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Microglial activation is attenuated in cell culture by pharmacological modulation of calcium homeostasis

PhD Thesis

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Introduction

Neuroinflammation is a complex inflammatory response in the central nervous system (CNS) mediated by microglia, the brain's organ-specific macrophage population. Activation of microglia is a common pathological hallmark of chronic neurodegenerative disorders and acute brain injuries. In healthy brains, microglia play a pivotal role in CNS development, maintaining homeostasis, pruning synapses, modulating neuronal plasticity, and regulating blood flow. Under physiological conditions, microglia have a small cell body and highly ramified processes. In response to exogenous or endogenous danger signals, microglia transform from a resting to an activated state. This activation leads to rapid changes in microglial morphology, function, and gene expression. Microglia are specialized phagocytes of the CNS and play a critical role in sensing and engulfing extracellular material.

Microglial activation can either promote neuroprotection or cause neuronal damage. The M1-M2 polarization state of microglia is a spectrum with intermediate, partially overlapping states. The inflammatory M1 subtype releases pro-inflammatory cytokines, leading to neuronal death. On the other hand, M2 microglia exhibit anti-inflammatory properties and serve a neuroprotective function. Single-cell RNA sequencing shows that microglia simultaneously express M1 and M2 activation markers, with transcriptomic studies revealing a broader transcriptional profile.

Autophagy is a crucial process in maintaining cell metabolism, contributing to cellular homeostasis. Autophagy can degrade and recycle cytoplasmic components under stress conditions, such as ischemia, hypoxia, and oxidative stress. Autophagy also impacts microglia function, with TLR4 acting as an upstream regulator. Lipopolysaccharide (LPS) can activate the PI3K/AKT/mTOR pathway in microglia, inhibiting autophagic flow and enhancing the inflammatory response. The autophagy inhibitor bafilomycin A1 (Baf) has been shown to block microglia pro-inflammatory polarization.

Intracellular Ca^{2+} concentration is crucial in regulating the immune effector state of microglia, as it acts as a second messenger in cellular signaling pathways. During activation, Ca^{2+} concentration increases rapidly, affecting microglial phagocytosis,

proliferation, cytokine production, and the release of reactive oxygen species. Calcium influx in microglia is achieved through various ion channels, with voltage gated L-type channels (LVGCCs) mediating the Ca^{2+} influx. The endoplasmic reticulum (ER) also plays a role in regulating mitochondrial and cytoplasmic calcium concentration during microglial activation. The ER regulates cytoplasmic Ca^{2+} concentration through Ca^{2+}release, and Ca^{2+}uptake via SERCA pumps.

Nimodipine is a dihydropyridine calcium antagonist, first synthesised in 1983. It is best known for its clinical application in preventing delayed ischemic deficit after subarachnoid hemorrhage. Nimodipine targets cerebrovascular smooth muscle cells, inhibiting Ca^{2+} influx through LVGCCs, reducing Ca^{2+}-dependent activation and increasing cerebral blood flow. Nimodipine is highly lipophilic and can cross the blood-brain barrier, making it a potential neuroprotectant. Recent studies suggest that microglia also express LVGCCs, potentially implicated in neuroinflammation. However, direct effects of nimodipine on microglia *in vivo* are difficult to separate from indirect actions, as LVGCCs are ubiquitously expressed in various brain cell types.

N,N-dimethyltryptamine (DMT), a naturally occurring indole alkaloid found in South American plants, has been shown to have psychedelic effects and cause hallucinations. It is a component of the traditional Ayahuasca brew used by indigenous tribes in the Amazon rainforest for spiritual and healing purposes. DMT has gained interest as a neuroprotectant in neurodegenerative diseases and acute ischemic brain injury. It has been found to protect human primary iPSC-derived cortical neurons and microglia-like cells from hypoxia, reduce infarct size, and show anti-inflammatory effects. DMT binds to sigma-1 receptors (Sig-1Rs) with high affinity, a potential cellular mechanisms to achieve ischemic neuroprotection. Sig-1R is an intracellular receptor found in the brain, immune cells, and peripheral organs, primarily regulating ATP synthesis and Ca^{2+} levels. It plays a chaperone role and supports cellular homeostasis and energy production. Sig-1Rs are ubiquitous in brain cells, including neurons, astrocytes, oligodendrocytes, and microglia. Studies have shown that Sig-1R activation reduces neuroinflammation by reversing M1 microglial polarization.

