NEURODEGENERATIVE DISORDERS

Restoring the balance

The precise pathophysiological mechanisms underlying neurodegenerative disorders such as Alzheimer's disease (AD) and Huntington's disease (HD) remain unclear, and no disease-modifying therapies currently exist. Now, two papers show that manipulating the kynurenine pathway (KP) of tryptophan degradation can ameliorate neurodegeneration in animal models of disease, thus revealing a promising new therapeutic approach for the treatment of neurodegenerative disorders. The research was performed in close collaboration with Robert Schwarcz, who pioneered studies linking the KP to neurodegeneration.

Abnormalities in the KP have previously been linked to neurodegenerative diseases. Indeed, levels of the neurotoxic metabolites quinolinic acid (which is associated with glutamate receptor excitotoxicity) and 3-hydroxykynurenine (3-HK) (which is associated with free radical generation) are elevated in the blood and brains of patients with AD and HD, whereas the concentration of the neuroprotective metabolite kynurenic acid (KYNA) is often decreased. Correcting this metabolite imbalance may therefore be therapeutically beneficial. One approach may be to inhibit kynurenine 3-monooxygenase (KMO), which functions at a key branching point in the KP — its inhibition shunts tryptophan metabolism towards enhanced production of KYNA.


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In the first paper, Muchowski and colleagues describe a novel small molecule, JM6, which is an orally bioavailable prodrug of an existing metabolically unstable KMO inhibitor (Ro 61-8048). As anticipated, JM6 was metabolized under the acidic conditions in the gut of rodents to slowly release active Ro 61-8048 into the blood. This resulted in increased levels of circulating kynurenine (the substrate of KMO), which entered the CNS by active transport, where it was converted to KYNA.

Next, they investigated the effects of JM6 in mouse models of neurodegenerative diseases. In a preclinical model of AD in which mice overexpressed the human β-amyloid precursor protein (APP), chronic oral JM6 treatment prevented spatial memory loss, anxiety deficits and synaptic loss, in conjunction with increased extracellular levels of KYNA and reduced levels of glutamate in the brain. In addition, oral JM6 treatment prolonged the survival of R6/2 mice (a widely used model of HD) when treatment was started at an early symptomatic stage; it also prevented synaptic loss, and decreased microglial activation and CNS inflammation.

Meanwhile, Giorgini and colleagues explored the therapeutic potential of KP manipulation using a *Drosophila melanogaster* model of HD (using Htt93Q flies, which express a mutated huntingtin exon 1 fragment). This model exhibits an increased 3-HK/KYNA ratio, which is indicative of a dysfunctional KP, in conjunction with loss of photoreceptor neurons (rhabdomeres), which is a robust readout for neurodegeneration. They found that genetic disruption of KMO or tryptophan 2,3-dioxygenase (the first and rate-limiting step in the KP) in Htt93Q flies ameliorated the HD phenotype: the 3-HK/KYNA ratio was dramatically decreased and rhabdomere loss was partially rescued. When KMO-deficient Htt93Q flies were fed 3-HK, this restored neurodegeneration; conversely, feeding Htt93Q flies with KYNA increased rhabdomere number and decreased the 3-HK/KYNA ratio.

Next, they tested the effects of the pharmacological KMO inhibitors UPF 648, Ro 61-8048 and JM6 (described above) in Htt93Q flies. All three were neuroprotective — they substantially rescued neurodegeneration and exerted a statistically significant shift towards KYNA synthesis.

Together, these studies demonstrate that intervening in the KP to decrease the ratio of 3-HK to KYNA may be therapeutically beneficial in neurodegenerative disorders such as AD and HD.

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ORIGINAL RESEARCH PAPERS Zwilling, D. *et al.* Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration. *Cell* **145**, 863–874 (2011) | Campesan, S. *et al.* The kynurenine pathway modulates neurodegeneration in a *Drosophila* model of Huntington's disease. *Curr. Biol.* **21**, 961–966 (2011)