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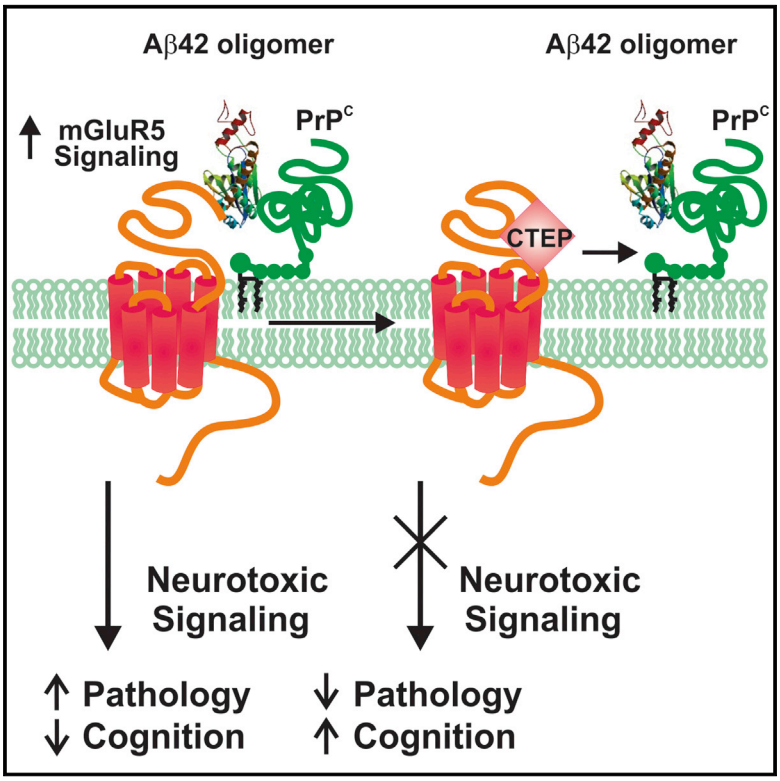
Report

Chronic Pharmacological mGluR5 Inhibition Prevents Cognitive Impairment and Reduces Pathogenesis in an Alzheimer Disease Mouse Model

Graphical Abstract



Highlights

- Chronic treatment with CTEP improves memory and cognitive function in an AD mouse
- Chronic treatment with CTEP reduces Aβ oligomers and Aβ plaques in an AD mouse
- mGluR5 antagonism may be a viable approach for the treatment of AD

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In Brief

Hamilton et al. demonstrate that chronic treatment of an Alzheimer disease mouse model with Basimglurant (CTEP) rescues the cognitive function and reduces disease pathology. The chronic pharmacological inhibition of mGluR5 signaling with CTEP might be effective for the treatment of cognitive deficits experienced by AD patients.

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Chronic Pharmacological mGluR5 Inhibition Prevents Cognitive Impairment and Reduces Pathogenesis in an Alzheimer Disease Mouse Model

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SUMMARY

Beta-amyloid (Aβ) oligomers contribute to the pathophysiology of Alzheimer disease (AD), and metabotropic glutamate receptor 5 (mGluR5) has been shown to act as a receptor for both Aβ oligomers and cellular prion proteins. Furthermore, the genetic deletion of mGluR5 in an APPswe/PS1ΔE9 mouse model of AD improves cognitive function and reduces Aβ plaques and Aβ oligomer concentrations. Here, we show that chronic administration of the orally bioavailable mGluR5-selective negative allosteric modulator CTEP, which is similar in structure, potency, and selectivity to Basimglurant (RO4917523), which is currently in phase II clinical development for major depressive disorder and fragile X syndrome, reverses cognitive decline in APPswe/PS1ΔE9 mice and reduces Aβ plaque deposition and soluble Aβ oligomer concentrations in both APPswe/PS1ΔE9 and 3xTg-AD male mice. These findings suggest that CTEP or its analogue Basimglutant might potentially be an effective therapeutic for the treatment of AD patients.

INTRODUCTION

Alzheimer disease (AD) is the most prevalent neurodegenerative disease, and the predominant neurotoxic species in the brains of AD patients is beta-amyloid (Aβ) protein, which is formed by the sequential cleavage of amyloid precursor protein (APP) (Citron et al., 1996; Kamenetz et al., 2003). These oligomers have been shown to be the most harmfully correlated with AD pathogenesis (McGowan et al., 2005; Shankar et al., 2008). Metabotropic glutamate receptor 5 (mGluR5) is a member of the G protein-coupled receptor (GPCR) superfamily that is activated by glutamate to couple to the heterotrimeric G protein $G\alpha_{q/11}$, resulting in the downstream second messenger-dependent release of intracellular Ca^{2+} that has been linked to a number of neurodegenerative diseases (Ribeiro et al., 2010). Aβ oligomers and cellular prion protein (PrP^C) interact with mGluR5 to cause the release of Ca^{2+} from intracellular stores, thus disrupting normal neuronal signaling and function (Renner et al., 2010; Sokol et al., 2011; Um et al., 2013; Haas et al., 2014). The genetic deletion of mGluR5 improves AD pathogenesis and cognitive decline in the APPswe/PS1ΔE9 mouse model of AD (Hamilton et al., 2014). Preclinical trials in fragile X syndrome and major depressive disorder with 2-chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1H-imidazol-4-yl) ethynyl) pyridine (CTEP) suggest that this mGluR5-selective allosteric modulator may be effective for the treatment of AD (Lindemann et al., 2011, 2015; Michalon et al., 2012). CTEP has high in vivo potency and is an orally bioavailable, brain-permeant, mGluR5-negative allosteric modulator of mGluR5; it has a half-life of 18 hr in vivo, allowing once a day administration that is effective for the treatment of fragile X in adult mice (Lindemann et al., 2011; Michalon et al., 2012). Moreover, CTEP is highly selective for mGluR5 versus more than 100 GPCR targets tested (Lindemann et al., 2011).

In the present study, we tested whether acute and/or chronic treatment with CTEP improved cognitive performance and reduced Aβ pathology in APPswe/PS1ΔE9 male mice. We found that chronic, but not acute, administration of CTEP by intraperitoneal injection rescues memory deficits in novel object recognition, Morris water maze (MWM), and reversal MWM (RMWM) memory paradigms in APPswe/PS1ΔE9 mice. Chronic CTEP treatment also significantly reduced Aβ oligomer concentrations and plaque formation in both APPswe/PS1ΔE9 and 3xTg-AD mouse models of AD. Our data provide further evidence of a central role for mGluR5 in AD, and they highlight the potential for repurposing the CTEP analogue Basimglurant as a treatment for AD.

RESULTS

Chronic, but Not Acute, Treatment with CTEP Rescues Memory Loss

To test whether CTEP treatment would ameliorate the behavioral and pathological phenotypes observed in AD mouse models, wild-type C57Bl/6, APPswe/PS1ΔE9, and 3xTg-AD mice male mice were raised to 9 months of age and treated with either