Primary microglial monocultures or co-cultures with neurons, astrocytes, or oligodendrocytes are widely used in studying microglial pathophysiology. These tools allow for reproducible, in-depth, and high-throughput analysis of microglial states, providing valuable insights into microglial biology. Cell culture models are essential for gaining valuable insights into microglial biology due to controlled manipulation, standardized experimental settings, and focused interpretation of results. Microglia cultures can be used to examine morphological phenotypes, functional aspects of microglia, and protein detection or gene expression profiling. However, rodent primary microglia cultures have limitations, such as lack of genetic diversity due to inbreeding and sterile living conditions. Human microglia can help overcome this issue. Co-culturing microglia with neurons and oligodendrocytes can help investigate their function in neuronal health and myelin production. Advanced techniques are facilitating enhanced study practices for microglial research, making them essential for exploring therapeutic opportunities to combat neurotoxic consequences of neuroinflammation associated with brain disorders.

Our aim here was to pharmacologically modulate microglia to suppress activation, and to elucidate the cellular mechanisms of pharmacological action:

1. We set out to analyze the effects of nimodipine on activated microglia at the level of morphological and functional phenotypes, as well as their transcriptomic profile. We hypothesized that nimodipine treatment suppresses microglial activation by acting on microglial Ca^{2+} homeostasis and associated changes in gene expression.
2. We sought to characterize the effects of DMT on microglial activation by morphological and functional profiling and by assessing changes in the microglial proteome. We anticipated an anti-inflammatory effect of DMT supported by an altered pattern of protein expression.
3. We aimed to identify the effect of the antibiotic bafilomycin on activated microglial autophagy. We assumed that bafilomycin mitigates microglial autophagy.

Materials and methods

Maintenance and treatment of primary microglia cell cultures

The culture was prepared from the cerebral cortex of newborn Sprague-Dawley rats. In our experiment, we used co-culture and microglia monoculture. Pure microglia culture was prepared by shaking the cultures. On day 6, the plated cells were activated with lipopolysaccharide (LPS; 20 ng/ml). In the first set of experiments, cultures were treated with nimodipine alone (5-10-20 μM) or in combination with LPS for 24 h. In the second set of experiments, cultures were treated with DMT (Sig-1R agonist) alone (5-10-20-50 μM) or in combination with LPS for 24 h. In the third set of experiments, microglial cultures were pre-treated with Baf A1 (50nM) for 3h, and activated with LPS for 24h. Microglial activation was evaluated by Iba1 immunolabeling. The degree of arborization was expressed by a transformation index (TI) calculated from the cell perimeter and surface area. Iba1 protein levels were quantified by Western blot analysis, and the phagocytic activity was visualized with fluorescent microbeads. TNF-α cytokine levels in the cell culture medium were measured with ELISA. Total RNA was isolated from collected cells and processed for RNA sequencing (RNA-seq) to determine differentially expressed genes (DEGs). Proteins were isolated from harvested cells and processed for proteomic analysis with mass spectrometry.

Immunohistochemistry

The study used a protocol for immunohistochemistry, involving primary co-cultures (DIV7) and microglia (subDIV7) monocultures on poly-L-lysine-coated coverslips. The cells were fixed in 4% formaldehyde, rinsed, and nonspecific sites were blocked. They were then incubated with primary antibodies (Iba1, p62), followed by secondary antibodies conjugated with Alexa Fluor dye. Finally, fluorescence microscopy images were taken to calculate the transformation index and to co-localize the markers.

