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

Barone E.

Di Domenico F.

Cassano T.

Arena A.

Tramutola A.

Lavecchia M.A.

Coccia R.

Butterfield D.A.

Perluigi M.

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.

3xTg-AD mice

Alzheimer disease

Biliverdin reductase-A

Insulin resistance

Oxidative stress

3 nitrotyrosine

4 hydroxynonenal

amyloid beta protein

biliverdin reductase a

carbonyl derivative

insulin

insulin receptor

insulin receptor substrate 1

mammalian target of rapamycin

messenger RNA

oxidoreductase

protein carbonyl

tau protein

tumor necrosis factor alpha

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