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Review

Exploring Neuroplasticity: The Role of LSD, Methamphetamine, Cannabis, and Ketamine in Psychiatric Disorders

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ABSTRACT

Psychoactive substances are chemical compounds that cause emotional and behavioral changes by altering perceptions and cognition. These substances can affect communication between brain cells and synaptic connections, thereby influencing neuroplasticity. Neuroplasticity is a key mechanism underlying various psychiatric disorders such as depression, anxiety, and post-traumatic stress disorder. The findings suggest that psychoactive substances could open new avenues in the field of neuropsychiatry. However, it is emphasized that these substances must be used safely and under controlled conditions, with consideration given to their side effects and risks, and more clinical research is needed. This review discusses the effects of psychoactive substances such as lysergic acid diethylamide, methamphetamine, dimethyltryptamine, cannabis, ketamine, and psilocybin on neuroplasticity, and how these effects could be beneficial in the treatment of depression, anxiety, and other psychiatric disorders.

Keywords: Dimethyltryptamine, methamphetamine, neuroplasticity, psychedelics, psychiatric disorders, psychopharmacology.

Psychological disorders are generally defined as illnesses that manifest through abnormal behaviors, emotions, and thoughts.[1] The types of psychological disorders include anxiety disorders, post-traumatic stress disorder (PTSD), schizophrenia, obsessive-compulsive disorder (OCD), personality disorders, mood disorders, and childhood disorders.[2]

Anxiety Disorder

Anxiety disorder refers to a condition in which an individual experiences a high level of anxiety and fear in response to events that may or may not happen, to the extent that it seriously threatens their daily functioning and well-being.[3]

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is a DSM-5-defined disorder characterized by intrusive thoughts that cause distress, and repetitive behaviors performed in response to these thoughts.[4]

Mood Disorders

Mood disorders are a group of conditions in which an individual experiences significant emotional fluctuations, including manic (extremely active) or depressive (profoundly low energy) episodes. Suicidal thoughts are also associated with these disorders.[5]

Post-Traumatic Stress Disorder

Post-traumatic stress disorder is a disorder that develops after intense traumatic experiences such as war, sexual assault, or natural disasters. Symptoms include negative thoughts, emotional numbness, and social isolation.[6]

Schizophrenia

Schizophrenia is a disorder that significantly disrupts daily life and is characterized by delusions, hallucinations, and severe difficulties in emotional and behavioral regulation. Genetic factors also play an important role in its development.[7]

Dissociative Disorders

Dissociative disorders are a group of conditions in which an individual experiences a loss of identity integrity and detachment from reality.[8]

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After researchers proposed the theory known as the monoamine hypothesis, they suggested that depression is caused by an imbalance among the chemicals responsible for communication between neurons.[9] Neurotransmitters are chemical substances that facilitate communication from one cell to another by crossing junctions called synapses. These molecules function as either excitatory or inhibitory agents.[10]

Antidepressants modulate serotonin (5-hydroxytryptamine, 5-HT) in the brain and enhance serotonergic transmission to the spinal cord. Among the various types of antidepressants are selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and noradrenergic and specific serotonergic antidepressants. Most of these drugs increase the concentration of monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) in neural tissue or act as agonists at their receptors. There are also antidepressants with different mechanisms of action.[11]

PSYCHOACTIVE SUBSTANCES

The use of psychedelics dates back to 1897 when Arthur Heffter isolated mescaline from the peyote cactus.[12] Additionally, magic mushrooms containing psilocybin, which are widely found across the world, appear to have been commonly used.[13]

The Eleusinian Mysteries, known as mystical and sacred rituals in Ancient Greece, were fundamentally based on special mixtures containing psychoactive compounds of the time. These ceremonies were a form of ritual that ancient societies turned to in order to experience spiritual transformation. Researchers suggest that participants in the Eleusinian Mysteries used various plant- and mushroom-based psychoactive substances to induce mystical awareness and a sense of unity. As for psychedelics, lysergic acid diethylamide (LSD) was first synthesized by Albert Hofmann in 1938 at the Sandoz laboratory in Switzerland.[14,15]

Mushrooms containing psilocybin, commonly known as "magic mushrooms," grow across a wide geographic range around the world and have been observed to be used by various cultures.[16]

Mescaline still holds a significant place in the rituals of the Native American Church in North America today.[17] In Brazil and the wider Amazon basin, a drink called ayahuasca is used in shamanic healing and spiritual ceremonies. Ayahuasca combines dimethyltryptamine (DMT) derived from plants and β-carboline MAOIs, and the synergy of these components induces profound spiritual experiences.[18]

