Testing Novel Anti-Inflammatory Compounds in Brain Microglial Cells

Ruwayd Abdalla, Prasad Gabbita, Giri Akkaraju

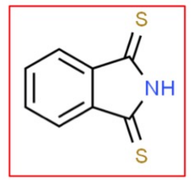
- Dept. of Biology
- P2D Bioscience

Abstract

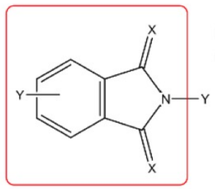
Alzheimer's Disease (AD) is the most common form of dementia that impacts the brain, specifically inducing neuronal cell death in the central nervous system. AD is characterized by the secretion of the protein Tau, and the formation of plaques made up of Beta-amyloid protein. Tau and Beta-amyloid plaques activate the secretion of inflammatory cytokines by microglial cells. The resulting inflammation triggers neuronal cell death, which leads to damage and cognitive decline over time. The cytokines secreted by microglia activate the NF-κB signaling pathway. Activation of Nf-κB results in gene expression and secretion of TNF-α, a pro-inflammatory cytokine known to be associated with inflammation. This leads to a feedback mechanism that results in greater inflammation.

Our lab has demonstrated that a variety of anti-inflammatory compounds derived from IDT (iso-indolin dithione), targets the Nf-κB pathway by reducing the levels of TNF-α at the protein/translational level. BV-2 cells, a mouse microglial cell line were used in this study. Inflammation was stimulated by exposing these cells to LPS to trigger the activation of the NF-κB signaling pathway. We hypothesize that the drugs tested reduce levels of TNF-α secreted by BV-2 mouse microglial cells, and therefore, block the development of disease-associated CNS inflammation seen in Alzheimer's disease

Structure of Compounds



IDT

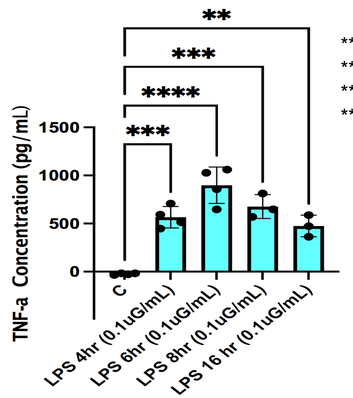


IDT derivatives
(P2D340, P2D2244)

X= O, S
Y= ALKYL, ARYL,
H, NH2, OH, etc.

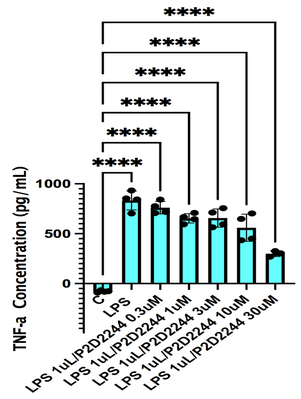
P2D2244 and P2D340

LPS-Stimulated TNF-α Production in BV-2 Cells



** p = 0.0050
*** p = 0.0004
**** p = <0.0001
**** p = 0.0007

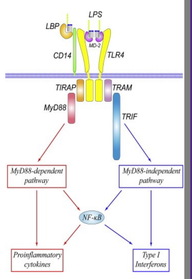
The Effect of P2D2244 on LPS-Induced Secretion of TNF-α



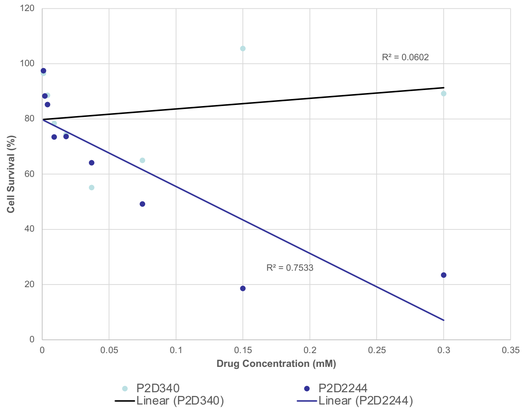
**** p = <0.0001

Background

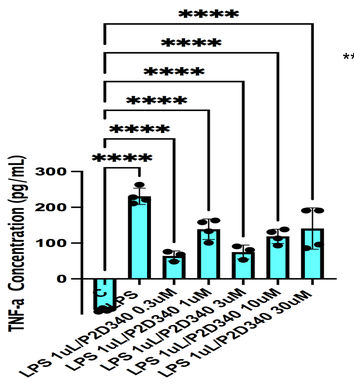
A-beta and tau accumulation in the brain induces the activation of microglial cells in the brain. This results in chronic inflammation which induces neuronal cell death, leading to cognitive decline overtime and results in the negative effects seen in Alzheimer's disease. The secretion of inflammatory cytokines by microglial results in the activation of the NF-κB pathway in surrounding cells. NF-κB is a transcription factor that when activated, turns on genes that results in the production of more cytokines, examples e.g.TNF-α. The TNF-α secreted from the cell, binds to receptors in surrounding cells, and continues the cycle of chronic inflammation. In this study, we test the ability of novel anti-inflammatory compounds to reduce the secretion of TNF-α. To stimulate this, microglia cells are treated with LPS, a component of the bacterial cell wall, which activates the NF-κB signaling pathway.



Cytotoxicity of the Compounds Tested



The Effect of P2D340 on LPS Induced Secretion of TNF-α



**** p = <0.0001

Conclusion

- The compounds P2D340 and 2244 reduce LPS-induced secretion of TNF-α.
- P2D2244 reduces LPS-induced secretion of TNF-a in a dose dependent manner.
- The mechanism by which TNF-a secretion is decreased needs to be explored.
- Citation: Gabbita, S Prasad et al. "Oral TNFα Modulation Alters Neutrophil Infiltration, Improves Cognition and Diminishes Tau and Amyloid Pathology in the 3xTgAD Mouse Model." *PloS one* vol. 10,10 e0137305. 5 Oct. 2015, doi:10.1371/journal.pone.0137305
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