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Metal nanoparticles in neuroinflammation: impact on microglial dynamics and CNS function

Masood Alaei,†[ab] Khadijeh Koushki,†[c] Kimia Taebi,†[ab] Mahdieh Yousefi Taba,[d] Samaneh Keshavarz Hedayati[e] and Sanaz Keshavarz Shahbaz ‡*[fb]

Microglia, the primary immune cells of the central nervous system (CNS), are crucial in maintaining brain homeostasis and responding to pathological changes. While they play protective roles, their activation can lead to neuroinflammation and the progression of neurodegenerative diseases. Metal nanoparticles (NPs), due to their unique ability to cross the blood–brain barrier (BBB), have emerged as promising agents for drug delivery to the CNS. In this way, we aim to review the dual role of metal-containing NPs, gold (AuNPs), silver (AgNPs), iron oxide (IONPs), zinc oxide (ZnONPs), cobalt (CoNPs), titanium dioxide (TiO_2NPs), and silica (SiO_2NPs) in modulating microglial activity. Some NPs promote anti-inflammatory effects, while others exacerbate neuroinflammation. We examine how these NPs influence microglial activation, focusing on their potential therapeutic benefits and risks. A deeper understanding of NP-microglia interactions is crucial for developing safe and efficient treatments for neuroinflammatory and neurodegenerative disorders.

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1. Introduction

Neuroinflammation is increasingly recognized as a pivotal factor in the pathogenesis of various central nervous system (CNS) disorders, including neurodegenerative diseases such as Alzheimer's and Parkinson's. This inflammatory response, while essential for maintaining homeostasis and responding to injury, can become detrimental when dysregulated, leading to neuronal damage and exacerbation of disease progression. Microglia, the resident immune cells of the CNS, play a dual role

[a]*Student Research Committee, Qazvin University of Medical Sciences, Qazvin, Iran*
[b]*USERN Office, Qazvin University of Medical Science, Qazvin, Iran. E-mail: Sanaz.ks_023@yahoo.com; sanaz.keshavarzshahbaz@jax.org*
[c]*Department of Neurosurgery, University of Texas Houston Health Science Center (UTHealth), Houston, TX, USA*
[d]*Department of Anatomy and Cell Biology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[e]*Department of Pharmacology, Faculty of Medicine, Qazvin University of Medical Science, Qazvin, Iran*
[f]*Cellular and Molecular Research Center, Research Institute for Prevention of Non-Communicable Disease, Qazvin University of Medical Sciences, Qazvin, 34197-59811, Iran*
† Should be considered joint author.
‡ Current affiliation: The Jackson Laboratory for Genomic Medicine, Farmington, CT, USA Phone (Fax): +982833790620-59 (cell).

Masood Alaei

Masood Alaei holds a Bachelor's degree in Medical Laboratory Sciences from Qazvin University of Medical Sciences. As a member of the Universal Scientific Education and Research Network (USERN), he has been actively involved in research, authoring review articles on nanotechnology and conducting original laboratory-based research projects.

Khadijeh Koushki

Khadijeh koushki is a researcher in the field of immunology, who works as a PostDoc researcher at The University of Texas Health Science Center at Houston (UTHealth). She has published several articles on topics such as asthma and allergy immunotherapy, drug delivery systems and autoimmune disorders. She has also received a PhD degree in immunology from Mashhad University of Medical Science.

in neuroinflammation; they are crucial for both protective responses and the development of inflammatory processes.[1]

Recent advancements in nanomedicine have highlighted the potential of polymer and metal nanoparticles (NPs) as innovative therapeutic agents capable of modulating microglial activity and influencing neuroinflammatory responses. Recently, we reviewed polymeric NP carriers applied to deliver microglial inhibition in neurological disorders with remarkable results, showcasing the promising role of these NPs in microglial modulation during drug delivery.[2]

In addition, due to the unique physicochemical properties—such as high surface area, tunable size, and functional versatility—Metal NPs can effectively cross the blood–brain barrier (BBB),[3] presenting new opportunities for targeted drug delivery in treating CNS disorders. Various metal-containing nanoparticles, including gold (AuNPs),[4] silver (AgNPs), iron oxide (IONPs), zinc oxide (ZnONPs), cobalt (CoNPs), titanium dioxide (TiO_2NPs), and silica (SiO_2NPs), have been shown to interact with microglia, either promoting anti-inflammatory effects or exacerbating neuroinflammation.[5]

In this way, this review aims to provide a comprehensive analysis of metal nanoparticles' impact on microglial dynamics and their implications for CNS function. By examining the complex interplay between these nanomaterials and microglial cells, we seek to elucidate their potential therapeutic benefits and risks in addressing neuroinflammatory conditions. Understanding these interactions is crucial for developing safe and effective treatments for neurodegenerative diseases and advancing the field of nanomedicine.

2. Microglia and their neuroinflammatory roles

Microglia are macrophage-like innate immune cells in the central nervous system (CNS), serving as the brain's primary effector cells that monitor the CNS for infections and injuries.[6–8] As the first responders to foreign pathogens and harmful particles in the brain, microglia act as key indicators of brain damage.[9–11] Constituting 20% of glial cells located in the brain, microglia originate from hematopoietic stem cells.[12] During brain development, these cells enter the brain *via* circulation and can exhibit neurotoxic or neuroprotective responses in their microenvironment.[13]

Kimia Taebi

Kimia Taebi earned a Bachelor's degree in Medical Laboratory Sciences from Qazvin University of Medical Sciences. She is a member of the Universal Scientific Education and Research Network (USERN) and has contributed to various scientific publications. Her work includes review articles in the field of nanotechnology as well as original research articles in laboratory sciences.

Samaneh Keshavarz Hedayati

Samaneh Keshavarz Hedayati is a researcher in the field of pharmacology and microbiology, who works as a research demonstrator in Qazvin University of Medical Science in Iran. She has also received a MSc. degree in microbiology.

Mahdieh Yousefi Taba

Mahdieh Yoosefi Taba earned a Master's degree in Anatomical Sciences and Cell Biology from Mashhad University of Medical Sciences. Her research focuses on aging models, with a particular emphasis on investigating the protective effects of therapeutic agents against oxidative stress in infertility and hippocampal dark neurons.

Sanaz Keshavarz Shahbaz

Sanaz Keshavarz Shahbaz is a researcher in the field of immunology, who works as a research assistant professor at Qazvin University of Medical Science in Iran and PostDoc research associates at The Jackson laboratory for genomic medicine, Farmington, CT, USA. She has published several articles on topics such as asthma and allergy immunotherapy, transplantation immunology, cancer, drug delivery systems and autoimmune disorders, neuroimmunology. She has also received a PhD degree in immunology from Mashhad University of Medical Science.

Neuroprotective functions of microglia include maintaining homeostasis by regulating the brain's internal environment, metabolic regulation, and facilitating immune responses.[14,15] In their resting state, known as the M0 phenotype, microglia clear apoptotic debris, remove dysfunctional synapses, and support pruning in developing brains. This process involves synaptic remodeling, phagocytosis of cells with intracellular inclusions, neuronal feedback,[16] facilitating myelination,[17] neurogenesis, and trophic maintenance of neurons.[18,19] These functions are crucial for preserving a healthy brain environment.

Microglia also have two activated states: the "M2" anti-inflammatory phenotype and the "M1" proinflammatory phenotype. M2 microglia are responsible for healing-related actions, such as maintaining homeostasis and promoting anti-inflammatory processes. They contribute to the generation of anti-inflammatory cytokines and neurotrophic agents.[10,20,21] In contrast, M1 microglia are the first line of defense, responsible for homeostasis and pro-killing functions. They can produce proinflammatory cytokines interleukin-1b (IL-1b), IL-17, IL-12, IL-6, IL-18, IFN-c, IL-23, inducible nitric oxide synthase (iNOS), tumour necrosis factor-alpha (TNF-α), cyclooxygenase-2 (COX-2), reactive oxygen species (ROS), prostaglandin E2 (PGE2), and (MHC-II).[22,23]

Although the pro-inflammatory functions of the M1 phenotype are protective in certain situations, excessive release of cytotoxic substances has been attributed to the development of neuroinflammatory disorders.[24] Many studies have shown that microglial activation plays a pivotal role in the pathogenesis of neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease (AD), psychiatric disease, ischemic disease, traumatic brain injury, and stroke.[10,25–27] Microglia become activated in response to pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), and certain nanostructures, triggering a pro-inflammatory response.

To perform their surveillance functions, microglia are equipped with different signaling immunoreceptors, such as Toll-like receptors (TLR4 and TLR2), complement phagocytic receptors (CR4 and CR3), and scavenger receptors (Cluster of Differentiation-36 (CD36) and CD204) to interact with extracellular species.[25,28,29] When neurons are exposed to harmful stimuli, they begin to generate "help me" signals, including fractalkine, interleukin-34 (IL-34), and CX3C chemokine.[30,31] In response, microglia become activated and release proinflammatory cytokines, including TNF-α and IL-1β, along with neurotoxic molecules, such as ROS.[32] Moreover, activated microglia can release glutamate, which causes an increase in the neuronal and neurite number, thereby contributing to neurodegenerative disorder exacerbation.[25,33]

Upon stimulation of microglial surface receptors, several signaling pathways become activated. They induce the production of inflammatory cytokines, the NLRP inflammasome activation, and beta-secretase enzyme (BACE) expression,[29] ultimately driving neuroinflammation and neuronal

