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Pharmacological Modulation of Neuroinflammation in Neurodegenerative Diseases: Current Insights and Future Perspectives

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Abstract: In the development of neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Huntington's disease, neuroinflammation has been recognized as a major role player. It is characterized by persistent microglia and astrocyte activation, excess release of cytokines, and oxidative stress leading to neuronal homeostasis disturbance and neurodegeneration. In this extended review, we provide a snap-shot of some of the key players and molecular constituents involved in chronic neuroinflammation. It also examines pharmacological modulation therapies via cytokine signaling, glial activation and oxidative stress pathways for the reduction of neuronal loss. Emerging data emphasizes the influence of novel therapeutic drugs like inflammasome antagonists, kinase inhibitors and neuroprotective nutraceuticals on modulation of inflammation. The review also considers challenges of translating preclinical observations to clinical benefit, such as restrictions associated with the blood–brain barrier, drug toxicity and heterogeneity in disease. Elucidating neuroinflammatory mechanisms may lead to safer and more effective pharmacological treatments for neurodegenerative diseases.

Keywords: Neuroinflammation; Neurodegeneration; Microglia; Astrocytes; Cytokines; Alzheimer's disease; Parkinson's disease; Multiple sclerosis; Pharmacological modulation; Neuroprotection.

I.INTRODUCTION

Neuroinflammation represents an endogenous defense mechanism of the CNS, elicited by infection, injury or abnormal proteins conformation. During physiological condition, glial activation provides protection, while long duration of the activated state leads to pathological inflammation and permanent loss of neurons [1]. Chronic neuroinflammation is now considered as a common denominator of various clinical entities in neurodegenerative diseases [2].

In the CNS, microglia are homeostatic tissue-resident immune cells that serve as sentinels. Upon exposure to stress or accumulated proteins, namely amyloid-β, α-synuclein, and mutant SOD1, microglia can be activated and polarized in the pro-inflammatory M1 region. These cells secrete TNF-α, IL-1β and NO leading to oxidative stress and neurotoxicity [3,4]. By contrast, M2-polarized microglia may contribute to repair by secreting IL-10 and transforming growth factor-β (TGF-β) [5]. Imbalance of this M1/M2 ratio is largely implicated in neuronal apoptosis and synapse dysfunction.

Astrocytes also contribute to the inflammatory background. Hypertrophy and up-regulation of glial fibrillary acidic protein (GFAP) highlight reactive astrocytosis. Acute protection is provided initially, with a chronic activation of astrocytes implicated in causing the maintenance of inflammation by cytokine release, glutamate excitotoxicity and

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blood–brain barrier (BBB) disruption [6]. Astrocytic signalling through JAK/STAT and NF-κB pathways sustains microglial activation, generating a feedforward toxic cycle [7].
Mitochondrial impairment (including generation of an excessive amount of ROS and RNS) results in inflammation, oxidative DNA damage and reduced ATP production [8]. In total, these processes establish a detrimental loop of inflammation inducing oxidative stress that further increases the inflammatory signalling [9].

Taken together, these cellular and molecular changes underscore the Janus-faced role of neuroinflammation: beneficial when limited in extent/regulatory but deleterious when persistent. Knowledge of this intricate balance has allowed for pharmacological manipulation to favor immune homeostasis within the CNS.

