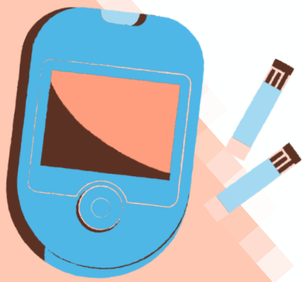

بسم الله الرحمن الرحيم

Type 3 diabetes mellitus and its association with type 2 diabetes

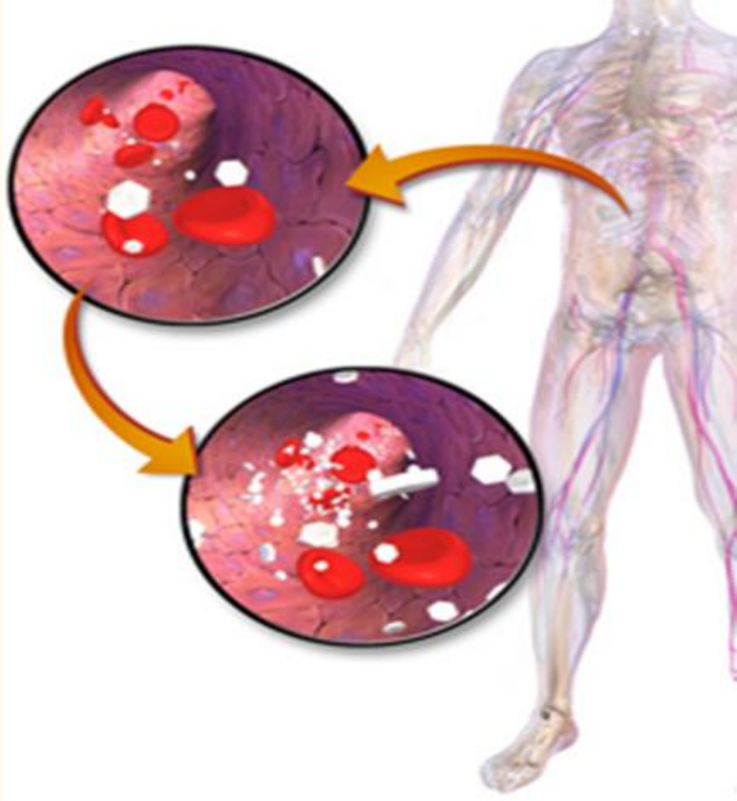
Created by: Kimiya Sadeghi



Topics

- Type 3 diabetes
- Risk factors for type 3 diabetes
- How to form type 3 diabetes
- Relationship between type 2 diabetes and Alzheimer's disease
- The role of insulin in Alzheimer's disease and diabetes
- diagnosis
- treatment

Diabetes mellitus



•Diabetes mellitus, often known simply as diabetes, is a group of common endocrine diseases characterized by sustained high blood sugar levels. Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body becoming unresponsive to the hormone's effects

Type 1	Type 2	Gestational diabetes
Type 3c	Type 3	

Enhancing flavor

TYPE 3 DIABETES

- Recently researchers proposed the term 'Type-3-Diabetes' for Alzheimer's disease (ad) because of the shared molecular and cellular features among Type-2-Diabetes and insulin resistance associated with memory deficits and cognitive decline in elderly individuals

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by progressive decline in memory, cognitive functions, and changes in behavior and personality.

Diabetes mellitus (DM) and Alzheimer's disease (AD) rates are rising, mirroring the global trend of an aging population

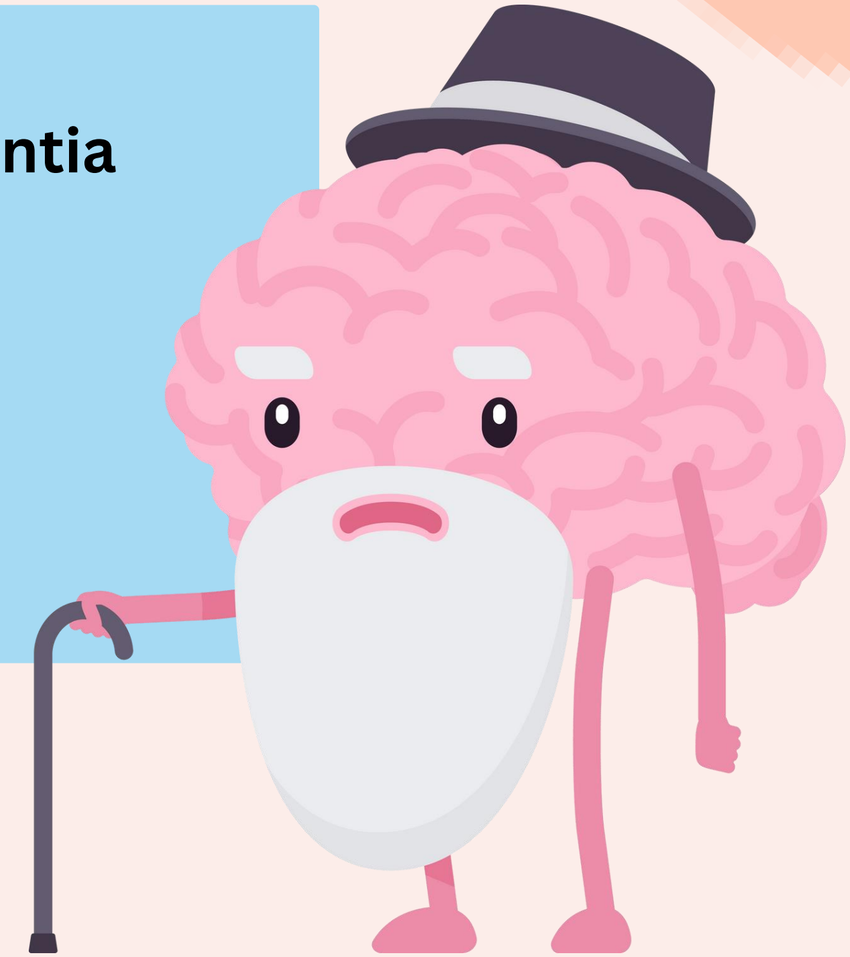
Numerous epidemiological studies have shown that those with Type 2 diabetes (T2DM) have an increased risk of developing dementia

AD is actually a neuroendocrine disorder that resembles type 2 diabetes

- AD is the main cause of dementia (72%).
- The global prevalence of dementia is currently 24 million people, which is expected to double every 20 years
- AD is the sixth leading cause of death in the United States and the fifth leading cause of death for people over age 65
- Nearly two-thirds of AD patients are women
- The prevalence of AD is lower in developing countries

AD RISK FACTORS:

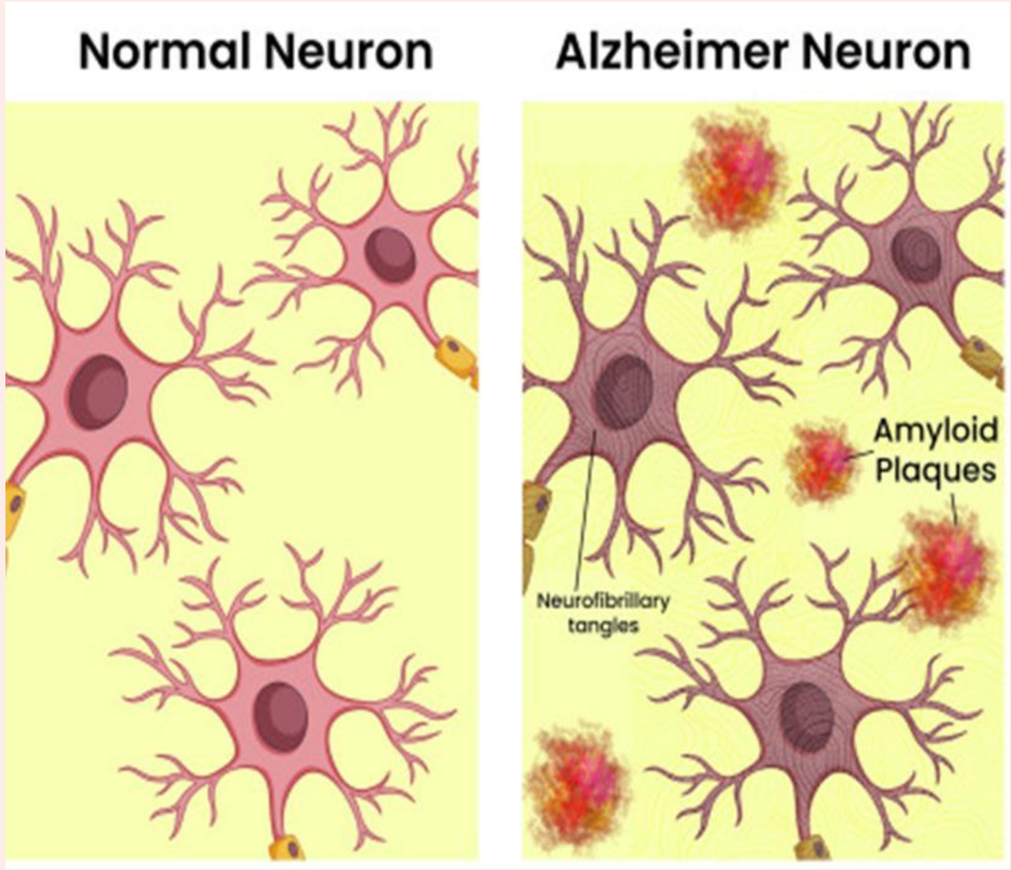
- age
- Positive family history of dementia
- Severe head injury
- Low level of education
- female gender
- Previous depression
- Vascular factors