Western blot analysis

Cells from primary co-cultures and microglial monocultures were harvested, homogenized, and centrifuged. Protein concentration was determined for quantitative Western blot analysis. Five-ten μg of protein was separated on an SDS-

polyacrylamide gel, transferred to a Hybond-ECL nitrocellulose membrane, blocked, and incubated with Iba1 and GAPDH primary antibodies. The membranes were then incubated with secondary antibodies and washed. Immunoreactive bands were detected using the enhanced chemiluminescence method.

In vitro phagocytosis assay

The fluid-phase phagocytic capacity of microglial cells in primary co-cultures and monocultures was determined by adding fluorescent microbeads. The cells were incubated at 37°C for 60 minutes, rinsed, fixed, and immunostained with Iba1 and DAPI.

Enzyme-linked immunosorbent assay (ELISA)

The concentrations of interleukin-10 (IL-10) and tumor necrosis factor-α (TNF α) were quantified in primary co-culture and microglial monoculture supernatants using ELISA kits. For both IL-10 and TNF-α, we obtained an internal coefficient of variation of less than 8%, indicating good measurement precision and supporting the reliability of the ELISA results.

NEB mRNA-Library and next generation sequencing

Total RNA samples were isolated and quantified using a Qubit 3.0 Fluorometer. NGS library preparation was done using the NEBNext Ultra™ II Directional RNA Library Prep Kit for Illumina. Next-generation sequencing was performed on the NovaSeq X Plus sequencing system. Quality control was performed using a D5000 ScreenTape instrument.

LC-MS/MS analyses

The samples were digested using trypsin according to the Strap micro protocol. They were redissolved in TEAB, reduced with TCEP, and alkylated with MMTS. 10% of the peptide mixtures were loaded onto C18 EvoTips for LC-MS analysis. Reversed-phase separation was performed using an Evosep One HPLC column, followed by data-dependent MS/MS acquisition using an Orbitrap Fusion Lumos Tribrid mass spectrometer. Data were collected using compensation voltages and high resolution.

Results

Nimodipine mitigates microglia activation

The morphological phenotype of microglia indicated their activation state. They had a ramified phenotype in the resting state, but their processes shortened upon activation, and the cells assumed a round amoeboid shape. In mixed cell culture, untreated control microglia cells showed more branches and exhibited a ramified shape. When we activated them with LPS, the TI of microglia cells significantly decreased, indicating an activated amoeboid phenotype. We added nimodipine to LPS-activated microglia cells, which increased the TI in both co- and monocultures, counterbalancing microglial activation.

Non-activated microglia cells exhibited low phagocytosis and engulfed few microbeads in both co- and monocultures. When we treated the cells with nimodipine alone, it did not alter phagocytosis levels. LPS activation increased microglial phagocytic activity and led to a higher number of engulfed microbeads. When we treated the LPS-activated cultures with nimodipine, phagocytosis decreased to near control levels in both co- and monocultures.

We used Iba1 expression in microglia to indicate their activation state. LPS-activated cells significantly increased Iba1 expression in both co- and monocultures. When we treated non-activated cultures with nimodipine, it did not alter Iba1 expression. However, when we added nimodipine to LPS-activated cultures, it reduced Iba1 protein levels, with significant effects at 10 and 20 μM concentrations.

We also examined the impact of nimodipine on the secretion of the pro-inflammatory cytokine TNF-α and the anti-inflammatory cytokine IL-10, measured in the culture medium. Our results showed that LPS, at the relatively low concentration of 20 ng/ml, did not alter IL-10 levels in either co- or monocultures. Nimodipine had no significant impact on IL-10 levels, regardless of whether the cultures were non-activated or activated. However, at a concentration of 20 μM, nimodipine reduced TNF-α concentrations in LPS-activated co-cultures to control levels. In LPS-activated monocultures, when we administered nimodipine at increasing concentrations, it

produced a stepwise reduction in TNF-α levels, although this did not reach statistical significance.

