

Diabetes Mellitus and Dementia



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Abstract

Diabetes mellitus increases the risk for developing dementia...BUT there is inconsistency with the subtypes of dementia...

Diabetes Mellitus (DM)

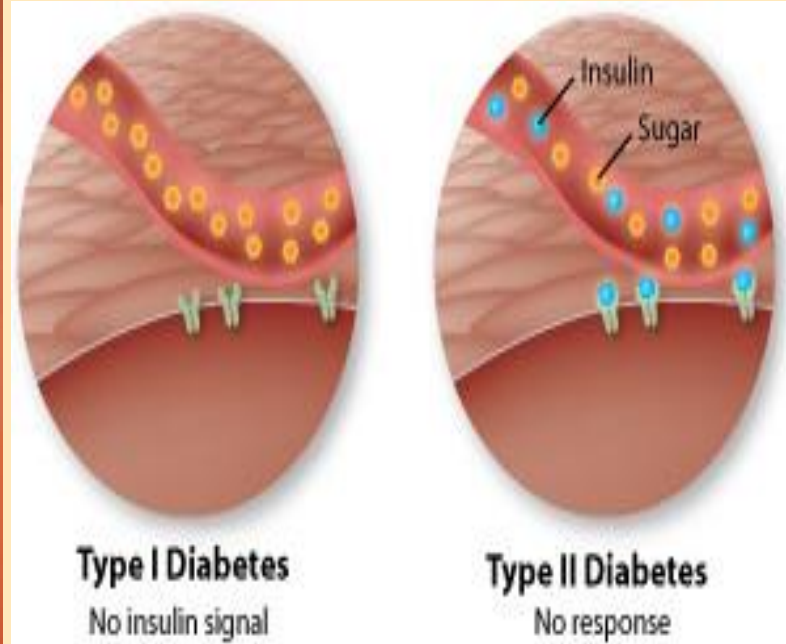
- defined as a problem of hyperglycemia
 - 366 million people worldwide → 552 million by 2030
- Type 1 DM
 - autoimmune disease: beta cells don't produce insulin
- Type 2 DM
 - “lifestyle” disorder: due to diet and exercise habits
- DM is a risk factor for vascular dementia and Alzheimer's

29.1 million American have diabetes

5% have
Type 1

95% have
Type 2

Source: American Diabetes Association, 2012



Polyuria
(Frequent Urination)



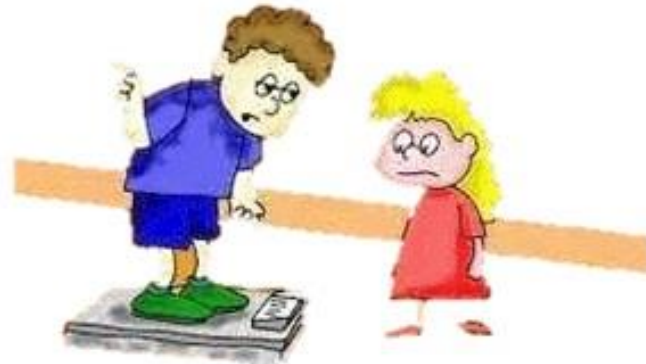
Polydipsia
(Excessive Thirst)



Polyphagia (Excessive
Hunger/Increased Appetite)



Involuntary Weight Loss



So what is dementia?

- “Syndrome that affects memory, thinking, behavior, and the ability to perform everyday activities”
- Two major subtypes
 - Alzheimer’s Disease (AD)
 - Vascular Dementia (VD)

Who has dementia?

- Currently, 35.6 million people worldwide
 - will double by 2030
- Think about the cost associated with it
 - caretakers, meds, etc
 - currently costs \$214 billion → projected to \$1.2 trillion by 2050

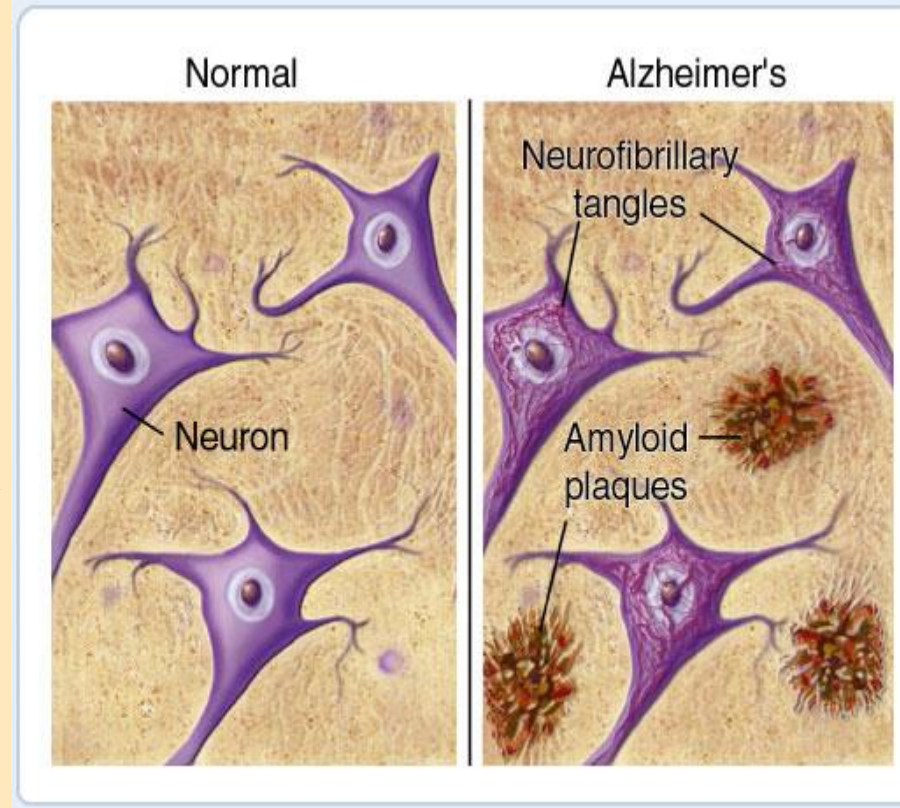


35.5 million people worldwide have dementia

Source - "Dementia: a public health priority" report, World Health Organization and Alzheimer's Disease International

Most Common Dementia: Alzheimer's

- Initially only thought of as only neurodegenerative
 - extracellular amyloid beta plaques (AB)
 - intracellular neurofibrillary tangles (tau)
- BUT now insulin might have a huge role