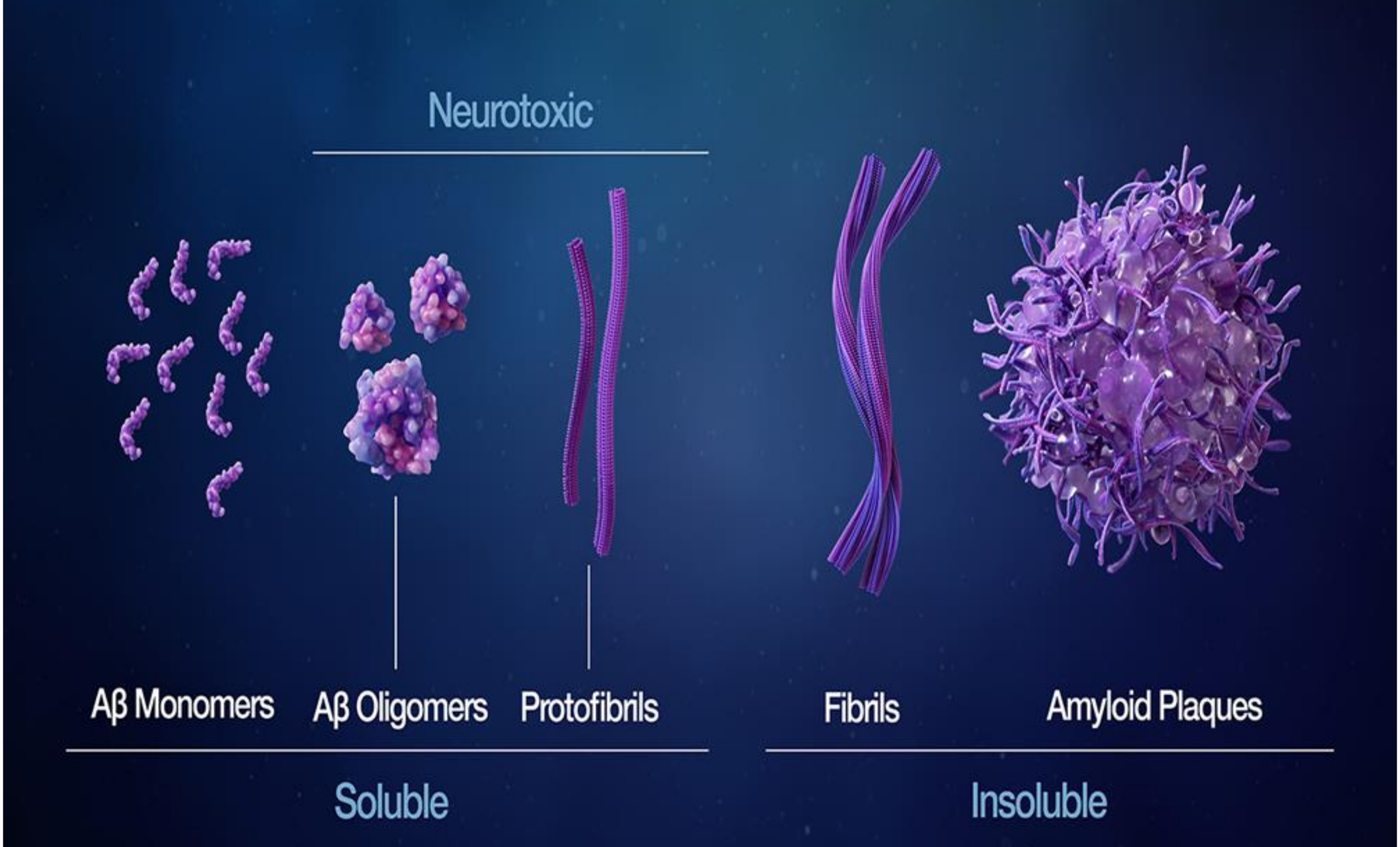


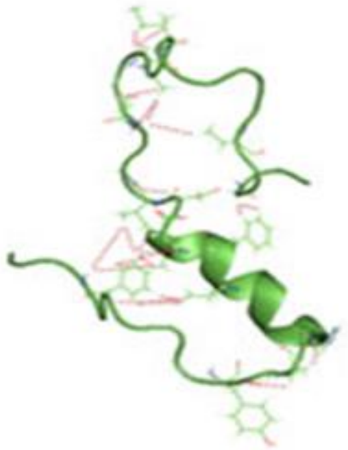
Alzheimer disease neuropathology

- extracellular accumulation of Aβ peptide

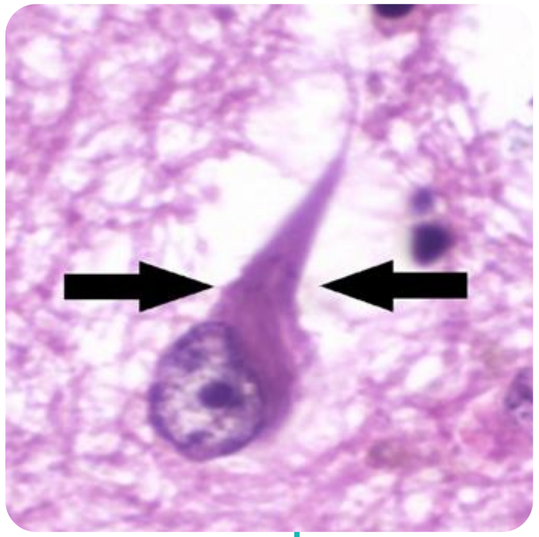
- intracellular aggregation of hyperphosphorylated tau



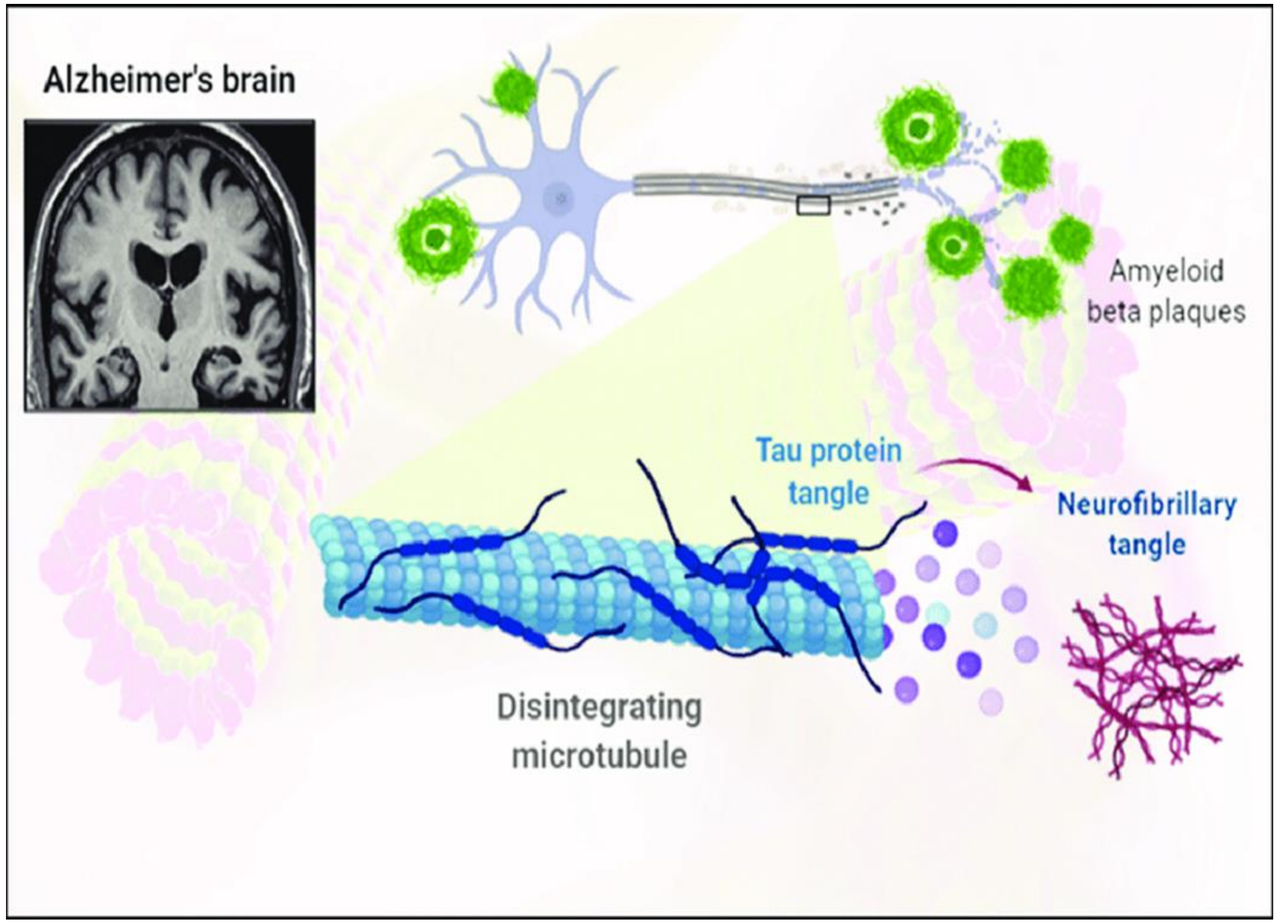

Neurotoxic
Aβ Monomers
Aβ Oligomers
Protofibrils
Fibrils
Amyloid Plaques
Soluble
Insoluble

