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REVIEW

The Missing Piece? A Case for Microglia's Prominent Role in the Therapeutic Action of Anesthetics, Ketamine, and Psychedelics

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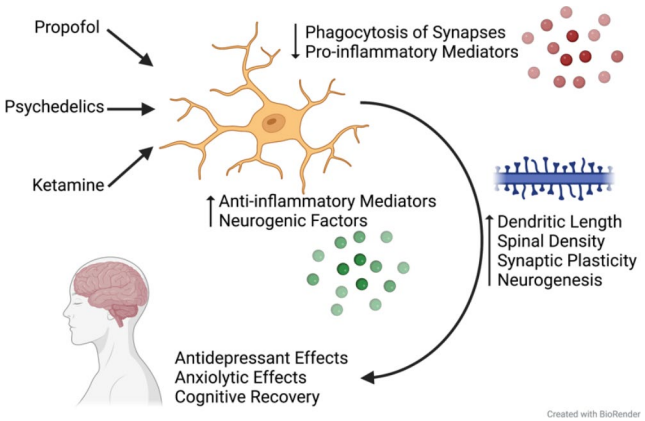
Abstract There is much excitement surrounding recent research of promising, mechanistically novel psychotherapeutics – psychedelic, anesthetic, and dissociative agents – as they have demonstrated surprising efficacy in treating central nervous system (CNS) disorders, such as mood disorders and addiction. However, the mechanisms by which these drugs provide such profound psychological benefits are still to be fully elucidated. Microglia, the CNS's resident innate immune cells, are emerging as a cellular target for psychiatric disorders because of their critical role in regulating neuroplasticity and the inflammatory environment of the brain. The following paper is a review of recent literature surrounding these neuropharmacological therapies and their demonstrated or hypothesized interactions with microglia. Through investigating the mechanism of action of psychedelics, such as psilocybin and lysergic acid diethylamide, ketamine, and propofol, we demonstrate a largely under-investigated role for microglia in much of the emerging research surrounding these pharmacological agents. Among others, we detail sigma-1 receptors, serotonergic and γ-aminobutyric acid signalling, and tryptophan metabolism as pathways through which these agents modulate microglial phagocytic activity and inflammatory mediator release, inducing their therapeutic effects. The current review includes a discussion on future directions in the field of microglial pharmacology and covers bidirectional implications of microglia and these novel pharmacological agents in aging and age-related disease, glial cell heterogeneity, and state-of-the-art methodologies in microglial research.

Graphical Abstract



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Introduction

Challenges in Neuropharmacology

The treatment, prevention, and diagnosis of injuries and disorders of the central nervous system (CNS) remain some of the most difficult challenges for medical and research fields to overcome. Pharmacotherapy is a primary mode of treatment for CNS disorders. Throughout history, numerous agents have been employed to treat and manage brain disorders and injuries with varying degrees of success (reviewed by [1]). This heterogeneity in the outcomes of psychopharmacotherapy stems from several implicit challenges in targeting the CNS. First, the CNS is immensely complicated with billions of neurons and even more non-neuronal cells in constant communication, which makes the identification and specific therapeutic targeting of cells and receptors an arduous process. Furthermore, the brain and body are constantly adapting to factors including age, environment, diet, stress, and hormonal cycles; drug design must take these numerous dynamic variables into account when aiming to induce a specific, desired effect. Additionally, the location and structural barriers of the brain are a natural physiological challenge. The blood-brain barrier (BBB) is an essential protective mechanism but, based on molecular size and chemical composition of the agent, it may present a significant obstacle to effectively delivering pharmaceuticals to the brain [2]. Further, research on the brain comes with inherent limitations, such as imaging capabilities, difficulties in validating translational potential from animal models to humans, and ethical considerations associated with both human and animal research. A large proportion of brain research must also be conducted post-mortem, which may lessen the potential for clinical translation. Finally, in medical research, conscious and unconscious cognitive biases play a large part in clinical outcomes, necessitating stringent means of acquiring objective and quantitative measures [3].

With all this in mind, treating CNS injuries and disorders is an ever-present challenge for pharmacological research, and unsurprisingly the number of available and effective, disease-modifying, pharmacological treatments is small [1]. For example, estimates suggest that up to a third of the adult population will meet clinical criteria for an anxiety disorder at some point during their lifetime [4], while clinically defined depressive disorders such as major depressive disorder (MDD) are a leading cause of global disease burden [5]. Even though pharmacotherapies for MDD and other mood disorders are available (e.g., selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors) as monotherapy or in combination, there are a number of drawbacks, including limited efficacy, side-effects, delayed onset of action (3–4 weeks), and inconsistent compliance due to requirements for daily intake [6, 7]. Despite decades of research, only 1 in 3 patients with MDD achieves remission with current first-line therapies [8], while response rates are higher, reaching 60–85%, for anxiety disorders [9]. As another example, there is a major lack of pharmacological treatment options for mild or severe traumatic brain injury (TBI; [1]). Current options focus on relieving post-concussive symptoms (commonly using antidepressants and anxiolytics) rather than treating the injury itself [10]. In a similar vein, many anti-psychotics used for the treatment of schizophrenia and other psychotic disorders entail debilitating side-effects, high non-adherence rates, and are altogether ineffective in a subset of patients [11]. Likewise, very few, if any, effective pharmacological treatments exist for age-related disorders such as Alzheimer's disease (AD; [12]). Hence, the development of novel pharmacotherapeutics for CNS disorders and the need for personalized medicine is of paramount importance.

Introduction to Microglia and Their Therapeutic Potential

Over recent years, a deep exploration of non-neuronal cells has revealed their critical role in CNS health and disease. Migrating to the CNS from the embryonic yolk sac in early stages of development, microglia are the primary resident immune cells of the CNS [13, 14]. For many years, microglia were described as mediating primarily adverse effects of disease and aging in the brain. However, research in the past two decades [14–17] has since revealed the critical role of microglia in healthy brain function. Microglia are extremely motile cells at steady-state; their processes constantly survey the CNS environment, allowing these cells to rapidly respond to homeostatic perturbations, quickly extending their processes and migrating to sites of injury or infection [15, 16]. Microglia have many complementary roles with astrocytes [18, 19] and are critical to the development of oligodendrocyte progenitors [20, 21], as well as maintain myelination throughout the CNS [22]. There is broad heterogeneity in microglial states across time, space, and environment; microglia display distinct morphologies, gene expression, and ultrastructure that vary between individuals depending on species, sex, region of the CNS, and age, as well as across environmental factors such as diet, sleep, stress, exercise, intestinal microbiome, and pathology [23–28]. Due to their ability to synthesize and release extracellular signalling molecules, such as anti- and pro-inflammatory cytokines, neurotrophic factors, and various enzymes, microglia are highly involved in managing the brain's inflammatory status [29]. Microglia control their CNS environment through multidirectional communication

with nearby neurons and other glial cells, such as astrocytes [30, 31]. Microglia play a critical role in modulating the BBB and neurovascular structures [32, 33] and were shown to actively contribute to establishing and altering the brain's neuronal networks [17, 34–36]. Microglia notably participate in neuronal remodelling through a number of mechanisms, including phagocytosis of whole or partial synapses [37–39] or selective nibbling of synaptic structures (trogocytosis; [40]), altering the extracellular matrix [41], and physically separating pre- and post-synaptic elements in a process called synaptic stripping [42]. In addition to their key role in the removal of synapses, microglia remodel neuronal networks through supporting of synapses and facilitating dendritic growth [43]. For example, Miyamoto and colleagues demonstrated that, in the early postnatal mouse (C57BL/6J) somatosensory cortex, microglia were directly responsible for inducing dendritic spine formation, while mice partially lacking microglia had significantly fewer functional synapses [44]. Moreover, microglia are key player in the synaptic pruning necessary for healthy brain development [45] and are important for the maintenance of synaptic integrity, activity and plasticity, as well as cognitive abilities during adulthood [46]. Given their extensive roles throughout the CNS, microglia were further heavily implicated in cognitive aging [47, 48] and pathogenesis of age-related brain disorders [49–52].

Because of their role in modulating the neuroinflammatory environment and regulating neuronal networks, microglia are emerging as a promising pharmacological target for treating a number of CNS disorders [53] – including mood disorders [54], TBI [55], schizophrenia [56], and neurodegenerative diseases [51]. Because microglial survival is reliant on colony stimulating factor 1 receptor (CSF1R), microglial depletion induced via pharmacology (CSF1R inhibitors, such as PLX3397) or genetic ablation (*Csf1r*-/-), has been investigated as a potential therapeutic approach to treat a range of brain related disorders [57–59]. Overall, while therapeutic effects of temporary and/or partial microglial elimination have been reported in rodent models, either in vivo or in organotypic slice cultures, and this CSF1R inhibition is deemed an effective tool for microglial research, the practicality of microglial elimination remains uncertain in a clinical setting (reviewed by [60]). In addition to impairing microglial physiological functions, this approach is associated with difficulties such as BBB passage, off-target action (e.g., circulating and tissue-specific macrophages, oligodendrocyte precursor cells), resultant immune susceptibility, partial effectiveness, as well as evidence that some distinct microglial states are unaffected by CSF1R inhibition [61–64]. Alternatively, numerous research studies found therapeutic efficacy of the tricyclic antibiotic, minocycline, across a number of disorders, due to its ability to normalize pro-inflammatory action and phagocytosis of microglia [65–70]. Therefore, it has been suggested that the use of pharmacological interventions to shape microglial activity could be a powerful method in discouraging negative effects of these cells, whilst promoting beneficial physiological functions [26].

In this review, we aim to discuss examples from three main categories of emerging pharmacological treatments for CNS disorders: anesthetics, psychedelics, and dissociative agents, focusing on their interactions with microglia. While recent research into these drug-types has uncovered surprising efficacy in treating a range of CNS disorders, there are still many questions relating to the mechanisms by which these drugs induce such powerful effects; microglia appear central in the mechanism, but this has remained largely unexplored. The current inquiry will describe both demonstrated and hypothesized pharmacodynamics involving microglia, and how those downstream effects lead to the neuroplasticity and neuronal regrowth associated with the therapeutic efficacy of these pharmacological agents. Ultimately, we hope this review will aid in the identification and design of novel therapeutic targets and pharmacological options for the treatment of CNS disorders.

Anesthetic Agents

General anesthetics are hypnotic substances that are traditionally used to induce a state of unconsciousness, typically for patients undergoing invasive surgery [71–74]. Commonly used general anesthetics include sevoflurane and isoflurane, which are administered via inhalation, as well as propofol and thiopental, delivered intravenously (IV; [75, 76]). In the current review, we will focus on propofol which represents the general anesthetic of choice for patients undergoing surgery and sedation, and for those in the intensive care unit requiring mechanical ventilation [71, 72, 74]. In fact, propofol has been the most frequently used IV anesthetic for the past three decades [71, 72, 74]. Propofol has a dose-dependent onset of action—typically less than a minute—and is a short-acting anesthetic: a typical induction dose exerts hypnotic effects for about 10 min, but prolonged or repeated administration causes accumulation in peripheral tissues and increases the duration of action [71, 74]. Importantly, general anesthetics are not only effective for the induction and maintenance of reduced consciousness; these medications can also exert anti-inflammatory and neuroprotective outcomes, yielding important implications for the treatment of a large variety of brain diseases and disorders [77–82].

Mechanism of Action

The mechanisms by which general anesthetics exert their effects have yet to be fully elucidated, hence remaining an active area of research [74, 83]. However, it has been determined that, like most general anesthetics, propofol is an agonist for γ-aminobutyric acid type A ($GABA_A$) receptors [72–74, 84]. While propofol's action on $GABA_A$ is primarily researched in the context of neuronal cells, $GABA_A$ is expressed throughout many cell types in the CNS, including microglia [85] and astrocytes [86, 87]. In neuronal cells, propofol binds to postsynaptic $GABA_A$ receptors at the β-subunit, which causes an influx of chloride ions (Cl^-) that hyperpolarize the postsynaptic dendrite [74, 83]. Furthermore, the effects of propofol are highly dose-dependent: at lower concentrations propofol potentiates GABA-induced Cl^- influx, but at higher concentrations it directly activates the Cl^- channel [83].

Critically, neuropharmacological research has identified propofol as an antagonist for the N-methyl-D-aspartate (NMDA) glutamate receptors (primarily investigated on neuronal cells), thereby acting as a CNS depressant through its influence on multiple neurotransmitter systems [88–92]. Specifically, propofol inhibits the influx of calcium ions (Ca^{2+}) resulting from NMDA receptor activation—a mechanism hypothesized to mediate propofol's neuroprotective effects [90]. As elucidated through the investigation of rat (Wistar) primary cortical and striatal neurons, propofol acts by increasing protein phosphatase 2 A activity, which in turn dephosphorylates the NR1 subunit on NMDA receptors [90]. NR1 subunit (de)phosphorylation is a primary mechanism by which NMDA receptors are regulated, however, the details of this mechanism remain incompletely characterized [93, 94]. Kingston and colleagues demonstrated that R1 dephosphorylation inhibits Ca^{2+} influx by measuring intracellular Ca^{2+} levels in rat cortical neurons across treatments with various NMDA receptor ligands and propofol [90]. The hypnotic effects of propofol are more likely attributable to $GABA_A$ receptor action, and less so NMDA, as many studies have shown that inhibition or loss-of-function mutations in $GABA_A$ receptors are sufficient to reverse the propofol-induced unconsciousness in rodent models [95–97].

