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Neurobiology

Hacking the tryptophan metabolic process to reduce neurodegeneration

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Oats, dried prunes, tuna fish, milk, chicken, bread, peanuts, and chocolate are fabulous foods that enrich our everyday meals. But apart from their culinary properties, they are also great sources of tryptophan. Tryptophan is an amino acid which is used by cells either as a building block for the synthesis of proteins or as a precursor in several metabolic pathways. Serotonin - our natural mood stabiliser - is an example of a product generated from tryptophan absorbed in our diet. However, the great majority of ingested tryptophan is used by a metabolic process called the kynurenine pathway. The final products of this process provide an ultra violet (UV) filter in our eyes which protects the retina from UV damage and are also used by cells in a diversity of other fundamental reactions. More interestingly, several intermediate products (metabolites) of the kynurenine pathway cause either damaging or protective effects to nerve cells (neurons). Indeed, the pathway can be divided into a "bad" or toxic section in which the metabolites 3-hydoxykynurenine and quinolinic acid are produced and a "good" or protective section which produces kynurenic acid (KYNA).

Neurodegenerative disorders is an umbrella term used to identify several human pathologies characterised by the progressive degeneration of neurons which ultimately culminate with their death in selective regions of the brain. Some examples of these pathologies are Alzheimer's, Parkinson's and Huntington's diseases - for which there are no cures. Although disease-specific clinical traits are shown by patients, all of these disorders are characterised by aberrant changes in levels of kynurenine metabolites. Indeed, while in normal health a fine balance between the "bad" and "good" metabolites is maintained, a shift towards the production of "bad" metabolites is observed in the brain of patients. Thus, exciting questions can be raised: Can we intervene to decrease the production of "bad" metabolites and increase levels of the "good" metabolite? Would this intervention be a valuable therapeutic avenue for treating these devastating diseases?

In order to address this question, we needed a simple yet reliable model to study. We found this in the common fruit fly *Drosophila melanogaster*, a robust system used for many decades to study several cellular processes relevant to human disease. Interestingly, fruit flies do not develop neurodegenerative diseases, but these can often be mimicked by inserting the defective human genes into flies and using appropriate genetic and molecular tools.

We focused on how diet can improve the condition of flies displaying symptoms of Huntington's disease. We found that an enriched tryptophan diet protects these flies from neuron loss by shifting the kynurenine metabolism towards production of the "good" metabolite KYNA. Similarly, by raising the dosage of the enzyme responsible for producing KYNA, an improvement in Huntington's disease-related defects was observed. Thus, the "good" metabolite can counteract the effects of the "bad" metabolites, prevent cells from dying, and thereby improve health in the flies.

Are there any other ways to raise levels of the protective metabolite in the flies? We demonstrated that "switching off" two critical enzymes - called TDO and KMO - of this pathway led to increased levels of the protective

metabolite. This change causes reversion of several disease-related defects not only in Huntington's disease model flies, but also in fly models of Alzheimer's and Parkinson's diseases. Furthermore, drug interventions which arrest TDO and KMO activities reduce neuronal death and other symptoms displayed by these neurodegenerative fly models.

As the current worldwide population lives longer, the number of people suffering from these neurodegenerative disorders is sadly increasing. These exciting results demonstrate that modulation of the kynurenine pathway constitutes a promising therapeutic avenue for design and development of drugs which could delay the onset and reduce the symptoms in a myriad of neurodegenerative disorders.