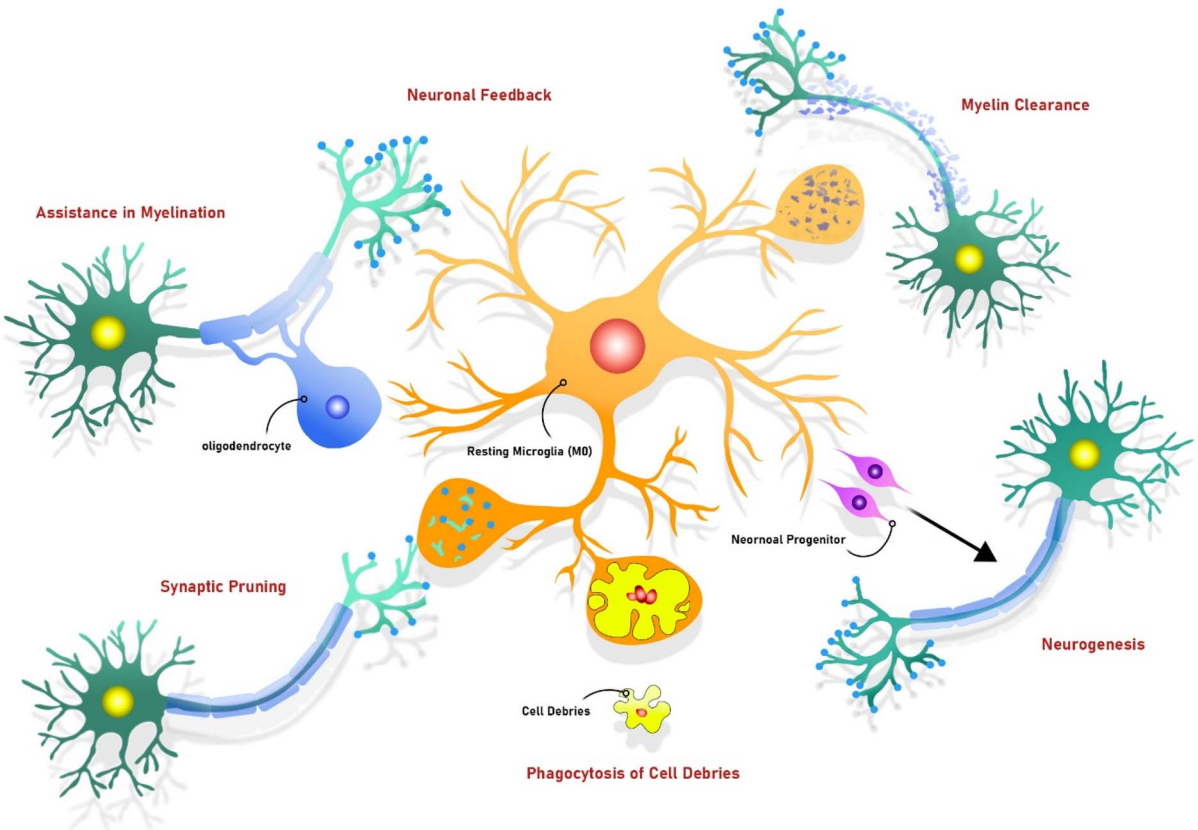

Fig. 1 Normal functions of microglia in the CNS.

death. Microglia can also accidently damage neurons while attempting to limit infections by producing cathepsin B, superoxide, nitric oxide, and derivative oxidants.[34] Furthermore, microglia-mediated reduction in insulin-like growth factor 1 (IGF-1) and nutritional brain-derived neurotropic factor (BDNF) contributes to neuronal death[35,36] (Fig. 1). These mechanisms highlight the potential of microglia M1 in the beginning and progression of neurodegenerative diseases.

Given the crucial role of microglia, particularly M1 microglia, in neuroinflammatory processes, potent inhibitors that target microglial immune activity may offer promising strategies for addressing these issues.

Resting microglia, known as M0 microglia, perform multiple health-promoting functions. They have the potential to support neuronal progenitors in the neurogenesis process. Additionally, they can appropriately eliminate cell debris and dead cell bodies through phagocytosis. Moreover, M0 microglia can phagocytose unnecessary synaptic connections (called synaptic pruning) to leave more space to form new connections between neurons. An oligodendrocyte is a cell that is responsible for forming myelin around axons. Interestingly, M0 microglia participate in this process by assisting oligodendrocytes. Microglia M0 also contribute to the neuronal feedback mechanism. When neurons are activated, microglia use negative neuronal feedback to prevent neuronal overactivation, thus leading to a balanced neuronal environment. Additionally, resting microglia can play a role in myelin clearance by attempting to phagocytose myelin debris to prevent impaired neurogenesis.

3. Inhibitors of microglial immune activity

According to microglia's vital role in neuroinflammation and the progression of neurodegenerative diseases, inhibiting their activity is a prominent therapeutic solution. Several compounds, including resveratrol, curcumin, cannabidiol,[37] ginsenosides, flavonoids, sulforaphane,[38] candesartan cilexetil,[39] propentofylline, luteolin,[40] quercetin,[41] and minocycline,[42] are available as conventional and potent inhibitors of microglial activity. Bellow, some of these compounds and their inhibitory effects on microglia are briefly discussed.

Resveratrol, a polyphenol abundant in peanuts, raisins, red grapes, and berries, possesses anti-inflammatory, antioxidant, and antiapoptotic properties.[43,44] Studies have illustrated that resveratrol can limit microglial activity and mitigate rotenone-induced neurotoxicity, CD11 (a microglial activity marker), TNF- α, and IL-1β.[45] Curcumin, another well-known inhibitor, is a potent anti-inflammatory and antioxidant agent found in turmeric. Interestingly, curcumin plays a suppressive role in microglial activity and decreases microglia-induced inflammatory cytokines.[46] It can also block the MAPK signaling pathway, which further inhibits the activation of NF-$\kappa\beta$.[47] Curcumin suppresses the production of COX-2 and other inflammatory cytokines by modulating TLR4 signaling.[48] Quercetin, a natural flavonoid present in vegetables and fruits, namely green tea, onions, apples, red grapes, and berries, is also a potent inhibitor of microglial activity due to its antioxidant and anti-inflammatory properties.[41] The treatment with quercetin reduces TLR-4 expression in the hippocampus and cortex, a key receptor involved in microglial activation.[49] In addition, it can reduce the expression of ionized calcium-binding adapter molecule 1 (Iba-1), IL-1β, TNFα, and COX2.[50] Minocycline, a well-known antibiotic, has also been extensively studied for its ability to inhibit microglial function, reducing the number of microglial inflammatory mediators.[51,52] Minocycline can also reduce MHC-II expression in microglia.[42]

While these drugs offer significant potential in mitigating microglial immune responses, drug delivery to the CNS is still a considerable challenge because of the restrictive nature of the blood–brain barrier (BBB). Its specific structure, surrounding cells, and molecular transport mechanisms limit the efficient delivery of many therapeutic agents. Therefore, the following section further discusses these challenges and potential solutions.

4. CNS drug delivery through the BBB and its challenges

BBB, along with extracellular matrix (ECM) and nonfenestrated monolayer of cells, significantly controls the microenvironment of CNS neurons. These structures protect the CNS from circulating toxins, infectious agents, and harmful substances, such as foreign microorganisms.[53–56] The BBB is formed by endothelial cells, whose proliferation is stimulated by neighboring cells such as astrocytes (which surround brain vessels) and pericytes (which help maintain the integrity of the BBB)[57]

Various transport systems control the traffic of substances across the BBB, including fenestra, transendothelial channels, pinocytotic vesicles, active efflux transport proteins, and breast cancer resistance proteins.[58] These systems are crucial in controlling the flow of specific drugs and essential nutrients into the CNS. Passive distribution *via* a paracellular or transcellular pathway for low molecular weight or lipophilic substances (the majority of CNS-targeting drugs); vesicular trafficking, such as adsorptive-mediated transcytosis (for positively-charged substances); receptor-mediated transcytosis (an energy-dependent pathway for proteins hormones and proteins); and carrier-mediated transport (for amino acids and glucose) are some examples.[59–61] The BBB's relative impermeability is primarily due to tight junctions between endothelial cells.[62,63] The mentioned mechanisms and complexes are potential obstacles for most drugs to enter the CNS, making drug delivery challenging with high failure rates and increased costs.[64] Even if drugs manage to cross the BBB, achieving therapeutic concentrations within the CNS can be difficult. Ensuring that drugs are effective without causing adverse side effects and neurotoxicity remains a critical challenge.[65] Also, CNS disorders often require targeted treatments that are tailored to individual patients. Achieving this specificity in drug delivery systems is complex and ongoing.[66] Moreover, many conventional therapeutic agents suffer from low bioavailability

due to rapid metabolism or elimination, leading to degradation. Therefore, encapsulating drugs can protect them from degradation and improve their pharmacokinetic profiles.[67] The ability to control drug release is also vital for maintaining therapeutic concentrations over time and avoiding excessive drug dosages, which many conventional drugs lack this ability.[68] These problems can lead to ineffective treatment for CNS disorders such as cerebral malignancies due to low brain penetration. Over the last decade, researchers have developed various technologies to overcome these challenges. One promising approach is using targeted vectors (peptides, proteins, antibodies, or specific formulations) to aid the transport of drugs across the BBB.[69] Additionally, nano-delivery systems have gained attention as a novel strategy. These systems offer the possibility to improve therapeutic precision and maintain medicine efficacy while minimizing toxicity.[23,70]

5. Nanoparticles for drug delivery to the brain

Advances in biotechnology have shifted therapeutic approaches from conventional medicine to nanotherapeutic agents.[71] Due to the challenges linked to macromolecular drugs crossing the BBB and their inability to target specific sites and ineffective dosages, nanotherapeutics have gained significant attention for drug delivery to the CNS and targeting microglia-related neuroinflammation.[72] Nanomaterials include nonpolymeric, lipid-based, polymer-based, and metal-based nanoparticles. These NPs range in diameter from 1 to 100 nanometers (nm). These ultrafine particles exhibit unique chemical and physical features that differ significantly from larger particles of the same substance because of their high surface area-to-volume ratio.[73,74] Some NPs exist in the environment, while others are engineered in industrial settings.[75]

Some NPs can traverse vessel walls and enter brain tissue. This ability is mainly attributed to their physiochemical characteristics, including size, shape, surface chemistry, surface charge, and surface traits.[76] Therefore, engineering the NPs to modify their morphological features enhances their ability to cross the BBB. One strategy involves designing the NPs in combination with elements specific to pathological sites and BBB-penetrating molecules, such as the spontaneous exploitation of NPs with *trans*-Golgi network (TGN) peptides and the cancer cell-specific aptamer AS1411. Such modification can remarkably improve BBB penetration and target delivery.[77] The shape and surface characteristics of NPs also influence how microglia internalize them;[78] for instance, spiky "urchin-shaped" gold NPs(AuNps) show higher levels of microglial uptake in contrast to rod or spherical-shaped AuNPs.[72,79] Hence, the way microglia take NPs up is highly dependent on the design of the NP surface and properties.[80] Microglia internalize NPs primarily through active processes like invagination and endocytosis.[69] However, certain NPs may also passively diffuse across the cell membrane. Furthermore, the uptake of NPs varies between microglial phenotypes. Compared with resting microglia, lipopolysaccharide (LPS)-activated microglia display greater dendrimer uptake, which is associated with increased endocytosis.[81]

