Can Lowering Mutant Huntingtin Limit Susceptibility to Oxidative Stress in 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. Oxidative stress in the brain is a feature of HD and causes degenerative damage to tissues and neurons. Wild type and mutant HTT primary neurons were cultured and treated with Antisense Oligonucleotides(ASOs) and Hydrogen peroxide(H202). H202 was the oxidative stressor and the ASO lowered HTT. A Western Blot was run to confirm the HTT lowering by the ASO. The antioxidant Glutathione was measured to see if neurons' oxidative stress response capacity changed with mutant HTT. Dead neurons (non-cell permeable stain and lactate dehydrogenase(LDH) release) and neurons undergoing apoptosis (caspase 3) were also measured. Reactive oxygen species(ROS), DNA damage and HTT protein aggregation(mutant HTT clumps together) were also tested in neurons. As expected, H202 had no effect on HTT protein amount. Huntingtin aggregation could not be determined because it is a progressive phenotype that has not yet developed in embryonic neurons. Cell death amounts lead to the conclusion that mutant HTT neurons are protected from oxidative stress early(theoretically as neurons age, they become more susceptible to oxidative stress with the progressive phenotype of HD). Mutant HTT neurons were found to have decreased capacities to deal with oxidative stress using the antioxidant glutathione and to have increased DNA damage. However, ASO HTT lowering limits oxidative stress by normalizing both glutathione function and DNA damage.