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REVIEW ARTICLE

From psychiatry to neurology: Psychedelics as prospective therapeutics for neurodegenerative disorders

Urszula Kozlowska[1,2] | Charles Nichols[3] | Kalina Wiatr[2] | Maciej Figiel[2]

[1]Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wroclaw, Poland

[2]Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznan, Poland

[3]Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA

Correspondence
Maciej Figiel, Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704, Poznan, Poland.
Email: mfigiel@ibch.poznan.pl

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Abstract

The studies of psychedelics, especially psychedelic tryptamines like psilocybin, are rapidly gaining interest in neuroscience research. Much of this interest stems from recent clinical studies demonstrating that they have a unique ability to improve the debilitating symptoms of major depressive disorder (MDD) long-term after only a single treatment. Indeed, the Food and Drug Administration (FDA) has recently designated two Phase III clinical trials studying the ability of psilocybin to treat forms of MDD with "Breakthrough Therapy" status. If successful, the use of psychedelics to treat psychiatric diseases like depression would be revolutionary. As more evidence appears in the scientific literature to support their use in psychiatry to treat MDD on and substance use disorders (SUD), recent studies with rodents revealed that their therapeutic effects might extend beyond treating MDD and SUD. For example, psychedelics may have efficacy in the treatment and prevention of brain injury and neurodegenerative diseases such as Alzheimer's Disease. Preclinical work has highlighted psychedelics' ability to induce neuroplasticity and synaptogenesis, and neural progenitor cell proliferation. Psychedelics may also act as immunomodulators by reducing levels of proinflammatory biomarkers, including IL-1β, IL-6, and tumor necrosis factor-α (TNF-α). Their exact molecular mechanisms, and induction of cellular interactions, especially between neural and glial cells, leading to therapeutic efficacy, remain to be determined. In this review, we discuss recent findings and information on how

Abbreviations: 5-MeO-DMT, 5-methoxy-N, N-dimethyltryptamine; AKT, protein kinase B; ALS, amyotrophic lateral sclerosis; APAF-1, apoptotic protease activating factor 1; Bax, Bcl-2-associated X protein; BBB, blood–brain barrier; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; CCL2, C-C motif chemokine ligand 2; CCL20, C-C motif chemokine ligand 20; c-Fos, Fos proto-oncogene; CHOP2, channelopsin-2; CNS, central nervous system; CREB, cAMP response element-binding protein; CXCL2, C-X-C motif chemokine ligand 2; DAMPS, danger-associated molecular patterns; DMT, N,N, dimethyltryptamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; ERK1/2, the extracellular signal-regulated kinase ½; ERS, endoplasmatic reticulum stress; FDA, food and drugs administration; fMRI, functional magnetic resonance imaging; GPXs, glutathione peroxidases; HO-1, heme oxygenase 1; ICAM-1, intercellular adhesion molecule 1; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferone γ; IgE, immunoglobulin E; IL, interleukin; IP3Rs, inositol 1,4,5-trisphosphate receptor; IRE1a, inositol-requiring enzyme-1a; Iκβ-α, NFKB inhibitor alpha; KYNA, kynurenic acid; LIMK1, LIM domain kinase 1; LSD, lysergic acid diethylamide; MAOi, monoamine oxidase inhibitors; MAP2, microtubule-associated protein 2; MCP-1, monocyte chemoattractant protein-1; MKP-1, mitogen-activated protein kinase (MAPK) phosphatase 1; mTOR, mechanistic target of rapamycin; NAD(P)H, nicotinamide adenine dinucleotide phosphate; NFAT, nuclear factor of activated T cells; NGF, neural grow factor; NIH, National Institute of Health; NMDA, N-methyl-D-aspartate receptor; NQO1, NAD(P)H Quinone Dehydrogenase 1; Nr4a1, nuclear receptor subfamily 4 group A member 1; Nrf2, nuclear factor erythroid 2–related factor 2; NSC/NPC, neural stem/progenitor cells; OPC, oligodendrocyte progenitor cells; PAK1, P21 (RAC1) activated kinase 1; PEA15, astrocytic phosphoprotein PEA-15; PECAM, platelet endothelial cell adhesion molecule; PERK, protein kinase RNA-Like ER kinase; PFC, prefrontal cortex; PKC, protein kinase C; PLCbeta, phosphoinositide phospholipase C; PLD1, phospholipase D1; PTSD, post-traumatic stress disorder; QUIN, quinolinic acid; Rac1, Ras-related C3 botulinum toxin substrate 1; RhoA, Ras homolog family member A; RIMA, reversible inhibitors of monoamine oxidase; RNS, reactive nitrogen species; ROCK, Rho-associated protein kinase; ROS, reactive oxygen species; rsFC, resting-state functional connectivity; RSK2, ribosomal protein S6 kinase alpha-3; SCA3, spinocerebellar ataxia type 3; SHH, sonic hedgehog; SNRIs, serotonin-norepinephrine reuptake inhibitors; SOD-1, -2, superoxide dismutase; SSRIs, selective serotonin reuptake inhibitors; SUD, substance use disorders; TAAR, trace amine-associated receptor; TBG, tabernanthalog; TCAs, tricyclic antidepressants; TJ, tight junction; TLR 4, toll-like receptor 4; TNF-α, tumor necrosis factor – α; TRD, treatment-resistant depression; TrkB, tropomyosin receptor kinase B; TRXPs, thioredoxin peroxidases; VCAM1, vascular cell adhesion protein 1; ZO, zonula occludens.

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psychedelics may act therapeutically on cells within the central nervous system (CNS) during brain injuries and neurodegenerative diseases.

KEYWORDS
blood–brain barrier, immunomodulation, microglia, neurodegenerative disorders, neuroprotection, psychedelics

1 | INTRODUCTION

We are in the midst of a renaissance of research into a class of drugs named psychedelics. This class of drugs was made illegal to use or possess worldwide in the late 1960s, but is now making a comeback as a possible clinical therapy for treating psychiatric conditions such as treatment-resistant depression (TRD), post-traumatic stress disorder (PTSD), and other neuropsychiatric diseases (Carhart-Harris et al., 2017, 2021; Griffiths et al., 2016; Krediet et al., 2020; Nutt et al., 2020). There is no doubt that psychedelics influence essential functions of the Central Nervous System (CNS). Therefore, they are increasingly recognized and being studied as therapeutic agents for psychiatric disorders. In modern pharmacology, the term "psychedelic" refers to a class of CNS active drugs that primarily produce their effects through serotonin 5-HT_{2A} receptor activation. Classic psychedelics are the natural products: psilocybin, N,N-dimethyltryptamine (DMT), 5-MeO-DMT, mescaline, and the semi-synthetic ergot derivative lysergic acid diethylamide (LSD). Non-classic psychedelics are newer derivatives of these classic compounds and also include DOx and 2C compounds such as (*R*)-DOI and 2C-B. CNS active drugs that can produce similar perceptual alterations such as ketamine, MDMA, and THC are not pharmacologically considered psychedelics because their effects are not mediated primarily through the 5-HT_{2A} receptor. However, recent phase-III-clinical trial data on MDMA-assisted psychotherapy demonstrated therapeutic benefits in patients with severe PTSD (Mitchell et al., 2021).

Research using psychedelics was essentially banned worldwide in the late 1960s and early 1970s, and this class of drug labeled dangerous with no medical value. Fortunately, research in this field has gained interest in recent years, and clinical trials in several areas show promise for these drugs as potential new therapeutics. For instance, so-called "magic mushrooms" are a well-known natural source of the classic psychedelic tryptamine psilocybin. Although known and used for millennia, psilocybin itself was not isolated until 1957 by Albert Hoffman from *Psylocibe mexicana*, who first synthesized it in 1958 (Passie et al., 2002). Psilocybin itself is a prodrug, rapidly converted to the active form, psilocin, in the body. Another classic psychedelic compound, N,N-Dimethyltryptamine (DMT), is found in significant concentrations in several plants such as *Mimosa tenuiflora*, *Psychotria viridis*, and *Diplopterys cabrerana*, among others. It is also produced in the mammalian body but at low levels. DMT was first synthesized in 1931 and isolated in 1942 from *M. tenuiflora* by Oswaldo Gonçalves de Lima. Its psychoactive properties, however, were not confirmed until 1956 (Gaujac et al., 2013). The β-carboline and monoamine oxidase inhibitors (MAOi) harmine, tetrahydroharmine, and harmaline in *Banisteropsis caapi* are often used to facilitate the oral activity of DMT in the Amazonian brew *ayahuasca*, which has also recently been studied for therapeutic benefits (Hamill et al., 2019; Jiménez-Garrido et al., 2020; Netzband et al., 2020; Palhano-Fontes et al., 2019; Sarris et al., 2021).

