The Alzheimer's disease: the unsolved puzzle

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Alzheimer's disease (AD) is the most common form of dementia and it is characterized to be an age-related and progressive neurodegenerative disorder which 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 hyperphosphorilated 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 "lasts pieces of the puzzle".

THE AMYLOID CASCADE HYPOTHESIS

- Deposition of Aβ peptides in early-onset AD due to mutations in APP, PSEN1 and PSEN2. In late-onset AD are associated with ApoE4.
- Amyloid plaques → neurotoxicity (ROS) and dysregulation of intracellular Ca^{2+}.
- Recent studies: AβOs 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-assembles into NTF which alter MT function, ↓ axonal trafficking → synapsis loss → cell death.

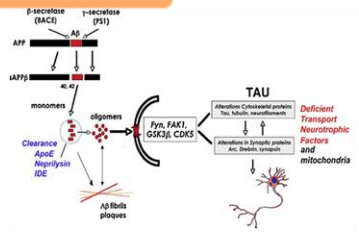

Figure 3. Possible AβO and tau interaction [1]

METABOLIC DISORDER HYPOTHESIS

It defends that a metabolic disorder precedes cognitive dysfunction and pathological 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:

IS AD A BRAIN-SPECIFIC FORM OF DIABETES?

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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.

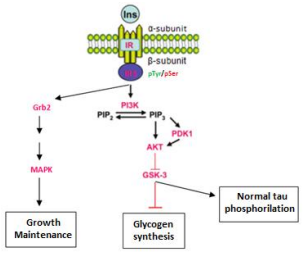


Figure 2. Insulin signal pathway [2]

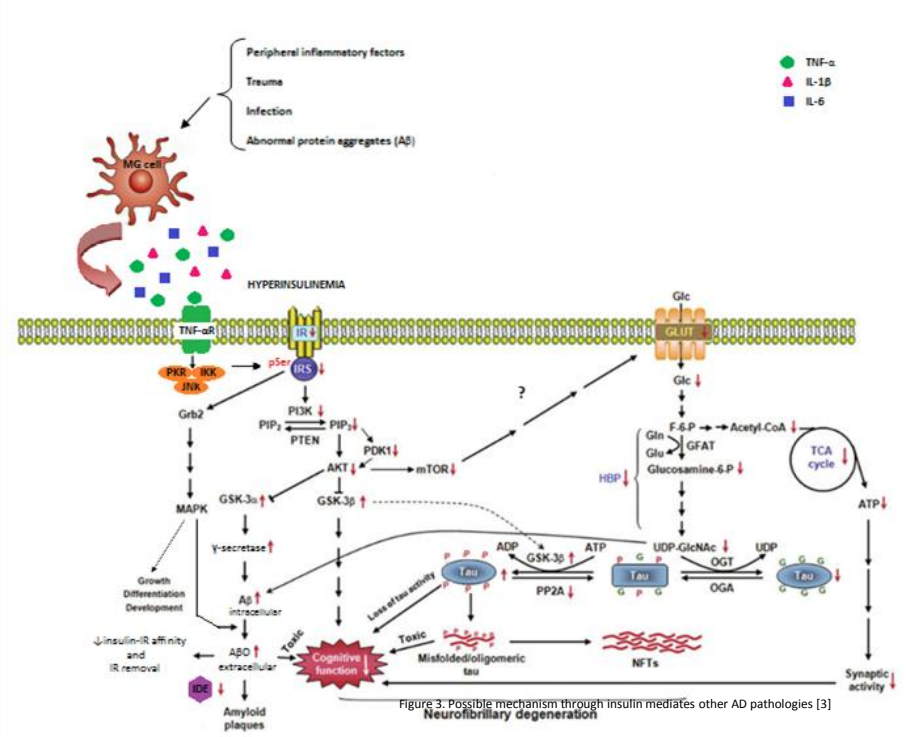


Figure 3. Possible mechanism through insulin mediates other AD pathologies [3]

GLUCOSE METABOLISM

It is suggested that insulin modulates CMRglu and glucose uptake within the hippocampus and cortex. Several hypotheses of the mechanism have been reported:

- Decrease of GLUTs could be due to insulin/IGF-1 signalling defects due to PI3K/Akt pathway.
- Insulin might influence CMRglu through GLUT4 (an insulin-sensitive GLUT)
- GLUT1 and GLUT3 may result from down-regulation of HIF-1 (possibly decreased in AD due to increased oxidative stress.

APP AMYLOIDOGENESIS

It has been proposed that insulin promotes Aβ formation and secretion into extracellular space in a PI3K-dependent manner.

- Disrupted insulin signalling could induce APP amyloidogenesi via PI3K/Akt/GSK-3α.
- 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 hyperinsulinemia situation there is ↓ IDE 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.

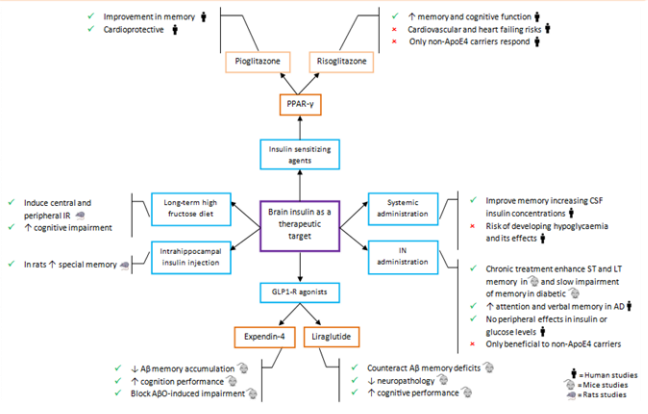
- MAPK, CdK5 and GSK-3β are the major tau kinases
- Insulin, via GSK-3β, could ↓ PP2A → ↑pTau
- A decrease of GLUTs may involve a ↓HBP flux → ↓ of O-GlcNAcylation →↑pTau

NEUROINFLAMMATION

It has been suggest that impaired insulin signalling could be due to pro-inflammatory signalling.

- Peripheral inflammatory factors, trauma, infection of abnormal protein aggregates activate MG → ↑TNF-α, IL-6 and IL-1β.
- TNF-α binds to TNF-αR and through stress-sensitive kinases (JNK, IKK and PKR) inhibits IRS function → ↑GSK-3α → ↑ APP amyloidogenesi
- ↑ APP amyloidogenesi, via Aβ aggregation, induces reactive MG.

BRAIN INSULIN AS A THERAPEUTIC TARGET OF AD



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.

Taking all those mechanism in account, it seems that brain insulin resistance is the common feature between them. It could confirm that there is a link between AD and T2DM and it has been thought that it would uncover the way to understand the pathogenic mechanism of AD and put together "the pieces of the puzzle". Hence, there is confidence in the fact that many therapy strategies based on insulin as a therapeutic target may yield promising results.

REFERENCES

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[1] C. R. Overk and E. Masliah, "Pathogenesis of synaptic degeneration in Alzheimer's disease and Lewy body disease," *Biochem. Pharmacol.*, vol. 88, no. 4, pp. 508–516, 2014.

[2] Adapted to Y. Liu, F. Liu, I. Grundke-Iqbal, K. Iqbal, and C.-X. Gong, "Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes.," *J. Pathol.*, vol. 225, no. 1, pp. 54–62, Sep. 2011.

[3] Adapted to Y. Chen, Y. Deng, B. Zhang, and C. X. Gong, "Deregulation of brain insulin signaling in Alzheimer's disease," *Neurosci. Bull.*, vol. 30, no. 2, pp. 282–294, 2014.