Neurogenesis, Neurodegenerative Diseases and Treatment Using Psilocybin

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Introduction

Neurogenesis refers to the process leading to the formation of new neurons in the brain. This is a crucial process during the formation and development of an embryo. The process, however, continues to other parts of the brain during after birth and across the lifespan. The brain consists of different sections which are responsible for executing different functions. Similarly, the brain has neurons with differing structure and connections. The hippocampus, a brain section responsible for spatial navigation and memory, consists of over 7 types of neurons. The notable diversity of neurons within the brain is a result of well-regulated neurogenesis during the development process of an embryo. It is during this process that differentiation of neural stem cells happens. It is for this reason that neurons become specialized cells for particular brain regions. Stem cells can indefinitely divide leading to the production of more stem cells. Stem cells can differentiate leading to the production of

specialized cells such as the neural progenitor cells. Neurogenesis may be impacted by different types of neurodegenerative conditions such as Alzheimer’s disease and Parkinson's. Treatment may include the use of different approaches with the use of psilocybin being the commonly known treatment for these health conditions. The purpose of this paper is to provide an in-depth insight about neurogenesis, neurodegenerative conditions and how psilocybin is used in treating these conditions.

Historical Perspective

Over the past few decades, there has been a growing recognition that neurogenesis, or the generation of new neurons, can occur in certain regions of the adult mammalian brain. This has challenged the long-held belief that neurogenesis only occurs during embryonic and prenatal development. One of the earliest indications of adult neurogenesis was found in the hippocampus of rats by Altman in the 1960s. Subsequent studies have confirmed that neurogenesis occurs in the hippocampus of many mammals, including humans. The hippocampus is an area of the brain that is important for learning, memory, and spatial navigation (Mahar et al., 2014). Goldman and Nottebohm reported on neurogenesis in the adult female canary brain, specifically in the ventricular zone. This region is involved in producing new neurons during embryonic development, but it was not previously thought to play a role in adult neurogenesis.

More recently, researchers have discovered neural stem cells (NSCs) in the adult mammalian brain. NSCs are cells that have the ability to differentiate into multiple types of cells, including neurons. These cells are found in specific regions of the brain, including the subventricular zone (SVZ) and the hippocampus. The discovery of adult neurogenesis has opened new avenues for research into the mechanisms underlying brain plasticity and the potential for brain repair following injury or disease. However, the functional significance of adult neurogenesis is still not fully understood, and there is ongoing debate among researchers about its relevance for brain function and behavior.

The introduction of BrdU, a synthetic analog of thymidine, allowed researchers to track the proliferation of cells and validate the existence of permanent neurogenesis in many mammalian species. This has led to substantial progress in the field of adult neurogenesis over the past decade. Active neurogenesis has been observed in three specific "neurogenic" regions of the brain under normal conditions. These regions include the subgranular zone (SGZ) in the dentate gyrus (DG) of the hippocampus, where new dentate granule cells are produced; the subventricular zone (SVZ) of the lateral ventricles, where newly generated neurons migrate through the rostral migratory stream (RMS) into the olfactory bulb to act as interneurons; and the hypothalamus (Choi et al., 2014).

The SGZ and SVZ are well-established regions of adult neurogenesis, while the discovery of neurogenesis in the hypothalamus is a more recent development (Choi et al., 2014). The hypothalamus is a region of the brain involved in regulating a wide range of physiological processes, including appetite, sleep, and reproductive behavior. While the functional significance of adult neurogenesis is still not fully understood, it is thought to play a role in learning and memory, mood regulation, and the response to stress. Additionally, there is growing interest in the potential of adult neurogenesis for brain repair and the treatment of neurological disorders.

The hippocampus is a region of the brain located in the temporal lobe and is responsible for memory, learning, and emotion. The hippocampus is composed of several distinct regions, including the Cornu Ammonis fields (CA1, CA2, and CA3) and the dentate gyrus (DG) (Choi et al., 2014). The newly formed DG neurons project to the CA2 region, which is important for social memory and contextual discrimination (Hitti & Siegelbaum, 2014). Adult neurogenesis is a complex process that is influenced by various physiological and pathological stimuli. In the adult hippocampus, neurogenesis can be altered by factors that affect structural plasticity, such as environmental stressors and learning. Researchers have made significant progress in understanding the neural subtypes involved in adult neurogenesis, as well as the microenvironment and stages of the process (Gu, Janoschka & Ge, 2013).

