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In This Issue

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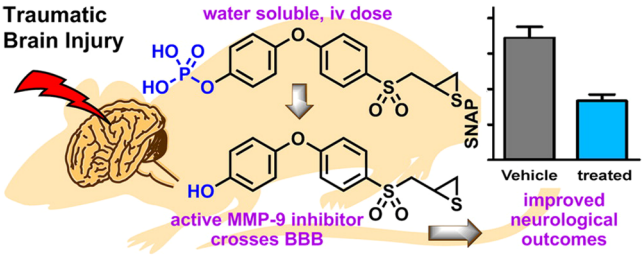
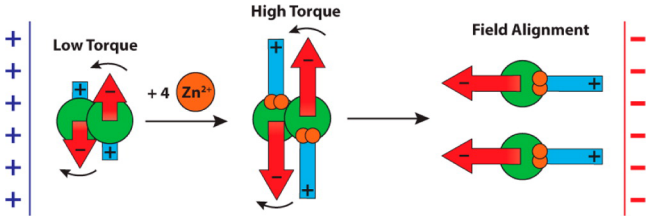
NEW WATER-SOLUBLE MMP-9 INHIBITOR



Matrix metalloproteinase (MMP)-9 represents an important target for intervention in several neurological diseases. The prototype inhibitor SB-3CT shows efficacy in animal models of stroke, traumatic brain injury, and spinal cord injury, and crosses the BBB. However, SB-3CT is readily metabolized, is poorly water-soluble, and cannot be administered intravenously, the preferred route of administration for the treatment of acute neurological conditions, such as traumatic brain injury.

In the current issue, Lee et al. (DOI: 10.1021/acschemneuro.5b00140) used a prodrug strategy to achieve >2000-fold improvement in water solubility. The prodrug is quantitatively hydrolyzed in human blood to the active MMP-9 inhibitor *p*-hydroxy SB-3CT, which distributes to the brain. The authors evaluated the prodrug/*p*-hydroxy SB-3CT in an animal model of severe traumatic brain injury and found significant reduction in brain damage and improvement of neurological outcomes.

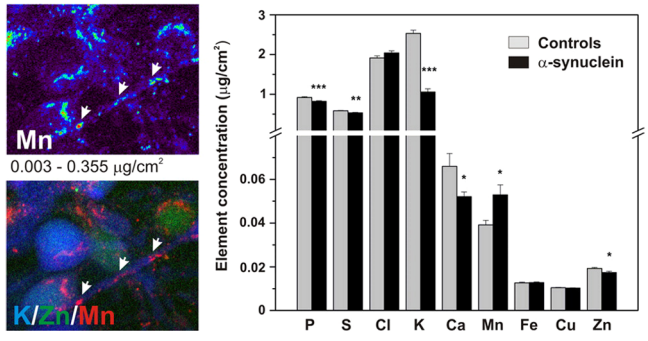
EFFECT OF ELECTRIC FIELDS ON SUPEROXIDE DISMUTASE-1 STRUCTURE



The monomerization of the homodimeric metalloenzyme, superoxide dismutase-1 (SOD1), has been previously identified as an early step in its aggregation, and the pathogenesis of amyotrophic lateral sclerosis (ALS). Monomerization of SOD1 requires, however, the reversal of two thermodynamically favorable post-translational modifications, that is, loss of active-site metal ions, and reduction of intramolecular disulfide bonds. Now, Shi et al. (DOI: 10.1021/acschemneuro.5b00146) demonstrate that monomeric SOD1 can be formed in vivo without the loss of these modifications.

The authors use amide-hydrogen−deuterium exchange, capillary electrophoresis, and "protein charge ladders" to show that the presence of an external electric field (of physiological strength) causes the fully "metalated", disulfide-intact SOD1 protein to rapidly monomerize and partially unfold (at room temperature), without the prior loss of metal ions or disulfide linkages. Field-induced monomerization was only observed in a zinc-replete ALS mutant of SOD1 (A4V SOD1), and not observed in metal-free A4V SOD1 or WT SOD1 (metal-free or replete). Theoretical modeling suggested a plausible mechanism for this effect.

ASSESSMENT OF METALS IN NEURONS THAT OVEREXPRESS α-SYNUCLEIN



α-Synuclein is a protein with a pivotal role in the pathogenesis of Parkinson's disease and other synuclein-related aggregopathies. Transition metals, which are involved in the pathogenesis of neurodegenerative disorders, bind to α-synuclein and alter its aggregation propensity, which likely contributes to the modulation of disease progression. Although several studies addressed the chemical interaction of α-synuclein and metals, not much is known about how α-synuclein regulates levels of transition metals on the cellular level. This is also due to the limitations in the subcellular elemental resolution using conventional microscopy methods.

In the current issue, Dučić et al. (DOI: 10.1021/acschemneuro.5b00093) demonstrate a quantitative and qualitative assessment of elemental distribution in primary neurons obtained by high-resolution synchrotron X-ray fluorescence. The authors show how overexpression of α-synuclein in neurons alters the distribution of Mn, Ca, K, S, P, and Zn. Correlation analyses and histochemical evaluation of DMT1 and MnSOD expression suggest that α-synuclein is involved in the regulation of the import and export of these metals. These findings significantly contribute to a better understanding of the functional link between α-synuclein and metals.

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