The Effect of Novel Anti-Inflammatory Compounds on NFκB Activation in TNF-Alpha-Induced HEK293 Cells

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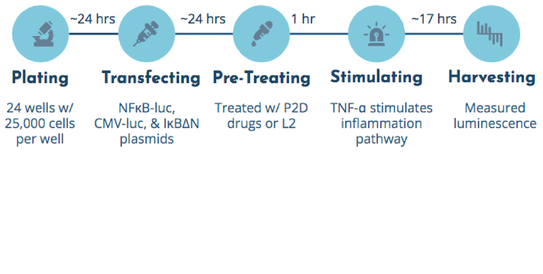
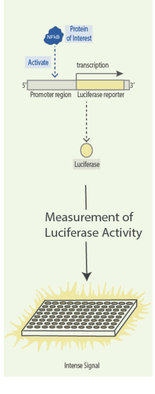
Abstract

Alzheimer's Disease (AD), the most common form of Dementia, is a brain disorder that affects memory, cognition, and behavior. It currently affects 6.7 million Americans in the United States and interferes with daily life. Neuroinflammation in the brain is thought to worsen symptoms and drive the progression of the disease. Inflammation is mediated by the transcription factor NFκB, which typically leads to transcription of pro-inflammatory cytokines, including TNF-alpha and IL-1β. The transcription of these cytokines can lead to a cycle of chronic inflammation if left unregulated. In collaboration with P2D Biosciences and the Green Lab, we focused on testing compounds for their ability to reduce inflammation. Some of the compounds tested here have been shown to reduce cognitive defects in a mouse model of AD. In this study we are trying to understand the mechanism of action of these drugs. We are looking at the effect on the transcription factor NFκB.

Methods

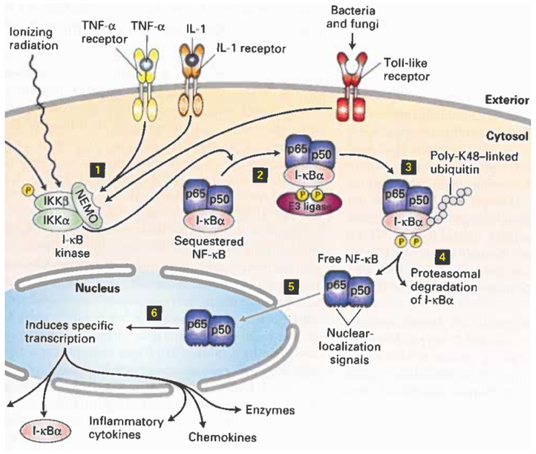




Hypothesis

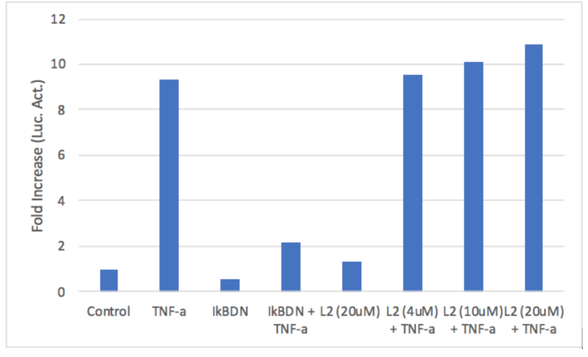
The novel compounds tested in this study reduce inflammation by inhibiting the activation of the transcription factor NFκB .

Background: NFκB Signaling Pathway



NFκB is an important transcription factor essential for the inflammatory response in the cell. Chronic inflammation in the brain can lead to damaged tissue or tissue death. We see this in diseases such as Alzheimer's Disease or Frontotemporal Dementia.

Results



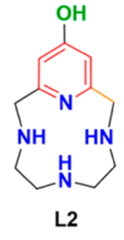


Figure 1: L2 does not inhibit the TNF-alpha-induced activation of NFκB. No significant reduction in luciferase activity was observed in cells treated with increasing concentrations.

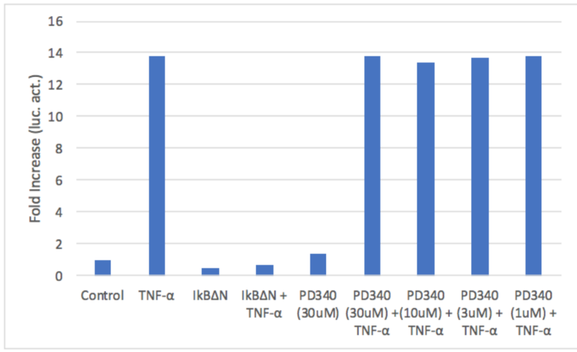


Figure 2: PD340 does not inhibit the TNF-alpha-induced activation of NFκB. No significant reduction in luciferase activity was observed in cells treated with increasing concentrations.

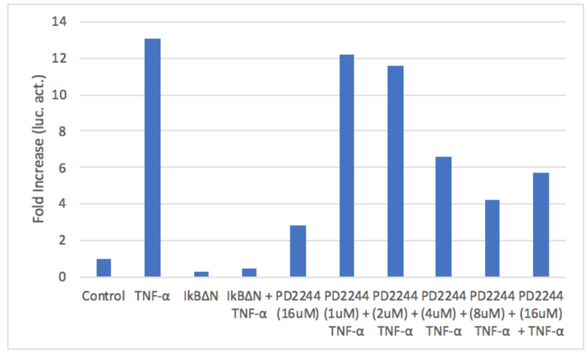


Figure 3: PD2244 exhibits a dose-dependent inhibition of TNF-alpha-induced activation of NFκB. A 50% reduction in luciferase activity was observed in cells treated with increasing concentrations.

Conclusion

In this study, we screened three drugs to look at their effect on inflammation. Two of the drugs, L2 and PD340, did not show a significant effect on the activation of NFκB. The drug, PD2244, showed a 50% reduction in the activation of NFκB. Further studies need to be conducted to pinpoint the exact part of the pathway that is being inhibited by this compound.

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