Exploring the Involvement of Polyamines in α-Synucleinopathies

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Abstract

Background and Objective:

Polyamines play vital roles in various organisms, encompassing multiple physiological functions including cell growth, survival, and the invocation of key biological processes, such as the synthesis of proteins and nucleic acids, stabilizing the structure of chromatin, regulating apoptosis, as well as safeguarding cells against oxidative damage. The impact of polyamine metabolism has been extensively explored in cancers, inflammatory bowel diseases, and neurodegenerative disorders. The mechanisms by which polyamine metabolism contributes to these diseases remains unclear. Our recent study found major increase in serum concentrations of three L-ornithine-derived polyamines (putrescine, spermine, and spermidine), each of which showed correlation to Parkinson's disease (PD) progression and its clinical subtypes. Given the key physiological roles of polyamines and their tight homeostatic regulation, we investigated whether the biomarker findings might offer biochemical insights into the neurodegeneration of PD (and possibly other neurodegenerative diseases involving proteinopathy).

Methods:

To further investigate the relationship between polyamine metabolism and PD, we engineered experimental changes in polyamine metabolism (knocking down critical polyamine interconversion enzymes) in *Drosophila* synucleinopathy models that overexpress neuronal α-synuclein. We analyzed sequential behavioral, histological, and biochemical changes, including longevity, motility, eye morphology assays as well as western and native blottings.

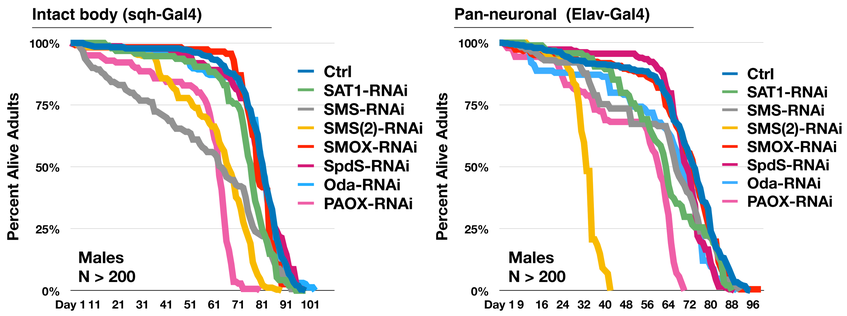
Results:

We observed substantial alterations in the lifespan and motility of Drosophila PD model when suppressing key enzymes such as spermine synthase (SMS), spermidine/spermine N1-acetyltransferase 1 (SAT1), Spermine Oxidase (SMOX), or polyamine oxidase (PAOX). We found the functional involvement of each polyamine in neuronal homeostasis and their regulation in relation to α-synuclein.

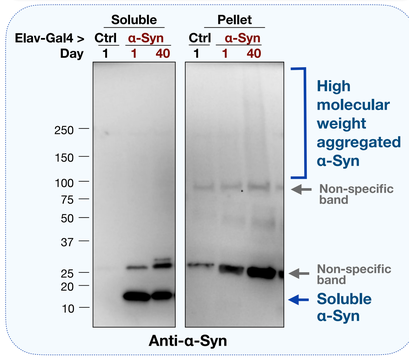
Discussion and Conclusion:

Our analysis provides insights into the origins of neuronal and systemic changes in polyamine metabolism. The Drosophila model of altering polyamine compounds and their metabolites may offer insights into the neurodegenerative process in PD via α-synuclein aggregation. These findings may also help to guide the development of clinical trials using therapeutic interventions targeting polyamine pathways.

