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In This Issue

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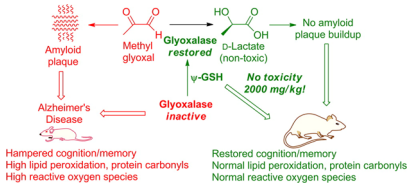
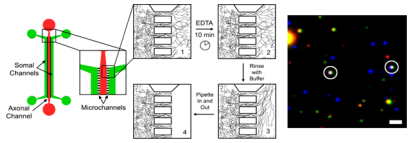
GLYOXALASE, AN ANTI-ALZHEIMER'S DRUG TARGET



Alzheimer's disease (AD) is a global health problem with no available cure. Reactive dicarbonyls such as methylglyoxal play an underlying role in neurodegenerative disorders such as AD. The glyoxylase enzyme system (GLO) is essential to combat oxidative stress by detoxifying dicarbonyls. In the current issue, More et al. (DOI: 10.1021/cn3001679) show that GLO cofactor, glutathione (GSH), increases GLO levels, counteracting AD-pathology, and has potential as a therapeutic.

The authors examined the effects of GSH administration to an AD-prone transgenic mouse model. GSH administration prevented the development of AD-pathology, demonstrated by lack of cognitive impairment, normal ROS levels, normal amyloid plaque levels, and normal lipid peroxidation indicators in the transgenic mouse. Importantly, GSH is nontoxic, even at high doses, increasing its suitability as a clinical drug candidate.

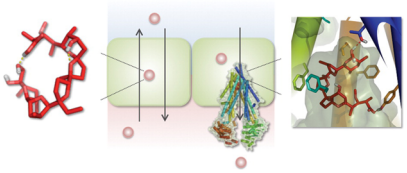
NEW METHOD FOR EXTRACTING AND ANALYZING AXONAL MATERIAL



Axonal transport maintains the polarized structure of neurons and facilitates the passage of synaptic proteins from the cell body to the synapse. To better understand the specificity and variance of protein transport in the central nervous system (CNS), Sgro et al. (DOI: 10.1021/cn300136y) report the development of a microfluidic approach that offers a more detailed analysis of axonal vesicles and carrier proteins at the single organelle level.

By growing hippocampal neurons inside a microfluidic device that separates axons from dendrites and cell bodies, the authors physically removed the axons to obtain a sample of pure CNS axonal material. Multiple antibody-labeling studies validated a previously discovered association between axonal transport motor, KIF1A, and synaptic vesicle protein, p38.This study provides new evidence for the interaction between KIF1A and vesicles containing SV2A and VAMP2.

RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND BBB PENETRATION



The blood brain barrier (BBB) tightly regulates the movement of molecules from blood into the brain. A major challenge to developing effective central nervous system (CNS) drug candidates is overcoming this barrier to reach the intended cellular target. In this issue, Dolghih and Jacobson (DOI: 10.1021/cn3001922) report a new computational approach for optimizing small molecule design for BBB penetration.

The authors present a way to differentiate between molecules with high and low efflux ratios in cell-based monolayer assays, an indicator of brain penetration. The approach also distinguishes between compounds which are expected to gain access to the CNS and those which are likely to be blocked. This new methodology provides guidance for developing new lead CNS drugs.

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