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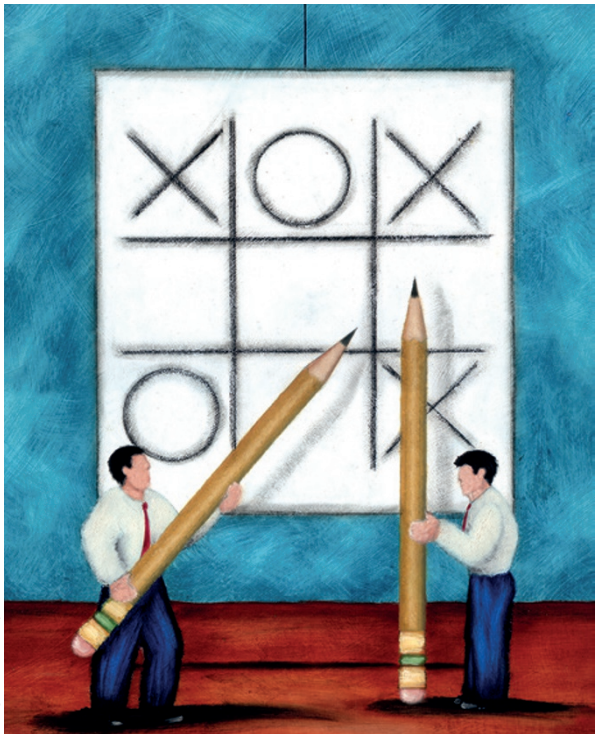
HUNTINGTON DISEASE

Boosting PPARδ blocks neurodegeneration

Huntington disease (HD) is a progressive autosomal-dominant neurodegenerative disorder caused by a CAG trinucleotide-repeat-expansion mutation in the huntingtin (HTT)-encoding gene. Precisely how mutant HTT results in HD pathogenesis remains unclear. Now, La Spada and colleagues reveal that mutant HTT represses peroxisome proliferator-activated receptor-δ (PPARδ) transactivation and show that pharmacological activation of this receptor effectively treats mouse models of HD.

Transcriptional dysregulation has emerged as a potentially important pathogenic mechanism in HD.



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Amino-terminal fragments of mutant HTT protein interfere with gene transcription in the early stages of the disease process. To further understand this transcriptional dysregulation, La Spada and colleagues first set out to identify transcription factors that interact with mutant HTT.

Using a transcription factor binding site array, they identified PPAR-response element (PPRE)-binding proteins as candidate mutant-HTT-interacting proteins. Further studies, using striatal-like cell lines derived from mutant *Htt*-knock-in mice and analysis of protein lysates from the cortices of BAC-HD97 mice (a highly representative HD mouse model), demonstrated that mutant HTT physically interacts with PPARδ, the most abundant PPAR subtype in the central nervous system (CNS).

Next, the authors investigated the consequences of the interaction of mutant HTT with PPARδ. Analysis of primary cortical neurons from BAC-HD97 mice revealed that the mutant HTT–PPARδ interaction repressed PPARδ transactivation. Increasing PPARδ activity in these BAC-HD97 neurons, through the overexpression of PPARδ or treatment with the PPARδ-selective agonist GW501516, ameliorated mitochondrial dysfunction and neurotoxicity.

In vivo studies further supported a pathogenic role of reduced PPARδ activity. In BAC-HD97 mice, the expression of PPARδ target genes was reduced in the striatum — where neurodegeneration and atrophy primarily occur in HD. Furthermore, transgenic mice expressing a dominant-negative PPARδ in the CNS exhibited widespread neurodegeneration, motor dysfunction, mitochondrial abnormalities, transcriptional dysregulation and striatal neuron loss.

The authors then investigated the therapeutic potential of boosting PPARδ activity. Treatment with the PPARδ agonist KD3010 — which penetrates the blood–brain barrier and has previously been tested in humans in a Phase Ib metabolic disease safety trial — rescued dominant-negative PPARδ-mediated transcriptional repression and mitochondrial dysfunction in BAC-HD97 neurons. Moreover, KD3010 prevented cell death in primary cortical neurons that had been transfected with mutant *Htt*.

In mice, intraperitoneal injection of KD3010 induced the expression of PPARδ target genes without any side effects. Furthermore, in the HD-N171-82Q mouse model of HD, injection of KD3010 5 times a week beginning at 6 weeks of age attenuated neurological dysfunction and improved motor function as compared to controls, extending lifespan by 16%.

Finally, demonstrating the potential application of these findings in humans, KD3010 was shown to reduce neurotoxicity in striatal medium spiny-like neurons that had been generated by differentiating induced pluripotent stem cells that had been derived from patients with HD.

This study suggests that PPARδ agonists that are capable of crossing the blood–brain barrier may represent a viable treatment strategy for HD and identifies KD3010 as a promising lead.

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ORIGINAL ARTICLE Dickey, A. S. *et al.* PPAR-δ is repressed in Huntington's disease, is required for normal neuronal function and can be targeted therapeutically. *Nat. Med.* **22**, 37–45 (2015)