Impairment of biliverdin reductase-A promotes brain insulin resistance in Alzheimer disease: A new paradigm

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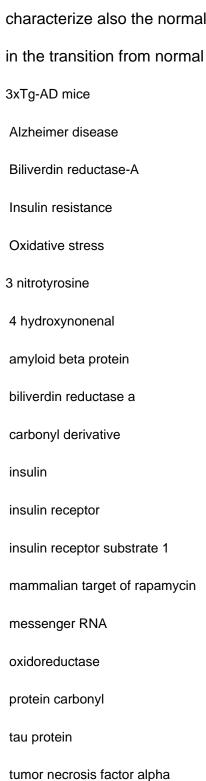
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Clinical studies suggest a link between peripheral insulin resistance and cognitive dysfunction. Interestingly, post-mortem analyses of Alzheimer disease (AD) subjects demonstrated insulin resistance in the brain proposing a role for cognitive deficits observed in AD. However, the mechanisms responsible for the onset of brain insulin resistance (BIR) need further elucidations. Biliverdin reductase-A (BVR-A) emerged as a unique Ser/Thr/Tyr kinase directly involved in the insulin signaling and represents an up-stream regulator of the insulin signaling cascade. Because we previously demonstrated the oxidative stress (OS)-induced impairment of BVR-A in human AD brain, we hypothesize that BVR-A dysregulation could be associated with the onset of BIR in AD. In the present work, we longitudinally analyze the age-dependent changes of (i) BVR-A protein levels and activation, (ii) total oxidative stress markers levels (PC, HNE, 3-NT) as well as (iii) IR/IRS1 levels and activation in the hippocampus of the triple transgenic model of AD (3xTg-AD) mice. Furthermore, ad hoc experiments have been performed in SH-SY5Y neuroblastoma cells to clarify the molecular mechanism(s) underlying changes observed in mice. Our results show that OS-induced impairment of BVR-A kinase activity is an early event, which starts prior the accumulation of A? and tau pathology or the elevation of TNF-?, and that greatly contribute to the

onset of BIR along the progression of AD pathology in 3xTg-Ad mice. Based on these evidence we, therefore, propose a new paradigm for which: OS-induced impairment of BVR-A is firstly responsible for a sustained activation of IRS1, which then causes the stimulation of negative feedback mechanisms (i.e. mTOR) aimed to turn-off IRS1 hyper-activity and thus BIR. Similar alterations characterize also the normal aging process in mice, positing BVR-A impairment as a possible bridge in the transition from normal aging to AD. © 2015 Elsevier Inc. All rights reserved.



unclassified drug

biliverdin reductase
oxidoreductase
target of rapamycin kinase
tumor necrosis factor
aging
Alzheimer disease
animal experiment
animal model
animal tissue
Article
comparative study
controlled study
enzyme activity
hippocampus
immunohistochemistry
immunoreactivity
in vitro study
insulin resistance
insulin treatment
longitudinal study
male
mouse
neuroblastoma cell
nitration
nitrosative stress
nonhuman

oxidative stress
priority journal
protein blood level
protein phosphorylation
129 mouse
Alzheimer disease
animal
C57BL mouse
enzymology
genetics
human
metabolism
protein processing
transgenic mouse
tumor cell line
Aging
Alzheimer Disease
Animals
Cell Line, Tumor
Hippocampus
Humans
Insulin Resistance
Male
Mice, 129 Strain
Mice, Inbred C57BL
Mice, Transgenic

Oxidative Stress

Oxidoreductases Acting on CH-CH Group Donors

Protein Processing, Post-Translational

TOR Serine-Threonine Kinases

Tumor Necrosis Factor-alpha