The Alzheimer’s disease: the unsolved puzzle

Alzheimer's disease (AD) is the most common form of dementia and is characterized to be an age-related and progressive neurodegenerative disorder where main consequences are cognitive impairment and memory loss. The AD brain histological hallmarks are the formation of senile plaques, composed of Aβ peptides, and neurofibrillary tangles (NFTs), formed by hyperphosphorylated tau (pTau) protein. The origin of the disease still remains unclear but some hypothesis have been proposed. The first were the amyloid cascade and the tau protein hypothesis. Recent evidence suggest a hypothesis that consist of a metabolic disorder, which consider insulin resistance as a pathological key that leads to the other features of AD. Because of the role that insulin plays in T2DM, it set up a link between AD and T2DM suggesting that studying both disease in parallel would bring some new clues to discover the "lost pieces of the puzzle".

**THE AMYLOID CASCADE HYPOTHESIS**
- Deposition of Aβ peptides in early-onset AD due to mutations in APP, PS1, and PS2. In late-onset AD are associated with APOE.
- Amyloid plaques ➔ neurotoxicity (ROS) and dysregulation of intracellular Ca2+.
- Recent studies: AD patients are the neurotoxic agents rather than plaques.

**THE TAU PROTEIN HYPOTHESIS**
- Tau is a MAP protein, regulates MT and axonal transport of organelles ➔ critical for neurotransmission.
- pTAU self-assemble into NFTs which alter MT function, ↓ axonal trafficking ➔ synapsis loss ➔ cell death.

**METABOLIC DISORDER HYPOTHESIS**
- It is suggested that metabolic disorder provokes cognitive dysfunction and pathologies of alterations of AD.
  - Metabolic abnormalities includes disrupted glucose uptake and impaired energy metabolism. It is associated with brain insulin deficiency and dysregulated signal transduction.
  - Those features resembles T2DM and carry some researchers to that question.

**BRAIN INSULIN EFFECT**
- Brain insulin is derived from peripheral insulin and transferred across the BBB but there is also data of local insulin synthesis in the brain.

**GLUCOSE METABOLISM**
- It is suggested that insulin modulates CMRglc and glucose uptake within the hippocampus and cortex. Several hypotheses of the mechanism have been reported:
  - Decrease of GLUTs may involve a ↓HBP flux.
  - Insulin might influence CMRglc through GLUT4 (an insulin-sensitive GLUT).
  - GLUT2 and GLUT3 may result from down-regulation of HIF-1 (possibly decreased in AD due to increased oxidative stress).

**APP AMYLOIDGENESIS**
- It has been proposed that insulin promotes APP formation and secretion into extracellular space in a PKB-dependent manner.
  - Disrupted insulin signaling could induce APP amyloidogenesis via PI3K/PIK3/GSK-3β.
  - Disrupted insulin seems to accelerate APP Aβ trafficking to extracellular space via MAPK.
  - Aβ peptides might reduce the affinity of the binding between insulin and IR.
  - In hyperinsulinaemia situation there is ↓ IR activity ➔ ↓ Aβ deposition.
  - Aβ peptides may induce the removal of IR from the membrane.

**HYPERPHOSPHRYLATION OF TAU**
- It has been reported that insulin and glucose metabolism regulate phosphorylation of tau, MAPK, GSK3β and GSK-30 are the major tau knowns.
  - Insulin, via GSK-3β could ↓ PPPA ➔ ↓ pTau.
  - A decrease of GLUTs may involve a ↓ HIF flux ➔ ↓ α of O-Glucosylation ➔ ↑ pTau

**NEUROINFLAMMATION**
- It has been suggested that impaired insulin signalling could be due to pro-inflammatory signalling.
  - Peripheral inflammatory factors, trauma, infection of abnormal protein-aggregates activate MG ➔ ↑ THF, ↓ GSK-3β and ↓ GSK-30.
  - THF-Aβ binds to IFN-cell and through stress-sensitive kinases (JNK, IKK and PKR) inhibits B5 R function ➔ ↓ GSK-3β ➔ ↓ APP amyloidogenesis.
  - ↑ APP amyloidogenesis, via Aβ aggregation, induces reactive MG.

**CONCLUSIONS**
AD is a multifactorial disease and that is why finding an efficient therapeutic treatment is so challenging. Apparently, the mechanism of the different pathological features are interconnected, and global vision it has been provided by the hypothesis of metabolic disorder.

**REFERENCES**