NEURODEGENERATIVE DISEASE

A neurobiological basis for depression in Huntington disease

Depression affects an estimated 40–50% of patients with Huntington disease (HD), and can precede the onset of motor symptoms by many years. A team from the University of British Columbia, Canada, has found evidence that depression in HD is at least partly attributable to the pathophysiological effects of the HD-causing mutation, raising the possibility that the depressive symptoms could be ameliorated by disease-modifying therapies.

"To eliminate the influence of psychosocial and environmental stressors, such as the knowledge of carrying a mutation for an incurable disease, we examined depressive phenotypes in transgenic YAC128 HD mice," say authors Mahmoud Pouladi and Michael Hayden. These mice express an expanded form of human huntingtin with 120 CAG repeats, and the resulting phenotype recapitulates many of the motor and cognitive deficits of human HD. The authors subjected the YAC128 mice to a forced swim test, in which increased immobility suggested depression, and a sucrose intake test, in which reduced sucrose consumption indicated anhedonia.

> "...[the YAC128 mouse] recapitulates many of the motor and cognitive deficits of human HD"

The YAC128 mice exhibited a depressive phenotype, which "was observed at an early stage of the disease, did not worsen over time, and was independent of CAG repeat length". These features were all consistent with the depression experienced by humans with HD. Also, like many cases of depression in HD, the depressive phenotype in the YAC128 mice failed to respond to antidepressants.

A key step in HD pathogenesis is the cleavage of mutant huntingtin at amino acid residue 586. Pouladi *et al.* found that the depressive phenotype was rescued in transgenic mice expressing a form of huntingtin that was resistant to cleavage at this residue, providing further evidence that depression in HD has a strong neurobiological basis.

"Our finding … suggests that therapies aimed towards inhibition of huntingtin cleavage are also likely to have beneficial effects on depressive symptoms in HD," say the authors. "We further aim to employ the YAC128 HD mice to evaluate the efficacy of candidate therapies in ameliorating the depressive, motor, and cognitive deficits [in HD]."

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Original article Pouladi, M. A. *et al.* Prevention of depressive behaviour in the YAC128 mouse model of Huntington disease by mutation at residue 586 of huntingtin. *Brain* [doi:1093/brain/awp006] (2009).