Procyanindin A-type dimer: A novel inhibitor of tau aggregation in vivo

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Country

USA

Title of project or programme

Procyanindin A-type dimer: A novel inhibitor of tau aggregation in vivo

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

387270.6422

Start date of award

15/07/2016

Total duration of award in years

1

Keywords

tau aggregation, dimer, Alzheimer's Disease, tau Proteins, Cinnamon - dietary

Research Abstract

Project Summary Basic research has identified ?-amyloid plaque formation and tau aggregation as the primary biomarkers of Alzheimer’s Disease (AD), which are hypothesized to be causally involved in AD progression. Molecular interventions of primarily ?-amyloid aggregation have over the last decade, however, been met with overt failure. Thus, alternative targets are now essential. Several inhibitors of tau aggregation in vitro have been identified, but only one, methylene blue, is currently being assessed for efficacy in vivo. Most small molecule chemical

inhibitors fail to enter the drug pipeline due to insolubility as well as inherent toxicity issues. Consequently, our laboratory has considered naturally occurring molecules present in edible plants as possible alternatives. Plant polyphenols have long been associated with various health beneficial effects owing classically to their anti-oxidant properties. However, distinct bio-activities of certain polyphenolic compounds are now believed to be responsible for a significant reduction in age-related diseases, cancer, cardiovascular diseases, and processes associated with neurodegeneration. We previously demonstrated that an extract of cinnamon containing a procyanidin A-linked trimer molecule (865 Da) was non-toxic and capable of inhibiting tau aggregation in vitro (Peterson et al., J. Alz. Dis., 2009, 17: 585-97). We now show that an aqueous extract of peanut skin (PSE) similarly inhibits tau aggregation. The bio-active component was isolated, and the purified compound contained intrinsic inhibitory activity. The compound was identified as a procyanidin A-linked dimer (576 Da). The corresponding, highly similar B-linked dimer did not inhibit, suggesting a specific interaction between tau and procyanidin oligomers of A-type linkage. Monomeric epicatechin, the molecule from which procyanidin oligomers are derived, do not inhibit, suggesting that the dimer is the smallest procyanidin molecule that retains tau aggregation inhibitory activity. Finally, peanut skin extract was orally administered to a mouse model of Alzheimer's disease, and preliminary data suggests the potential of the extract to inhibit tau pathology in vivo. In this grant application, we propose to test if purified procyanidin A-linked dimer administered orally to Alzheimer's disease mice displays efficacy to inhibit tau pathology and the behavioral symptoms associated with AD. We hypothesize that procyanidin A-linked dimer present in a common and inexpensive food source may offer potential as a novel and effective intervention of tau aggregation in humans.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A