Inhibitors of soluble epoxide hydrolase and p38 kinase as Alzheimer's therapeutics

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Technology description

A Potent Neuroprotective Mechanism for Alzheimer’s Disease

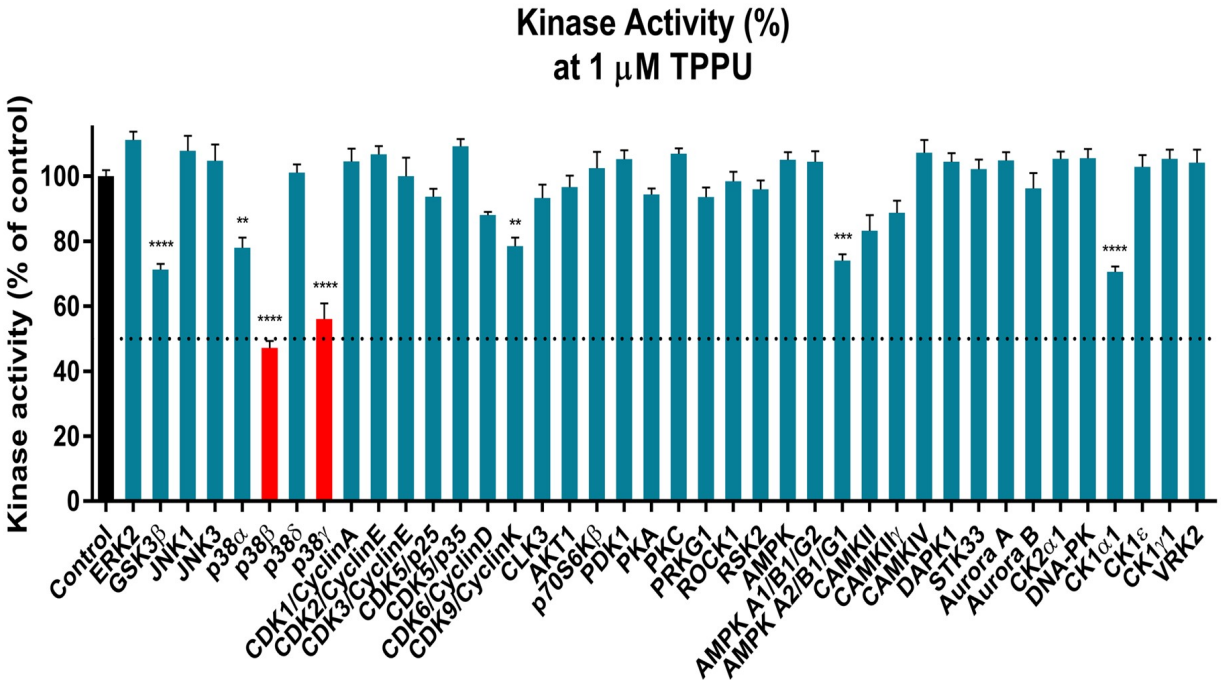
Background

Alzheimer’s disease (AD) is the most common neurodegenerative disorder. Neuroinflammation is a prevalent pathogenic stress leading to neuronal death in AD. Targeting neuroinflammation to keep neurons alive is an attractive strategy for AD therapy. 1-Trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU) is a potent and blood-brain barrier permeable inhibitor of soluble epoxide hydrolase (sEH). It has a good efficacy on a wide range of chronic inflammatory diseases in preclinical animal models. However, the anti-neuroinflammatory effects and molecular mechanisms of TPPU for potential AD interventions remain elusive.

Technology Overview

Researchers at the University of Hawaii’s Molecular Biosciences and Bioengineering Department have developed a novel method using TPPU to treat AD.

TPPU selectively inhibits both sEH and p38β kinase, showing a neuropharmacology in multiple AD signaling pathways. TPPU effectively prevents neuronal death by mitigating amyloid toxicity, tau hyperphosphorylation and mitochondrial dysfunction in the human neuron SH-SY5Y cells, and promoting neurite outgrowth and suppressing activation and nuclear translocation of NF-κB for inflammatory responses.



Advantages

TPPU selectively inhibits soluble epoxide hydrolase (sEHs);
TPPU selectively inhibits p38 kinase;
TPPU protects neurite outgrowth against Aβ42 neurotoxicity;
TPPU and epoxyeicosatrienoic acids (EETs) prevent Aβ-induced cytotoxicity in SH-SY5Y cells;
TPPU attenuates tau hyperphosphorylation induced by Aβ42 in human SH-SY5Y cells;
TPPU and EETs prevent Aβ-induced depolarization of mitochondrial membrane potential and mitochondrial dysfunction; and
TPPU suppresses activation and nuclear translocation of the transcription factor NF-κB in differentiated SH-SY5Y cells.
TPPU is a potential disease-modifying therapy for AD.

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