Clinical Potential of Propofol

Beyond its use in general anesthesia, propofol demonstrates potential in treating a wide array of conditions, including TBI [77, 81], status epilepticus [82, 98], delirium tremens [78, 99], status asthmaticus [100], treatment resistant MDD [101], cerebral ischemia [79, 80, 102], Parkinson's disease (PD; [103]), and AD [104, 105] – to name a few. Propofol exerts anxiolytic, analgesic, anticonvulsant, and amnesic effects, making it a highly versatile medication [71–73]. In virtue of being a general CNS depressant, propofol has shown promise in treating epilepsy, delirium tremens, and status asthmaticus—all conditions which are characterized by hyperactivity in the peripheral and central nervous systems [78, 82, 98–100]. By contrast, propofol's neuroprotective properties are more surprising, and largely involve the various functions of microglia—ranging from microglial release of pro-inflammatory cytokines, to caspase activation and microglia-mediated apoptosis [84, 102, 106–108]. Thus, the next section will discuss propofol as an emerging treatment for TBI, cerebral ischemia, and neurodegenerative diseases and emphasize a central role for microglia in its therapeutic efficacy.

Propofol, Brain Inflammation, and Microglia

The mechanistic pathways underlying propofol's general anti-inflammatory and neuroprotective activities, irrespective of a specific disease context, have been more extensively studied than for many other anesthetics [84, 107–112]. Various studies using primary mouse microglia[1] exposed to lipopolysaccharide (LPS)[2] have identified mechanisms by which propofol influences microglial pro-inflammatory

[1] It is important to highlight limitations of in vitro methodologies as their use is discussed throughout this review and those respective results must be approached with appropriate caution. Cell culture methodologies in neuroscience are a simplified representation of the in vivo brain that allow for specific, controlled investigation of single culture or co-culture of neural cells. However, there are several drawbacks specific to primary microglial cell cultures and immortalized cell lines, such as BV2 microglia. Numerous studies have demonstrated that culturing primary microglia leads to changes in these cells affecting their molecular profile, morphology, ultrastructure, and possibly metabolism (reviewed by [113]). In vivo, microglia are highly respondent to and interwoven with their environment and therefore, growing them in a foreign and impoverished environment likely alters many of their cellular functions. There is also indication that age and sex are critical factors in culturing microglia particularly when used as a model of aging microglia [114]. Research findings investigating exclusively BV2 microglia (and other immortalized microglial cell lines) are not discussed in this review because of growing evidence suggesting their inherent insufficiencies in modeling primary and in vivo microglia [115–118].

[2] LPS is a pathogen associated membrane pattern found on the cell wall of gram negative bacteria that is frequently used in primary cell cultures and rodent models of immune challenges because of its ability to induce a pro-inflammatory environment in the brain[119, 120]. Importantly, LPS is known to activate the pattern recognition receptor, Toll-like receptor (TLR)-4, expressed by microglia [121]. This activation of TLR4 mediates microglial reactivity via the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription factors, resulting in an increased production of pro-inflammatory cytokines, altered morphological characteristics, and exacerbated phagocytic activity across animal models [122]. For these reasons, LPS is a functional model to test a pharmacological agent's ability to impact the brain's inflammatory environment, as discussed throughout the current review.

cytokine production. For example, propofol was found to reduce mRNA expression of genes associated with the NF-κB pathway (e.g., *Ticam1*, *Myd88*, *Irf3*, and *Nfkb1*) in LPS-exposed primary mouse (C57BL/6J) microglial culture—thereby emphasizing the importance of the NF-*κ*B signaling pathway and its influence on microglia [110]. Another study measuring changes in protein expression in primary mouse (C57BL/6J) microglia found that propofol inhibits NF-*κ*B signaling pathways by downregulating the multifunctional enzyme transglutaminase 2 (TGM2), while attenuating the downstream pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β and IL-6 [107]. Additionally, ectopic expression of TGM2 or constitutively active IκB kinase complex β (IKK-β) impaired the anti-inflammatory activity of propofol—implicating the role of TGM2 and IKK-β in influencing NF-*κ*B signalling [107]. Finally, propofol can reduce microglial cytokine production by targeting the miR-221/222 and interferon regulatory factor 2 (IRF2) axis: propofol was shown to downregulate miR-221 and miR-222 expression, which in turn downregulated IRF2 and reduced pro-inflammatory cytokine production in primary mouse (C57BL/6J) microglia [111]. In cumulation, these studies show that propofol's ability to lessen microglial pro-inflammatory cytokine production results from many different cellular pathways participating in its complex mechanism. While further research is warranted, these findings support microglia as an important target of propofol that may contribute to many of the immunomodulatory effects of this widely used anesthetic.

Propofol and Traumatic Brain Injury

Propofol is an effective neuroprotective agent in mouse and rat models of mechanical TBI [77, 81, 123], and a randomized control trial in humans demonstrated that propofol treatment can result in better recovery and reduced mortality rates, relative to morphine, across moderate and severe TBI patients [124]. More recent clinical trials have found propofol to be significantly more effective than sevoflurane in reversing cognitive deficits induced by oxidative stress [125]. With respect to animal models, propofol was found to significantly reduce cellular damage, relative to no treatment, in hippocampal brain slices from 6 to 8 day-old mice (C57BL/6, Charles River) that received acute, focal mechanical trauma [81]. Propofol was found to reduce "total injury" over the entire hippocampal slice as well as "secondary injury" surrounding the primary impact site, in a dose-dependent manner [81]. Another study compared the neuroprotective effects of propofol and thiopental, using whole cell patch-clamp and field recordings from granule cells in rat (Wistar) hippocampal slices, revealing that propofol induced greater survival rates in neurons subjected to dendritic amputation via mechanical incision [77]. Critically, neuroprotective effects were only observed when hippocampal slices were exposed to propofol before or during (but not after) dendritic amputation, and they became increasingly potent with higher propofol concentrations [77]. Of note, the neuroprotective influence of the anesthetics was inhibited when hippocampal slices were exposed to $GABA_A$ receptor antagonists (e.g., picrotoxin, bicuculline) and were mimicked by the $GABA_A$ receptor agonist (muscimol), suggesting that propofol prevented neuronal death by agonizing $GABA_A$ receptors [77].

Using an adult rat (Sprague-Dawley; SD) model of lateral fluid percussion TBI, it was found that propofol treatment reduced neuronal death in the cerebral cortex, but not in the hippocampus nor in the thalamus [126]. This same study revealed that the neuroprotective effects of propofol are largely mediated by microglia, as propofol reduced microglial expression of various cytotoxic compounds and enzymes, including inducible nitric oxide synthase (NOS), nitric oxide (NO), TNF-α, IL-1β, reactive oxygen species (ROS), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [126]. The propofol treatment, compared to isoflurane, caused a significant decrease in "bushy" or ameboid microglial states (large cell bodies and many short processes) that are typically associated with a pro-inflammatory environment [126]. Overall, significantly less microglial-induced neurotoxicity was observed in the cortex of propofol *versus* isoflurane treated rats [126]. Propofol was hypothesized to mediate this effect through upstream inhibition of NADPH oxidase [126], considering that this effector induces a cytotoxic and pro-inflammatory microglial state [127, 128].

It is worth noting that while some studies have found significant neuroprotective effects of propofol [77, 81, 124], other work rejects these conclusions [129] in the context of TBI. This may be due to the nuanced effects of propofol, as higher dosage (intended to model the higher end of clinically utilized propofol concentration or exposure time) of the general anesthetic are cytotoxic to primary mouse (C57, Shanghai Model Organisms Center) microglia in both control and LPS-exposed conditions [110]. Thus, depending on concentration, propofol may not only attenuate LPS-induced microglial activity, but indiscriminately increase apoptosis in microglia as well [110]. This cytotoxicity similarly applies to neurons in neonatal mice, rats, and rhesus monkeys, as large concentrations of propofol significantly increased neuronal apoptosis, reduced spontaneous behavioral activity, and impaired learning assessed using maze completion tasks [130–133] – thus, it has implications in the clinical application of high propofol concentrations for human anesthesia.

Propofol and Cerebral Ischemia

With respect to ischemic stroke, a large amount of evidence suggests that propofol can exert neuroprotective effects [79, 80, 134–136]. For instance, when ischemic strokes are induced in the striatum of conscious rats (adult, Wistar) via local vasoconstriction endothelin injection, propofol significantly reduced infarct size relative to intralipid vehicle control [135]. In this experiment, propofol was effective at reducing brain damage when administered immediately or one hour after the stroke occurred, thus providing evidence that both concurrent and delayed propofol treatment is neuroprotective [135]. At a propofol dose of 25 mg/kg/h administered immediately or delayed (one hour) after injury (endothelin injection), infarct volume was significantly reduced compared to intralipid controls [135]. The benefits of propofol treatment are not limited to focal injuries, as a rat (adult, SD) model of global cerebral ischemia-reperfusion injury revealed that propofol significantly reduces the brain concentration of malondialdehyde (an index of oxidative stress) compared to rats receiving a saline solution [136].

Mechanistically, evidence suggests that the neuroprotective effects and reduced infarct size in rat (adult, Wistar) hippocampi result from propofol's ability to reduce mitochondrial swelling [80], which can cause the organelle to rupture, thereby releasing proapoptotic molecules (e.g., cytochrome C) into the cytoplasm [137, 138]. Furthermore, propofol appears to protect against excitotoxicity associated with cerebral ischemia, as stroke causes excessive glutamate release and dysregulation of glutamate transporters [139]. This implicates the involvement of neurons, astrocytes, oligodendrocytes, microglia and/or endothelial cells forming the BBB, since all these cell types can express glutamate transporters [79, 140–142]. Microglia express the glutamate transporter-1 (GLT1) and glutamate–aspartate transporter (GLAST), increasing their protein expression after brain injury, as notably shown in post-mortem immunohistochemistry studies of humans diagnosed with focal cerebral ischemia [143–145]. However, the application of 3-methyl-glutamate, an inhibitor of GLT1, did not have a measurable effect of propofol's neuroprotective ability in a model of ischemia using rat (Wistar) cortical neuron-glia co-cultures, suggesting that propofol acts primarily on glutamate transporters other than GLT1 [79]. Furthermore, as mentioned, there is extensive evidence suggesting that propofol reduces microglial release of pro-inflammatory cytokines [107, 110–112] and that these cytokines supress the expression and proper functioning of glutamate transporters [146–149]. Thus, propofol may influence microglia directly through GLAST or indirectly via microglial release of cytokines which can disrupt the function of glutamate transporters [150, 151].

There is also evidence suggesting that propofol may exert its neuroprotective effects via caspases, enzymes which modulate a number of microglial activities in addition to cellular apoptosis [102, 104, 106]. Indeed, administration of a non-specific caspase inhibitor was found to reduce lesion size in a rat (adult, SD) model of striatal focal ischemia [102]. Furthermore, pre-treatment with an NMDA antagonist had a synergistic effect and was able to increase the efficacy of the caspase inhibitor treatment [102]. Thus, propofol may be acting via two pathways: by (1) preventing excitotoxicity via its antagonistic action on NMDA receptors [89–91] and (2) controlling microglia-mediated inflammation via caspase activity in rodent models [102, 104, 106]. Indeed, the study by Schulz and colleagues suggests that focal ischemia induces neuronal death via two steps: first by acute exposure to an excitotoxic environment, then by excessively activating caspases [102]. Caspase-3, -7, and -8 have demonstrated ability to regulate microglial-induced apoptosis in neurons via NF-κB signaling across cell cultures and rodent models [106, 152, 153]. Caspase-1, in contrast, promotes the maturation of pro-inflammatory cytokines released from microglia, such as IL-1β, IL-18 and IL-33, demonstrated also in cell cultures and rodent models [154–156]. Thus, global caspase inhibition is widely hypothesized to promote a neuroprotective environment by impairing microglia-induced neurotoxicity and chronic inflammation [106, 154, 156].

Finally, rat (adult, SD) models of cerebral ischemic injury and reperfusion suggest that propofol has an important regulatory influence over connexin 43 (CX43) expression in microglia [157]—CX43 facilitates intercellular communication via gap junction formation [158]. Notably, two models were used: an in vivo middle cerebral artery occlusion model to obtain primary microglia, and an in vitro model in which primary rat (SD) microglia were cultured under glucose free and hypoxic conditions, then reoxygenated [157]. This study found increased microglial production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), microglial upregulation of CX43, increased neuronal expression of Cav3.2, and reduced neuronal expression of microtubule associated protein 2 (MAP2), which caused more frequent neuronal apoptosis [157]. Notably, CX43 upregulation after ischemia is hypothesized to facilitate the spread of cytotoxic molecules (e.g., apoptotic factors, TNF-α, IL-1β), cellular debris, and dying cells into surrounding healthy tissue, thereby exacerbating cellular damage via gap junction signalling [159–161]. Therefore, an upregulation of CX43 in microglia may worsen brain inflammation by means of spreading pro-inflammatory and neurotoxic signals [162, 163]. Furthermore, excessive Ca^{2+} influx from

CaV3.2 channels was shown to contribute to ischemic cytotoxicity by damaging mitochondria [164]. Lastly, MAP2 is an index of synaptic plasticity, as the protein enhances the synthesis of microtubules and is concentrated in dendritic trees [165, 166]. Critically, propofol-treated rats, relative to untreated controls, showed decreased infarct volume and neuronal apoptosis [157]. These results were accompanied by a reduction in pro-inflammatory cytokine levels, CX43 expression, CX43 phosphorylation, and CaV3.2 levels, while MAP2 expression was increased [157]. Thus, propofol appears to reduce the spread of proapoptotic signals and cellular debris in tissue surrounding the primary infarct site (by downregulating CX43), lessen the severity of excitotoxicity (by reducing the number of CaV3.2 channels), and it promotes synaptic plasticity (by increasing MAP2 expression in neurons) largely via interactions with microglia.

