The Role of Aging, Antioxidants, and Mutant Huntington Lowering in the Oxidative Stress Response of HD Neurons

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Huntington’s disease (HD) is a fatal neurodegenerative disorder which affects around 1 in every 10,000 people. This autosomal dominant genetic disorder is caused by an expansion of the polyglutamine coding CAG tract in the huntingtin (HTT) gene on chromosome 4. When oxidants overwhelm antioxidants naturally in the brain, it results in oxidative stress (OS) which causes neurodegeneration. Previous work shows that HD brains have been damaged by OS, suggesting that OS may play a role in HD. However, if OS is an HD disease onset driver or a bystander is yet to be known. To investigate this, wild type and mutant HTT primary neurons were cultured and treated with hydrogen peroxide (H202), to induce OS. Damage in neurons with mutant HTT were lower compared to wild type neurons, even in response to H2O2 treatment. This may demonstrate that mutant HTT is neuroprotective against OS in early embryonic neurons, and, theoretically as neurons age, they become more susceptible to oxidative stress along with onset and the progressive phenotype of HD. To further investigate this hypothesis, neurons were aged with progerin. Progerin is a mutated protein that causes heightened aging in the disease Progeria. Progerin treatment showed Huntingtin oligimerization and a decrease of lamin B1 protein, both age related markers. Cell death is increased in aged HD neurons stressed with H202, implying a hypersensitivity to stress with age in HD neurons. This further supports the idea that as HD neurons age, they become more susceptible to OS-induced damage than WT neurons.

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