Several studies have also investigated the effects of new-born neurons on existing neuronal circuitries and their contribution to brain functions under both physiological and pathological conditions. However, there is still ongoing debate and questions regarding whether adult

hippocampal neurogenesis occurs in humans, due to contradictory findings (Gu, Janoschka & Ge, 2013). While early studies suggested that adult neurogenesis might occur in the human brain, more recent research has cast doubt on this idea. For example, some studies have reported no evidence of adult neurogenesis in the human hippocampus, while others have reported limited or localized neurogenesis. Overall, more research is needed to fully understand the extent and functional significance of adult neurogenesis in the human brain.

Furthermore, studies have demonstrated that adult neurogenesis plays a critical role in the regulation of emotional and cognitive behaviors, such as learning, memory, and mood regulation (Palmer, Takahashi & Gage, 1997). For example, studies in rodents have shown that environmental enrichment and physical activity can increase neurogenesis in the hippocampus, leading to enhanced learning and memory performance (Shihabuddin, Ray & Gage, 1997). On the other hand, chronic stress has been shown to decrease neurogenesis, leading to cognitive deficits and depression-like behaviors. Despite the advances in the field, the functional significance of adult neurogenesis in the human brain remains unclear. While there is evidence to suggest that adult neurogenesis occurs in the human hippocampus, it is still debated whether this process contributes to cognitive and emotional functions in humans (Arsenijevic & Weiss, 1998). Furthermore, the extent to which adult neurogenesis occurs in other regions of the human brain is still unknown.

Despite the lack of evidence for neurogenesis in the adult human hippocampus in the Sorrells et al. study, other studies have reported evidence for adult neurogenesis in the human brain. For example, a study by Gu, Janoschka & Ge (2013) reported the presence of neuroblasts and **immature neurons in the hippocampus of adult humans**, although the number of these cells was significantly lower compared to rodents. Another study by Shihabuddin, Ray & Gage (1997) reported the presence of neural progenitor cells in the human striatum, a region involved in motor control and reward processing. Overall, the evidence for adult neurogenesis in the human brain remains inconclusive, and further research is needed to clarify this issue. It is possible that the process of adult neurogenesis in humans is more limited compared to other species, or that it occurs in other brain regions outside of the hippocampus. Nevertheless, the potential for adult neurogenesis to contribute to brain plasticity and functional recovery remains an area of active research and interest.

These findings highlight the complex and dynamic nature of adult neurogenesis in the human brain and its potential relevance to cognitive and emotional functioning. While the initial study by Sorrells et al. suggested that adult hippocampal neurogenesis may be absent or extremely rare (2018), subsequent studies have challenged this view and suggested that neurogenesis may indeed occur in the human hippocampus and other brain regions (Sorrells et al., 2018). The potential role of adult neurogenesis in human cognition and emotional resilience is an area of active research and interest. It is possible that ongoing neurogenesis may contribute to the maintenance of cognitive function and emotional well-being throughout life, and declines in neurogenesis may be associated with compromised resilience and susceptibility to age-related cognitive decline and mental health disorders. Further research is needed to elucidate the mechanisms and functional significance of adult neurogenesis in the human brain, as well as its potential for therapeutic applications in the treatment of neurological and psychiatric disorders.

The Evolution of Adult Neurogenesis

Rakic's paper, "Limits of Neurogenesis in Adult Primates," argued that sophisticated brains choose constancy over flexibility and that newborn neurons would disrupt intricate neuronal networks. Rakic also suggested that validating adult neurogenesis in humans would put us at equal levels with lobsters, rodents, and perhaps birds. However, nowadays, adult hippocampal neurogenesis in humans has been established (Drew, Fusi & Hen, 2013). Rakic's dispute mainly targeted cortical neurogenesis, but the hippocampus, which is part of the archicortex, was not completely discounted from the debate.