Once NPs reach the brain tissue, they can release their therapeutic cargo at the target location in a time-dependent way and navigate the drugs (genes, small molecular agents, and biomolecules) to the target organelle without being trapped in endo/lysosomes. Various strategies have been developed to facilitate lysosomal escape. One common approach is the proton sponge effect, where pH-sensitive nanoparticles swell and disrupt the lysosomal membrane upon exposure to the acidic environment, leading to the release of their contents into the cytosol. Other methods include osmotic lysis, which results from the disassembly of nanoparticles in response to low pH, and mechanical disruption techniques that utilize nano-mechanical actions or photochemical processes to destabilize lysosomal membranes.[82] This controlled release mechanism decreases the required drug dosage and side effects of using nanomaterials.[56,83,84] Engineering NPs is also critical for drug delivery. One example involves using stimulus-sensitive bonds to ensure the accurate release of cargo in the expected areas in response to spatial variations in redox capacity.[85] Additionally, NPs designed with epidermal growth factor (EGF) and two types of bioresponsive bonds that enhance vascular permeability[86] can deliver drugs directly to subcellular organelles, improving drug efficacy in the brain.[87,88] Such designs have been employed to deliver DNA-binding agents and ROS-generating drugs into mitochondria,[76,89] facilitating the treatment of stroke, glioma, epilepsy, and AD. Besides, the unique electrical and optical traits of some nanoparticles enable them to treat CNS disorders.[71]

Put simply, NPs favor the treatment of neurodegenerative disorders by delivering essential drugs to the brain, which is partially impossible for macromolecular drugs to reach alone. Nonetheless, metal-containing NPs hold promise for enhancing drug delivery performance compared to NPs alone. However, they also present side effects such as toxicity in the brain by switching M0 microglia to the M1 phenotype. Alternatively, they may alleviate the neuroinflammation by promoting the M2 phenotype. Therefore, the following section further discusses how metal-containing NPs, as multifaceted substances, influence brain health and neuroinflammatory conditions in detail.

6. Metal-containing NPs: a double-edged sword

Inorganic NPs, including metals (such as iron, silver, and gold) and metal oxides (including zinc oxide, iron oxide, titanium dioxide, cerium oxide, *etc.*), have gained considerable interest in recent years because of their diverse usages across medical, sunscreen, cosmetic, and industrial fields.[90] These metal-containing NPs possess unique physicochemical features, making them helpful in diagnosing and treating CNS disorders.[91] Their ability to translocate into the CNS through the BBB, eye-to-brain, nerve signaling pathways, and cell uptake opens new possibilities for therapeutic interventions.[75]

Once inside the brain, metal-containing NPs are immediately internalized by microglia and astrocyte-like (ALT) cells. M1 microglia produce CCL2 and proinflammatory cytokines, for instance, NO, IL-12, IL-1β, and IL-6, which result in acute neuroinflammatory reactions. On the contrary, the M2 phenotype releases anti-inflammatory cytokines such as TGF-β, IL-10, and IL-4, aiding the resolution of neuroinflammation and repairing the damaged brain.[92] Metal-containing NPs can influence this polarization, with some promoting M1 activation and exacerbating inflammation, while others encourage the M2 phenotype, facilitating neuroprotection and recovery.[93]

Metal NP-induced M1 phenotype can exert neurotoxic effects through various mechanisms, including the generation of ROS, which leads to oxidative stress, inducing neuronal apoptosis and necrosis and contributing to neurodegenerative diseases.[94] Furthermore, metal NPs can trigger the activation of microglia, leading to the release of pro-inflammatory cytokines, exacerbating neuroinflammation, and compromising neuronal health.[95] The neurotoxic potential of metal NPs is significantly influenced by their physicochemical properties. Smaller NPs generally exhibit higher reactivity and greater cellular uptake, which can enhance their therapeutic efficacy but also increase the risk of toxicity. Surface modifications, such as PEGylation, can alter NP-cell interactions, improve circulation time, and reduce immunogenicity, potentially mitigating some toxic effects.[96] The neurotoxicity of metal NPs is often dose-dependent, with low concentrations potentially eliciting beneficial effects by modulating microglial activity and promoting anti-inflammatory responses. Higher concentrations can overwhelm cellular defense mechanisms, leading to toxicity. This highlights the crucial need to optimize dosages in therapeutic applications to maximize efficacy while minimizing adverse effects.[97] Chronic exposure to metal NPs may lead to cumulative neurotoxic effects that are not immediately apparent. NP prolonged exposure potentially results in significant alterations in microglial function and neuronal integrity, leading to long-term cognitive deficits or the exacerbation of existing neurological conditions.[98]

For instance, silver nanoparticles (AgNPs) are able to promote M1 polarization and induce neurotoxicity. Duffy *et al.* reported that AgNPs triggered the production of proinflammatory cytokines like TNF-α in BV2 microglial cells, leading to neuroinflammatory responses.[99] Additionally, AgNPs have been shown to enhance the level of the proinflammatory chemokine CXCL13 in microglia, astrocytes, and Neuro2a (N2a) cells, further elevating the levels of IL-1β.[100] Besides silver, other metal-based NPs, like titanium dioxide nanoparticles (TiO_2NPs), have been linked to neuroinflammatory responses. TiO_2NPs can activate inflammasomes and nuclear factor-κB (NF-κB), activating microglia and subsequent inflammation.[75]

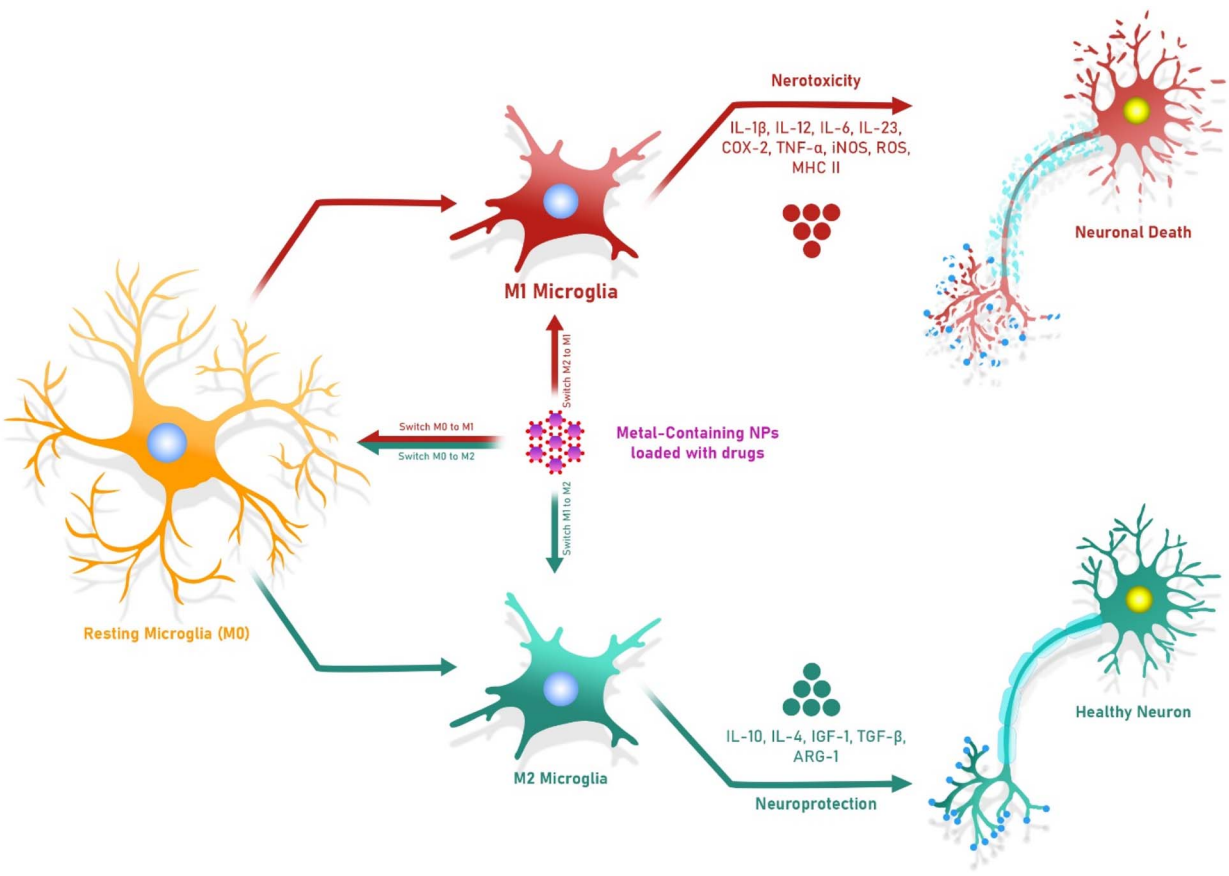

Fig. 2 The possible functions of metal-containing nanoparticles in microglial activation.

Despite these proinflammatory effects, some metal-containing NPs also exhibit anti-inflammatory properties. AuNPs, for instance, have been evidenced to prevent the proinflammatory reactions in microglia by promoting M2 phenotype, thereby contributing to CNS repair.[101] Similarly, exposure to AgNPs has been found in another article to be associated with a reduction in inflammation. This could be possibly due to the detoxification of silver ions through sulfidation and the activation of hydrogen sulfide-synthesizing enzymes.[102] Moreover, iron oxide nanoparticles (IONPs) have been demonstrated to inhibit the production of IL-1β in LPS-stimulated microglia, further underscoring the potential neuroprotective role of metal-based NPs.[103] (Fig. 2).

Although remarkable endeavors have been made to understand the neurotoxic and neuroprotective effects of metal-containing NPs, much remains to be learned about their role in neuroinflammation. Additionally, since studies have shown that microglia activation can serve as an early warning and defensive response against exogenous NPs that invade and accumulate in the CNS, it is crucial to investigate the interaction between various metal-containing NPs conjugated with specific drugs and microglia. Hence, additional exploration is needed to fully exploit the ability of nanotechnology to treat CNS disorders.

In the following section, we aim to comprehensively discuss some well-known metal-containing NPs and their conjugation with certain drugs, highlighting how NP uptake by microglia influences treatment outcomes (Table 1).