II.MOLECULAR MECHANISMS AND PATHWAYS OF NEUROINFLAMMATION

2.1 Microglial Polarization
Microglia are the main modulators of the neuroinflammatory response. The M1 type is activated in the presence of interferon-γ and lipopolysaccharide, whereas the M2 type in response to IL-4 and IL-13. M1 microglia cells express iNOS and subsequently produce ROS, NO, and pro-inflammatory cytokines, whereas M2 microglial cells secrete Arg-1, IL-10, neurotrophic factors [10]. Loss of phenotypic transition leads to durable neurotoxicity. Pharmacological agents with the ability to redirect microglial reactivity towards the M2 phenotype including minocycline, resveratrol, and pioglitazone have been proposed as potential drugs for attenuating disease progression [11,12].
2.2 Astrocyte-Mediated Inflammation
Astrocytes control synaptic transmission and barrier of BBB. In the pathological environment, they produce IL-6, MCP-1 and MMPs destructing networks of the neurons [13]. Excess S100B and glutamate from reactive astrocyte leads to excitotoxicity and Ca2+ overload. Further, crosstalk with microglia by way of IL-1β and TNF-α maintains expression of inflammatory genes [14]. Inhibition of astrocyte activation by JAK/STAT inhibitors or natural flavonoids has been discussed as an adjuvant therapy.
2.3 The NF-κB Pathway
The transcriptional complex of nuclear factor-κB (NF-κB) governs inflammation. It is induced by TLRs, TNF receptors and oxidative stress. Now free from IκB, NF-κB translocates to the nucleus and induces the up-regulation of TNF-α, IL-1β and COX-2. Chronic NF-κB activation has been described in the hippocampus of Alzheimer's disease and the substantia nigra of Parkinson's disease [15]. It inhibits this pathway to decrease cytokine production and salvage neurons.
2.4 NLRP3 Inflammasome Activation
The NLRP3 inflammasome is a sensor for cellular stress and drives the maturation of IL-1β and IL-18 via caspase-1 activity. The misfolded Aβ, α-synuclein and environmental toxins serve as strong third-party activators. Small molecules that inhibit NLRP3 like MCC950 block microglia activation and neuronal loss in animal models [16].
2.5 MAPK and JAK/STAT Signalling
The mitogen-activated protein kinase (MAPK) family including ERK, JNK and p38 regulates glial cytokine expression and apoptosis. Hyperactivation of p38 MAPK promotes tau hyperphosphorylation and synaptic dysfunction [17]. On the other hand, the JAK/STAT pathway mediates cytokine signals in astrocytes and microglia, with STAT3 activation associated with astrocytic reactivity. Pharmacologic inhibitors that potently target a specific kinase can therefore regulate the intensity of neuroinflammation.

Table 1. Key Molecular Pathways in Neuroinflammation [18]

Pathway	***Primary Role***	***Effect on CNS***	***Therapeutic Modulators***
NF-κB	Cytokine gene transcription	Chronic inflammation and apoptosis	Curcumin, Celastrol
NLRP3 Inflammasome	IL-1β/IL-18 maturation	Neuronal pyroptosis	MCC950, OLT1177
MAPK (p38, JNK, ERK)	Glial activation, stress signalling	Tau phosphorylation	SB203580, U0126
JAK/STAT	Astrocyte signalling	Sustained GFAP expression	Tofacitinib, Ruxolitinib
ROS/NO Pathway	Oxidative damage mediator	Lipid peroxidation, DNA injury	NAC, Coenzyme Q10

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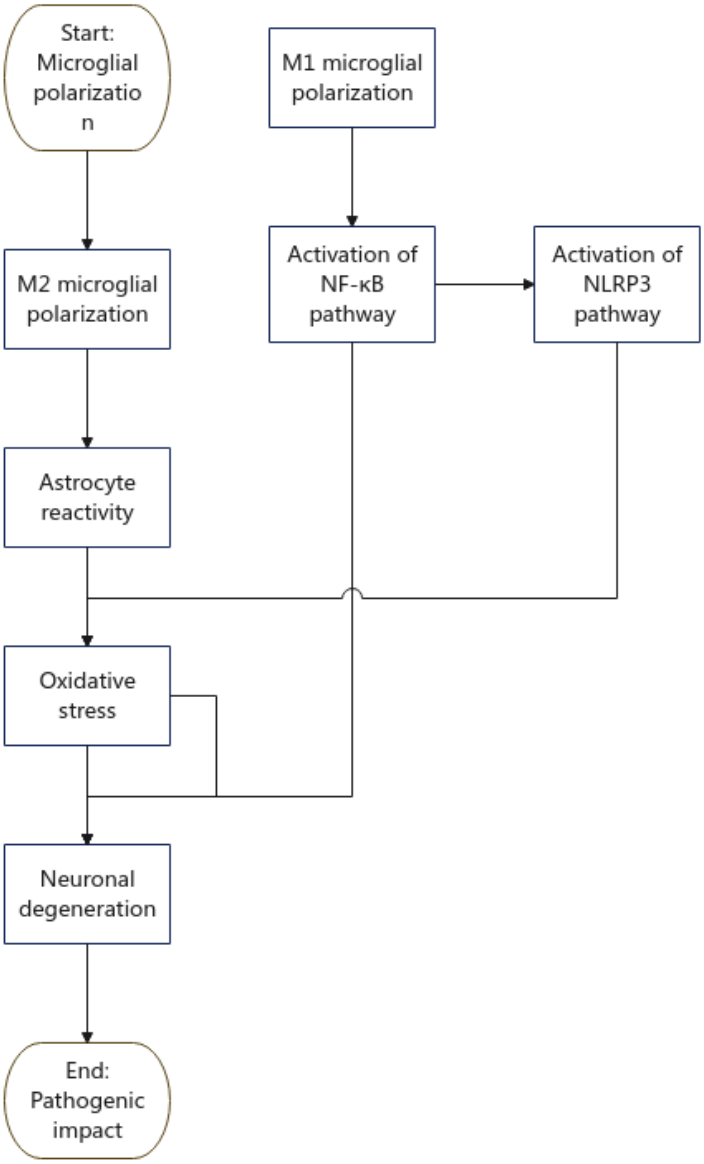

