Talk

Role of the GABA receptor in the mechanism of action of STX64

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ABSTRACT

Aging is a degenerative process that underlie the major risk factor for disease and death. Previous studies have shown that the loss of function of sul-2 gene, the Caenorhabditis elegans homologue gene for steroid sulfatase (STS), raises the pool of sulfated steroid hormones, increases longevity, and ameliorates protein aggregation diseases. Treatment with the specific steroid sulfatase inhibitor, STX64, mimics these effects in a wild-type background in C. elegans and it also ameliorates cognitive impairment and aggregation in mouse models of Alzheimer's disease. All these data suggest that the protective effect is produced by the action of sulfated hormones [1]. Sulfated hormones or neurosteroids have been to negatively regulate neurotransmitter receptors in the nervous system. The only neuroreceptor that when mutated increase longevity is the one affected in the GABA receptor encoded by gbb-1 gene [2]. The mechanism by which gbb-1 mutants increase longevity is similar to that described for sul-2 mutations [1,2]. Additionally, it has also been described that reducing the activity of this receptor leads to an increase in cholinergic activity [3]. These results suggest a possible participation of GABA receptor in aging and neurodegenerative process by cholinergic pathway. In this project, we will investigate the mechanism by which this factor is involved in these processes.

Methods: Lifespan assays, mutant isolation, Aldicarb assays, thrashing assay and paralysis assay.

Results: Increased cholinergic activity was found in both the gbb-1 mutants and the sul-2(gk187);gbb-1(tm1406) double mutants, with no additive effect. We are currently studying the effect of both mutants in longevity.

Conclusions: Inhibition of the sulfatase of steroid hormones increase cholinergic activity as also gbb-1 mutant with no additive effect, suggesting that both are in the same pathway regulating neurotransmission. We will discuss the effect on longevity.

REFERENCES

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