Healthy Aging and ADRD ECHO

Elizabeth Disbrow PhD

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Improving Brain Health Through Diet and Exercise

Speaker

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Disclosure

In the past 24 months, I have not had any financial relationships with any ineligible companies.

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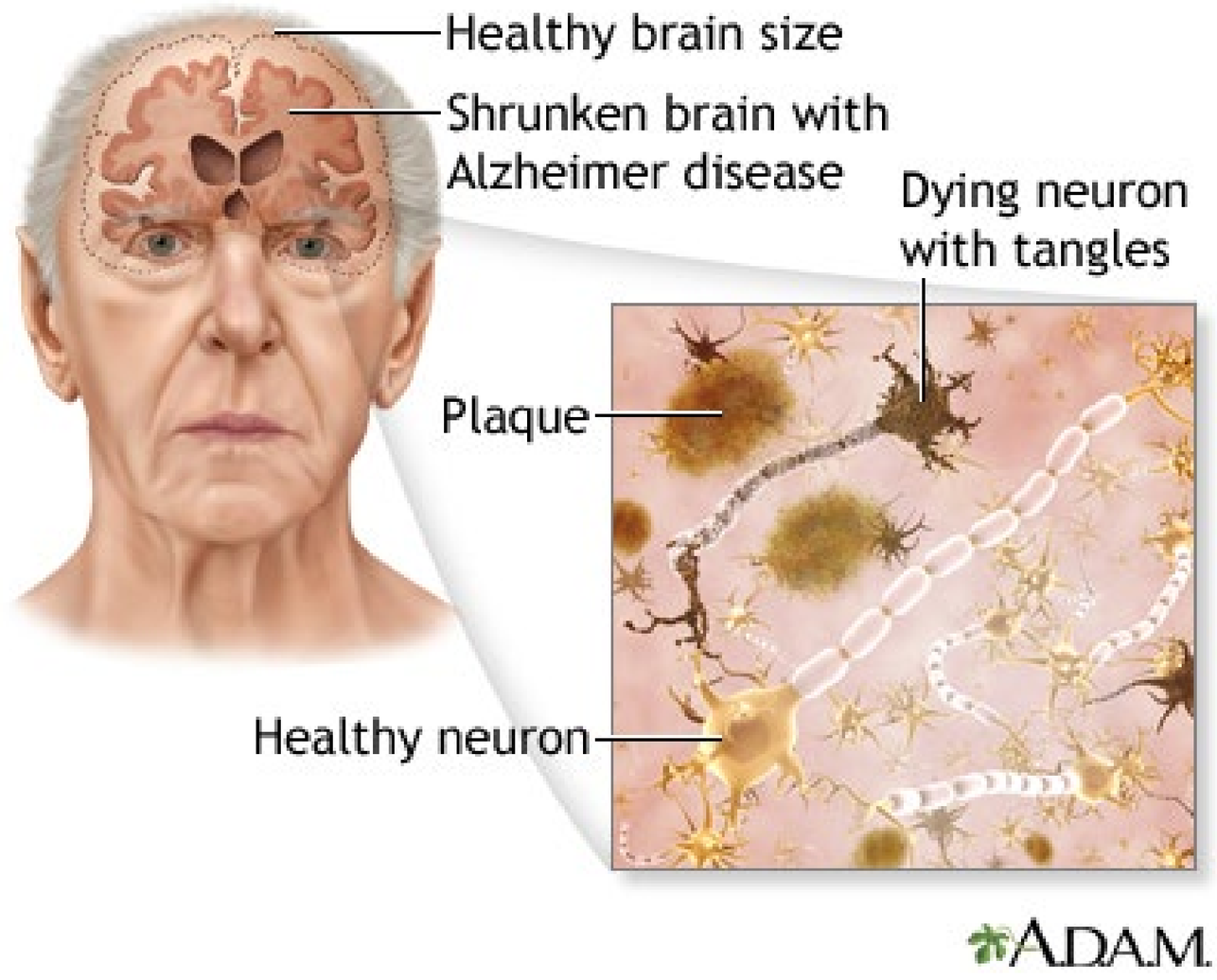
Objectives

