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Shifting from Neurotoxic to Neuroprotective States: Exploring Therapeutic Approaches to Modulate Microglial Polarization M1/M2 in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a rapidly growing neurodegenerative disorder, characterized by the progressive loss of dopaminergic neurons and neuroinflammation, particularly mediated by microglial activation. The transition between pro-inflammatory M1 and anti-inflammatory M2 microglial phenotypes plays a crucial role in PD pathogenesis. This paper explores therapeutic strategies aimed at modulating microglial polarization, focusing on the potential of Apilarnil (API), a bee-derived compound, and Rho-associated protein kinase (ROCK) inhibitors. We examine how these therapies influence key molecular pathways, such as AKT/mTOR, NF-κB, and PPAR-γ, which regulate microglial function and contribute to neuroinflammation in PD. Studies reveal that API, through its dose-dependent effects, improves motor function, restores dopamine (DA) metabolism, reduces α-synuclein aggregation, and shifts microglial polarization towards the neuroprotective M2 phenotype. Similarly, ROCK inhibitors, such as Fasudil and Y-27632, modulate microglial activity and promote neuroprotection by targeting inflammatory pathways. These findings highlight the potential of API and ROCK inhibition as therapeutic approaches for PD, with a focus on reducing neuroinflammation and promoting neuronal survival. However, further clinical research is required to assess their safety and efficacy in human PD treatment.

Keywords: Parkinson's disease, microglial polarization, Apilarnil, Rho-associated protein kinase, neuroinflammation, neuroprotection, AKT/mTOR, NF-κB, PPAR-γ, therapeutic strategies

Introduction

Parkinson's disease (PD) is the fastest growing, outpacing even Alzheimer's in terms of growth. According to the Global Burden of Disease Study, approximately 6.2 million individuals currently have PD. There is also direct proportionality between aging and the incidence of PD, and with the aging

world population, the number of affected individuals is expected to rise significantly in the coming years.

With its increasing prevalence worldwide, PD mirrors many features typically associated with pandemics, except for an infectious etiology. In most populations, genetic mutations in established Parkinson's disease-associated genes account for approximately 3-5% of cases, representing monogenic forms of the disease. In contrast, 90 identified genetic risk variants collectively explain nearly 16-36% of the heritable susceptibility to non-monogenic Parkinson's disease. Additional risk factors include a family history of Parkinson's disease or tremor, chronic constipation, and non-smoking status, each of which is associated with at least a twofold increase in disease risk.

Apart from microglia-mediated neuroinflammation, hallmark manifestations of PD include rigidity, tremor, and difficulty with balance and coordination. However the clinical presentation is multifaceted and extends to a wide range of non-motor manifestations.

Microglia are glial cells which are located in CNS . They are the resident macrophages which clear up wastes and toxins from the brain and spinal cord and act as an active form of immune response .

Microglia have two activated type M1 [pro-inflammatory] and M2 which is

[anti-inflammatory]. Both of them have different effects on the glucose , lipid ,amino acids and iron metabolism. Mitochondrial dysfunction does play a role in microglial function . In PD related models we have noticed α-SYN, paraquat, and lipopolysaccharide (LPS) can mediate the microglial metabolic reprogramming and results in Neuroinflammation and neuronal death of dopaminergic neurons can be reduced effectively by inhibiting certain metabolic pathways in M1 microglia or changing M1 to M2 phenotype .(Huang et al., 2023)

M1 And M2 microglia phenotypes

Macrophages can be polarised upon recognizing PAMPS /DAMPS . These PAMPS /DAMPS activate resting microglia via ATP receptors orTLRs . In the presence of IFN-γ and LPS, resting microglia are typically polarised to M1 phenotype , which produces pro inflammatory mediators like TNF-α, IL-1β, IL-6, CCL2, nitric oxide (NO) and ROS , leading to blood brain barrier disruption and neuroinflammation .

