ACS Chemical Neuroscience

In This Issue

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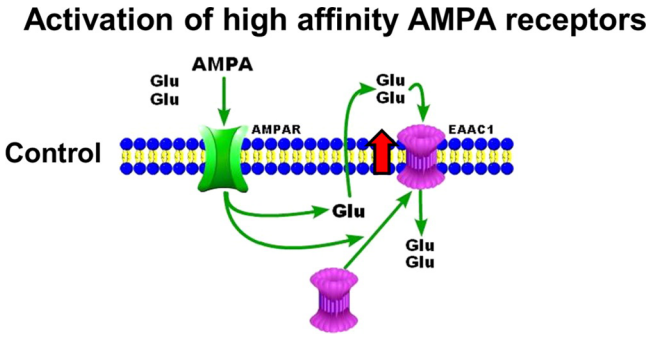
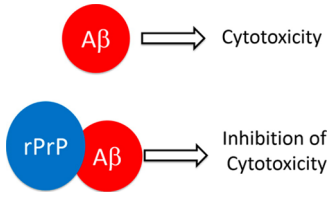
MODULATORS OF GLUTAMATE RELEASE IN THE CEREBELLUM



During glutamatergic neurotransmission, neurons release glutamate which is sensed by postsynaptic neurons mainly through the ionotropic glutamate receptors NMDA and AMPA, whose activation increases extracellular glutamate levels. As excessive activation of glutamate receptors induces neuronal death, extracellular glutamate must be tightly controlled. The glutamate transporter EAAC-1 plays a main role in this task.

In the current issue, Cabrera-Pastor et al. (DOI: 10.1021/acschemneuro.5b00212) show that activation of AMPA and NMDA receptors induces transient increases of extracellular glutamate in the cerebellum in vivo, which are rapidly reduced due to enhanced membrane expression of the EAAC1 transporter. Chronic hyperammonemia alters this interplay which would contribute to the impaired neurotransmission and cognition in hyperammonemia.

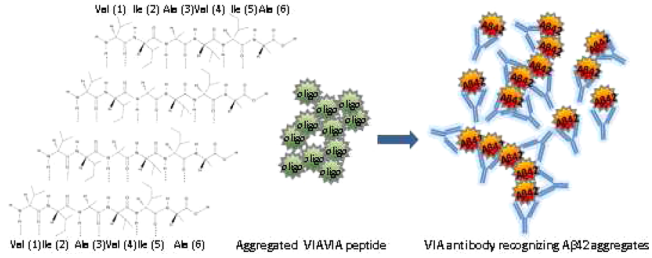
INSIGHT INTO PROTECTIVE EFFECT OF PRION PROTEIN



It is generally believed that the main neurotoxic species in Alzheimer's disease are soluble amyloid Aβ oligomers, and recent data suggest that at least some of the toxic effects of Aβ are mediated by the normal form of the prion protein. Furthermore, recent studies indicate that the assembly of Aβ into toxic species and the cytotoxic action of the oligomers can be strongly inhibited by soluble recombinant prion protein (rPrP) and its fragments. However, the mechanism by which rPrP interacts with Aβ oligomers and prevents their toxic effects is unknown, and studies in this regard are hindered by large heterogeneity of commonly used preparations of Aβ oligomers.

To overcome the aforementioned heterogeneity problem, Williams et al. (DOI: 10.1021/acschemneuro.5b00229) used well-defined oligomeric species of Aβ that were trapped by chemical cross-linking. The authors found that rPrP alters the size distribution of small Aβ oligomers, and that both the binding affinity between rPrP and Aβ as well as the protective effect of rPrP against Aβ cytotoxicity are oligomer size dependent. This mechanistic insight should aid in future development of PrP-based therapeutics for Alzheimer's disease.

AN ANTIBODY TO PROTECT AGAINST ALZHEIMER'S DISEASE



Alzheimer's disease is the most prevalent neurodegenerative disease and currently has no effective treatment. It is characterized by the toxic buildup of a misfolded protein, amyloid-beta (Aβ), that forms clumps interfering with the communication between cells in the brain. Aβ can exist in multiple different pathological forms, with small aggregates of the longer form of the protein called Aβ-42 oligomers being the most toxic. In order to study this pathological form of the protein, Bodani et al. (DOI: 10.1021/acschemneuro.5b00231) have created a specific antibody recognizing Aβ-42 oligomers.

The authors found that these oligomers could be found both in human Alzheimer's disease brains and in Alzheimer's mouse model brains. They also found evidence that this antibody could be used to protect against toxicity in cells. These results could contribute to potential future therapeutics for Alzheimer's disease that are designed to fight against the detrimental effects of Aβ-42 oligomers.

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