The Role of Copper in Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative protein-folding diseases involve the misfolding and aggregation of a naturally occurring protein that plays a role in the progressive deterioration of neurons. For a number of years, metals have been implicated in a number of neurodegenerative diseases including Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), prion diseases, and Huntington’s disease. However, their precise roles in the disease pathologies have been difficult to elucidate. Redox active metals, specifically copper and iron, are of significant interest because they are capable of forming reactive oxygen species (ROS) through Fenton chemistry. In this reaction, reduced iron and copper catalyze the production of hydroxyl radicals that damage proteins, DNA, and lipids through oxidative modification. This process results in oxidative stress and eventual cell death. In the diseased state, it is thought that metal homeostasis is disrupted, resulting in poor control of potentially toxic metal ions. Therefore, determining the role of metal ions in these diseases has become an important part of understanding these diseases and finding a treatment or a cure.

Synchrotron-based microscopy and imaging have grown in popularity over recent years due to rapid developments in x-ray sources, optics, and detectors. One particular field that has benefited from these improvements is the area of neurodegeneration, where complicated tissue and cell heterogeneity demand micro- and nanoscale spatial resolution and sub-ppm detection sensitivity of metal distribution, concentration, and speciation [1]. In this presentation, examples will be described that involve the use of X-ray fluorescence microscopy (XFM) and spectroscopy (micro-XANES) for the study of metal homeostasis in mouse models of neurological protein-folding diseases such as Alzheimer’s disease [2-5] and amyotrophic lateral sclerosis (ALS) [6-7]. These studies were be performed in conjunction with behavioral studies of cognitive performance. The overall hypothesis is that elevated Cu+ content in the misfolded aggregates is correlated with cognitive decline, hence identifying a potential mechanistic explanation for brain cell death in AD and providing a potential diagnostic marker and therapeutic target for ameliorating cognitive impairment. In addition to the current findings, the ongoing needs for high spatial resolution, data collection rates, tomography, and speciation will be discussed.

REFERENCES