Methylene blue modulates huntingtin aggregation intermediates and is protective in Huntington's disease models

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Abstract

Huntington's disease (HD) is a devastating neurodegenerative disorder with no disease-modifying treatments available. The disease is caused by expansion of a CAG trinucleotide repeat and manifests with progressive motor abnormalities, psychiatric symptoms, and cognitive decline. Expression of an expanded polyglutamine repeat within the Huntingtin (Htt) protein impacts numerous cellular processes, including protein folding and clearance. A hallmark of the disease is the progressive formation of inclusions that represent the culmination of a complex aggregation process. Methylene blue (MB), has been shown to modulate aggregation of amyloidogenic disease proteins. We investigated whether MB could impact mutant Htt-mediated aggregation and neurotoxicity. MB inhibited recombinant protein aggregation in vitro, even when added to preformed oligomers and fibrils. MB also decreased oligomer number and size and decreased accumulation of insoluble mutant Htt in cells. In functional assays, MB increased survival of primary cortical neurons transduced with mutant Htt, reduced neurodegeneration and aggregation in a Drosophila melanogaster model of HD, and reduced disease phenotypes in R6/2 HD modeled mice. Furthermore, MB treatment also promoted an increase in levels of BDNF RNA and protein in vivo. Thus, MB, which is well tolerated and used in humans, has therapeutic potential for HD.