Discuss the link between disease mechanisms and diet and exercise

- **Beta Amyloid**
- **Neuroinflammation**
- **Mitochondrial Function**
- **Cardiovascular Function**

PLAQUES & TANGLES



THEORIES OF DISEASE MECHANISM

Neuroinflammation

Activated Microglia

↓

Release of cytokines/chemokines/ROS

↓

Cell Death

↓

Release of neurotoxins

↓

AD

Extended from de la Torre (2004)

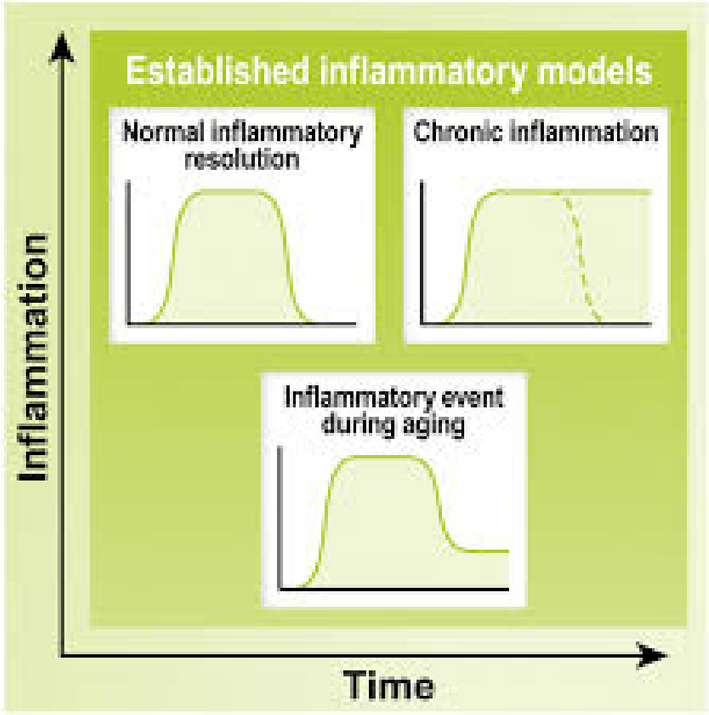
Neuroinflammation

Neuroinflammation is characterized by activation of microglia, the brain's resident immune cells

The **brain's innate immune system is triggered following a challenge** such as injury, infection, exposure to a toxin, neurodegenerative disease, or aging.

This inflammation is mediated by the production of cytokines, chemokines, reactive oxygen species, and secondary messengers.

The accumulation of amyloid fibrils causes tissue **damage** and elicits immune cell infiltration into tissue and proinflammatory cytokine production.



Newcombe et al., 2018

Exercise and Neuroinflammation

Exercise maintains homeostasis of the brain and **prevents brain pathology** by modulating the activation of glia, pro-inflammatory cytokines, and neuroinflammation, thereby preventing neurodegenerative diseases such as AD, PD, ALS, and MS.

As little as 20 minutes of exercise could have anti-inflammatory effects.

Evidence That Diet Influences Neuroinflammation

Nutritional patterns can modulate inflammatory signaling in the brain through effects on the gut microbiome, immune system, and microglial activation.

- Diets high in saturated fats, refined carbohydrates, and ultra-processed foods are associated with increased systemic inflammation, which can promote inflammatory signaling in the central nervous system.
- Animal and human studies suggest that dietary factors influence the gut-brain axis, altering production of inflammatory mediators and affecting blood-brain barrier integrity.
- Emerging evidence indicates that dietary interventions may reduce neuroinflammatory biomarkers and support cognitive health (i.e. Mediterranean, MIND, DASH).

Take-home message: The relationship between diet and neuroinflammation is biologically plausible and supported by growing mechanistic and epidemiologic evidence.

Oral Health & Neuroinflammation

Bacteria that cause gum disease are also associated with the development of Alzheimer's disease and related dementias, especially vascular dementia.

