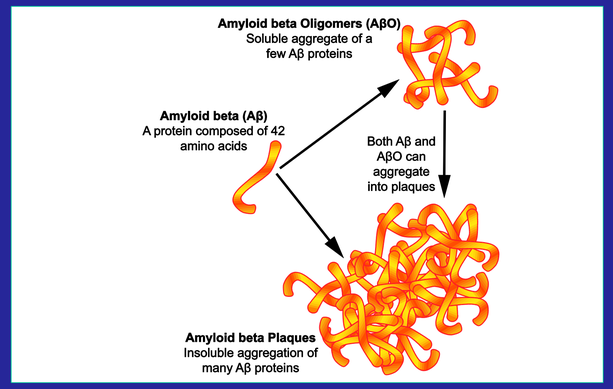
Amyloid Beta, Zinc and Neurodegeneration in Alzheimer's Disease

Busciglio Lab
Dept. of Neurobiology and Behavior,
Institute for Memory Impairments and Neurological Disorders
University of California, Irvine, CA

Introduction

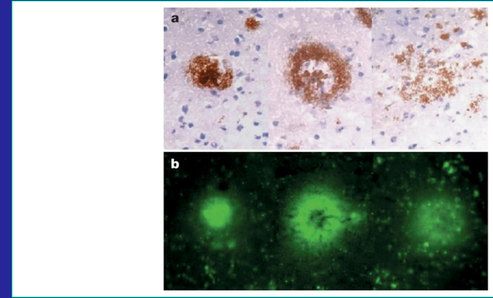
Alzheimer's disease (AD) is the leading cause of dementia, a progressive condition marked by deteriorating cognitive abilities such as memory, judgment, orientation, understanding and communicating. It is ultimately fatal, usually within 4-6 years after diagnosis. Current treatments slow the worsening of symptoms, but do not stop the death of brain cells that results in cognitive impairment. The primary pathology of AD consists of aberrant regulation of two proteins, amyloid beta (Aβ) and tau.

Amyloid beta (Aβ)



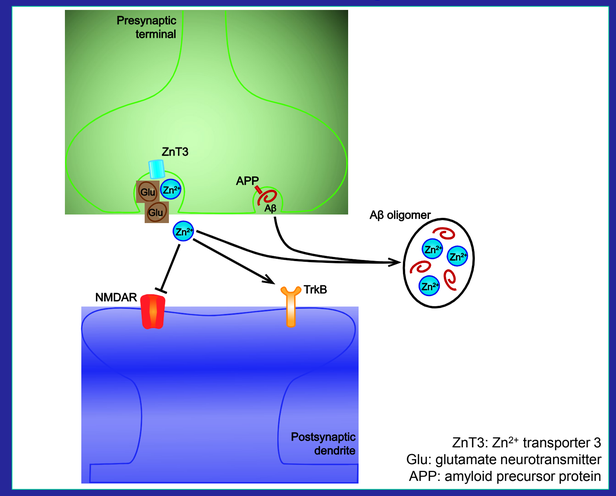
Aβ is a protein that aggregates into soluble oligomers and insoluble plaques. The oligomeric form is the more toxic species, damaging neurons and interfering with synaptic functions.

Aβ and Zn^{2+}



Aβ plaques are enriched with zinc.
a) Aβ plaques are labeled with a brown stain in brain tissue of an AD patient.
b) Zinc is labeled with fluorescent green in the plaques seen above.

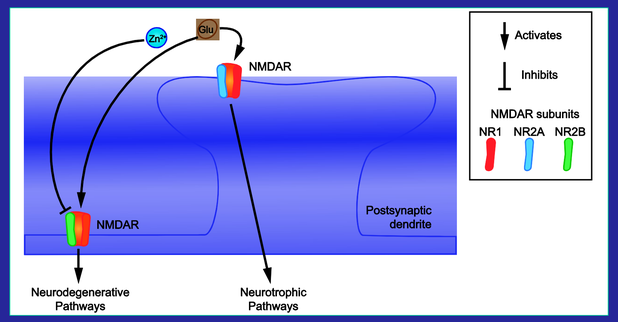
Zn^{2+} at the Synapse



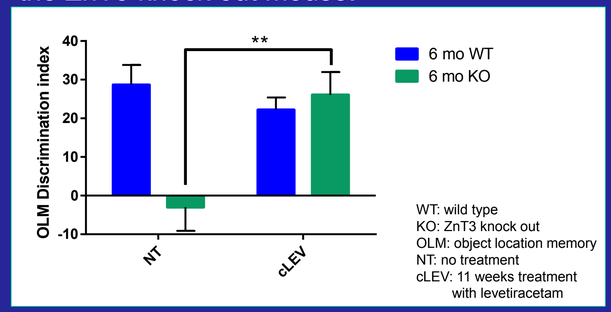
Zinc (Zn^{2+}) is released during neurotransmission and modulates several neuronal signaling pathways. Interaction between Zn^{2+} and AβO is implicated in AD pathology because the release of Zn^{2+} increases localization of AβO at the synapse, where AβO binds to Zn^{2+} and interferes with the role of Zn^{2+} in neurotransmission, including inhibition of NMDA receptors and activation of neurotrophic TrkB receptors.

Results from our lab

We have found that interference with Zn^{2+} neurotransmission results in excessive excitatory neurotransmission (seizure activity in the brain) and impairs neurotrophic signaling. Zn^{2+} inhibits the NR2B subunit, but not the NR2A, of NMDARs, altering the balance between synaptic and extra-synaptic NMDAR signaling, leading to neurodegeneration.



We have also found that treatment with an anti-seizure drug prevents the age-dependent development of cognitive impairment found in a transgenic mouse that lacks synaptic Zn^{2+}, the ZnT3 knock out mouse.

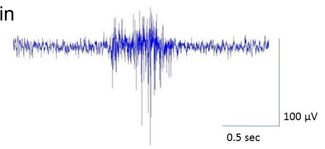


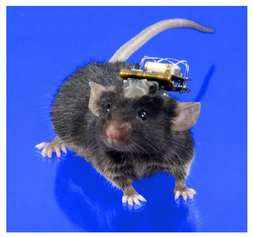
Therapeutic implications

Patients with mild cognitive impairment (MCI) in conjunction with elevated activity in a specific region of the brain are at greater risk of converting to AD than other MCI patients. This group of patients may benefit from treatment with an anti-seizure drug to reduce the elevated brain activity and prevent further impairment of cognition.

However, this strategy does not address the underlying dysregulation of synaptic Zn^{2+}; it treats one of the results of dysregulation. Another strategy would focus on maintaining Zn^{2+} homeostasis in the brain. A drug for this has been successful in treating mouse models of AD and has had success in a limited clinical trial on humans. Our results support the maintenance of Zn^{2+} homeostasis as a relevant therapeutic strategy for AD.

Epileptiform activity recorded in aged ZnT3 knock out mouse





The Neurologger pictured on this mouse can record EEG in freely moving subjects while performing behavioral tasks to assess the effects of experimental treatments on cognitive impairment.

Future Directions

Our lab is working on:

- Investigating the role of seizure activity in the impairment of cognition.
- Analyzing EEG to investigate age-dependent alterations in seizure activity.
- Assessing the effects of treatments that restore zinc homeostasis in the seizure activity found in some mouse models of AD.

Acknowledgments

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