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The mechanism of hallucinations caused by lysergic acid diethylamide

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Abstract:

Lysergic acid diethylamide (LSD) is a semi-synthetic hallucinogen that induces intense hallucinogenic effects. There are various ways that hallucinations can occur, but classic psychedelics like LSD differ significantly in their effects from those caused by other means. The primary focus of current research is on activating 5-HT2A receptors within the serotonin system, which is essential for causing hallucinations and related behavioral responses in humans. In addition, through functional magnetic resonance imaging (fMRI), people can clearly observe the changes in cerebral blood flow influenced by LSD. This research presents the mechanism behind LSD's hallucinatory effects from perspectives such as molecular biology and neuroanatomy spanning nearly half a century. As the understanding of its mechanism deepens, it can link the hallucinations caused by LSD to perceptual disorders and other diseases in humans, thus identifying more treatment methods. The analysis of the hallucination mechanism can also be beneficial for developing new treatment methods and understanding the specific physiological changes caused by drugs in hallucinations.

Keywords: LSD; hallucination; hallucinogens; 5-HT receptors.

1. Introduction

Hallucinogens are a class of compounds that can cause hallucinations and induce unconventional sensory perceptions, such as visual and auditory. Hollister proposed in 1968 that hallucinogens at therapeutic doses can alter perception, emotion, and cognition but have few or virtually no neuropsychiatric side effects and are not likely to lead to addiction; this concept has been widely adopted. Therefore, not all compounds that cause hallucinations are classed as hallucinogens; substances like cannabinoids, ketamine, 3,4-methylenedioxymethamphetamine (commonly known as ecstasy), and the kappa-opioid receptor agonist salvinorin A [1]. Lysergic acid diethylamide (LSD) is a semi-synthetically produced hallucinogen. It triggers a series of responses in the central nervous system of the brain, resulting in intense hallucinogenic effects. LSD interacts with serotonin receptors in the brain, disrupting the normal functions of neurotransmitters like dopamine and serotonin and altering the way information input is processed in the brain. LSD can affect a variety of brain receptors, such as dopamine receptors, adrenergic receptors, and glutamate receptors, though most research focuses on its stimulation of the serotonergic receptor 5-HT2A.

The hallucinogenic effects of LSD are due to its interference with the normal functioning of neurotransmitters in the brain, altering the way information is processed from the senses into the brain. Ingesting ten micrograms of LSD might cause a sense of euphoria, while 50-200 micrograms can lead to hallucinations. Physiologically, LSD is generally safe, primarily used to alter the state of consciousness of the user without causing life-threatening changes in cardiovascular, renal, or hepatic functions [2]. LSD does not produce dependency or addiction, but one adverse consequence of using hallucinogens is „flashbacks." These are re-experiencing certain sensory effects caused by the hallucinogen even when there is no LSD present in the body after the drug's effects have dissipated. Most flashback effects are visual hallucinations that can last for months or even years, and there is no correlation between the frequency of LSD use and the occurrence of flashbacks. However, persistent perception disorder (flashbacks) from hallucinogens like LSD can occur years after use. Relatively low doses of LSD have been shown to disrupt normal exploratory activity patterns, increase avoidance of new and central areas of activity monitors, and suppress feeding activities within 10 minutes after administration [2].

Hallucinations are complex perceptual phenomena rooted in errors in the brain's processing of information. They are visual patterns experienced by individuals in the absence of physical stimuli. Hallucinations are perceptual disorders, including auditory, visual, tactile, and other

sensations, with visual hallucinations being very common. They can have defined contours like animals or plants, as well as formless auras and lights. Disturbances in touch and taste are also possible. For example, users may taste metal in their mouths or smell unusual odors after taking LSD. Auditory hallucinations are infrequent among users. Both genuine hallucinations (perceptual) and pseudo-hallucinations (illusory) can occur. True hallucinations, also known as complete or perceptual hallucinations, are unwaveringly believed by the patient, accompanied by corresponding thought, emotional, and volitional behavior responses. Pseudo-hallucinations, also known as incomplete hallucinations or illusory, are not as vivid, arise in the subjective space such as within the brain or body, and despite being distinct from general perception, patients are often certain they did hear or see and are convinced of its reality.