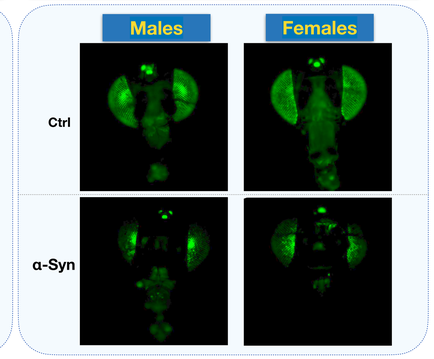
Knocking down of polyamine interconversion enzymes affects fly lifespan



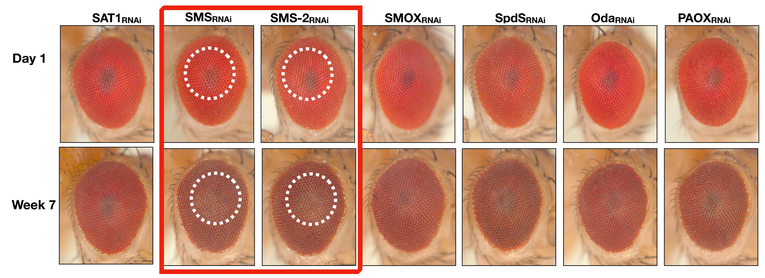
α-Syn aggregation in Day 40 flies



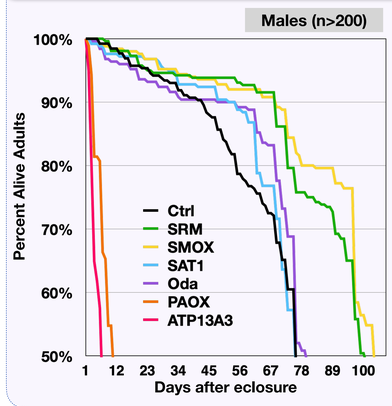
α-Syn diminishes fly eye integrity



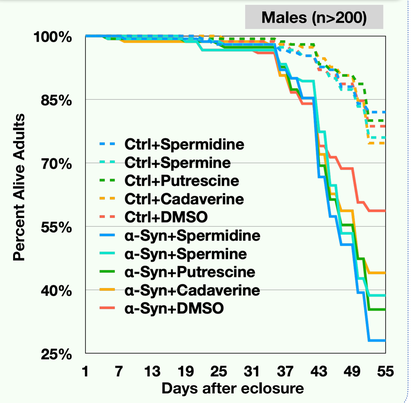
Knocking down of polyamine interconversion enzymes affects external fly eyes



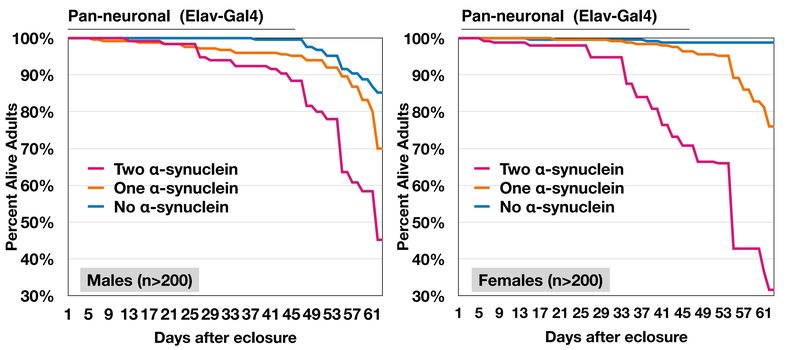
Knocking down enzymes in Polyamine pathway affects the lifespan and motility of Parkinson's disease fly model



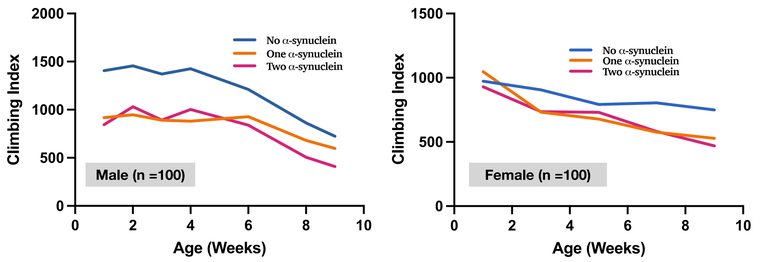
Feeding flies polyamines reduces the lifespan and motility of Parkinson's disease model in flies