Propofol and Neurodegenerative Diseases

AD, defined by pathological accumulation of extracellular amyloid-β plaques and intracellular neurofibrillary tangles, and PD, characterized by atrophy of dopaminergic pathways essential for regulating movement, are common neurodegenerative diseases in which microglia have been extensively investigated as a potential therapeutic target. The propofol-caspase-microglial pathways mentioned earlier have implications for AD and PD treatment [103, 104, 106, 107]. For example, propofol administration was found to improve performance on the Morris water maze task—a common behavioral assessment of spatial navigation—in aged wild type mice (C57BL/6J) as well as in transgenic mouse models of AD pathology (B6.Cg-Tg (APPswe, PSEN1dE9) 85Dbo/J; [104]). Furthermore, both aged wild-type and transgenic mice showed significantly lower levels of caspase-3 and -9 in both cortical and hippocampal tissue, relative to saline-treated controls [104]. Mechanistically, it is hypothesized that propofol protects against mitochondrial dysfunction in cerebral ischemia [80, 104, 164]. Further evidence supporting the previously described hypothesis that propofol acts upon microglia via inhibition of the IKK-β/NF-κB pathways comes from findings that microglial caspase-3 and -8 are significantly more active in the post-mortem frontal cortex of humans with AD, relative to matched controls [106]. These findings provide evidence for a mechanistic link between propofol's action on $GABA_A$ receptors and microglial/caspase pathways perhaps through direct agonism of microglial GABA receptors (see more in Sect. 5.1.4.).

Further support comes from studies of post-mortem brain samples showing that caspase-3 and -8 are significantly more active, as indexed via double immunolabelling and confocal imaging analysis, in the ventral mesencephalon of PD patients relative to age- and sex-matched healthy controls [106]. Caspases associated with inflammation (e.g., caspase-1) may also contribute to propofol's effects on PD, considering that rat (Wistar) models of PD were found to express 16-fold greater IL-1β mRNA levels in the substantia nigra, relative to control rats treated with a vehicle [103]. Indeed, PD may be especially susceptible to microglia-related treatments, as the substantia nigra has one the highest concentrations of microglia among the mammalian brain [167, 168]. Although more research is needed, propofol appears to be a promising avenue for the treatment of age-related disorders, particularly through its impact on microglia.

Introduction to Psychedelics

Psychedelics are agents that substantially modulate sensory perceptions, mood, and cognition [169, 170]. For millennia, humans across diverse geographical and cultural landscapes have made use of psychedelics for ceremonial, medicinal, and recreational purposes [171]. Psychedelics can cause altered visual and auditory perceptions, as well as temporal and spatial awareness, hallucinations, and increases in positive affect [172, 173]. Early clinical trials have highlighted clinical potential for psychedelics in the treatment of depression, anxiety, and other psychiatric disorders. Despite promising initial results, political pressures and shifting cultural values in the mid-20th century prompted the illegalization of psychedelic drugs and a cessation of all associated research in Canada and the United States [170]. Recently, however, psychedelics research has regained momentum, culminating in numerous clinical trials yielding promising results for a range of psychiatric conditions [171, 174].

Psychedelics are traditionally grouped into three broad classes [173, 175]. The tryptamines include psilocybin and its active metabolite psilocin, N,N-dimethyltryptamine (DMT) and its derivative 5-methoxy-DMT (5-MeO-DMT), as well as ibogaine. The second class, called ergolines, comprise lysergic acid diethylamide (LSD) and its derivatives. The third group, psychedelic phenylethylamines, are derivatives of phenylethylamine or amphetamine (α-methylphenylethylamine) and encompass naturally occurring mescaline, as well as synthetic 2,5-dimethoxy-4-methylamphetamine derivatives (DOx compounds), 2C compounds, and 3,4-methylenedioxymethamphetamine (MDMA). Traditionally, classical psychedelics such as psilocybin (through its active metabolite psilocin), DMT, LSD, mescaline and their derivatives are drugs exerting their primary effects through agonism of the serotonin neurotransmitter receptor $5\text{-}HT_{2A}$ considered to be mainly localized on neuronal cells [173, 175]. Compounds such as ibogaine and

MDMA also stimulate 5-HT_{2A}, but exert pleiotropic effects through other receptor interactions and are often classified separately [173, 176–178]. Although some evidence indicates that MDMA may not be hallucinogenic [175], this substance will be discussed as a psychedelic for the purposes of this Review, particularly in light of the large body of evidence highlighting its interactions with the central and peripheral immune systems.

Clinical Potential of Psychedelics

Anxiety and Mood Disorders

In recent years, psychedelics have re-emerged as promising agents for the treatment of conditions ranging from mood disorders to neurodegenerative diseases. A growing body of preclinical research has culminated in two landmark clinical trials showing a significant benefit of psilocybin in terminal cancer patients with related depression or anxiety. Single or multiple doses of psilocybin were efficient in improving clinical depression and anxiety scores, as well as subjective quality of life ratings, with effects persisting for at least six months post-treatment [179, 180]. Psychedelics have continued to show clinical benefits in modern randomized controlled trials, with a recent meta-analysis of 12 clinical trials indicating that treatment with psilocybin, LSD or the plant-derived psychedelic brew ayahuasca can significantly reduce negative mood symptoms in clinically depressed patients, and, remarkably, in healthy volunteers [181]. Importantly, psychedelics tend to require fewer doses than traditional antidepressants such as SSRIs, even demonstrating efficacy after a single administration, and their benefits often manifest more rapidly and persist longer post-treatment [171].

The neurobiological processes underlying the success of psychedelics in treating mood and anxiety disorders remain a topic of intense investigation [177, 182–184]. Animal and human studies have provided insights into some mechanisms underlying the therapeutic actions of psychedelics. Classical psychedelics activate serotonin receptors on neurons throughout all regions of the brain [185]. Serotonin receptors are also expressed on microglia [186–189]; however, the impact of psychedelics on microglia has not yet been directly investigated – but could be central to therapeutic efficacy (see more on this in Sect. 5.1.). 5-HT_{2A} receptor activation in layer V cortical pyramidal neurons is thought to mediate the hallucinogenic effects of psychedelics [185, 190]. The activation of 5-HT_{2A} in post-synaptic neurons increases downstream glutamate release, raising glutamate levels in the brain and leading to increased excitatory neuronal activity through activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), NMDA and mGluR receptors [185, 191–193]. Glutamate-mediated AMPA signalling was shown to augment the release of brain derived neurotrophic factor (BDNF; [194]). Likewise, BDNF release, measured by serum BDNF levels, is acutely and persistently increased in response to a single administration of LSD in human subjects [195, 196]. As impairments in BDNF-mediated neurogenesis are thought to underlie the pathology of depression and anxiety [197–200], psychedelics may thus promote adult neurogenesis and beneficial circuit rewiring in patients with these disorders (see more on microglial BDNF in Sect. 5.1.1.; [182, 184]). In line with this, DMT, psilocin, 2,5-dimethoxy-4-iodoampethamine (DOI), MDMA, LSD, and noribogaine were recently shown to increase neurite growth and dendritic arbour complexity in cultured rat (SD) cortical neurons through a mechanism involving 5-HT_{2A} receptor stimulation, TrkB signalling, and AMPA activation [201, 202]. Further testing with DMT demonstrated its potential to increase dendritic spine growth in the prefrontal cortex (PFC) of adult rats [201]. In addition to glutamate-mediated neurogenesis, attenuation of inflammation and increased synaptic plasticity allowing for rewiring of pathological circuitry are potential mechanisms underlying the benefits of psychedelics in anxiety and mood disorders, which will be discussed further below in the context of other psychiatric conditions.

Addiction and Alcohol Use Disorder

Alcohol use disorder (AUD), as defined by diagnostic statistics manual-5 (DSM-5) criteria, carries a lifetime prevalence of nearly 30% [203]. Psychotherapeutic and behavioral approaches to its treatment can show benefits in a subset of patients, but pharmacological options for AUD are limited [204]. Psychedelics represent a novel and promising approach for the treatment of alcohol-associated addiction. A meta-analysis of clinical trials comprising a total of 536 subjects demonstrated a significant benefit of LSD in reducing alcohol misuse in patients with AUD [205]. Observational evidence also indicates an association of LSD and other psychedelics in promoting the cessation of alcohol consumption by alcohol-dependent patients [206], while clinical trials have similarly shown the capacities of psilocybin and MDMA to enhance the outcomes of psychotherapy in treating AUD [207, 208].

AUD and other substance use disorders are characterized by pathological remodelling of the reward circuit, which is strongly influenced by nearby microglia [209–211], through positive and negative reinforcement of behaviors [204]. Neural circuit remodelling in response to positive stimuli involves neuroplastic changes in neurotransmitters, such as serotonin and dopamine, in the major reward pathways of the brain, comprising striatum, ventral tegmental area

(VTA), and nucleus accumbens [212]. Meanwhile, negative reinforcement mechanisms involve hyperactivation of stress response axes, including changes in corticotropin release [212]. Moreover, long-term alcohol administration in mice (C57BL/6, Guangdong Provincial Laboratory Animal Center; GPLAC) was shown to reduce hippocampal dendritic spine density and synaptic protein expression, while increasing microglia-mediated synaptic elimination [213].

The putative mechanisms for the antidepressant actions of psychedelics may also contribute to their potential in treating addiction. As discussed, glutamate-mediated neuroplasticity may play a key role in rewiring detrimental functional connections within and between specific brain regions while promoting beneficial connections [177, 182]. For instance, systemic administration of the psychedelic ibogaine in an ethanol-addiction model in rats (Long-Evans) increased glial cell-line-derived neurotrophic factor (GDNF) expression in the VTA, correlating with a decreased alcohol preference in two-bottle choice and alcohol self-administration tests [214]. Similarly, psilocybin, LSD and other psychedelics exert neurotrophic effects [201, 202, 215], and thus may act similarly in the context of addiction-reward circuitry. It was also proposed, based on evidence from functional magnetic resonance imaging (fMRI) studies in humans, that psychedelics induce a state of increased brain entropy and relax rigidly held pre-existing beliefs and associated neural connectivity, allowing the brain to revise and reform thoughts, beliefs and behavioral patterns [183, 216]. Notably, patients attribute alcohol use cessation to the subjective psychedelic experience, describing life-changing realizations and highly meaningful cognitive experiences during psychedelic treatment [206], suggesting that increased neuroplasticity in acute psychedelic treatment may promote adaptive rewiring of the brain pathological circuitry through active cognitive processes [183, 184].

Recent neurochemical research has led to the development of non-hallucinogenic analogues of classical psychedelics that demonstrate efficacy in treating animal models of addiction and mood disorders [217, 218]. Specifically, tabernanthalog (TBG), an analogue of the psychedelic ibogaine, does not induce the head-twitch response commonly utilized method to indicate hallucinogenic effects in rodents. Despite this, TBG demonstrated anti-addictive outcomes by reducing heroin and alcohol seeking behavior and reduced depressive-like and anxiety-like behaviors in a chronic unpredictable stress mouse (8 week-old, C57BL/6J) model [217]. These therapeutic effects were correlated with a recovery of structural plasticity and dendritic spine formation in the frontal and somatosensory cortices of these mice, particularly through agonism of 5-HT_{2A} receptors [218]. While these analogues have not yet been tested in clinical studies, this provides evidence that the cellular and molecular activities of psychedelics may be sufficient to induce beneficial therapeutic effects independently of their hallucinogenic effects (reviewed by [219]).

MDMA and PTSD

An estimated 1 in 15 people will develop in their lifetime post-traumatic stress disorder (PTSD), a condition characterized by intrusive re-experiencing of distressing memories secondary to a significant traumatic life event [220]. Symptoms include avoidance behavior, negative affect, and increased reactivity/arousal [221]. Although a substantial proportion of the population is exposed to traumatic experiences during their lifetime, many individuals cope effectively with trauma and display resilience to the effects of stress, and thus only a subset develop PTSD [203]. PTSD occurs in association with impaired fear extinction and a decreased ability to distinguish danger from neutral stimuli [222, 223]. Neurobiologically, PTSD pathogenesis is mediated by synaptic loss among brain regions such as the PFC and hippocampus, increased synaptic density in the nucleus accumbens, and alterations in glutamate and monoamine neurotransmission [222, 224–227]. Microglia are emerging as a therapeutic target in the context of PTSD as they play an important role in modulating the synaptic loss observed in humans suffering from and animal models of PTSD [228–235]. Interestingly, classical anti-depressants, such as SSRIs, also demonstrate clinical benefits in PTSD [236].

The atypical psychedelic MDMA, which is often classified as distinct from the classical psychedelics due to its pleiotropic receptor interactions, affinity for 5-HT_{2A} receptors, and action upon multiple alternative pathways, has generated excitement in the medical community following remarkable successes in clinical trials for PTSD. Recently, in a Phase III trial of 90 PTSD patients, nine MDMA-assisted psychotherapy sessions were found to significantly reduce clinical symptom scores, with benefits persisting at least two months beyond the treatment period [237]. Earlier trials further support the use of MDMA in PTSD psychotherapy, with meta-analyses revealing consistent benefits such as reducing clinical symptoms [238, 239].