M2 phenotype consists of various subtypes M2a cells induced by IL-4 and IL-13 ,suppress NF-κB signalling and promote an anti-inflammatory response . M2b cells activated by the immune complex and LPS generate NO and anti-inflammatory cytokines like IL-10. M2c cells ,activated by IL-10, TGFβ and glucocorticoids support remodelling and immunosuppression . M2 microglia express markers like ARG1, CD36, and CD163 and release anti-inflammatory cytokines , aiding in inflammation resolution

. Additionally ,microRNAs like miRNA-155 and miRNA-124 regulate M1 and M2 polarization, respectively.(Huang et al., 2023)

MICROGLIAL REPROGRAMMATION

M1 Microglia subtype

Microglia can be reprogrammed in its M1 and M2 types . When mTOR pathways are activated in M1 microglia it induces a series of metabolic pathways in the metabolism of iron, lipids, glucose, and amino acids. . The NF-κBpathways which gets activated in M1 types leads to a large number of inflammatory factors which causes damage and injury to DA neurons which leads to onset of PD . (Huang et al., 2023)

M2 Microglia subtype

In M2 pathways different receptors activate mTOR pathways in M2 Microglia which in turn induces Metabolic changes . The PPAR-γ pathway gets activated in M2 phenotype which plays a neuroprotective role .(Huang et al., 2023)

Iron metabolism and signalling pathway Role

In M1 microglia PAMPS /DAMPS activate TLRs which leads to initiation of AKT/mTOR/HIF signaling pathways .The transcription factor HIF-α promotes the expression of IRP1 and its leads to inhibition of (HAMP) hepcidin transcription .

This decrease in hepcidin promotes FPN1 expression ,whereas the increase in IRP1 inhibits FPN1 and promotes DMT1 expression . This imbalance leads to increased Iron uptake which gets deposited in the cell .

The excess Iron produces (ROS) , which activates HIF-α and creates a feedback loop.Increased activity of(PPP) pentose phosphate pathway in M1 microglia leads to ROS production while NO and PPP suppress oxidative phosphorylation which promotes ROS production .

Lipid droplet accumulation and Iron buildup serves as a ROS source . This excess ROS activates NF-κB pathway and through inhibition of AMPK and SIRT1 by glycolysis indirectly triggers neuroinflammation . ROS and NO lead to activation of MAPK pathways ,further enhancing NF-κB activation.(Huang et al., 2023)

In M2 microglia ,activation of IL-4R and TREM2 triggers the AKT/mTOR signalling pathways . APOE ,either through TREM2 or in combination with LPL enters the cell and releases fatty acids .These fatty acids along with mTOR activation ,stimulate PPAR-γ pathway. This regulates the transcription of key genes including APOE ,LPL,Arg ,IL-4 and NRF2. Glutamine plays a role in both TCA cycle and synthesis of UDP-GlcNAc..These metabolic pathways and signals contribute to anti-inflammatory

function of M2 microglia .. This promotes tissue repair and immune regulation . The interplay between lipid metabolism and amino acids pathways and gene expression PPAR-γ and mTOR ensures the proper function of M2 microglia in resolving inflammation and maintaining tissue homeostasis.(Huang et al., 2023)

Apilarnil exerts neuroprotective effects and alleviates motor dysfunction by rebalancing M1/M2 microglia polarization, regulating miR-155 and miR-124 expression in a rotenone-induced Parkinson's disease rat model(Salama et al., 2024)

Apilarnil (API) is a bee-derived product made by lyophilizing the larvae of drones.(Salama et al., 2024)

The dose-dependent improvement in locomotor behavior following Apilarnil (API) treatment, particularly at the high dose (800 mg/kg), suggests its potential as an intervention for ROT-induced impairments in Parkinson's disease (PD).

API treatment helps in restoring motor function and enhancing PD-related locomotor behaviors in rats. Our findings demonstrate that various doses of API not only improves behavioral performance but also had a notable impacts on key PD-related biochemical markers, such as dopamine (DA) regulation, α-synuclein (α-syn) expression, and tyrosine hydroxylase (TH) levels. Loss of dopaminergic neurons and disruption of DA metabolism are hallmarks of PD, and our results showed a marked reduction in DA levels in the ROT-treated group.

