmission may explain its therapeutic potential, as similar mechanisms have been implicated in the antidepressant effects of ketamine (Passie et al., 2008).

LSD's influence on dopamine has been studied (due to its effects on reward processing), but the exact nature of this interaction is unclear. (Gobbi, 2024). Some animal studies suggest that LSD's affinity for D2 receptors may contribute to its effects, drawing parallels to dopamine-mediated symptoms observed in schizophrenia (Liester, 2015). However, human studies indicate that LSD does not act as a direct dopamine-releasing agent (Liechti, 2017). LSD exhibits mixed effects on dopamine release, acting as an agonist for D1 and D2 receptors as well as for the 5-HT_{2C} receptor, which in turn inhibits dopamine release. As such, LSD is hypothesised to modulate the dopamine response (Liester, 2015). Moreover, LSD's pharmacodynamics are fundamentally rooted in its ability to alter brain networks and cognitive processes. Neuroimaging studies have demonstrated that LSD alters the balance between excitation and inhibition in the brain, particularly by disrupting the default mode network (DMN), which is responsible for self-awareness and ego functioning (Carhart-Harris et al., 2012). This disruption is thought to contribute to the sense of ego dissolution and the mystical altered state of consciousness, a key feature of the psychedelic experience.

While LSD's modulation of serotonergic pathways is central to its hallucinogenic and introspective effects, the variability in user experiences suggests a complex interaction between multiple neural circuits. Emerging research indicates that LSD may enhance synaptic plasticity, potentially contributing to its lasting cognitive and emotional effects, with therapeutic implications for disorders like depression and PTSD (Gobbi, 2024). However, further investigation is needed to clarify how serotonin, glutamate, and dopamine signaling interact to produce LSD's hallucinogenic and therapeutic effects, as well as to determine its full clinical potential.

Drug Effects

Few substances can so profoundly alter human perception, cognition, and emotion, bolstering LSD as a subject of renewed scientific interest in neuroscience and mental health. LSD induces a spectrum of physiological and behavioral effects, ranging from transient hallucinations to long-term changes in mood and cognition (Liechti, 2017). The effects of LSD are strongly influenced by the set and setting in which it is used; this refers to the mental state of the individual as well as their physical and social environment (Liester, 2015). One of its most well-documented effects is the altered states of consciousness, including ego dissolution, synesthesia, and time distortion (Carhart-Harris et al., 2016). Dr. Hofmann himself expressed his transformative experience with LSD, recounting, "*Waves of ineffable happiness flowed through my body. I had experienced the grace of God."* (Hofmann, 2017).

These effects are mediated primarily by 5-HT_{2A} receptor activation in the prefrontal cortex, which enhances cortical excitation and disrupts normal sensory integration (Kraehenmann et al., 2017). LSD's psychoactive effects begin around 40 minutes of ingesting the drug and generally last 8-12 hours (Liester, 2015). It exerts dose-dependent autonomic effects (Liester, 2015), including mild increases in blood pressure, heart rate, and body temperature (Holze et al., 2021). In a placebo-controlled study by Holze et al. (2021), moderate doses (50-100 µg) produced mild sympathomimetic effects,

while higher doses (200 μg) resulted in greater cardiovascular activation and increased pupil dilation. However, the physiological impact of LSD is less pronounced than that of stimulants like amphetamines (Herian, 2022). One limitation with administering a high clinical dose of LSD (100 μg or more) is the subjects' cognitive impairment and inability to cooperate due to the intensity of the drug, while lower doses may not properly capture all effects. (Passie et al., 2008)

With a medium dose of LSD, typical perceptual effects include sensory alterations and illusions, intense colour perception, and metamorphosis-like changes in objects and faces (Passie et al., 2008). Subjects may also experience cognitive effects such as impaired judgement, shortened attention span, and mind-wandering (Liester, 2015). LSD also increases primary process thinking, a form of cognition associated with dream states and psychotic experiences (Kraehenmann et al., 2017). This effect, characterized by enhanced associative thinking and decreased cognitive filtering, underlies both the creative insights and psychotic-like states induced by LSD. Interestingly, transcendental and mystical experiences are often reported, with a renewed sense of unity and self (Liester, 2015). However, not all users experience positive psychological effects - some may experience the "bad trip" with anxiety, paranoia, or transient psychotic episodes, particularly at higher doses (Carhart-Harris et al., 2016). Furthermore, a study by Liechti (2017) showed that LSD reduces fear perception by altering amygdala function, leading to a decreased response to threatening stimuli. This effect may explain its potential in treating anxiety disorders and post-traumatic stress disorder (PTSD), as it facilitates emotional processing and fear extinction.