Over-expression of α-Syn in neurons shortens the lifespan of *Drosophila*



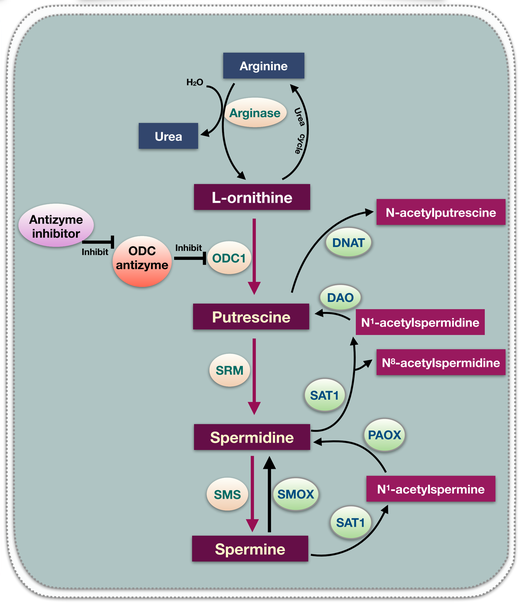
Over-expression of α-Syn in neurons decreases fly climbing ability



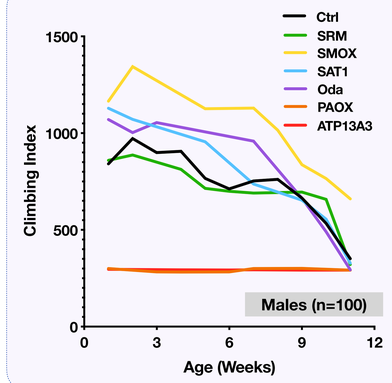
CSF compounds differentiating PD and healthy control

MULTIVARIATE ANALYSIS	Fold Change
benzoate	1.04
cis-4-decenoyl carnitine	1.03
N-acetylglucosamine/N-acetylgalactosamine	0.95
taurine	0.93
succinate	0.92
glycerophosphoglycerol	0.91
ascorbate	0.87
2-aminooctanoate	0.84
2-deoxyuridine	0.81
pantothenate	0.76
N-acetylglucosaminylasparagine	0.75
ergothioneine	0.65
PRESENT IN BOTH ANALYSES	
N-acetyl-cadaverine	2.33
N-acetylputrescine	1.56
ornithine	1.37
urea	1.33
N°, N°, N°-trimethyllysine	1.16
indoleacetate	0.75
N-acetylglutamate	0.71
carboxyethyl-γ-aminobutyrate	0.71
acisoga	0.68
5-hydroxyindoleacetate	0.52
paraxanthine	0.48
UNIVARIATE ANALYSIS	
prolyl-4-hydroxyproline	1.94
(S)-1-pyrroline-5-carboxylate	1.39
glycine	1.36
γ-glutamylvaline	1.35
propionylcarnitine	1.30
γ-glutamylleucine	1.29
threonine	1.27
asparagine	1.13
glutamine	1.07
4-acetamidobutanoate	0.81

Polyamines Pathway



Knocking down enzymes in Polyamine pathway affects the lifespan and motility of Parkinson's disease fly model



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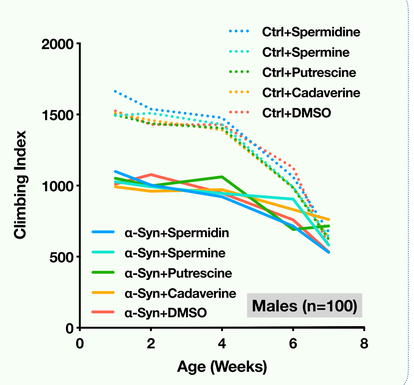

Future Directions:

We aim to investigate the impact of modified polyamine compounds and their metabolites in a *Drosophila* model of PD, shedding light on the underlying neurodegenerative processes associated with α-synuclein aggregation in PD. Our focus will be on exploring the role of SMOX in PD. The outcomes of our research hold the potential to provide valuable insights that could inform the development of future clinical trials, specifically targeting the polyamine pathways, as therapeutic interventions for PD.

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