Viewpoint

Mechanistic actions of psychedelics on neurogenesis: Re-building the tapestry of consciousness

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Abstract:
Throughout history, many naturally occurring psychedelic substances have been recognized for their ability to alter emotions, cognition, and perception. These same compounds have recently been studied to better understand their role in adult neurogenesis. Adult neurogenesis is the creation of new neurons beyond fetal development in specific brain regions, which are then integrated into existing neural circuitry. These adult-born neurons play a key role in understanding how psychedelics can help promote healthier brain activity and lead to reversible effects for neurodegenerative conditions. Recent implicative studies of adult neurogenesis have shown its significance in the areas of Alzheimer's, Post Traumatic Stress Disorder, Schizophrenia, stress, and various other non-neurotypical conditions. This literature review will focus on what has already been discovered about adult neurogenesis through the use of LSD, Ayahuasca, and Peyote, as well as the future use of psychedelics in a clinical setting.

Keywords: LSD, ayahuasca, peyote, psychedelic, therapeutics, neurogenesis, depression

INTRODUCTION

According to the World Health Organization (WHO), neurological disorders are a major concern for public health, and many rural populations have taken charge of providing treatments by pulling resources from their naturally occurring environment. This concept of ethnobiological treatment has proven itself positively among populations. Thus, WHO is beginning to stress the importance of inspecting these traditional medicinal plants and seeing if any of the compounds being used can be utilized in the prevention and treatment of psychological illnesses worldwide [1]. One such study was conducted on a rural population in Chota Nagpur Plateau, India--a place full of plant, animal, and population diversity in terms of indigenous communities. The results of this study reported 65 knowledgeable and traditional medicine men and 47 traditional formulations from plants and animals to use against 13 neurological and psychological disorders [2].

Given this knowledge, there has been an interest in studying naturally-occurring psychedelics and similar synthetically produced psychedelics that diverse cultures across the globe have used. There has been a particular interest in serotonergic psychedelics, as serotonin is implicated in many prevalent mental disease states such as Major Depressive Disorder, anxiety, and addiction. The mechanism of therapy proposed by existing literature shows that a psychedelic compound's efficacy lies in "destabilizing networks in the brain and amplifying neurons," allowing the brain to "reset" itself [2]. This phenomenon is referred to as neurogenesis. Both interconnectivity and neurogenesis play a role: Interconnectivity or neuroplasticity is the ability for the brain to form new connections and pathways from already established neurons and adapt based on learning and injury. Neurogenesis on the other hand is the ability to form new neurons and from those neurons, create new connections. Furthermore, psychedelics show promise in treating inflammatory diseases, with some mechanisms of action being more advantageous than existing anti-inflammatory agents currently on the market.

A study conducted in 2015 sampled 130,000 adults in the United States to see if there was a correlation between psychedelic use and mental health issues. Researchers concluded that there was no such link between the two. Additionally, psychedelic use is not prone to addiction or excessive use, furthering the interest in researching psychedelic compounds to be used as therapeutic drugs [3]. Aside from the physical remodeling of the brain induced by psychedelic compounds, psychotherapists also envision practical applications for their use in therapy. Psychologists propose that these substances can help a patient confront traumatic events by inhibiting the "fear response," help the patient build intimate communication, and foster a strong relationship between the patient and therapist [4]. Thus, this literature review will discuss physical, emotional, and psychological responses brought about by LSD, Ayahuasca, and Peyote as suggested therapeutics.

LSD AND ADULT NEUROGENESIS

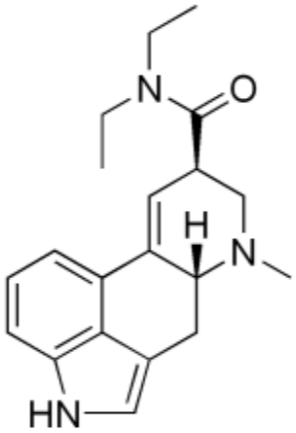

Figure 1: Common Name - Lysergic Acid Diethylamide (LSD), IUPAC Name - (6aR,9R)-N,N-diethyl-7-methyl-6,6a,8,9-tetrahydro-4H-indolo[4,3-fg]quinoline-9-carboxamide, Molecular Weight - 323.44 g/mol, Molecular Formula - $C_{20}H_{25}N_3O$