API, particularly at the high dose, effectively elevated DA levels, supporting the importance of maintaining optimal DA concentrations for alleviating PD symptoms. Furthermore, elevated DA metabolites, DOPAC and HVA, indicative of disrupted DA metabolism, were reduced by API treatment across all doses, especially at the high dose.(Salama et al., 2024)

API also significantly reduced the elevated expression of α-syn and DA turnover observed in the ROT group, consistent with studies highlighting the neuroprotective effects of reducing α-syn aggregation. Additionally, API treatment increased the expression, particularly at the higher doses, aligning with research suggesting that enhancing the activity can restore DA production in PD.(Salama et al., 2024)

The dose-dependent improvement in locomotor behavior following Apilarni

API treatment also reduced GFAP levels in a dose-dependent manner, suggesting it may protect against neurodegeneration by halting astrogliosis. Additionally, API influenced microRNA expression, with miR-155 levels increasing and miR-124 decreasing after ROT exposure, indicating heightened neuroinflammation. The regulation of these microRNAs, particularly miR-155, is linked to increased

M1 microglia activation and pro-inflammatory cytokine production, underscoring the therapeutic potential of API in modulating neuroinflammation in PD.(Salama et al., 2024)

Modulation of Microglial Activity by Rho-Kinase (ROCK) Inhibition as Therapeutic Strategy in Parkinson's Disease and Amyotrophic Lateral Sclerosis

Therapeutic studies targeting Rho-associated protein kinase (ROCK) have examined various methods to reduce its activity in models of neurodegenerative diseases.ROCK inhibition can be achieved through pharmacological agents like Fasudil and Y-27632, which target both ROCK isoforms, or selectively targeting ROCK2 with drugs such as SR3677. Additionally, genetic approaches, such as shRNA or siRNA, can be used to suppress ROCK expression. In Parkinson's disease (PD) models, ROCK inhibition has demonstrated neuroprotective effects. For example, treatment with Fasudil in an MPTP-induced mouse model preserved dopaminergic neurons and improved motor performance. Similar effects were observed with Y-27632 treatment, where neuroprotection was attributed to both direct effects on neurons and inhibition of microglial activation.However, in the more severe 6-OHDA model, ROCK inhibition failed to prevent dopaminergic degeneration, suggesting that in models with significant damage, additional therapies may be needed. Overall, ROCK inhibition helps protect dopaminergic neurons by modulating microglial activity and providing direct neuroprotection.(Roser et al., 2017)

Recently, a range of pharmacological ROCK inhibitors has been developed, primarily derived from isoquinoline (e.g., Fasudil, Ripasudil) or aminopyridine (e.g., Y-27632) compounds. Most of these inhibitors are Type 1 ATP-competitive kinase inhibitors, which prevent the transfer of a phosphate group from ATP to the substrate. Fasudil and Y-27632 are the most commonly used ROCK inhibitors in research, though their broader kinase selectivity and limited potency may lead to off-target effects, potentially impacting study results. As a result, there is limited information on the effects of isoform-selective ROCK inhibition, particularly for ROCK2, which is the predominant isoform in the central nervous system. Targeting ROCK2 specifically is important for treating neurodegenerative diseases, as it could minimize the risk of hypotension, a known side effect of non-selective ROCK inhibitors. Currently, Fasudil and Ripasudil are the only ROCK inhibitors approved for clinical use, with good tolerability and minimal adverse effects.(Roser et al., 2017)

Methodology

The study utilizes narrative research design to examine the role of microglia in Parkinson's disease . The main objective is to explore microglial activation , polarization and their involvement in neuroinflammation within the context of PD . how to modulate the polarisation of M1and M2 and promote conversion to M2 through various pathways .

By using qualitative methods, the study aims to provide a deeper understanding of how microglial activity contributes to the pathophysiology of PD and its potential therapeutic implications.