Dementia vs. Alzheimer's

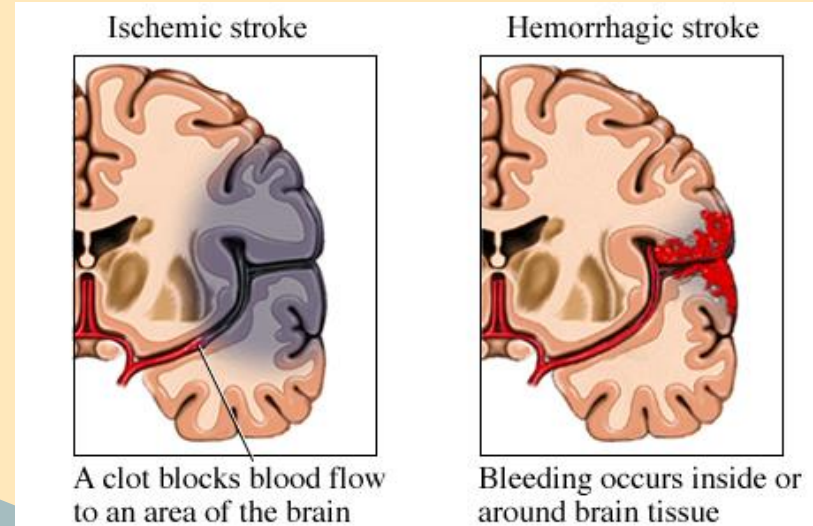
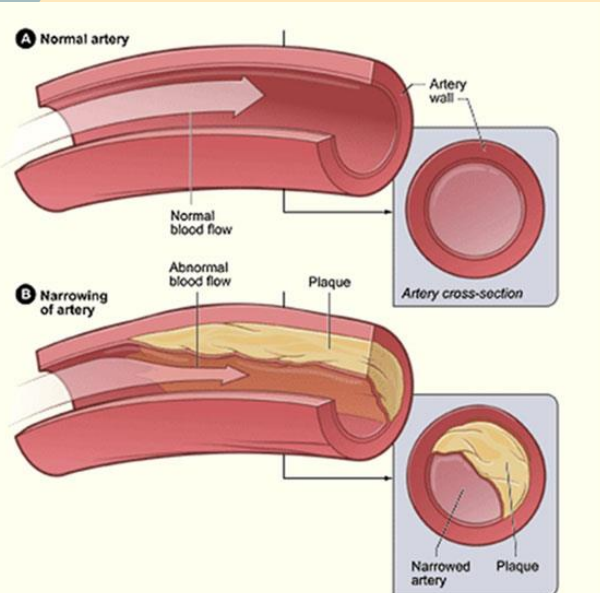
Dementia

Alzheimer's Disease

	Dementia	Alzheimer's Disease
General Definition	A brain related disorder caused by diseases and other conditions.	A type of dementia. But the most common type.
Cause	Many, including Alzheimer's disease, stroke, thyroid issues, vitamin deficiencies, reactions to medicines, and brain tumors.	Unknown, but the "amyloid cascade hypothesis" is the most widely discussed and researched hypothesis today.
Duration	Permanent damage that comes in stages.	Average of 8 to 20 years.
Typical Age of Onset	65 years and older.	65 years but can occur as early as 30.
Symptoms	Issues with memory, focus and attention, visual perception, reasoning, judgment, and comprehension.	Difficulty remembering newly learned information. With advancement, disorientation, mood and behavior changes may occur.

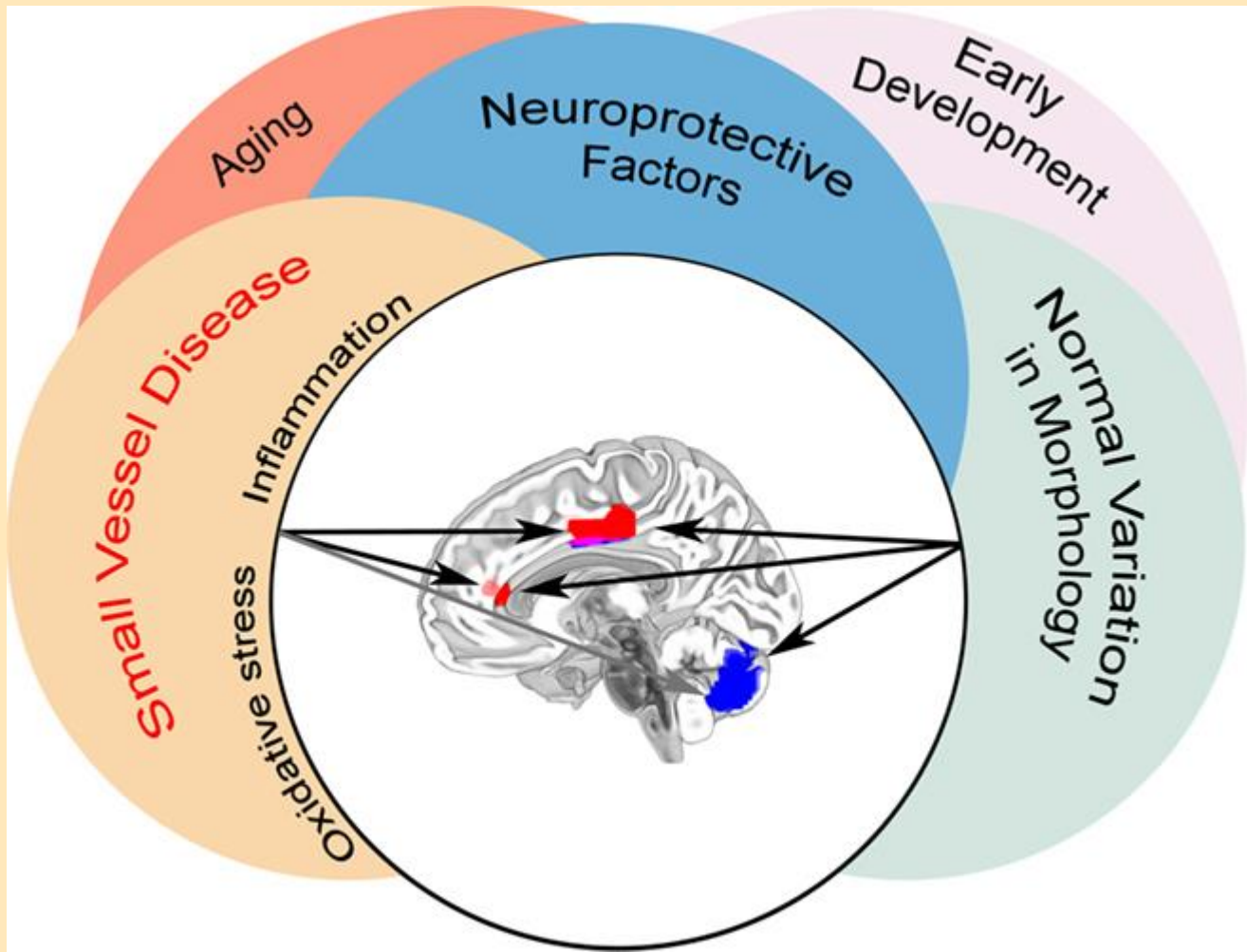
Second most common: Vascular Dementia

- Small vessel disease → strokes → vascular dementia (VD)
 - causes permanent cognitive damage



Clinical features	Vascular Dementia	Alzheimer's Disease
History of atherosclerotic diseases	Transient ischemic attack, strokes, atherosclerotic risk factors e.g., diabetes mellitus, hypertension	Less common
Onset	Sudden or gradual	Gradual
Progression	Slow or stepwise progression	Slow, progressive decline
Neurological examination	Neurological deficits	Normal
Gait	Often disturbed early	Usually normal
Memory	Mild impairment in early phase	Prominent in early phase
Executive function	Marked impairment and early	Impaired later
Type of dementia	Subcortical	Cortical
Hachinski Ischemic Score	≥ 7	≤ 4
Neuroimaging	Infarction or white matter lesions	Normal or hippocampal atrophy

Source: Roman GC, 2003;¹¹ Muangpaisan W et al., 2005.¹⁸



Epidemiological Evidence

- They used MEDLINE via Ovid computer search (1946-2013)
 - keywords used: diabetes mellitus, dementia, epidemiologic studies
- yielded 795 research articles → exclusion requirements → 18 specific articles reviewed

From the 18 studies...