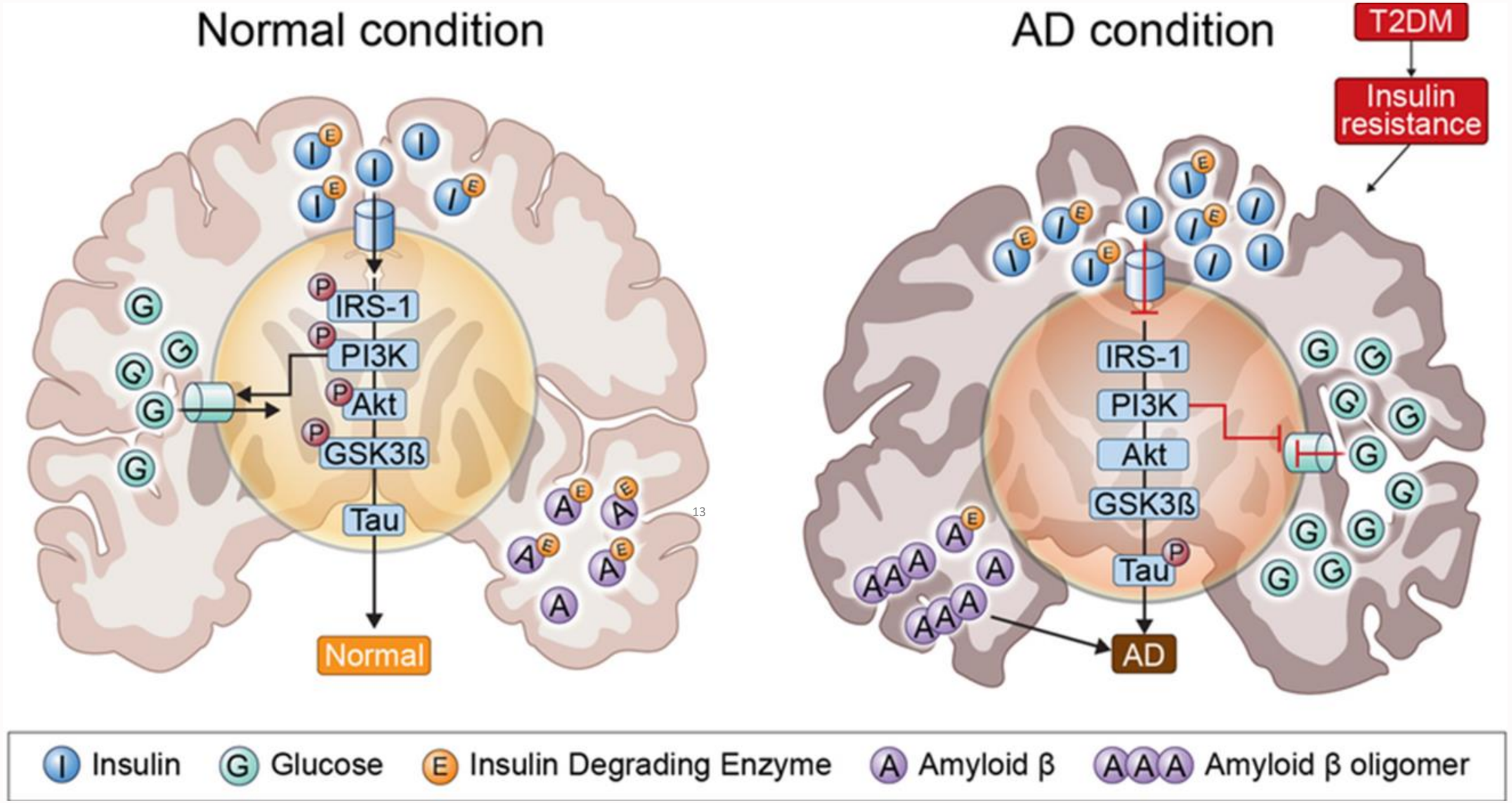


protein tau

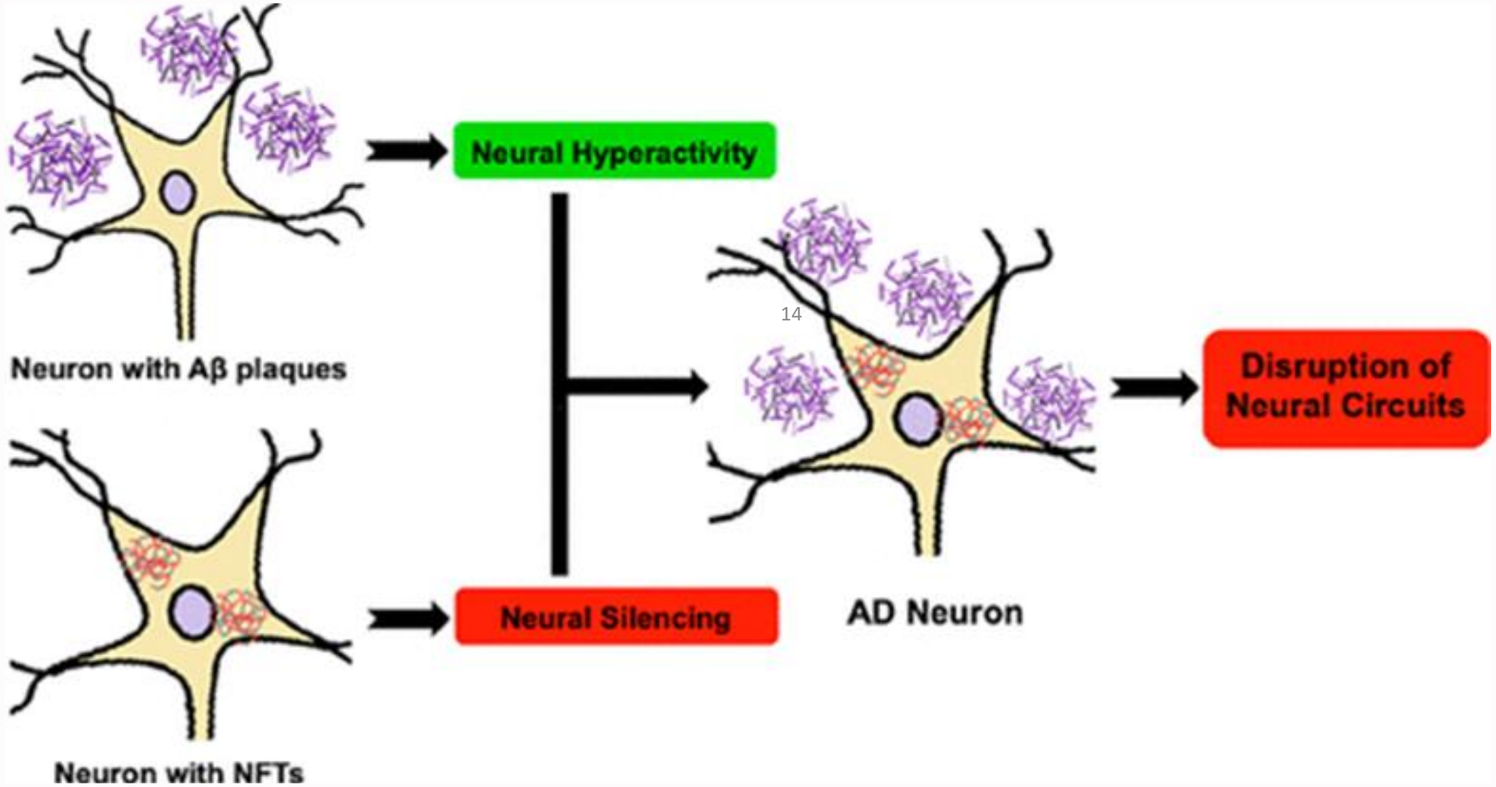


NFTs




Normal condition
AD condition
T2DM
Insulin resistance
IRS-1
PI3K
Akt
GSK3ß
Tau
Normal
AD
Insulin
Glucose
Insulin Degrading Enzyme
Amyloid β
Amyloid β oligomer

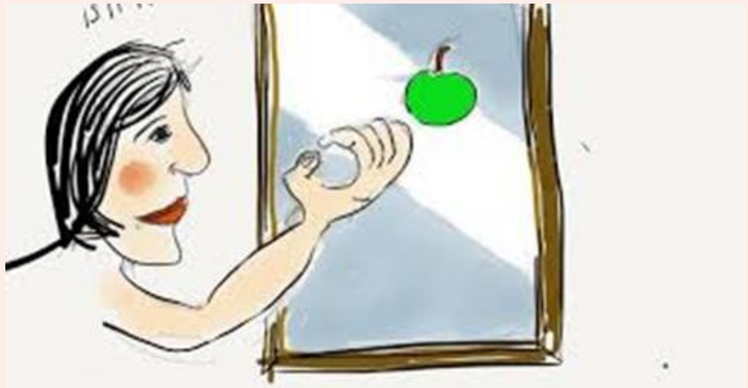
•Accumulation of Aβ in the cortex or of neurofibrillary tangles (NFTs) in the medial temporal lobe may precede the initial symptoms by decades



Following that preclinical phase of AD, clinical signs may be separated into two groups:

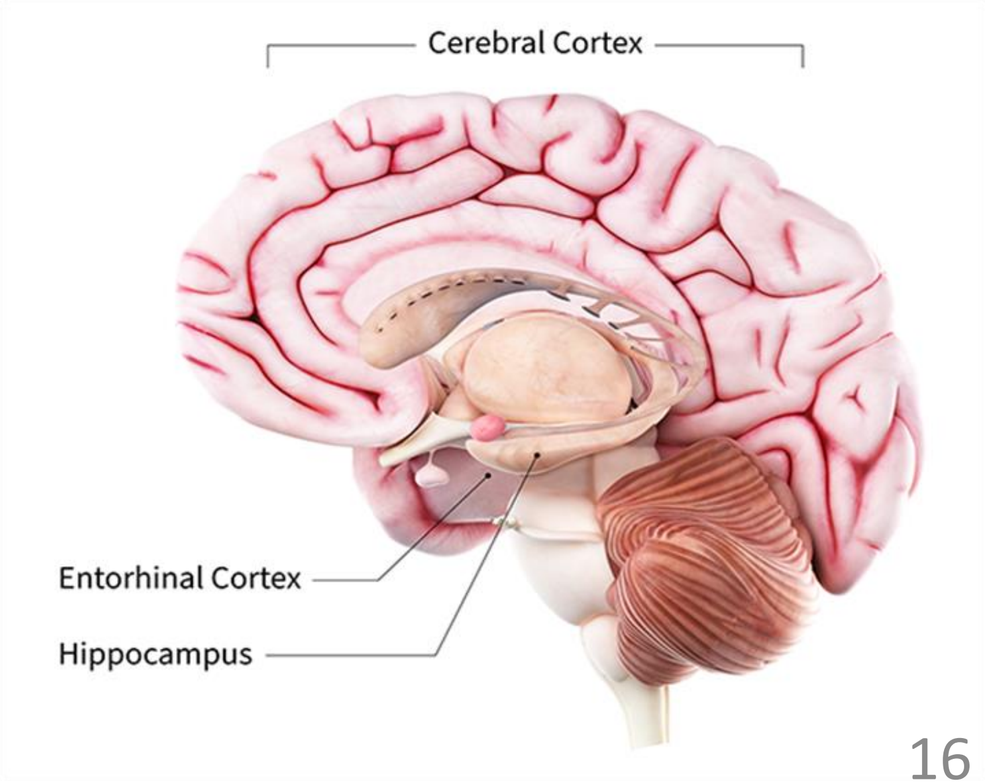
1. amnestic syndrome (related to hippocampal lesions)