Hallucinations are most commonly visual (VH) and auditory (AH), and therefore, the mechanism behind their occurrence will be explored using visual and auditory hallucinations as examples. Currently, pure visual hallucinations are considered to be characteristic of neurological disorders such as Parkinson‘s and Bonnet syndrome. Both Parkinson‘s and Bonnet syndrome are also associated with ocular diseases, affecting the retina, the primary visual pathways within the eye, and the secondary ventral and dorsal pathways [3]. There are many research models regarding VH, and current studies on VH models mainly focus on the Default Mode Network (DMN) decoupling model. This hallucinatory activity is caused by changes in thalamic function and dysregulation of brain neurotransmitters. Historically, dopamine has been considered the primary driver of VH in synucleinopathies. Dopaminergic pathways originate in the midbrain, specifically in areas like the ventral tegmental area (VTA) and substantia nigra, projecting to various regions of the brain; projections to the cortex and ventral striatum are known as mesocortical and mesolimbic dopaminergic projections, respectively. The pathogenesis of VH involves the dysfunction of the nigrostriatal pathway in this context.

This research focuses on the classic hallucinogen LSD, summarizing research in pharmacology and neuroscience, with an emphasis on discussing the electrophysiological pathways through which LSD induces hallucinations. It encompasses past experiments on the possible effects of hallucinogens on human neuronal receptors, neural networks, and brain regions, along with the resulting physiological responses. To investigate the mechanism behind hallucinogen-induced hallucinations, this research approaches the subject from two main angles: receptor-drug binding and the activation of receptor-coupled electrosignaling pathways, including the activation of neural network connections. The research specifically examines the early experimental methods used to localize the 5-HT2A receptor, the content of experiments using hallucinogens on rats, cerebral blood flow measurement, statistics from magnetic resonance imaging, and the main symptoms affected, offering a comprehensive summary and organization of the mechanism behind the hallucinatory effects of hallucinogens. This research also explores the link between the generation of hallucinations and perception to present some more comprehensible extensions.

2. LSD-based hallucination mechanism analysis

2.1 Direct connection between hallucinogens and hallucinations

The core effect of hallucinogens is to induce hallucinations. The hallucinations produced by hallucinogens have tested populations that often have various influences, such as religious and cultural factors, making it difficult to quantify with biological markers. These studies involve multiple disciplines, including psychology, anthropology, and religious studies. The most common method for studying the hallucinatory effects of hallucinogens on the human body has been to administer psychological insight surveys to subjects. These surveys attempt to standardize the evaluation of all aspects of the hallucinatory experience, including changes in sensation, emotion, and cognition. LSD was given to psychiatrists and researchers between 1949 and 1966 to „further understand the world of psychiatric patients“ and aid in psychotherapy. LSD has been a crucial instrument for neuroscience and drug development and has also had an impact on art and society. Political pressure resulted in the halting of clinical research on LSD in the early 1970s due to its widespread and uncontrolled use. Hollister summarized the symptoms of the clinical use of hallucinogens, which included somatic, sensory, and mental symptoms [4]. Current toxic reactions caused by hallucinogens are primarily manifested as perceptual changes, mainly including synesthesia, intensified sensations, enhanced empathy, personality disintegration, distorted perception of the outside world, and changes in emotion. The sensations experienced by users often combine, akin to a journey. This intensification of mental activity can also appear when the individual is sober. Mental disorder is one of the main side effects of hallucinogens. It is estimated that out of every 10,000 LSD users, eight may experience psychotic episodes.

