Role of brain c-Jun N-terminal kinase 2 in the control of the insulin receptor and its relationship with cognitive performance in a high-fat diet pre-clinical model

Busquets O.

Eritja À.

López B.M.

Ettcheto M.

Manzine P.R.

Castro-Torres R.D.

Verdaguer E.

Olloquequi J.

Vázquez-Carrera M.

Auladell C.

Folch J.

Camins A.

Insulin resistance has negative consequences on the physiological functioning of the nervous system. The appearance of type 3 diabetes in the brain leads to the development of the sporadic form of Alzheimer's disease. The c-Jun N-terminal kinases (JNK), a subfamily of the Mitogen Activated Protein Kinases, are enzymes composed by three different isoforms with differential modulatory activity against the insulin receptor (IR) and its substrate. This research focused on understanding the regulatory role of JNK2 on the IR, as well as study the effect of a high-fat diet (HFD) in the brain. Our observations determined how JNK2 ablation did not induce compensatory responses in the expression of the other isoforms but led to an increase in JNKs total activity. HFD-fed animals also showed an increased activity profile of the JNKs. These animals also displayed endoplasmic reticulum stress and up-regulation of the protein tyrosine phosphatase 1B (PTP1B) and the suppressor of cytokine signalling 3 protein. Consequently, a reduction in insulin sensitivity was detected and it is correlated with a decrease on the signalling of the IR. Moreover,

cognitive impairment was observed in all groups but only wild-type genotype animals fed with HFD showed neuroinflammatory responses. In conclusion, HFD and JNK2 absence cause alterations in normal cognitive activity by altering the signalling of the IR. These affectations are related to the appearance of endoplasmic reticulum stress and an increase in the levels of inhibitory proteins like PTP1B and suppressor of cytokine signalling 3 protein. (Figure presented.). Cover Image for this issue: doi: 10.1111/jnc.14502.

ER stress

high-fat diet

JNK

metabolism

neuroinflammation

PTP1B

biological marker

insulin receptor

isoprotein

mitogen activated protein kinase 9

protein tyrosine phosphatase 1B

suppressor of cytokine signaling 3

X box binding protein 1

insulin receptor

mitogen activated protein kinase 9

animal cell

animal experiment

animal model

Article

cognition

cognitive defect

controlled study

dendritic spine

endoplasmic reticulum stress

enzyme activity

genotype

hippocampus

insulin sensitivity

lipid diet

macroglia

male

metabolic parameters

microglia

mouse

nervous system inflammation

nonhuman

novel object recognition test

priority journal

protein expression

protein function

regulatory mechanism

signal transduction

upregulation

wild type

adverse event

animal

brain

C57BL mouse

cognition

disease model

insulin resistance

knockout mouse

lipid diet

metabolism

physiology

Animals

Brain

Cognition

Diet, High-Fat

Disease Models, Animal

Endoplasmic Reticulum Stress

Insulin Resistance

Male

Mice

Mice, Inbred C57BL

Mice, Knockout

Mitogen-Activated Protein Kinase 9

Receptor, Insulin