

Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease.

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Huntingtin is a 350_kilodalton protein of unknown function that is mutated in Huntington's disease (HD), a neurodegenerative disorder. The mutant protein is presumed to acquire a toxic gain of function that is detrimental to striatal neurons in the brain. However, loss of a beneficial activity of wild_type huntingtin may also cause the death of striatal neurons. Here we demonstrate that wild_type huntingtin up-regulates transcription of brain-derived neurotrophic factor (BDNF), a pro-survival factor produced by cortical neurons that is necessary for survival of striatal neurons in the brain. We show that this beneficial activity of huntingtin is lost when the protein becomes mutated, resulting in decreased production of cortical BDNF. This leads to insufficient neurotrophic support for striatal neurons, which then die. Restoring wild_type huntingtin activity and increasing BDNF production may be therapeutic approaches for treating HD.