P96: Effects of transthyretin stabilization by wine polyphenols in the modulation of Alzheimer's disease

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Introduction: Alzheimer's disease (AD) is the most common type of dementia, accounting for 60% to 80% of all cases worldwide. Senile plaques, one of AD hallmarks, are mainly constituted of A peptide. Transthyretin (TTR) has been described to exert a neuroprotective effect in AD by interacting with A. This activity is dependent on its stability, thus compounds that stabilize TTR tetrameric fold increase TTR/A binding. Most of the compounds identified as TTR stabilizers belong to the group of non-steroid anti-inflammatory drugs and compete with thyroxine (T_4), the natural TTR stabilizer.

Objectives: Investigate the neuroprotective potential of wine polyphenols (Resveratrol, Catechin, Malvidin and Polyphenolic Extract) by exploring their ability to improve TTR/A interaction.

Materials and Methods: In this work we evaluated *in vitro* the ability of wine polyphenols to compete with T_4, their capacity to improve TTR stability and ability to improve TTR/A interaction. We also optimized a cellular model with A plaque formation, which was used to evaluate the effect of TTR. Finally, we evaluated the *in vivo* effects of Resveratrol using an AD/TTR transgenic mouse model.

Results and Discussion: Regarding the *in vitro* results, Resveratrol competed with T_4 and stabilized TTR, and TTR/A binding was improved by Resveratrol and the Polyphenolic Extract. In the amyloid plaque cellular model, TTR not only inhibited plaque formation as also disrupted pre-formed plaques, decreasing their number and size. Concerning the *in vivo* results the administration of Resveratrol resulted in a diminishment of A plaque burden and A_{42} brain levels.

Conclusion: The neuroprotective effects of Resveratrol can be related to increasing TTR tetrameric stability. The combined administration of wine polyphenols might produce synergistic enhanced neuroprotection.

References

1. Ribeiro, C., Saraiva, M. J., & Cardoso, I. (2012). Stability of the Transthyretin Molecule as a Key Factor in the Interaction with A-Beta Peptide. PLoS One, 7(9). doi:10.1371/journal.pone.0045368