Neurogenesis is the process of generating new neurons from neural precursor cells, which occurs throughout the lifespan in different regions of the brain. The two regions where adult neurogenesis is well-established are the hippocampus and the subventricular zone (SVZ)/olfactory bulb (Choi et al., 2014). In the hippocampus, adult neurogenesis gives rise to excitatory neurons that contribute to adaptable memory development. These neurons arise from precursor cell populations in the dorsal region of the hippocampus. Neuroblasts that originate from the SVZ in humans travel to multiple brain regions, such as the frontal cortex and the cingulate cortex in the infant brain and the striatum in the adult brain (Van Praag et

al., 2002). In the SVZ, progenitor cells grow and migrate along the rostral migratory stream to the olfactory bulb, where they differentiate and mature into interneurons. These interneurons contribute to the processing of sensory input. Interestingly, some researchers have reported that adult hippocampal neurogenesis in the SGZ is conserved in most mammals, while others have shown that new neurons develop from neural precursor cells in the SGZ and mature into excitatory neurons.

The two types of mammalian adult neurogenesis, in the DG and the olfactory bulb, evolved to handle considerably distinct challenges and demands, and were thus formed by relatively dissimilar evolutionary forces. Neurogenesis in the olfactory system is evolutionarily old and vastly preserved, whereas the DG is a young substructure of the hippocampus whose neuronal network and specific role is exclusive to mammals. While some have claimed that adult neurogenesis must be an atavism or, at best, a heritage from our ancestors, this notion may be true for the olfactory system but not for the hippocampus (Van Praag et al., 2002). The DG and its associated processes, such as learning and memory, are unique to mammals, and the evolution of adult neurogenesis in this region is likely related to the demands of these processes. Therefore, adult neurogenesis in the hippocampus is not merely a vestige of ancestral evolution, but rather a crucial adaptation that provides mammals with unique cognitive abilities.

The Functional Significance of Neurogenesis

It is believed that adult neurogenesis has existed for the past three decades. Studies have revealed that neurogenesis happens in different species which include humans. Studies are, however, yet to establish the behavioral significance of neurogenesis. Nonetheless, studies have shown that hippocampus executes a significant role in learning, memory as well as neural plasticity mechanisms like LPT (long-term potentiation).

Neurogenesis and Behavior

Studies have revealed that animals which live in an enriched environment usually have more new neurons. It has further been found that these animals perform better on the spatial learning task. Neurogenesis has been found to decline with aging. However, when exposed

into an enriched environment, a restoration of neurogenesis usually occurs, leading to enhanced performance of the organism.

Electrophysiology

Although the histological and morphological methods are used in identifying new granule cells, one of the most significant questions that remain is to whether young cells have a lower threshold for LPT and were impacted by GABA-A inhibition which suggests enhanced plasticity in the young cells (Van Praag, 2002). Studies have found that hippocampal neurogenesis is linked to memory function. Animals with stimulated neurogenesis usually record high performance on learning tasks. The relationship between behavior and neurogenesis is more casual than it is correlational because the occurrence of electrophysiological measurable shifts is more in brain regions in which the occurrence of adult neurogenesis is evident.

Neurodegenerative Diseases

Neurodegenerative disorders are a group of chronic and progressive conditions that result from the gradual loss of neurons in the brain and nervous system. These disorders, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, traumatic brain injury, and stroke, are characterized by the accumulation of abnormal proteins in the brain, inflammation, oxidative stress, and genetic mutations. As the population ages, the incidence of these conditions is expected to increase, representing a significant socioeconomic burden on healthcare systems worldwide. Currently, available treatments for neurodegenerative disorders are largely palliative, meaning they only manage the symptoms of the disease without halting or reversing its progression. However, there is increasing hope that new drugs that slow, halt, or even reverse the process of neurodegeneration can be developed, thanks to advances in our understanding of the underlying biology of these conditions.

The incidence and prevalence of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis, are on the rise, representing a significant healthcare burden worldwide. According to data presented by Will Richardson of GlaxoSmithKline, the prevalence of Alzheimer's disease is expected to triple by 2050, with

1.5 million patients in Italy, the United Kingdom, Spain, Germany, and France combined. In the same regions, Parkinson's disease is predicted to have a prevalence of 1.1 million, with multiple sclerosis not far behind at 0.5 million. Despite the high prevalence of these conditions, no disease-modifying therapies are yet available for Alzheimer's disease and Parkinson's disease. Symptomatic drugs are available but are associated with serious side effects in Parkinson's disease and provide only modest improvements in cognitive status in patients with probable Alzheimer's disease.

Recombinant interferons have been approved in many countries for the treatment of relapsing-remitting multiple sclerosis, but their ability to modify the disease course has not been clearly established. The lack of disease-modifying therapies highlights the urgent need for the development of new pharmacotherapies that can halt or slow the progression of these devastating conditions. While there has been significant progress in understanding the underlying biology of neurodegenerative disorders, developing effective treatments remains a complex and challenging task. However, there is hope that with continued research and development, new therapies will emerge that can improve the lives of millions of patients suffering from these conditions.