The hallucinogenic signaling pathways of LSD through the distribution of the 5-HT2A receptor are located using autoradiographic techniques to map the central nervous distribution of the 5-HT2A receptor. The initial radioligands used were primarily [3H] spiropiperidine, [3H]

ketanserin, [3H] LSD, and [125I] DOI, but these ligands are not highly selective for the 5-HT2A receptor, meaning that they are not specific only to the 5-HT2A receptor, resulting in some uncertainty in the localization outcomes [5]. The 5-HT2A receptor is mainly distributed in the cerebral cortical areas, with other regions including the hippocampus, mammillary bodies of the hypothalamus, thalamic nuclei, and various nuclei of the midbrain [6]. The distribution of the 5-HT2A receptor in the human brain differs from its distribution in the brains of rats. Transgenic approaches with gene promoters can be used to enhance the expression of the 5-HT2A receptor tagged with green fluorescent protein in mice, thereby pinpointing the specific cell populations expressing the receptor, which includes pyramidal cells in layer V of the prefrontal cortex, GABAergic interneuron subgroups in the intermediate layers of the cortex, and non-pyramidal cells in layer VIb [5].

For those researchers related to the brain regions activated by the LSD molecule, cerebral blood flow is primarily used as a measure of neuronal activity, or sometimes researchers will use functional magnetic resonance imaging (fMRI) to identify highly connected neural networks. As shown in Fig. 1, the changes in cerebral blood flow indicate the alterations post-LSD ingestion. LSD significantly increases the functional connectivity between the primary visual cortex and subcortical brain regions, suggesting that a larger proportion of the brain is involved in processing visual information than under normal circumstances. This also corroborates the role of LSD in producing hallucinations due to its intense activation of the 5HT2A receptor, with the main distribution areas of this receptor also experiencing increased oxygen demand and concentrated blood flow due to high cortical activity. From this, it can also be inferred that the intense visual hallucinatory experiences are derived from the heightened activation of the visual cortex.

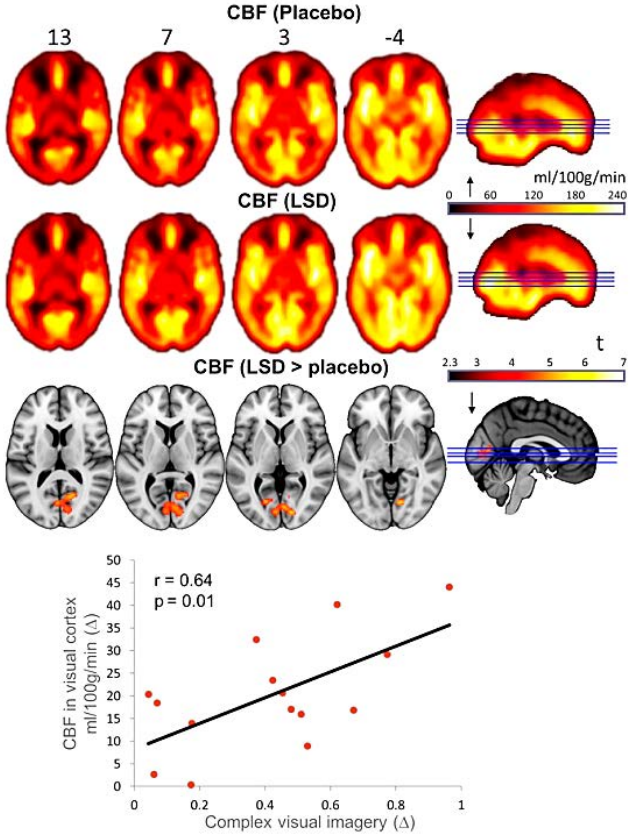

Fig. 1 Whole brain cerebral blood flow and difference maps under placebo and LSD conditions [7].

LSD has been found to significantly reduce the network's functional integrity and the segregation between them. At the global brain level, LSD increases the functional connectivity between different brain regions. LSD also increases the measure of something called „brain entropy" for many functional systems. „Brain entropy" refers to the level of neuronal states accessible by the brain and is used to measure the brain's capability to process complex information. fMRI data show that LSD enhances functional connectivity across different brain areas and networks, including key regions such as the medial prefrontal cortex, anterior and posterior cingulate cortex, and insular cortex.