We conducted next-generation RNA sequencing on microglial monocultures and identified 13,866 genes, out of which 9,720 were differentially expressed (DEGs) due to LPS activation or nimodipine treatment. We examined LPS-induced gene expression changes and found that several phagocytosis-related genes were upregulated, while genes directly involved in macroautophagy remained unchanged. We found that LPS increased the expression of the TRPM2 channel and the P2X4 purinergic receptor, suggesting an elevated influx of Ca^{2+} into the cytoplasm through these pathways. In contrast, LPS downregulated the expression of genes encoding VGCCs, which suggested that this downregulation might serve as a compensatory mechanism for the increased expression of TRPM2 and P2X4. Alongside the upregulation of P2X4 receptors and TRPM2 channels, we observed compensatory changes in the expression of ryanodine and IP3 receptor genes, as well as SERCA pump genes (Atp2a2 and Atp2a3) at the ER. LPS downregulated ryanodine and IP3 receptors, which release Ca^{2+} from the ER into the cytoplasm, while it upregulated SERCA, which pumps Ca^{2+} from the cytoplasm back into the ER lumen. These changes suggested that the Ca^{2+} concentration increase caused by P2X4 and TRPM2 during microglial activation was counterbalanced by regulatory mechanisms at the ER.

When we treated microglial monocultures with both nimodipine and LPS, we observed changes in the expression of 110 genes—29 were upregulated and 81 were downregulated. The influence of nimodipine was opposite to that of LPS. Our analysis showed that 20 of the genes affected by nimodipine were linked to the microglial immune response, 7 were associated with cell adhesion, 2 were involved in autophagy regulation, and 4 played roles in intracellular calcium homeostasis.

DMT modulates microglial activation

We observed that DMT alone, at all concentrations, tended to promote the resting state of microglia, as indicated by an increased transformation index. Low transformation index values observed with LPS treatment revealed that the cells were activated.

When we administered DMT at 20 and 50 μM, the transformation index significantly increased, indicating that microglial cells shifted toward more ramified, and thus resting, phenotypes.

We found that DMT treatment reduced the proportion of phagocytic cells in each culture, while LPS treatment increased the ratio of phagocytic cells, with a corresponding decrease in non-phagocytic cells. When we combined DMT with LPS at 20 and 50 μM concentrations, it reduced phagocytic activity to control levels.

LPS activation caused a significant increase in Iba1 protein expression compared to the absolute control. DMT did not reverse the LPS-induced Iba1 expression; in fact, DMT alone tended to upregulate Iba1.

We performed proteomic analyses and identified a total of 2,793 proteins, out of which 244 showed altered expression. When we compared the groups, we found that LPS upregulated 111 proteins and downregulated 33 proteins compared to the control. When we added DMT to LPS-treated cultures, 76 proteins were upregulated and 86 were downregulated compared to the control, indicating the effect of DMT. Finally, co-administration of DMT and LPS led to the upregulation of 21 proteins and downregulation of 84 proteins compared to LPS alone. We then identified proteins whose expression was altered by LPS and subsequently reversed by DMT, including eight that were upregulated and twelve that were downregulated. Among these, we found that two proteins induced by LPS and attenuated by DMT were inducible nitric oxide synthase (iNOS) and phospholipase A2 (PLA2), both of which are clearly related to the pro-inflammatory function of activated microglia.

Suppression of autophagy in the presence of Baf

We investigated the regulation of autophagy, which is crucial for microglial functions, and focused on the role of p62/SQSTM1 in this process. LPS treatment did not significantly affect microglial cell numbers, but when we pretreated the cultures with bafilomycin (Baf), it led to a significant reduction in microglial proliferation. Western blot analysis showed that LPS treatment caused a slight increase in p62 protein levels, while Baf pretreatment did not change the amount of p62 protein. We observed that the distribution of p62/SQSTM1 immunoreactivity was uniform throughout the

cytoplasm, with p62/SQSTM1-labeled autophagosomes predominantly appearing as puncta in the perinuclear region. We found a similar number of p62/SQSTM1-labeled autophagosomes in cultures treated with LPS, regardless of the presence or absence of Baf.