Alzheimer’s Disease

Roger Bullock from Kingshill Research Centre presented a clinical perspective on Alzheimer's disease (AD) at the meeting. He highlighted the complexity of AD and the challenge of developing effective therapies that can halt the disease. While preclinical research tends to focus on reductionist approaches, the clinical manifestation of AD is a complex disorder that may have different subtypes requiring different therapies. Bullock noted that targeting a single biochemical pathway, such as amyloid beta (Aβ), may not be sufficient to halt the disease. He suggested that some of the processes being targeted may have physiological importance, and reducing their activity may have unwanted side effects (Alzheimer’s Society, 2019). For example, while hyperphosphorylation of the tau protein is a hallmark of AD, it is a normal process that regulates the protein's binding to and stabilization of microtubules. Bullock also highlighted the limitations of the clinical instruments used to assess cognitive decline in AD, such as the ADAS-cog. These instruments may not be appropriate for evaluating the effectiveness of new therapeutic approaches that focus on improving the activities of daily living.

Studies have found that Mutations in the tau protein can result in inherited frontotemporal dementia and parkinsonism linked to Chromosome 17, and these mutations can cause neuronal loss and patterns of abnormal tau deposition similar to those seen in Alzheimer's disease. It is likely that abnormalities in tau protein contribute to the development and progression of Alzheimer's disease, and interventions that target these abnormalities may be effective therapies for the disease (Alzheimer's Society, 2019). Tau protein plays an important role in stabilizing microtubules and aiding in the transport of organelles within neurons. Mutations in tau can lead to a loss of this function and result in the abnormal deposition of tau protein into paired helical filaments, which are the main component of neurofibrillary tangles seen in Alzheimer's disease.

Inherited forms of fronto-temporal dementia and parkinsonism linked to Chromosome 17 are caused by mutations in the tau gene, and these mutations lead to similar patterns of abnormal tau deposition as seen in AD. Targeting CDK5, a kinase involved in the hyperphosphorylation of tau, could be a potential therapeutic approach for treating Alzheimer's disease. Pfizer is currently working on finding selective inhibitors of CDK5, and two promising compounds, CP-668863 and CP-681301, have been identified as potent and selective inhibitors of CDK5 (Van Praag, 2002). It will be interesting to see how these compounds progress in preclinical and clinical trials and whether they could eventually lead to the development of a new treatment for Alzheimer's disease.

> *Note: Recent findings have cast doubt on many studies citing research that exposure to the amyloid beta subtype Aβ*56 was compromised.

Parkinson's Disease

Parkinson's disease (PD) is a movement disorder that is primarily characterized by the loss of dopamine neurons in the substantia nigra of the ventral midbrain. This loss leads to a loss of dopamine innervation of the neostriatum (caudate nucleus and putamen) and subsequent motor dysfunction. The main symptoms of PD include muscle rigidity, tremor, bradykinesia (slowness of movement), and akinesia (complete loss of movement in extreme cases) (Van Praag, 2002). In addition to these primary symptoms, PD can also lead to the loss of cognitive function and subtle language problems as secondary symptoms. Rational therapies

for PD and other movement disorders depend on understanding the underlying changes in neural pathways and the involvement of specific neurotransmitters and receptors.

The main therapies for PD include levodopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors. Levodopa is a precursor of dopamine and is converted to dopamine in the brain, where it acts to restore dopamine levels in the striatum. Dopamine agonists directly stimulate dopamine receptors and are often used in combination with levodopa to reduce the dose required and decrease side effects (Van Praag, 2002). MAO-B inhibitors increase dopamine availability by inhibiting the enzyme that breaks down dopamine, while COMT inhibitors block the enzyme that breaks down levodopa, increasing its availability in the brain. However, all of these therapies have limitations and can cause side effects, such as dyskinesias, hallucinations, and cognitive impairment.