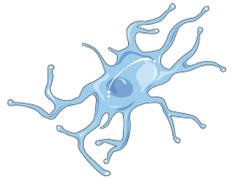
Gum disease is caused by infection of oral tissue. Bacteria and inflammatory molecules they make can travel through the bloodstream from the mouth to the brain.

Gum disease, mouth infections and antibodies to the bacteria *Porphyromonas gingivalis*, the most common cause of gum disease, were associated with greater risk of dementia and death.

P. gingivalis, is also associated with increased βA plaque production.

THEORIES OF DISEASE MECHANISM

Neuroinflammation



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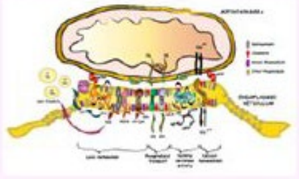
MAM hypothesis



Altered lipid raft formation

↓

Altered Ca^{2+} homeostasis

↓

Altered APP/tau processing

↓

Plaques / Tangles / Lipid droplets

↓

Neurodegeneration

↓

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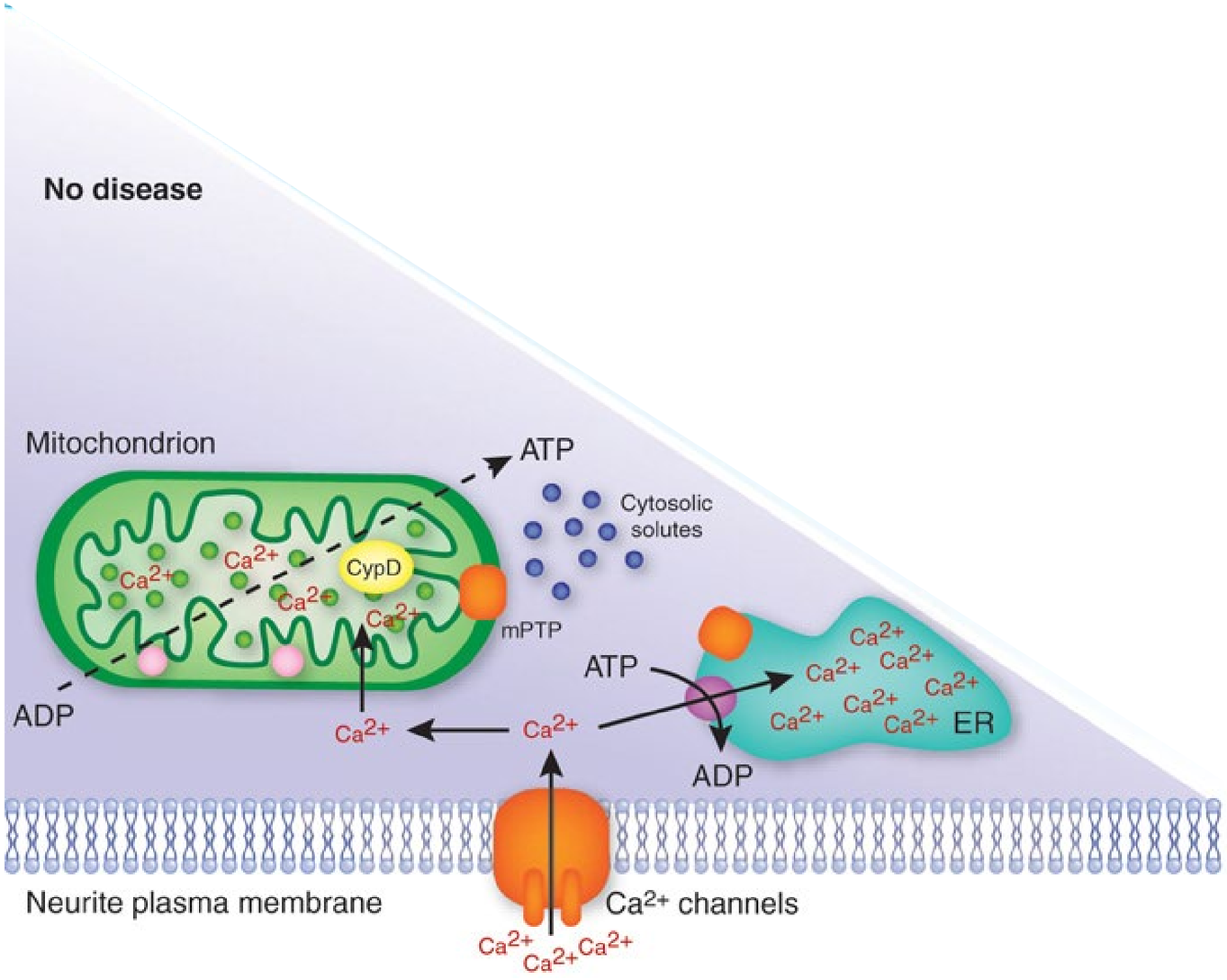
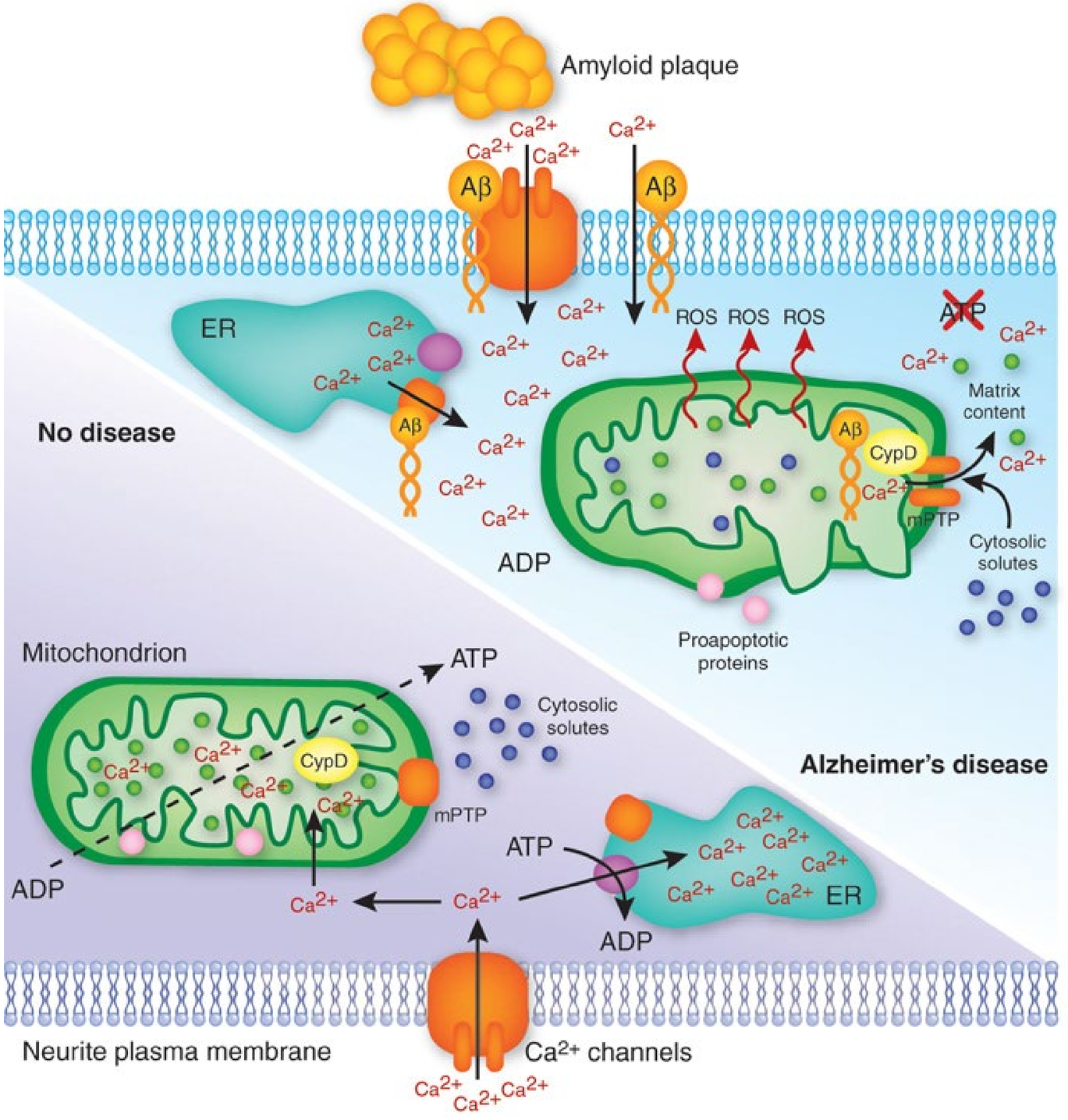
Mitochondrial Associated Membrane Hypothesis




