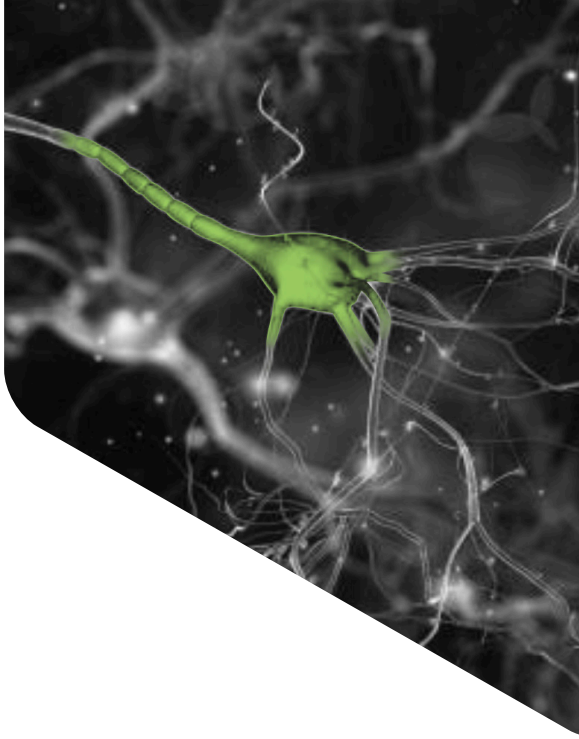

# Targeting neuroinflammation in neuroscience research

Toronto Research Chemicals
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It is becoming clear neuroinflammation contributes to neurodegenerative diseases

# Introduction

Inflammation is a host defence mechanism designed to protect the body from injury. While it plays a key role in protecting the central nervous system (CNS), it also has the potential to damage it. It is becoming increasingly clear that neuroinflammation contributes to neurodegenerative diseases such as Parkinson's, Alzheimer's and Huntington's. (1) These diseases are characterised by a progressive loss of the structure and function of neuronal materials, causing cognitive and motor dysfunction and dramatically impacting patients' quality of life. (2)

Current treatment options can alleviate symptoms but do not treat the root cause of neurodegeneration, and therefore cannot prevent its onset or progression. Neuroinflammation represents a potential therapeutic target, but further research is necessary in order to develop a greater understanding of the process and its relationship to neuronal damage.

# Neuroinflammation and the immune system

The CNS has both innate and acquired immunities, the former referring to inborn resistances to infections and the latter to immunity developed over time in response to foreign substances. As neurodegeneration can be induced by viral infection, the immune response is important in the pathogenesis of neurodegenerative diseases. (3) Microglia and other immune cells help regulate the brain, maintaining homeostasis and accumulating in response to neuronal cell injury or foreign entry, in a process termed 'reactive gliosis'. (4)

Acute neuroinflammatory response activates the innate immune system to minimise injury, and is therefore beneficial - however, the inflammatory response can be over-sustained by feedback from microglia and astrocytes, leading to chronic inflammation. This sustained release of proinflammatory cytokines prolongs microglial activation and can also lead to the recruitment of more immune cells, upregulating the inflammatory response and causing neurotoxicity and further tissue degeneration. (2)

Toll-like receptors play an important role in innate immunity by recognizing pathogens

The varying activation of microglia in the immune response regulates neuroinflammation and can either trigger neuroprotection or neurotoxicity. The mechanism controlling this is not clearly understood, but it is likely that aging plays a role, as control over the adaptive immune system decreases with age, compromising the immune response. Microglia also become 'reactive' or 'sensitized' with age, meaning they are more likely to orchestrate an inflammatory response. This potentially contributes to their prolonged activation in the CNS in response to infection. (5)

This decline in both innate and adaptive immune response leaves the elderly more vulnerable to infections, which can trigger sensitized microglia into prolonged activation. This may contribute to the transition from neuroprotective to neurodegenerative processes. Further study into the differential response of microglia as immune effectors is imperative, in order to improve our understanding of both their beneficial and harmful effects. (5)

# Research strategies

A variety of targets within neuroinflammatory pathways are being investigated to advance understanding and provide insight into potential therapeutic points of interest. Three main categories are outlined below.