Parkinsonism and various involuntary movement disorders, also known as dyskinesias, are well-replicated in animals using neurotoxins such as 6-hydroxydopamine (6-OHDA) and 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) (Van Praag, 2002). These animal models provide an opportunity to study the mechanisms of these disorders at the cellular and molecular levels and identify potential therapeutic targets. In Parkinson's disease (PD), the loss of dopamine neurons in the substantia nigra of the ventral midbrain and the resulting loss of dopamine innervation in the neostriatum (caudate nucleus and putamen) can be modeled in experimental animals using these neurotoxins (Agin-Liebes et al., 2020). Researchers can use a histological section that shows the key brain nuclei involved in the main symptoms of PD to explore the mechanism of action and side effects of the main therapies available.

Researchers have heavily relied on the direct (D1-mediated) and indirect (D2-mediated) pathways from the putamen to the globus pallidus external and internal segments as a model of basal ganglia connectivity (Kim et al., 2007). They can rationalize the effects of current dopamine-based therapies as the imbalance of excitatory (glutamate and aspartate) and inhibitory (γ-aminobutyric acid) regulation of the subthalamic nucleus (Van Praag, 2002). Currently, L-dihydroxyphenylalanine (L-DOPA) is still the gold-standard therapy for PD.

While its initial pharmacological effect in PD is dramatic, the period for which L-DOPA therapy successfully treats the symptoms of PD (tremor and bradykinesia) diminishes with duration of treatment (Agin-Liebes et al., 2020). Dyskinesias and freezing that patients taking L-DOPA suffer represent serious side effects, and treating these iatrogenic problems is currently an active area of research.

The basal ganglia is a complex structure within the brain that plays a crucial role in motor control, cognition, and emotion. It contains various receptors and neuropeptides, including opioid, nicotinic, muscarinic, adrenergic, histaminergic, serotonergic, and adenosinergic receptors (Van Praag, 2002). The diversity of receptors and neuropeptides in the basal ganglia provides a range of targets for pharmacological interventions in Parkinson's disease (PD) and other movement disorders. PD is a neurodegenerative disorder that affects dopaminergic neurons in the substantia nigra, leading to a depletion of dopamine in the basal ganglia. The loss of dopamine results in the characteristic motor symptoms of PD, such as tremors, rigidity, and bradykinesia (Agin-Liebes et al., 2020). The most common treatment for PD is L-DOPA, which is converted into dopamine in the brain and restores dopamine levels. However, long-term use of L-DOPA can lead to side effects such as dyskinesias, which are abnormal involuntary movements.

One approach to improving PD therapy is to develop agents that allow longer use of existing agents without incurring serious side effects. For example, the recently launched methyl-esterified form of L-DOPA (melevodopa) and the monoamine oxidase type B inhibitor rasagiline have been shown to improve the motor symptoms of PD without causing dyskinesias (Van Praag, 2002). Additionally, dopamine receptor agonists, which mimic the effects of dopamine, are being tested in clinical trials. Nondopaminergic treatments are also being explored as a means of improving PD therapy. Alpha-2 adrenergic receptor antagonists and adenosine A2A receptor antagonists are two types of agents that are currently in clinical trials. These agents target receptors other than dopamine receptors and may provide additional benefits or reduce side effects of dopaminergic therapy.

One approach to treating PD is to replace the lost dopamine neurons through transplantation of embryonic dopamine cells or stem cells into the affected area of the brain. Early studies in animal models of PD demonstrated functional recovery after transplantation of embryonic dopamine cells into the striatum, the region of the basal ganglia that is most affected by the disease (Van Praag, 2002). Clinical trials using tissue from the adrenal glands, however, showed little improvement in symptoms and are no longer used. Embryonic nigral grafts have been shown to alleviate simple motor asymmetries and restore lateralized motor learning in experimental animals, but their use in clinical trials has been limited by poor survival of the transplanted tissue and ethical issues surrounding the use of fetal material.

To overcome these limitations, researchers are actively searching for a more suitable and robust donor source for dopamine-producing cells. Adult stem cells are a promising option because they can be obtained from a patient's own tissues, reducing the risk of rejection and ethical concerns. Additionally, advances in stem cell technology have made it possible to generate dopamine-producing neurons from induced pluripotent stem cells (iPSCs), which can be derived from a patient's skin or blood cells. While the use of stem cells for PD therapy is still in the early stages of development, preclinical studies have shown promising results (Agin-Liebes et al., 2020). One approach is to transplant stem cell-derived dopamine neurons directly into the affected area of the brain, while another approach is to use stem cells to produce dopamine in vitro and then transplant the dopamine-producing cells into the brain.