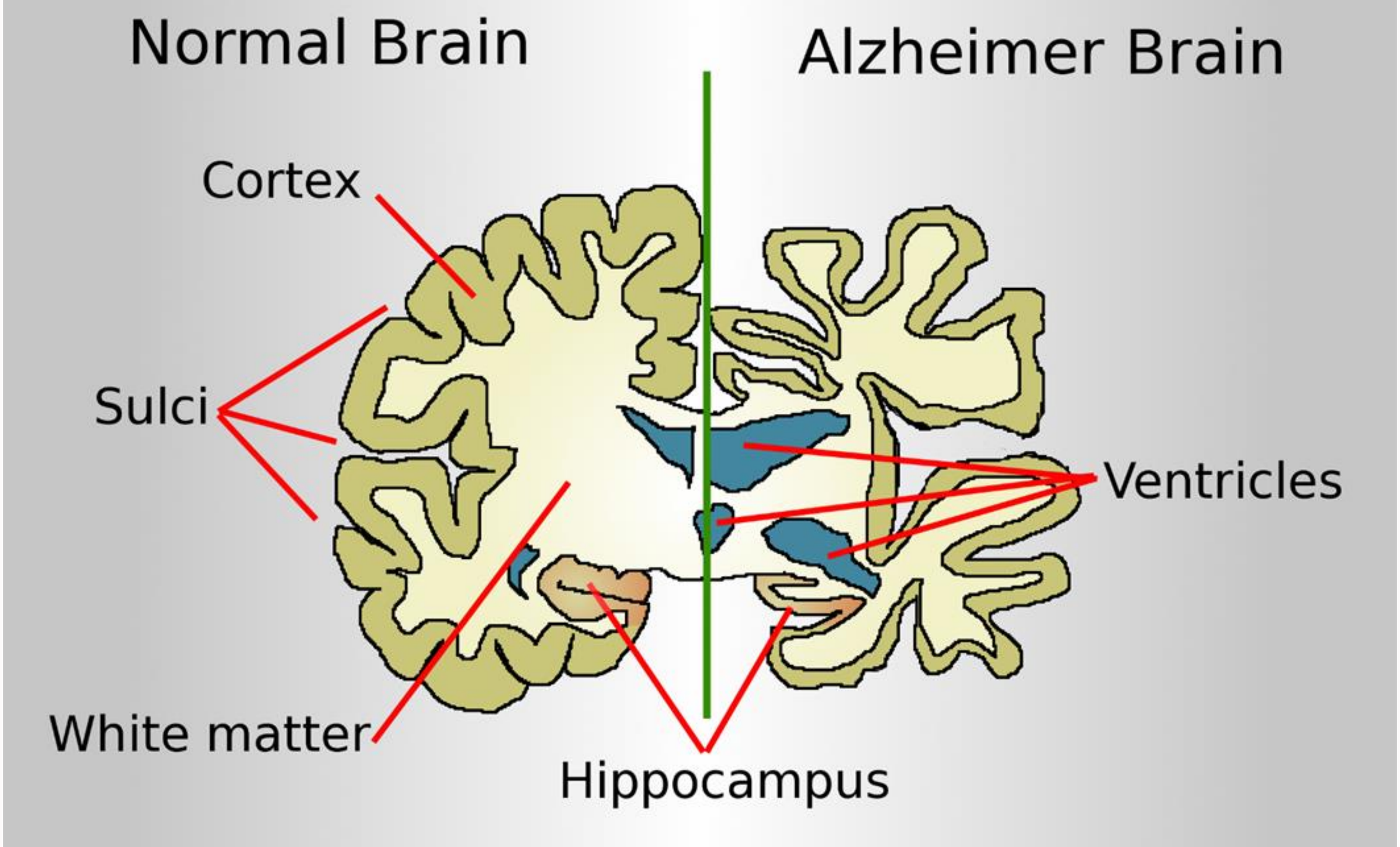
2. so-called focal signs (caused by limited lesions in the neocortex responsible, e.g., for visual agnosia or progressive aphasia)

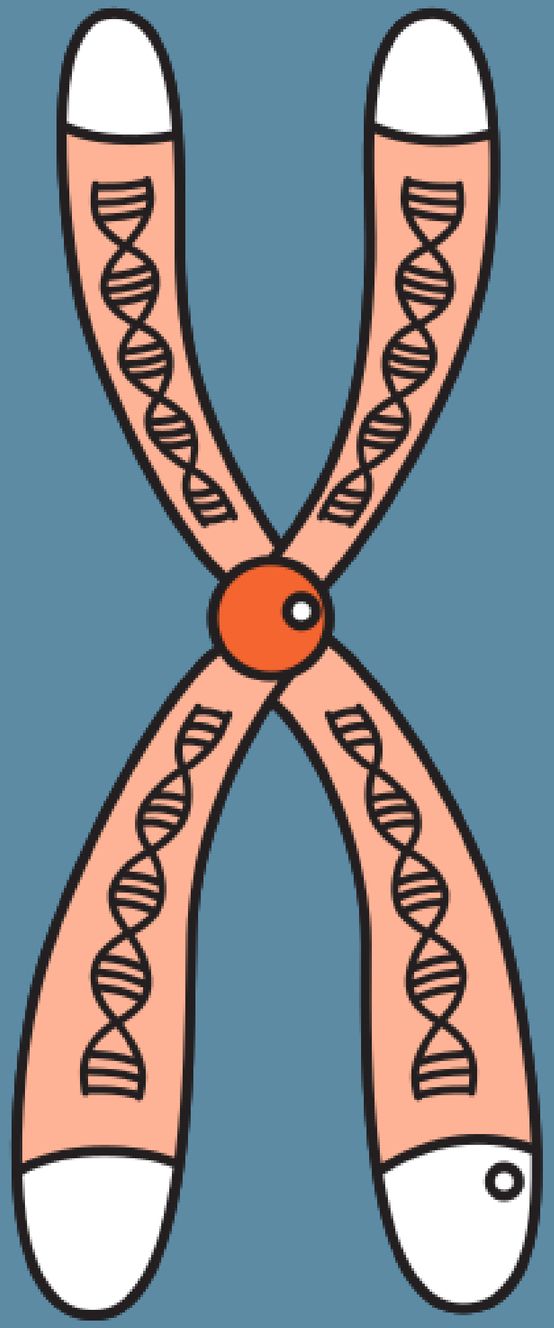


Atrophy involves areas affected by tau pathology and takes years to develop.

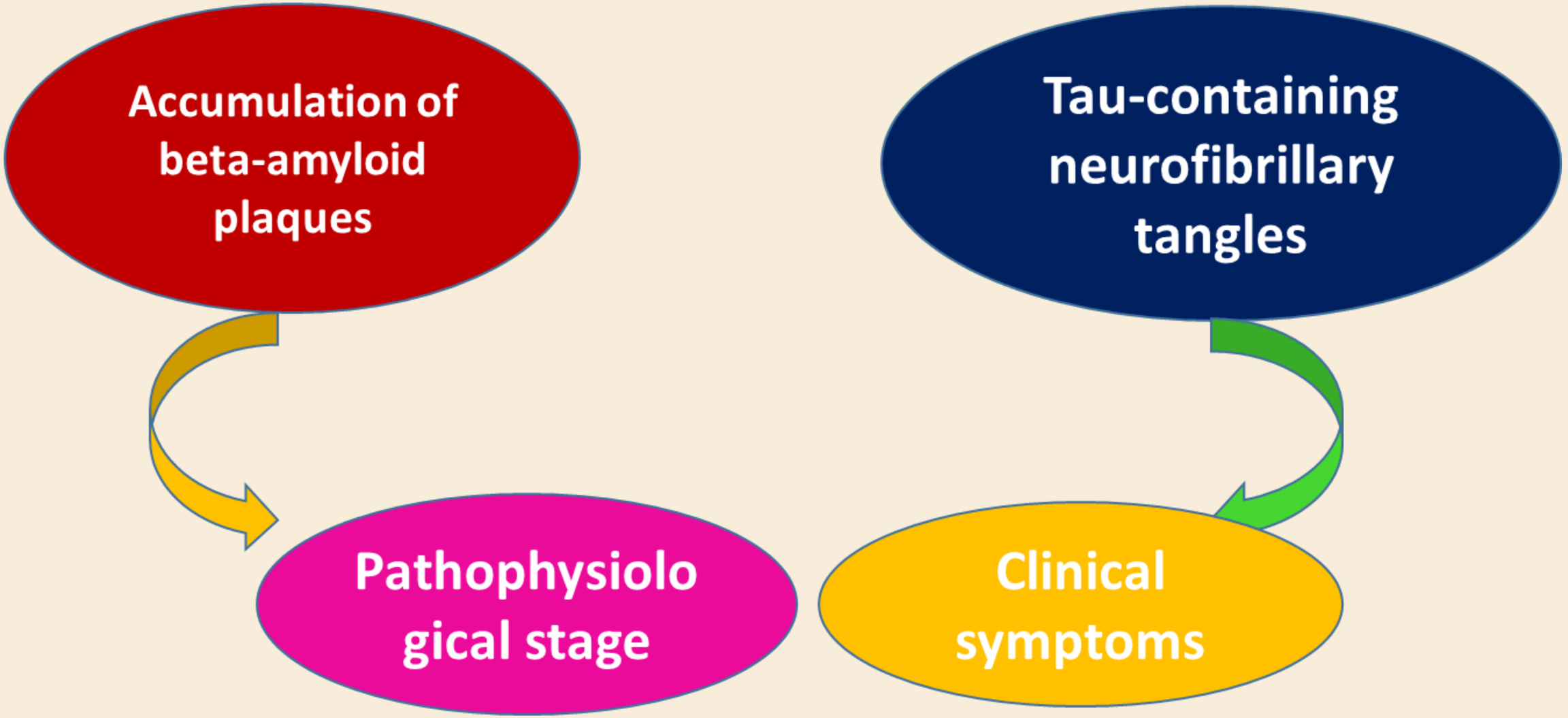
Most atrophic are the regions that are first involved by tau pathology, such as the entorhinal cortex, the hippocampus, and the amygdala.