Psychedelics have long captured the interest of neuroscientists.[19] These molecules can affect perception, alter cognition, and create unique experiences. The ability of psychedelic drugs to modulate perceptions can be utilized as a powerful tool for exploring the human mind. Additionally, psychedelics have the potential to benefit patients diagnosed with a wide range of neuropsychiatric disorders, such as depression, anxiety, and substance use disorders.[20-22]

EFFECTS OF PSYCHOACTIVE SUBSTANCES ON THE BRAIN AND NEUROPLASTICITY

Neuroplasticity refers to the brain's capacity to adapt and change in response to new experiences. It encompasses not only morphological changes but also biochemical and pharmacological alterations (such as intracellular pathways, receptors, and synaptic proteins). This process includes changes in neuronal networks (modifications in connections, dendritic remodeling, and alterations in the number and morphology of dendritic spines) and the formation of new neurons (adult neurogenesis). Neuroplasticity serves as a significant gateway to understanding the pathophysiology and treatment of psychiatric and neurological disorders.[23]

Serotonin is an evolutionarily conserved monoamine neurotransmitter that regulates psychophysiological functions across species through various pathways. The human brain synthesizes this substance in the raphe nuclei and is reflected in afferent and efferent pathways. Disruptions in the 5-HT system are thought to contribute to disorders such as depression, anxiety, and migraines in the brain.[24,25]

Psychedelics, such as psilocybin derived from mushrooms, are compounds that have long intrigued researchers and hold therapeutic potential. The first study on LSD in the English literature was published in 1950, and these types of psychedelic substances garnered significant interest in the fields of psychology and psychiatry for a brief period. During this time, the profound experiences and expanded awareness induced by substances like LSD excited

psychiatrists and researchers alike.[26]

However, the implementation of restrictive laws in the mid-1960s significantly hindered psychedelic research and the therapeutic use of such substances. During this period, studies exploring the potential therapeutic effects of psychedelics also decreased sharply. Notably, potential benefits were observed in treating challenging psychological issues, such as alcoholism and mood disorders.[27]

In recent years, there has been a resurgence in the research and therapeutic use of psychedelics. The renewed interest and studies are providing new insights into how these substances can be utilized in the field of mental health. Notably, research on natural psychedelics like psilocybin is drawing attention to their potential effectiveness in treating mental health issues such as depression and anxiety. In this context, the history and therapeutic potential of psychedelic substances remain important topics of interest and investigation within the scientific community.[28]

A study conducted by Calvin Ly et al.[29] demonstrates that psychedelics have the potential to enhance neuroplasticity in the brain. This research revealed effects such as synaptic growth, an increase in dendritic spines, enhanced protein synthesis, and elevated levels of brain-derived neurotrophic factor (BDNF). It is a critical protein for the health and growth of nerve cells, as well as for the formation of new synaptic connections. The study found that psychedelics like LSD, DMT, and psilocybin increased dendritic arbor complexity and strengthened synaptic connections, showing similar results to ketamine. Moreover, psychedelics significantly promoted the formation of new synaptic connections by increasing both the number of dendritic branches and their total length. Dose-response studies indicated that LSD, in particular, exhibited high potency and was effective even at low concentrations. These findings support the potential therapeutic use of psychedelics in treating mental health disorders by enhancing structural and functional neuroplasticity in neurons.

When psychedelics bind to the 5-HT2A receptors in the brain, they trigger complex biochemical processes within cells. This binding causes the activation of proteins known as Gq. The activated Gq proteins initiate a series of reactions in the cell membrane and break down a molecule called PIP2 into two important components: IP3 and DAG. IP3 increases calcium release within the cell, while DAG activates an enzyme known as protein kinase C. Protein kinase C alters the functioning of other proteins within the cell, thereby amplifying the effects of psychedelics. This process affects how brain cells communicate with each other, changing the intensity of psychedelic experiences. Additionally, 5-HT2A receptors also signal through other pathways; for example, some psychedelics stimulate the release of arachidonic acid via these receptors, leading to the production of different chemical messages by the cells.[32] The effects of psychedelics on cells and the overall psychedelic experiences in the brain are shaped by these complex signaling pathways and protein kinases within the cells.[33]

Lysergic Acid Diethylamide

The first insights into the therapeutic use of LSD were proposed by Albert Hofmann, who suggested that doses should be gradually increased during the treatment process. He identified two methods for the therapeutic use of LSD: *Psycholytic Therapy*, which involves administering low doses across multiple sessions and integrating the experiences through group discussions, and *Psychedelic Therapy*, which requires intensive preparation and aims for mystical experiences with higher doses of LSD. Psychedelic peak therapy is the closest approach to today's psychedelic-assisted psychotherapy protocols. In the treatment room, patients, accompanied by a therapist and a nurse, close their eyes, listen to music, and focus on their experiences.[34]