Figure 1. Schematic representation of microglial polarization and neuroinflammatory signaling in neurodegeneration.

III.PHARMACOLOGICAL MODULATORS OF NEUROINFLAMMATION

Pharmacological modulation aims to interrupt inflammatory cascades at multiple points. Both synthetic drugs and natural molecules have been explored to counteract microglial activation, cytokine release, and oxidative stress.

3.1 Non-Steroidal and Steroidal Anti-Inflammatory Agents

Non-steroidal anti-inflammatory drugs (NSAIDs), including indomethacin, ibuprofen and naproxen [1–3], also suppress the activity of COX enzymes to decrease prostaglandin synthesis. Epidemiological evidence indicates that long-term use of NSAID is associated with reduced risk for Alzheimer's disease, however clinical benefits are modest because of gastrointestinal and cardiovascular side effects [19]. Corticosteroids are effective, but have poor BBB infiltration and systemic toxicity limit long-term application [20].

3.2 Natural Compounds and Nutraceuticals

Polyphenols such as curcumin, resveratrol and epigallocatechin gallate (EGCG) have antioxidant and anti-inflammatory activities. These agents regulate NF-κB and MAPK signaling pathways, suppress microglial activation and promote the expression of neurotrophic factors [21]. The pharmacokinetic challenges are being addressed with development of curcumin analogs that have increased bioavailability. Omega-3 fatty acids and vitamins E and D also influence cytokine production and neuronal resistance [22].

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3.3 Inflammasome and Kinase Inhibitors

Selective targeting of inflammasome and kinase signalling pathways: a new therapeutic approach. MCC950, CY-09 and dapansutrile all interfere with NLRP3 activation to reduce IL-1β secretion. Inhibition of p38 MAPK (SB203580) or JAK/STAT (tofacitinib, ruxolitinib) reduces cytokine-overuse in glial cells in a similar fashion [23]. Cotreatment with such agents and antioxidant may potentiate the effectiveness of drugs and reduce toxicity.

3.4 Neuroprotective Peptides and Monoclonal Antibodies

Therapeutic Approaches to Treatment/Mitigation The damage caused by venom is reversible if therapeutic agents are available ideally at the time of envenomation, but in some cases early use may still be very helpful. Monoclonal antibodies against pro-inflammatory cytokines like anti-TNF-α (infliximab) and anti-IL-6 (tocilizumab) – have been suggested promising in the experimental models of multiple sclerosis and Parkinson's disease [24]. Neurotrophic peptide cerebrolysin has anti-apoptotic and anti-inflammatory activities that support survival of neurons [25].