- Most studies in Western countries (US, CAN, Euro) and two in Japan
- diagnosis of DM based on
 - self reports
 - medical records
 - anti-diabetes meds
 - oral glucose tolerance test

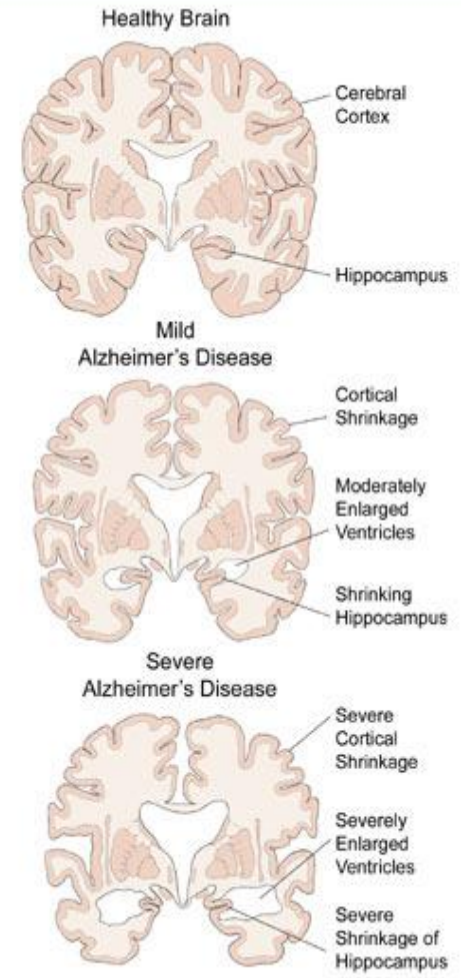
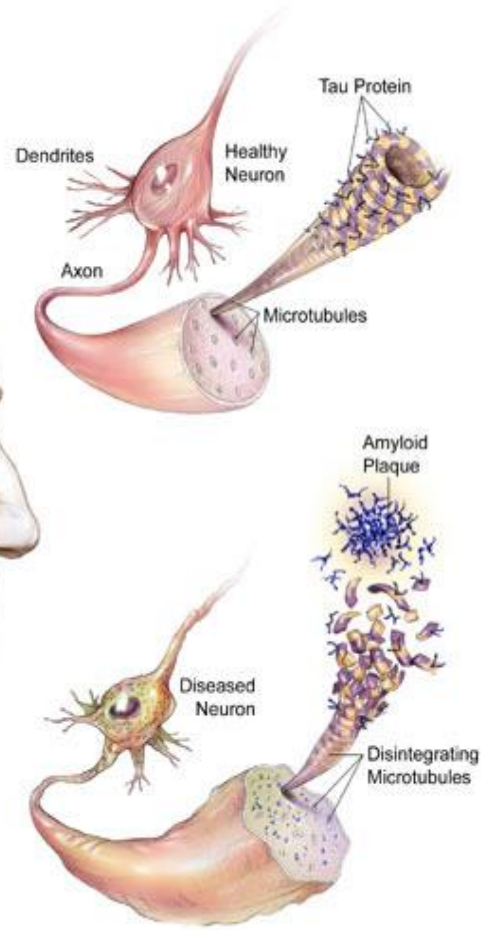
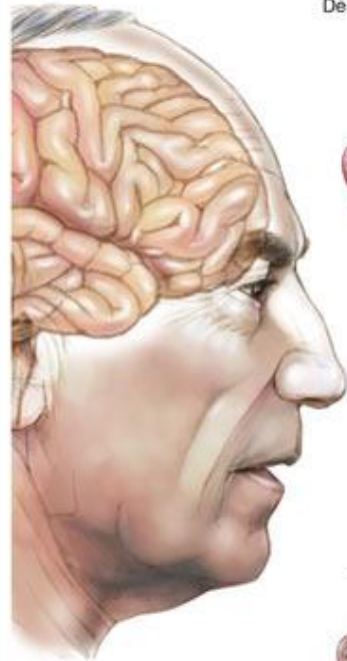
Out of the 18 studies...

- 15/18: DM increased risk of all dementia
 - about a 1.7x increase
- 14/18: Addressed DM and AD specifically
 - so 5/14 demonstrated a significant increased risk
 - 9/14 didn't show a significant difference because of experimental method differences

Major Correlations

- Risk of AD is 1.6x greater with DM
- Risk of Vascular Dementia is 2.2x greater with DM
- “People with DM have a 1.5-2.5x greater risk of dementia than those without it among community-dwelling elderly people”

Morphologic Changes in the Brain



Hisayama Study

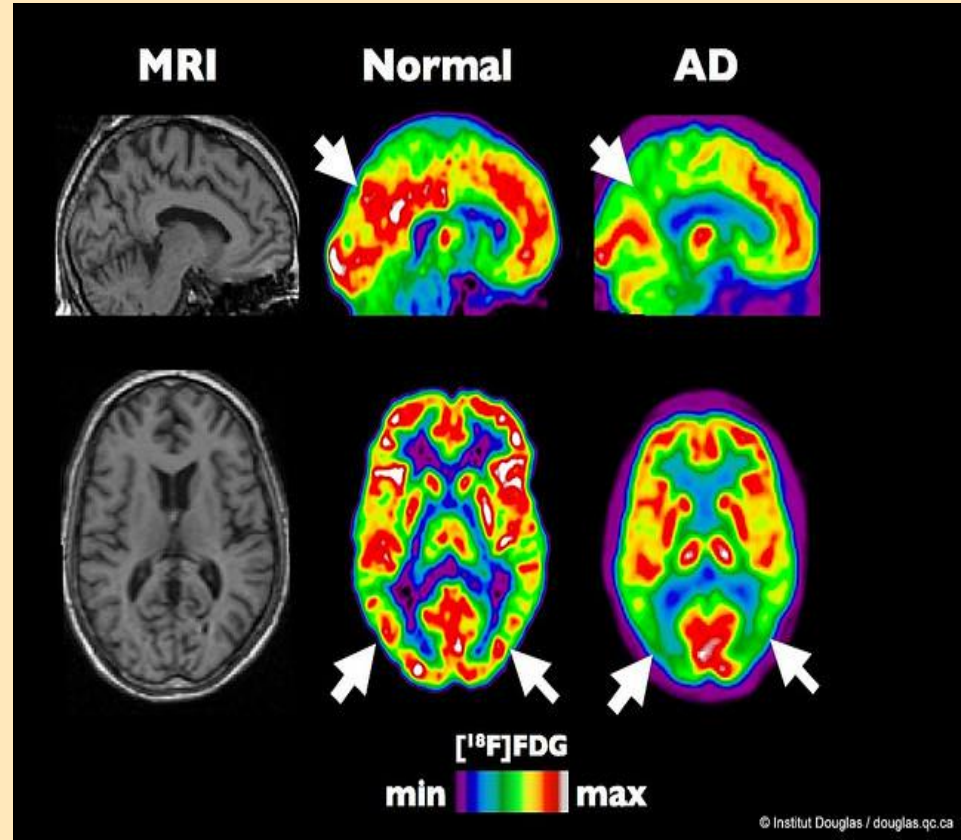
- In Japan, the diabetes diagnosed by glucose tolerance test
 - measured the 2 hour post-load plasma glucose (2PG) and the fasting plasma glucose (FPG)
- 2PG levels linked to increased risk of AD and VD
 - 2PG associated with strokes