Metal-containing nanoparticles have serious impacts on microglia in the CNS. They can directly influence resting microglia (M0) to switch them to the M1 or M2 phenotype. They can also induce this effect on the M1 and M2 phenotypes, resulting in a phenotypic switch between M2 and M1. In case of a switch to the M1 phenotype, proinflammatory and inflammatory cytokines are likely to be released, resulting in an inflammatory state in the CNS and, consequently, neuronal death. On the other hand, if a phenotype switch occurs to the M2 phenotype, it is probable that anti-inflammatory cytokines will be released, leading to a protective state in the CNS and healthy neurons.

6.1. Gold nanoparticles (AuNPs)

AuNPs possess distinctive physicochemical characteristics, including surface plasmon resonance and high biocompatibility, making them notably attractive for several biomedical uses, such as photothermal and photodynamic therapies. These properties enable targeted heating of tissues and enhanced imaging capabilities, making them versatile tools for both treatment and diagnosis of CNS disorders.[104,105] Gold nanoparticles possess inherent antibacterial properties that make them effective against a range of pathogens, including antibiotic-resistant strains.[106] Their ability to amplify signals also makes them valuable tools in clinical settings as potent biosensors.[107,108] They have been explored in fields like pharmacology, drug delivery, cancer therapy, biosensing, and bioimaging because of their suitable shape and size.[109] This section summarizes the results of some studies on the effects of these NPs on microglia-mediated neuroinflammation during drug delivery to CNS.

Several researchers have confirmed the anti-inflammatory function of AuNPs in the CNS by influencing microglia. For example, Ozdal *et al.* revealed that gold-quercetin NPs exhibited superior anti-inflammatory and therapeutic effects compared to free quercetin. These NPs notably reduced the translational and transcriptional levels of inflammation-associated enzymes, PGE2, and nitric oxide (NO) in LPS-stimulated microglia without causing cytotoxic effects. This highlights the potential of AuNPs as carriers to address solubility issues of therapeutic compounds like quercetin.[110] Another example involves dihydrolipoic acid (DHLA)-functionalized AuNPs, which act as neuroprotective antioxidants. These GNPs polarize microglia to M2-like phenotype, effectively reducing oxidative stress and NF-κB signaling. Additionally, they support microglial survival by preventing apoptosis.[101] Moreover, Kuschnerus and colleagues reported that AuNPs coated with a hard corona composed of fibrinogen (FIB) and bovine serum (BS), *in vitro*, significantly enhanced cellular uptake and lowered oxidative stress and ROS production in microglia more effectively than AuNPs-FIB, protein corona (PC), and BS-T120W3-AuNPs each alone. This selective formation of AuNP-corona complexes may offer a promising strategy for controlling oxidative stress and improving cellular uptake.[111] Additionally, in an *in vitro* study, *E. sinica* Stapf extract (ES)-functionalized AuNPs lowered proinflammatory cytokine levels by downregulating the NF-κB and Janus kinase/signal transducers and activators of transcription (JAK/STAT) in LPS-stimulated microglia, thereby suggesting that ES-functionalized AuNPs may mitigate neuroinflammation and neurodegenerative disorders.[112] Also, Diaz and colleagues[113] evaluated microglial responses to intracerebrally injected PEGylated AuNPs (polyethylene glycol-coupled AuNPs). The results indicated a transient and predominantly localized cellular response of microglia and astrocytes at the injection site with minimal harmful effects on the brain for 3 to 90 days. It was suggested that neural tissues could tolerate PEGylated GNPs well. Interestingly, Hutter *et al.* discovered that AuNP exposure caused a limited and transient upregulation of TLR-2 and inflammatory markers like IL-1α, NO, and GM-CSF in microglia. Notably, microglial activation occurred in a limited number at a slow pace, highlighting their ability for long-term drug delivery to the CNS.[114]

AuNPs have also shown privileges in treating neurodegenerative diseases like Parkinson's disease (PD). In this regard, a study utilizing *Paeonia moutan*-functionalized AuNPs (PM-AuNPs) in a PD mouse model showed that these NPs significantly inhibited the production of NO and inflammatory cytokines and scavenged ROS in LPS-stimulated BV2 microglia all without causing cytotoxic effects. PM-AuNPs reduced levels of COX2 and iNOS, key markers of inflammation, while improving motor coordination in the PD model.[115] Consistently, Zhao *et al.* observed that PM-AuNPs reduced α-synuclein internalization and oligomer formation, as well as decreasing TNF-α and IL-6 levels *in vitro*. This supports PM-AuNPs' role in managing PD-related neuroinflammation.[116] Additionally, AuNPs have been used to treat Alzheimer's disease (AD). As a study has shown,

Table 1 The outcomes of using metal-containing NPs in other studies[a]

NP type	The surface coating	NP properties	Cell type/animal models	Mechanisms & outcomes	Ref
Au	Gold-quercetin NPs	27 nm, 100, 200, 400 μg mL^{-1}	LPS-stimulated microglia	Significant decrease in both the transcriptional and translational levels of inducible NO synthase, cyclooxygenase-2; COX-2 and iNOS Inhibiting the release of NO and proinflammatory PGE2 from LPS-stimulated microglia without causing any cytotoxic effect	110
Au	AuNP-FIB-BS hard corona	50–3 nm, dose: 26 μg mL^{-1}	Murine BV2 microglia	Significant decrease in oxidative stress and ROS generation Significant increase in cellular uptake	111
Au	*Ephedra sinica* Stapf extract extract-capped AuNPs	57.6 ± 3.07 nm	Microglia	Decrease in the production of the proinflammatory cytokines, including IL-1β, IL-6, and TNF-α in LPS-stimulated microglia through the downregulation of JAK/STAT, NF-κB, IKK-α/β, JNK, and p38 MAPK signaling pathways Upregulation of NQO1 and HO-1 Activation of AMPK and Nrf2	112
Au	Polyethyleneglycol-coupled GNPs	8.09 ± 3.60 nm (85×10^6 nL^{-1})	Microglia	Self-limited, transient, and predominantly localized cellular response of microglia at the injection site within 3 to 90 days following intracerebral injection No chronic microglial response by NPs	113
Au	*Paeonia moutan*-functionalized GNPs	100 nm, 5, 10 and 20 μg mL^{-1}	BV2 microglia and C57BL/6 mice/ mouse model of parkinsonian	Inhibiting the inflammatory cytokines (IL-1β, IL-6, and TNFα) and NO synthesis Trapping the reactive oxygen in LPS-stimulated BV2 murine microglia suffering from PD Significant reduction in the expression of inflammatory COX2 and iNOS Increase in the expression of tyrosine hydroxylase Improving motor coordination and alleviating the neuroinflammation in the Parkinson model	115
Au	*Paeonia moutan*-functionalized GNPs	190–450 nm	BV2 microglia	Decrease in formation of intracellular *α-syn* oligomers, pro-inflammatory cytokines (IL-6 and TNF-α) secretion, and *α-syn* internalization, *in vitro* Lowered *α-syn*-induced production of ROS and NO in microglia Nuclear translocation of NF-κB Suppression the expression of Iba-1 by *α-syn*-challenged microglia	116
Au	Anthocyanin-loaded poly (ethylene glycol)-AuNPs	135 ± 5 nm	Aβ1-42-induced mouse model and BV2 microglia	Reduction in Aβ1-42-induced neuroapoptotic markers and neuroinflammation by restricting the *p*-GSK3β/NF-κB/*p*-JNK pathways in both *in vivo* and *in vitro* AD models	118

Table 1 (*Contd.*)

NP type	The surface coating	NP properties	Cell type/animal models	Mechanisms & outcomes	Ref
				Significant mitigation in Aβ-induced apoptosis in both BV2 microglia and the mouse hippocampus by reducing Cyt. c release, Bax protein expression, and increasing Bcl2 protein levels Reduction in the production of Iba-1 and GFAP in microglia Mitigating the expression of iNOS and *p*-NF-κB proteins	
Ag	AgNPs	20 nm, 50 μg mL^{-1}	Mouse BV-2 microglia	Decrease in microglial growth by AgNPs and CdTe-QDs by stopping the cells in the G1 phase (CdTe-QDs) or S phase (AgNPs and CeO_2NPs) of the cell cycle	129
Ce	Cerium oxide NPs	25 nm, 100 μg mL^{-1}		Significant reduction in Aβ uptake by BV-2 microglia with AgNPs and CeO_2NPs, but not CdTe-QDs	
	Cadmium telluride quantum dots	3.8 nm, 3 or 10 μg mL^{-1}		No impacts on the secretion of IL-6, IL-1b, and IFNg by Aβ, nor NPs or their combinations Significant increase in TNFa secretion by CeO_2NPs	
Ag	—	20 nm, dose: 50 μg mL^{-1}	Mouse BV-2 microglia	Efficiently blocking the Aβ uptake by microglia	130
Ag	—	20 nm	Mouse BV-2 microglia	Impairing Aβ clearance by BV-2 microglia by competing with Aβ for scavenger receptors	131
Ag	—	10 nm, 6, 3, and 1 μg mL^{-1}	BV2 microglia	Releasing soluble factors like NO and H_2O_2 from glial cells Significantly inhibiting the induced ROS and cytokines (TNF-α, MCP-1, and IL-6) from LPS-activated BV-2 Decreasing cell viability of BV-2 by releasing H_2O_2 from ALT cells through indirect AgNP exposure	121
Ag	—	23 nm diameter	Glial cells	Destruction of the cerebellum granular layer, causing cerebellar ataxia-like symptoms in rats	124
Ag	—	23.44 ± 4.92 nm, 5 μg mL^{-1}	BV2 microglia cell lines of mouse	AgNPs-induced M1 polarization of microglia in a time- and dose-dependent way by inhibiting the fusion of autophagosomes with lysosomes Increasing the expression of pro-inflammatory genes such as IL-1β, TNF-α, Iba-1, NF-κB, and MCP-1 in BV2 cells Reducing the mRNA expression of anti-inflammatory cytokines	126
Ag	—	3–5 nm, dose: 5–12.5 μg mL^{-1}	Murine BV-2 microglia	Inducing pro-inflammatory cytokine secretion such as IL-1β secretion and gene expression of CXCL13, GSS, and macrophage MARCO	100

Table 1 (*Contd.*)