Despite these emotional and cognitive alterations, LSD does not appear to induce compulsive drug-seeking behaviors, a key distinction from substances, like stimulants and opioids, with high addiction potential (Herian, 2022). While LSD does bind to dopamine receptors, its effect on dopamine release in the nucleus accumbens is minimal compared to addictive substances (Liechti, 2017). Furthermore, LSD does not produce physical dependence and withdrawal symptoms - with the absence of addictive properties often attributed to the drug's interactions with the 5-HT_{2C} receptor (Liester, 2015; Gobbi, 2024). Some individuals may crave LSD's altered states of consciousness or use it excessively for personal exploration, spiritual experiences, or escape from reality. However, this is not the same as a substance use disorder (SUD), since there is no uncontrollable drug-seeking behavior.

LSD induces rapid tolerance with repeated use, mainly due to downregulation of 5-HT_{2A} receptors, which mediate its psychedelic effects (Herian, 2022; Liechti, 2017). Studies indicate that after just a few consecutive doses, LSD produces significantly diminished effects, requiring higher doses to achieve the same subjective experience (Passie et al., 2008). This tolerance develops within 2-3 days of repeated administration and dissipates within a week of abstinence, distinguishing it from substances with longer-lasting tolerance mechanisms (Liechti, 2017). In this way, LSD lacks the neurochemical properties of traditional addictive drugs, but excessive use could indicate habitual psychological reliance rather than true addiction. LSD does not produce sensitization, meaning that repeated exposure does not lead to an increased response over time (Passie et al., 2008). Additionally, due to its cross-tolerance with other serotonergic psychedelics, such as psilocybin and mescaline, users who develop tolerance to LSD may experience reduced effects from

these compounds as well. The rapid tolerance development and lack of sensitization contribute to LSD's low potential for compulsive use and addiction (Herian, 2022).

LSD has a paradoxical influence on behavior, producing both increased social bonding and altered risk perception. Studies indicate that LSD enhances feelings of connectedness and trust, likely through increased oxytocin release and altered functional connectivity in the brain's default mode network (DMN) (Liechti, 2017). At the same time, LSD impairs cognitive control and sensorimotor gating, leading to increased suggestibility and altered decision-making (Carhart-Harris et al., 2016). Some studies even report that LSD acutely disrupts impulse regulation, although this effect is transient and dose-dependent (Holze et al., 2021). The distinct effects of LSD at low (serotonergic) and high (dopaminergic) doses could be the pharmacological basis of why LSD has some beneficial effects in elevating mood and well-being while also inducing a hallucinogenic effect with mystical-like properties (Gobbi, 2024). More research is required to form a stronger correlational relationship between dose and response in humans; nevertheless, researchers accept that the hallucinogenic effects of LSD are mediated by both D2 and 5-HT_{2A} receptors.

LSD induces a complex array of physiological, psychological, and behavioral effects, largely mediated by its serotonergic, glutamatergic, and dopaminergic interactions (Herian, 2022). While mild autonomic stimulation and increased neuroplasticity contribute to its physiological impact, its deep cognitive alterations highlight both its therapeutic potential and risks. Notably, LSD's low addictive potential and unique effects on social cognition and fear processing demonstrate a distinct pharmacological profile (Liechti, 2017). However, further research is needed to clarify individual variability in responses and long-term effects, particularly in clinical applications. LSD remains one of the most enigmatic substances in neuroscience, offering both challenges and opportunities for research. As modern science revisits its therapeutic applications, LSD's journey from accidental discovery to psychiatric tool and cultural phenomenon continues to shape our understanding of consciousness and brain function.

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