Hisayama Study Cont.

- Presence of plaques increased with increases in 2PG levels (not FPG), fasting insulin, and insulin resistance
 - increase in ApoE4 increases these risks
 - ApoE is a gene on chrom. 19 (strong genetic factor for AD)
 - produced by astrocytes, liver, and macrophages
 - 7 receptors→ variety of effects

Rotterdam Scan Study

- Based on MRI, hippocampus and amygdala of DM patients was smaller than those without DM



Honolulu Heart Program Study

- DM + ApoE4 allele → increases number of plaques and tangles in the brain (cortex and hippocampus to be specific)
- Risk of cerebral amyloid angiopathy was higher in DM patients and ApoE4 than without it
 - associated with worse cognitive function

Honolulu Heart Program Study Cont.

- Perhaps the link between DM, AD, and ApoE4 is due to an increased risk of cerebral amyloid angiopathy formation
 - cerebral amyloid angiopathy= Amyloid protein builds up in arteries of brain



Potential Biological Mechanisms

Cardiovascular Risk Factors

1) In Type 2 DM

- a) obesity, insulin resistance, atherogenic dyslipidemia, hypertension, proinflammatory states
 - i) clustering of these risk factors accelerates stroke, small vessel disease, and subsequent vascular dementia
 - (1) increasing exposure to hyperglycemia → ruins capillaries → decreases oxygen supply to brain → physical damage of artery → vascular dementia

Cardiovascular Risk Factors Cont.

2) Standard strategies of risk reduction among the elderly are not effective in treating dementia

a) anti-hypertension meds, anti-platelet therapy, and statin treatment

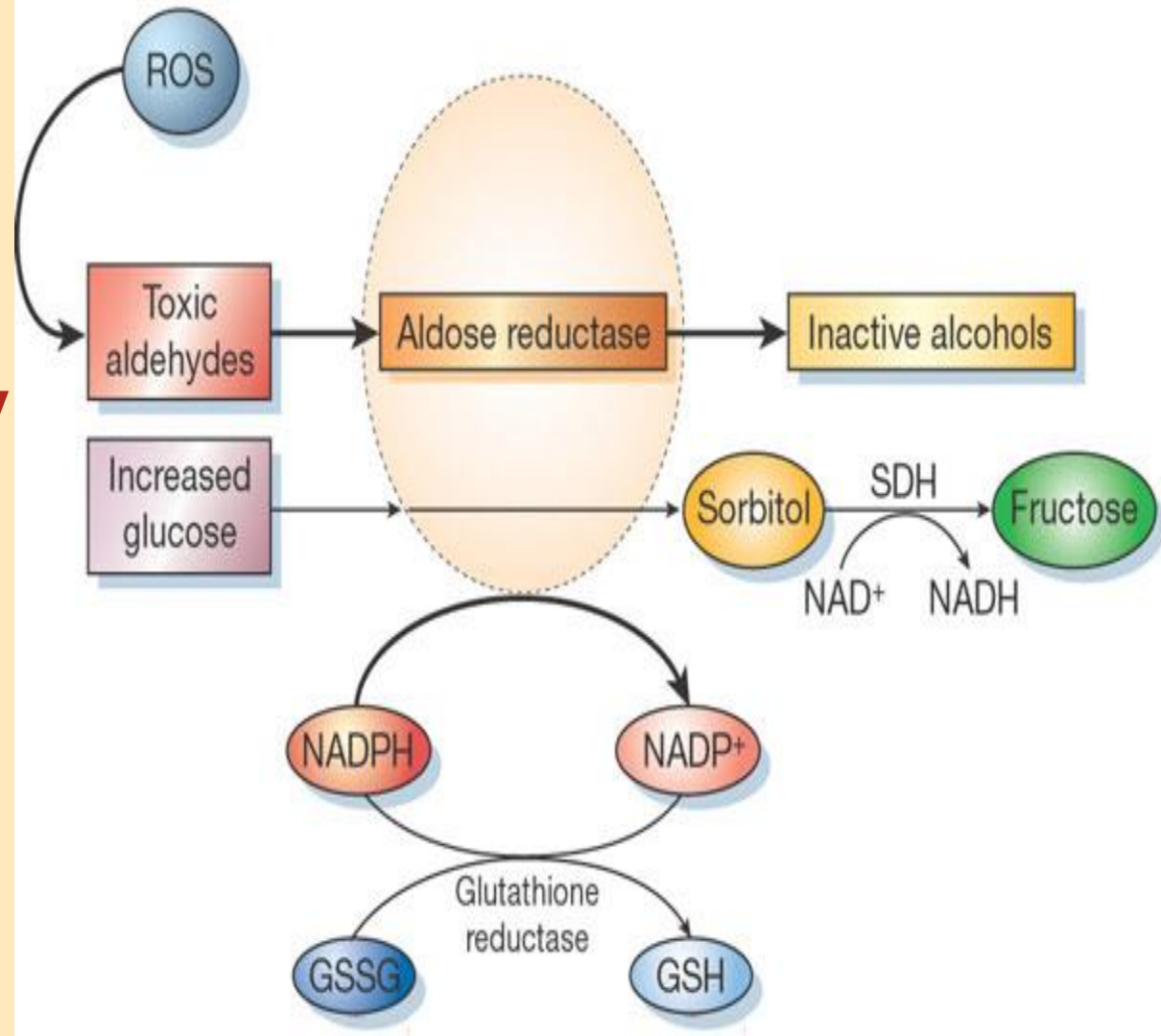
i) suggests that that maybe there's more to cardiovascular diseases than just cardiovascular agents