Amyloid plaque
Aβ
Aβ
Ca2+
ER
No disease
ROS ROS ROS
ATP
Matrix content
CypD
mPTP
ADP
Cytosolic solutes
Proapoptotic proteins
Mitochondrion
ATP
Cytosolic solutes
Alzheimer's disease
ADP
ATP
ER
ADP
Neurite plasma membrane
Ca2+ channels

Exercise & Mitochondrial Function

- Exercise improves mitochondrial energetics not only in skeletal muscle but also in other tissues like neurons.

- Exercise is associated with improved memory, neurogenesis, synaptic plasticity and mitochondrial biogenesis in the brain.

Sarcopenia is Linked to Dementia

- Sarcopenia is the loss of muscle tissue associated with normal aging

- Dementia and sarcopenia may be linked
  - Weak grip strength and reduced muscle mass are common in dementia (Shin et al. 2011)
  - Loss of muscle mass may be associated with loss of brain cells (Burns et al., 2010)
  - Also associated with cognitive decline (Boyle et al., 2009; Moon et al., 2019; Ohta et al., 2019)
  - Inactive lifestyle is associated with sarcopenia and decreased brain volume (Halloway et al., 2019)

Sarcopenia is Linked to Dementia

- Exercise can slow sarcopenia and dementia
  - Significant changes in muscle mass and cognitive function have been observed after 6 months of moderate exercise (Pereira et al. 2007)
  - Resistance training only once per week can reduce cognitive decline and improve muscle strength (Ambrose et al., 2009; Taaffe et al., 1999)

- The mechanism is unclear, but exercise may address shared pathways

  - Exercise improves mitochondrial quality and function by stimulating turnover (Safdar et al., 2011; Cartee et al., 2016; Joseph et al., 2016).
  - Exercise improves mitochondrial ATP synthesis (Han and Kim, 2013; Yoo et al., 2019)

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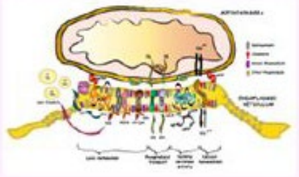