Lysergic acid diethylamide, LSD, is a hallucinogen that mediates excitatory and inhibitory input in structures of the cortex located along the midline. Although its synthesis is quite extensive, the starting product is always lysergic acid, which then gets activated and reacts with diethylamine or N,N-carbonyldiimidazole. LSD acts as an agonist on frontocortical 5-hydroxytryptamine 2A-serotonin (5-HT2A) receptors and as an agonist at D1 and D2 dopamine receptors. 5-HT2A helps regulate the production of Brain-Derived Neurotrophic Factor (BDNF), which in turn helps regulate neurogenesis and neuroplasticity. These serotonin receptors show nootropic benefits, especially within areas essential for learning and memory. Furthermore, the drug's serotonergic action is also implicated in anxiolytic and antidepressant cognition. Studies have shown that the 5-HT2A receptors specifically located in the fronto-parieto-occipital cortex play a role in invoking a positive mood [5]. Given this information, researchers have begun a closer examination of how the drug works employing electrophysiology, neuroimaging, and molecular analysis techniques to test its efficacy in therapeutics [6]. Functional clustering analysis has demonstrated that LSD enhances pathways involved in neurotransmission, energy metabolism, neuropeptide signaling, and, most importantly, synaptic plasticity [7].

However, with chronic LSD use, there has been an increase in tolerance, leading to decreased 5-HT2A receptor binding and increased pathways involved in the pathogenesis of schizophrenia and related psychotic illnesses, which is supported by a study of LSD in populations of children with autism and adults. The study showed that children with autism were less likely to develop tolerance and the associated schizophrenia-like adverse effects than adults.[6] Further clinical research has proven that when only two doses of LSD are used, patients suffering from anxiety report a significant reduction of symptoms for up to 2 months after exposure [7]. Numerous published case studies have found that therapeutic uses of LSD lead to an overall increase

in mental-health positivity. For example, Dr. Grob, a pediatric psychiatrist, has even administered psychedelics to treat anxiety during terminal-stage cancer treatments, aiming to address psychological, spiritual, and existential crises often encountered in patients facing terminal conditions. These patients go through psycho-spiritual revelations that lead to decreased usage of narcotic pain medications as well as sustained improvement in mood and anxiety [8].

Various studies have shown that LSD increases learning new conditioned behavior rates in rabbits, with increased doses of hallucinogens resulting in faster learning [9]. Researchers' results treating psychological conditions such as Major Depressive Disorder using therapeutic psychedelics are auspicious. In a randomized, placebo-controlled cross-over study, LSD was used twice a week for patients with life-threatening physical diseases; A high dose (200 µg) was compared with a very low dose (20 µg) as an active placebo. The two sessions were embedded in a psychotherapeutic process that lasted for several months. Two months after administration of the high dosage, reductions in the state-trait Anxiety Inventory (STAI) were found in the "trait anxiety" (d = 1.1; p = 0.033) and "state anxiety" (d = 1,2; P = 0.021). No complications were reported that persisted beyond one day after ingestion of the substance. The reduction of anxiety symptoms was still detectable after 12 months [10]. While studies have not been able to prove that BDNF directly causes increased learning capabilities, there is an increase in the expression of BDNF within the hippocampus during learning tasks. Comparatively, genetically modified mice that do not produce BDNF show behaviors similar to psychiatric illnesses such as eating disorders and OCD. Studies conducted on these mice "indicate that endogenous BDNF is critical for the normal development and function of central 5-HT neurons and for the elaboration of behaviors that depend on these nerve cells. Therefore, BDNF+/− mice may provide a useful model to study human psychiatric disorders attributed to dysfunction of serotonergic neurons [11]." Currently, no study has been conducted on the direct effects of psychedelics and increases of BDNF through 5-HT2A receptor activation within the hippocampus. If performed, this experiment should be designed to show that an animal could learn a new task faster after taking LSD with primary endpoints looking at the level of BDNF in the hippocampus.. There have been strict regulations on studies of LSD. However, there is much anecdotal evidence that microdosing in quantities less than that causes perceptual disturbances that can lead to increased productivity and positive changes in thought patterns. Dr. Fadiman's early results presented at the Psychedelic Science 2017 showed that people reported lowered depression and procrastination followed by increased energy and creative thinking. [12].