This review will discuss the current state of the art of how psychedelics influence neural tissue homeostasis and activity. We hypothesize that psychedelics can also be used as therapeutics in the treatment of neurodegenerative diseases and brain injuries. We will mainly focus on neuroimmunology and how data from recent research in the context of neuroinflammation support the hypothesis that psychedelics may have a beneficial outcome in restoring the balance of neural tissue function (Frecska et al., 2016; Inserra, 2019). In this context, we will also discuss psychedelic-induced neuroplasticity, neurogenesis, and gliogenesis. We propose that psychedelic research in studies of neurodegeneration may be beneficial for future development in this field. We hope that this review will provide information useful to support future psychedelic research in the area of regenerative medicine and the treatment of neurodegenerative disorders and brain injuries.

2 | PSYCHEDELICS IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

Numerous research studies of psychedelics in psychiatry were performed between the 1950s and 1970s that suggested their use for the treatment of TRD and PTSD (Byock, 2018; Pahnke et al., 1970). For example, prior to the scheduling and restrictions on the use of LSD, the NIH funded over 130 research projects on its prospective therapeutic benefits (Nutt et al., 2020). Unfortunately, the rigor of those studies was not up to current standards, and most were not adequately controlled (Bonson, 2018). However, these historical trials gave reason to suspect efficacy in the treatment of MDD and SUD. Currently, 264 million people are suffering from depression globally, and among them 60–70% do not respond to the first treatment, and 30–40% do not respond to any pharmacotherapy. Worldwide, every year about 800 000 people commit suicide, and suicide is the second leading cause of death among young people between 18 and 29 years old (De Gregorio et al., 2018).

Several drugs are used to treat MDD. These include reversible inhibitors of monoamine oxidase (RIMA), tricyclic antidepressants

(TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and others (Ionescu et al., 2015). However, about one-third of patients do not respond to these conventional treatments (Ionescu et al., 2015) and are termed treatment-resistant depression (TRD). A new medicine for TRD is (*S*)-ketamine (Esketamine, Sprivato®), a non-monoaminergic antagonist of NMDA receptors that was recently approved by the FDA as a nasal spray formulation for TRD in conjunction with an oral antidepressant. Esketamine treatment is rapid acting (i.e., within hours), and appears to be a useful tool in the treatment of TRD, but the cost of the therapy is relatively high (Bahr et al., 2019), and there are abuse issues that may present with long-term use necessary for sustained therapeutic effect.

The first evidence that psychedelics may elicit therapeutic benefits in the treatment of MDD appeared from studies conducted between the 1950s and 1970 (Pahnke et al., 1970). More recently, this concept has been further explored with modern scientific rigor in clinical trials. Two groundbreaking studies demonstrated psilocybin improves well-being of cancer patients when used together with psychotherapy (Griffiths et al., 2016; Ross et al. et al., 2016). They found that just a single administration of psilocybin to patients brought significant relief from cancer-related psychosocial distress, with the positive behavioral effects lasting through the studies' 6-month duration. Patients reported improvement in life attitude, mood, social interactions, and clinically rated remission for MDD and anxiety. A long-term follow-up study on a small group of patients has suggested positive outcomes lasting at least 4.5 years (Agin-Liebes et al., 2020). The clear advantage of psychedelic-assisted psychotherapy is the administration of one or two doses, which are at least equally effective as an everyday dose of classical antipsychotics. The psychedelic-assisted psychotherapy sessions are reported to be satisfactory for a treatment of an anxiety and major depressive disorder (Agin-Liebes et al., 2020; Carhart-Harris et al., 2021; Griffiths et al., 2006, 2016; Ross et al. et al., 2016).

Imaging studies using fMRI to scan the brains of depressed individuals have mapped functional changes in neural network connectivity, and these may be relevant to the therapeutic effects of psilocybin (Carhart-Harris et al., 2017). One proposed antidepressant mechanism of psychedelics involves stimulation of 5-HT_{2A} receptors, and subsequent effects on resting-state functional connectivity (rsFC) to disintegrate the default mode network (DMN) and produce a net hyperconnectivity. In this scenario, for a subset of patients, MDD is associated with rigid, predictable reality processing through fixed neural connections, making it difficult to escape negative thought patterns (Carhart-Harris et al., 2014). This network hyperconnectivity then gives way to more normal connections and a "resetting" of the brain and a shedding of rigid and negative network states as the acute effects of psilocybin diminish (Carhart-Harris et al., 2017; Nichols et al., 2017), similar to a defibrillator re-synchronizing electrophysiological signals within the heart. In reality, MDD affects several aspects of neurobiology, from network connectivity to cellular function. Psychedelics activate ensembles of excitatory neurons, inhibitory interneurons, and non-neuronal cells like astrocytes and glia in a regionally dependent manner (Martin & Nichols, 2016) as well as increase synaptic density and connections between neurons (Ly et al., 2018). Complex heterogeneous effects at the cellular and molecular level in response to psychedelics likely underlie the observed normalization in network connectivity, leading to therapeutic effects.

It remains unknown, how just a single administration of a psychedelic can produce such long-term therapeutic effects. An interesting theory proposed by Flanagan and Nichols suggests that this may occur because of psychedelic induced anti-inflammatory responses whereby the psychedelic reduces neuroinflammation associated with MDD, which could otherwise facilitate relapse back into a depressed state (Flanagan & Nichols, 2018; Kyzar et al., 2017). Anti-inflammatory pathways could involve activation of 5-HT_{2A}, Sigma-1, and TAAR receptors present in multiple cell types involved in the immunomodulation of the CNS. These concepts will be discussed later in this review. Reducing inflammation is a recently proposed antidepressant strategy, as a large percentage of depressed individuals have elevated inflammatory biomarkers. Traditional antidepressant drugs such as SSRIs and SNRIs are reported to lower inflammation and promote hippocampal neurogenesis (Gałecki et al., 2018; Samuels et al., 2015; Santarelli et al., 2003; Warner-Schmidt et al., 2011). Psychedelics have also been shown to reduce proinflammatory biomarker expression in several models, including in vitro, animal, and human studies (Flanagan & Nichols, 2018; Flanagan et al., 2019; Nardai et al., 2020; Szabo et al., 2014; Uthaug et al., 2020), but it remains to be investigated if this anti-inflammatory mechanism is also involved in the antidepressant effects of psychedelics to treat MDD. One of the possible mechanisms would be the prevention of inflammatory-mediated tryptophan metabolism via the IDO/kynurenine pathway (Miura et al., 2008). Tryptophan is one of the amino acids required for serotonin synthesis, however, it may be metabolized to kynurenine by indoleamine 2,3-dioxygenase (IDO). The IDO enzyme is produced by immune cells, such as monocytes, macrophages, and microglia in response to proinflammatory cytokines (for instance, IFN-γ, IFN-α) (Munn & Mellor, 2013; Robinson et al., 2005). In the IDO/kynurenine pathway, tryptophan is metabolized into kynurenic acid (KYNA) and quinolinic acid (QUIN), an NMDA receptor agonist. The involvement of QUIN and KYNA in the development of MDD has recently been investigated (Liu et al., 2018; Steiner et al., 2011). The anti-inflammatory properties of psychedelics may therefore involve prevention of immune cells to synthetize IDO, and disruption of IDO/kynurenine pathways.

The therapeutic effect may also depend on the subjective mind-altering experiences that occur during the treatment sessions apart from any acute biological mechanisms. Life-changing experiences that do not depend on drug administration, such as motivation to quit an addiction, can and do regularly occur (Griffiths et al., 2006; Morris, 2006). Although there is a promise in the psychedelic-assisted therapy, is that approach better than the current standard of care using traditional antidepressants and psychotherapy? In a recently published clinical study, which was the first head to head comparison of psilocybin versus an SSRI (escitalopram) to treat MDD, both compounds appeared to have similar therapeutic effects

(Carhart-Harris et al., 2021). However, the fact remains that during this trial, only two doses of psilocybin were administered compared to chronic dosing of SSRI. Additional ongoing or planned clinical trials studying the use of psychedelics to treat addiction, PTSD, cluster headaches, major depressive disorder in Mild Cognitive Impairment and Alzheimer's Disease will soon inform on the broader applicability of psychedelics to treat neuropsychiatric disorders.

In general, the application of novel therapies is justified only if the risks do not outweigh the benefits, and there are some concerns when considering therapeutic applications of psychedelics. Although it is generally accepted that this class of the drug has little to no addictive potential (Fábregas et al., 2010; rev in Dos Santos et al., 2018; rev in Johnson et al., 2018), there is a slight risk for certain patients to experience sporadically occurring adverse psychological effects (Sarris et al., 2021). This includes the risk of developing symptoms of psychosis or schizophrenia (rev in Paparelli et al., 2011). Clinical trials to date have specifically excluded participants with first-degree relatives with certain psychiatric disorders like psychosis and schizophrenia to minimize risk. Furthermore, it may not be prudent to administer psychedelics to individuals with certain other psychiatric conditions such as borderline personality disorder or bipolar disorder (Holmes et al., 2009; Kulacaoglu & Kose, 2018; Reddy et al., 2014; Studerus et al., 2011).

