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Noradrenergic control of neuroinflammation and cognitive function in Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease, directly affecting about 24 million people worldwide. Currently, there is no effective treatment for AD to prevent, cure, or slow its progression, emphasizing the need for a novel therapeutic strategy. The lack of effective AD therapies can be attributed to the complex array of factors involved in its development and progression. Given the complex nature of AD, therapeutic agents that simultaneously modulate different key target points of AD pathology would represent the most ideal and comprehensive therapy. Beta1-adrenergic receptor (ADRB1), which is involved in multiple key aspects of AD, is a unique and therapeutically attractive target for AD that could enable a comprehensive strategy for the treatment and management of the disease. Here, we demonstrate that specific activation of G-protein signaling of ADRB1 leads to beneficial effects on impaired cognitive function and pathology associated with the disease in two independent mouse models of AD. In 2 different

transgenic models in which mice either express 5 mutations related to Familial Alzheimer's Disease, [5XFAD; 3 mutations in the amyloid precursor protein and 2 in presenilin 1] or 2 mutations in amyloid precursor protein (T41B), transgenic and wildtype male mice were chronically dosed with vehicle or with the G-protein biased ADRB1 partial agonist, xamoterol (5XFAD, 6 mg/kg daily oral gavage or 3 mg/kg subcutaneous pump; T41B, 0.3-1.0 mg/kg daily subcutaneous injection). When chronically dosed, the G-protein biased ADRB1 partial agonist improved novel object recognition and spatial learning in 5XFAD mice, and reduced hyperactivity and improved contextual fear conditioning in T41B mice. Chronic dosing with xamoterol also decreased amyloid beta and modulated indices of neuroimmune activation in both models. Reduction in tau pathology was also observed with chronic dosing with xamoterol in 5XFAD mice. Together, our findings suggest that activation of the ADRB1 G-protein signaling pathway may be a therapeutic approach for AD.

Biography

Mehrdad Shamloo has received his doctoral degree in 1999 from the Wallenberg Neuroscience Center of Lund University in Sweden. He was recruited to the San Francisco Bay Area the same year where he held several positions at biopharmaceutical companies, including Affymax and AGY Therapeutics, until 2008. During this time he was responsible for the discovery and development of novel neuroprotective and regenerative small molecule and peptide therapeutics for multiple diseases. As the program leader for neuroprotection and regeneration programs at AGY Therapeutics, his work enabled several patent applications, scientific publications, and an IND application and subsequent clinical trials. These years of experience in industry built on his extensive background in CNS drug discovery and preclinical development. In 2008, Mehrdad joined Stanford University Stanford University School of Medicine. He is a faculty in school of medicine and director of Stanford behavioral neuroscience laboratory. He has published more than 55 papers in reputed journals.

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