Glucose Toxicity

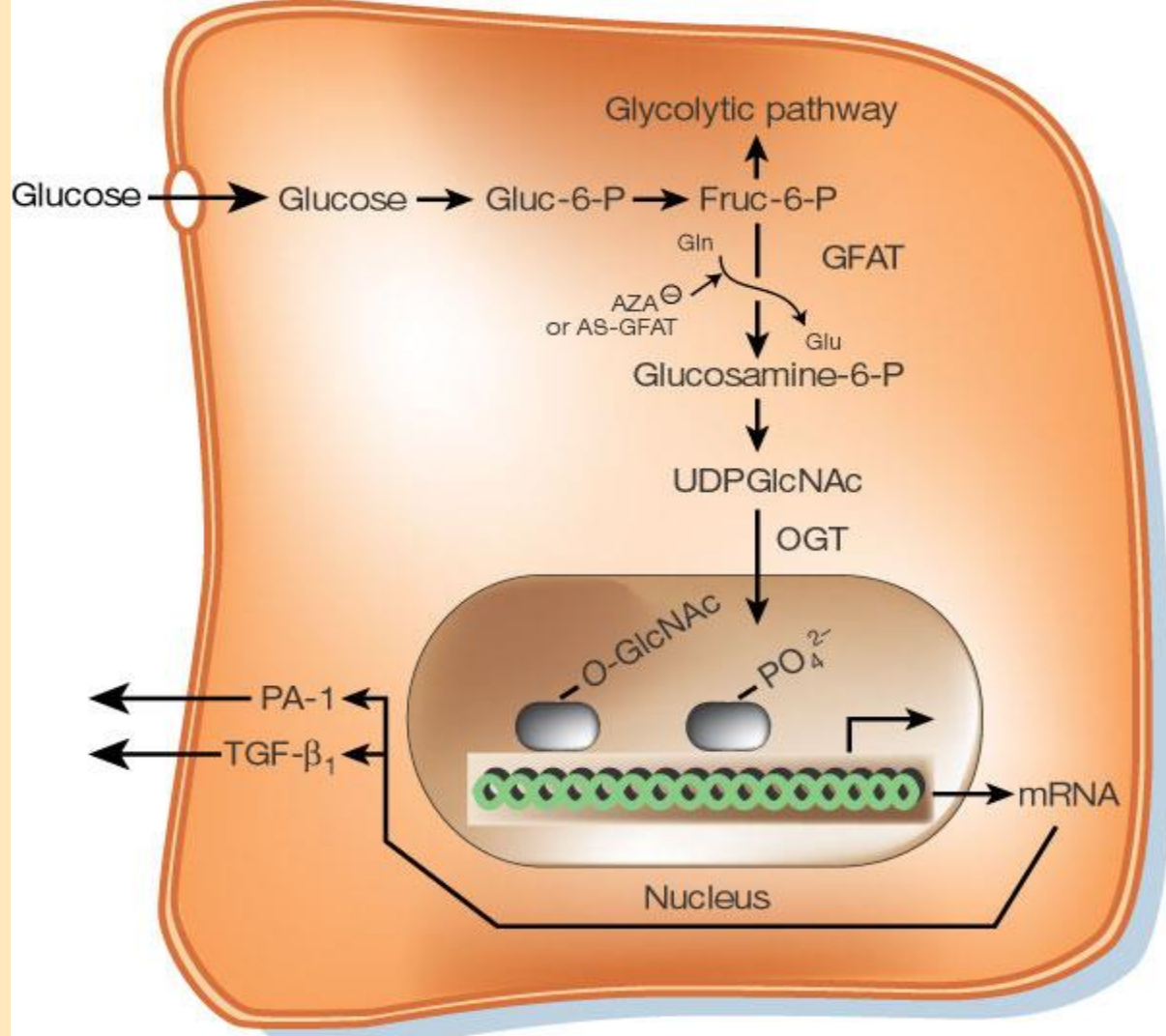
1) Mediated By:

- a) increase flux of glucose through the polyol and hexosamine pathway
- b) an increased production of oxidative stress
- c) accumulation of advanced glycation end-products (AGEs)
 - i) proteins or lipids that become glycated after exposure to sugars
 - ii) prevalent in the diabetic vasculature
 - (1) believed to play causal role in blood vessel complications in DM
 - iii) believed to speed up oxidative damage to cells

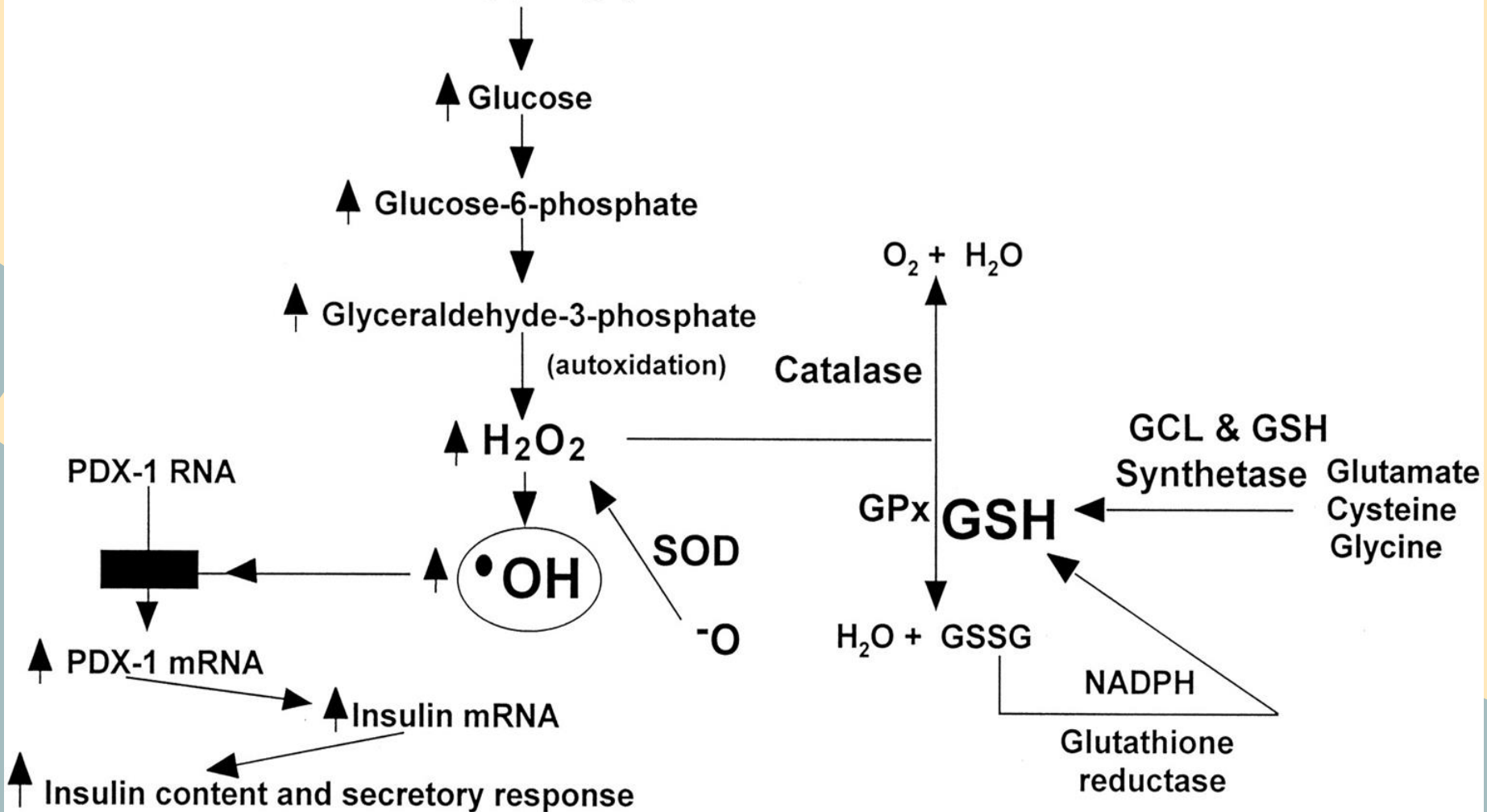
Hyperglycemia Increases Flux Through Polyol Pathway



