

AMPK amplifies Huntington's disease

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A new study describes how hyperactivation of AMP-activated protein kinase (AMPK) promotes neurodegeneration in Huntington's disease (HD). The article appears online on July 18, 2011, in *The Journal of Cell Biology*.

The aggregation of mutant [Huntingtin protein](#) in HD disrupts many [cellular processes](#), including metabolism. [AMPK](#)-a protein that balances a cell's energy production and usage-is abnormally active in the brains of mice with HD, but whether the kinase protects neurons from the metabolic imbalances associated with HD or whether AMPK contributes to neuronal death is unknown.

Yijuang Chern and colleagues determined that the alpha1 isoform of AMPK was specifically activated and translocated into the nuclei of neurons in a mouse model of HD, whereas AMPK-alpha2 was unaffected. An inhibitor of Ca²⁺/calmodulin-dependent [protein kinase II](#) reduced AMPK activity, suggesting that AMPK-alpha1 is activated by this kinase, probably because Ca²⁺ signaling is disrupted in HD neurons.

Further stimulation of AMPK by injection of the AMPK-activating drug AICAR increased neuronal death and decreased the lifespan of HD mice. AICAR also promoted the death of neuronal cell lines, an effect reversed by an AMPK inhibitor. Active, nuclear AMPK-alpha1 promoted neuronal apoptosis by reducing expression of the cell survival factor Bcl2. Bcl2 levels and cell survival were restored by CGS21680, a drug that alleviates the symptoms of HD mice.

AMPK was also hyperactivated in the brains of human HD patients, suggesting that the kinase could be a therapeutic target. Chern now wants to investigate how AMPK-alpha1 and -alpha2 isoforms are differentially regulated in neuronal tissue.

More information: Ju, T.-C., et al. 2011. *J. Cell Biol.*
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