

# Biliverdin reductase-A impairment links brain insulin resistance with increased A $\beta$ production in an animal model of aging: Implications for Alzheimer disease

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Brain insulin resistance is associated with an increased A $\beta$  production in AD although the molecular mechanisms underlying this link are still largely unknown. Biliverdin reductase-A (BVR-A) is a unique Ser/Thr/Tyr kinase regulating insulin signalling. Studies from our group, demonstrated that BVR-A impairment is among the earliest events favoring brain insulin resistance development. Furthermore, reported a negative association between BVR-A protein levels/activation and BACE1 protein levels in the parietal cortex of aged beagles (an animal model of AD), thus suggesting a possible interaction. Therefore, we aimed to demonstrate that BVR-A impairment is a molecular bridge linking brain insulin resistance with increased A $\beta$  production. Age-associated changes of BVR-A, BACE1, insulin signalling cascade and APP processing were evaluated in the parietal cortex of beagles and experiments to confirm the hypothesized mechanism(s) have been performed in vitro in HEK293APP<sub>swe</sub> cells. Our results show that BVR-A impairment occurs early with age and is associated with brain insulin resistance. Furthermore, we demonstrate that BVR-A impairment favors CK1-mediated Ser phosphorylation of BACE1 (known to mediate BACE1 recycling to plasma membrane) along with increased A $\beta$  production in the parietal cortex, with age. Overall, our results suggest that the impairment of BVR-A is an early molecular event contributing to both (I) the onset of brain insulin resistance and (II) the increased A $\beta$  production observed in AD. We, therefore,

suggest that by targeting BVR-A activity it could be possible to delay the onset of brain insulin resistance along with an improved regulation of the APP processing. © 2018 Elsevier B.V.

Alzheimer disease

BACE1

Bilivedin reductase-A

Canine

Dog

Insulin resistance

3 nitrotyrosine

amyloid beta protein

amyloid precursor protein

beta secretase 1

biliverdin

biliverdin reductase A

insulin

oxidoreductase

unclassified drug

amyloid precursor protein

APP protein, human

aspartic proteinase

BACE1 protein, human

biliverdin reductase

cyclin dependent kinase inhibitor

oxidoreductase

secretase

aged

aging

Alzheimer disease

animal experiment

animal model

animal tissue

Article

beagle

cell membrane

controlled study

embryo

HEK293 cell line

human

human cell

human tissue

in vitro study

in vivo study

insulin resistance

insulin signaling

male

nonhuman

parietal cortex

priority journal

protein function

protein phosphorylation

protein processing

aging

Alzheimer disease

animal

brain

disease model

dog

insulin resistance

metabolism

phosphorylation

Aged

Aging

Alzheimer Disease

Amyloid beta-Protein Precursor

Amyloid Precursor Protein Secretases

Animals

Aspartic Acid Endopeptidases

Brain

Cyclin-Dependent Kinase Inhibitor Proteins

Disease Models, Animal

Dogs

HEK293 Cells

Humans

Insulin Resistance

Male

Oxidoreductases Acting on CH-CH Group Donors

Phosphorylation