Hyperglycemia Increases Flux Through Hexosamine Pathway



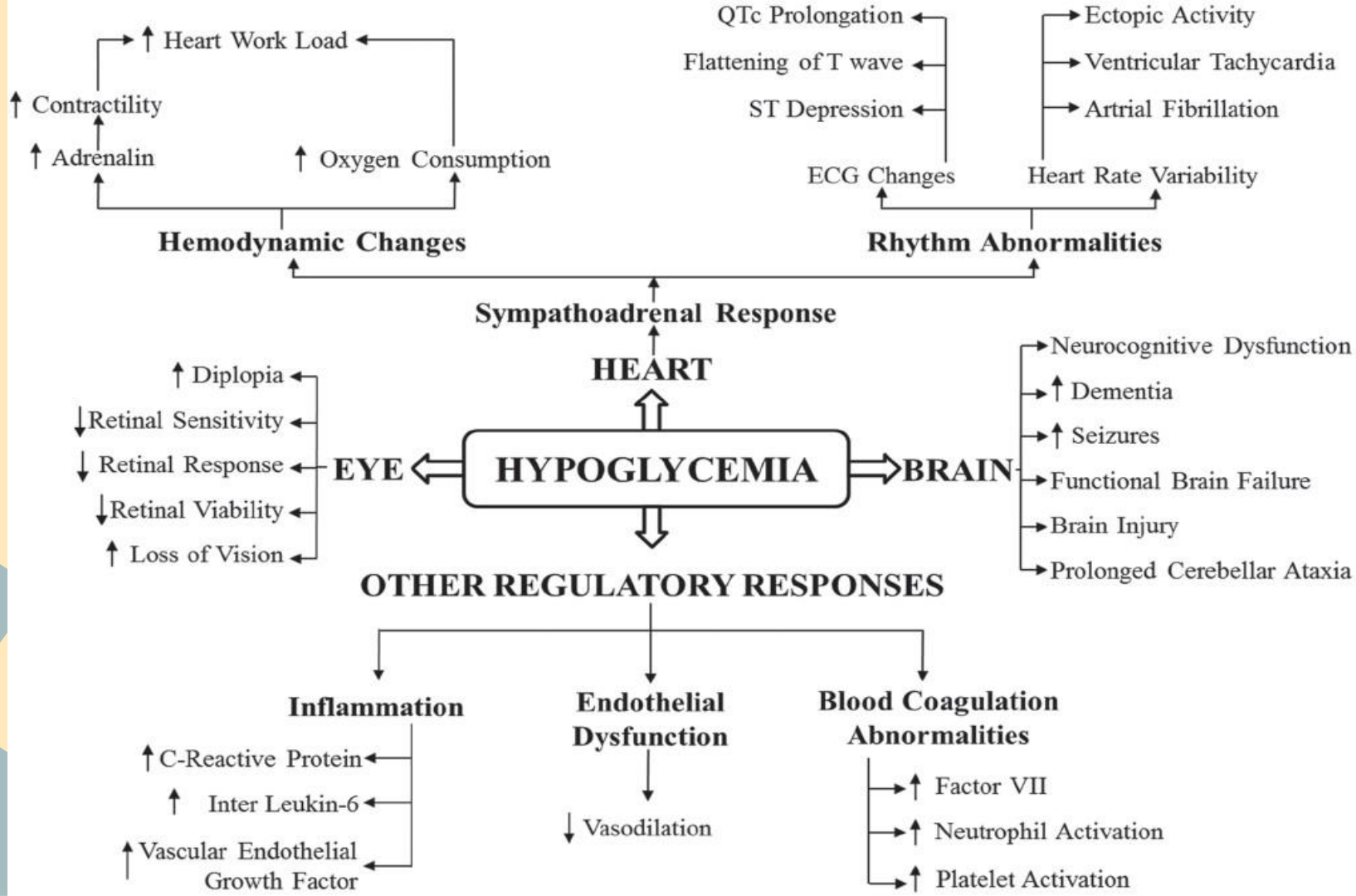
Chronic Hyperglycemia



Hypoglycemia

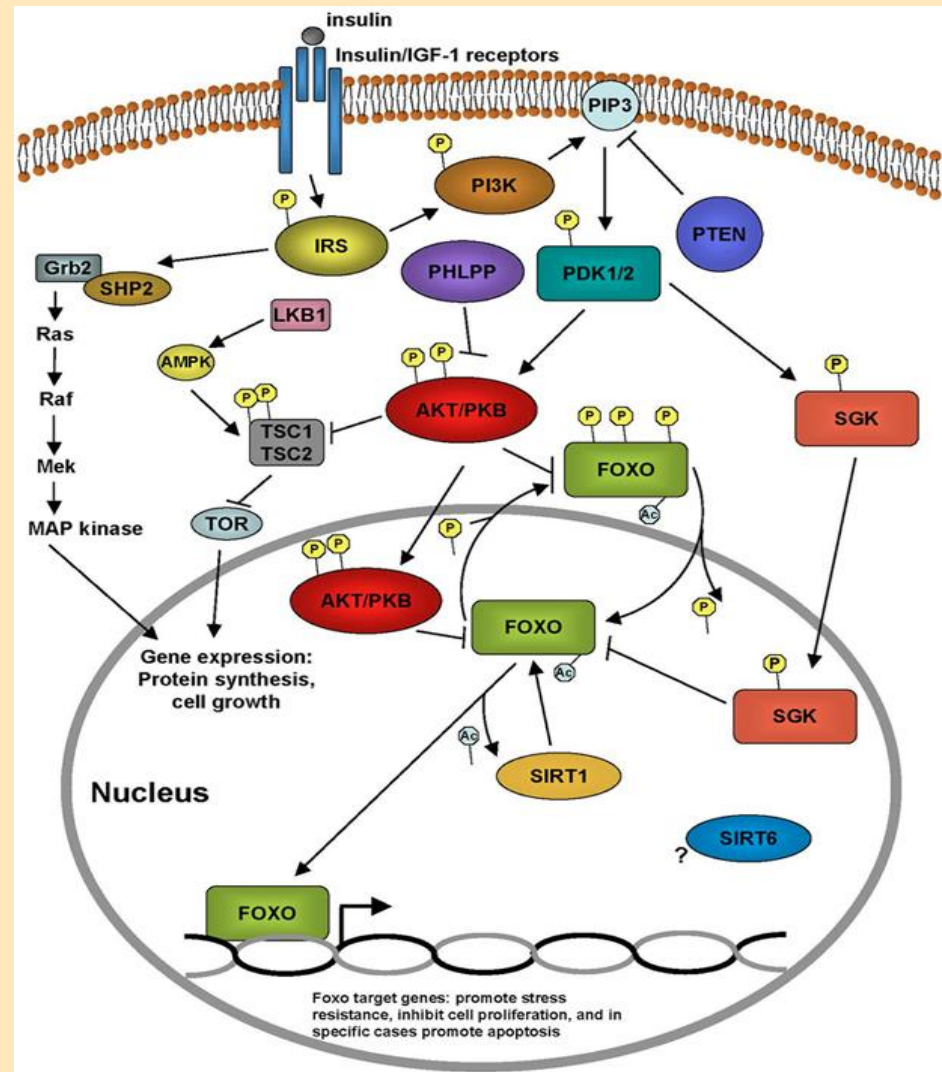
1) In Type 2 Diabetes Patients

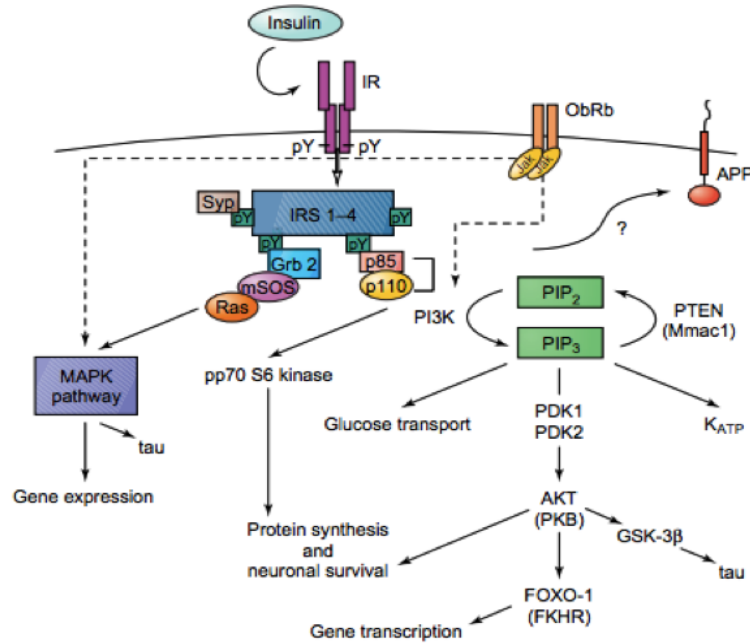
- a) 1.5-2.0 times greater risk of the development or deterioration of cognitive impairment
- b) can induce permanent neurologic sequelae:
 - i) neuronal cell death
 - ii) increase in platelet aggregation and fibrinogen formation
- c) could cause neurological changes that render older patients more susceptible to dementia



Changes (Disruption) in Insulin Sensitivity

- 1) Insulin Resistance + Hyperinsulinemia
 - a) typical of early type 2 DM
