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mGluR5 Contribution to Neuropathology in Alzheimer Mice Is Disease Stage-Dependent

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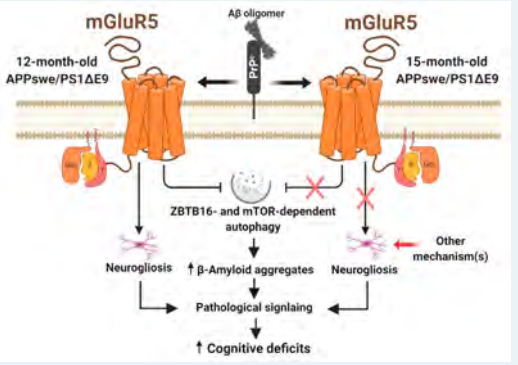
ABSTRACT: Alzheimer's disease (AD) is the most prevalent neurodegenerative disease and is characterized by a progressive cognitive decline in affected individuals. Current therapeutic strategies are limited in their efficacy and some have proven to be even less effective at later disease stages or after extended use. We previously demonstrated that chronic inhibition of mGluR5 signaling using the selective negative allosteric modulator (NAM) CTEP in APPswe/PS1ΔE9 mice can rescue cognitive function, activating the ZBTB16-mediated autophagy pathway to reduce Aβ, the principal neurotoxic species in AD brains. Here, we evaluated the efficacy of long-term treatment with CTEP in 6 month old APPswe/PS1ΔE9 mice for either 24 or 36 weeks. CTEP maintained its efficacy in reversing working and spatial memory deficits and mitigating neurogliosis in APPswe/PS1ΔE9 mice when administered for 24 weeks. This was paralleled by a significant reduction in Aβ oligomer and plaque load as a result of autophagy activation via ZBTB16 and mTOR-dependent pathways. However, further extension of CTEP treatment for 36 weeks was found ineffective in reversing memory deficit, neurogliosis, or Aβ-related pathology. We found that this loss in CTEP efficacy in 15 month old APPswe/PS1ΔE9 mice was due to the abolished contribution of ZBTB16 and mTOR-mediated signaling to AD neuropathology at this advanced disease stage. Our findings indicate that the contribution of pathological mGluR5-signaling to AD may shift as the disease progresses. Thus, we provide the first evidence that the underlying pathophysiological mechanism(s) of AD may unfold along the course of the disease and treatment strategies should be modified accordingly to ensure maximal therapeutic outcomes.



KEYWORDS: *Alzheimer's disease, autophagy, mGluR5, neuroglia, age, beta amyloid*

Alzheimer's disease (AD) is a neurodegenerative disorder primarily characterized by progressive memory loss and cognitive decline. It is the most common form of dementia affecting people over 65 years of age[1] with more than 40 million people diagnosed with AD worldwide.[2] At present, AD has no known cure and the existing treatments only provide symptomatic relief with limited disease-modifying efficacy.[3,4] With an aging population the incidence of AD is continuing to rise,[1] emphasizing the need for effective, safe, long-term and/or late stage therapeutic strategies for the treatment of AD.

Associated with the neurotoxic effects that characterize AD is the protein amyloid β (Aβ). In its fibrillar plaque form, Aβ forms one of the main hallmarks for AD. However, it is the soluble oligomeric $A\beta_{1-42}$ that is believed to be the more neurotoxic amyloid species.[5,6] AD is known to be associated with a disruption of glutamatergic signaling, and this is believed to be due to the enhanced binding of Aβ oligomers to metabotropic glutamate receptor 5 (mGluR5) in association with cellular prion proteins.[7] Specifically, mGluR5 can act as an extracellular scaffold for a Aβ/ cellular prion protein (PrP^c) complex that results in impaired lateral diffusion and enhanced clustering of the receptor leading to excessive release of intracellular Ca^{2+} and neurotoxicity.[8−10] We have previously shown that the genetic deletion of mGluR5 in the APPswe/PS1ΔE9 mouse model of AD prevented memory loss and reduced Aβ-related neuropathology in male animals.[11] We then showed that the pharmacological inhibition of mGluR5 using a selective negative allosteric modulator (NAM) CTEP (2-chloro-4-[2[2,5-dimethyl-1-[4-(trifluoromethoxy) phenyl] imidazol-4-yl] ethynyl] pyridine) in two male mouse models of AD, APPswe/PS1ΔE9 and 3xTg-AD, rescued deficits in learning and memory and enhanced autophagic clearance of Aβ oligomers and plaques from the brain.[12,13] Others have also reported that mGluR5 silent allosteric modulators can improve cognitive impairment but not Aβ deposition in an AD mouse model.[14] More so, mGluR5 positive allosteric modulator was proven to reverse Aβ-mediated neurotoxicity but was not successful in reversing cognitive deficits in an AD mouse

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