3 | PSYCHEDELIC INDUCED NEUROPLASTICITY AND NEUROGENESIS: WHAT IS ALREADY KNOWN—WHAT COULD BE PROPOSED

The term "neural plasticity" describes changes in functional neural connectivity. The mechanisms are mostly associated with neural cells, but the process reaches beyond the plasticity of neural synapses (Sampaio-Baptista & Johansen-Berg, 2017). The adaptive changes in the fMRI-measurable macro-scale come from changes in local micro-scales within multicellular interactions, involving neurons, astrocytes, microglia, and oligodendrocytes (Chagas et al., 2020; Dzyubenko et al., 2016). These cellular interactions are characterized by complicated homeostatic processes employing both paracrine and direct cell-to-cell communication. Neural plasticity is still poorly understood, but some mechanisms have already been described (Vatansever et al., 2017). Psychedelics may induce a so-called elevated brain entropy state, resulting in an increased ability to learn and "unlearn" certain information. Such action may be therapeutic, and is likely associated with increased neural plasticity mechanisms at the cellular level (Carhart-Harris et al., 2014). Acute changes in the density and complexity of synaptic architecture induced by psychedelics and 5-HT_{2A} receptor activation have been shown by several investigators in both in vitro and in vivo models. These changes involve multiple mechanisms. For example, increases in spine density and morphology can involve direct signaling downstream of 5-HT_{2A} receptor stimulation by psychedelics through serotonylation and activation of Rac1 and kalirin-7 (Jones et al., 2009; Mi et al., 2017), or indirect modulation of synaptic architecture by elevated glutamate levels acting through BDNF/TrkB and mTOR signaling (Figure 1) (Ly et al., 2018). A feature of psychedelic therapy is the long-lasting effect after only a single treatment. The reason for this is unclear, but likely involves changes in gene expression and/or epigenetic factors underlying the maintenance of neural processes normalized by treatment. There are several known genes involved in synaptic plasticity whose expression is changed in response to psychedelics (Jefsen et al., 2021; Nichols & Sanders-Bush, 2004). Neurogenesis may also be a factor; the administration of DMT induces neural progenitor cells proliferation and adult hippocampal neurogenesis in vivo via activation of Sigma-1 receptors in C57BL/6 mouse (Morales-Garcia et al., 2020). Taken together, neurotrophic signaling and neuroplasticity promoting pathways activated by psychedelics are hypothesized to be key to the mechanism(s) of action for therapeutic effect(s).

A potential key mechanistic component not taken into account for nearly all proposed models is the involvement of microglia for therapeutic effect, as most if not all attention has been focused on neurons in the mechanism of action of psilocybin and other psychedelics. Microglia are tissue-specific, self-renewable CNS macrophage-like cells that are different from other cell types since they appear in the brain and spinal cord during fetal development in the process of primitive hematopoiesis (Alliot et al., 1999). During their life-long residency inside the CNS environment, microglia assume specific immune cell characteristics and functions. Microglia are very mobile, continually scanning the environment, ready to respond to injury and infections, and take an active part in synaptic rearrangement and neural tissue regeneration (Chagas et al., 2020). They modulate the deletion of unnecessary connections and the formation of new ones (Heneka et al., 2015; Ledo et al., 2016). It is tempting to speculate that psychedelics may stimulate neural plasticity through microglia regulation, especially since many receptors targeted by certain psychedelics like psilocybin and LSD are also present on microglia, including 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{7} receptors (Quintero-Villegas & Valdés-Ferrer, 2019), and the Sigma-1 receptor (Gekker et al., 2006; Ray, 2010). Interestingly, in vitro application of DMT and 5-MeO-DMT to monocyte-derived dendritic cells (moDCs) reduce mRNA and protein expression of IL-1β, IL-6, TNF-α, IL-8, and increase expression of regulatory and tolerogenic IL-10 (Szabo et al., 2014).

Another interesting phenomenon is the reciprocity in the dynamics of neuron–microglia interactions. For instance, activation of NMDA receptors on a single neuron's dendrites can stimulate the growth of microglial extensions (Eyo et al., 2018). Further research may help better understand how neuronal–microglia interactions affect learning and memory, neurodegeneration, and possibly the progression of certain mental illnesses. Microglia may be regulating synaptic pruning or growth by signals from neurons themselves (Sandvig et al., 2018). These regulatory signals may rely on the electrochemical transmission or the complement system, which is also involved in the process of synaptic pruning. During this process, unnecessary synapses are tagged with specific complement proteins that are detected and phagocytized by microglia. Errors in this process during childhood may lead to the development of autism,

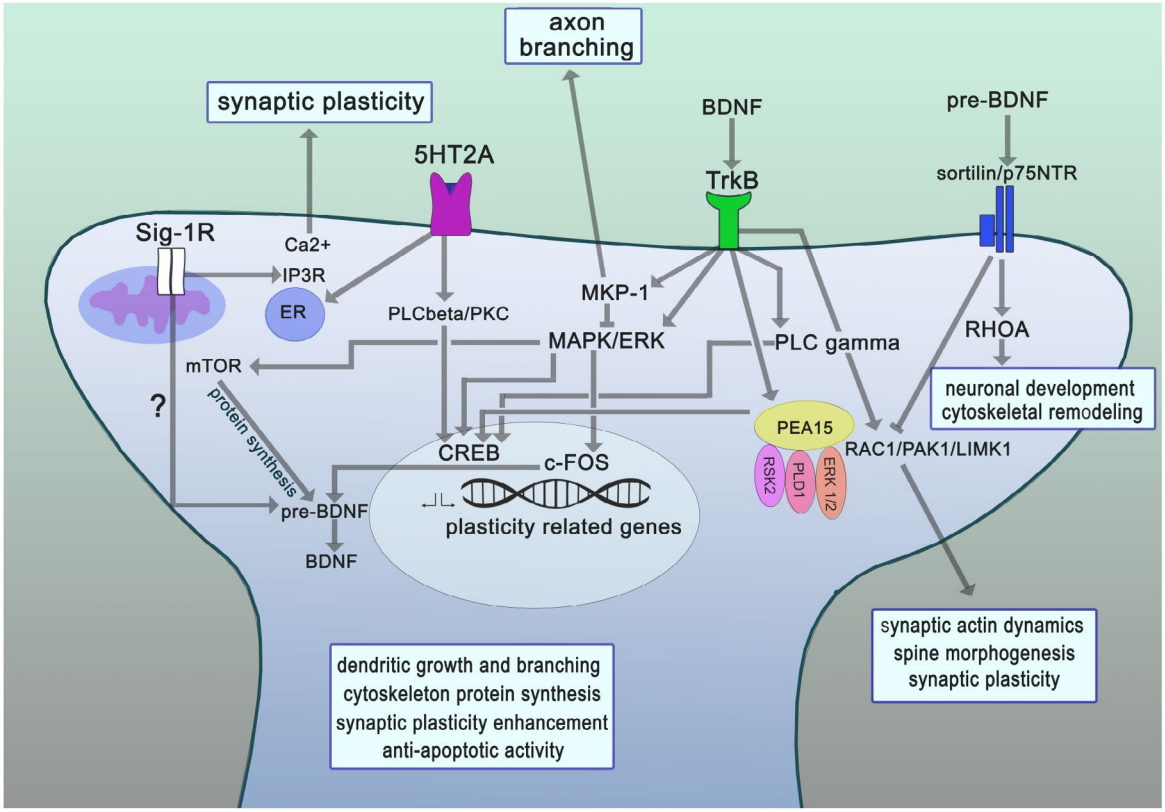

FIGURE 1 Model of neuroplasticity pathways induced by 5-HT_{2A} and Sigma-1 receptors in response to psychedelics treatment. 5-hydroxytryptamine receptor 2A (5-HT_{2A}) and Sigma-1 (Sig-1R) receptor are activated by binding psychedelics (LSD, DMT, psilocin), which induces transcription of brain-derived neurotrophic factor (BDNF) through PLCbeta/PKC signaling in the case of 5-HT_{2A} and unknown pathway in the case of Sig-1R. BDNF exerts various effects in the cell leading to increased neural plasticity. Precursor BDNF (pre-BDNF) is acting on the sortilin-p75 receptor, which results in neuronal development and cytoskeletal remodeling. Mature BDNF as well as other neurotrophins: NGF and NT-3 by binding to their receptors activate main signaling pathways: PLC-gamma and MAPK/ERK. Those pathways activate transcription regulators such as CREB and c-FOS, which leads to expression of plasticity-related genes involved in neurite outgrowth, branching, neuronal survival, and synapse plasticity. In addition, MAPK/ERK activation leads to mTOR-regulated translation of BDNF and ERK1/2 in the complex with PLD1, RSK2, and PEA15 which promote BDNF transcription through CREB. Interaction of BDNF with TrkB receptor activates several other signaling cascades: RAC1/PAK1/LIMK1 involved in synaptic actin dynamics and MKP-1 leading to axon branching. Neuroplasticity induced by 5-HT_{2A} and Sig-1 receptors is also mediated through calcium signaling released from endoplasmic reticulum (ER)

schizophrenia, or mental retardation, and in adult also result in degenerative diseases (Eroglu & Barres, 2010; Presumey et al., 2017). The cellular phenotype and activity of microglia, the involvement of the complement system, and the neuronal signals relevant to synaptic plasticity upon psychedelics stimulation are probably critical aspects of the psychedelic therapeutic mechanism.

