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Microglia in drug addiction: A perspective from neuroimmunopharmacology

Drug addiction refers to a state of dependence that arises from habitual drug intake and can result in specific withdrawal symptoms upon cessation. The most commonly abused substances include psychostimulants, cannabinoids, and opioids. When drugs are consumed, they stimulate the release of dopamine, a neurotransmitter crucial for the pleasure and reward centers of the brain. With repeated drug use, the brain undergoes various changes, leading to tolerance, dependence, and addiction (Lüscher et al., 2020). The mechanisms involved in drug addiction are highly complex and involve diverse cell types within the brain.

As important immune cells of the central nervous system (CNS), microglia play a significant role in drug addiction progression. When exposed to drugs and other insults, microglia are activated and release pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS). These inflammatory mediators down-regulate the expression of glutamate transporters and γ-aminobutyric acid (GABA) receptors, while up-regulating the expression and functionality of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and N-methyl-D-aspartic acid (NMDA) receptors (Limón et al., 2021) (Figure 1A). Furthermore, they enhance the release of neurotransmitters and synaptic transmission, leading to an increase in neuronal excitability at multiple sites within the circuitry implicated in substance abuse. Such alterations play a pivotal role in the development of various neuropathological aspects associated with drug abuse, including neuronal toxicity, synaptic dysfunction, and emergence of addictive behaviors.

Consequently, the “xenobiotic hypothesis” of drug addiction has been proposed, positing that substance abuse involves the introduction of exogenous (foreign) molecules, which are recognized by the innate immune system within the CNS. This recognition triggers neuroinflammatory responses, which subsequently contribute to the development and persistence of drug addiction.

Chronic abuse of drugs, such as opioids, cocaine, and methamphetamine, can activate microglia, resident immune cells in the brain, via Toll-like receptor 4 (TLR4) (Wang et al., 2020). This activation triggers the production of cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), as well as ROS and reactive nitrogen species (RNS), leading to neuroinflammation, disruption of normal brain homeostasis, and damage to neurons and glial cells.

Activated microglia can also release chemokines, including monocyte chemoattractant protein-1 (MCP-1), which attract immune cells from the periphery to the CNS, thereby exacerbating neuroinflammation (Squillace & Salvemini, 2022). Moreover, chronic drug abuse can induce microglial priming, where microglia become hypersensitive to subsequent stimuli, leading to exaggerated responses to further insults. This priming effect may contribute to the persistent neuroinflammation observed in drug abuse-induced neuroinflammation.

Prolonged exposure to drugs can result in inflammation within the brain and other tissues, as evidenced by increased levels of inflammatory markers in individuals with substance use disorders. Animal studies have demonstrated that inhibition of inflammatory responses can diminish drug-seeking behavior, highlighting the role of microglial activation in the initiation and perpetuation of drug addiction. Consequently, targeting microglia and their activation presents a potential therapeutic approach for mitigating drug addiction and associated neuroinflammatory disorders.

One such strategy includes the inhibition of drug-induced microglial activation and neuroinflammation by targeting specific receptors and signaling pathways involved in microglial immune responses. For example, inhibiting the signaling of TLR4, which is implicated in microglial activation induced by drug abuse, has shown potential in reducing neuroinflammation and the behavioral effects associated with drug addiction (Figure 1B). TLR4 antagonists with good blood-brain barrier (BBB) permeability, such as (+)-naloxone and (+)-naltrexone (Wang et al., 2016), have demonstrated the ability to reduce neuroinflammation and curb drug cravings in animal models of drug abuse, including alcohol, opioids, cocaine, and methamphetamine.

Additionally, the depletion of microglia through pharmacological methods has emerged as a potential therapy for drug addiction treatment. The colony-stimulating factor 1 receptor (CSF1R) plays a role in regulating the proliferation, differentiation, and function of microglia via its ligand CSF1. CSF1 is responsible for maintaining microglial homeostasis and facilitating their activation in response to inflammatory signals. The highly effective pharmacological tool PLX5622 (Figure 1B) has been shown to inhibit CSF1R, leading to