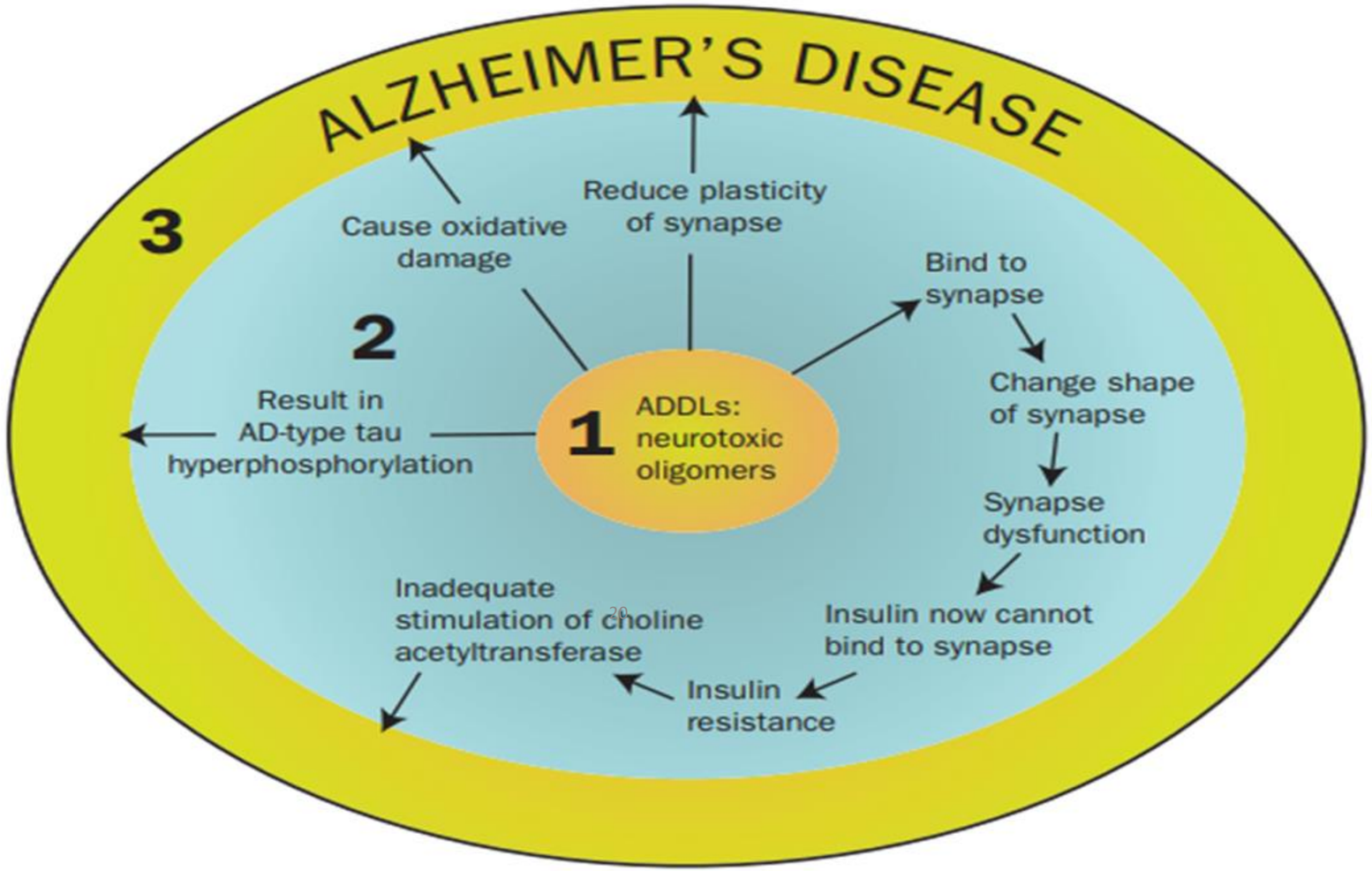

Normal Brain
Alzheimer Brain
Cortex
Sulci
Ventricles
White matter
Hippocampus



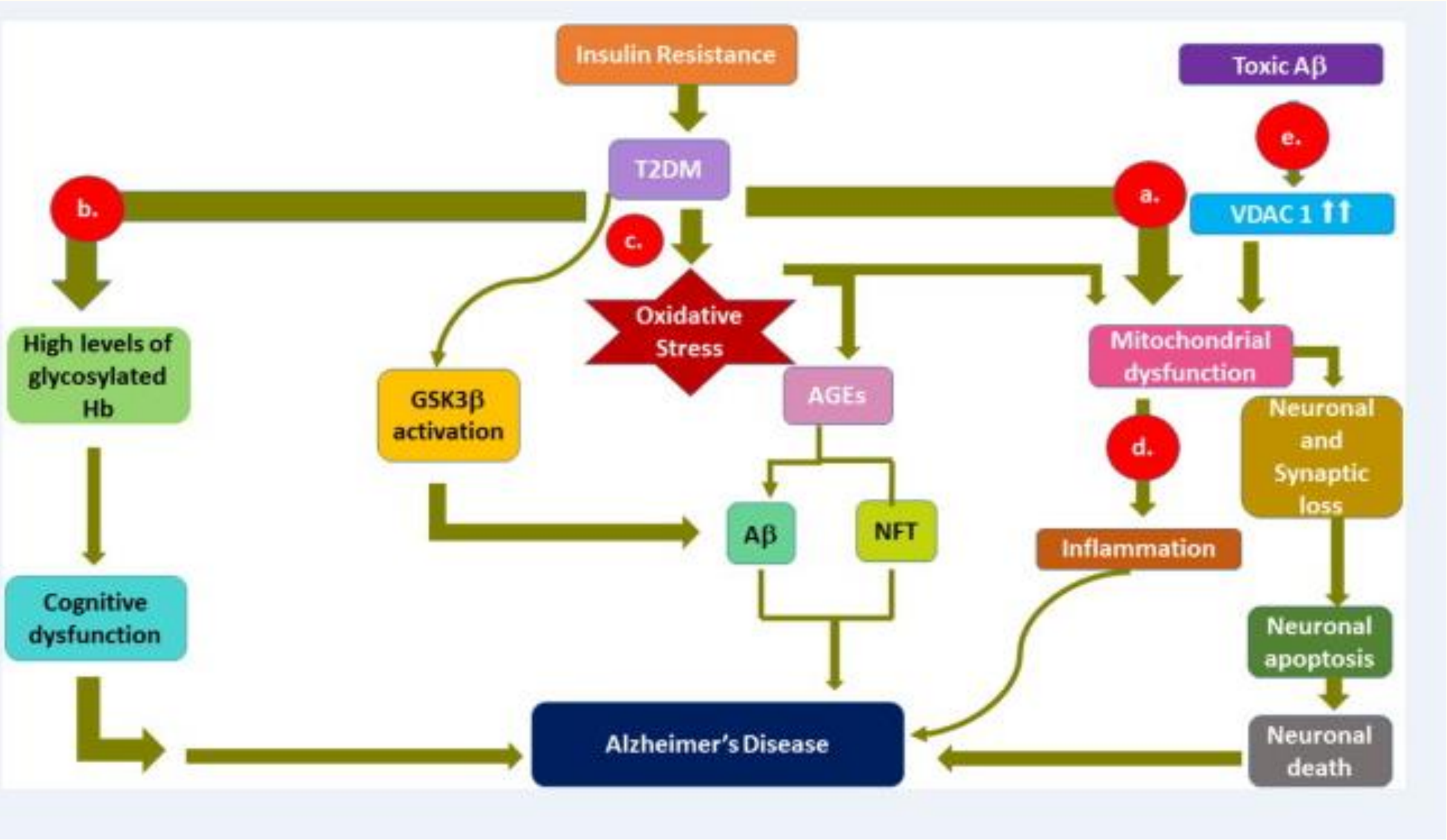
- **All the mutations associated with AD are located on the APP gene or on genes involved in its metabolism.**


Accumulation of beta-amyloid plaques
Tau-containing neurofibrillary tangles
Pathophysiological stage
Clinical symptoms

ADDL



1. ADDLs = amyloid beta-derived diffusible ligands
2. Mechanism of action of ADDLs
3. End-point of ADDLs


Insulin Resistance
Toxic Aβ
T2DM
e.
b.
a.
VDAC 1 ↑↑
c.
Oxidative Stress
High levels of glycosylated Hb
GSK3β activation
AGEs
Mitochondrial dysfunction
Neuronal and Synaptic loss
d.
Aβ
NFT
Inflammation
Cognitive dysfunction
Neuronal apoptosis
Alzheimer's Disease
Neuronal death