MDMA and its active metabolites bind to 5-HT_{2B}, 5-HT_{2C} receptors, trace amino acid receptors (TAARs), adrenergic receptors, and competitively inhibit synaptic monoamine reuptake through their interactions with neuronal dopamine, norepinephrine and serotonin transporters [176, 178]. Increased synaptic serotonin concentrations led to downstream increases in glutamate-mediated excitatory neurotransmission, which, as observed with the classical psychedelics, may result in a neuroplastic rewiring of neuronal connections ([201] see Advances in Microglial

Research Methodology section). In rodents, MDMA ablates fear conditioning by promoting extinction of learned fear reactions to conditioned stimuli [240, 241]. Recent research suggests that this reopens the critical period of social reward learning, enhancing sensitivity to social reward cues via an oxytocin-dependent mechanism [242]. These mechanisms may account for the observed increase in the efficacy of psychotherapy when combined with MDMA treatment, as enhancing social learning could allow to strengthen the essential therapeutic alliance between psychotherapist and patient [242].

Psychedelics, Inflammation, and Microglia

Anti-inflammatory Effects of Classical Psychedelics

Classical psychedelics have been largely reported to exert anti-inflammatory effects [169, 243, 244]. One important mechanism for this phenomenon is linked to 5-HT_{2A} receptor activation. Although serotonin is well-established as a key mediator of peripheral inflammation [169, 245] and stimulates pro-inflammatory cytokine production in human monocytes [246], psychedelics may promote anti-inflammatory effects by stabilizing the 5-HT_{2A} receptor in an alternative conformation that mediates a preferential recruitment of anti-inflammatory downstream signalling molecules [169]. Stimulation of smooth muscle cells with the psychedelics (*R*)-DOI, 2 C-BCB, LSD and lysergic acid 2,4-dimethylzetidide decreased TNF-α production and expression of the leukocyte adhesion molecules ICAM and VCAM [247], which could have implications for preventing loss of BBB integrity, immune cell infiltration, and inflammation. Although more mechanistic evidence is needed, modulating the CNS inflammatory environment through serotonergic receptor ligands likely involves direct binding to microglial serotonergic receptors or indirectly modulating microglial activity and inflammatory signals expression.

The direct effects of classical psychedelics on microglia remain largely undetermined. However, existing literature suggests an anti-inflammatory effect, in line with research on peripheral immune cells [248]. Psychedelics additionally activate the Sigma-1 receptor (S1R), an endoplasmic reticulum-associated molecular chaperone expressed on microglia that controls mitochondrial ATP synthesis through the regulation of calcium signalling [249–251]. The tryptamines DMT and 5-MeO-DMT are endogenous agonists of S1R [252] that were shown to modulate microglial function in various disease contexts (for further discussion of S1R, see Sect. 5.1.2.). In cultured human monocyte-derived macrophages, widely used to model some aspects of microglial biology in vitro, DMT or 5-MeO-DMT decreased the ability of monocyte-derived macrophages to promote the differentiation of pro-inflammatory T-cell subsets [253]. These compounds also inhibited production of the pro-inflammatory cytokines IL-1β, IL-6, IL-8 and TNF-α, while increasing tolerogenic IL-10 [253]. Similarly, DMT decreased pro-inflammatory cytokine expression and promoted expression of IL-10 and BDNF, as well as increased neuronal and astrocyte survival, in rodent models of ischemic stroke [249, 251]. Further research has demonstrated that DMT enhances the survival of monocyte-derived macrophages under hypoxic conditions through S1R-mediated induction of hypoxia-induced factor (HIF)-1α [250]. Increased resistance to hypoxia in microglia could be advantageous in certain pathologies, such as ischemic stroke and TBI, where a lack of brain tissue perfusion is a major cause of cell death. However, it should be noted that HIF-1α is a key inducer of glycolytic metabolism, which is also linked to pro-inflammatory microglial function [254–256]. Thus, further research is necessary to determine whether DMT modulates microglia beneficially across various disease contexts.

Pro-inflammatory Effects of MDMA

Unlike classical psychedelics, MDMA, as well as other synthetic phenylethylamines and higher doses of ibogaine, are typically associated with inflammation and immune cell reactivity [178]. Although MDMA is typically well-tolerated in clinical trials, significant neurotoxicity can result when it is used in unsupervised settings or with uncontrolled dosing [208, 257, 258]. Microglia are important mediators of the pro-inflammatory and neurotoxic effects of MDMA [259], with microglial reactivity, as quantified by isolectin-B_4 immunostaining, proposed to be a specific marker of amphetamine neurotoxicity in microglia [260]. In MDMA-treated rats, microglia were observed to become more abundant in the hippocampus, striatum, hypothalamus, and parietal/frontal cortices, adopting a highly phagocytic state with amoeboid morphology [257, 261, 262]. Treatment with minocycline, a tetracycline antibiotic that normalizes microglia-mediated inflammation [65], attenuated the neurotoxic effects of MDMA in adult Dark Agouti rats [261] and Balb/cAnNCrICrIj mice [262]. Although mechanistic studies are scarce, current evidence suggests that MDMA-induced hyperthermia contributes to microglial-associated neurotoxicity [263, 264]. Furthermore, genetic deletion of the monomeric GTPase Rhes increased microglial reactivity (measured by a significant increase in CD11b immunopositivity) in the mouse (C57BL/6, source unspecified) substantia nigra pars compacta in an age- and sex-dependent manner, suggesting a possible role for G-protein signalling in suppressing MDMA-induced microglial functional transformation [263].

Overall, microglia appear to act as a double-edged sword in the context of psychedelic therapies. Although microglia mediate key beneficial effects of psychedelics on neuroplasticity, neurogenesis, and inflammation – all of which may yield clinical benefits for patients with neuropsychiatric disorders among others – microglia can also exacerbate inflammation and neurotoxicity depending on context. Thus, further research is necessary to unravel the molecular interactions of psychedelics and microglia, as required to develop optimized immune-informed strategies for novel psychedelic therapies.

Introduction to Ketamine

Ketamine is a psychoactive derivative of phencyclidine, synthesized in 1962 by Calvin Stevens [173, 176–178]. Ketamine differs itself from both psychedelics and anesthetics because of its ability to induce a 'dissociative' experience and its distinctive and broad mechanism of action in the CNS [173, 178]. When given at subanesthetic dose in humans, ketamine induces a pronounced alteration in state of mind consisting of hallucinatory state, derealization, depersonalization, synesthesia, altered proprioception, disorganized speech, and blunted affect, comprising a constellation of behavioral phenotypes that have been proposed to resemble schizophrenic psychosis [265–267]. The scientific and broad medical study of ketamine, and other related arylcyclohexylamine dissociative agents, gradually emanated from the initial discovery of ketamine's ability to suppress sensory responses of central neurons through blockade of NMDA receptors in 1983 [268, 269]. Overall, ketamine is a unique and promising dissociative, anaesthetic agent implemented in clinical and research contexts because of its diverse abilities in anesthesia, pain management, and psychiatric disorders (reviewed by [270]).

The psychotherapeutic applications of ketamine in clinical practice have since been investigated for a large number of psychiatric and non-psychiatric conditions (e.g., depression [271], chronic pain [272], insomnia [273], PTSD [274], asthma [275]), either as a monotherapy or in combination with other medications. To date, according to ClinicalTrials.gov, over 500 registered clinical trials have been completed that list ketamine as a drug intervention for the treatment of a broad range of disorders. However, the safety of a prolonged therapeutic usage of ketamine remains inconclusive; in fact, an increasing body of evidence reveals an emergence of memory impairment, depressive tendency, cystitis, gastritis, and liver dysfunction following chronic usage in humans (reviewed by [276]). Additionally, ketamine is a highly addictive and regulated substance – thus, posing a risk of substance abuse (reviewed by [277]). Thus, no definitive judgement has been made yet in regards to its long-term clinical utility as an chronic antidepressant [278, 279].

Ketamine's Mechanism of Action

The neuropharmacological action of ketamine is quite extensive: ketamine is reported to act on the serotonergic, dopaminergic, opioid, cholinergic, and GABA systems in the brain (reviewed by [280]). Ketamine pharmacodynamics largely resemble its precursor phencyclidine, but its quantitative anaesthetic action is shorter in duration and presents reduced psychotomimetic effects (reviewed by [279]). This could be attributed to its pharmacokinetic properties, such as rapid dissolution in hydrophobic and hydrophilic solutions, low protein binding, and quick transfer across the BBB (reviewed by [281]). Importantly, the racemic mixture (R and S enantiomers) of ketamine has been identified in several studies as a key factor in determining its pharmacological activities (reviewed by [278]). The S-enantiomer of ketamine (esketamine) is largely reported to be more potent at the NMDA receptor binding site compared to phencyclidine [282, 283]. It is also known to possess stronger analgesic and anaesthetic effects relative to the R-ketamine [284]. Although the precise molecular and cellular mechanisms underlying anti-depressant and neuroprotective effects of ketamine's enantiomers still remain unclear, R-ketamine has currently demonstrated a superior antidepressant effect with a more tolerable adverse profile than esketamine [285, 286].

Ketamine's primary mechanism of action in the CNS is as a non-competitive antagonist of the phencyclidine binding site inside the Ca^{2+} channel of NMDA receptors; these NMDA receptors are widely distributed at GABAergic interneurons present in spinal, thalamic, and cortical sub-fields [287]. This NMDA receptor blockade results in downstream activation of other glutamate receptors including AMPA receptors [269, 276]. Given that GABA binding to glutamatergic pyramidal neurons decreases glutamate release, the antidepressant effects of ketamine are postulated to result from inhibition of the NMDA receptor co-localized on GABAergic neurons [287, 288], which leads to disinhibition of glutamate release and increased subsequent AMPA receptor activation. AMPA receptor activation subsequently mediates the induction of other signaling pathways, notably through the mammalian target of rapamycin (mTOR), a key molecular target for Ca^{2+}/calmodulin-dependent kinase eukaryotic elongation factor 2 (EEF2) kinase, extracellular signal regulated kinase (ERK) and Akt [289–293]. These joint activations have been linked to altered structural plasticity via increases in the expression of synaptosome proteins, neurotrophic factors, binding elements, and increased

dendritic spine density through the disinhibition of BDNF release [201, 289, 290, 294, 295]. Although less mechanistic information is available for these pathways, the secondary mechanisms occur through ketamine's action on norepinephrine transporter, mu (μ) opioid receptors, serotonin transporter, and S1Rs [269]. Important to this review, ketamine's antidepressant effects are hypothesized to work in combination of NDMA receptor antagonist activity and S1R agonism (more on S1Rs in Sect. 5.1.2.; [296]).

Ketamine and Microglia

In recent years, research findings have indicated a crossroad between the anti-inflammatory mechanisms of ketamine and its rapid antidepressant effects [289, 297–299]. There is evidence that ketamine involves modulation of both the peripheral and central inflammatory milieu through interactions with microglia [299, 300]. Quinolinic acid (QA) is a metabolite of the kynurenine pathway (KP) of tryptophan metabolism primarily produced by microglia that has largely pro-inflammatory effects throughout the CNS via its agonist action on NMDA receptors [301] – mechanistically opposite to ketamine. Experimental and clinical findings indicated that subanaesthetic doses of ketamine induce a shift in the microglial KP of tryptophan metabolism by suppressing QA and increasing kynurenic acid (KA) production [302]. In fact, Verdonk and colleagues found that ketamine decreases the microglial production of plasmatic QA relative to LPS-treated mice (9–11 week-old, C57BL/BJRj), contributing to ketamine's antidepressant effect (more details on the KP metabolism in Sect. 5.1.5. [302, 303]). In another study, LPS treatment led to increased brain levels of QA levels and associated depressive-like behaviors in mice (12 week-old C57BL/6J), while ketamine attenuated behavioral impacts of LPS driven through an increase in AMPA signaling [304].

The impact of ketamine on microglial-associated pro- and anti-inflammatory cytokines has emerged with some mixed results; however, recent research is largely emphasizing ketamine's neuroprotective effects via modulation of microglial cytokine release. In one study, ketamine administration had no significant impact on IL-1β, IL-6, nor BDNF mRNA levels and the therapeutic effect was instead primarily driven through the NDMA receptor blockade [304][3]. Yang and colleagues found that pre-treatment with the esketamine had a significant impact on pro-inflammatory (TNF-α, IL-1β) cytokine and NF-κB expression in the dorsal striatum, but not in the PFC nor anterior cingulate cortex in an adult rat (SD) model of PTSD [305]. On the other hand, Xie and colleagues found that a single-dose of ketamine attenuates depressive-like behaviors in a rat (6–8 week-old, SD) model of neuropathic pain as well as exerts immunomodulatory effects by decreasing serum levels IL-1β and IL-6 in depressive-like animals [306]. Yang and colleagues also found that ketamine reduced IL-1β and IL-6 levels, specifically in the PFC and hippocampus of mature rats (Wistar) and improved performance on the forced swim test [307]. Ketamine protected against LPS-induced increases in TNF-α, IL-1β, and nitrite production in primary rat (Wistar) microglia [308] and TNF-α, but not nitrite, production in primary rat (Wistar) mixed glial cell culture [309]. Administering ketamine (and two active ketamine metabolites) to HMC3 (human microglial cell line) cells identified microglial signal transducer and activation of transcription 3 (STAT3) as an important factor down-regulated in ketamine's immunomodulatory effects [310]. STAT3 is known to regulate inflammatory response within microglia, particularly, as an important transcription mediator for pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β [311–313]. STAT3 is largely inflammatory in the brain parenchyma and has demonstrated interactions with EEF2, a molecule critical to ketamine's anti-depressant effects [314]. Further support for ketamine's ability to modulate the brain's inflammatory environment is from Wang and colleagues who demonstrated that esketamine reduced pro-inflammatory cytokine (TNF-α and IL-6) levels in serum and medial PFC (mPFC) of a mouse (7-week-old, C57BL/6, GPLAC) model of post-operative depression [315]. Esketamine also rescued post-operation associated depressive-like behaviors and NF-κB over-expression in the mPFC [315]. Similar results were found in a chronic restraint stress mouse (mature, Kunming) model: ketamine alleviated increased brain and serum levels of TNF-α, IL-1β, and IL-6 as well as rescued depressive-like behavior, particularly through down-regulation of the TLR4/p38 pathway [316]. There is also evidence that anti-depressant effects of ketamine are dependent on microglia, as partial depletion of microglia in the PFC via a CSF1R inhibitor (PLX3397) also reversed the observed anti-depressant effects of R-ketamine in a chronic social defeat stress (CSDS) mouse (8 week-old, C57BL/6, Japan SLC inc.) model of depression [317]. Specifically, Zhang and colleagues revealed therapeutic efficacy of R-ketamine was dependent on microglial transforming growth factor (TGF)-1β (and its receptors) in the same mouse model [317]. Lastly, when murine TNF-α was injected (via tail-vein) into adult mice (C57BL/6J), ketamine administration successfully alleviated the increased motor dysfunction, decreased necroptosis of HT-22 hippocampal neurons, and reduced quantity of IBA1/CD68

[3] To explain finding no alteration in BDNF mRNA levels post-ketamine administration, Walker and colleagues cite the 6-hour post-treatment measurement time which likely missed the acute increase in BDNF from ketamine administration [304].

double immunopositive microglia – emphasizing ketamine's neuroprotective effects [318].