### Signalling pathways

Key intracellular signalling pathways are activated in response to brain injury or infection, triggering inflammation. (6) Understanding these pathways and the molecules they involve is therefore crucial for neurodegeneration research into therapeutic targets. There is variation in the exact inflammatory response across different neurodegenerative diseases, but aspects of the pathways are common between them. These include the involvement of toll-like receptor (TLR) signalling, mitogen-activated protein (MAP) kinase mediation and inflammatory cytokines, such as tumour necrosis factor α (TNFα) and interleukin-1β (IL-1β). (6)

Toll-like receptors play an important role in innate immunity by recognizing pathogens and activating the immune response. TLR signalling results in the activation of proteins such as MAP kinases. (6) These are a family of protein kinases that mediate intracellular signalling in the CNS and are implicated in the development of neurodegenerative diseases through the activation of microglia and the resulting neuroinflammation. (7)

# A possible means of controlling neuroinflammation is through MAPK inhibitors

There are three major MAP kinases involved in regulating the inflammatory response: extracellular signal-regulated kinases (ERK), p38 MAPK and c-Jun N-terminal kinases (JNK). (8) These proteins regulate diverse cellular processes, including the expression of pro-inflammatory cytokines, such as TNFα and IL-1β. The complex signalling cascade involved in the activation of MAP kinases induces and promotes inflammation. MAP kinases activate microglia, which can then activate astrocytes, upregulating the inflammatory response. (6) This occurs as a neuroprotective mechanism, but excessive production of cytokines and insufficient inhibition sustains the response, causing inflammation to become chronic and damaging, as explained above. (7) MAP kinases are therefore promising therapeutic targets due to their mediating role in the key signalling pathways that control the inflammatory response.

A possible means of controlling neuroinflammation is through MAPK inhibitors, which act as anti-inflammatory drugs by blocking the signalling pathway that results in the production of pro-inflammatory compounds. Inhibiting p38 MAPK and JNK pathways has been found to reduce both the production of pro-inflammatory cytokines and the associated intracellular signalling, helping to prevent chronic neuroinflammation. (6) Further research will allow more targeted manipulation of these pathways to improve patient outcomes.