Data Collection -

A thorough literature review will be performed to collect existing research and identify key themes related to the role of microglia in Parkinson's disease (PD). The review will focus on studies that investigate microglial activation, polarization (specifically M1 vs. M2 phenotypes), neuroinflammation, and their impact on the progression of PD. Relevant articles will be sourced from databases such as PubMed, Scopus, and Google Scholar, using search terms like “microglia,” “Parkinson’s disease,” “neuroinflammation,” and “microglial polarization.”

A thorough Literature review was performed to collect existing research and identify key themes related to the role of microglia in PD . the review focused on investigation regarding microglia activation , polarization , neuroinflammation and their impact on the progression of PD . Relevant articles were sourced from data bases such as PubMed, Scopus,ScienceDirect and Google Scholar, using search terms like “microglia,” “Parkinson’s disease,” “neuroinflammation,” and “microglial polarization.”

Results

Therapeutic strategies targeting microglial polarization in Parkinson’s Disease (PD) models have revealed key molecular mechanisms for neuroprotection. Apart from Apilarnil (API) and ROCK inhibitors, several pathways influence microglial activation, shifting them from neurotoxic M1 to neuroprotective M2 phenotypes. The AKT/mTOR and NF-κB pathways play significant roles in microglial activation. In the M1 phenotype, these pathways drive the production of pro-inflammatory cytokines and reactive oxygen species (ROS), contributing to dopaminergic neuronal damage. Inhibition of mTOR has been shown to shift microglia toward the M2 phenotype, reducing inflammation and promoting tissue repair.

The PPAR-γ pathway, activated in M2 microglia, supports anti-inflammatory responses and tissue remodeling, while the TREM2/AKT pathway enhances phagocytosis and neuronal protection. API, a bee-derived compound, improved motor function and DA metabolism in a rotenone-induced PD rat model. API also modulated microglial activity by altering microRNA expression, favoring an anti-inflammatory M2 phenotype and reducing neuroinflammation.

ROCK inhibitors like Fasudil and Y-27632 also reduce M1 microglia activation by targeting the AKT/mTOR and NF-κB pathways, promoting neuroprotection. However, in severe PD models like 6-OHDA, ROCK inhibition alone was insufficient to prevent degeneration, suggesting that combination

therapies may enhance therapeutic outcomes. Together, these findings highlight promising strategies to shift microglial polarization toward neuroprotective states in PD.

Discussion

Parkinson's disease (PD) is rapidly growing, with increasing incidence linked to the aging global population. Both genetic factors and environmental influences, along with neuroinflammation, play key roles in the progression of PD, emphasizing the need for effective treatments.Microglial activation, particularly the shift between pro-inflammatory M1 and anti-inflammatory M2 phenotypes, is a crucial factor in PD pathology. . Disruption of dopaminergic signaling and neuroinflammation in PD models underscores the importance of modulating microglial activation.Apilarnil (API), a bee-derived substance, demonstrates promising neuroprotective effects in PD. API influenced microglial polarization, decreased α-synuclein expression, and regulated key microRNAs like miR-155 and miR-124, which are involved in inflammatory responses in PD. These findings support the potential of API to reduce neuroinflammation and improve motor function, offering a novel therapeutic avenue for PD.

Conclusion

In conclusion, Apilarnil (API) demonstrates significant therapeutic potential for Parkinson's disease (PD), showing both behavioral and biochemical improvements in PD models. The dose-dependent effects of API, particularly its ability to restore dopamine levels, reduce α-synuclein buildup, and regulate microglial polarization, highlight its neuroprotective properties. By modulating inflammatory pathways and regulating microRNAs such as miR-155 and miR-124, API effectively addresses neuroinflammation while promoting neuronal survival and function. These results align with ongoing research emphasizing the importance of balancing microglial activity and restoring dopamine production in PD treatment. As such, API shows promise as an intervention for PD, with the potential to improve motor function and slow disease progression. However, further clinical trials are needed to evaluate its efficacy and safety in humans.

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