NEURODEGENERATIVE DISEASE

A mechanism for axonal transport defects in HD

Inhibition of fast axonal transport might be an early event in the molecular pathology of a number of neurodegenerative disorders. Various studies have indicated that the mutant form of the huntingtin protein (HTT), which causes Huntington disease (HD), can inhibit such transport; however, the mechanism underlying this effect has remained unclear. A report published in *Nature Neuroscience* has revealed that mutant HTT seems to inhibit fast axonal transport via activation of cJun N-terminal kinase (JNK) 3 and subsequent phosphorylation of molecular motors. "Results from our work thus identified a molecular mechanism for pathogenesis in HD," states co-principal investigator Gerardo Morfini, of the University of Illinois at Chicago.

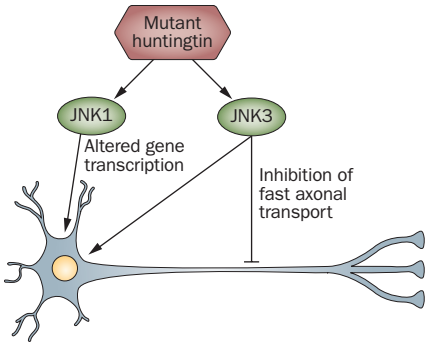

Figure 1 | Neuronal effects of mutant huntingtin mediated by JNK activity. Both JNK1 and JNK3 can affect the expression of neuronal genes. JNK3 can also phosphorylate molecular motors, thereby inhibiting fast axonal transport. Abbreviation: JNK, cJun N-terminal kinase.

Possible mechanisms explaining how mutant HTT could inhibit fast axonal transport include a direct interaction with or a blockade of the transport machinery. Morfini *et al*. were, however, unable to find evidence that mutant or wild-type HTT at endogenous levels binds to molecular motors—directly or indirectly. Mutant HTT, but not the wild-type protein, was able to inhibit axonal transport at very low concentrations in isolated squid axoplasm. "This observation suggested that mutant HTT inhibits fast axonal transport through a mechanism involving one or more enzymatic activities," explains fellow co-principal investigator Scott Brady.

On the basis of their findings and previous evidence implicating deregulation of kinases in HD, the researchers investigated the involvement of JNK activity in the inhibition of axonal transport caused by mutant HTT. JNK inhibitors blocked the inhibitory effect of mutant HTT on axonal transport in squid axoplasm, indicating the involvement of JNK in the signaling cascade. Moreover, expression of mutant HTT led to an increase in JNK activity in cellular and animal models of HD. Further study revealed that while mutant HTT could activate all three JNK isoforms, JNK3 was the principal mediator of fast axonal transport inhibition.

JNK3 was shown to phosphorylate kinesin 1—a molecular motor involved in anterograde axonal transport. Using mass spectrometry, the researchers demonstrated that Ser176 was the main site of JNK3-induced phosphorylation in kinesin 1. Mutation of this serine residue to mimic phosphorylation impaired axonal transport of kinesin 1 in cultured hippocampal neurons. Thus, the researchers succeeded in establishing a mechanistic link between mutant HTT and axonal transport defects (Figure 1).

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Original article Morfini, G. A. *et al*. Pathogenic huntingtin inhibits fast axonal transport by activating JNK3 and phosphorylating kinesin. *Nat. Neurosci.* **12**, 864–871 (2009).