Recent research has implicated the microglial NOD-like receptor pyrin domain containing protein 3 (NLRP3) inflammasome in the rapid anti-depressant effects of ketamine [319]. The inflammasome, containing NLRP3, a pro-caspase-1 precursor, and apoptosis-associated speck-like protein containing a caspase recruiting domain, is known to trigger caspase-1 which in turns activates IL-1β [320] – often coupling with NF-κB in this process [321]. The NLRP3 inflammasome is highly implicated in MDD because of its increased expression in humans suffering from and rodent models of MDD [320, 322–324]. The NLRP3 inflammasome is also known to modulate autophagic cellular activities (reviewed by [325]). In a chronic restraint stress rat (8 week-old, Wistar-Kyoto) model of depression, blocking microglial autophagic activities with an inhibitor (Baf A1) also blocked ketamine-induced (1) rapid anti-depressant effects, (2) amelioration of increased NLRP3 activation and IL-1β expression in the PFC and hippocampus, and (3) increase in synaptic plasticity markers (BDNF and synaptophysin) also in the PFC and hippocampus [319]. This study, along with others relating to ketamine and propofol, implicate the regulation microglial NLRP3 and associated autophagic activities as critical to their therapeutic effects in the brain [319, 326, 327].

Another mechanism of action involves ketamine's ability to induce the disassembly of perineuronal nets, an extracellular matrix component responsible for neuronal development, synaptic plasticity, and maintenance of the balance between inhibition and excitation, through modulation of microglial activity [328]. Specifically, Venturino and colleagues blocked microglial signalling pathways using a CSF1R inhibitor (PLX5622) and purinergic receptor, G-protein coupled, 12 (P2Y12) blocker (clopidogrel[4]), which both, independently, prevented ketamine-induced disassembly of mature perineuronal nets and associated neuroplasticity in mice (8–12 week-old, C57BL/6J; [328]) – proposing a novel mechanism of ketamine-induced, microglial-dependent neuroplasticity.

Another recent paper isolated the microglial high motility group box 1 (HMGB1)-advanced glycation end products (RAGE) receptor pathway as key to the therapeutic effects of ketamine [327]. Ketamine decreased LPS-induced upregulation of HMGB1 and its translocation into the cytoplasm and rescued LPS-induced depressive-like behaviors in mice (8–10 week-old, C57BL/6, Charles River; [327]). In the same study, ketamine attenuated LPS-induced microglial upregulation of CD68 and downregulation of CD206, as well as significantly decreased LPS-induced heightened mRNA levels of pro-inflammatory mediators (TNF-α, IL-1β, monocyte chemoattractant protein-1, CD16, and CD32) and increased anti-inflammatory mediator mRNA levels (Arg-1, CD206, TGF-β, IL-10, YM-1) in the CA1, CA3, and dentate gyrus regions of the hippocampus – effects dependent on HMGB1-RAGE pathway suppression by ketamine [327]. Strikingly, Wu and colleagues also demonstrated that ketamine can regulate autophagic activity in microglia through the HMGB1-RAGE pathway and is critical to therapeutic effects in mice (8–10 week-old, C57BL/6, Charles River; [327]). This recent finding implicating the HMGB1-RAGE interactions adds to the plethora of potential therapeutic mechanisms of ketamine, driven through its impact on microglia.

Discussion: Investigating the Important Targets of Microglial Pharmacology

Microglia as a Target for Inducing Adult Neurogenesis

The scientific understanding of neurological disorders has evolved over the last decades to integrate research emphasizing the importance of the immune system and the inflammatory environment of the CNS. As microglia are the primary resident immune cells of the CNS and are central to maintaining or altering the brain's inflammatory environment, this has implicated microglia in the maintenance of homeostasis, but also in many CNS disorders and injuries. These findings have emphasized the value of looking at the brain on a more holistic level, integrating neuronal with non-neuronal cells in our understanding of health and disease.

MDD is a prime example of a psychiatric condition whose scientific understanding has changed with further research in neuroimmunology. Although the monoamine theory has been comprehensively investigated in depressed patients and animal models of MDD [330–332], more recently other theories have increasingly received attention, including neuroimmune dysfunction [299]. In this regard, experimental animal studies and post-mortem clinical findings have demonstrated a close association between MDD and microglial pro-inflammatory activity [54, 333–336]. Inflammatory challenges, such as injection of LPS and pathogenic agents, cause depressive-like behaviors in mice [337–339], while treatment with pro-inflammatory cytokines or endotoxin leads to depressive symptoms in humans [340–342]. Conversely, antidepressant treatment can attenuate underlying inflammation [343, 344], while anti-inflammatory agents can ameliorate clinical depression scores [345]. Inflammation may also be a key mediator linking chronic stress to

[4] Clopidogrel is known to disable microglial purinergic signalling via P2Y12 receptor, a signalling pathway that is critical to microglial response to injury and has an important role in neuroplasticity [329].

the development of mood disorders [337, 342, 346]. Under chronic stressful conditions, microglia respond to glucocorticoids and produce pro-inflammatory cytokines, contribute to increased BBB permeability, and recruit peripheral immune cells to the brain parenchyma [54, 337, 346–349]. Increased microglial ionized calcium binding adaptor molecule-1 (IBA1)[5] immunopositivity, thought to indicate a pro-inflammatory microglial state, and increased expression of pro-inflammatory cytokines, have been observed in animal models of MDD [336, 337, 347, 352] and human patients diagnosed with MDD [353]. Specifically, several post-mortem studies have confirmed the existence of excessive central and peripheral concentrations of inflammatory proteins and cytokines such as IL-1β, IL-6, TNF-α, and C-reactive protein in patients with chronic depression [354–356]. Further, the transformation of microglial activity from largely homeostatic and surveying behavior to pro-inflammatory and/or highly phagocytic – a likely result of prolonged immune challenges as well as a combination of contextual susceptibility factors (such as stress, lifestyle, diet, genetics) – are associated with the expression of key surface inflammatory markers such as CD86, major histocompatibility complex-II (MHC-II), and chemokines (e.g., CCL3, CCL7, CCL8, CCL11), as well as correlated with depressive-like behavior [357, 358]. Across rodent and human research, increased microglial density and arborization in stress-susceptible brain regions – such as CA1 and CA3 of the hippocampus, the nucleus accumbens, anterior cingulate, PFC, and mediodorsal thalamus – have been implicated in the pathogenesis of MDD [359–364] and are hypothesized to be involved in suicidal behavior [365].

Additionally, microglial involvement in alcohol dependence is well-supported [366]. Specifically, in AUD and other substance use disorders, microglia contribute to pathological rewiring of the reward circuits through the production of pro-inflammatory cytokines, remodelling of synaptic connections, and prevention of neurogenesis through elevated phagocytosis of neural progenitors [210, 367, 368]. Recent research indicates that microglia also play detrimental roles in transgenic mice (8–16 week-old, *CX3CR1*^{creER} and *iDTR*) subjected to context-specific electric shocks, a model for PTSD, and their genetic or pharmacological ablation using microglia-specific inducible diphtheria toxin susceptibility or modulation with minocycline attenuates pathological behaviors, such as fear context-induced freezing time [232].

Impaired adult neurogenesis of cortical and limbic regions of the brain has been identified as key to many CNS disorders, such as mood disorders [369–371], substance use disorders [372], PTSD [373], and AD [374]. Therefore, a current theory for the quick antidepressant effects and long-term efficacy of both psychedelics and ketamine presumes the drug's ability to promote neurogenesis in specific stress-susceptible brain regions resulting in a rescue of depleted synaptic density [182, 315, 375, 376]. Specifically, regeneration of layer V and II/III frontocortical pyramidal neurons appears crucial for therapeutic efficacy in rodent models [315, 376]. Critically, this neuronal regrowth is directly associated with behavioral improvements, symptom reduction, and sustained therapeutic effects in both human and animal research (reviewed by [375]). In fact, inhibition of neurogenesis through genetic ablation of BDNF abrogates ketamine-mediated improvements in synaptic density and depressive-like behaviors in mice (1–2 month-old, C57BL/6J and *Thy1*-GFP-M; [218]), emphasizing the role of BDNF in this process. Further support to this hypothesis comes from research showing that adult hippocampal neurogenesis is necessary for the beneficial effects of antidepressants, while its inhibition causes depressive-like and anxiety-like behaviors in rodents [199, 200, 377, 378]. For these reasons, drugs with the ability to rescue decreases in synaptic density and dendritic length have been termed 'psychoplastogens' [201, 379]. While most research has focused on the anti-depressant effects of these agents, their 'plastogenic' effects may be implicated and applied to other CNS disorders characterized by corticolimbic neuronal atrophy, such as AD, substance use disorders, TBI, or PD – suggesting a novel therapeutic target. As microglia are key to synaptic remodelling, notably through phagocytic activity, modulate the inflammatory environment, and demonstrate morphological changes and differences in density among key brain regions associated with CNS disorders, we hypothesize that microglia are central to the action of 'psychoplastogenic' drugs. Clear support is found in a recent paper by Wang and colleagues demonstrating that esketamine significantly reduced CD68+/IBA1 + co-expression in the mPFC of a mouse (7 week-old, C57BL/6, GPLAC) model of post-operative depression [315]. On top of the decreases in microglial immunoreactivity for CD68, a marker of phagolysosomal activity, reductions in mPFC dendritic spine density and quantity of parvalbumin-positive neurons as well as depressive-like behaviors were rescued with esketamine treatment [315] – similar neurogenic results were seen using a single-dose of psychedelic substance, psilocybin, in mice (6–8 week-old, C57BL/6J; [376]). Although more research is necessary to elucidate full mechanisms, we hypothesize that the ability of these 'psychoplastogenic' agents to modulate microglial structure and function involves several integrated mechanisms comprising microglial production and release of BDNF, expression

[5] The validity of IBA1 as a specific marker of microglial 'activation' (a term rejected by the field [24]) or reactivity has recently been questioned, and thus results using exclusively IBA1 should be interpreted with appropriate caution[350, 351].

of 5-HT receptors and S1Rs, and direct impacts on KP metabolism. These different mechanisms are summarized in Fig. 1 and will be described in detail below.

Microglial BDNF and its Relevance in Pharmacological Therapy

The neurotrophic factor BDNF is commonly associated with neuronal maintenance and synaptic plasticity. When released into the extracellular space, BDNF binds with high affinity to the tyrosine kinase B (TrkB) receptor (found pre- and post-synaptically) which activates downstream intracellular cascades involving phospholipase-Cγ (PLC-γ), Ras-mitogen activated protein Kinase (MPAK), mTOR, and phosphatidylinositol-3-kinase (PI3K) [380]. The downstream effects of TrkB receptor agonism often create a positive feedback loop on the recipient cell, resulting in increased expression of the transcription factor CREB and synthesis of BDNF [381, 382]. In many CNS disorders (e.g., MDD, AD, PD, stroke) dysregulation of the TrkB/BDNF pathway and decreases in synaptic plasticity and density are central phenotypes (reviewed by [383]). Evidence suggests that BDNF released from microglia is essential to maintaining synaptic plasticity in the brain, particularly in recovery from CNS disorders. A central study by Parkhurst and colleagues demonstrated that microglial BDNF increases TrkB phosphorylation on neurons and that depletion of microglia (using a *CX3CR1*^{CreER} transgenic mouse model) leads to decreased synapse related proteins and glutamatergic signalling [43]. Further, this study demonstrated that BDNF knockout in microglia (1–2 month-old, *CX3CR1*^{CreER}:*BDNF*^{flox} mice) resulted in significant deficits in learning-dependent spine formation and associated behavioral performance over 2 days, without affecting the overall basal level densities of cortical nor hippocampal neurons and synapses [43] – however, this was only measured under homeostatic conditions. Using a similar model (*CX3CR1*^{CreER}:*BDNF*^{flox} mice) under pathological conditions, it was subsequently demonstrated that microglial BDNF is important for hippocampal plasticity during recovery from TBI [384]) as well as recovery of cortical plasticity and reducing pain hypersensitivity in a neuropathic pain model [385]. Further, the release of BDNF from neurons appears to prevent microglial engulfment of mossy fibre synapses in the CA3 of mice (8–12 week, C57BL/6J; [386]). Microglial BDNF production was also shown to regulate GABA release at cortical interneurons, demonstrating the ability of microglia to alter network excitability and cortical functions [35, 387]. Altogether, there is a tight relationship between microglial dynamics (motility, surveillance, phagocytosis), BDNF, and synaptic plasticity.

