Evaluating the Effect of Novel Drugs on LPS- and ATP- Induced Inflammation Using Enzyme-Linked Immunosorbent Assay

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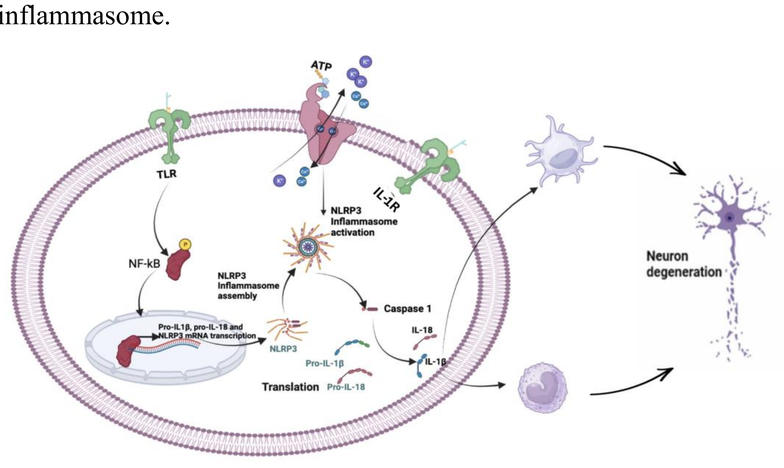
Neuroinflammation plays a key role in many neurodegenerative diseases and is characterized by the over-activation of immune cells within the central nervous system. Activated microglia and astrocytes release pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF- α), as well as reactive oxygen species that contribute to neuronal damage. These inflammatory responses are mediated through signaling pathways including the NF-κB pathway and the NLRP3 inflammasome. Alzheimer's disease (AD) is the most common neurodegenerative disease and the leading cause of dementia worldwide. In AD, accumulation of β-amyloid plaques (Aβ) stimulates chronic neuroinflammatory responses and contributes to neuronal dysfunction and disease progression. Elevated levels of inflammatory cytokines, particularly IL-1β, have been strongly associated with Aβ plaque deposition and the onset of AD. Based on this relationship, targeting neuroinflammatory signaling pathways might be a promising therapeutic strategy for AD. PD2244, a novel compound synthesized by P2D Biosciences, is hypothesized to reduce neuroinflammation by suppressing the production of pro-inflammatory cytokines involved in AD pathology. PD2244 was tested on several cells related to AD pathology, including microglial, neuronal, and monocytic. These cells were pretreated with increasing concentrations of PD2244 prior to inflammatory stimulation. IL-1β production was quantified using Enzyme Linked Immunosorbent Assay (ELISA), a highly sensitive technique commonly used to detect pro-inflammatory cytokine production.

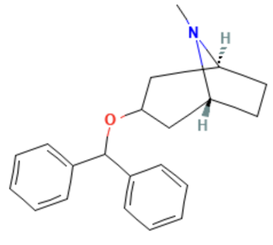
Background

- Alzheimer's disease (AD) is the most common neurodegenerative disease and the leading cause of dementia worldwide.
- In AD, accumulation of β-amyloid plaques (Aβ) stimulates chronic neuroinflammatory responses and contributes to neuronal dysfunction and disease progression.
- Elevated levels of inflammatory cytokines, particularly IL-1β, have been strongly associated with Aβ plaque deposition and the onset of AD.
- These inflammatory responses are mediated through signaling pathways including the NF-κB pathway and the NLRP3 inflammasome.