 - b) impaired cognitive function
- 2) Insulin and Insulin Receptors
 - a) important roles in cognitive performance via modification of activities of excitatory and inhibitory postsynaptic receptors and activation of specific signaling pathways →





TRENDS in Endocrinology & Metabolism

Insulin receptor signal transduction with respect to neuronal function:
 Insulin binds to and activates the insulin receptor (IR). The receptor undergoes a conformational change resulting in the phosphorylation of intracellular insulin receptor substrate (IRS) proteins on tyrosine residues.

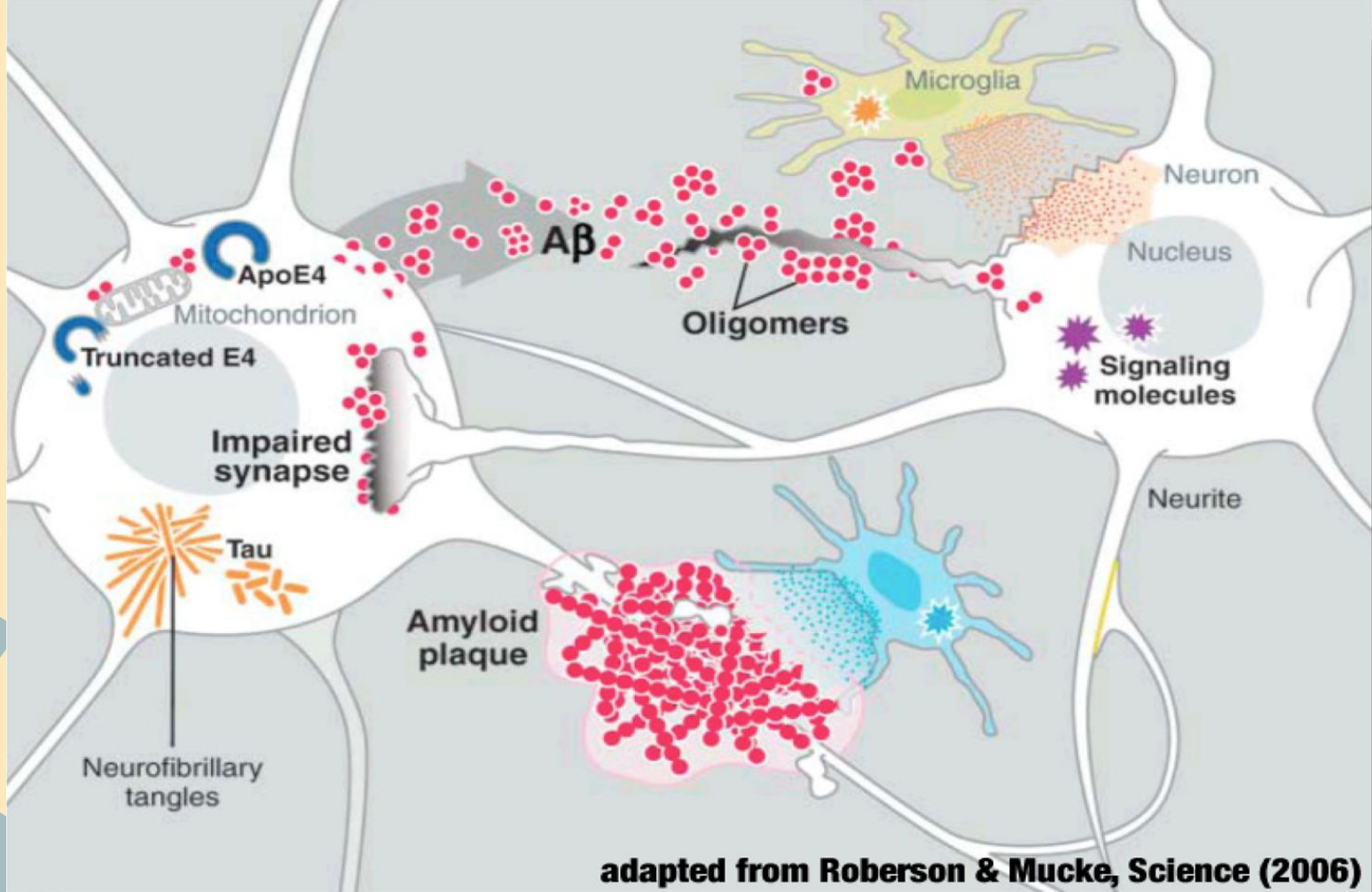
Changes (Disruption) in Insulin Sensitivity