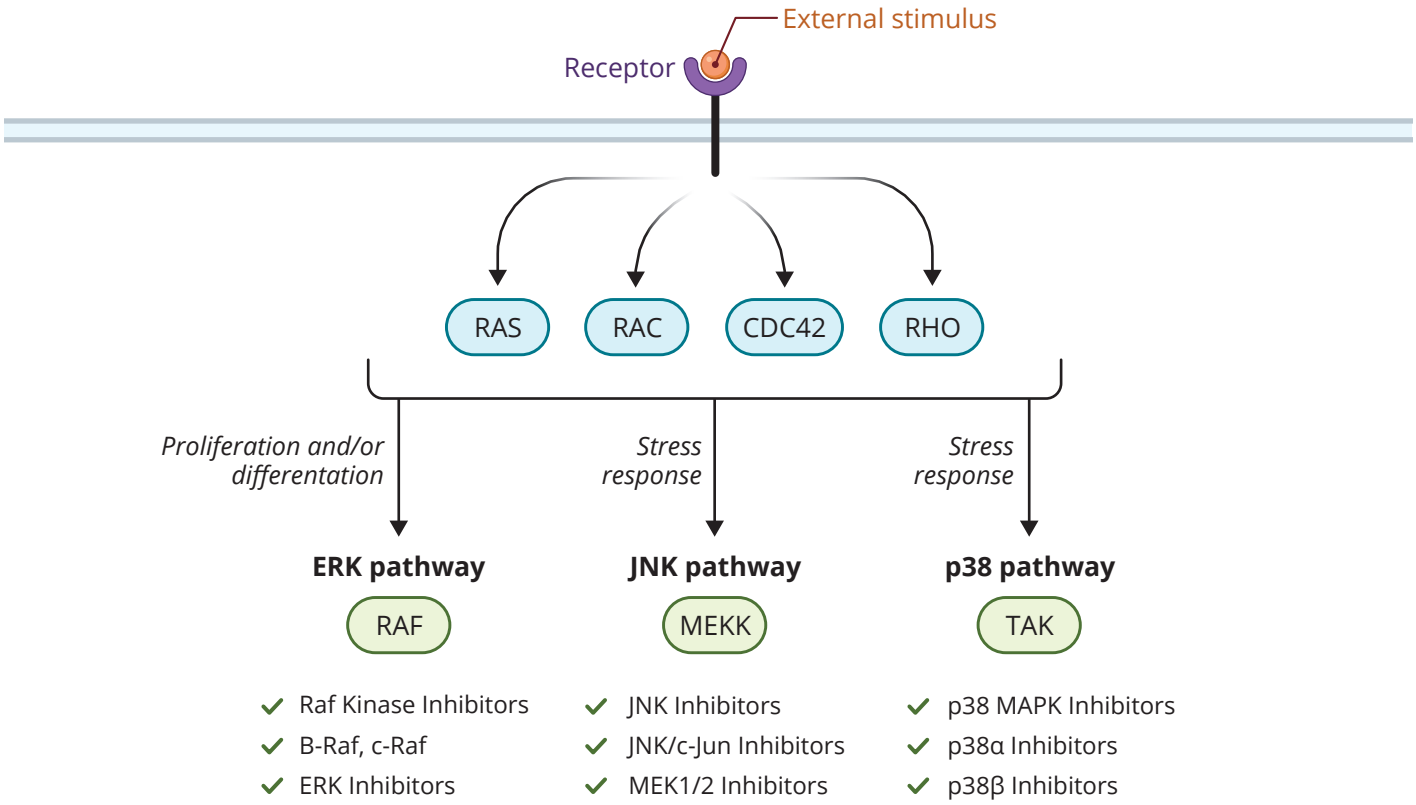



**Figure 1:** Pharmacological targets for major MAP kinase pathways: ERK, JNK, p38

Other receptor targets include G-protein-coupled receptors (GPCRs)

**Receptors**

Receptors for key neurotransmitters involved in neuroinflammation also represent promising targets for further research and potential treatments. Proinflammatory cytokines produced by microglia play a key role in initiating and prolonging inflammation, and research is currently ongoing into the impact of blocking receptors for these in experimental models. (4)

Other receptor targets include G-protein-coupled receptors (GPCRs) - proteins that activate cellular responses. They have many roles within eukaryotes, including the detection of neurotransmitters within the brain and in the modulation of immune responses, making them an interesting target for neurodegenerative disease treatment.

The G-protein-coupled receptor 55 (GPR55) expressed in immune cells (including microglia) is involved in the modulation of inflammation. Data suggests that this receptor plays a crucial role in mediating neuroinflammation via inverse agonistic activity. (9) GPR55 antagonists might therefore be an effective therapeutic option for the treatment of neuroinflammation and the resulting neurodegeneration. It is important, however, to consider the impact that modulators may have on other fundamental proteins within the CNS, and a thorough understanding of the complex functions of the immune system in the CNS is crucial when identifying appropriate therapeutics.

Controlling reactive gliosis, the immune response to injury or infection in the CNS, represents a promising strategy in the fight against neurodegeneration. Molecules that are able to restore physiological functions and reduce proinflammatory responses in microglia and astrocytes may offer therapeutic opportunities. For instance, an anti-inflammatory effect achieved by modulating the enzyme glycogen synthase kinase-3β has been identified. (4) Selective glia inhibitors have also been found to be effective in suppressing microglial activation and therefore reducing the production of cytokines, conferring neuroprotection. (10)