Discussion

Primary microglia cultures are suitable to study the pharmacological modulation of microglial activation

Our research was conducted to analyze the morphological, functional, and gene expression characteristics of microglia co-and monocultures, following treatment with nimodipine or DMT in unstimulated or LPS-activated cultures. Activated microglial cultures are instrumental in the testing of drugs that target neuroinflammation, as they facilitate the evaluation of drug effects on microglia without the interference of other brain cells. Our study assessed various functional aspects, including phagocytosis, autophagy, and gene and protein expression profiles.

Microglial states can be identified through protein detection or gene expression profiling, such as single-protein ELISA or multiplex ELISA, mass spectrometry, Western blot, and RNA sequencing. Upon activation, microglia exhibit dual capacity for pro- and anti-inflammatory responses, exhibiting a continuum of polarization towards either a neurotoxic (M1) or beneficial (M2) state in response to injury.

The results highlighted the complex beneficial effects of both drugs, classifying them as excellent candidates for preventive neuroinflammatory therapy with well-balanced properties of enhanced anti-inflammatory and subdued proinflammatory effects.

Microglial activation is characterized by changes in calcium homeostasis, which serve as a target to attenuate neuroinflammation. Intracellular Ca^{2+} concentration in microglia regulates immune effector state transition. Here we targeted microglial Ca^{2+} homeostasis by manipulating Ca^{2+} influx across the plasmalemma with nimodipine and activating intracellular Sig-1Rs with DMT. These approaches suppressed microglial activation by modulating gene expression or protein translation, affecting

morphological and functional phenotypes. The study highlights the importance of Ca^{2+} homeostasis in the microglial immune response.

Benefits of nimodipine application for neuroinflammation

Microglial activation is linked to an increase in intracellular Ca^{2+} concentration when exposed to danger signals, with LPS being one of the most commonly used activators. We investigated whether manipulating microglial Ca^{2+} homeostasis via LVGCC antagonism inhibits microglial activation. The results showed that LPS exposure induces a shift in microglial morphological and functional phenotype and upregulates the expression of mRNA encoding proteins involved in Ca^{2+} influx. The latter suggests that Ca^{2+} accumulation during microglial activation may be manifested through these pathways. The expression of ryanodine and IP3 receptor genes and SERCA pump genes at the ER were altered in a compensatory manner, suggesting that the Ca^{2+} concentration, which presumably increases via P2X4 receptors and TRPM2 channels upon microglial activation, is counterbalanced by mechanisms at the ER.

Nimodipine consistently inhibited the phenotypic shift of microglia in co-cultures and monocultures, suggesting that microglia were reliably targeted by the treatment. The study suggests that nimodipine finely modulates intracellular signaling pathways by inhibiting LVGCC to induce gene expression changes. The anti-inflammatory effect of nimodipine must be achieved by modulating intracellular Ca^{2+} signaling, which is a well-known intracellular second messenger involved in the control of gene expression.

Previous studies suggested that nimodipine may also target alternative cellular sites, such as Kv1.3 voltage-gated potassium channels, mineralocorticoid receptors, and CFTR chloride channels, contributing to its anti-inflammatory effect. In conclusion, nimodipine's potential for attenuating neuroinflammation in acute brain injury or chronic neurodegeneration is highlighted.

The therapeutic potential of DMT for neuroinflammation

DMT, a compound known for its psychedelic properties, has been shown to have neuroprotective effects and potential therapeutic applications. Endogenous DMT has been recognized to play a critical role in the central nervous system, particularly under stress conditions, by protecting neurons, reducing inflammation, and promoting neuroplasticity through mechanisms such as the elevation of brain-derived neurotropic factor (BDNF). Sig-1Rs, intracellular receptors located on the ER membrane and targeted by DMT, regulate Ca^{2+} balance, inhibit ROS production, and promote cell survival in stress conditions.