Oxidative reaction

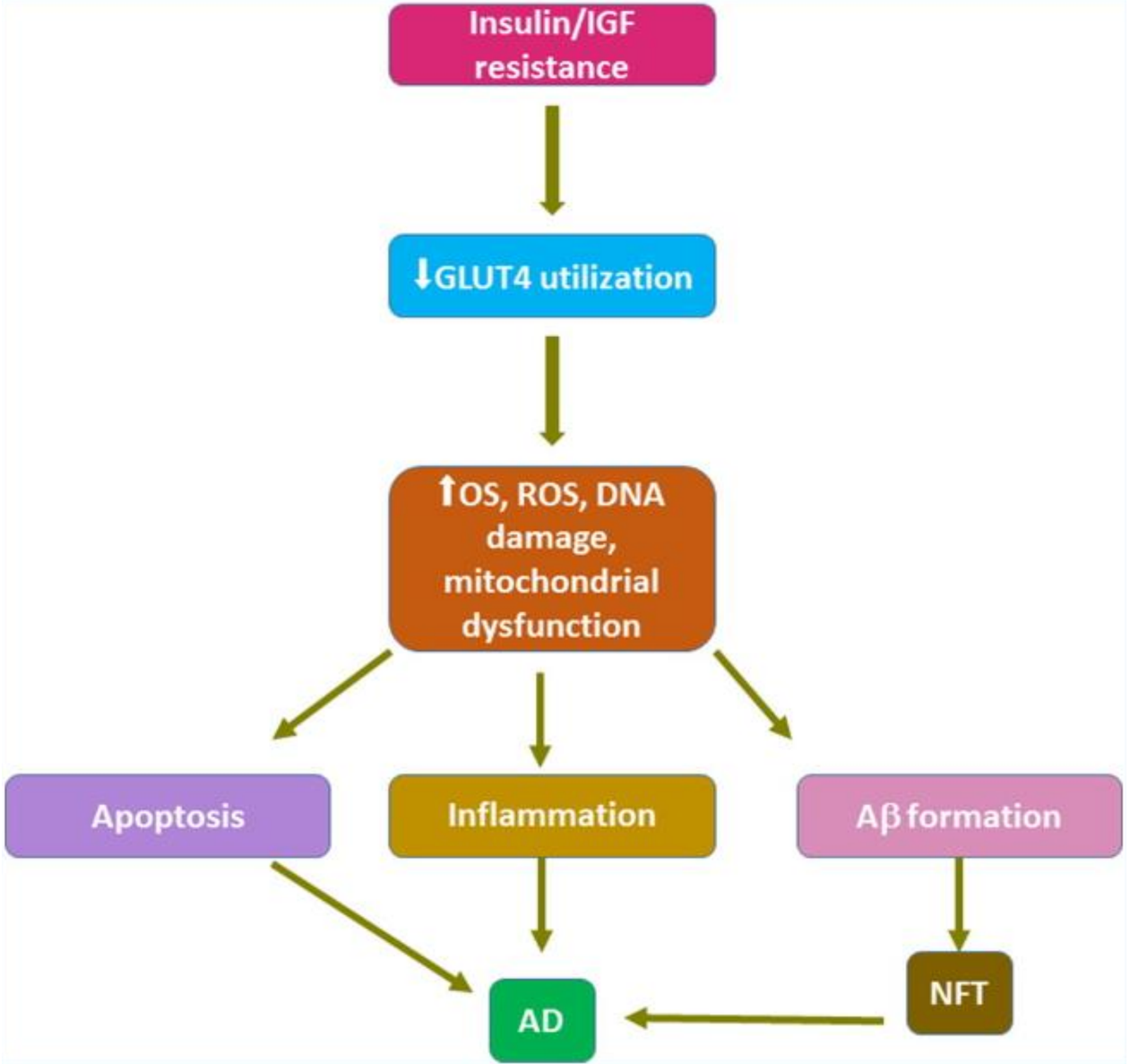
double edged swords

- AD
- T2DM
- Huntington's disease (HD)

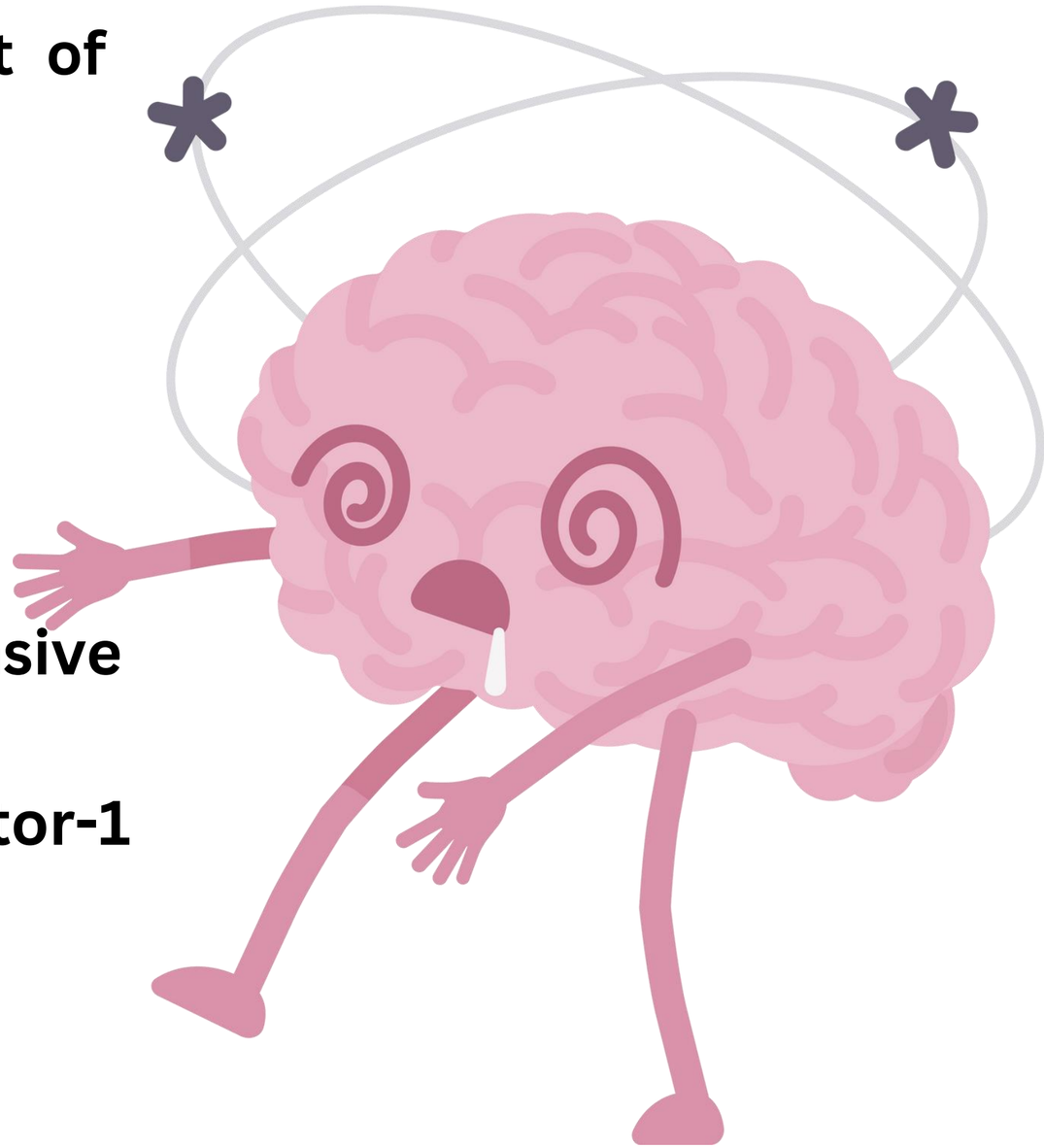
T2DM AND AD

- Insulin resistance
- Insulin growth factor (IGF) signaling
- Inflammatory response
- Oxidative stress
- Glycogen synthase kinase 3β (GSK3β) signaling mechanism
- Formation of amyloid beta (Aβ) from amyloid precursor protein (APP)
- Neurofibrillary tangles formation
- regulates acetylcholinesterase activity

Oxidative stress, mitochondrial dysfunctionin T2DM and AD



In the past, the brain was thought to be an insulin-insensitive tissue. Until now, there was a lot of evidence for brain insulin.



The concept that the brain is an insulin-responsive organ is supported by the presence of glucose transporter 4 (GLUT-4), insulin-like growth factor-1 (IGF-1), and other receptors on the surface of neurons..

Functions of insulin

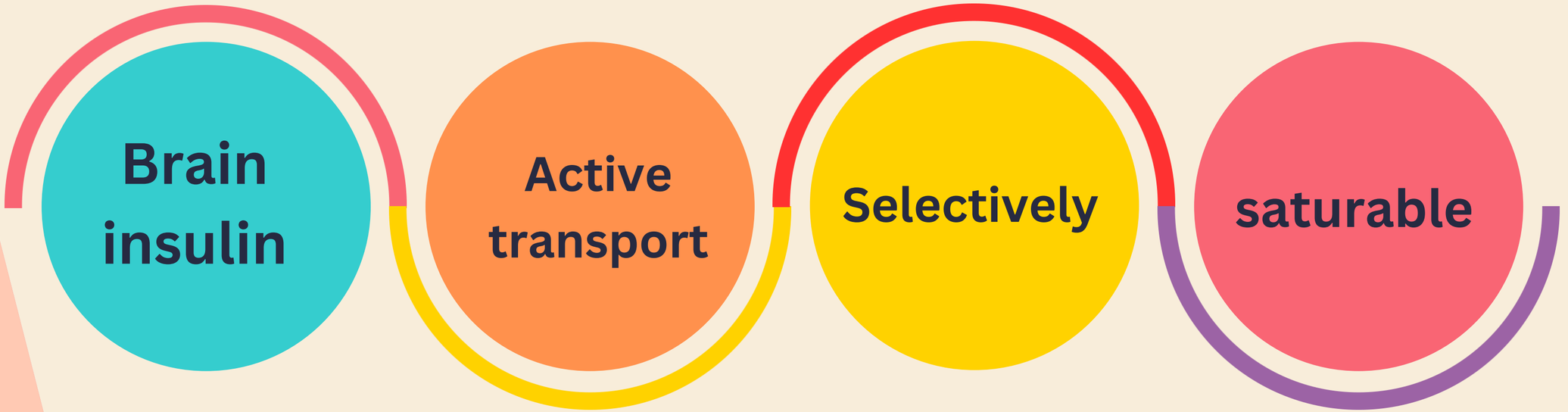
- Formation of neural circuits
- Synaptic plasticity
- Dendritic arborization
- Expression of neurotransmitters
- Survival of neurons
- signal transmission
- Memory function

THE ORIGIN OF INSULIN IN THE BRAIN

SYNTHESIS OF INSULIN IN THE BRAIN	→	ITS PRODUCTION IS INSIGNIFICANT
TRANSFER OF PANCREATIC INSULIN TO THE BRAIN	→	ORIGINAL SOURCE

It has been found that insulin crosses the blood-brain barrier in different animal species

