

Neurodegeneration and aldehyde load: from concept to therapeutics

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A vast amount of data has been generated over the last 30 years regarding neurodegenerative mechanisms. The basic question that has still not been answered is, how can selective cell populations degenerate? Specifically, N. basalis cholinergic neurons in Alzheimer's disease (AD), nigral dopaminergic neurons in Parkinson's disease, upper and lower motor neurons in amyotrophic lateral sclerosis (ALS), oligodendrocytes in multiple sclerosis (MS) and neurons in the penumbra of an ischemic focus. Perhaps the most pivotal observation from studies of preclinical models may be that, after the loss of mitochondrial integrity and the associated efflux of cytochrome c with activation of the caspase cascade, the cell death cascade has probably passed a point of potential pharmacological intervention. Despite intense efforts to define points of intervention to stop this loss of mitochondrial function, translation of basic research knowledge into clinical practice has been extremely limited.

Another question that has been interrogated by several research groups is that of the possibility that there might be a common mediator or class of mediators responsible for a diverse number of neuropathologies involving selective neuronal losses. In this regard, the production of reactive aldehydes and the associated accumulation of their adducts in neurological disorders is well established.¹ The potential sources of these aldehydes are complex, involving lipid peroxidation, glycation reactions, polyamine metabolism, pyrimidine catabolism, monoamine metabolism, and the intermediary metabolism of carbohydrates, amino acids and phospholipids.

In models of ischemia-reperfusion injury, work from the laboratory of Kevin J. Tracey² has established a key role for the aminoaldehyde, 3-aminopropanal in the delayed cell

death of the penumbra, acting at the premitochondrial phase of apoptosis and necrosis. The source of 3-aminopropanal is metabolism of the polyamines spermine and spermidine to putrescine by polyamine oxidase (PAO) and spermine oxidase. In this regard, inhibition of PAO and the use of aldehyde-sequestering agents have both been demonstrated to be neuroprotective in the rat middle cerebral artery occlusion and global brain ischemia models and in the gerbil global brain ischemia model.

These data have formed a sound groundwork for the study of aldehydes in cell death in models of delayed neuronal cell death not involving ischemia. Such studies of the trimethyltin model of delayed CA3 hippocampal cell death in the rat have revealed that, as in brain ischemia, massive increases in 3-aminopropanal precede neuronal cell death and that aldehyde-sequestering agents provide 100% neuroprotection in this model.³

These data are the first to suggest that reactive aldehydes are key mediators of neuronal cell death in both ischemic and non-ischemic paradigms. Therefore, the next logical question might be, "Which clinical conditions are associated with increased aldehyde load, as reflected by accumulation of protein-aldehyde adducts?" First, in the case of MS, oligodendrocytes possess high levels of polyamines and PAO. Arginase and ornithine decarboxylase (ODC), enzymes that supply the precursors for augmented polyamine metabolism, are elevated in murine models of MS, and aldehyde-protein adducts are elevated in both animal models and in MS patients. In ALS, increases in CSF arginase and aldehyde-protein adducts have been reported. In AD, neocortical ODC, putrescine and aldehyde-protein adducts are all elevated. Of major consequence is the recent demonstration that increased aldehydes and

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aldehyde-protein adducts are present in the CSF of patients with mild cognitive impairment, a clinical condition that generally precedes AD.⁴

In summary, a number of neurodegenerative diseases are associated with a high aldehyde load. The efficacy of aldehyde-sequestering agents in preclinical models of delayed neurodegeneration suggests that these agents may provide a new generation of therapeutics for the treatment of devastating neurological disorders.

Competing interests: None declared

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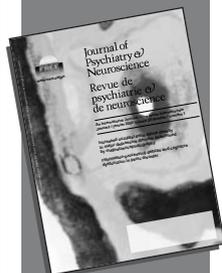
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