A clinical study conducted in Canada evaluated the effects of LSD-assisted therapy on individuals with alcohol dependence. The study included a group receiving a dose of 800 mcg of LSD and a control group receiving 60 mg of ephedrine sulfate. The LSD group was designed as a double-blind study, whereas there was no blinding between the ephedrine sulfate group and the placebo group. Participants, assessed by independent evaluators, consisted of alcoholic men and women with a long history of uncontrolled drinking. Measurements included a drinking history questionnaire, a 6-month abstinence rate, the Maudsley Personality Inventory, the Haigh-Butler Q, the Rorschach test, and the Wechsler Adult Intelligence Scale. The results demonstrate the effectiveness of such therapeutic approaches in assessing the potential impacts of LSD on alcohol dependence treatment.[35]

In a study conducted by Gasser et al.[36] in 2014, the effects of LSD on anxiety were examined in 12 participants with serious health issues. This randomized controlled, cross-over study involved participants receiving 200 µg of LSD and a low dose of

20 µg as a placebo. The LSD sessions were conducted under the supervision of trained psychotherapists over two separate sessions, with a one-week interval between them. Participants received psychological support both before and after their LSD experiences. The study's results indicated that LSD significantly reduced anxiety levels and improved participants' quality of life. Side effects were generally mild and transient, and the study concluded that LSD was safe in this context. These findings suggest that LSD could be a potential therapeutic agent for treating anxiety in individuals with serious health conditions.

In a study conducted by Osorio et al.[37] in 2015, the therapeutic effects of psilocybin were investigated in six participants diagnosed with depression. Psilocybin was administered to the participants in a controlled environment, and depression symptoms were assessed both before and after treatment. The findings indicated that psilocybin significantly reduced symptoms of depression and provided long-lasting positive effects in some participants. Additionally, no serious side effects were observed during the use of psilocybin, highlighting its safety. This study presents significant findings, suggesting that psilocybin could be a potential therapeutic option for patients with treatment-resistant depression.

Methamphetamine

Methamphetamine was first used by soldiers during World War II to reduce fatigue and suppress appetite, and it became widely prescribed for the treatment of depression and obesity in the 1950s and 1960s. However, it was banned and restricted in 1970. Since the late 1990s, methamphetamine use has increased, particularly in the 2000s. In recent years, there has been a resurgence in both the production and use of methamphetamine. This increase has been accompanied by the development of new methods for methamphetamine production and a rise in the smuggling of chemicals used in its manufacture.[38]

The pleasurable effects of methamphetamine are linked to the release of the neurotransmitter dopamine; however, prolonged use of methamphetamine alters the molecular structure of the dopamine system and can lead to damage at nerve terminals, impaired motor skills, cognitive deficits, and psychotic disorders. These brain changes can persist for years after cessation of use. In a conducted evaluation study, the efficacy of cannabidiol (CBD)-rich cannabis extract was examined in children with autism spectrum disorder (ASD). In this randomized, double-blind, placebo-controlled clinical trial, 60 children aged between five and 11 years were divided into two groups: the treatment group received the CBD-rich cannabis extract, while the control group received a placebo. Both groups used their respective products for a duration of 12 weeks. According to the study's results, the CBD-rich cannabis extract improved social interaction, which is one of the diagnostic criteria for ASD, and demonstrated positive effects on symptoms commonly associated with ASD. Additionally, only three children in the treatment group (9.7%) experienced side effects such as dizziness, insomnia, colic, and weight gain. No serious side effects were reported. This study presents significant findings by evaluating the potential therapeutic effects and safety of CBD-containing cannabis extract on social interaction and other symptoms in children with ASD, positioning it as an alternative treatment option.[39]

Mammalian target of rapamycin (mTOR) is a protein kinase regulated by various signaling pathways within the cell. It receives information from membrane receptors such as dopamine D1/D2, glutamate NMDA/AMPA, or BDNF-TrkB at the synaptic level. Utilizing this information, mTOR regulates synaptic protein synthesis and controls various biological processes, including cellular growth, proliferation, metabolism, and neuroplasticity. In a study conducted on mice, the activation of mTOR in striatal regions through mTORC1 was examined. Daily administration of methamphetamine activated the mTORC1 signaling pathway, leading to increased behavioral sensitivity. These findings indicate that the mTORC1 signaling pathway plays a critical role in the development of behavioral sensitivity associated with methamphetamine use and may serve as an important therapeutic target in the neuroadaptive processes related to psychostimulant substance use.[40]