Our unpublished data suggest that psilocin increases the protein expression of triggering receptor expressed on myeloid cells 2 (TREM2) on microglia while reducing p65, TLR4, and CD80 proinflammatory markers (Kozlowska, Klimczak, Wiatr et al., 2021). TREM2 is involved in the regulation of several microglial functions, including phagocytosis and synaptic refinement. Microglia deficient in TREM2 expression results in synaptic pruning defects, increased excitatory neurotransmission, and reduced long-range functional connectivity (Filipello et al., 2018). The down-regulation of TREM2 was also observed in brain samples of patients suffering refractory epilepsy (Koenig & Dulla, 2018). According to our pilot data, psychedelics may prevent neuronal damage in microglia-neuron co-culture, however, it is presently unknown if the protective mechanisms of psychedelics are mediated by microglial TREM2.

4 | PATHOLOGICAL MECHANISMS IN NEURODEGENERATION—A POTENTIAL TARGET FOR PSYCHEDELICS

Because the brain is very fragile and hardly an accessible organ, only limited therapeutic approaches can be proposed for the treatment of brain-specific neurodegeneration. These can be pharmacological, stem cell, or gene therapy approaches. Unfortunately, results to date with these approaches have not been very successful (Durães et al., 2018; Pen & Jensen, 2017; Sudhakar & Richardson, 2019). Interestingly, one recently proposed solution

is the application of traditional psychiatric drugs because they have been shown to prevent neural loss and stimulate neurogenesis (Santarelli et al., 2003), Neuroprotection and induction of neurogenesis may be a fruitful avenue to treat MDD as the histopathology of depressed individuals sometimes show signs of subtle neurodegeneration. For example, post-mortem brain studies have revealed neural loss and atrophy in the prefrontal cortex (PFC) and the hippocampus (Manji et al., 2003; Sheline et al., 2003). Neural protective mechanisms (e.g., neuroprotection, neurogenesis, neuroplasticity) have been shown to be induced by psychedelics, which are effective in the treatment of MDD (Flanagan et al., 2019, 2020; Ly et al., 2018; Morales-Garcia et al., 2020; Morales-García et al., 2017; Nardai et al., 2020; Szabó et al., 2021). Here, we discuss pathologies that occur in neurodegenerative disorders that may potentially be targeted by psychedelics for therapeutic effect. We speculate that their application at early disease stages may result in the delay of pathological symptoms (Figure 2).

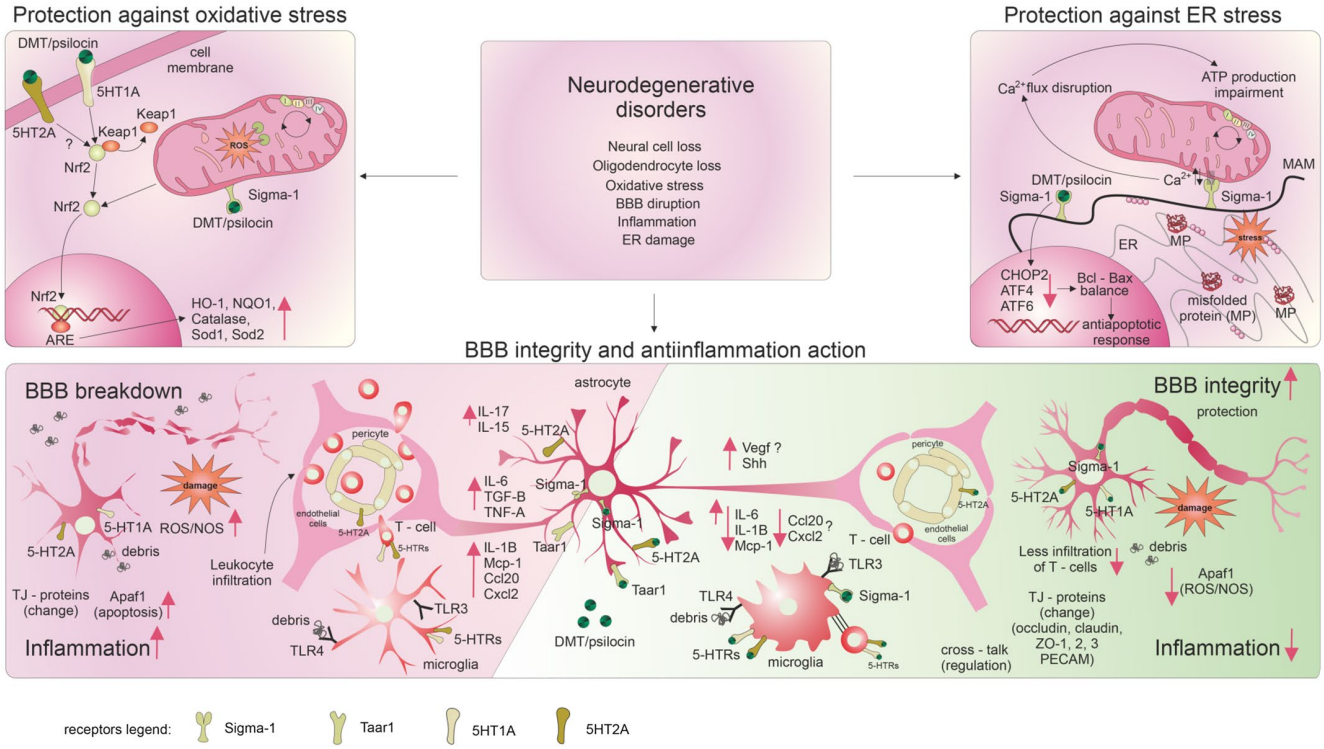

FIGURE 2 The concept of possible therapeutic mechanisms of psychedelics in several inflammation-related pathophysiological events in neurodegenerative disorders. Protection against oxidative stress: the psychedelic-based drugs may act via stimulation of 5-HT_{1A}, 5HT_{2A}, and Sigma-1, which initiates Nrf2 signaling and results in the up-regulation of antioxidant genes and proteins expression (HO-1, NQO1, Catalase, SOD1, SOD2). Protection against ER stress: a multiprotein complex consisting of receptors (IP3Rs), ion transporters, and anchoring proteins builds the ER-mitochondria interface. It sustains direct tunneling and constant supply of Ca2+ between the two organelles stimulating mitochondrial metabolism and ATP synthesis. Disruption of Ca+/ATP production and exchange may lead to neuronal pathogenesis, structural damage, and disrupted protein folding. Activation of Sigma-1R by psychedelics may protect the cells against the ER damage-mediated stress via down-regulation of CHOP2, ATF4, ATF6, and the creation of bax (apoptotic) versus bcl2 (anti-apoptotic) equilibrium. Maintenance of BBB integrity and the anti-inflammatory properties of psychedelics: Left side presents inflammation-related mechanisms in neurodegeneration, neural tissue damage. Disease-related inflammation occurs in response to pathogenic signals (e.g., NOS/ROS, viruses, prions, toxic proteins, damaged myelin, danger-associated proteins). Those signals stimulate astrocytes and microglia to secrete proinflammatory cytokines and chemokines (IL-1β, IL-6, IL-15, IL-17, TNF-α, MCP-1, CCL-20 CXCL2), eventually attracting leukocytes to cross BBB and infiltrate brain parenchyma. BBB breakdown may also be the result of elevated ROS/NOS deleterious concentration. Right side of the scheme presents the concept of how psychedelics may target the mechanisms via 5-HTRs, Sigma-1, and TAAR1 receptor stimulation. Psychedelics might elicit neuroprotective activity by decreasing the protein levels of APAF-1 and proinflammatory cytokines while up-regulating the expression of neurogenic and anti-inflammatory factors (BDNF, GDNF, IL-10). The activation of 5-HTRs, Sigma-1, and TAAR1 would also stimulate microglia-T-cell crosstalk in favor of achieving their equilibrium (regulation). As the result of anti-inflammatory mechanisms, the up-regulation of TJ protein levels (SHH, ZO-1, 2, 3, occludin, claudin, PECAM-1) would maintain BBB integrity. We propose that the application of classical psychedelics may be beneficial in treating neurodegenerative disorders such as Alzheimer's Disease, Amyotrophic Lateral Sclerosis, and Spinocerebellar Ataxia type 3. The therapeutic actions of psychedelics via 5-HT2A, 5-HT2B, Sigma-1R, and Trace Amine-Associated Receptor 1 (TAAR1) would protect from reactive oxygen species (ROS), neuro-inflammation, and toxic proteins aggregation, simultaneously supporting neurotrophy. The possible pathways activated during the psychedelic effect could include down-regulation of indoleamine 2,3-dioxygenase (IDO) and Nuclear Factor of Activated T cells NFAT, up-regulation of neurotrophy factors such as c-Fos and cAMP Response Element-Binding Protein (CREB), and sustaining blood–brain barrier (BBB) integrity

4.1 | Oxidative stress

Oxidative cell damage is often a reported in brain-specific neurodegeneration. This damage usually occurs because of an imbalance between free radicals, reactive oxygen species (ROS), and reactive nitrogen species (RNS), and the presence of antioxidants and anti-oxidative proteins, such as superoxide dismutases (SOD), hioredoxin peroxidases (TRXPs), glutathione peroxidases (GPXs) (Snezhkina et al., 2019). In a typical situation, if reactive species are held in balance, they play an essential role in regulating essential cellular processes including phagocytosis, apoptosis, and cellular signaling. However, when cells are unable to neutralize excesses of reactive molecules, these molecules may induce damage to mitochondria, cellular and nucleolar membrane, and DNA, and over time result in organ and/or tissue degeneration (Burton & Jauniaux, 2011; Dizdaroglu et al., 2002; Liguori et al., 2018). Elevated oxidative stress and disruption in redox balance are observed in many psychiatric conditions such as MDD, schizophernia, bipolar disorder, anxiety disorder (Bajpai et al., 2014; Salim, 2014). Importantly, disruption of redox homeostasis occurs in the pathology of ALS, PD, AD, and DNA repeat expansion disorders such as HD and SCAs (Niedzielska et al., 2016; La Rosa et al., 2020).