BDNF, as it is repeatedly found to be an important factor in neuronal regrowth and associated with cognitive and behavioral therapeutic efficacy, is critical for the therapeutic mechanism of the topical pharmacological agents [315, 376]. Building on the neuronal production of BDNF in the CA1 and CA3 of the hippocampus, which contributes to the therapeutic efficacy of ketamine [388], Yao and colleagues demonstrated that ERK-NRBP1-CREB (CREB being a well-established primary transcription factor for BDNF [389]) signalling in microglia is essential to the anti-depressant effects of R-ketamine. In this study, ketamine-induced phosphorylation of the ERK pathway in microglia led to an increased production of BDNF and anti-inflammatory cytokines, while reducing pro-inflammatory cytokines in the mPFC of mice (8 week-old, C57BL/6, Japan SLC inc. [390]). These findings emphasize the importance of ERK-NF-κB signalling in the regulation of microglial BDNF and hence synaptic plasticity [384, 385, 387]. We hypothesize that microglial BDNF is key to the previously proposed mechanisms of psychedelic- and ketamine-induced neuroplasticity [379], which extends to propofol's therapeutic mechanisms of action (see Fig. 1).

Sigma-1 Receptors

As briefly described above, S1Rs are intracellular transmembrane receptors chaperones at the mitochondria-associated membrane (MAM) – specifically the mitochondria-ER interface – that are important for mitochondrial ATP synthesis, intracellular Ca^{2+} homeostasis, and they regulate various cellular functions, including stress response, lipid metabolism, and neuroplasticity [391–393]. As molecular chaperones, S1Rs support the folding of intracellular proteins and can translocate from the MAM to various cellular locations to form heterologous structures with other proteins or receptors, such as NMDA or inositol triphosphate receptors (reviewed by [394]). S1Rs are expressed throughout most CNS cells including neurons, microglia, astrocytes, and oligodendrocytes [391, 395], particularly, but not exclusively, in the hippocampus and PFC of human and rodent brains [396–399]. The S1R has been implicated in a number of CNS disorders including AD [400], Huntington's disease [401], PD [402, 403], mood disorders [404–406], schizophrenia [407], TBI [408, 409], and stroke [410], identifying S1Rs as novel therapeutic targets for a range of conditions. S1R agonism is progressively being investigated for its immunomodulatory role in the CNS, specifically on glial cells [411, 412]. For example, S1R expression is significantly increased following TBI in humans and mice, and CRISPR/Cas9-mediated knockout of S1R in mice (6–8 week-old, C57BL/6, Experimental Animal Laboratories of the Academy of Military Medical Sciences (EALAMMS), Beijing, China) significantly increases ER stress following TBI [413]. Previous findings demonstrated

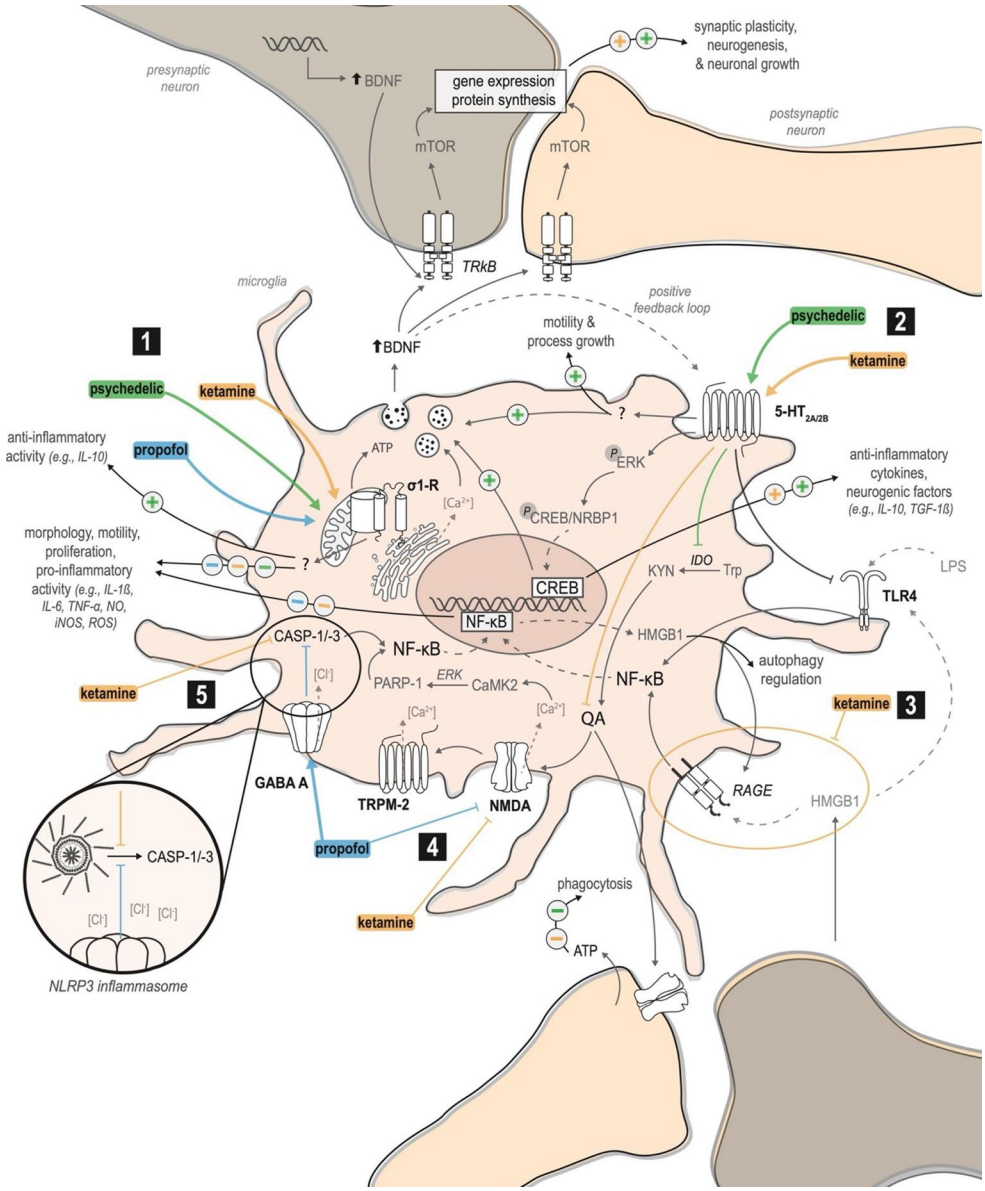

Fig. 1 A summary of the putative intracellular signalling pathways of psychedelics, anaesthetics (e.g., propofol), or ketamine action on microglia. These substances can act as: (1) agonists of a sigma-1 receptor – involved in regulation of microglial inflammatory activity, morphology changes, proliferation, and motility as well as BDNF signalling through several mechanisms including mitochondrial ATP synthesis and calcium signalling; (2) agonists of $5\text{-HT}_{2A/2B}$ receptors – regulating key microglial signalling pathways: (a) positive regulation of microglial motility and process growth; (b) stimulation of ERK/CREB/NRBP1-dependent expression and release of BDNF, as well as anti-inflammatory cytokine or pro-neurogenic factors release; (c) inhibition of kynurenine pathway by acting on IDO or downstream QA – an endogenous agonist of NMDA receptors – hence contributing to inhibition of NF-κB pathway and phagocytic activity; (d) blockade of NF-κB and downstream inflammatory pathway by inhibition of TLR4, a pathogen pattern recognition receptor; (3) inhibitors of microglial HMGB1-RAGE signalling – a key player in control of microglial inflammatory activity as well as autophagy processes; (4) antagonists of NMDA receptor – preventing CaMK2/PARP-1 pathway mediated activation of NF-κB and inflammation; and (5) inhibitors of the caspase cascade activation by NLRP3 inflammasome through acting on $GABA_A$ receptors or unspecified mechanism – blocking the NF-κB and inflammatory pathway activation. $5\text{-HT}_{2A/2B}$ – 5-Hydroxytryptamine/Serotonin receptor 2 A/2B; σ1-R – Sigma-1 receptor; ATP – Adenosine tri-phosphate; BDNF – Brain-derived neurotrophic factor; $[Ca^{2+}]$ – calcium ion; CaMK2 – $^{Ca2+}$/Calmodulin-dependent protein kinase II; CASP-1/-3 – Caspase-1/-3; $[Cl^-]$ – chloride ion; CREB – cAMP-response element binding protein; NRBP1 – Nuclear receptor-binding protein; ERK – Extracellular signal-regulated kinase; $GABA_A$ – γ-Aminobutyric acid type A receptor; HMGB1 – High Mobility Group Box 1; IL-1β – Interleukin 1 beta; IL-6 – Interleukin 6; IL-10 – Interleukin 10; iNOS – inducible Nitric oxide synthase; KYN – Kynurenine; LPS – Lipopolysaccharide; MAPK – Mitogen-activated protein kinase; mTOR – Mechanistic target of rapamycine; NFκB – Nuclear factor kappa B; NLRP3 – NLR family pyrin domain containing 3; NMDA – N-methyl-D-aspartate receptor; NO – nitric oxide; PARP-1 – Poly [ADP-ribose] polymerase 1; QA – Quinolinic acid; RAGE – Receptor for advanced glycation endproducts; ROS – Reactive oxidative species; TLR4 – Toll-like receptor 4; TNF-α – Tumor necrosis factor alpha; TRκB – Tropomyosin receptor kinase B; Trp – Tryptophan; TRPM-2 – Transient receptor potential cation channel subfamily M Member 2. Made with Adobe Illustrator

that immune-activation via LPS treatment in primary rat microglia [121] and chronic stress in rats (adult, SD; [414]) led to downregulation of S1R. Shi and colleagues also observed that agonism of S1R (via PRE-084) was neuroprotective, considerably reducing ER stress, reactive microglia, and microglia-associated pro-inflammatory mediators (e.g., TNF-α, IL-6, iNOS, IL-β) in mice (6–8 week-old, C57BL/6, EALAMMS; [413]). Similar reductions in microglia-mediated inflammation were observed using an S1R agonist (SKF10047) in an adult rat (SD) stress-induced model of hypertension [414]. Alternatively, treatment of mice (CD1, age unspecified) with an S1R antagonist (S1RA or E-52,862/MR309) yielded quicker functional recovery and reduced infarct volume following ischemic stroke compared to vehicle-treated controls [415]. Nevertheless, S1Rs appear to have a central role in neuroprotection and immunomodulation, specifically through altering microglial activity.

The three major drug categories discussed in the current review have been reported to act on the S1R. As discussed earlier, both endogenous and exogenous DMT appear to have neuroprotective effects (increasing anti-inflammatory and decreasing pro-inflammatory cytokines) driven through its agonism of S1Rs on immune cells [249–251, 253]. Additionally, some evidence suggests that propofol is an antagonist of S1R [416]. Using rat (adult, Wistar) brain samples, it was found that propofol causes a reduction in the maximum binding capacity of N-allylnormetazocine, a selective S1R agonist [416]. Further, propofol administration selectively interferes with the effects of another S1R agonist (pentazocine): namely, propofol reduced *c-fos* expression, but not bradykinin-induced intracellular Ca^{2+} concentration, in cells of the posterior cingulate and retrosplenial cortex [416]. Therefore, the immunomodulatory effects of propofol may be partially mediated by the S1R given S1Rs' impact on the neuroimmune environment [402, 411, 417].[6]

There is also evidence that S1Rs may be involved in regulating addiction through the dopaminergic system [420–422], potentially contributing to the reported anti-addictive properties of many psychedelics and ketamine. Therefore, this supports the evidence that microglia play a role in regulating the rewiring of motivational circuits and cognitive structures of addiction [210, 367, 368] and warrants further investigation to provide mechanistic detail. Although more research is needed to fully understand the downstream effects of S1R agonism (and antagonism), psychedelics, propofol, and ketamine have all been reported to act on the S1R and this receptor presents strong evidence of being central to their therapeutic mechanisms, particularly through its impact on microglia. It is important to emphasize that this receptor is ubiquitously expressed in the CNS and further research, isolating S1R and its downstream effects in microglia, is required to fully elucidate the role of microglia in the therapeutic mechanisms of these agents.

