BILIVERDIN REDUCTASE-A IN BRAIN INSULIN SIGNALING AND OXIDATIVE STRESS-MEDIATED NEURODEGENERATION

https://neurodegenerationresearch.eu/survey/biliverdin-reductase-a-in-brain-insulin-signaling-and-oxidative-stress-mediated-neurodegeneration/

Name of Fellow
Institution
Funder

European Commission FP7-Seventh Framework Programme

Contact information of fellow
Country

EC

Title of project/programme

BILIVERDIN REDUCTASE-A IN BRAIN INSULIN SIGNALING AND OXIDATIVE STRESS-MEDIATED NEURODEGENERATION

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€ 179,740

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The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Alzheimer disease | ageing | biliverdin reductase | diabetes | insulin resistance | oxidative stress | redox proteomics | 3xTg-AD

Research Abstract

Alzheimer disease (AD) is the most common form of dementia among the elderly, whose care in Europe demands an amount of financial resources which is rising dramatically making AD a financial problem. Delaying AD onset by 5 years would decrease its prevalence by 50% with an enormous impact on the financial resources involved in AD care. Hence, it is necessary to understand the mechanisms related to the earlier phases before the symptoms onset. Insulin resistance is associated with a higher risk to develop AD. Post-mortem analysis of brains from AD subjects revealed a markedly downregulated expression of the insulin receptor (IR) and its downstream targets, which progresses with severity of neurodegeneration. Biliverdin reductase-A (BVR-A) is a pleiotropic enzyme that not only catalyzes the synthesis of the powerful antioxidant bilirubin but through its Ser/Thr/Tyr kinase activity modulates cell signaling networks including the two main arms of insulin signaling: MAPK and PI3K. Further, BVR-A is directly activated, via Tyr phosphorylation, by IR. Thus, being BVR-A an up-stream effector in the IR-mediated signaling cascade I hypothesize that the impairment of BVR-A activity contribute substantially to the progression of insulin resistance observed in AD, likely due to the oxidative damage as reported in the brain of aMCI and AD subjects. The aim of this project is to provide evidence about age-associated BVR-A-dependent changes of (i) oxidative/nitrosative stress levels; and (ii) the insulin-induced signaling pathways in 3xTg-AD mice model of AD. Finally, the effect of intranasal insulin (INI) administration, will be evaluated to describe age-dependent insulin effects on IR/BVR-A-dependent signaling pathways and cognition, to rule out if defects in insulin singling are associated with age-dependent changes of BVR-A expression and/or activity.

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