NP type	The surface coating	NP properties	Cell type/animal models	Mechanisms & outcomes	Ref
				Altering protein and gene expressions of Aβ deposition by inducing the expression of amyloid precursor protein (APP) gene	
Ag	—	49.7 ± 10.5 nm	Microglia	Reducing LPS-stimulated NO, TNF-α, and ROS production Significant anti-inflammatory effects Reducing microglial toxicity to dopaminergic neurons	133
Ag	—		Human microglia cells (HMC3)	M1 to M2 phenotype switch Enhancing the expressions of anti-inflammatory markers including transforming TGF-β and IL-10 A significant reduction in mRNA expressions of TNF-α and IL-6 Biogenic AgNPs were protected against oxidative stress and neuroinflammation by targeting Nrf2/HO-1 and TLR4/MyD88 signaling pathways	134
Ag	—	18 ± 1.8 nm	Microglia	Neurobehavioral alterations in offspring Body fat increase Long-term gut dysbiosis Reducing the microglial counts	172
IO	—	~65 nm	Cultured rat microglia	Time- and concentration-dependent uptake Longer incubation periods of exposure or higher concentrations or severely attenuated cell viability	136
IO	—	58.7 nm, 1–510 μ Fe/mL	Primary murine microglia	Attenuation of the IL-1β production, but not TNF-α, mediated by their accumulation in lysosomes and affecting the secretory lysosomal pathway of cytokine recessing Suppression of IL-1β converting enzyme in IONP-treated murine microglia by decreasing the activity of cathepsin B	137
Magnetic iron oxide (γ-Fe_2O_3)	—	11 ± 3.5 nm	rTg4510 tau-mutant mice	A significant decrease in the number of activated microglia in comparison with the same concentration of the free peptides by stabilizing the peptide to the γ-Fe_2O_3 NPs	138
Fe_2O_3	—	γ -Fe_2O_3: (31 ± 17) nm α-Fe_2O_3NP: (22 ± 5) nm Dose: 0.02, 0.2, 2 mol Fe/L of Fe_2O_3-NP suspensions or $FeCl_3$ solution	BV2 microglia	Proliferation of microglia Increased phagocytosis Higher release of ROS and NO by microglia	139
Co	—	50 nm	C57BL/6J mice brain	Toxic effects and inflammatory responses in BV2 microglia and mice by activating the NOX2 (NADPH oxidase 2)	142
		Dose: 1.25, 2.5 and 5 μg mL^{-1}	BV2 microglia	Catalyzing ROS production, IL-1β, NLRP3, accompanied by tau phosphorylation	
Co	—	96 and 123 nm	Microglia	Microglial activation	143

Table 1 (*Contd.*)

NP type	The surface coating	NP properties	Cell type/animal models	Mechanisms & outcomes	Ref
ZnO	—	38.52 ± 2.82 nm, dose: 6.6 μg mL^{-1}	Mouse microglia N9 cell line	Disrupting the MMP activity and subsequently inducing the apoptotic pathway in the microglia by NADPH oxidase-independent ROS and ATP depletion Disrupting mitochondrial membrane potential Microglia apoptosis, involving altered intracellular calcium (Ca^{2+}) level, mitochondrial ROS production, caspase-9 and -3 activation, ERK and p38 phosphorylation, and cytochrome-c release	146
ZnO	—	50 nm, dose: 10 μg mL^{-1}	Murine BV-2 microglia	Increase in the ROS levels and oxidative stress in BV-2 cells in a time-dependent manner through autophagy and PINK1/parkin-mediated mitophagy Increasing count of swollen mitochondria and autophagosomes	150
ZnO	—	20 nm (5, 10, 20, 40, and 80 μg mL^{-1})	Murine BV-2 microglia	Influencing the lysosomal destabilization Inducing extensive cellular and organelle (mitochondria, lysosome), ROS accumulation, and consequently nonapoptotic cell death, leading to the release of lysosomal enzymes Promoting inflammation by cell debris and accumulating ROS at the CNS level	151
ZnO	—	42.31 ± 17.94 nm, dose: 30 μg mL^{-1}	BV2 microglia cell line	Driving microglia and inflammatory responses in the CNS by activating the Ca^{2+}-dependent ERK, p38, NF-κB pathways	152
ZnO	—	26.4 ± 2.3 nm, 5 μg mL^{-1}	BV2 microglia	Microglial activation and proliferation by ERK and Akt signaling pathways	153
ZnO	—	50 nm	Microglia	Induction of tau protein expression, microglia activation, and oxidative stress in the brain, resulting in neurotoxicity	154
ZnO	Luteolin/ZnO NPs	17 nm	Microglia	Regulating microglia polarization by targeting C/EBPA and alleviating inflammatory injury by modulating the redox-sensitive signal transduction pathways	155
TiO_2	TiO_2 NPs (Degussa P25)	330 nm, dose: 2.5–120 ppm	BV2 microglia	Upregulation of NF-κB and ERK/MAPK Stimulating BV2 microglia to have an prolonged and immediate release of ROS Damaging neurons at low concentrations in cultures of the brain striatum, probably by microglial-generated ROS Influencing genomic pathways linked to cell cycling, upregulation of apoptotic pathways, inflammation, mitochondrial bioenergetics, and downregulation of energy metabolism	148
TiO_2	—	20–30 nm, 0.1 to 200 μg mL^{-1}	BV2 microglia	TiO_2NP accumulation in BV-2 cells	157

Table 1 (*Contd.*)

NP type	The surface coating	NP properties	Cell type/animal models	Mechanisms & outcomes	Ref
				Induction of oxidative stress and mitochondrial dysfunctions Damaging the permeability of cell membranes, inhibiting cell adhesion with a loss of mitochondrial transmembrane potential. Induction of ROS overproduction and reducing cell viability	
TiO_2	—	1–100 nm	Microglia	Producing excessive ROS *via* the oxidative burst Interfering with mitochondrial energy production *in vitro* Damaging membrane integrity	158
TiO_2	TiO_2 NPs (Degussa P25)	30 nm	BV2 microglia	Formation of free radicals in cellular and morphological expressions	159
TiO_2	—	21 nm, 25–200 μg mL^{-1}	Male C57BL/6 mice and murine BV2 microglia cell line	Stimulating inflammatory mediators in the brain and neurons *in vitro* Significantly elevating pro-inflammatory cytokine (TNF-α and IL-1β) mRNAs and IL-1β protein levels in the brains of LPS-exposed mice Enhancing TNF-α production and NF-κB binding activity by LPS-stimulated BV2 microglia Causing neuroinflammatory responses by enhancing microglial activation in the preinflamed brain and leading microglia N9 to apoptosis	160
TiO_2	TiO_2NPs HAP-NPs	20–60 nm/0.25 mg mL^{-1} and 0.5 mg mL^{-1}	Primary microglia	Inducing a significant expression of iNOS and subsequent NO secretion Upregulating the expression levels of MIP-1 and MCP-1 from NP-stimulated microglia by inducing NF-κB activation Increasing the production of TNF-α, IL-6, and IL-1β by TiO_2-NPs and HAP-NPs	162
TiO_2	—	35 nm, dose: 4–125 μg mL^{-1}	Microglia N9	Inducing TiO_2-induced apoptosis	173
TiO_2	—	6 nm, dose: 100–5 μg mL^{-1}	BV-2 microglia	Inducing IL-1β production and ROS production Clathrin-dependent endocytosis, phagocytosis, and a slow translocation to the lysosome in BV2 cells More TiO_2NP uptake in LPS-activated BV-2 than normal BV-2, resulting in more released ROS, IL-6, IL-1β, and MCP-1 levels	174
SiO_2	Fluorescein isothiocyanate -tagged SiO_2 NPs	115 nm	Male C57BL/6N mice & microglia	Increasing Iba-1 antibody in the hippocampus	166
SiO_2	Silica-coated magnetic NPs containing	50 nm	Murine BV2 microglia	Increasing the expression of Iba1 Increasing the serine protein, especially excitotoxic D-serine secretion in the growth	169

Table 1 (*Contd.*)

NP type	The surface coating	NP properties	Cell type/animal models	Mechanisms & outcomes	Ref
	rhodamine B isothiocyanate dye			medium of activated microglia from primary rat microglia Activation of primary microglia Accumulation of ubiquitinated proteins and increasing the inclusion bodies in primary cortical and dopaminergic neurons, cocultured with activated primary microglia Reduction of intracellular ATP levels and proteasome activity in cocultured neuronal cells, especially in primary cortical neurons, by D-serine secretion	
Si	—	48.53 ± 3.12 nm	Murine BV2 microglia	Significantly increasing caspase-1, ASC, and NLRP3 after stimulation by LPS and SiNPs Raising the production of inflammatory factors, including IL-6, IL-1β, and TNF-α Decreasing the cell viability by increasing the concentration of NP Changing the ultrastructure Invading the cytoplasm Activating the NLRP3 inflammasome Releasing a large number of inflammatory factors Disrupting cellular antioxidant function Inducing ferroptosis Increasing intracellular ferrous ion levels	170
SiO_2	—	—	Microglia	Elevating oxidative stress levels Activation of microglial functions	
Si	—	150–200 nm	Primary rat microglia	Significantly increasing intracellular RNS and ROS productions Decreasing TNF-α gene expression Increasing the expression of COX-2 gene Inducing a small but detectable IL-1β release	149

[a] Abbreviations: Au, gold; Ag, silver; IO, iron oxide; Co, cobalt; ZnO, zinc oxide; TiO_2, titanium dioxide; SiO_2, silica; Si, silicon.

anthocyanins-loaded GNPs successfully crossed the BBB. They inhibited a key inflammatory pathway in microglia-induced neuroinflammation, *p*-GSK3β, without harming neurons. GSK-3β mainly regulates the balance between proinflammatory and anti-inflammatory agents in microglia. Intriguingly, it activates the JNK and NF-κB pathways, resulting in enhanced chemokine and cytokine production[117] by microglia in AD models. Therefore, anthocyanins-loaded GNPs could also indirectly inhibit NF-κB and JNK pathways. Anthocyanins conjugated with PEG-GNPs (AnPEG-GNPs) could also reduce the expression of Aβ1–42-escalated neuroapoptotic markers in BV2 microglia in mouse AD models, making it a promising therapeutic approach.[118]

Overall, AuNPs offer considerable advantages, including their anti-inflammatory properties and ability to cross the BBB, making them promising carriers for drug delivery in neurological disorders like AD and PD, with minimal microglia-mediated side effects for neurons and the brain. Nonetheless, more investigation is necessary to address the potential for even mild and transient neuroinflammatory responses associated with AuNPs, ensuring their safety and efficacy in CNS treatments.

