Role of *aak-2* in neuroprotective action in Alzheimer's and Parkinson's disease models in *C. elegans*

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ABSTRACT

Caenorhabditis elegans is an important model organism as it shares genetic and physiological similarities with humans.. Age-related diseases, such as Alzheimer's or Parkinson's, are caused by the progressive decline of proteostasis during the aging, characterized by the appearance of protein aggregates, which can cause cell function failure in addition to cell death (1).

An increase in sulfated steroid hormones has been shown to extend lifespan and ameliorate diseases caused by aging. For this purpose, *sul-2* mutants were generated. *Sul-2* is a sulfatase of steroid hormones. When the sulfatase gene is deleted, the ability to remove sulfate from hormones is lost and there is an increase in sulfated steroid hormones in the organism, and a reduction in symptoms of neurodegenerative diseases and an increase in longevity. Treatment with the drug STX64, a specific inhibitor of the steroid sulfatase enzyme, in *C. elegans* and in murine models has been shown to produce the same beneficial effects (2).

Recently in our laboratory, results obtained in a RNA seq show that *sul-2* mutants share expression patterns with AMPK activation mutants. There are two AMPKα subunit homologs in *C. elegans*, *aak-1* and *aak-2*. *aak-2* is the homologous gene of AMPK in humans, a cellular fuel sensor that regulates cellular energy homeostasis and functions in stress resistance and to extend lifespan (3). The results of a research show that AMPK activation also has neuroprotective effects in Huntington's disease, its activation can preserve striatal neurons to combat the consequences of toxicity in murine models and protects *C. elegans* neurons from the dysfunction induced by human exon-1 huntingtin expression (4).

To know if *aak-2* has a role in the neuroprotective effects of *sul-2* mutants, we have constructed *aak-2* mutants in Alzheimer's and Parkinson's models to check the effects of *aak-2*. The different strains are subjected to different assays, Alzheimer's model show a paralysis phenotype when they are shifted to 25ºC and Parkinson's models show slow movement in buffer, so we perform thrashing assays. In subsequent assays, an *aak-2;sul-2* double mutant will be generated to test whether the neuroprotective action of *sul-2* mutants is reversed. At the same time, we have started assays with STX64, another way of looking at the consequences of *sul-2* deletion.

The aim of the project is to understand the role of *aak-2* in proteostasis and neurodegenerative diseases and in this way provide a better understanding of the mechanism of action of the drug STX64.

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