AYAHUASCA AND ADULT NEUROGENESIS

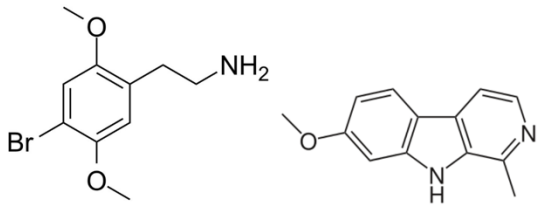

Figure 2: Left -Common Name - DMT, IUPAC Name - 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine, Molecular Weight - 218.3 g/mol, Molecular Formula-$C_{13}H_{18}N_2O$
Right -Common Name - Harmine, IUPAC Name - 7-methoxy-1-methyl-9H-pyrido[3,4-b]indole, Molecular Weight - 212.252 g/mol, Molecular Formula - $C_{13}H_{12}N_2O$

Ayahuasca is a vine with hallucinogenic properties found in the Amazon that can exert its effects for up to 4 to 8 hours after ingestion. Indigenous populations of the Amazon

have concocted a tea of Ayahuasca and leaves from the Psychotria virdis shrub. The shrub contains N,N-dimethyltryptamine (DMT), an agonist of the serotonergic 5-HT2A receptor. DMT is synthesized starting with L-tryptophan, which is decarboxylated to form tryptamine. This compound undergoes methylation to produce N-methyltryptamine, which again gets methylated to produce N,N-dimethyltryptamine [13]. Harmine, a beta-carboline alkaloid, is responsible for the brain remodeling effects of Ayahuasca and works through a mechanism that inhibits monoamine oxidase (MOA) and tyrosine-phosphorylation-regulated kinase (DYRK1A) [14]. Harmine is synthesized from tryptophan, which is then decarboxylated to produce tryptamine; upon the addition of an alpha-keto acid, this is converted to beta-carboline carboxylic acid, which is decarboxylated to produce 1-methyl beta carboline. This compound will finally be oxidized to yield harmaline, which will be dehydrated to produce harmine [14]. A study was done in which human neural progenitor cells (hNPCs) were cultured with harmine and the number of cells in the group of hNPCS increased by 71.5%. It was specifically the DYRK1A inhibition mechanism that was responsible for this neurogenesis, as it has been shown to have a major role in mediating cellular proliferation and development of the brain. This neurogenic finding has significant implications for Ayahuasca usage as a therapeutic drug as rodent models of Major Depressive Disorder show that classic antidepressants exert their effects by stimulating neuronal proliferation [14].

Neuroimaging has revealed increased blood perfusion to the fronto-medial and anterior cingulate cortices of the frontal lobe and medially located structures of the temporal lobe; this correlates with improvement in planning and inhibitory control following the administration of Ayahuasca. Additionally, “applying spectral analysis and source location techniques to cortical electrical signals showed changes in neuronal activity that predominated in more posterior sensory-selective areas of the brain [15].” This study established a connection between two contradictory findings “by simultaneously enhancing endogenous cortical excitability and reducing higher-order cognitive control, ayahuasca temporarily disrupts neural hierarchies allowing inner exploration and a new outlook on reality [16].” Other findings also report increased positive mood, amended visual sensations, and anti-depressant qualities without characteristics of addiction. Unlike LSD, both acute and chronic use of Ayahuasca did not lead to psychopathology or deficits in cognition. One study found that Ayahuasca can lead to cortical thinning of the posterior cingulate cortex, a part of the default mode network, which is more active during restful states than in task-performing states [17]. This brain area is also responsible for introspection. An fMRI study revealed that Ayahuasca leads to decreased activity throughout the network, mimicking altered brain states brought about by meditation and sleep. This alteration increases mindfulness, allowing one to think less emotionally and be better equipped to handle trauma and other highly emotional events, only increasing the therapeutic power of Ayahuasca [13].

