ACS Chemical Neuroscience

In This Issue

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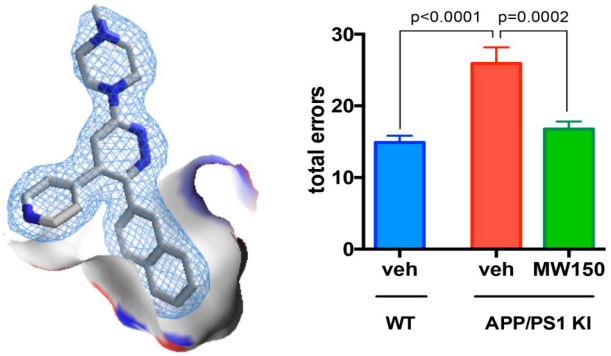
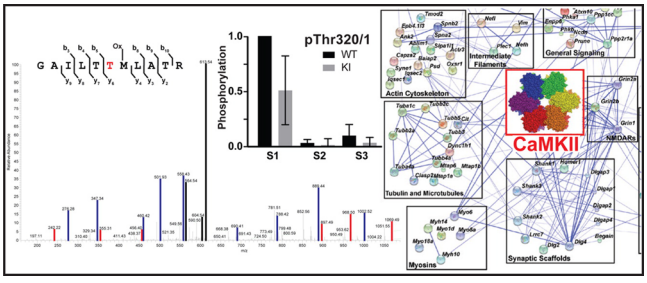
## MODULATING STRESS-RELATED BEHAVIOR




Currently, a void exists for serine/threonine protein kinase inhibitor drugs and CNS disease indications. Clinical and preclinical data implicate the stress kinase, p38$\alpha$MAPK, in neuroinflammation and synaptic dysfunction, pathophysiology phenotypes shared across diverse neurodegenerative and neuropsychiatric disorders. However, the lack of isoform selective inhibitors for CNS indications and the variable efficacy in prior mixed kinase inhibitors in peripheral tissue disorders has thwarted progress in the field. Now, Roy et al. (DOI: 10.1021/acschemneuro.5b00002) report an isoform selective p38$\alpha$MAPK inhibitor, MW01-18-150SRM (= MW150), that is efficacious in suppression of hippocampal-dependent associative and spatial memory deficits in two distinct synaptic dysfunction mouse models.

The authors describe a scalable synthetic scheme and characterization of the biocompatible product, summarize outcomes from pharmacological screens that derisk development potential, and present high resolution crystallography studies that document active site binding, reveal an apparent low energy conformation of the bound inhibitor, and provide a structural hypothesis for MW150s exquisite target selectivity.

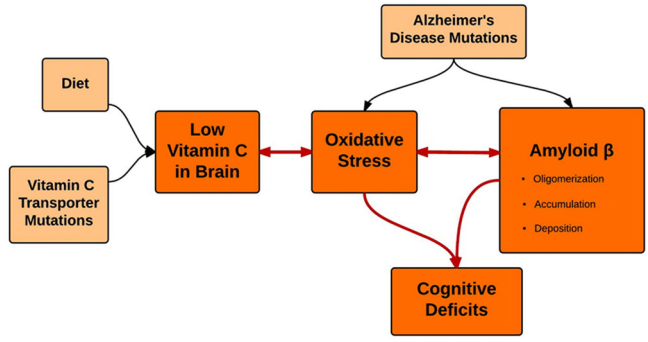
## PROTEOMIC ANALYSIS OF THE MOUSE FOREBRAIN CaMKII




Calcium/calmodulin-dependent protein kinase II (CaMKII) is a serine/threonine kinase that is critical for normal neuronal function and normal learning and behavior. CaMKII has catalytic activity toward itself (autophosphorylation) at multiple sites on the kinase. Specifically, autophosphorylation at Thr286 and Ser305/Ser306 of the CaMKII$\alpha$ isoform and Thr287 and Ser306/Ser307 of the CaMKII$\beta$ isoform regulate the location of the kinase in the neuron and normal neuronal function. In the current issue, Baucum et al. (DOI: 10.1021/cn500337u) extend these findings and identify novel phosphorylation sites in CaMKII$\alpha$ and CaMKII$\beta$ that are modulated by preventing autophosphorylation at Thr286 and that are enriched in specific neuronal compartments.

The authors use new mass-spectrometry-based proteomics approaches to identify and quantify novel CaMKII interacting proteins that are regulated by prevention of CaMKII$\alpha$ autophosphorylation at Thr286. These studies provide novel insight into CaMKII phosphorylation and protein−protein interactions, allowing for a greater understanding of the molecular mechanisms that underlie normal learning and memory processes.

## VITAMIN C DEFICIENCY IMPAIRS COGNITION




Oxidative stress is a critical feature of the pathogenesis of Alzheimer's disease. Vitamin C is a critical antioxidant that humans must obtain through the diet. Although severe clinical deficiency (scurvy) is rare, suboptimal or depleted levels are relatively common in aged, institutionalized, and disease populations. In this study, Dixit et al. (DOI: 10.1021/cn500308h) limited transport of vitamin C into the brain in a mouse model of Alzheimer's disease to induce prolonged vitamin C deficiency and elevated oxidative stress to test the impact on cognitive ability and amyloid accumulation.

The authors report that low vitamin C did indeed lead to elevated oxidative stress, increased amyloid accumulation and deposition, and cognitive deficits compared to mice with normal vitamin C in the brain. The authors propose that avoiding vitamin C deficiency throughout life is a far more important strategy for disease prevention than late-stage dietary intervention, and one that should receive greater focus in future.

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