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Neurodegeneration

↓

AD

Vascular hypothesis

Advanced ageing and vascular risk factor

↓

Brain hypoperfusion

↓

Neuroglial energy crisis

↓

Mild cognitive impairment

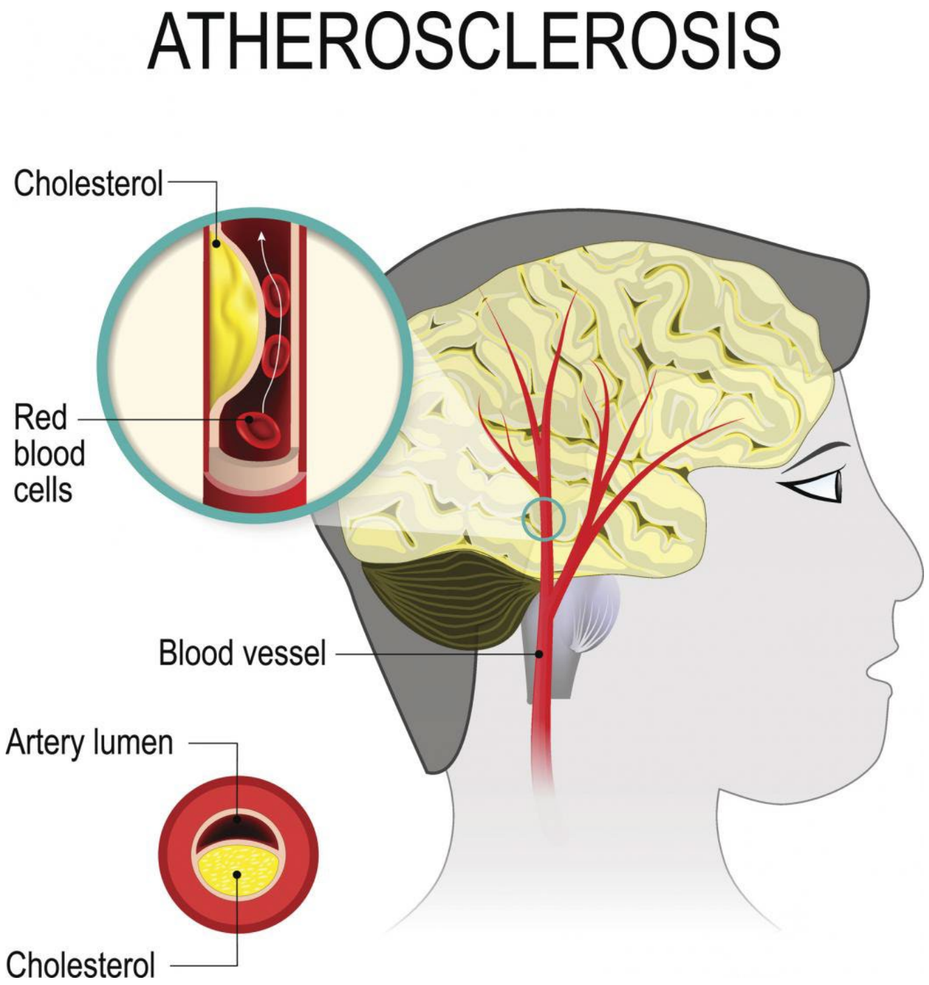
↓

Neurodegeneration

↓

AD

Extended from de la Torre (2004)



VASCULAR DYSREGULATION HYPOTHESIS

Imbalance between blood flow-based substrate delivery and brain energy requirements intensify common cardiovascular risks for dementia

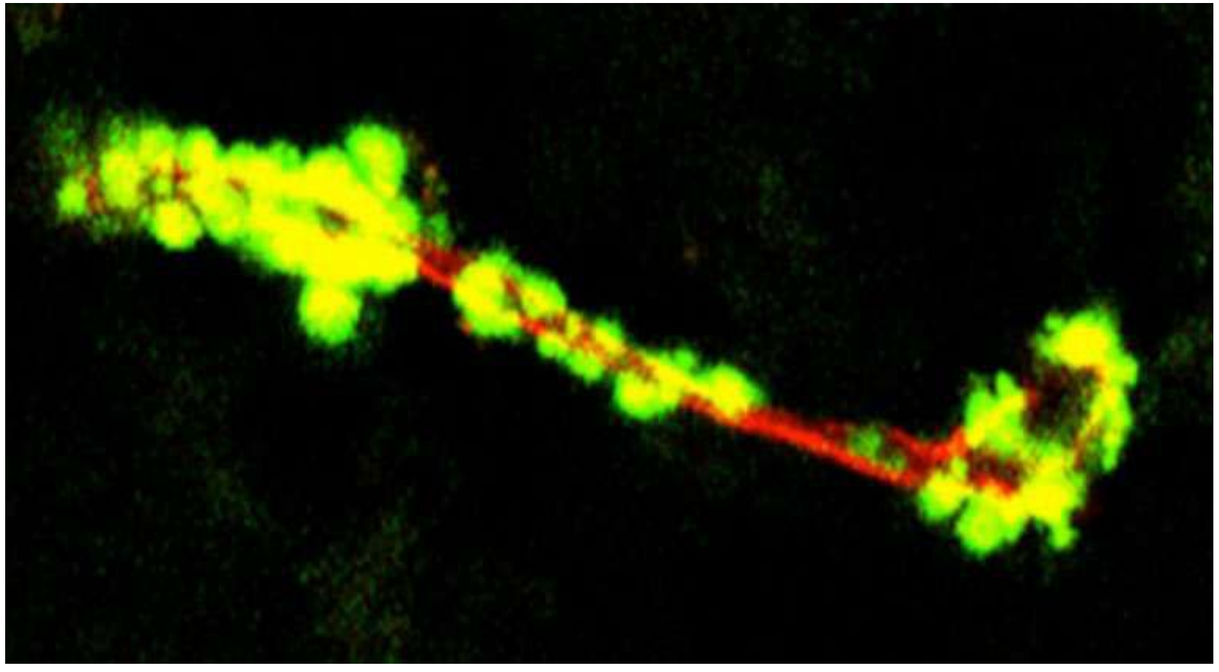
- Hypertension
- Cerebrovascular Disease
- Sedentary lifestyle