5-HT Receptors and Microglia

As discussed, many psychoactive effects of psychedelics are exerted through their interaction with serotonin receptors. While there are seven major categories of serotonergic receptors, the 5-HT_2 receptor subtypes are the best-characterized with respect to the psychopharmacological agents discussed here, particularly psychedelics [423]. Psychoactive and therapeutic effects of psychedelics are driven primarily through 5-HT_{2A} receptors, with a minor contribution of the 5-$HT_{2B/2\,C}$ subtypes [379, 423]. Using RNA extraction and PCR amplification from isolated microglia in early postnatal and adult mice (C57BL/6, source unspecified), Krabbe and colleagues demonstrated the adult expression of multiple serotonin receptors, including 5-$HT_{1A,}$ 5-$HT_{1F,}$ 5-$HT_{2A,}$ 5-$HT_{2B,}$ 5-HT_{2C}, 5-HT_{3B}, 5-$HT_{5A,}$ and 5-HT_7 receptors [189]. Despite wide expression of 5-HT receptors, microglial research has primarily focused on the unique expression of the 5-HT_{2B} receptor, particularly during healthy development, where it plays a critical role [189]. Primary mouse (C57BL/6, source unspecified) microglia from whole-brain [189] and hippocampi [424] of neonatal mice (C57BL/6, Institut du Fer à Moulin) appeared to exclusively express 5-HT_{2B} receptors, suggesting development-related differences in microglial serotonergic receptor expression. There is possibility that 5-HT_{2B} receptor agonism may represent a mechanism underlying therapeutic effect of psychedelics, such as DMT and psilocin [248]. However, there are few investigations of the role of serotonergic signalling on microglia in adulthood. Béchade and colleagues, using 129S2/SvPas mice, demonstrated that 5-HT_{2B} receptor knockout was associated with an increase in LPS-induced brain inflammation and weight loss during development, although the same effect was not observed in adulthood [425]. Similarly, despite 5-HT_{2B} receptor outlined as a therapeutic target for amyotrophic lateral sclerosis (ALS), particularly the 5-HT_{2B} expression on microglia [426], a 5-HT_{2B} receptor agonist (BW723C86) was unable to rescue degenerative effects in an adult mouse model of acute ALS (*Sod1*^{G86R} on FVB/N background [427]). Furthermore, Cameron and colleagues reported the

[6] S1Rs may also mediate the nuanced and dose-dependent effects of propofol (e.g., how propofol transitions from neuroprotective to neurotoxic at high enough concentrations; [416, 418]). For instance, propofol's ability to lessen the binding potential of N-allylnormetazocine to S1Rs occurred in a dose-dependent manner, with a higher anesthetic concentration resulting in greater agonist competition [416]. The neurotoxic effects of high concentrations of general anesthetic are indeed hypothesized to be the result of disrupted intracellular calcium homeostasis, as mediated by S1Rs, thereby activating pro-apoptotic mechanisms [84, 418, 419].

development of psychedelic analogues with agonistic activity on 5-HT_{2A} and with simultaneous antagonistic activity on 5-HT_{2B} receptors [217]. Although analysis of microglial activity was not performed, these novel compounds, while antagonistic for 5-HT_{2B} receptors, were capable of maintaining therapeutic efficacy in treatment of depressive-like behaviors in mice (8 week-old, C57BL/6J; [217]). These findings together suggest that while 5-HT_{2B} receptor agonism may regulate the CNS inflammatory environment and 5-HT_{2B} receptor expression on microglia is critical during development, agonism of this receptor may not be required for the therapeutic effects of psychedelics in the CNS during adulthood.[7] Regardless, assessing location-dependent and developmental differences in expression of 5-HT receptors in neurons and non-neuronal cells will be crucial when investigating their involvement in the therapeutic mechanism of these pharmacological agents. Further work is urgently needed to fully understand possible location-dependent up- and down-regulation of various 5-HT receptors in microglia and other neural cells across the lifespan under homeostatic, inflammatory, and treatment conditions.

There is some evidence that 5-HT receptor agonism on microglia may contribute to the therapeutic effects of psychedelics and ketamine. Glebov and colleagues revealed in primary mouse (C57BL/6J) microglia that serotonin agonism on 5-$HT_{2A/2B/4}$ receptor cause release of microglial exosomes, membranous vesicles that contain various lipids and proteins prepared for extracellular release [187]. Given this, one hypothesis is that 5-HT_{2A} receptor agonism via psychedelics or ketamine on microglia produces a wave of exosome release. While the cargo of these vesicles appears to vary [429] and depends on a number of factors such as localization, age, sex, and particular context of health and disease, if the cargo includes microglial derived neurotrophic factors, such as BDNF or insulin-like growth factor-1, this rapid exosome release could speculatively contribute to the quick neuroplastic effects in synaptic density reported in psychedelic and ketamine treatment. Of note, Krabbe and colleagues did not observe an increase in nitric oxide or cytokine (TNF-α, macrophage inflammatory protein (MIP)-1α, and IL-6) release by primary mouse (C57BL/6, source unspecified) microglia in response to serotonin application [189]. However, the production of anti-inflammatory cytokines or neurotrophic factors was not measured in this study. Importantly, activation of the 5-$HT_{2A/2B}$ receptors has demonstrated an increase in microglial motility, process growth, and decreases in phagocytic activity in primary mouse (C57BL/6, source unspecified) microglia [189] as well as in young (< 1 month-old) and adult (2 month-old) mouse ($CX3CR1^{GFP/+}$) slices of the thalamus [186]. Altogether, evidence supports 5-$HT_{2A/2B}$ receptor agonism as important for regulating microglial activity as well as 5-HT_{2A} being critical to the therapeutic effects of psychedelics and ketamine, while more work is needed to understand the impact of these pharmacological agents on microglial receptors specifically.

Targeting GABA Receptors on Microglia

Another important receptor family found on microglia are GABA receptors, which are particularly implicated in the mechanism of propofol. Microglial expression of both $GABA_A$ (ionotropic subtype) and $GABA_B$ (metabotropic subtype) receptors has been demonstrated across postnatal and adult mice (Naval Medical Research Institute; NMRI; [430]), in primary rat (Wistar) microglia [85], and primary human microglia [431]. Microglial response to GABA signalling is essential during neurodevelopment [432], particularly in shaping the developing inhibitory circuits [433]. In primary rat (Wistar) microglia stimulated with LPS, Kuhn and colleagues demonstrated that a $GABA_B$ receptor agonist (baclofen) attenuates the release of IL-6 and IL-12-p40, without influencing TNF-α or NO levels. By contrast, in LPS-stimulated primary human microglia, Lee and colleagues found that the GABA, $GABA_A$ agonist (muscimol), and baclofen all lead to decreases in microglial TNF-α and IL-6 levels [431]. GABA release from neurons also impacted surveillance and morphology by decreasing process velocity as shown using in vivo imaging of microglia in retinal explants from *CX3CR1*$^{+/GFP}$ mice [434]. There is evidence that GABA, dependent on concentration and exposure time, can induce an inflammatory reaction by microglia – echoing similar findings as propofol. Lang and colleagues demonstrated that sustained GABA response from a cold exposure stress mouse (6-week-old, C57BL/6, Experimental Animal Center of Vital River, Beijing) model was essential to inducing the inflammatory reaction (measured via expression of IL-1β and IBA1 in Western blot and immunofluorescence; [435]). Additionally, there is some indication that GABA activity increases microglial ROS in primary rat (SD) microglia [436] and MIP-1β production in postnatal and adult mouse (NMRI) brain [430]. To our knowledge, no studies have investigated propofol's impact on microglial GABA channels; however, given its $GABA_A$ agonistic

[7] However, it is often the case that molecules or proteins expressed abundantly in development with corresponding low levels in adulthood are upregulated in disease states or in exposure to environmental risk factors – TREM2, TAM kinases, and the complement pathway in microglia are exemplars of this trend[27, 428]. Given this pattern appears to apply to its expression in microglia, 5-HT_{2B} receptors may yet play an important role in therapeutic efficacy of 5-HT ligands in the brain. It could be hypothesized that if 5-HT_{2B} is found to be of higher expression in certain diseased states, it may be that the antagonist activity on 5-HT_{2B} receptors (demonstrated with TBG [217]) may contribute to the therapeutics effects of agonistic 5-HT_{2A} receptor activity.

activity, we would expect this mechanism to contribute to propofol's anti-inflammatory activity at low concentrations.

Targeting the Kynurenine Pathway Through Microglia

As briefly mentioned above, tryptophan is an amino acid whose metabolism is critical to the functioning of a healthy CNS as a precursor for necessary psychoactive metabolites, such as serotonin, melatonin, and KA (reviewed by [437]). Specifically, the KP of tryptophan metabolism results in a number of downstream metabolites, including QA, KA, picolinic acid, and nicotinamide adenine dinucleotide (NAD^+), with a range of actions in the CNS (reviewed by [438]). Tryptophan metabolism homeostasis is strongly implicated in health and diseases of the CNS; including the pathology of AD [439], mood disorders [440], schizophrenia [441], and PD [442]. Depletion of serotonin during CNS inflammation is associated with increased tryptophan catabolism (via the KP) to kynurenine (KYN), QA, and KA, and may contribute to depressive symptomatology [443, 444]. Clinical evidence suggests that elevated serum QA and KA can be used as biomarkers of depression severity [445, 446]. At steady state, brain KP metabolism occurs primarily in astrocytes [447]; however, under conditions of immune challenges or brain disorders associated with a disruption to the inflammatory balance of the brain, such as MDD or TBI, microglia can modulate KP metabolism by preferentially generating certain metabolites [301, 302]. For example, under conditions of acute and chronic immune activation, such as chronic LPS or pro-inflammatory cytokine (TNF-α or IL-6) exposure, microglia increase the expression of indoleamine 2,3-dioxygenase (IDO) which promotes elevated production of QA [300, 448]. Critical to its downstream effects, QA is a powerful NMDA agonist which can mediate glutamatergic hyperactivity [300, 449]. Kubesova and colleagues found increased serum levels of QA and other KP metabolites in an early postnatal, LPS-induced rat (Wister/Hann) model of depression compared to controls [450]. These elevated QA levels correlated with reduced hippocampal volume, increased astrogliosis, and decreased dopaminergic neurons in the substantia nigra pars compacta (implicated in the pathogenesis of PD; [450]). Steiner and colleagues also demonstrated in human brain tissue that increases in microglial production of QA[8] were correlated to atrophy of subregions of the anterior cingulate cortex and increased depressive severity [360]. Interestingly, Busse and colleagues examined post-suicide human brain tissue and found a reduction in microglial production of QA in the CA1/2/3 regions of the hippocampus without corresponding changes in hippocampal size. The authors proposed that this contrasting finding may have resulted from possible compensatory neuroprotective mechanisms, an insufficient sample size, variation in disease state severity and/or region-specific differences in microglial metabolism [451]. The dysregulation of KP metabolism was identified as a prominent mechanism underlying CNS inflammation-induced upregulation of glutamatergic neurotransmission, particularly through agonistic binding of QA to NMDA receptors impacting synaptic plasticity [332, 452]. Taken together, this research supports the neuroplasticity hypothesis of depression and other CNS disorders, providing mechanistic evidence for the perturbed neuroplasticity and decreases in dendritic spine density commonly observed in patients with MDD and animal models of depression [451, 453, 454].

It is hypothesized that one of the mechanisms of action for these pharmacological agents is by altering KP metabolism, likely through targeting microglial production of QA. In support, Verdonk and colleagues demonstrated that ketamine decreased microglial production of QA compared to vehicle in a LPS-induced mouse (9–11 week-old, C57BL/BJRj) model of depression [302]. Further, ketamine rescued LPS-induced depressive-like behaviors, decreased brain-wide levels of pro-inflammatory cytokines (IL-1α, IL-6 and TNF-α) and altered microglial morphological characteristics (decreasing cell body area and increasing ramification significantly in the mPFC, but non-significantly in the hippocampus) in the same mice. From a mechanistic point of view, Lisak and colleagues found that ANAVEX2-73 and other S1R agonists were neuroprotective against the effects of QA, citing S1R's ability to manage the microglial response to immune challenges [455]. Additionally, it was demonstrated that injection of QA inhibits the DOI-induced hallucinogenic-like state, assessed based on the head twitch reflex of MF1 mice in a dose-dependent manner [456]. This mechanism was not mediated through direct or indirect antagonism of $5\text{-}HT_{2A}$ receptors as ligand binding assays demonstrated no interaction between QA and $5\text{-}HT_{2A}$ receptors [456], emphasizing that QA must disrupt the downstream effects of $5\text{-}HT_{2A}$ receptor agonism through alternative mechanisms. The NMDA receptor agonism of QA appears to be the most likely an alternative mechanism; QA is known to increase oxidative stress [457] and disrupt cytoskeletal elements in neurons and astrocytes [458] which likely play into QA's ability to perturb downstream effects of $5\text{-}HT_{2A}$ receptor agonism. As discussed previously, S1R agonism is implicated in NMDA receptor activity and synaptic plasticity (reviewed by [459]). Also important to this mechanism, KA, an alternative metabolite of KP metabolism, is an uncompetitive antagonist of the NMDA receptor

[8] In research by Steiner and colleagues and Busse and colleagues, all cells immune-positive for QA were classified and analyzed[360, 451] – in both cases, QA immunoreactivity was exclusively found around microglia and vascular monocytes.

[438]; similar to the antagonist NMDA receptor activity of propofol (see more in Sect. 2.2.1.). Generally, QA and KA work in opposition of each other; in fact, low KA/QA blood serum ratios are suggested as a predictor of depression severity in humans [460] in addition to predicting ketamine response in treatment-resistant depression [302]. Overall, the impact of KA and QA on the NMDA receptor is central to synaptic plasticity and is heavily implicated in MDD (reviewed by [461]). Although more research is needed to fully elucidate, with mechanistic insight, the spatiotemporal relationship between depressive symptoms, alterations in synaptic density and plasticity, QA production, microglial structure/function, and changes in the CNS inflammatory environment, one potential mechanism of psychedelics, ketamine, and propofol is their ability to modulate microglial impacts on KP of metabolism in the brain parenchyma.