Serotonin (5-HT) is a primary neurotransmitter involved in severe depression and is also the main system through which hallucinogens produce their effects. Hallucinogens, such as LSD, have a strong association with their binding capacity to 5-HT receptors. Neurons expressing 5-HT receptors are distributed throughout the brain, with the highest concentration in the dorsal raphe nucleus (DRN). The 5-HT neurons of the DR are inhibited by dendritic autoreceptors. Antidepressants, selective serotonin reuptake inhibitors (SSRIs), act on the 5-HT transporter and then activate the 5-HT1A autoreceptor, reducing the firing rate. LSD and psilocybin hallucinogens do not bind directly to glutamate receptors. Glutamate has a downstream effect on the overall effects of LSD and hallucinations, with significant non-genomic actions and impacts. The time-dependent increase in glutamate levels in the prefrontal cortex (PFC) occurs when systemic hallucinogens are used, an effect that is impeded by the selective 5-HT2A antagonist MDL100907. LSD has a profound influence on dopamine system deficiencies due to its psychotomimetic properties. The D2 receptor is the dopaminergic receptor with which LSD has a high affinity [2].

Hallucinogens will be completely substituted in animals trained to distinguish the typical hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) by binding to the 5-HT2A receptor. Consequently, hallucinogens are commonly classified as classical hallucinogens or serotonergic hallucinogens. Two major structural classes are used to categorize classical hallucinogens: tryptamines and phenethylamines. Phenethylamine hallucinogens are specifically suited to 5-HT2 receptors, which include 5-HT2A, 5-HT2B, and 5-HT2C. In contrast, the tryptamine class binds non-selectively to 5-HT receptors. The neurotransmitter serotonin has potent vasoconstrictive effects, particularly in the rat uterus and guinea pig ileum. The development of radioligand receptor technology allowed for the study of 5-HT receptors by applying this methodology. The radioligand [3H]spiperone has been introduced to counteract dopaminergic activity. It was established that [3H]spiperone was not binding to the 5-HT receptor in the same way as the sites labeled by [3H]5-HT. [3H]LSD labeled both 5-HT1 and 5-HT2 receptors, which were identified as the sites labeled by 5-HT and [3H]spiperone [1].

LSD is a hallucinogen that primarily exhibits agonist activity on 5-HT receptors 2A-C, 1A/B, 6-7, as well as dopamine D2, D1 receptors. LSD can effectively bind to many neural receptors. However, ketanserin (ket), a selective antagonist for 5-HT2A and α-adrenergic receptors, was found to be completely blocking LSD‘s hallucinogenic effects. This illustrates that ket should block the neural effects of LSD. The distribution of 5-HT2A receptors in the brain should have a strong correlation with the networks regulated by LSD [8]. The publication utilized the latest advances in human cortical gene expression atlases to understand the spatial topography of data-driven connectivity changes induced by neuroactive drugs. The literature hypothesized that the changes in global brain connectivity (GBC) caused by LSD would accurately match the expression pattern of the gene encoding for the 5-HT2A receptor. Hypothesis was made that 5-HT2A would be prioritized for this effect, rather than other receptors, and that the removal of artifacts would lead to a significant improvement in spatial matching. The 5-HT2A receptor‘s role in LSD‘s neuropharmacology was confirmed by the fusion of neuropharmacology and gene expression atlas [8]. This neuroimaging pharmacology study addressed the data-driven effects of LSD, which are very sensitive to the removal of global signal (GS), suggesting that the 5-HT2A receptor has been implicated in LSD‘s neuropharmacology, which involves both subjective and neural effects, and that mapping spatial expression pattern of 5-HT2A receptor gene can help identify cortical effects of LSD.

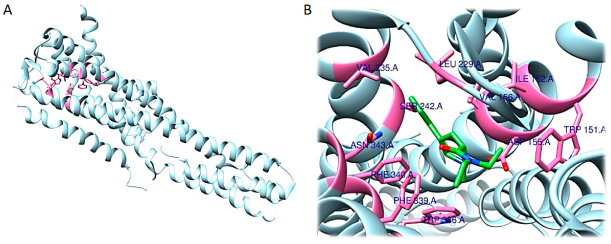

Fig. 2 3-D structure for PDB and 5-HT2B-LSD complex [9]. (A) A 3-D model of the 5-HT2A receptor (A). (B) Detailed view of residue (pink) interacting with LSD (green).