In the psychedelic brew ayahuasca, two components, harmine and harmaline, are monoamine oxidase inhibitors with antioxidant properties (Berrougui et al., 2006; Li et al., 2018) and have the capability to induce gliogenesis and neural progenitor cell migration (Morales-García et al., 2017). Another anti-oxidative effect of psychedelics such as psilocybin and/or DMT may come as a result of 5-HT_{1A} receptor activation. The 5-HT_{1A} receptor agonist 8-OH-DPAT induces expression of the anti-oxidative factor metallothionein-1/-2 (MT-1/-2) and Nfr2 (Miyazaki & Asanuma, 2016; Miyazaki et al., 2013). In retina pigment epithelial cell line (ARPE-19), 8-OH-DPAT reduces damage caused by paraquat, an oxidative herbal agent, through elevation of *MT1*, *heme oxygenase*-1 *(HO1)*, *NAD(P)H: quinone acceptor oxidoreductase 1 (NqO1)*, *superoxide dismutase* 1 and 2 (*SOD1*, *SOD2)*, and *catalase* (*Cat)* mRNA expression. 8-OH-DPAT also reduces oxidative stress damage in retinal pigment epithelium/choroid in *Sod2* knockout mice (Biswal et al., 2015).

4.2 | Endoplasmatic reticulum stress (ERS)

Some psychedelics (e.g., DMT) target the Sigma-1 receptor, which is reported to protect cells from various insults (Ryskamp et al., 2019). ER stress induces up-regulation of Sigma-1 expression and modulates the action of PERK, IRE1α, and ATF6 proteins in mitochondria-associated membrane (MAM) (Hayashi & Su, 2007). Stimulation of Sigma-1 may prevent ERS-mediated cellular apoptosis by regulation of ATF4, ATF6/ C/EBP homologous protein (CHOP), and the balance between Bax and Bcl-2 in granulosa cells (Jiang et al., 2020). Because ERS damage is reported in MDD (Mao et al., 2019) and several neurodegenerative disorders (Doyle et al., 2011), targeting Sigma-1 receptors with psychedelics is proposed as a novel therapeutic strategy.

4.3 | Blood–brain barrier disruption

The vasculature system in the brain is equipped with a special feature called the blood–brain barrier (BBB). The BBB is composed of a tight layer of astrocytes, is selectively permeable, and separates the intracerebral circulatory system from the peripheral blood to protect the brain against chemical and biological insults. The BBB also contains other cells types, such as microglia cells, perivascular macrophages, and pericytes. The whole structure is embedded in the basal membrane, with extracellular matrix secreted by endothelial cells and pericytes (Daneman & Prat, 2015; Hawkins & Davis, 2005). The endothelial cells inside the blood capillaries form tight junctions (TJ), multi-protein complexes composed of occludins, claudins, and tight junction proteins ZO-1, -2, -3. Breakdown of this system is associated with brain-specific damage and neurodegeneration, and may be the cause of serious illness (Daneman & Prat, 2015; Hawkins & Davis, 2005). Breakdown can originate from prolonged exposure to oxidative stress and/or immune cell activity. For example, microglia inflammatory cytokines acting via IL-1β on Sonic Hedgehog (SHH) can down-regulate tight-junction proteins in astrocytes, resulting in BBB leakage (Argaw et al., 2006). Moreover, suppressing SHH in astrocytes leads to increased secretion of pro-inflammatory chemotactic proteins (e.g., CCL2, CCL20, and CXCL2) and immune cell activation (Wang et al., 2014). Microglia also secrete IL-1β via inflammasome-dependent mechanisms in response to proinflammatory cytokines, DAMPS, β-amyloid (Parajuli et al., 2013; Walsh et al., 2014), or other toxic protein aggregates. In a C57BL/6 healthy male mouse model, chronic social stress causes BBB disruption via claudin-5 down-regulation, which leads to the infiltration of proinflammatory factors and depression-like behaviors (Dudek et al., 2020). Disruption of the BBB is also observed in a genetic mouse model of schizophrenia (Crockett et al., 2021), and may be involved in bipolar disorder pathology (Patel & Frey, 2015). BBB disruption is also observed in multiple neurodegenerative disorders including ALS, AD, and SCA3 (Duarte Lobo et al., 2020; Sweeney et al., 2018).

Conceptually, inflammation-based BBB leakage could be prevented to some degree by the presence of psychedelics. The drugs N,N-DMT and 5-MeO-DMT, applied into LPS and polyI:C – activated dendritic cells in vitro, result in down-regulation of expression of IL-1β, IL-6, IL-8, TNF-α, and up-regulation of IL-10 as measured by mRNA and protein expression through stimulation of Sigma-1 receptors (Szabo et al., 2014). This observation has also been confirmed in vivo in a Wistar rat model of stroke, where N,N-DMT administration significantly decreased IL-1β, IL-6, and TNF-α, but increased IL-10, measured by mRNA and protein expression (Nardai et al., 2020). Furthermore, N,N-DMT-treated rats demonstrate improved motor skills post-stroke (Nardai et al., 2020). Although not validated yet in brain tissues, several psychedelics, including DOI, LSD, and psilocybin, have been shown to have potent anti-inflammatory effects of suppressing many of these same proinflammatory biomarkers in peripheral tissues (Flanagan et al., 2020), and they may represent effective therapies for inflammation-related neuropathologies.

4.4 | Oligodendrocyte pathology

Oligodendrocytes protect and support neurons and their axons by providing myelin that improves electric signal transmission. Unfortunately, their active role in immune response and neural regeneration has long been overlooked. Microglia and oligodendrocytes actively work to regulate each other's functions (Peferoen et al., 2014). Moreover, oligodendrocytes' pathology occurs in many neurodegenerative diseases, including Alzheimer's and Parkinson's Disease, ALS, Multiple Sclerosis, Spinal Cord Injury (Almad et al., 2011; Ettle et al., 2016), but also non-degenerative psychiatric conditions including MDD, schizophrenia, and Alcohol Use Disorder (Bøstrand & Williams, 2021). For example, in MDD, abnormalities in oligodendrocyte density are observed in the PFC and amygdala (Rajkowska & Miguel-Hidalgo, 2007). Interestingly, oligodendrocytes are extremely vulnerable to oxidative stress and prolonged exposure to proinflammatory factors secreted by microglia. The previously discussed psychedelic-mediated reduction in cytokine secretions may play a protective role in myelin and oligodendrocyte cell survival (Peferoen et al., 2014). Certain psychedelics can target Sigma-1 receptors, which are essential in stimulating OPC differentiation (Hayashi & Su, 2004). Together, these findings indicate that more attention should be paid to the influence of psychedelics on oligodendrocyte biology.

5 | PSYCHEDELICS AS IMMUNOMODULATORS

The study of psychedelics at target receptors and the activation of effector pathways have brought new, but still limited, insights into their immunomodulatory potential (see Table 1). Classic psychedelics like LSD, DMT, 5-Meo-DMT, and psilocin have the potential to interact with several 5-HT receptor subtypes, Sigma-1R, and TAAR, which are present in CNS and other tissues, including cells of innate and adaptive immunity like macrophages, monocytes, dendritic cells, and T cells (Barker, 2018; Casas-Engel et al., 2013; Herr et al., 2017; Quintero-Villegas & Valdés-Ferrer, 2019). These receptors are mediators of immunological response, and serotonin is considered a critical factor in immune homeostasis. Therefore, psychedelics can regulate both adaptive and innate immune responses. A review of putative molecular mechanisms in which psychedelics may act as immunomodulators was published by Szabo, emphasizing cross-talk between pattern recognition receptors (PRR), such as Toll-Like Receptor 4 (TLR4), 5-HTRs, and Sigma-1R, and regulation of inflammatory response via NFκB/IRF signal transduction pathways. Although these modulations result in changes in IFN-α, IL-8, IL-1β, IL-6, and TNF-α gene expression, the immunological response regulation also involves intracellular Ca2+ mobilization via 5-HT and Sigma-1R (Szabo, 2015). 5-HTRs, Sigma-1, and TAAR seem to play a crucial role in immune response, and all three of them can be stimulated by psychedelics.