Dimethyltryptamine

Dimetiltriptamin is a powerful psychedelic found in many plants and animals and is also produced endogenously in the human body. When used in smoking form, it produces extremely intense and short-lasting effects. Dimethyltryptamine was first synthesized in the Western world in 1931 by Canadian chemist Richard Manske.[41] However, during this period, its pharmacological effects on humans had not been studied. In 1946, microbiologist Oswaldo Gonçalves de Lima discovered that DMT occurs naturally in plants.[42] The hallucinogenic properties of DMT emerged in 1956 when pioneering Hungarian chemist and psychiatrist Stephen Szára extracted DMT from the Mimosa hostilis plant and administered

the extract intramuscularly to himself. This sequence of events established a link between modern science and the historical use of many DMT-containing plants as cultural and religious sacraments. At the same time, the chemical structure of DMT and its effects on the psyche began to be studied.[43]

Cannabis

Cannabis is a flowering plant genus, best known for its species Sativa, Indica, and Ruderalis. In its dried flower bud form, it is referred to as marijuana.[44]

The resinous form of the plant is known as hashish. Flavonoids, cannabinol, terpenoids, and cannabinoids are some of the bioactive molecules that determine the characteristics of different cannabis species. The ratios of cannabinoid varieties in a specific species determine the potency of its psychoactive effects.[45]

Of the approximately 100 types of cannabinoids, the most well-known and clinically significant are delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, and CBD, an anti-inflammatory agent. The THC is a partial agonist of the cannabinoid receptor 1 (CB1), meaning that it binds to and partially activates the receptor, producing psychoactive effects. Cannabidiol, on the other hand, is a negative allosteric modulator of the CB1 receptor, meaning it binds to a different site on the receptor and reduces the effects of agonists like THC.[46,47]

The active components of cannabis exert their effects by binding to receptors in the body called CB1 and CB2. The CB1 receptors are primarily concentrated in the central nervous system and are responsible for functions such as reward, memory, and learning.[48] The CB2 receptors, on the other hand, are primarily found in immune cells and play a role in regulating inflammation.[49] Cannabis binds to these receptors, increasing dopamine release while reducing the release of neurotransmitters like acetylcholine and norepinephrine. These changes affect pain perception, mood, and stress responses. By stimulating the endocannabinoid system, cannabis also inhibits the release of neurotransmitters such as gamma-aminobutyric acid and glutamate, leading to overall calming and relaxing effects.[50]

Ketamine

Ketamine is a compound synthesized in 1962 by Calvin Stevens and is structurally similar to phencyclidine (PCP).[51] Ketamine, by exhibiting fewer of these side effects, has facilitated recovery after anesthesia. In early clinical trials, ketamine demonstrated a potent anesthetic effect and produced a unique alteration of consciousness, which was termed "dissociative anesthesia." With the Food and Drug Administration approval, it was used as a battlefield anesthetic in 1970 and is still preferred in situations where airway management is difficult.[52] Additionally, ketamine has been found to have potential effects in the treatment of depression, anxiety, and other psychiatric disorders. Its use in sub-anesthetic doses has been shown to be effective in conditions such as depression, anxiety, and OCD in studies conducted in Iran.[53] In Argentina and Mexico, ketamine has been used in psychedelic psychotherapy sessions, contributing to therapeutic processes. It has also been shown to be potentially effective in the treatment of alcoholism. Randomized controlled trials for depression treatment conducted in 2000 produced positive results. Originally developed for anesthesia purposes, ketamine was designed to have short-lasting effects with less "emergence delirium" compared to PCP. Emergence delirium refers to a state that occurs during recovery from anesthesia, characterized by confusion, agitation, or hallucinations.[54,55]

In conclusion, the body of knowledge regarding the effects of psychoactive substances on the brain and innovative approaches to neuroplasticity is increasingly expanding. Psychoactive substances serve as treatment options for conditions such as depression, anxiety, and PTSD. Substances like LSD have been shown to accelerate the neuroplasticity process and aid in the reconnection of brain cells, providing significant advantages in the repair or reorganization of damaged neural networks. They support learning and memory processes and expedite rehabilitation. However, alongside their positive aspects, the risks and adverse effects associated with the use of psychoactive substances must also be considered. These substances should be used safely and in a controlled manner, with strict oversight. More information about side effects, individual differences, and long-term outcomes is needed, and further clinical research is required. In conclusion, these substances are opening new horizons in the field of neuropsychiatry. Adhering to ethical and scientific principles throughout this process will enable us to obtain reliable results.

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