PEYOTE AND ADULT NEUROGENESIS

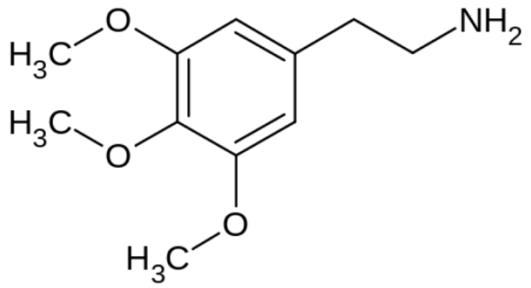

Figure 3: Common Name - Mescaline, IUPAC Name - 2-(3,4,5-trimethoxyphenyl)ethanamine, Molecular Weight - 211.161 g/mol, Molecular Formula - $C_{11}H_{17}NO_3$

Peyote is a cactus that grows close to the ground that produces euphoric and psychoactive effects. The succulent synthesizes a hallucinogenic compound known as mescaline which causes a wide range of effects from spiritual insight to hallucinations. The plant is consumed through chewing or made into tea. Tribes in regions of Mexico even use peyote buttons as an anesthetic or for pain relief. Today, Native American tribes continue to use it for its curative properties. Mescaline or 3,4,5 - trimethoxyphenethylamine is a naturally occurring alkaloid in the phenethylamine class comparable to LSD and psilocybin. The synthesis of Mescaline begins with dopamine in Lophophora williamsii (Peyote), using Catechol O-Methyl Transferase (COMT) and Guaiacol O-Methyl Transferase (GOMT) enzymes. Other biosynthetic pathways can also lead to the production of mescaline, using either Phenylalanine or Tyrosine as the starting amino acids. In vivo synthesis has been proposed as the following: oxidation of tyrosine to produce dopa, decarboxylation of dopa to yield dopamine, followed by oxidation of dopamine to produce 3,4,5-trihydroxy-phenyethylamine, which then gets methylated, resulting in mescaline. Synthetic synthesis of mescaline can occur through variousroutes, starting with acetal, nitro alkene, or chromium complex.

The stimulating compound, mescaline, is a non-selective serotonin receptor agonist. Like other hallucinogens, the drug's stimulatory actions are postulated to come from its interactions at the 5-HT2A serotonin receptors. Mescaline peaks in the brain 60 minutes after ingestion and remains constant for another hour. "Human subjects given C14-mescaline by mouth excrete an average of 87% of the dose during the first 24 hours and an average of 92% during the first 48 hours. Average half-life of mescaline in six hours [18]." Hallucinogenic effects due to increased blood flow to the frontal cortex induced by the drug include intense mental images, synesthesia, increased sensory stimulation, distortion of reality, fixation on thoughts, and deceptive sense of body weight. The G-coupled protein receptors and ligand-gated channels on which this drug acts are responsible for releasing hormones in addition to neurotransmitters. "These receptors play an important role in a variety of processes, such as anxiety, cognition, aggression, learning, memory, nausea, sleep and mood. As a result, they are the target of therapeutic agents, as well as illicit drugs, including hallucinogens [19]." Thus, the drug mimics physiological effects produced by norepinephrine and epinephrine, such as increased heart rate and temperature, nausea, dizziness, sweating, dilated pupils, and anxiety. Symptoms produced by toxic amounts of this drug can be alleviated with valium or chlorpromazine.

Decreased amounts of serotonin are seen as a biochemical model for Major Depression. Although there is not much information in the literature on mescaline use as a therapeutic tool, its positive action on serotonergic receptors could have significant implications for its ability to be utilized. However, research shows that drugs that cause less distortion of reality than mescaline or LSD can be used as supplements in treating such illnesses. These specific drugs belong to the phenylisopropylamine subgroup of phenylalkylamines and are called entactogens [4]. Entactogens promote a brain state of open mindedness, "interpersonal closeness, intimacy, and empathy." [21] Research postulates that entactogens would be a good addition to psychotherapy treatment plan, as they would help the patient feel more prone to opening up to the therapist about traumatic events [20].

CONCLUSION:

There is much to learn about adult neurogenesis. Neurogenesis and neuroplasticity are two interlocking concepts that are not fully understood. The substances mentioned in this

paper, alter the brain in ways that can increase our understanding of how the brain changes and adapts in both short and long term exposures and diseased states. These findings have massive implications in the understanding and treatment of diseases such as Alzheimers and Traumatic brain injury. More in depth, larger scale research trials are needed to fully understand the impact of these substances on adult neurogenesis and future treatment options.

AUTHOR INFORMATION

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