6.2. Silver nanoparticles (AgNPs)

Silver nanoparticles (Ag nanoparticles) have been studied for their capability of crossing the BBB and are valuable for addressing challenges linked to the delivery of therapeutic agents to the CNS.[119] Microglia mainly take up these NPs,[120,121] suggesting that AgNPs can polarize these cells toward either M1 or M2 phenotypes.[122] This section discusses various studies exploring the effects of AgNPs on microglia during drug delivery to the CNS.

Several studies have shown that AgNPs can induce neurotoxic effects through microglial activation. For instance, one study evidenced that prenatal AgNP exposure led to cognitive dysfunctions and abnormal behaviors in adults, which were linked to microglial activation.[123] Another survey by Hsiao *et al.* found the toxic effects of AgNPs on neurons were indirectly mediated by the release of NO and H_2O_2 from glial cells. Although, cytokines, namely IL-6 and TNF-α, were not involved in this process.[121] Additionally, in an animal study, intranasal administration of 23 nm AgNPs resulted in microglial activation, destructing the cerebellum granular layer. This process caused cerebellar ataxia-like symptoms in rats, as well as motor dysfunction and impaired locomotor activity.[124] Autophagy significantly affects microglial inflammation and phenotype transformation.[125] Shang *et al.*[126] explained that AgNPs promoted M1 polarization and inflammation in microglia in a time- and dose-dependent manner by avoiding the fusion of autophagosomes with lysosomes, thereby altering the lysosomal function and impairing autophagy. This finding provides insights into the molecular mechanisms behind AgNP-induced neurotoxicity.[127] Moreover, Huang *et al.* reported that AgNPs promoted neuroinflammation, oxidative stress, and Aβ deposition in microglia, which was mediated by the secretion of IL-1β, the production of CXCL13 (C-X-C motif chemokine 13), macrophage receptor with collagenous structure (MARCO), and glutathione synthetase (GSS).[100] One of the key concerns about AgNPs is their potential to exacerbate neurodegenerative diseases like AD. Aβ deposits cause toxicity to neurons as they cause proinflammatory responses and oxidative stress in the CNS.[128] Since AgNPs and Aβ both are taken up by microglia *via* the scavenger receptor 1 (Scara1), AgNPs may compete with Aβ for uptake, potentially impairing Aβ clearance and worsening AD pathology.[129–131] Sikorska *et al.* also observed that the AgNPs accompanied by cerium oxide nanoparticles (CeO_2NPs) reduced microglial phagocytic activity and amyloid-β (Aβ) uptake by BV-2 microglia, which may assist in the AD pathogenesis. AgNPs also attenuated the microglial viability once combined with cadmium telluride quantum dots (CdTe-QDs), favoring the pathogenesis of AD.[129]

On the contrary, some studies suggest that AgNPs can exhibit anti-inflammatory and neuroprotective properties. For example, AgNPs, in combination with CdTe-QDs or CeO_2NPs, even at relatively nontoxic concentrations, could decrease microglial growth by arresting the cell cycle at the G1 phase or S phase, respectively. This suggests a new approach to alleviate neuroinflammation and further disorders.[129] Likewise, Lyu *et al.* confirmed that using AgNPs reduced the number of microglia, supporting their anti-inflammatory role.[132] Moreover, citrate-capped AgNPs have demonstrated both anti-inflammatory and antioxidant effects in microglia. These AgNPs were specifically absorbed by microglia and further reduced LPS-stimulated NO, ROS, and TNFα production, leading to less neurotoxicity of microglia for dopaminergic neurons. Also, LDH release, following AgNP treatment, showed a significant reduction, underscoring the role of AgNPs in heightening neuronal cell viability (Fig. 3).[133] Furthermore, the inhibitory role of biogenic AgNPs in LPS-induced neuro-inflammation by HMC3 microglial cells was studied. Cotreatment with AgNPs significantly decreased the production of inflammatory markers while increasing anti-inflammatory markers, facilitating a shift from M1 to M2 phenotype in microglia. Therefore, biogenic AgNPs are able to defend CNS against oxidative stress and neuroinflammation.[134]

Consequently, the effects of AgNPs on microglia in the context of neurodegenerative diseases remain controversial. While some studies highlight the proinflammatory and neurotoxic potential of AgNPs, others demonstrate their anti-inflammatory and neuroprotective effects. Therefore, AgNPs act as a double-edged sword in neuroinflammation. Further investigation is required to better perceive their mechanisms and ensure their safe and appropriate use to treat CNS disorders.

6.3. Iron oxide nanoparticles (IONPs)

IONPs are a class of magnetic NPs that have garnered considerable interest for their potential applications in biomedicine and bioengineering. IONPs have recently been explored for drug delivery systems, particularly for their ability to modulate microglia activity and reduce neuroinflammation.[135] Along with it, this section reviews several studies to determine the effect of

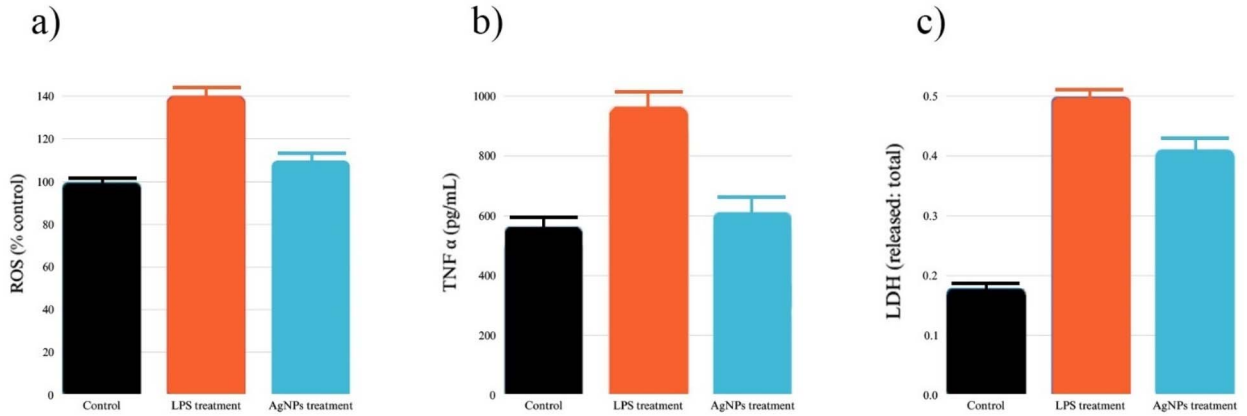

Fig. 3 Anti-inflammatory effects of AgNPs on microglial cells (a and b) N9 microglial cells were treated with LPS (500 ng mL^{-1}) with or without AgNPs for a 1 h pulse period. Then, a 24 h chase period was considered. Microglial inflammation was assessed through evaluation of (a) ROS production and (b) TNFα release following AgNP treatment. (c) N9 microglia were treated for 1 h (pulse) with AgNP (50 μg mL^{-1}) and/or LPS (500 ng mL^{-1}). Then, a 24 hours chase period was considered with only LPS present. The medium was then transferred to N27 neurons and incubated for 48 hours. Afterward, the cell viability was assessed through LDH release examination. Adapted from Gonzalez-Carter *et al.*[133]

this NP on microglia-mediated neuroinflammation during drug delivery.

Iron oxide-based metal NPs are primarily internalized by microglia, mainly through clathrin-mediated endocytosis and macropinocytosis, after which they accumulate in the lysosomal compartment.[136] This accumulation in lysosomes plays a crucial role in modulating microglial activity. Interestingly, Wu *et al.* showed that accumulated IONP attenuated the expression of IL-1β in LPS-stimulated microglia by affecting the secretory lysosomal pathway. In addition, the IL-1β converting enzyme (ICE) was inhibited in microglia following the treatment with IONP by preventing the activity of cathepsin B, an enzyme responsible for IL-1β activation. These findings suggest that IONPs efficiently suppress IL-1β production, highlighting their potential for use in drug-delivery systems that target inflammation.[137] Another critical area of investigation is the ability of microglia to alleviate tau pathology in neurodegenerative conditions such as AD. In this regard, Glat *et al.*[138] showed the efficacy of iron oxide (γ-Fe_2O_3) NPs in delivering fibrin γ377–395 peptides to nervous tissue. Stabilizing the peptide to γ-Fe_2O_3 NPs significantly decreased the activated microglia in comparison with the same concentration of the free peptides. Therefore, the authors suggested γ-Fe_2O_3 NPs as suitable carriers for the controlled release of medicine in the CNS. Wang *et al.*[139] also observed that Fe_2O_3 NPs induced the proliferation of microglia, enhanced phagocytosis, and increased ROS and NO production in microglia. However, the study noted no significant production of inflammatory cytokines, namely, IL-6, IL-1β, and TNF-α, implying that IONPs may boost some microglial functions without causing overt inflammation.

Despite their promising applications, many studies have evidenced the potential detrimental impacts of IONPs on microglia. As reported by Petters *et al.*,[140] IONP exposure triggered ROS production by microglia, causing cellular and tissue damage. Additionally, the IONP accumulation in microglia could lead to changes in microglial morphology and function, potentially disrupting their usual tasks in the brain. Similarly, Luther *et al.* noted that prolonged exposure to IONPs compromised microglial cell viability, raising concerns about long-term use of these NPs in the brain.[136]

IONPs offer a noteworthy ability to deliver drugs, particularly in their ability to regulate microglial activity and mitigate neuroinflammation. However, the dual nature of their effects—both as modulators of inflammation and potential toxicity sources—necessitates further investigation. While some studies have shown their efficacy in reducing proinflammatory cytokine production and promoting drug delivery to the CNS, others have indicated possible adverse outcomes, such as the generation of ROS and compromised microglial viability. Consequently, more comprehensive research is required to make sure IONPs are safe and efficient as therapeutic agents for CNS-related conditions.

6.4. Cobalt nanoparticles (CoNPs)

CoNPs have been extensively utilized due to their catalytic, electrical, and magnetic properties. Intriguingly, it has been reported that CoNPs can enter the CNS, possibly due to their resemblance to local air pollutants, which can be inhaled.[141] Prolonged exposure to cobalt dust in occupational settings has been associated with cognitive impairments, including reduced memory deficits and attention, showing that cobalt over-intake may contribute to neurodegenerative changes.[142] However, the exact effects of CoNPs on triggering neurodegeneration and the underlying mechanisms remain mostly unexplored.

