Proteomic identification of altered protein O-GlcNAcylation in a triple transgenic mouse model of Alzheimer's disease

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PET scan analysis demonstrated the early reduction of cerebral glucose metabolism in Alzheimer disease (AD) patients that can make neurons vulnerable to damage via the alteration of the hexosamine biosynthetic pathway (HBP). Defective HBP leads to flawed protein O-GlcNAcylation coupled, by a mutual inverse relationship, with increased protein phosphorylation on Ser/Thr residues. Altered O-GlcNAcylation of Tau and APP have been reported in AD and is closely related with pathology onset and progression. In addition, type 2 diabetes patients show an altered O-GlcNAcylation/phosphorylation that might represent a link between metabolic defects and AD progression. Our study aimed to decipher the specific protein targets of altered O-GlcNAcylation in brain of 12-month-old 3×Tg-AD mice compared with age-matched non-Tg mice. Hence, we analysed the global O-GlcNAc levels, the levels and activity of OGT and OGA, the enzymes controlling its cycling and protein specific O-GlcNAc levels using a bi-dimensional electrophoresis

(2DE) approach. Our data demonstrate the alteration of OGT and OGA activation coupled with the decrease of total O-GlcNAcylation levels. Data from proteomics analysis led to the identification of several proteins with reduced O-GlcNAcylation levels, which belong to key pathways involved in the progression of AD such as neuronal structure, protein degradation and glucose metabolism. In parallel, we analysed the O-GlcNAcylation/phosphorylation ratio of IRS1 and AKT, whose alterations may contribute to insulin resistance and reduced glucose uptake. Our findings may contribute to better understand the role of altered protein O-GlcNAcylation profile in AD, by possibly identifying novel mechanisms of disease progression related to glucose hypometabolism. © 2018

Alzheimer disease

Glucose metabolism

Insulin signaling

O-GlcNAcylation

Phosphorylation

glucose

glucose transporter 3

insulin

proteome

serine

tau protein

threonine

beta n acetylhexosaminidase

hexosaminidase C

insulin receptor substrate

IRS1 protein, human

n acetylglucosamine

n acetylglucosaminyltransferase

OGT protein, human

protein

protein kinase B

acylation

Alzheimer disease

animal experiment

animal model

animal tissue

Article

cerebellum

controlled study

enzyme activity

glucose metabolism

glucose transport

hippocampus

homogenate

immunofluorescence

insulin resistance

insulin signaling

male

mass spectrometry

molecular pathology

mouse

mouse model

neuropathology

non insulin dependent diabetes mellitus

nonhuman

priority journal

protein degradation

protein phosphorylation

protein targeting

proteomics

transgenic mouse

two dimensional electrophoresis

Western blotting

Alzheimer disease

animal

brain

disease model

female

genetics

human

metabolism

phosphorylation

procedures

proteomics

Acetylglucosamine

Alzheimer Disease

Animals

beta-N-Acetylhexosaminidases

Brain

Disease Models, Animal

Female

Humans

Insulin Receptor Substrate Proteins

Male

Mice

Mice, Transgenic

N-Acetylglucosaminyltransferases

Phosphorylation

Proteins

Proteomics

Proto-Oncogene Proteins c-akt