Future Directions in Microglial Pharmacology

Glial Heterogeneity and Communication

Overall, this review has primarily focused on microglia and their importance in neuropharmacology in the context of existing as well as emerging therapeutic strategies. However, despite the progression of research during the last decades within the field of microglia, much remains unknown. For example, there is a growing abundance of research pointing to a number of heterogenous states within microglial populations in human and rodent brains, such as disease-associated (DAMs) and dark microglia, differentiated based on their expression and transcriptomic profile, localization, morphology, ultrastructure, as well as disease specificity [462–464]. It is likely that certain microglial states may be of greater or lesser relevance as pharmacological targets due to their differential expression of key molecules, such as membrane proteins. For example, dark microglia tend to downregulate expression of IBA1, CX3CR1, and purinergic receptor P2Y, G-protein coupled, 12 (P2RY12) while strongly upregulating CD11b, compared to homeostatic microglia [27, 462]; therefore, pharmacologically targeting microglia via the P2RY12 receptor may not be an effective method for targeting dark microglia. Specific to the current review, single-cell RNA sequencing data from Keren-Shaul and colleagues suggest a slight upregulation (~0.6-fold increase) of S1R in disease-associated microglia compared to homeostatic microglia in an ALS mouse (C57BL/6-SJL background) model [463] – suggesting that treatment with S1R agonists may preferentially target this transcriptomic state and may lead to further therapeutic efficacy of these drugs in ALS. Overall, differences in BDNF synthesis, 5-HT receptor and S1R expression, and preferential impact on KP metabolism (to be elucidated across sub-populations and states of microglia) might impact pharmacological treatment efficacy. Distinguishing how heterogenous glial states might enhance, attenuate, or prevent the therapeutic efficacy of emerging pharmacotherapies is a future challenge in the fields of microglial biology and pharmacology.

While the role of astrocytes was not a focus in the current review, there is evidence pointing to their role in the therapeutic effect of ketamine [465], psychedelics [466], and anesthetics [467, 468], as well. Therefore, another critical step toward fully understanding the pharmacodynamics of these novel therapeutics is developing a deeper understanding of glia-glia and neuron-glia communication which highlights the critical impact of the local intercellular communication on pharmacodynamics. Researchers in the astrocyte and microglia fields continue to emphasize the importance of glial cell crosstalk in the maintenance of health and the progression of psychiatric disorders [469], neurodegenerative conditions [470, 471], and brain injury [472]. An important future challenge is to determine how research from multiple fields (e.g., microglia, astrocytes, neurovasculature) may be integrated to achieve a more complete understanding of drug effects in the CNS.

Psychedelic and Anesthetic Implications in Aging and Neurodegenerative Disorders

The 'plastogenic' effects of pharmacological agents covered in this review, perhaps unsurprisingly, have been suggested to disrupt the aging process in the CNS [84, 473] and these agents are suggested to influence the progression of age-related disorders [248]. Microglia among other glial cells are highly implicated in the aging process of the CNS [474]; in fact, as the brain ages, microglia respond more acutely to inflammatory challenges, adopting a "primed" microglial state [475]. Keane and colleagues emphasized microglial mTOR as upregulated in the aging process and highlighted the difference in outcomes of mTOR activation across the lifespan (using aged C57BL/6J mice; [476]). As mTOR is highly implicated in underlying the 'psychoplastogenic' effects of drugs like psychedelics [379], when investigating these drugs for anti-aging effects, a focus on their impact on microglia is pertinent. Overall, however, there are obstacles in generating adequate models for investigating aging microglia and fully elucidating their role in neurodegeneration, such as difficulties in obtaining aged animals, as well as expenses and time associated with aging animals. Accelerating the aging of primary microglial cultures and other in vitro models was also mostly unsuccessful [477].

There is some limited evidence that agonists of 5-HT_{2A} (psychedelics, ketamine) may be detrimental in AD. Previously, 5-HT_2 receptor agonism has been implicated in AD pathogenesis [478]. Two recent studies demonstrated that

antagonism or inverse agonism of the 5-HT_{2A} receptors reduces Aβ pathology in APP/PS1 mice. Yuede and colleagues utilized 5-HT_{2A} receptor inverse agonist, Pimavanserin, to demonstrate reduction of interstitial fluid levels of Aβ by 50% within hours in aged APP/PS1 mice (C3H/B6 background) – an effect that was dependent on 5-HT_{2A} receptors and sustained with chronic (4 months) treatment [479]. Chronic Pimavanserin treatment also reduced Aβ aggregation in post-mortem immunohistochemical examination and improved anxiety-like behaviors and cognitive function deficits of aged APP/PS1 mice [479]. Interestingly, downstream activation of NMDA receptor/ERK pathway to activate α-secretase was found to be necessary for 5-HT_{2A} suppression of Aβ [479]. To our knowledge, no research has investigated the impact of Pimavanserin on microglia. Along similar lines, Lu and colleagues found that an antiallergic drug (desloratadine; DLT), with demonstrated selective 5-HT_{2A} receptor antagonism, was therapeutic in aged APP/PS1 mice (B6C3F1 background) via reducing Aβ plaque burden, upregulating microglial expression of TLR2/4, and increasing their phagocytosis [188]. DLT also improved short-term working memory, spatial working memory and learning, and long-term memory tests on APP/PS1 mice, as well as promoted synaptic integrity and induced plasticity in the CA1 of the hippocampus [188]. Mechanistically, DLT antagonism of 5-HT_{2A} reduced Aβ driven inflammation in aged APP/PS1 mice, through suppressing the NLRP3 inflammasome and NF-κB, while 5-HT_{2A}/cyclic adenosine monophosphate (cAMP)/phosphate kinase A (PKA)/CREB/glucocorticoid receptor (GR) was critical to microglial upregulation of TLR2/4 which was also required for increased phagocytosis of Aβ [188]. While neither of these studies investigated the impact of a 5-HT_{2A} receptor agonist in their models, both provide evidence that antagonist activity on these receptors is therapeutic in aged APP/PS1 mice, hence agonism may be detrimental in the context of AD and other age-related disorders.[9]

The KP pathway of tryptophan metabolism is particularly associated with aging and age-related diseases, specifically because of its production of NAD^+ and impact on mitochondria (reviewed by [485]). Mitochondrial dysfunction (e.g., production of ROS, mutations to mitochondrial DNA, structural deterioration and changes in energy production) tends to increase with age [486]. It is suggested that NAD^+ helps protect mitochondria from age-related dysfunction, which was mostly explored in animal models [487–489]. Additionally, QA, which is one of the primary metabolites of tryptophan metabolism, increased tau phosphorylation (leading to the neurofibrillary tangles, a hallmark of age-related degenerative disease) in primary fetal human neuron culture [490] and impaired learning and memory in a rat (Wistar) pup model of lead-induced neurotoxicity [491]. Aβ plaques were shown to increase microglial production of QA [449] and QA's downstream effects (e.g., increases in ROS production and pro-inflammatory cytokine release), thus creating a positive-feedback loop that contributes to the multifaceted cascade of neurodegeneration. For details on propofol's neuroprotective role in neurodegenerative disease, see Sect. 2.2.4.

In a mouse (C57BL/6, source unspecified) Aβ oligomer-injection model of AD pathology, the non-psychedelic selective S1R agonist PRE-084 further promoted neurogenesis by stimulating the proliferation of hippocampal neuronal progenitor cells and attenuated astrogliosis [492]. Treatment of PRE-084 or DMT did provide a significant decrease in microglial density in the hippocampus; however, IBA1

[9] While both studies investigated the effect of 5-HT_{2A} receptor antagonism in an AD mouse model (APP/PS1), with appropriate caution, more mechanistic detail on the role of 5-HT_{2A} receptor agonism on microglia can be extrapolated from these findings across different disease conditions. Firstly, antagonism of 5-HT_{2A} receptors upregulated TLR2/4 levels on microglia and increased phagocytic activity in aged APP/PS1 mice [188]) – this supports reverse hypotheses that agonism of these receptors would decrease phagocytosis, likely through suppression of the same 5-HT_{2A}/cAMP/PKA/CREB/GR pathway. TLR4 has been highly implicated in depression [480, 481] and is one of the primary targets of LPS which induces microglial phagocytic activity, production of inflammatory cytokines, and depressive-like behaviors in mouse models [121]. On the other hand, TLR2s effects seem to be more mixed [482, 483], and it has even been suggested to work in opposition to TLR4 in regulating mood-related response to stress [482] – emphasizing the need to measure TLR2 and TLR4 levels separately. Given the association between TLR4 levels and depression, it would be unsurprising to find that 5-HT_{2A} receptor agonism would lead to the downregulation of TLR4 on microglia as part of the psychedelic and ketamine therapeutic mechanism of action, thus reducing production of microglial pro-inflammatory cytokines and phagocytosis. Secondly, 5-HT_{2A} receptor inverse agonism relied upon downstream NMDA receptor activity and ERK to increase α-secretase (an enzyme that cleaves amyloid precursor proteins) activity – inhibition of NMDA receptor activity reversed therapeutic efficacy of Pimavanserin in the context of AD pathology [479]. However, in the case of MDD pathology (e.g., decreases in cortical spinal density), reducing microglial phagocytic activity would be more desirable, emphasizing our previous hypotheses that inhibiting NMDA receptor activity is key to dampening microglial pro-inflammatory response [484] and is one of the central therapeutic mechanisms of psychedelic and anesthetic agents – citing ketamine's ability decreasing microglia QA release and propofol's antagonist activity on NMDA receptor, for example. Overall, these findings provide novel evidence demonstrating the nuanced nature of functional changes in microglia across disease states and health. As an example, in an AD pathology mouse model, an increase in phagocytic activity provides therapeutic relief by increased phagocytic engulfment of Aβ therefore, antagonist activity on 5-HT_{2A} receptor is emerging as a new therapeutic target for AD [188, 479]. But in depressive disorders, a decrease in phagocytic activity instead is therapeutic and hypothesized to be driven by 5-HT_{2A} receptor agonism in the context of psychedelics and ketamine. Altogether, these findings emphasize the importance of further research into microglial 5-HT receptors because of their apparent ability to regulate cellular activity and their emerging role as a therapeutic target across several CNS disorders.

immunostaining only was used to assess microglial inflammatory status [492]. Further analysis of microglial morphology or changes in other immunomarkers (e.g., CD68, Cd11b) may provide additional valuable understanding of microglial activity following this treatment. It can be hypothesized that psychedelic S1R agonists could simultaneously promote hippocampal neurogenesis and reduce inflammation, thus improving the pathology of depression, anxiety, substance use and related disorders. However, other findings from the same study provide a note of caution: although direct injection of DMT (without Aβ oligomer-injection) decreased inflammation and microglial density, DMT also impaired hippocampal neurogenesis. The authors speculated that this detrimental effect was mediated through 5-HT_{2A} receptor stimulation of DMT, as PRE-084 mediated pro-neurogenic as well as anti-inflammatory effects [492]. Thus, although DMT and other psychedelics may enhance the treatment of psychiatric disorders by increasing BDNF, promoting neurogenesis and modulating inflammation, further research is necessary to differentiate their molecular mechanisms of action with regard to microglia, and potentially to develop compounds or strategies for modulating microglial function in a more specific manner. Overall, the role of psychedelics, anesthetics, and ketamine in reducing microglial QA production support their proposed neuroprotective and anti-aging effects. While the complex relationship between the 'psychoplastogens', microglia, and aging is still largely unexplored, we hypothesize that as these drugs continue to be investigated for their anti-aging and pro-cognitive effects in the future, their modulation of microglial function will emerge as a central mechanism.

Advances in Microglial Research Methodology

As the importance of microglia in neuropharmacological research and future therapeutic options continue to grow in recognition, accurate and effective research methods and techniques for studying microglia are crucial. As an important note in microglial research methodology, anesthetics and ketamine are commonly used in the euthanasia process in animal research and is a factor to keep in mind when studying minute changes in the CNS, post-mortem. It is likely that, given the immediate, established effects of these drugs on microglia, there will be a swift change in cellular activity induced by these drugs which may have an impact on the morphology, location, gene expression, and inflammatory status of these cells and surrounding tissue which may confound some research findings. One example of this, Venturino and colleagues demonstrated that treatment with the ketamine/xylazine/phenothiazine tranquilizer acepromazine led to an immediate, significant increase in colocalization of perineuronal nets with microglia, and a further significant increase after 20 min in mice (8–12 week-old, C57BL/6J; [328]). To further characterize these effects, Hristovska and colleagues demonstrated that a ketamine/xylazine protocol enacted an extensive reduction in microglial morphological process complexity and both ketamine/xylazine and pentobarbital significantly reduced microglial motility in frontal cortex and hippocampus of mice (6–10 week-old, CX3CR1$^{eGFP(+/-)}$) – further questioning the functional utility of ketamine as an anesthetic in microglial research methodologies [493].

Promising research is emerging from single-cell RNA sequencing and other 'omics techniques, allowing for the establishment of microglial states based on the gene expression profile of each individual cell [23, 28, 464, 494, 495]. This method will allow for the differentiation of microglial subtypes and differential changes in gene expression pre- and post-drug treatment, potentially allowing for identification of the precise biological mechanisms mediated by these therapeutics. Another technique applied to further classify microglia is electron microscopy, which provides cellular and sub-cellular analysis of phenotypic expression, organelles, and visualization of microglial states via morphology, cellular contacts, cytosol density, and others [25, 496]. Put together, single-cell RNA sequencing and other 'omics techniques combined with electron microscopy (particularly via advanced immunohistochemical staining and three-dimensional ultrastructural imaging) can bring the field closer to understanding microglial functional dynamics at steady-state and the effects of pharmacological interventions. Overall, technical advancements made in microglial research will accelerate pharmacological research looking to target microglia in order to influence the brain's immune status and neuronal plasticity throughout the CNS.

Altogether, this review emphasizes the importance of investigating the involvement of microglia in neuropharmacology and has outlined several demonstrated or theoretical pathways of microglial pharmacology that can be leveraged in developing novel drug therapies for a wide variety of CNS disorders.

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Declarations

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