5.1 | 5-HT receptors

Serotonin is one of the most critical factors during fetal brain development and neurogenesis, and is responsible for the formation of axons and dendrites (Trakhtenberg & Goldberg, 2012), and adult axonal regeneration (Perrin & Noristani, 2019; Sobrido-Cameán et al., 2018). Serotonin receptors are present on most, if not all, types of cells in the CNS. In neurons, for example, their activation can influence cellular membrane polarization states through multiple mechanisms. Serotonin also plays significant roles aside from being a neurotransmitter. There are several receptor subtypes expressed in mammalian peripheral tissues and cells outside the CNS, including adaptive and innate immune cells. Serotonin itself has an endocrine effect on the regulation of whole-body homeostasis, such as heart rate, intestinal motility, and last but not least: the immune response (Berger et al., 2009; Herr et al., 2017).

Although 5-HTRs are primarily described as activators of proinflammatory pathways, they surprisingly have anti-inflammatory properties when activated by certain, but not all, psychedelics. The selective 5-HT_2 receptor agonist (*R*)-DOI, reduces mRNA expression of proinflammatory adhesion molecules ICAM-1 and VCAM-1 as well as mRNA levels for proinflammatory cytokines MCP1, IL-1β, and IL-6 in various tissues like intestine and aorta, and circulating levels of IL-6 in TNF-α treated mice (Jr et al., 2013). Several of these findings were confirmed in a high fat-fed $ApoE^{-/-}$ knockout moue model of cardiovascular and metabolic disease. An increase in levels of VCAM-1, IL-6, and MCP-1 mRNA expression was observed in animals fed a high-fat and -cholesterol "Western diet" compared to control mice fed regular food, and this increase was prevented in mice fed the Western diet and treated with (*R*)-DOI (Flanagan et al., 2019). The precise mechanism underlying why 5-HT_{2A} receptors, which are widely described as inflammation inducers, induce anti-inflammatory processes after activated by (*R*)-DOI and some other psychedelics is not known. The hypothesis proposed by Flanagan and Nichols involves the concept of functional selectivity, in which different ligands induce slightly different conformations of the receptor to recruit different sets of effector pathways. Psychedelics are hypothesized to recruit and activate anti-inflammatory effector signaling pathways, whereas serotonin itself recruits proinflammatory pathways (Flanagan & Nichols, 2018; Kim et al., 2020). In rodent models of allergic asthma, nasal administration of (*R*)-DOI at a very low dose (EC_{50}: ~0.005 mg/kg) completely prevents symptoms, including airways hyperresponsiveness, pulmonary inflammation, and mucus overproduction in response to allergen (Flanagan et al., 2020; Nau et al., 2015). Further examination of the lung tissue revealed prevention of eosinophilia and a reduction in Th2 cell recruitment. Interestingly, the behavioral potency of different psychedelics does not correlate with anti-asthma efficacy (Flanagan et al., 2019). Significantly, therapeutic drug levels in these models are orders of magnitude lower than the levels necessary to induce measurable behavioral responses. These findings suggest that subperceptual

TABLE 1 Research and concepts of psychedelic-mediated anti-inflammatory mechanisms

Psychedelic ligands	Receptor	Effect	Literature
(R)- DOI	5-HT_{2A}	In smooth muscle cells in vitro: Prevention of Nf-κβ nuclear translocation and inhibition of nitric-oxide synthase activity In aortic arch and small intestine in vivo: Down-regulation of TNF-α-mediated Cx3CL1, Icam-1, Vcam-1, MCP-1, IL-6, IL-1β In OVA-treated asthma-model lung in vivo: Suppression of Th2-related genes: *Mcp-1*, *Il-13*, *Il-5*, *and Gm-csf*, Inhibition of neutrophil infiltration, Inhibition of mucus hyperproduction	Yu et al. (2008) Nau et al. (2013) Nau et al. (2015
DMT, 5-MeO-DMT	Sigma-1	Down-regulation of: IL-1 β, IL-6, TNF-α, IL-8 Up-regulation of: IL-10 (gene and protein expression) Decrease of Th1 and Th17 activation after E. coli or H1N1 co-culture	Szabo et al. (2014)
5-MeO-DMT	5-HT_{2A} (?) 5-HT_{2c} (?)	In human cerebral organoid in vitro model: Down-regulation of Nf-κβ pathways (involved in the immune response) Down-regulation of Nuclear Factor of Activated T cells (NFAT) (T-cell activation, stem cell differentiation) Modulation of Gaq-Rho-ROCK pathway (cytoskeletal rearrangement, phagocytosis)	Dakic et al. (2017)
DOI, DMT, Psilocin	5-HT_{2B}	(Reported with BW723C86 5-HT_{2B} ligand) In CD1+ moDC down-regulation of: TNF-α, IL-6, IL-8/CXCL8/IP-10/CXCL10 after TLR2, and TLR6/7 activation, In TLR3-activated CD1+ moDC: down-regulation of CD80, CD83, CD86 (anti-inflammatory, tolerogenic) Prevention of Th1, Th17 lymphocyte polarization	Szabo et al. (2018)
DMT	Sigma-1	In in vivo model of stroke: Down-regulation of: IL-1β, IL-6, IL-8, TNF-α, NOS, APAF-1 (proinflammatory, proapoptotic) Up-regulation of BDNF and IL-10 (tolerogenic, neurogenic)	Nardai et al. (2020)
(Hypothetically) DOI, DMT, Psilocin, LSD, mescaline	TAAR1, TAAR2	(Not tested yet with psychedelics) Lymphocyte migration, increase in IL-4 secretion, Th1/Th2/Th3 phenotype modulation, mediation of IgE-secretion	Babusyte et al. (2013)

levels of some psychedelics may be an exciting alternative to currently available steroid drugs in the treatment of asthma and other inflammatory-related disease (Nau et al., 2015).

Given the high level of expression of 5-HT_{2A} receptors in the brain on multiple cell types, it may be that psychedelics have similar anti-inflammatory properties against neuroinflammation. In vitro application of 5-MeO-DMT in human cerebellar organoids results in down-regulation of NF-κβ and nuclear factor of activated T cells (NFAT) pathways, as well as modulation of the Gαq-RhoA-ROCK pathway involved in cytoskeleton rearrangement (Dakic et al., 2017) and phagocytosis (Kim et al., 2017).

Classical psychedelics have mid affinity for and efficacy at 5-HT_{2B} receptors. Interestingly, the activation of this receptor type with the agonist (BW723C86) regulates immune responses in CD1+ monocyte-derived dendritic cells (moDC). The application of BW723C86 resulted in down-regulation of CD80, CD83, and CD86 proinflammatory molecules on CD1+ moDC. Furthermore, stimulation of 5-HT_{2B} down-regulates TLR2, TLR3, and TLR7/8-mediated proinflammatory cytokine protein expression (e.g., TNFα, IL-6, IL-8/CXCL8, IP-10/CXCL10, IL-12). It also prevents moDC-mediated activation of T cells toward inflammatory Th1 and Th-17 phenotypes (Szabo et al., 2018). Furthermore, certain immune stimulators such as the molecule polyI:C, which is a TLR3 agonist, up-regulate the expression 5-HT_{2B} receptor protein. Together, these observations suggest that 5-HT_{2B} agonism may participate in some aspects of their anti-inflammatory mechanism. However, in the allergic asthma model, *(R)*-DOI was not effective in reducing pulmonary inflammation in the 5-HT_{2A} receptor knockout mouse indicating that for at least asthma and pulmonary inflammation 5-HT_{2A} receptor activity is necessary and sufficient for therapeutic effect (Flanagan et al., 2020).

5.2 | Sigma-1 receptor

The sigma-1R is a transmembrane protein located in mitochondria and the endoplasmatic reticulum (ER). It is abundantly present within the CNS in neurons, astrocytes, oligodendrocytes, and microglia, where it mediates a neuroprotective effect (Gekker et al.,

2006; Gundlach et al., 1986; Hayashi & Su, 2004; Ruscher et al., 2011; Zhao et al., 2014). Sigma-1R activity promotes neural function and survival via modulation of Ca^{2+} homeostasis, mitigation of oxidative stress, regulation of gliosis, neuroplasticity, and glutamate activity (Ruscher and Wieloch, 2015, 1; Nguyen et al., 2015, 1, 2017, 1).

Stimulation of Sigma-1R in oligodendrocyte progenitor cells (OPC) results in oligodendrocyte differentiation (Hayashi & Su, 2004), and stimulation in astrocytes improves the BDNF secretion (Da et al., 2017; Malik et al., 2015). This suggests that targeting Sigma-1R may be a promising therapeutic strategy for psychiatric and neurodegenerative conditions (Ryskamp et al., 2019; Wang et al., 2016) Interestingly, Sigma-1R activity is involved in the transition between M1-like proinflammatory and M2-like proregenerative and tolerogenic microglia phenotypes. These mechanisms are not very well understood (Chao et al., 2017; Hall Aaron et al., 2009; Jia et al., 2018). Moreover, as microglia are cells of complicated biology and are somewhat difficult to study, the concept of M1/M2 polarization may be too simplistic to address many aspects of microglia function (Ransohoff, 2016). It has been recently proposed that microglia displaying a proinflammatory phenotype are crucial for their role in neural tissue reorganization and regeneration (Chagas et al., 2020).

