Mitochondrial permeability transition pore contributes to mitochondrial dysfunction in fibroblasts of patients with sporadic Alzheimer's disease

Pérez M.J.

Ponce D.P.

Aranguiz A.

Behrens M.I.

Quintanilla R.A.

In the last few decades, many reports have suggested that mitochondrial function impairment is a hallmark of Alzheimer's disease (AD). Although AD is a neurodegenerative disorder, mitochondrial damage is also present in patients? peripheral tissues, suggesting a target to develop new biomarkers. Our previous findings indicate that AD fibroblasts show specific defects in mitochondrial dynamics and bioenergetics, which affects the generation of adenosine triphosphate (ATP). Therefore, we explored the possible mechanisms involved in this mitochondrial failure. We found that compared with normal fibroblasts, AD fibroblasts had mitochondrial calcium dysregulation. Further, AD fibroblasts showed a persistent activation of the non-specific mitochondrial calcium channel, the mitochondrial permeability transition pore (mPTP). Moreover, the pharmacological blockage of mPTP with Cyclosporine A (CsA) prevented the increase of mitochondrial superoxide levels, and significantly improved mitochondrial and cytosolic calcium dysregulation in AD fibroblasts. Finally, despite the failure of CsA to improve ATP levels, the inhibition of mitochondrial calcium uptake by the mitochondrial calcium uniporter increased ATP production in AD fibroblasts, indicating that these two mechanisms may contribute to mitochondrial failure in AD fibroblasts. These findings suggest that peripheral cells present similar signs of mitochondrial dysfunction observed in the brain of AD patients. Therefore, our work creates possibilities of new targets to study for early diagnosis of the AD.

Alzheimer´s disease

Calcium homeostasis

Fibroblasts

Mitochondria

mPTP

adenosine triphosphate

calcium

calcium channel

cyclosporine

mitochondrial permeability transition pore

superoxide

adenosine triphosphate

calcium

carrier protein

mitochondrial permeability transition pore

aged

Alzheimer disease

Article

biosynthesis

calcium cell level

calcium homeostasis

calcium transport

clinical article

controlled study

cytosol

disease course

disorders of mitochondrial functions

human

human cell

pathophysiology

priority journal

protein function

skin fibroblast

very elderly

Alzheimer disease

female

fibroblast

male

metabolism

mitochondrial membrane potential

mitochondrion

pathology

Adenosine Triphosphate

Aged

Aged, 80 and over

Alzheimer Disease

Calcium

Female

Fibroblasts

Humans

Male

Membrane Potential, Mitochondrial

Mitochondria

Mitochondrial Membrane Transport Proteins