Recent studies have paved the way for understanding the potential neurotoxic and pro-inflammatory effects of CoNPs. In this way, Li *et al.* illustrated that CoNPs induced toxicity and inflammatory responses in microglial BV2 cells by activating NADPH oxidase 2 (NOX2). CoNPs in both BV2 cells and mouse brains (the hippocampus and cortex) further catalyzed ROS production and upregulation of IL-1β and NLRP3, which are inflammation-related proteins. Additionally, CoNP exposure was linked to increased tau phosphorylation, which is a hallmark of neurodegenerative diseases.[142] Similarly, a survey by Zheng *et al.* reported that CoNPs were capable of inducing

microglial activation, leading to the expression of oxidative stress-related substances NRF2, heme oxygenase-1 (HO-1), and malondialdehyde (MDA) in the hippocampus and cortex of the rat brain.[143] These results indicate that CoNPs can induce significant inflammation and oxidative stress in the brain.

While these studies provide initial insights into the impacts of CoNPs, the limited research on this topic underscores the need for further investigations. The potential proinflammatory effects of CoNPs during drug delivery warrant a deeper understanding of their interactions with microglia and their long-term implications for neurodegenerative processes. Continued research is essential to elucidate how CoNPs may contribute to neuroinflammation and cognitive decline, ultimately identifying their safe application in biomedical contexts.

6.5. Zinc oxide nanoparticles (ZnONPs)

ZnONPs can be easily found in various forms. Some physicochemical properties of ZnONPs, including their surface charge, morphology, concentration, purity, and size impact the interaction of ZnO with microglia. ZnONPs have been found to cause neurotoxicity through microglial activation, which is a significant cause of concern.[144,145]

Several studies have shown that ZnONPs trigger apoptosis in the murine microglial cell line N9 by generating ROS and depleting cellular energy,[146,147] leading to neuronal damage[148] or self-destructive processes.[149] Wei *et al.* indicated that ZnONPs significantly raised ROS levels and oxidative stress in a time-dependent way in BV-2 cells, which occurred through autophagy and PINK1/parkin-mediated mitophagy.[150] Moreover, Sharma *et al.* found that ZnONPs disrupted matrix metalloproteinases (MMPs) and subsequently activated the apoptotic pathway in microglia *via* NADPH oxidase-independent ROS generation and ATP depletion. This microglial apoptosis exacerbates the existing neuroinflammation.[146] Also, it has been reported that ZnONPs induce a nonapoptotic mode of cell death in microglia, which is probably driven by ROS accumulation, leading to lysosomal destabilization and extensive damage to mitochondria and lysosomes. This nonapoptotic cell death can severely damage the brain by accumulating ROS and releasing lysosomal enzymes and cell debris, resulting in severe neuroinflammation.[151] ZnONPs have also triggered several inflammatory responses. For instance, a study claimed that ZnONPs activate NF-κB, Ca^{2+}-dependent extracellular signal-regulated kinase (ERK), and p38 pathways in BV2 microglia following tongue instillation.[152] Similarly, Liu *et al.* revealed that even nontoxic concentrations of ZnONPs led to BV2 proliferation and activation through the Akt (protein kinase B) and ERK signaling pathways.[153] Another paper studied the acute outcomes of pulmonary exposure to ZnONPs in a rat model. The results indicated that acute exposure to ZnONPs induces microglial activation, tau protein expression, and oxidative stress in the brain, contributing to neurotoxicity.[154]

Despite the concerns associated with ZnONPs, some studies have reported potential benefits. In this respect, a survey by Moustafa *et al.* on diabetic patients revealed that luteolin/ZnONPs could regulate microglial polarization by targeting brain CCAAT/enhancer-binding protein (C/EBPA mRNA). These NPs also alleviated inflammation by modulating redox-sensitive signal transduction pathways. Therefore, it was concluded that luteolin/ZnONPs may offer a novel approach to protecting BBB and preventing neurological complications.[155]

The adverse effects of ZnONPs on microglial neuroinflammation appear to outweigh their potential benefits in promoting brain health. Urgent and comprehensive studies should be conducted to thoroughly investigate the possible positive and negative effects of ZnONPs on microglia-related neuroinflammation. This is crucial to determine a safer dosage with minimal side effects for patients suffering from neurodegenerative disorders.

6.6. Titanium dioxide nanoparticles (TiO_2NPs)

TiO_2NPs are widely applied across various sectors, including chemical, electrical, electronic, medical, cosmeceutical, and industrial fields. TiO_2NPs can enter the brain directly through the olfactory bulb and accumulate in the hippocampus. Recent studies have raised concerns about the potential harm TiO_2NPs pose to biological systems, particularly regarding their toxicity to the CNS.[156] Nonetheless, the toxicity of TiO_2NPs to the CNS has been poorly investigated so far.

Rihane *et al.* evidenced that TiO_2NPs predominantly accumulate in BV-2 cells, promoting mitochondrial dysfunction following oxidative stress. These NPs also cause various side effects, such as damaging the permeability of cell membranes, ROS overproduction, and inhibiting cell adhesion with a loss of mitochondrial transmembrane potential, thereby leading to microglia apoptosis.[157] Additionally, Sheng *et al.* highlighted that TiO_2NPs contribute to the apoptosis of primary hippocampal neurons and microglia.[158] On top of that, recent reports have indicated that low concentrations of TiO_2 stimulate BV2 microglia to undergo immediate and prolonged release of ROS, damaging neurons in brain striatum cultures.[148,159] Shin *et al.*[160] reported that ultrafine TiO_2NPs stimulate the release of inflammatory mediators, encompassing IL-1β, TNF-α, and mRNA in the brains of LPS-exposed mice. These NPs also enhanced NF-κB binding activity in LPS-stimulated BV2 microglia. Therefore, the study suggests that nanosized TiO_2-NPs promote exaggerated neuroinflammatory responses by activating microglia. In line with this, another study found that LPS-activated BV-2 cells took more TiO_2NPs up compared to non-activated cells, leading to increased IL-6, ROS, MCP-1, and IL-1β.[161] Along with it, Xue *et al.*[162] showed that TiO_2NPs induced significant iNOS expression and subsequent NO secretion, accompanied by upregulation of chemokines through NF-κB activation in NP-stimulated microglia *in vitro*. This study also indicated raised levels of pro-inflammatory cytokines.

To conclude, TiO_2NPs activate microglia and neuroinflammation using various pathways. Given the small number of papers written on TiO_2NPs and the scarcity of positive findings, additional research is essential to comprehensively understand the mechanisms in charge of the harmful effects of TiO_2NPs on microglia-related neuroinflammation. These

findings will facilitate the evolution of strategies for the secure and efficient employment of TiO_2NPs in the treatment of neurodegenerative diseases.

6.7. Silica nanoparticles (SiO_2NPs)/Silicon nanoparticles (SiNPs)

Silica nanoparticles (SiO_2NPs), one of the most widely employed types of NPs, have been applied across various industries.[163] Nanosized SiO_2 can cross the BBB, making them valuable for delivering therapeutic and diagnostic agents.[164] The exposure to SiO_2 does not significantly influence the viability of various neural cells, and it also does not cause neuroinflammation.[165] However, long-term exposure to these NPs can cause cognitive impairment, mood dysfunction, and synaptic alterations, potentially by activating mitogen-activated protein kinases (MAPKs).[166] Therefore, the potential of SiO_2NPs for treating microglia-induced neuroinflammation merits further exploration.

SiO_2NPs have shown potential in activating microglia. In line with this, in a study, after exposure to fluorescein isothiocyanate-tagged SiO_2NPs (FITC-SiO_2-NPs),[167,168] the number of Iba-1- stained microglia significantly rose in the hippocampus in comparison with the controls.[166] Consistently, a study showed that silica-coated magnetic NPs containing rhodamine B isothiocyanate dye (MNPs@SiO_2(RITC)) morphologically activated BV2 murine microglia and increased Iba1 expression, an activation marker protein.[169] The study also demonstrated that microglia activation elevated serine protein levels in the growth medium. Notably, the secretion of excitotoxic D-serine from primary rat microglia was significantly upregulated, which in turn decreased intracellular ATP and activity of the proteasome in cocultured neuronal cells, particularly in primary cortical neurons. This led to the accumulation of ubiquitinated proteins and the formation of inclusion bodies in cortical and primary dopaminergic neurons cocultured with activated microglia. Thus, the activation of microglia by MNPs@SiO_2(RITC) initiates excitotoxicity in neurons through the secretion of D-serine, underscoring the neurotoxic processes triggered by microglial activation.[156] SiO2NPs are likely to produce inflammatory agents and cause neuroinflammation. In this way, Xue *et al.* demonstrated that SiO_2NPs enhance the proinflammatory cytokines (TNF-α, IL-1β, and IL-6).[162] Additionally, the findings of another study illustrated that deficient SiNP levels could change microglial function. In turn, alteration in proinflammatory genes, cytokine release, and heightened RNS and ROS production adversely affect not only microglial function but also surrounding neurons.[170] Correspondingly,