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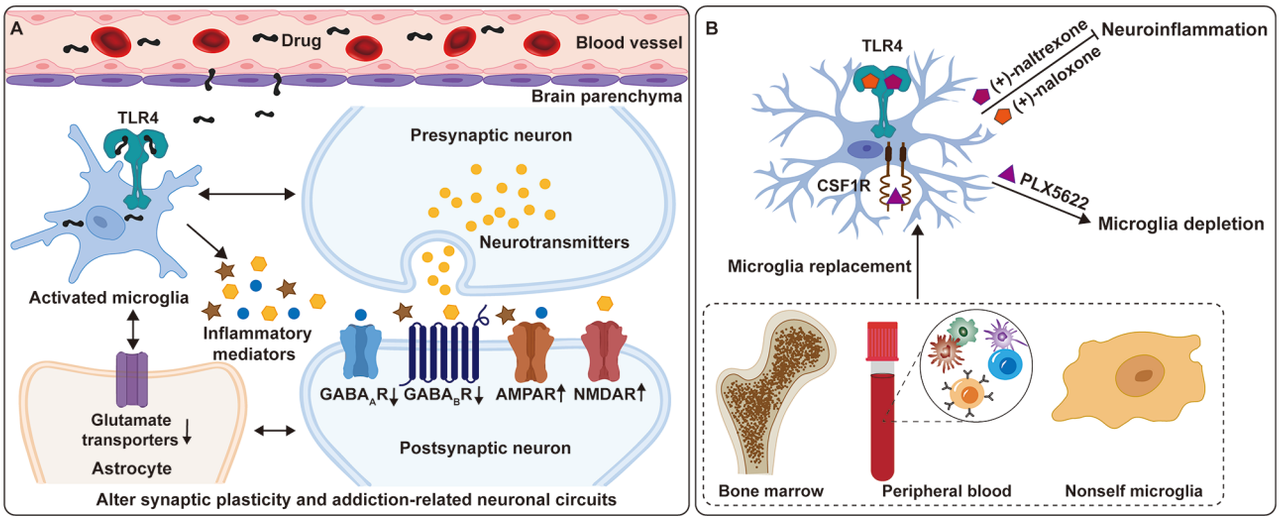

Figure 1 Role of microglia in drug abuse and microglial-targeting strategies for drug addiction treatment

A: As xenobiotic substances, drugs of abuse are recognized by TLR4 on microglia, resulting in microglial activation and inflammatory mediator release. These mediators damage neurons and astrocytes, reducing astrocytic glutamate transporters and inhibitory GABA receptors (specifically, $GABA_AR$ and $GABA_BR$) on postsynaptic neurons, while increasing excitatory AMPA and NMDA receptors on postsynaptic neurons, thereby affecting synaptic plasticity and addiction-related neural circuits. B: For drug addiction treatment, various interventions, such as TLR4 antagonists (+)-naltrexone or (+)-naloxone for microglial inhibition, CSF1R antagonist PLX5622 for microglial depletion, and microglial replacement strategies, have been used to effectively block the production of inflammatory mediators.

microglial depletion. Furthermore, studies have indicated that microglial depletion induced by PLX5622 is crucial for the development and progression of alcohol use disorders (Warden et al., 2020). However, further investigation is needed to determine whether microglial depletion exhibits therapeutic effects on addiction induced by other drugs. Nonetheless, the potential of this approach in the treatment of drug addiction highlights the need for additional research and exploration.

Recently, microglial replacement has been proposed as a possible strategy for restoring the loss of “homeostatic” microglia induced by drugs in the adult brain. The concept of microglial replacement entails the introduction of engrafted microglia into specific brain regions by bone marrow transplantation, peripheral blood replacement, and non-self-microglial replacement, enabling these cells to assume the characteristics of native microglia (Xu et al., 2020). This approach aims to replace dysfunctional or activated microglia associated with drug addiction and restore normal microglial function, thereby mitigating the detrimental effects of drug abuse on the brain. Before microglial replacement can be considered a practical therapeutic strategy for drug addiction, several challenges must be addressed, including optimizing the source and transplantation method of microglia, as well as ensuring their survival and successful integration into the existing microglial network.

The discovery of precise biomarkers for microglial changes associated with addiction has the potential to facilitate the diagnosis of susceptibility to and the progression of addiction. This development could prove invaluable for tailored interventions and personalized treatment strategies. The utilization of specific microglial biomarkers to advance imaging technologies, such as two-photon microscopy and positron emission tomography (PET), may yield more in-depth insights into microglial activity within the brains of individuals affected by addiction. These methodologies enable real-time tracking of microglia and their interactions with other cells across various regions of the brain.

Microglia can assume diverse functional states in response to repeated stimulation, underscoring the importance of differentiating these complex states to develop more selective and effective therapeutic strategies. Based on variations in cell surface antigens, microglia can be categorized into different subgroups, each potentially serving distinct roles in drug addiction. Further exploration into the specific functions of these microglial subgroups will deepen our understanding of the mechanisms involved in drug addiction. Additionally, targeting particular microglial subgroups presents a promising avenue for the development of novel therapeutic strategies for drug addiction, facilitating the development of microglial activation antagonists or depletion agents.

Undoubtedly, the area of microglial research related to addiction is burgeoning and holds significant promise. It offers valuable insights into the neurobiological underpinnings of addiction and potentially new pathways for effective treatments and interventions.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS

C.L. wrote the original draft and drew the figure. X.W. wrote and edited the manuscript. All authors read and approved the final version of the manuscript.

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