Multiple Sclerosis

Kenneth J. Smith from King's College London discusses the potential mechanisms underlying axonal degeneration in multiple sclerosis (MS). MS is a condition characterized by degeneration of neuronal axons, which can lead to creeping paralysis, especially in progressive forms of the disease (Van Praag, 2002). While the exact mechanisms underlying axonal degeneration in MS are not yet known, pathological studies suggest that inflammation or inflammatory mediators, including the free radical nitric oxide (NO), may play a role. It has been shown that NO-mediated axonal damage can result in axonal degeneration, especially if the axons are electrically active while exposed to NO. The cause of the

degeneration is not fully understood. However, the available evidence suggests that NO exposure inhibits mitochondrial function so that ATP production is impaired (Van Praag, 2002). The ATP-dependent sodium/potassium pump therefore fails to cope with the enhanced sodium ion entry due to the electrical activity, and so the intra-axonal sodium ion concentration rises.

Professor Smith suggested that a high concentration of sodium in the axon permits the sodium/calcium exchange molecule to operate in reverse mode, importing damaging calcium ions that eventually activate endogenous degradative enzymes resulting in axonal degeneration. Recent research has shown that sodium channels may play a role in the symptomatology of MS, causing permanent axonal destruction and modulating the intensity of immune activity. Sodium channels may also provide a potential avenue to achieve axonal and neuronal protection in MS, impeding the otherwise relentless advance of permanent neurological deficit (Van Praag, 2002). The symptoms of MS are largely determined by the conduction properties of axons, which in turn are largely determined by sodium channels. The number, subtype, and distribution of sodium channels, as well as modifications in channel function resulting from local factors such as inflammation, are all important in understanding the disease.

Recent research has confirmed that sodium channels may contribute to axonal degeneration, which is primarily responsible for permanent neurological deficits in MS. The proposed mechanism involves intra-axonal sodium accumulation, which promotes the reverse action of the sodium/calcium exchanger and thereby a lethal rise in intra-axonal calcium (Van Praag et al., 2002). Partial blockade of sodium channels may protect axons from degeneration in experimental models of MS, and the sodium channel-blocking agents flecainide and lidocaine have been shown to protect axons from NO-mediated degeneration in rats with chronic relapsing experimental autoimmune encephalomyelitis (CR-EAE). These findings indicate that sodium channel-blocking agents may provide a novel approach for axonal protection in patients with MS. Lamotrigine, a phenyltriazine that is widely used as a broad-spectrum antiepileptic drug and a use-dependent blocker of sodium channels, has shown efficacy in EAE models of MS. Based on this research, Professor Smith and his colleagues have initiated

a clinical trial in patients with secondary progressive MS to establish if lamotrigine can slow disease progression.

The use of Psilocybin in Treating Neurodegenerative Diseases

Psilocybin is classified as a Schedule I drug in the United States, meaning it is considered to have a high potential for abuse and no accepted medical use. However, research into its potential therapeutic effects has been growing in recent years. Studies have shown promise for its use in treating depression, anxiety, and addiction, as well as improving quality of life for individuals with terminal illnesses (Aday et al., 2020). Psilocybin-assisted therapy involves administering the drug in a controlled setting with the guidance of a trained therapist to help facilitate a transformative experience (Agin-Liebes et al., 2020). While further research is needed, the potential benefits of psilocybin therapy are currently being explored and debated by researchers and policymakers.

While there is currently limited research specifically examining the potential of micro-dosing psychedelics for treating Alzheimer's disease (AD), there is growing interest in the role of these substances in promoting neuroplasticity and neurogenesis in the brain (Bravermanová et al., 2018). The 5HT2A-R agonists psilocybin and LSD have been shown to have therapeutic potential for a range of psychiatric and neurological disorders, and there is some evidence that they may be able to promote the growth of new neurons and synapses in the brain (Anderson et al., 2019). In the context of AD, which is characterized by the progressive degeneration of brain tissue and the loss of neurons and synapses, the potential of psychedelics to promote neurogenesis and neuroplasticity could be particularly significant. While more research is needed to explore the specific mechanisms by which micro-dosing psychedelics may impact the progression of AD, there is reason to believe that these substances could have a role to play in the development of novel therapeutic approaches for this devastating disease.