Production of IL-1β (Adapted from Al-Qahtani, *et al*)

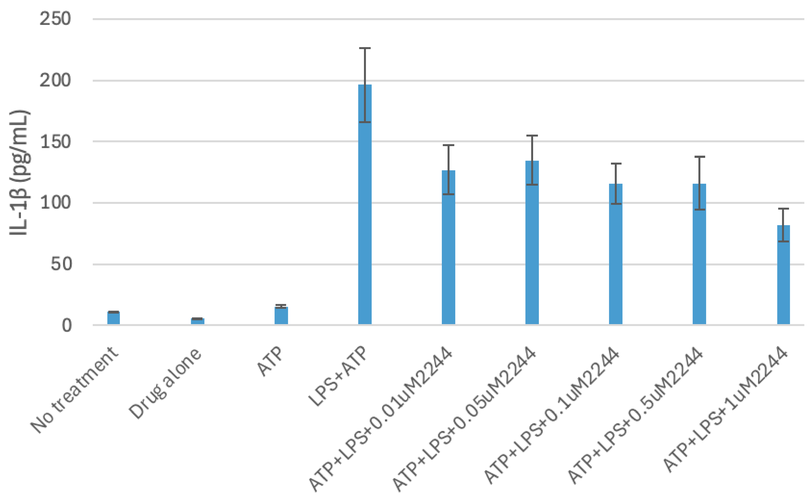
Compounds used in this study



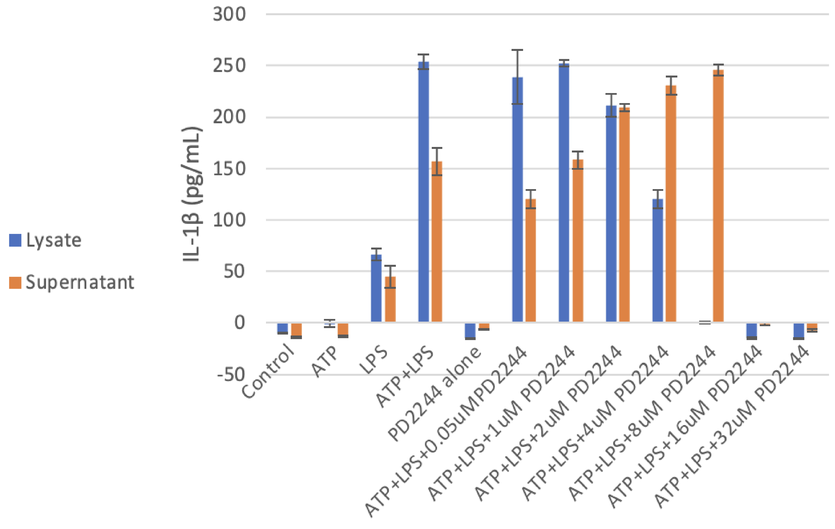
PD2244

Results

I. Effect of PD2244 on LPS-and ATP-induced IL-1β production in BV2 cells

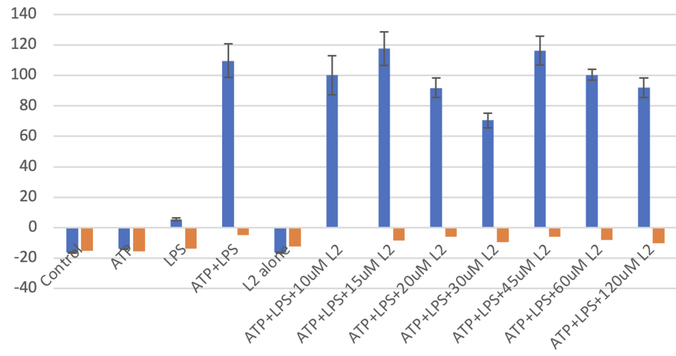


II. Effect of PD2244 on LPS- and ATP- induced IL-1β production in THP-1 cells



Results

III. Effect of L2 on LPS-induced IL-1β production in THP-1 cells



Conclusions

PD2244 inhibits IL-1β production in LPS- and ATP-stimulated BV2 cells in a dose-dependent manner with an average IC_{50} of 0.75μM ± 0.06.

PD2244 inhibits IL-1β production in LPS- and ATP-stimulated THP-1 cell lysate in a dose-dependent manner with an average IC_{50} of 4.13μM

PD2244 has shown potential as an anti-inflammatory molecule

Bibliography

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