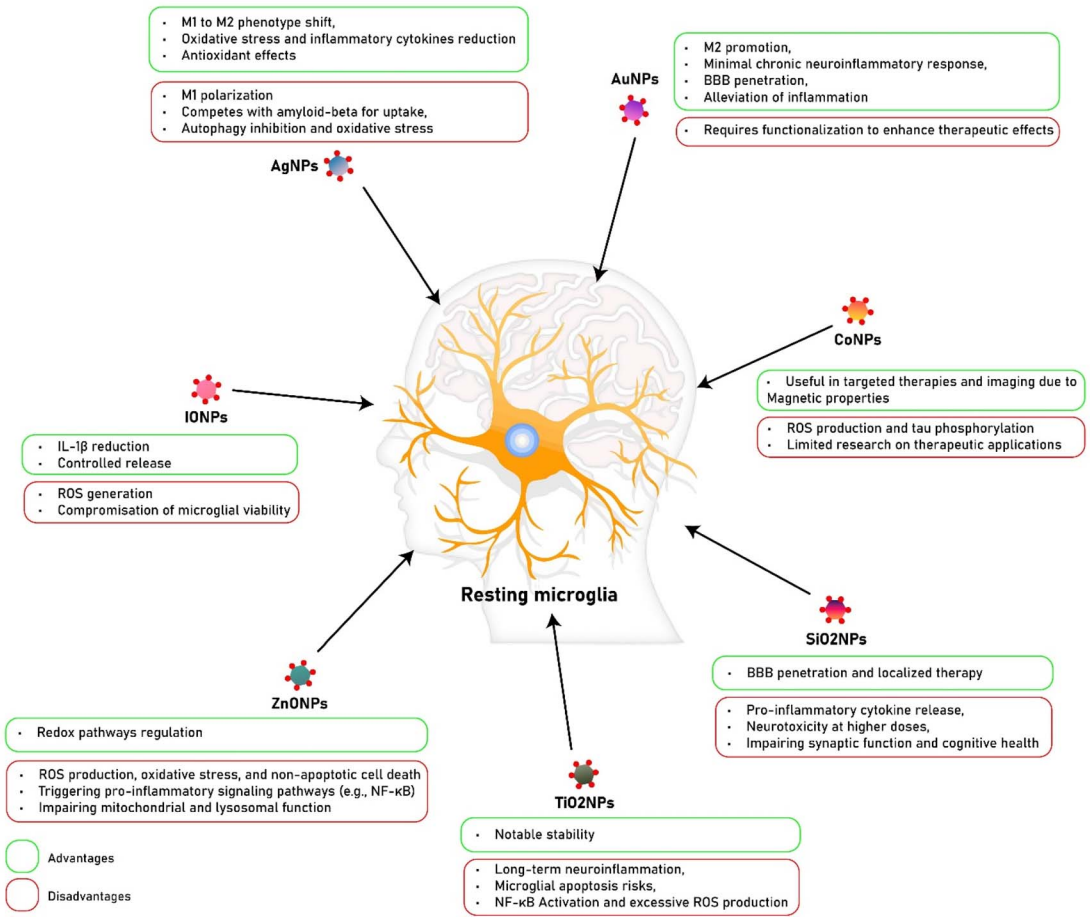

Fig. 4 The advantages and disadvantages of drug-loaded metal NPs in microglia-induced neuroinflammation.

MNPs@SiO_2(RITC) were shown by another study to enhance ROS production in a dose-dependent manner.[171] The findings of another research indicated that the viability of MNPs@SiO_2(-RITC) was gradually reduced with increasing SiO_2NP concentration and exposure duration. The findings indicated that SiNPs could penetrate the cytoplasm, alter the ultrastructure, activate the NLRP3 inflammasome, release a multitude of inflammatory molecules, and start inflammatory reactions. SiNPs were also discovered to induce ferroptosis, increase intracellular ferrous ion levels, and disrupt cellular antioxidant function.[170]

In summary, the studies reviewed suggest that SiO_2NPs possess the potential to induce microglial activation and neuroinflammation, negatively impacting neuronal health. Due to the scarcity of studies on the positive influences of these NPs on microglia-related neuroinflammation, the potential of SiO_2NPs for treating neuroinflammation deserves further research to fully elucidate the risks of exploiting this nanoparticle.

Regarding the explained studies, Fig. 4 illustrates the advantages and disadvantages of each metal NP in the inhibition of microglia-mediated neuroinflammation.

7. Conclusion

Microglia are central to neuroinflammation and neurodegeneration, capable of both protecting and harming the CNS. Metal nanoparticles offer exciting potential for targeting microglial activity due to their ability to cross the BBB and move medicines directly to the brain. However, their dual effects, ranging from neuroprotection to exacerbation of inflammation, necessitate careful consideration. While AuNPs and certain IONPs show promise in reducing neuroinflammation, other NPs like AgNPs, ZnONPs, and TiO_2NPs have been linked to increased neurotoxicity. As the field progresses, future research is proposed to focus on deciphering the specific mechanisms underlying nanoparticle–microglia interactions, paving the way for targeted and safe interventions for neurodegenerative diseases. A comprehensive understanding of these interactions will enhance the therapeutic potential of nanoparticles and ensure neural homeostasis. In this dynamic landscape, interdisciplinary collaboration and continued exploration are essential to address these challenges and unlock the full therapeutic potential of nanoparticles in neurodegenerative disorders.

8. Challenges

Despite the promising potential of metal nanoparticles (NPs) in treating neuroinflammation and modulating microglial activity, several critical challenges remain.

8.1. Toxicity and biocompatibility

The biocompatibility of NPs is a key factor in their clinical translation. Although some NPs, such as gold nanoparticles (AuNPs), are considered relatively safe, others, like silver nanoparticles (AgNPs), can induce oxidative stress and pro-inflammatory responses in microglial cells at higher concentrations. The dose-dependent duality of these effects necessitates precise dose optimization and the development of biocompatible coatings to mitigate toxicity.

8.2. Blood–brain barrier (BBB) permeability

While the nanoscale size of certain NPs facilitates their ability to cross the BBB, their transport efficiency and distribution in targeted brain regions remain inconsistent. Surface charge, hydrophilicity, and interactions with serum proteins can impact their BBB permeability and bioavailability, limiting therapeutic outcomes.

8.3. Stability in biological environments

The physicochemical stability of NPs in the dynamic and complex CNS environment is a significant challenge. Non-functionalized NPs are prone to aggregation and premature clearance, while improperly stabilized particles may lose activity before reaching their target. Effective functionalization strategies are required to enhance stability, circulation time, and targeted delivery.

8.4. Long-term safety and accumulation

The long-term effects of NPs, including potential accumulation in brain tissues, remain poorly understood. Chronic exposure could lead to neurotoxicity, inflammation, or immune system interference. Comprehensive *in vivo* studies are needed to evaluate their safety profiles under prolonged use.

8.5. Immune system interactions

NPs may inadvertently activate peripheral or central immune responses, complicating their therapeutic use. Understanding and mitigating these interactions is critical for reducing adverse effects and enhancing therapeutic specificity.

9. Future perspective

9.1. Development of advanced nanoparticle designs

The engineering of next-generation NPs with precise targeting capabilities is paramount. Functionalization with ligands specific to inflammatory markers or activated microglia can enhance therapeutic specificity while reducing off-target effects. Stimuli-responsive NPs that release their therapeutic payload in response to pH, temperature, or inflammatory signals could provide controlled and localized treatment.

9.2. Exploration of biodegradable nanoparticles

The development of biodegradable NPs that degrade into non-toxic byproducts after delivering their cargo is crucial for minimizing long-term risks. Materials such as polymers, lipid-based carriers, or naturally derived compounds should be further explored to ensure both efficacy and safety.

9.3. Combination therapies

Leveraging the co-delivery capabilities of NPs to carry multiple therapeutic agents, such as anti-inflammatory drugs, antioxidants, or gene therapy vectors, can target multiple pathways simultaneously. These approaches could provide synergistic effects, particularly in complex disorders like Alzheimer's disease or Parkinson's disease.

9.4. In-depth mechanistic studies

Detailed studies on the molecular mechanisms of NP-microglia interactions are essential. Investigating how NPs influence microglial polarization between pro-inflammatory (M1) and anti-inflammatory (M2) states can guide the design of more effective therapeutic strategies.

9.5. Preclinical and clinical translation

Long-term safety, pharmacokinetics, and efficacy studies in animal models are vital for bridging the gap between preclinical research and clinical application. Establishing standardized protocols for NP synthesis, characterization, and biological testing will also facilitate regulatory approval and clinical trials.

9.6. Interdisciplinary collaboration

The successful translation of NP-based therapies requires collaboration across disciplines, including materials science, neuroscience, pharmacology, and toxicology. Integrating advanced imaging, computational modeling, and machine learning techniques can accelerate NP design and optimize therapeutic outcomes.

By addressing these challenges and exploring these prospective directions, nanoparticle-based therapies could revolutionize the treatment of neuroinflammation and related CNS disorders.

List of abbreviations

CNS	Central nervous system
AuNP	Gold nanoparticle
AgNP	Silver nanoparticle
IONP	Iron oxide nanoparticle
SiO_2NP	Silica nanoparticle
ZnONP	Zinc oxide nanoparticle
CoNP	Cobalt nanoparticle
TiO_2NP	Titanium oxide nanoparticle
TNF-α	Tumour necrosis factor alpha
DAMPs	Danger-associated molecular patterns
PGE2	Prostaglandin E2
PAMPs	Pathogen-associated molecular patterns
CR and CR	Complement receptors
CD	Cluster of differentiation
IL	Interleukin
ROS	Reactive oxygen species
TLR and TLR	Toll-like receptors
BACE	Beta-secretase enzyme
iNOS	Inducible nitric oxide synthase
COX2	Cyclooxygenase-2
BBB	Blood–brain-barrier
ECM	Extracellular matrix
NPs	Nanoparticles
TGN	*Trans*-Golgi network
Iba-1	Ionized calcium-binding adapter molecule
ALTs	Astrocyte-like
N2a	Neuro2a
NF-κB	Nuclear factor-κB
SPIONPs	Superparamagnetic iron oxide nanoparticles
MPI	Magnetic particle imaging
DHLA	Dihydrolipoic acid
FIB	Fibrinogen
BS	Bovine serum
PC	Protein corona
JAK/STAT	Janus kinase/signal transducers and activators of transcription
PEGylated AuNPs	polyethyleneglycol-coupled AuNPs
PM-AuNPs	*Paeonia moutan* to functionalize GNPs
CeO_2NPs	Cerium oxide nanoparticles
Aβ	Amyloid-β
GSS	Glutathione synthetase
AD	Alzheimer's disease
MMP	Matrix metalloproteinases
AnPEG-GNPs	Anthocyanins conjugated with PEG-GNPs
MAPKs	Mitogen-activated protein kinases
MARCO	Macrophage receptor with collagenous structure
FITC	Fluorescein isothiocyanate
ERK	Extracellular signal-regulated kinase

Data availability

This article does not include primary research data, software, or code. It is a review article that discusses findings from various studies in the field with all data and figures cited from previously published sources. No new data were generated or analyzed in the preparation of this article.

Author contributions

Masood Alaei, Khadijeh Koushki, and Kimia Taebi contributed to the conceptualization and methodology, collected data, and drafted the manuscript. Masood Alaei illustrated the figures and charts. Mahdieh Yousefi Taba and Samaneh Keshavarz Hedayati co-operated in writing and drafting the manuscript. Sanaz Keshavarz Shahbaz participated in supervising, providing critical review, commentary, and revising the final draft of the manuscript.

Conflicts of interest

All the authors declare no conflicts of interest related to this manuscript.

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