3) AD Patients

- a) lower insulin levels in cerebrospinal fluid (CSF)
- b) higher plasma insulin levels
- c) drastically reduced densities of insulin receptor in the brain

4) Amyloid Beta ($A\beta$) Protein

- a) Higher levels of plasma insulin → limit degradation of $A\beta$ protein (via direct competition for the insulin-degrading enzyme) → amyloid accumulation
- b) lower insulin levels in CSF + impaired response to insulin and insulin-like growth factor-1 → inhibit the transportation of $A\beta$ carrier proteins (albumin and transthyretin) → decrease the clearance of $A\beta$ protein



adapted from Roberson & Mucke, Science (2006)

Inflammation

1) DM Patients

- a) type 2 have higher levels of circulating inflammatory markers.
- b) Elevated circulating levels of inflammatory markers were associated with worse cognitive ability

2) AD patients

- a) increase levels of: interleukin-1, interleukin-6, tumor necrosis factor - α
- b) Macrophage inflammatory protein-1 α in reactive astrocytes nearby $A\beta$ plaques in the brain

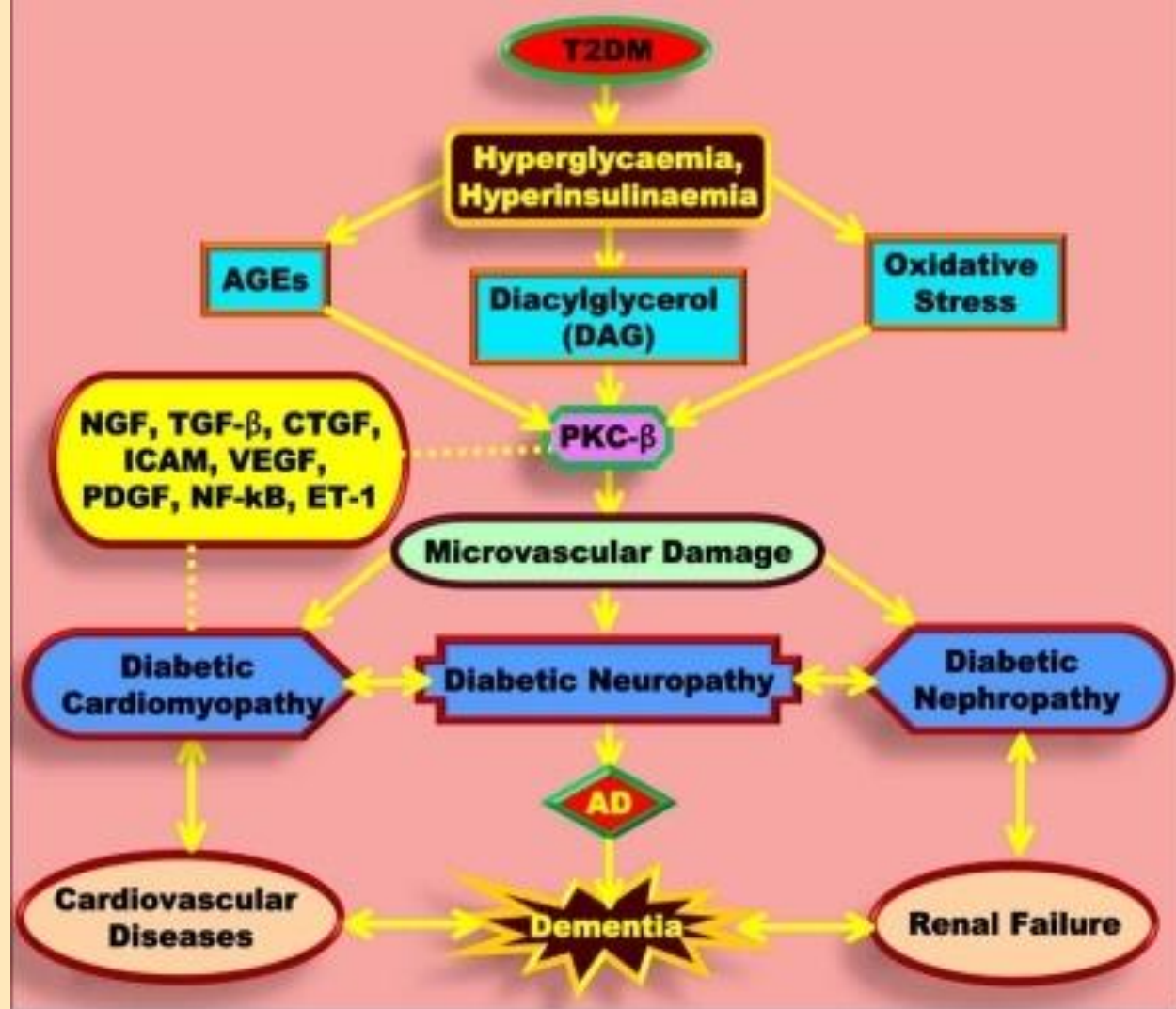
3) Dementia patients

- a) Evidence of activated inflammatory response of microglial cells

Conclusions

- 1) Diabetes mellitus is a significant risk factor for vascular dementia and Alzheimer's disease.
- 2) Good control of cardiovascular risk factors could be expected to reduce the risk of dementia
- 3) Chronic hyperglycemia may cause cognitive impairments and abnormalities in synaptic plasticity.
- 4) Hypoglycemia is a risk factor for cognitive impairments
- 5) Prolonged hyperinsulinemia induces an impaired response to insulin through a decreased expression of insulin receptors at the blood brain barrier and brain and consequently inhibits the insulin transportation into CSF and brain tissues → $A\beta$ protein build up
- 6) Chronic inflammation may play a role in accelerated cognitive impairment.

Conclusions



THANK
YOU