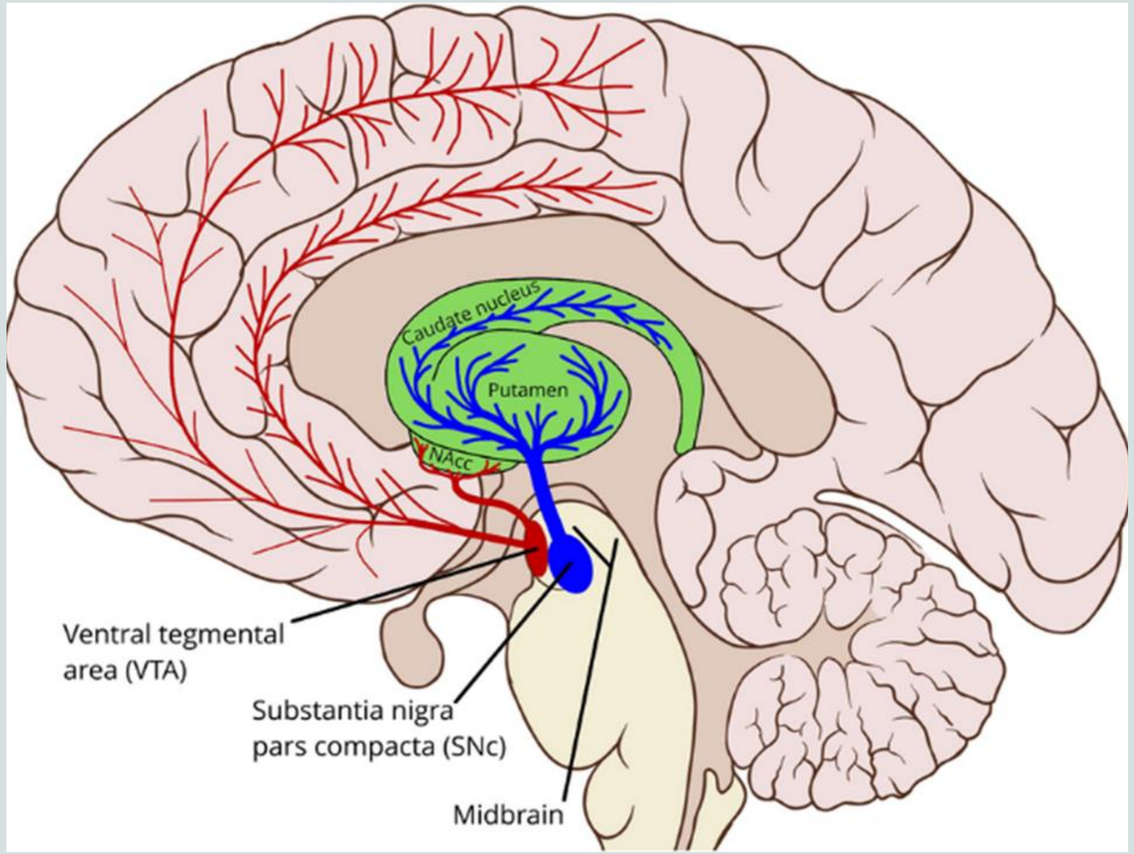
How does insulin cross the blood-brain barrier with a large molecular structure and not soluble in fat?



- Control of food consumption
- Effect on cognitive functions, memory and regeneration of damaged nerve cells in disorders

INSULIN RECEPTORS

Insulin receptors and its mRNA expression have been observed in wide areas in the brain including the substantia nigra, olfactory bulb, hypothalamus, hippocampus, cerebellum, amygdala and cerebral cortex



There are two types of insulin receptors in the mammalian brain:

NUMBER	STATEMENT
1.	The type of **environment** that exists only in glial cells and insulin regulates glucose metabolism in glial cells through this receptor
2.	1.A special type in **brain neurons** that do not play a role in glucose metabolism

(Insulin receptors are found on the dendrites of neurons in areas related to cognitive processes such as the hippocampus)

Insulin function in the brain

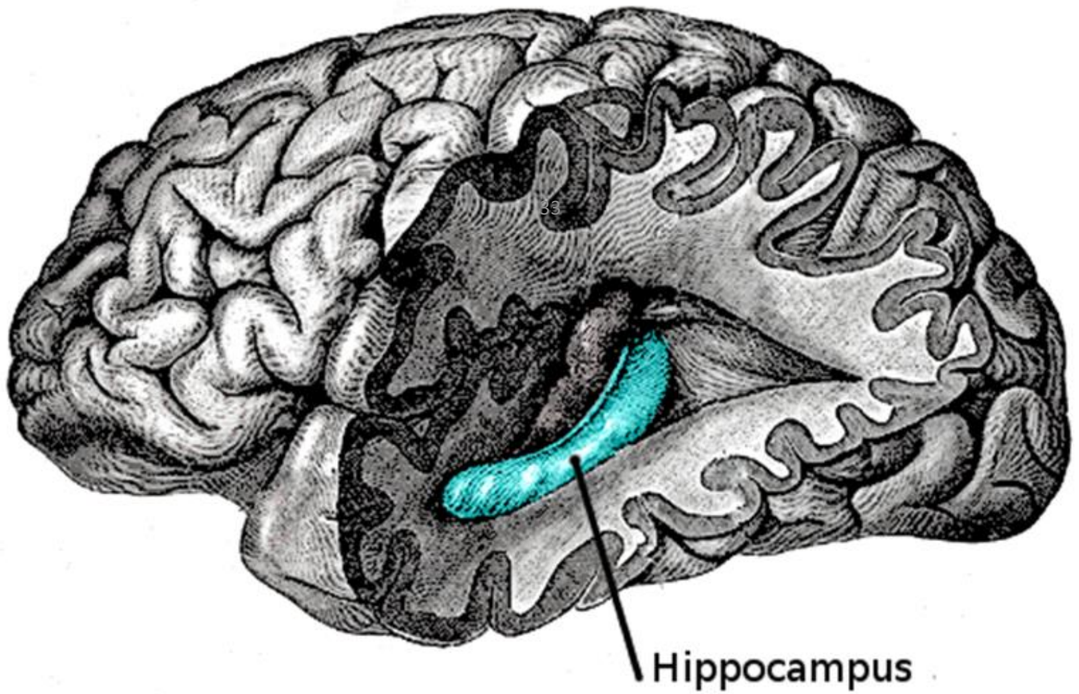
Metabolic effects

- Effect on the amount of glucose uptake
- Regulating the function of enzymes involved in carbohydrate, fat and protein metabolism
- Regulation of enzyme gene expression

Non-metabolic effects

- The function of presynaptic and postsynaptic neurons is modulated

- Insulin receptors exist in different areas of the brain, especially in the cerebral cortex and hippocampus, which play an important role in learning, memory consolidation, and cognitive activities.



Insulin receptor in the hippocampus

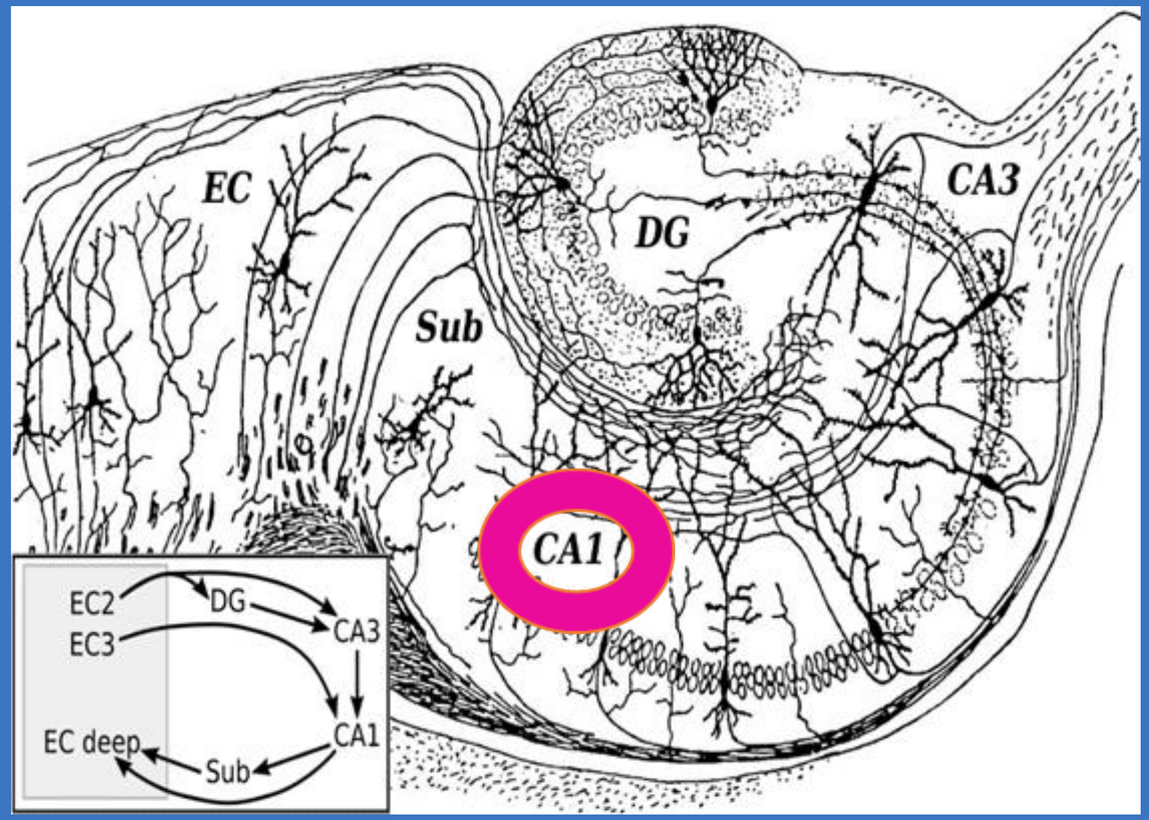
The hippocampus contains both insulin receptors and glucose-regulated insulin receptors (GluT4).

Dependence of glucose metabolism on insulin in the hippocampus

Changes in the function of insulin receptors play an important role in memory formation

Increasing plasma insulin levels increases insulin-sensitive receptors in the plasma membrane of hippocampal neurons and improves cognitive and behavioral activities.

