

Succinate Receptor 1 (SUCNR1) Antagonists to Treat Neuroinflammation

A promising therapeutic target for the prevention and/or treatment of neurodegenerative diseases.

Technology Overview

The inventors have identified a small molecule Succinate Receptor 1 (SUCNR1) antagonist (termed "compound 7a") that interferes with SUCNR1 signaling in microglia and suppresses neuroinflammation. In recent work, the inventors have developed an oral topical gelformulation of compound 7a, which has been shown to reduce both periodontitis and central nervous system (CNS) inflammation and may represent an efficacious therapeutic agent for the prevention and/or treatment of neurodegenerative diseases. As described in unpublished proof-of-concept (POC) studies, oral treatment with compound 7a reduces neuroinflammation in a mouse model of periodontitis by decreasing levels of the cytokine IL1β both systemically and locally in gingiva, hippocampus, and cerebellum.

Current Development Stage

Lead-like compounds are currently being tested in mouse-model POC studies.

Background

Both chronic neuroinflammation and immune dysregulation in the periphery represent key contributors to the development and progression of non-hereditary neurodegenerative diseases, such as Alzheimer's disease, Parkinson's Disease, and Multiple Sclerosis. These diseases can be induced and/or accelerated through dysbiosis (homeostatic imbalance) of microbiota in the mouth and gut, leading to abnormal activation of host immune responses and dissemination of pro-inflammatory cytokines and other signaling compounds into the CNS. Among these, succinate, a common metabolite of mammalian and bacterial cells, has been found to exert a pro-inflammatory response in the CNS through the activation of Succinate Receptor 1 (SUCNR1) and its downstream signaling pathway. Therefore, inhibition of SUCNR1 represents a promising therapeutic strategy to block succinate-mediated, pro-inflammatory signaling cascades and prevent and/or treat neurodegenerative diseases. Such treatments could be further augmented with microbiome-targeted therapeutics to restore succinate homeostasis.

Applications

Technology ID

LI06-03

Category

Life Sciences/Biochemicals &
Small Molecules
Life Sciences/Neuroscience
Life
Sciences/Therapeutics/Inflammat
Disease
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- **Neurodegenerative conditions:** Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis, among others
- Periodontitis
- Potential therapeutic target for oxidative and metabolic stress-related conditions: Atherosclerosis, metabolic syndrome, and diabetes complications (e.g., osteoporosis, retinopathy, and hypertension)
- **Potential therapeutic target for chronic inflammatory conditions:** Ulcerative colitis and rheumatoid arthritis

Advantages

- Target topology is favorable for pharmacological intervention: SUCNR1 is a membrane G protein-coupled receptor with an extracellular surface accessible to drug targeting
- Method of compound administration: Compound 7a can be administered orally
- Well-characterized, disease-implicated signaling pathway: The succinate/SUCNR1 signaling pathway has been previously implicated in multiple conditions, including ulcerative colitis, rheumatoid arthritis, diabetic retinopathy, hypertension, liver fibrosis and atherosclerosis
- New therapeutic target for neuroinflammation: There are no FDA-approved drugs targeting SUCNR1 or the succinate/SUCNR1signaling pathway

Intellectual Property

A U.S. non-provisional application and a PCT application have been filed covering the chemical composition of the compounds and their method of use.