Studies on micro-dosing psychedelics such as LSD and psilocybin have produced mixed results on cognitive function. Controlled studies on younger adults found no significant effects, while an uncontrolled trial reported increased cognitive fluency, flexibility, and originality (Deco et al., 2018). A recent study on older adults found no difference in adverse events or cognitive impairment between those taking LSD and those on a placebo. However, caution is needed in interpreting these results, as some studies had small sample sizes, lacked a placebo control group, or were subject to selection bias (Family et al., 2020). Studies on micro-dosing psychedelics such as LSD and psilocybin have produced mixed results on cognitive function. Controlled studies on younger adults found no significant effects, while an uncontrolled trial reported increased cognitive fluency, flexibility, and originality. A recent study on older adults found no difference in adverse events or cognitive impairment between those taking LSD and those on a placebo (Gasser, Kirchner & Passie, 2015). However, caution is needed in interpreting these results, as some studies had small sample sizes, lacked a placebo control group, or were subject to selection bias.

The research cited suggests that 5HT2A-R activation plays an important role in neuroplasticity, neurogenesis, and memory processes. Specific polymorphisms of the 5HT2A-R can impair verbal memory recall and object recognition, while reduced 5HT2A-R density in brain areas responsible for memory processes is associated with worse cognitive performance (Bryson et al., 2017). Low-dose psychedelics have been shown to enhance hippocampal long-term potentiation, promote neurogenesis, and enable the re-consolidation of fear conditioning in the amygdala. However, higher doses may suppress these effects beyond a certain threshold (Carhart-Harris et al., 2012). In rats, 5HT2A-R activation stimulates neurogenesis and BDNF expression in the neocortex but consistently inhibits the same process in the hippocampus (Carhart-Harris et al., 2018). The dose-dependent effect of 5HT2A-R activation on neurogenesis suggests an optimal dose range for therapeutic purposes. In cultured rat neurons, activation also stimulates dendritic spine proliferation and growth. These findings suggest that the 5HT2A-R pathway may be an important cross-species evolutionary pathway for promoting neurogenesis and synaptogenesis.

Research suggests that 5HT2A-R polymorphisms and reduced 5HT2A-R density in areas of the brain responsible for key memory processes are associated with worse cognitive

performance. However, pre-task 5HT2A-R activation in mice enhances post-task hippocampal long-term potentiation and enables the re-consolidation of fear conditioning in the amygdala, supporting a critical role in neuroplasticity. In rats, 5HT2A-R activation appears to stimulate neurogenesis and brain-derived neurotrophic factor (BDNF) expression in the neocortex but inhibits the same process in the hippocampus, potentially in a dose-dependent manner (Aday et al., 2020). Both low and high dose psychedelics can lead to the resolution of fear responses, but this process may be more rapid at lower doses where hippocampal neurogenesis is unimpaired. LSD and psilocybin also promote neurogenesis and synaptogenesis in a dose-dependent manner, suggesting a potential therapeutic dose range. Tolerance to mental effects from psychedelics can develop quickly with repeated administration but may be minimized with infrequent dosing schedules, as seen in a recent safety study in older adults.

Gamma frequency oscillations have also been found to be modulated by various neurotransmitters, including acetylcholine, norepinephrine, and dopamine, which are involved in attention, memory, and learning. In particular, acetylcholine has been shown to enhance gamma oscillations in the hippocampus, and dysfunction in the cholinergic system is a hallmark of AD (Aday et al., 2020). Cholinesterase inhibitors, which are the mainstay of AD pharmacotherapy, increase the availability of acetylcholine and have been shown to enhance gamma activity and improve cognitive function in AD patients. In addition, non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been used to modulate gamma oscillations in AD patients with promising results (Van Amsterdam et al., 2006). TMS has been shown to increase gamma activity in the hippocampus and improve memory in AD patients, while tDCS has been shown to enhance gamma oscillations in the dorsolateral prefrontal cortex and improve executive function in AD patients.

