

## Can mGluR5 antagonists be utilized to reduce beta-amyloid levels in Alzheimer's disease and other neurological disorders

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Messenger RNA (mRNA) binding proteins, which modulate ribosomal access and initiation, regulate dendritic translation. One of the best-known examples is the fragile X mental retardation protein (FMRP), which represses the translation of a subset of dendritic mRNAs whose products affect synaptic plasticity and function. Metabotropic glutamate receptor 5 (mGluR5) signaling causes pulsatile translation of post-synaptic mRNAs by repressing FMRP. We have demonstrated that FMRP binds to and controls the post-synaptic translation of amyloid-beta protein precursor (APP) mRNA and that mGluR5 signaling increases APP production. APP is cleaved to beta-amyloid, the predominant protein in the senile plaques in Alzheimer's disease (AD) and Down syndrome. Chronic treatment with the mGluR5 inhibitor fenobam reduces beta-amyloid levels in AD mice. APP and beta-amyloid are also up-regulated in a mouse model for Fragile X syndrome (FXS), a disorder characterized by lack of expression of FMRP. mGluR5 antagonists are under intense investigation as a possible therapeutic treatment for FXS. We hypothesize that mGluR5 antagonists improve FXS phenotypes by modulating APP and beta-amyloid levels and that these inhibitors are potential therapeutics for AD and DS as well. There is currently a dearth of potent therapeutics for beta-amyloid reduction, and the mGluR5 antagonist fenobam has been previously approved for phase I and II clinical trials in humans. Thus, this drug could be rapidly extrapolated to humans.

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