In experimental focal cerebral ischemia, DMT has been shown to be neuroprotective, reducing brain infarct size, improving motor function, and inhibiting the transcription of pro-inflammatory cytokines in the brain. *In vivo* studies have demonstrated that microglia also express the target of DMT, Sig-1R. However, the effect on microglia is complex and difficult to isolate in intact tissue or organism.

As shown here, in microglia cultures, DMT administration induces alterations in microglial morphology and functionality. When added to activated microglia cultures at concentrations of 20 and 50 μM, DMT resulted in more ramified cell shapes and reduced the proportion of phagocytosing cells in the culture. Proteomic analysis revealed substantial changes in protein concentrations, with DMT reversing the expression of specific pro-inflammatory proteins that have been previously induced by LPS.

The inhibition of microglial activation observed in this study is consistent with previous findings that DMT was protective in macrophage cultures of monocyte origin exposed to hypoxia. It was also demonstrated that agonism of Sig-1R with DMT may be protective for microglial cells under lethal conditions. In a rodent model of focal cerebral ischemia, DMT inhibited the mRNA transcription of pro-inflammatory cytokines, including TNF-α, and thus an anti-neuroinflammatory effect was reported.

DMT treatment in inflammatory processes exerts an anti-microglial activation effect reflected by the modulation of the levels of the proteins involved. These observations

may be useful in the development of drugs for diseases in which neuroinflammation impairs the chances of recovery. DMT has also recently attracted the attention of pharmaceutical companies, with Canada's Algernon Pharmaceuticals having completed a clinical phase study with DMT, aiming to introduce DMT in ischemic stroke medication.

The suppression of microglial autophagy is coincident with an increase in p62/SQSTM1 protein

The study explores the role of autophagy regulation in microglial functions, focusing on the protein p62/SQSTM1. Autophagy and microglial cells are crucial for maintaining cellular homeostasis and responding to stressors in the central nervous system. Autophagy facilitates the degradation and recycling of damaged cellular components, particularly under pathological conditions like ischemia and hypoxia. Inflammation is closely linked to autophagy and inflammatory processes, with critical regulatory molecules like p62/SQSTM1 playing pivotal roles.

The study highlights the intricate role of p62/SQSTM1 in regulating autophagy within microglial functions, particularly under inflammatory conditions induced by LPS. The notable reduction in microglial proliferation upon bafilomycin pretreatment underscores the complex interactions between autophagy and inflammation. The observed increase in p62 protein levels in response to LPS, alongside its stable concentration with bafilomycin pretreatment, suggests a nuanced role of p62 in inflammatory states that warrants further investigation.

The study provides additional evidence to support the role of bafilomycin in modulating autophagic processes and its potential effects on cellular responses and autophagy-related pathways. The interplay between ion homeostasis and signaling pathways, notably through TLR4 and VGCCs, underscores microglia cells' regulatory roles in inflammatory responses post-injury. Understanding the nuanced behavior of microglia and their modulation represents a promising therapeutic avenue for addressing central nervous system disorders, particularly in optimizing responses following ischemic strokes.

Main observations

1. The study showed that nimodipine, an L-type voltage-gated calcium channel blocker, reduces microglial activation, most probably by modulating intracellular Ca^{2+} signaling. The LPS-induced microglial activation was attenuated as nimodipine altered gene expression, and suppressed inflammation. These findings highlight its potential in reducing neuroinflammation in brain injury and neurodegenerative diseases.
2. The study found that DMT reduces microglial activation by inducing more ramified morphology and lowering phagocytic activity. Proteomic analysis showed that DMT reversed the LPS-induced upregulation of some pro-inflammatory proteins like iNOS and PLA2, likely via Sig-1R activation. These effects support DMT's anti-inflammatory potential in microglial regulation.
3. The study examined how autophagy relates to inflammation in microglia. LPS combined with Bafilomycin A1 (Baf) inhibited autophagy, shown by increased p62/SQSTM1 levels, suggesting disrupted autophagy may contribute to sustained inflammation. These findings highlight the key role of autophagy in regulating microglial function and its interaction with ion homeostasis and signaling after injury.

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Articles to serve as the basis of the thesis

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