How defects in pantothenate metabolism cause neurodegeneration

Susan J. Hayflick¹, Randy Woltjer¹, Lindsay Reese², Jeffrey Hamada¹ and Brian Richardson¹

¹Oregon Health & Science University, Portland, USA
²University of Vermont, Burlington, USA

Inborn errors of coenzyme A biosynthesis lead to neurodegenerative disorders in humans. Pantothenate kinase-associated neurodegeneration (PKAN) manifests with damage to brain, retina and testis and is caused by mutations in PANK2, the gene encoding the mitochondrial form of pantothenate kinase, a key regulatory enzyme in CoA synthesis. How does a defect in CoA production result in this specific phenotype? Why are these tissues selectively vulnerable? And what is the underlying neurodegenerative process arising from defective pantothenate kinase 2?

Insight into the pathophysiology of PKAN has come from various models of disease, including flies and mice as well as directly from humans. The tissue types damaged by defective pantothenate kinase 2 share several important features that are likely to contribute to their selective vulnerability. These include the presence of a blood-tissue barrier, the milieu with respect to oxidative stress, tissue metabolic demand, differential expression of PANK genes, and membrane composition of cells in these tissues.

In PKAN, brain pathology is largely limited to a specific population of neurons in basal ganglia. These neurons are selectively vulnerable to defective pantothenate kinase 2. The features of this neuronal population, their milieu and other contributing factors will be examined with the goal to begin to delineate how defects in pantothenate metabolism cause neurodegeneration.