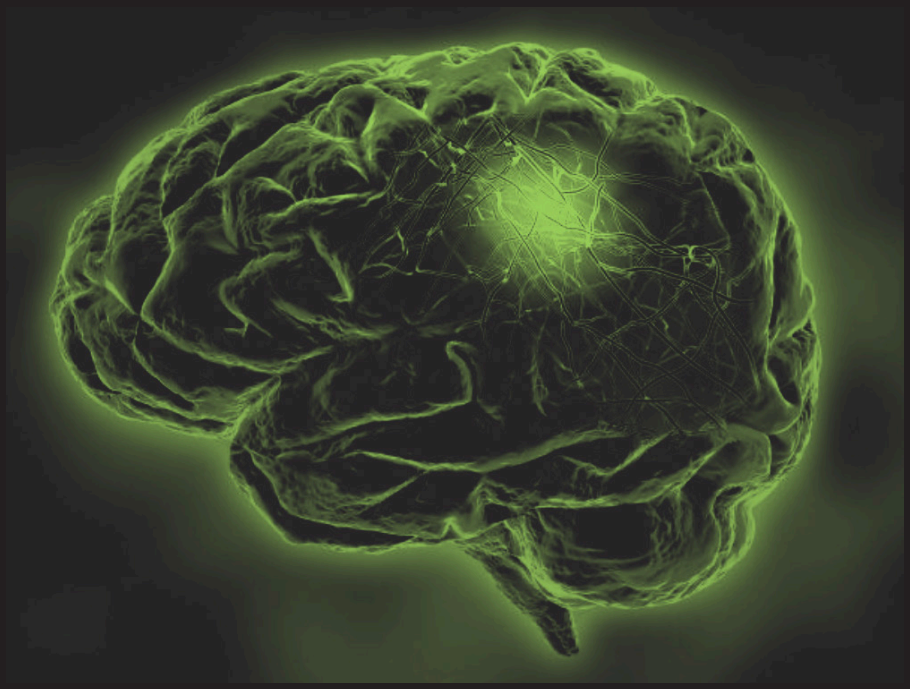
Small-molecule-based approaches are well suited to modulating glial phenotypes, as small molecules are better able to cross the blood-brain barrier. An example of this approach is the use of a novel small-molecule compound that can inhibit the phenotypic switch from neuroprotective to neurotoxic by modulating mitochondrial function. (10) This suggests it may be possible to modulate glial phenotypes via their metabolic pathways.

Backed by a complete portfolio of selective, non-selective and labelled inhibitors, agonists, antagonists and modulators, TRC provides both the resources and the expertise needed to support research in this important area.

## Ongoing research

Studies on the mechanism of inflammation in Parkinson's disease have shown that activation of the inflammatory process in microglia via the protein NLRP3 is a critical step for neuronal loss and the resulting motor issues associated with the condition. (11) A deficiency in NLRP3 decreases motor dysfunctions and dopaminergic neurodegeneration in MPTP-mouse models. This shows that MPTP, a key neurotoxin involved in neuronal death in Parkinson's, activates the NLRP3 inflammasome and causes subsequent neurodegeneration.

This understanding is important as it highlights key pathways in the pathogenesis of Parkinson's, and may highlight therapeutic targets. One such therapeutic target is discussed in another study, which finds that modulation of specific receptors can prevent the activation of the inflammatory response. Selectively modulating the S1P1R receptor provided neuroprotection in response to MPTP neurotoxicity, suggesting this receptor is a promising target for Parkinson's therapy. (12) Both of these studies used MPTP obtained from TRC to induce the symptoms of Parkinson's using *in vitro* models.



A further study explores the anti-inflammatory properties of dibenzoylthiamine (DBT) in mouse models. The findings indicate that administering DBT stopped motor dysfunction in the case of amyotrophic lateral sclerosis (ALS), a neurodegenerative disease, using novel coenzyme-independent mechanisms. (13) This promising research also found an anti-oxidative effect, targeting oxidative stress as another contributor to neurodegeneration.

# Conclusion

While no cure for neurodegeneration has yet been realised, extensive research is ongoing to help bring next-generation medicines to market. Scientific advances have uncovered a strong link to neuroinflammation, leading to a host of potential drug targets. These include several signalling pathways, of which the MAP kinase pathways are of particular interest. Receptors, such as GPCR55, and controlling glial activation through identifying and modulating key enzymes are also promising strategies. Further investigation into how best to utilize these potential drug targets to halt or even reverse neurodegeneration is an important next step. Recent advances in our understanding of the mechanisms of Parkinson's disease also highlight the importance of continued research into identifying new targets.

Many challenges still lie ahead, including those related to appropriate dosage. These must be overcome in order to avoid negative side effects in elderly patients and diminish the risk of neurotoxicity. (9) However, every advance in our understanding of the elements that influence the onset and progression of neurodegeneration brings the world one step closer to effective therapies.

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