Alzheimer’s disease (AD) is a neurodegenerative disorder manifested by a progressive impairment of cognitive functions. Current pharmacological therapies for AD improve symptoms but do not significantly modify disease progression, thus offering limited and transient benefits to patients. A pressing need in AD management is to diagnose and apply treatments at the early stage of AD in order to ameliorate or slow down the disease progression.

The large conductance, Ca2+-dependent K+ (BK) channel offers a potential “disease modifying” therapy in AD. BK channels are expressed widely in the central nerve system and their activation requires neuronal depolarization together with a rise of intracellular Ca2+. By rapid repolarization of the presynaptic action potential, BK channels diminish synaptic transmission by downregulating calcium signals necessary to trigger transmitter exocytosis. Therefore, BK channels are thought to be an ‘emergency brake’ that reduces excessive excitatory activities.

Using electrophysiological recordings in hippocampal slices in vitro, we have recently shown that BK channels are activated in the AD transgenic mice but not in wild type controls. Such BK activation is responsible for the downregulation of hippocampal field EPSPs in the mutant animals (Ye et al, Neurobiol Aging, 2008). We provide convergent evidence suggesting that dis-regulation of Ca2+ homeostasis and subsequent activation of BK channels manifest at the early stage of disease in the mutant mice.

We hypothesize that excessive glutamatergic excitation is an important factor in AD pathological processes, and that the down-regulation of glutamatergic transmission by BK channel activation serves as an intrinsic protective mechanism against such excessive excitation in AD. Pharmacological activation of BK channels via BK channel openers has been used in clinical trials and animal models of stroke to protect against brain neuronal injuries. Currently, we are testing whether administration of the BK channel openers offers long-term benefits in AD.