DMT is an agonist of Sigma-1Rs, and found to be produced by specific tissues in the brain. Szabo et al. observed that the application of DMT into human iPSC-derived cortical neuron cultures in vitro resulted in better survival under hypoxia conditions, but that the protective effect vanished after Sigma-1R gene knockdown with siRNA (Szabo et al., 2016). This suggests that DMT can protect cells from hypoxia-induced apoptosis via Sigma-1 receptor stimulation. This observation was later confirmed in an in vivo rat model of stroke, where continuous administration of DMT reduced the size and number of lesions, and decreased levels of IL-1β while up-regulating IL-10, and BDNF protein and mRNA levels (Nardai et al., 2020). Similar results were found with another Sigma-1 agonist (PRE-084) after embolic stroke to significantly reduce the size of lesions, improve neuronal deficits, and reduce concentrations of some proinflammatory cytokines while elevating levels of some anti-inflammatory cytokines like IL-10 (Allahtavakoli & Jarrott, 2011). Interestingly, application of the Sigma-1R selective antagonist (MR309), had similar neuroprotective effects (Sánchez-Blázquez et al., 2018). It is tempting to speculate that elevated anti-inflammatory cytokine levels after DMT administration in these stroke models may be caused by Sigma-1R mediated changes in microglia phenotypes. For example, in a study by Moritz et al., stimulation of Sigma-1R "switched off" activated microglia and made them migrate away from the location of damaged tissue (Moritz et al., 2015). Moreover, in the LPS-treated microglial BV2 cell line, application of Sigma-1R agonist SKF83959 (6-chloro-2,3,4,5-tetrahydro-3-methyl-1-(3-methylphenyl)-1H-3-benzazepine-7,8-diol) results in the prevention of M1-like phenotype switching by microglia, and a decrease in TNF-α, IL-1β, and inducible NOS levels (Wu et al., 2015). A similar effect was reported in a model of traumatic brain injury (TBI) (Dong et al., 2016), and Parkinson's Disease (Francardo et al., 2014).

5.3 | TAAR

Trace amine-associated receptors (TAARs) are G-protein-coupled receptors abundantly present in the CNS. In most vertebrates, they exist in nine isoforms. Only TAAR1 has been studied in-depth, however. This receptor is relatively non-selective and has an affinity for endogenous trace amines as well as the classical neurotransmitters serotonin and dopamine, and multiple psychoactive drugs, including amphetamines, ergoline derivatives, psilocin, DMT, and mescaline (Berry et al., 2017; Rutigliano et al., 2018). TAAR1 is a modulator of neurotransmission induced by canonical dopamine, serotonin, and glutamine receptors, and its aberrations and rare variants may contribute to the etiology of schizophrenia (John et al., 2017). TAAR1 is also expressed in non-CNS tissues such as the thyroid, stomach, pancreas, and intestine, where it may regulate body functions in an endocrine manner (Mühlhaus et al., 2017).

Although abnormalities in TAARs expression or function may be related to the development of schizophrenia (John et al., 2017), data suggest involvement in additional neuropsychiatric conditions. For example, stimulation of TAAR1 in an experimental model of Parkinson's Disease results in L-DOPA-related dyskinesias (Alvarsson et al., 2015), and TAAR1 knockout mice are reported to be more vulnerable to various substance addiction (Liu & Li, 2018). Targeting TAAR1 has also been suggested as a possible therapeutic target for the treatment of bipolar depression, fibromyalgia syndrome, and diabetes (Alvarsson et al., 2015; Berry et al., 2017).

TAAR are found in immune cells and can elicit immunomodulatory effects; however, our knowledge about TAARs and immune responses is limited. TAAR1 is expressed in polymorphonuclear leukocytes (PMN), T cells, and B cells, whereas TAAR2 is also abundant on NK cells and monocytes. In T cells, stimulation of TAAR1 and TAAR2 receptors induce IL-4 production and modulation of Th1, Th2, and Th3 markers, whereas silencing of these receptors reduces IgE secretion in B cells after induction with trace amines. TAAR1 and TAAR2 are also reported to be involved in PMN chemotactic migration (Babusyte et al., 2013). DMT, (*R*)-DOI, d-LSD, and 5-MeO-DMT are TAAR1 agonists (Bunzow et al., 2001), and it is, therefore, possible that psychedelics may regulate immune cells to respond and regulate neural tissue homeostasis via TAAR1 activation.

6 | RESEARCH PERSPECTIVES FOR PSYCHEDELICS IN PREVENTING NEURODEGENERATION

In this review, we have highlighted the beneficial outcomes of psychedelic treatment for MDD. Our primary focus was on processes in neural tissue microenvironments which can be affected by psychedelics. These include the induction of neurogenesis and neuroplasticity and reduction of inflammation and oxidative stress. These characteristics of psychedelics may play crucial roles in restoring

long-term healthy homeostasis in depressed patients. We also emphasized potential areas of therapeutic actions in brain-specific neurodegeneration in which psychedelics may be beneficial. These include oxidative stress, inflammation, BBB disruption, and loss of oligodendrocytes and myelin.

In Europe, around 7 million people suffer from dementia-related disorders, and the aging of society is expected to double this number by 2040. Around 15 mln people worldwide and 1,12 mln in Europe experience a stroke every year, with 5 mln of those being fatal incidents (650 000 in Europe), and another 5 mln of patients suffer post-stroke severe disability (Shrivastava et al., 2013; Wafa et al., 2020). Each year 10 mln new dementia cases are being diagnosed globally, and 60–70% of them are Alzheimer's Disease. In 2015 ALS was diagnosed in 222 801 people worldwide, and that number is predicted to grow by 69%, reaching 376 674 new ALS cases annually by 2040 (Arthur et al., 2016). Therefore, neurodegenerative diseases are a serious and growing burden for modern societies. Moreover, the development of effective therapeutics lags behind other fields such as cardiovascular diseases and cancer. Therefore it is a top priority to search for novel candidates for therapeutic approaches to revert these dire statistics (Strafella et al., 2018).

Psychedelics represent such a novel approach. Certain psychedelics, with demonstrated therapeutic efficacy for psychiatric disorders in clinical trials, have been used safely for centuries by indigenous populations. The beneficial therapeutic dosages of these substances have been shown to be well-tolerated, and they present a favorable safety profile in treating a variety of disorders (Carhart-Harris et al., 2017; Heuschkel & Kuypers, 2020; Krediet et al., 2020; Moreno et al., 2006). Clinical trials are investigating therapeutic efficacy for anorexia nervosa (Foldi et al., 2020), the early stage of Alzheimer's Disease, and traumatic brain injury, among other CNS disorders.

Psychedelics (e.g., DOI, DMT, LSD) promote structural plasticity via BDNF signaling and are thus proposed as potential therapeutics for MDD and related disorders. Neuropsychiatric disorders are well known to be associated with atrophy of neurons and abnormal neuronal circuits (Ly et al., 2018; Forrest et al., 2018). Among neurodegenerative disorders, commonalities in pathological characteristics may be seen in polyQ disorders such as spinocerebellar ataxia type 3 (SCA3) (Lee et al., 2020).

Similar to many other neurodegenerative disorders, the down-regulation of BDNF is observed in SCA3 cells and in dentate neurons of SCA3 patients (Evert et al., 2003). Moreover, several essential proteins belonging to the BDNF signaling pathway are also down-regulated in mouse models. For example, Rac1, acting downstream of BDNF and TrkB (Hedrick et al., 2016), is down-regulated in the cerebral cortex and cerebellum of young SCA3 mice (Wiatr, Marczak, Pérot, et al., 2021; Wiatr et al., 2019). Together with another down-regulated protein, RhoA, Rac1 mediates proplasticity properties evoked by BDNF by facilitating sLTP (structural long-term potentiation) and regulating actin cytoskeleton in dendritic spines. Furthermore, MAPK1 (a.k.a. Erk) and MAP2K1 are also down-regulated in the young SCA3 mice, and Erk signaling is down-regulated in MDD (Wang & Mao, 2019; Wiatr, Marczak, Pérot, et al., 2021; Wiatr et al., 2019). Importantly, BDNF is an immediate upstream regulator of the MAPK (mitogen-activated protein kinase) cascade. Activation of MAPK (ERK) signaling by neurotrophins is involved in long-term synaptic plasticity and the structural remodeling of the spines in the excitatory synapses (Alonso et al., 2004).

