An expanded polyglutamine tract in huntingtin (Htt) causes Huntington’s disease (HD). HD neurons become dysfunctional and die by mechanisms not fully understood. Patients with HD succumb within 15 years of disease onset. There is no treatment to slow disease progression. Evidence of oxidative damage is observed in the brain of HD patients but the sources of oxidative stress in early HD are unclear. We examined the activity of the superoxide generator NADPH oxidase which functions in intracellular and plasma membranes. The gp91-phox-containing NADPH oxidase activity was markedly elevated in postmortem brain of HD patients compared to normal controls. The cortex and striatum, which degenerate in HD, had significantly elevated activity and the highest activity was present in a patient presymptomatic for HD. We studied synaptosomes from the cortex and striatum of a mouse model of HD (HD140Q/140Q) and found that compared to those of WT mice, HD synaptosomes had significantly higher levels of NADPH oxidase activity before the onset of disease phenotypes. Elevated ROS coincided with significantly increased ROS activity in cortical and striatal primary neurons of the HD140Q/140Q mice and treating the HD neurons with NADPH oxidase inhibitors significantly reduced ROS and increased neuronal viability. Marked neuronal swelling, a hallmark of oxidative stress, were also prevented in the HD neurons by inhibitors of NADPH oxidase. These increases in ROS coincided with significant increases in NADPH oxidase activity from cortical and striatal HD neurons with NADPH oxidase inhibitors significantly reduced ROS and neuronal death. The cortex and striatum, which degenerate in HD, had significantly higher levels of NADPH oxidase activity before the onset of disease phenotypes. These findings suggest that excess NADPH oxidase is an early source of oxidative stress in HD neurons and contributes to synaptic dysfunction and cell death.

Study funded by CHDI to MD, NDF and Fundacion Mexicano en Harvard, A.C. in A.V. 

MOUSE MODEL: Homozygous knock-in HD mice with 148 CAG repeats and their wild-type counterpart C57BL/6.

METHODS

ABSTRACT

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1. NADPH oxidase activity is elevated early in HD patient brain and HD mouse brain synaptosomes and primary neurons

2. Reactive oxygen species are elevated in cortical and striatal HD neurons

3. NADPH oxidase inhibitors reduce ROS and neuronal death in cortical and striatal HD neurons

RESULTS

CONCLUSIONS

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