2.2 Signaling pathway of 5-HT receptors

Regarding the hallucinogenic response caused by LSD, serotonin signaling is involved in this response. Activation of 5-HT2A receptors solely within the cerebral cortex is enough to trigger a hallucinogenic response at the cortical level, suggesting that cortical pathways are central to the hallucinatory response. LSD is considered a partial agonist for the 5-HT2A receptor. Through thalamic input, LSD can activate the 5-HT2A receptor and lead to the rise of cortical glutamate levels. As shown in Fig. 2, hydrophobic interactions were identified as being related to lle152, Asn343, Leu229, Val156, Trp336, Trp151, Val235, Phe340, and Phe339 [9]. This explains why blood-brain barrier can be crossed by LSD. LSD induces an increase in functional brain connectivity between the thalamus and the sensorimotor cortical regions, as well as from the thalamus to the posterior cingulate cortex, while also reducing

connections with the temporal lobe cortex.

The main hypotheses on how LSD affects 5-HT are as follows: LSD preferentially inhibits the firing of serotonergic neurons, thereby preventing the upregulation/downregulation of postsynaptic serotonin receptors. Generally, 5-HT is primarily an inhibitory neurotransmitter that suppresses sensations, thus preventing sensory overload in the brain. LSD inhibits the release of 5-HT in the locus coeruleus (LC), raphe nuclei (RN), and the cerebral cortex. When 5-HT activity is reduced, the downstream neurons in the chain are no longer inhibited, thus becoming more active. LSD is now understood to be partially agonistic to the 5-HT2A receptor. Activation of 5-HT2A causes the increase of cortical glutamate levels, and this raised glutamate release results in changes in cortico-cortical and cortico-subcortical transmission. Experiments using genetically modified mice that express the 5-HT2A receptor only in the cerebral cortex have shown that they are adequate to generate hallucinogenic effects. This may suggest that hallucinatory effects are mainly mediated by cortical-cortical neural circuits, rather than the thalamo-cortical circuits. LSD‘s activation of receptors is time-dependent; it can activate rats‘ 5-HT2A receptors within 15-30 minutes, while after 90 minutes, the main part of the LSD response may be mediated by D2 receptors [10]. This data could explain the effects of LSD on humans.

It is widely believed that the main molecular target for the cellular, electrophysiological, and behavioral effects of hallucinogens in rodents is the expression of 5-HT2A receptors in pyramidal neurons of the frontal cortex, but the activation of mGlu2 receptors also plays a role in this process. Compared with wild-type littermates, LSD-induced head-twitch response in mGlu2 gene knockout mice is impaired, suggesting that mGlu2 has a role in the specific head-twitch behavior enticed by hallucinogens. Activating mGlu2 receptors can prevent the electrophysiological effects of 5HT2A agonists, which can lead to hallucinations, demonstrating that 5-HT2A receptors and mGlu2 receptors are involved in crosstalk. Gq/11-coupled 5-HT2A receptors and Gi/o-coupled mGlu2 receptors form a specific GPCR heteromer complex when co-expressed heterologously, meaning that in the frontal cortex, a GPCR heteromer complex is formed by the co-expression of 5-HT2A receptors and mGlu2 receptors [11]. According to this information, the 5-HT2A-mGlu2 receptor complex is necessary for the hallucinogen-like behaviors caused by 5-HT2A receptor agonists.

3. Conclusion

This research provides an overview of the hallucinatory mechanism induced by the representative hallucinogen LSD. This research discusses in detail the role of LSD, especially its effects on the nervous system, including the receptors it interacts with, the role of different neurotransmitters in the hallucinatory response, and the electrophysiological pathways through which LSD induces hallucinations. Of course, research into the hallucinogenic drug LSD still has its limitations. Current studies on hallucinations are challenging to quantify with biological markers, and the most common methods involve psychological surveys of subjects, although these are often influenced by religious, cultural, and anthropological factors. With the deeper understanding of LSD‘s mechanism of action in the 21st century, it can explore its tremendous potential for treating neurological disorders, in order to conquer diseases that currently have no effective treatments.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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