Another protein necessary for BDNF signal transduction to the nucleus is Pea15, which is also down-regulated in SCA3 mice (Wiatr, Marczak, Pérot, et al., 2021). Silencing of Pea15 results in inhibition of BDNF retrograde signaling (Ammar et al., 2015). Pea15 acts as a scaffolding protein for PLD1, RSK2, and ERK1/2, and the formation of this complex is triggered by BDNF in cortical neurons. Therefore, the potential use of psychedelics could affect the levels of several proteins (Rac1, Rhoa, Mapk1, Map2k1, Pea15, and BDNF itself), which are down-regulated in the SCA3 model probably by an increase in BDNF which may promote synaptic plasticity. The role of BDNF signaling in the survival of neurons has been well documented in other neurodegenerative disorders, such as Huntington's, Parkinson's, and Alzheimer's disease (Murer et al., 2001; Zuccato & Cattaneo, 2007).

Psychedelics have also been shown to reduce oxidative stress, which is a significant issue in neurodegenerative disorders. Several oxidative stress biomarkers are elevated in models of neurodegenerative disorders (Fan et al., 2019; Hueso et al., 2020; Wiatr, Marczak, Pérot, et al., 2021). Other anti-oxidative proteins, which play an essential role in reducing oxidative stress by breaking down ROS (Gstp1, Sod2, Fth1), are down-regulated in the SCA3 model (Wang et al., 2015; Wiatr et al., 2019, 2021). Moreover, Txn down-regulation in SCA3 mice might increase the vulnerability of neurons to ROS (Sewastianik et al., 2016; Wiatr, Marczak, Pérot, et al., 2021). Therefore, psychedelics' anti-oxidative properties could be a beneficial component of a therapeutic strategy for SCA3 and other neurodegenerative disorders (Jiang et al., 2016; Sorolla et al., 2008).

The strategy of serotonergic signaling modulation by psychedelics in SCA3 is also strongly supported by studies showing a therapeutic effect for SCA3 through 5-HT_{1A}R activity, which is activated by several psychedelics including psilocybin and LSD. Targeting of the 5-HT_{1A} serotonin receptor orthologue SER-4 in *C. elegans* ameliorates motor dysfunction and reduced mutant ATXN3 aggregation (Pereira-Sousa et al., 2021). Furthermore, treatment with partial agonists of 5-HT_{1A} receptors has been demonstrated to reduce ataxia, pain, insomnia, and depressive symptoms in patients with SCA3 and other forms of SCA (Takei et al., 2005, 2010). The SSRI citalopram has beneficial therapeutic effects in animal models of SCA3 and preclinical trials (Ashraf et al., 2019; Esteves et al., 2019; Teixeira-Castro et al., 2015). Thus, activation of serotonergic signaling in SCA3 patients with psychedelic agents is a promising therapeutic strategy.

6.1 | Non-hallucinogenic psychedelics approach

The "hallucinogenic" effects of psychedelics have been proposed to be directly associated with their therapeutic potential in

psychedelic-assisted psychotherapeutical approach as the subjective peak intensity has a high correlation with therapeutic efficacy (Yaden & Griffiths, 2021). However, in patients suffering brain-specific neurodegeneration, psychotropic effects of psychedelics may be a serious limitation, especially if because of the disease physiology, the medicine would have to be administrated more often and in higher doses. Furthermore, correlation is not causation, and subjective peak experiences may merely indicate that sufficient drug has been administered to produce therapeutic efficacy at cellular and molecular targets and circuits. Although ibogaine is not classified as a psychedelic, it is a type of hallucinogen that may have therapeutic efficacy to treat substance use disorder. Recently, analogs of ibogaine have been reported by two different investigators to attenuate behaviors associated with substance abuse in rodent models, in a similar way to ibogaine. One is peer reviewed (Cameron et al., 2021), and the other awaiting peer review (Havel et al., 2021). Because of the low toxicity and lack of hallucinogenic properties of these new molecules, they represent potential non-hallucinogenic derivatives of hallucinogenic parent molecules with therapeutic effect. With regard to psychedelics, their demonstrated potency in multiple animal models of disease suggests it may not be necessary to eliminate hallucinogenic behaviors from effective molecules because the dose is so low that effects on behaviors would not be seen at relevant therapeutic levels. Regardless, work by Flanagan et al. (2020) suggest that it may be possible to engineer hallucinogenic effects away from therapeutic effects to develop non-hallucinogenic 5-HT_{2A} receptor agonists with anti-inflammatory potential. Development of a 5-HT_{2A} receptor agonist therapeutic devoid of hallucinogenic effects would conceivably allow higher levels to be used, especially for those with weaker potencies, which may allow for greater efficacy in certain circumstances.

6.2 | Prospect implications for regenerative medicine

Besides the prevention and regulation of pathology in neurodegenerative disease, the immunomodulatory properties of psychedelics may also be relevant to regenerative medicine. Neural Stem/Progenitor Cell (NSC/NPC) transplantation is a recently developed and promising therapeutic tool. However, the limitation of such a strategy is poor graft survival because of immune response (Kozlowska, Klimczak, Bednarowicz, et al., 2021; Piquet et al., 2012). Our recent study revealed that DMT and psilocin down-regulate CD80 co-stimulatory molecule expression on the surface of microglial cells, with and without LPS stimulation (Kozlowska, Klimczak, Wiatr et al., 2021). The co-stimulatory signal is crucial for recruiting adaptive immune cells; therefore, blockade of co-stimulatory molecules an attractive immunosuppressive strategy (Lan et al., 2020). The unique properties of psychedelics in suppressing inflammatory responses (Szabo et al., 2014; Flanagan & Nichols, 2018; Nardai et al., 2020), and promoting neural survival (Szabo et al., 2016) and plasticity (Ly et al., 2018), could be a strong rationale for the hypothesis that psychedelics might support grafted cells and facilitate their survival for therapeutic benefits.

6.3 | Therapeutic perspectives for microdosing

One dosing method of psychedelics is the use of so called "microdoses"—very low concentrations of various psychedelics that do not reach the threshold of perceivable behavioral effects. This is usually 10% of active recreational doses (e.g., 10–15 μg of LSD, or 0.1–0.3 g of dry "magic mushrooms") taken up to three times per week. This regimen is popular in underground settings without medical guidance (Kuypers et al., 2019). Microdosing is believed to improve the creative thinking, cognitive function, and overall psychological well-being, and is described mostly in the context of self-application by healthy enthusiasts. There have been few rigorously controlled studies of microdosing, and the therapeutic effects of psychedelic microdoses for the treatment of psychiatric disorders are questionable. According to a self-blinding study involving 191 healthy volunteers, in which the mood changes were measured using various questionaries, the authors concluded that anecdotal psychological improvements are more likely associated with the placebo effect rather than drug effect (Szigeti et al., 2021). Furthermore, Family et al. (2020) reported that repeated administration of LSD (5–20 μg) in healthy individuals in a blinded placebo-controlled clinical trial produced no significant changes in several cognitive outcome measures. However, a recent study using fMRI showed that 13 μg of LSD changes connectivity inside the limbic circuits 90 min after drug administration compared to the placebo control, which was associated with positive mood changes as measured with a Positive and Negative Affect Schedule (PANAS) (Bershad et al., 2020). Each of these reports has been in healthy individuals, and there have been no rigorous and controlled studies to date on microdosing in patients with diagnosed depressive disorder. The application of psychedelic microdosing in the context of the treatment of brain-specific neurodegenerative disorders has not been yet directly investigated, however, researches speculate that it may influence the hippocampal neurogenesis (Vann Jones & O'Kelly, 2020). Importantly, a Phase I feasibility and safety study on repeated low-dose LSD administration has been conducted in an elderly healthy population in preparations for later phase clinical trials to treat Alzheimer's Disease (Family et al., 2020).

7 | CONCLUSION

Psychedelics stimulate neuro- and gliogenesis, reduce inflammation, and ameliorate oxidative stress. Therefore, they are promising candidates for future therapeutics for psychiatric, neurodegenerative, and movement disorders. Importantly, psychedelics hold the promise of being disease-modifying therapeutics, and not simply just providing symptomatic relief. Current clinical trials have demonstrated both safety and efficacy for their therapeutic use in controlled

clinical settings, and psilocybin, has even been designated with "Breakthrough Therapy" status by the FDA in the United States for two different Phase III clinical trials. Often only just one or two therapeutic administrations produce profound and persistent effects. Preclinical research has shown promise in several disease models for both psychiatric and non-psychiatric diseases. Therefore, the use of psychedelics as therapeutics is very promising and should be further developed, paying special attention in the future to prospect applications in neurodegenerative diseases.

CONSENT FOR PUBLICATION

All authors consent for this version of the manuscript to be published.

CONFLICT OF INTERESTS

Charles D. Nichols is Scientific Advisor for Eleusis Therapeutics, has a Sponsored Research Agreement with Eleusis Therapeutics, and is an advisor to Palo Santo Venture Fund. Urszula Kozlowska declares no conflict of interest. Kalina Wiatr declares no conflict of interest. Maciej Figiel declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data were generated for this Review article.

ORCID

Urszula Kozlowska https://orcid.org/0000-0003-0213-0215
Charles Nichols https://orcid.org/0000-0002-0615-0646
Kalina Wiatr https://orcid.org/0000-0002-8422-9229
Maciej Figiel https://orcid.org/0000-0003-3961-4635

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