Table 2. Major Pharmacological Strategies Targeting Neuroinflammation

Drug/Class	***Mechanism of Action***	***Therapeutic Potential***
NSAIDs (Ibuprofen, Naproxen)	COX inhibition, reduced prostaglandins	Mild symptomatic relief in AD, PD
Corticosteroids	Broad immunosuppression	Limited by systemic toxicity
Curcumin, Resveratrol	NF-κB and MAPK inhibition	Multi-target neuroprotection
MCC950, CY-09	NLRP3 inflammasome inhibition	Reduction in IL-1β, neuronal survival
Tofacitinib, Ruxolitinib	JAK/STAT pathway inhibition	Attenuation of astrocyte reactivity
Coenzyme Q10, NAC	Antioxidant activity	Redox balance restoration

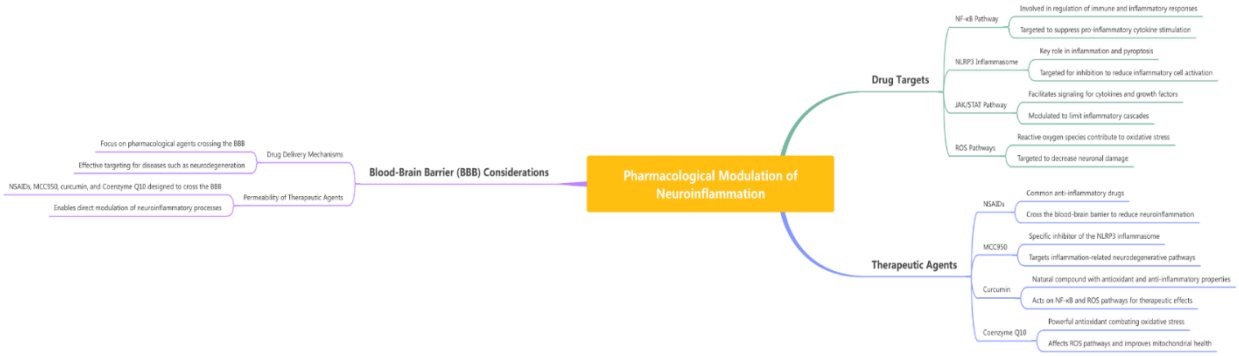

Figure 2. Pharmacological modulation of neuroinflammatory pathways in neurodegenerative diseases.

IV. CLINICAL AND TRANSLATIONAL INSIGHTS

However, even though preclinical data are promising, the transition to clinically effective anti-neuroinflammatory agents is difficult. The CNS drug delivery is limited by the blood–brain barrier, and a large number of molecules are poorly bioavailable [26]. Furthermore, inflammatory signatures were heterogenous across neurodegenerative diseases and require personalized treatment.

Nanocarrier systems (such as liposomes, polymeric NPs, and solid lipid NPs) enable better penetration of the BBB and controlled drug release [27]. Beneficial effects of nanoparticles-mediated curcumin or MCC950 delivery have been explored and better neuroprotection was achieved in experimental models. Biologics targeting anti-TNF and anti-IL-6 have led to limited benefit in clinical trials, indicating that early intervention before irreversible neuronal loss is necessary. Anti-inflammatory drugs could also be synergistic with antioxidants, mitochondrial agents or neurotrophic factors [28].

V. FUTURE PERSPECTIVES

Future neuropharmacological strategies should make way for multi-target interventions combining immunomodulation, antioxidant defence as well as neurorestoration. Gene-editing tools like CRISPR/Cas9 may contribute to fine-tuning of inflammatory gene expression. Omics and AI-aided discovery of drugs will make it increasingly easier to pinpoint new targets and biomarkers [29]. In addition, lifestyle interventions (diet, exercise and cognitive stimulation) synergize with pharmacotherapy by decreasing systemic inflammation and promoting resilience of neural circuits.

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VI. CONCLUSION

Neuroinflammation at the convergence of immunity and neurodegeneration. The overlap of glial reactivity, oxidative stress and cytokine dysregulation highlights its status as a cause and effect of neuronal degeneration. Pharmacologic intervention directed at the NF-κB, NLRP3, MAPK and JAK/STAT pathways could emerge as a potential therapeutic approach. Despite translational hurdles, combination therapy of multi-target drugs and nanocarriers with nutraceuticals may represent viable approaches in future neuroprotective treatments. Long-term interdisciplinary efforts between pharmacologists, neurologists and bioengineers are required to turn these molecular understandings into promising clinical candidates against chronic neurodegenerative diseases.

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