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Pterostilbene as a promising therapeutic approach against age-related cerebral and muscular decline

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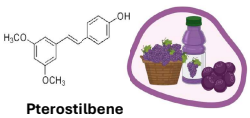
Background

Aging and neurodegenerative diseases pose significant challenges to global health. They are characterized by cellular and molecular dysfunctions that include mitochondrial impairment and metabolic alterations. In this context, pterostilbene (3,5-dimethylresveratrol; Pt), a natural plant phenol, holds therapeutic promise due to its ability to cross the blood-brain barrier and reach therapeutically active concentrations in target tissues such as the brain and skeletal muscle.

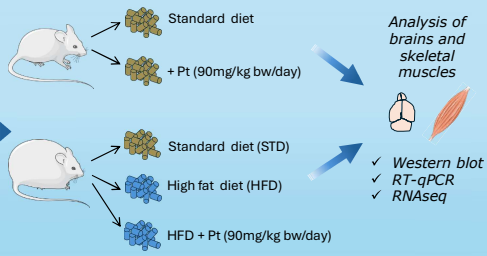


Methods

In the view of developing a nutraceutical intervention contrasting aging and/or preventing neurodegeneration, we focused our study on the analysis of the *in vivo* effects of chronic Pt administration. The impact of prolonged Pt treatment was studied in wt C57BL/6J mice in standard conditions (healthy mice fed with chow diet) as well as in a mouse model of diet- induced obesity (obesogenic diet is known to induce alterations in the central nervous system resembling those observed during aging and neurodegeneration). Brains and skeletal muscles, which are tissues heavily impacted by aging, were analyzed at the transcription and protein level with Western blot, RT-qPCR and RNAseq experiments.

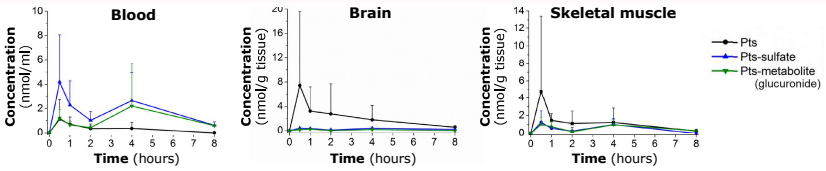
Preliminary studies:

- ✓ *Pharmacokinetic studies to assess tissue distribution of Pt and the most suitable dosage*
- ✓ *Stability studies to ensure Pt stability in food during the experiments*



Pharmacokinetic studies

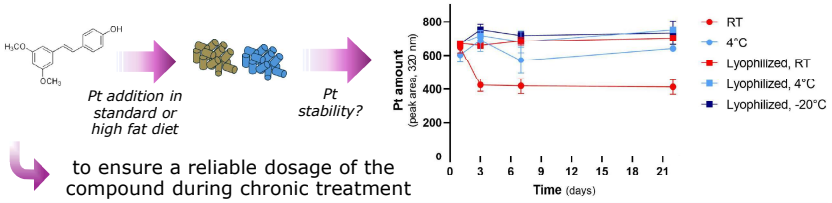
✓ Pharmacokinetic profile after oral Pt administration was assessed in wt C57BL/6J mice



Stability studies

✓ Stability of Pt in standard and high fat diet was assessed through HPLC/UV analysis.

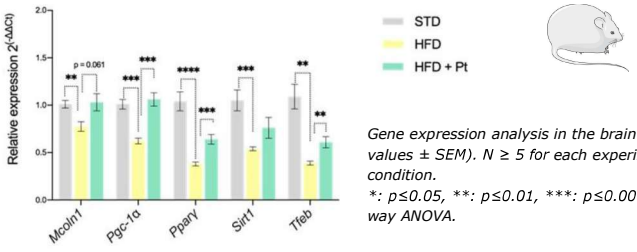
✓ Different work up protocols and storage conditions were assessed



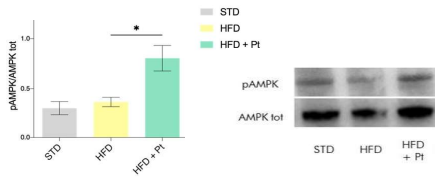
to ensure a reliable dosage of the compound during chronic treatment

Results – *diet induced obesity model*

Chronic treatment with Pt during a high-fat diet ragimen increases phosphorylation levels of AMPK, as well as the expression of *Tfeb*, *Pgc-1α* and *Ppary* genes in the brain.



Gene expression analysis in the brain (mean values ± SEM). N ≥ 5 for each experimental condition.
**: p≤0.05, **: p≤0.01, ***: p≤0.001. One-way ANOVA.*

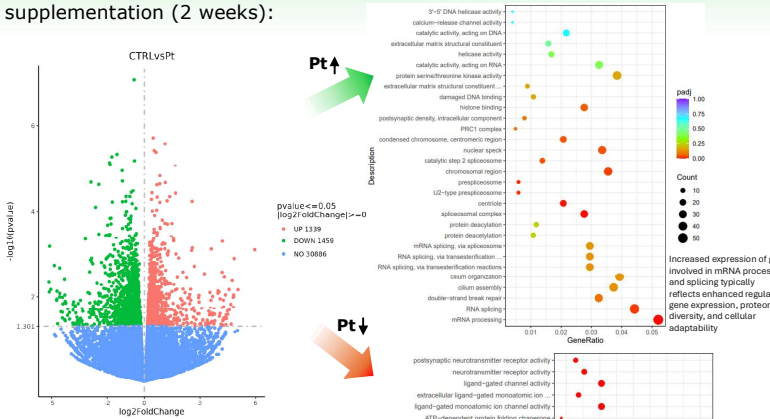


Western blot analysis of phosphorylated AMPK (Thr 172) in the brain (mean values ± SEM). N ≥ 6 for each experimental condition.

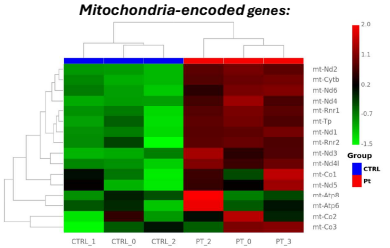
Results – *wt mice*

Western blot and RT-qPCR analyses of brains from wt mice treated with Pt highlighted changes coherent to those observed in obese mice.

RNAseq analysis shed light to a more comprehensive view of gene expression changes induced in the brain by chronic Pt supplementation (2 weeks):



Mitochondria-encoded genes:



Work in progress

✓ Analysis of skeletal muscles from the same mice are in progress

✓ Evaluation of the molecular changes induced by another interesting compound (Nicotinamide riboside) is also under way

Conclusions

Our results suggest the therapeutic potential of chronic Pt supplementation for the amelioration, prevention and/or treatment of aging-related pathologies.