A metabolic perspective of late onset Alzheimer's disease

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After decades of research, the molecular neuropathology of Alzheimer's disease (AD)is still one of the hot topics in biomedical sciences. Some studies suggest that soluble amyloid ? (A?)oligomers act as causative agents in the development of AD and could be initiators of its complex neurodegenerative cascade. On the other hand, there is also evidence pointing to A? oligomers as mere aggravators, with an arguable role in the origin of the disease. In this line of research, the relative contribution of soluble A? oligomers to neuronal damage associated with metabolic disorders such as Type 2 Diabetes Mellitus (T2DM)and obesity is being actively investigated. Some authors have proposed the endoplasmic reticulum (ER)stress and the induction of the unfolded protein response (UPR)as important mechanisms leading to an increase in A? production and the activation of neuroinflammatory processes. Following this line of thought, these mechanisms could also cause cognitive impairment. The present review summarizes the current understanding on the neuropathological role of A? associated with metabolic alterations induced by an obesogenic high

fat diet (HFD)intake. It is believed that the combination of these two elements has a synergic effect, leading to the impairement of ER and mitochondrial functions, glial reactivity status alteration and inhibition of insulin receptor (IR)signalling. All these metabolic alterations would favour neuronal malfunction and, eventually, neuronal death by apoptosis, hence causing cognitive impairment and laying the foundations for late-onset AD (LOAD). Moreover, since drugs enhancing the activation of cerebral insulin pathway can constitute a suitable strategy for the prevention of AD, we also discuss the scope of therapeutic approaches such as intranasal administration of insulin in clinical trials with AD patients. © 2019 Elsevier Ltd

Alzheimer's disease

c-Jun N-terminal kinase inhibitors

Insulin

Licochalcone A

Neuroinflammation

Reticulum stress

Type 2 diabetes mellitus

amyloid beta protein

anthra[1,9 cd]pyrazol 6(2h) one

antiobesity agent

azeliragon

ceramide

chalcone derivative

cholinesterase inhibitor

exendin 4

gastric inhibitory polypeptide

glitazone derivative

hm 15211

hydromethylthionine

insulin

insulin detemir

insulin glulisine

insulin receptor

licochalcone A

licochalcone E

linolenic acid

liraglutide

lixisenatide

metformin

pioglitazone

placebo

quercetin

rosiglitazone

sr 11935

sr 3306

stress activated protein kinase inhibitor

unclassified drug

unindexed drug

amyloid beta protein

ceramide

Alzheimer disease

antiinflammatory activity

antineoplastic activity

antioxidant activity

apoptosis

cognitive defect

disease association

disorders of mitochondrial functions

drug efficacy

drug mechanism

drug response

drug safety

endoplasmic reticulum stress

epilepsy

human

lipid diet

metabolic disorder

nerve cell necrosis

nerve degeneration

nervous system inflammation

neuropathology

neuroprotection

non insulin dependent diabetes mellitus

nonhuman

obesity

pathogenesis

priority journal

Review

senile plaque

signal transduction

Alzheimer disease

animal

cognitive defect

complication

metabolism

obesity

Alzheimer Disease

Amyloid beta-Peptides

Animals

Ceramides

Cognitive Dysfunction

Diabetes Mellitus, Type 2

Endoplasmic Reticulum Stress

Humans

Obesity