The Involvement of Peripheral and Brain Insulin Resistance in Late Onset Alzheimer?s Dementia

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Nowadays, Alzheimer?s disease (AD) is a severe sociological and clinical problem. Since it was first described, there has been a constant increase in its incidence and, for now, there are no effective treatments since current approved medications have only shown short-term symptomatic benefits. Therefore, it is imperative to increase efforts in the search for molecules and non-pharmacological strategies that are capable of slowing or stopping the progress of the disease and, ideally, to reverse it. The amyloid cascade hypothesis based on the fundamental role of amyloid has been the central hypothesis in the last 30 years. However, since amyloid-directed treatments have shown no relevant beneficial results other theories have been postulated to explain the origin of the pathology. The brain is a highly metabolically active energy-consuming tissue in the human body. It has an almost complete dependence on the metabolism of glucose and uses most of its energy for synaptic transmission. Thus, alterations on the utilization or availability of glucose may be cause for the

appearance of neurodegenerative pathologies like AD. In this review article, the hypothesis known as Type 3 Diabetes (T3D) will be evaluated by summarizing some of the data that has been reported in recent years. According to published research, the adherence over time to low saturated fatty acids diets in the context of the Mediterranean diet would reduce the inflammatory levels in brain, with a decrease in the pro-inflammatory glial activation and mitochondrial oxidative stress. In this situation, the insulin receptor pathway would be able to fine tune the mitochondrial biogenesis in neuronal cells, regulation the adenosine triphosphate/adenosine diphosphate intracellular balance, and becoming a key factor involved in the preservation of the synaptic connexions and neuronal plasticity. In addition, new targets and strategies for the treatment of AD will be considered in this review for their potential as new pharmacological or non-pharmacological approaches.

Alzheimer?s disease

insulin resistance

Mediterranean diet

neuroinflammation and neurodegeneration

obesity

type 2 diabetes mellitus

adenosine diphosphate

adenosine triphosphate

amyloid beta protein[25-35]

chlorogenic acid

exendin 4

guggul

insulin

insulin receptor

inulin

liraglutide

lixisenatide

memantine

metformin

peroxisome proliferator activated receptor gamma agonist

pioglitazone

plant medicinal product

silymarin

somatomedin C receptor

stress activated protein kinase 1

sulfonylurea derivative

unclassified drug

Alzheimer disease

blood brain barrier

cognition

Curcuma longa

dietary supplement

disease association

energy consumption

enzyme activation

frontal cortex

glia cell

glucose metabolism

glucose utilization

hippocampus

human

hypothalamus

hypothesis

insulin resistance

lipid diet

long term potentiation

Mediterranean diet

mild cognitive impairment

mitochondrial biogenesis

mitochondrion

nerve cell

nerve cell plasticity

neuroprotection

non insulin dependent diabetes mellitus

nonhuman

obesity

obesogenic diet

oxidative stress

protein phosphorylation

protein targeting

Review

risk factor

sugar intake

synaptic transmission

Western diet