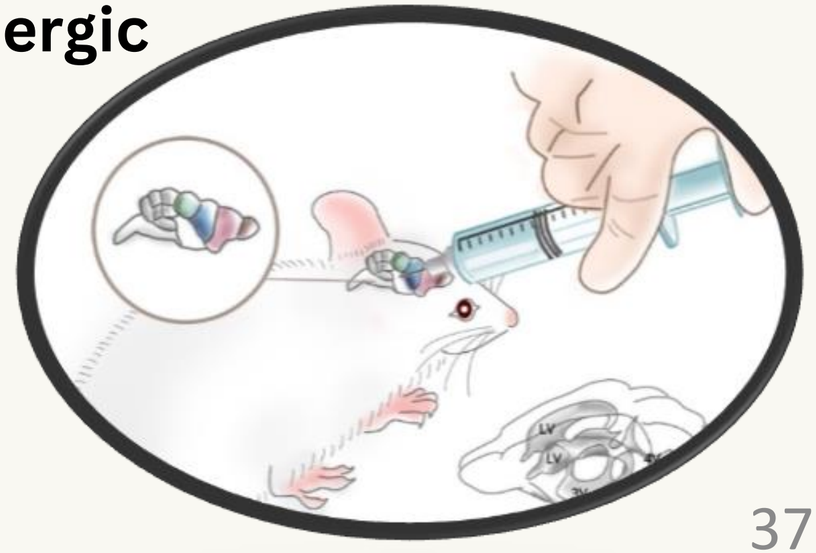
Spatial learning process is effective on insulin receptor gene expression Insulin activates the synthesis of some proteins involved in synaptic structures through the PI3K/Akt/mTOR pathway and plays an essential role in synaptic plasticity and the process of learning and memory



Insulin increases the activity of alpha-1-adrenergic receptors in the hippocampal cells and increases the level of epinephrine in the prefrontal cortex, and increases the process of attention and concentration, which is dependent on the activity of the noradrenergic system.

It is not known to what extent cognitive actions are affected by direct administration of insulin, but research results show.....

- Intraventricular injection of insulin is effective in the process of memory processing and consolidation by affecting cholinergic nerves and increases the concentration of serotonin and acetylcholine in presynaptic neurons and decreases the concentration of dopamine.



•Administering insulin through the nose (Intranasal) to bypass the liver increases insulin in the cerebrospinal fluid and improves memory function.

- **Insulin has a greater effect on cognitive functions in women than in men, so that insulin administration improves hippocampus-dependent memory and working memory in women compared to men.**

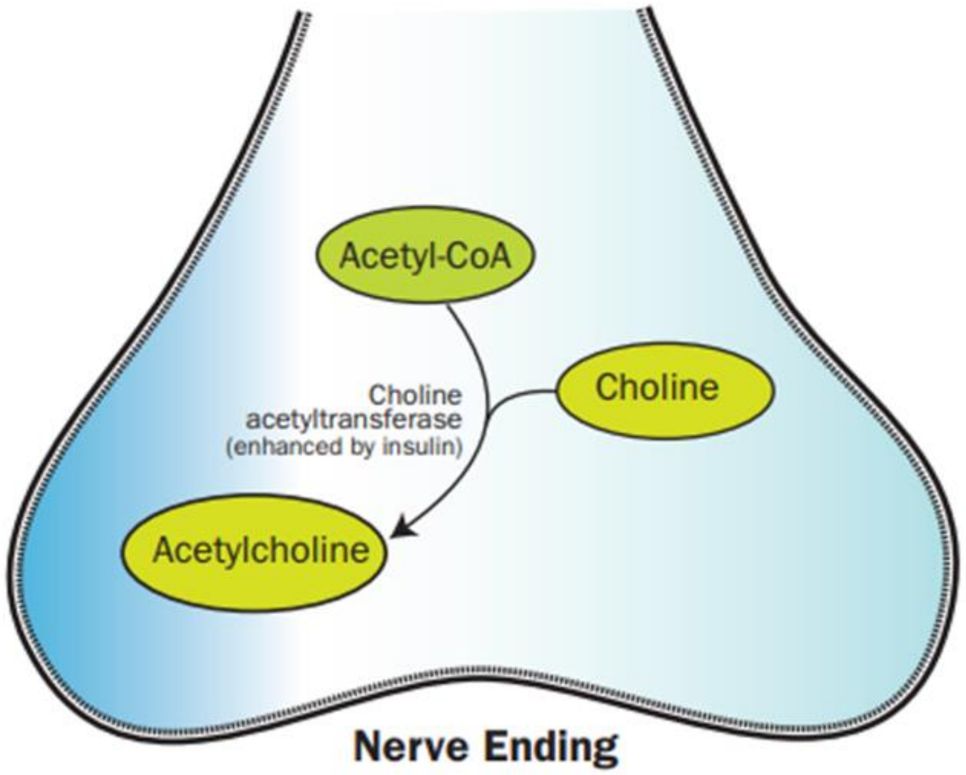
Insulin and the cholinergic hypothesis

centration in cerebrospinal fluid. Of 30 subjects, ADDL concentrations were found to be higher in those diagnosed with AD compared to non-AD patients. This test is not readily available and less invasive testing is underway.[26] An ADDL vaccine is being studied and ADDL-blocking drugs are being considered by Klein et al.[27]

Insulin and the Cholinergic Hypothesis

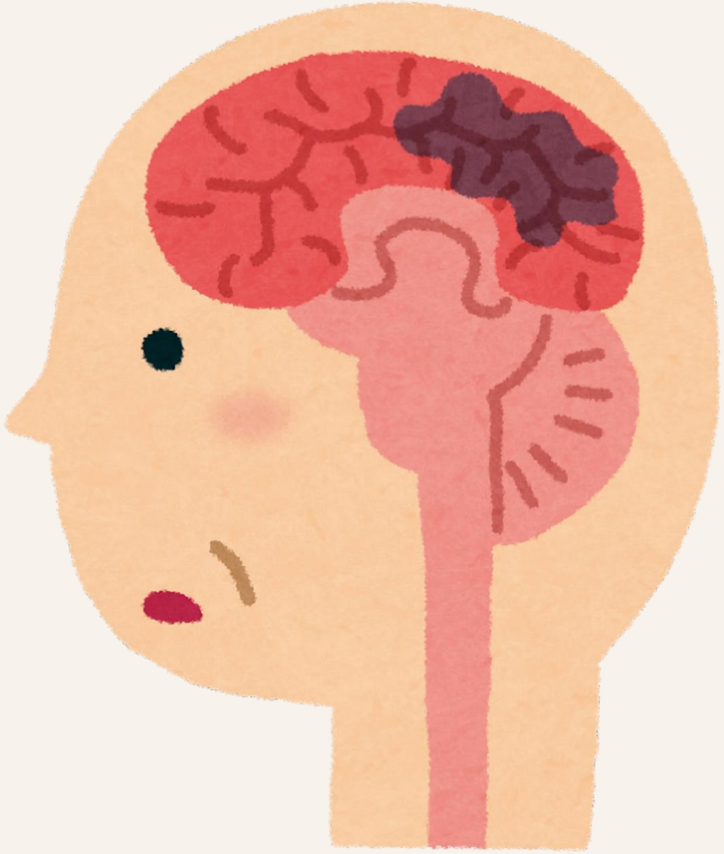
The cholinergic hypothesis that suggests AD is caused by an inadequate production of acetylcholine may also have links to blood sugar abnormalities and insulin resistance. The researchers at Brown point out that insulin also participates significantly in neurological function by stimulating the expression of choline acetyltransferase (ChAT), the enzyme responsible for acetylcholine

Figure 2. Insulin's Role in the Cholinergic Hypothesis: The Importance of Insulin in Memory Formation



Vascular issues

- Microvascular dysfunction and vascular problems are observed in both AD and diabetes.
- in T2D rat model, altered cerebral blood flow is considered the probable reason behind the development of AD-like cognitive dysfunction in diabetes



Diagnosis

- A family history of T2DM is considered as a possible risk factor for AD, as well as low brain glucose metabolism as an important biomarker for the development of dementia and AD.
- Repeated tests of fasting glucose and insulin and detection of insulin resistance (HOMA-IR)
- MRI
- PET

Anti-diabetes drugs effect on AD:

- **Target genes** (Meng et al., 2022)
- **GLP-1** (Cheng et al., 2022)
- **Intranasal insulin** (Lochhead et al., 2019)
- **Metformin** (Lu et al., 2020)
- **Amylin analogs** (Jackson et al., 2013)
- **SGLT2 inhibitors** (Lin et al., 2021)

Anti-AD drugs effect on diabetes

- Tacrine (Cui et al., 2018)
- Donepezil (Aggarwal et al., 2022)
- Rivastigmine (Matsuda and Hisatsune, 2017)
- Galantamine (Meng et al., 2023)

CONCLUSION

Epidemiological evidence indicates a common pathophysiological relationship between type 2 diabetes and Alzheimer's disease, so much so that it has been hypothesized that AD may be type 3 diabetes.

Insulin resistance can also occur in the brain, which is associated with Alzheimer's disease

Insulin and the insulin signaling pathway are important for neuronal survival

True or false? Alzheimer’s disease is type 3 diabetes: Evidences from bench to bedside

Type 3 Diabetes and Its Role Implications in Alzheimer’s Disease

Association Between Type 2 Diabetes Mellitus and Alzheimer's Disease: Common Molecular Mechanism and Therapeutic Targets

Type 3 Diabetes Mellitus: A Novel Implication of Alzheimers Disease

{#29 2013 }نقش انسولین در عملکردهای شناختی در سیستم مرکزی اعصاب

Is Alzheimer's disease a Type 3 Diabetes? A critical appraisal

How does brain insulin resistance develop in Alzheimer's disease?

IS ALZHEIMER’S DISEASE A TYPE 3 DIABETES? A REVIEW

Alzheimer’s Disease as Type 3 Diabetes: Common Pathophysiological Mechanisms between Alzheimer’s Disease and Type 2 Diabetes

Type 2 diabetes mellitus and Alzheimer’s disease

Relationship between Alzheimer’s Disease and Diabetes: Type 3 Diabetes?

Alzheimer disease{Knopman, 2021 #17}

Alzheimer disease{Castellani, 2010 #18}

Alzheimer disease{Kumar, 2018 #19}

Chapter 23 - Alzheimer disease{Calderon-Garcidueñas, 2018 #20}

THANK YOU