Pharmacodynamics

Glutamate is the main excitatory neurotransmitter in the brain and plays a key role in synaptic plasticity, learning, and memory. Studies have shown that psilocybin can increase glutamate levels in the prefrontal cortex, which is involved in higher cognitive functions such as

decision-making and social behavior (Mason et al., 2020). Psilocybin also increases the connectivity between different brain regions, particularly between the default mode network (DMN) and the task-positive network (TPN). The DMN is a network of brain regions that are active during rest and self-referential processing, while the TPN is active during goal-directed behavior and external attention. The increased connectivity between these networks may underlie the profound changes in perception, thought, and emotion that are commonly reported after taking psilocybin. Psilocybin has been shown to have therapeutic potential in the treatment of several psychiatric disorders, including depression, anxiety, and addiction. The rapid and sustained neuroplasticity induced by psilocybin may underlie its therapeutic effects. For example, psilocybin-assisted psychotherapy has been shown to reduce symptoms of depression and anxiety in cancer patients, with effects lasting up to six months or longer (Grieshaber et al., 2001). Psilocybin has also been shown to reduce alcohol and tobacco use in clinical trials, and may have potential for treating other types of addiction (Meyer et al., 2011). The therapeutic effects of psilocybin may be mediated by its ability to promote neuroplasticity, as well as by its effects on serotonin and other neurotransmitter systems (Baselt, 2008).

Pharmacokinetics

It is important to note that the effects of psilocybin can vary greatly depending on the individual's mindset and the setting in which the drug is taken. Psilocybin is a powerful psychoactive substance and should be used with caution and under the guidance of a trained professional. Psilocin is metabolized in the liver, where it undergoes a first-pass effect before entering the systemic circulation (Baselt, 2008). Psilocin is broken down by the enzyme monoamine oxidase to produce several metabolites that can circulate in the blood plasma. Psilocin is also glucuronated by the glucuronosyltransferase enzymes UGT1A9 in the liver, and by UGT1A10 in the small intestine. About 50% of ingested psilocybin is absorbed through the stomach and intestine, and within 24 hours, about 65% of the absorbed psilocybin is excreted into the urine, with a further 15-20% excreted in the bile and feces (Mason et al., 2020).

Psilocybin can still be detected in the urine after 7 days, although most of the remaining drug is eliminated within 8 hours. Clinical studies show that psilocin concentrations in the plasma of adults average about 8 μg/liter within 2 hours after ingestion of a single 15 mg oral psilocybin dose, and psychological effects occur with a blood plasma concentration of 4-6 μg/liter (Van Amsterdam et al., 2006). Psilocybin is about 100 times less potent than LSD on a weight per weight basis, and the physiological effects last about half as long. It is important to note that combining psilocybin with MAOIs or other drugs can have serious and potentially life-threatening consequences, such as serotonin syndrome. Therefore, it is not recommended to combine psilocybin with MAOIs or other drugs without consulting a medical professional (Van Amsterdam et al., 2006). Additionally, the use of psilocybin and alcohol or tobacco should be approached with caution, as individual reactions and experiences may vary.

Conclusion

Neurogenesis is the process by which new neurons are generated in the brain. This process involves the division of neural stem cells, migration of the new cells to their final location, and their differentiation into mature neurons with specific functions.

Currently, it is believed that there are only two areas in the adult brain where neural stem cells reside and proliferate: the subventricular zone (SVZ) lining the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. These stem cells give rise to neurons that are involved in the olfactory bulb and hippocampus, respectively. Neurodegenerative disorders are a group of diseases characterized by the progressive loss of function and death of neurons in the brain or spinal cord. Examples of neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease, Lewy body dementia, and motor neuron disease. These disorders are typically associated with the accumulation of abnormal proteins in the brain, leading to the death of neurons and a decline in cognitive and motor function. Recent research into psychedelics such as psilocybin and LSD has shown promising results in their potential therapeutic role in a range of psychiatric and neurological conditions. These substances have been shown to stimulate neurogenesis, provoke neuroplastic changes, and reduce neuroinflammation, which may contribute to their

therapeutic effects. Studies have suggested that psychedelics may be effective in treating depression, anxiety, addiction, and post-traumatic stress disorder (PTSD). One theory is that they work by disrupting rigid patterns of thinking and behavior, allowing individuals to gain new perspectives and insights into their experiences. This, in turn, may lead to a reduction in symptoms and improved psychological well-being. Micro-dosing or taking small amounts of psychedelics on a regular basis, has also gained attention as a potential way to enhance cognitive function, creativity, and productivity. However, the evidence supporting the effectiveness of micro-dosing is still limited, and there are concerns about potential adverse effects and long-term consequences of regular use. Despite the promising findings, it is important to note that the use of psychedelics for therapeutic purposes is still highly regulated and restricted. There is still much research to be done to fully understand the potential benefits and risks of these substances, and more rigorous clinical trials are needed before they can be considered as a standard treatment option.

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