People who have had a stroke have a far greater risk of developing dementia than people who have not had a stroke.

THE LINK BETWEEN HEART & BRAIN HEALTH

- Longitudinal data indicates that persons with a history of high blood pressure or cholesterol are twice as likely to get Alzheimer's disease. Those with both are four times as likely to become demented.
- Heart disease risk factors in midlife such as diabetes, elevated blood pressure, and smoking cigarettes—are associated with an increased risk for dementia.
- If cerebrovascular disease is present, it takes fewer plaques and tangles to produce the same degree of dementia.

Brain Blood Vessel Amyloid

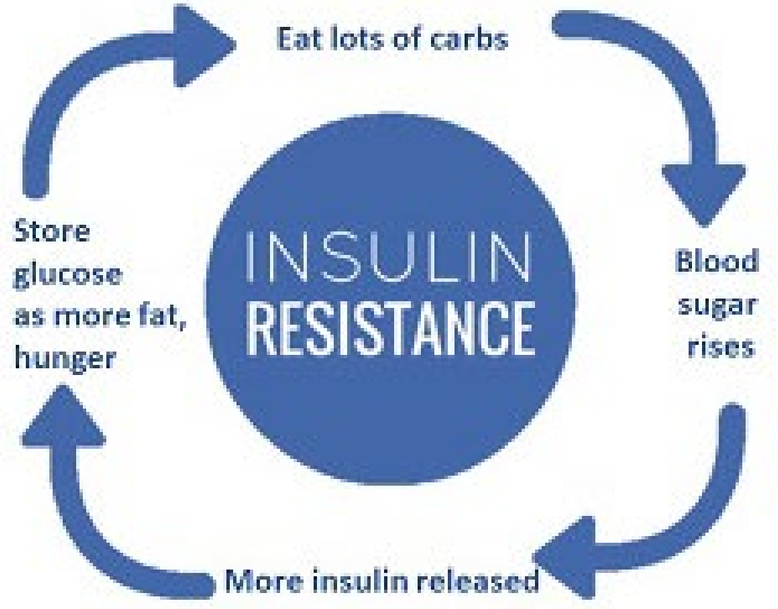


Brain blood vessel amyloid could promote different pathological responses, i.e., inflammation, which likely contributes differently to cognitive impairment and dementia than neuron amyloid.

DIABETES & AD

- Diabetes may increase risk of AD by:
  1) directly influencing the underlying Alzheimer's disease process through the interactions of insulin and beta-amyloid
  2) exacerbating diabetic microvascular disease, which affects the finer blood vessels in the body.

- Diabetes may result in:
  Abnormal vascular insulin exchange in the brain
  Oxidative stress
  Inhibition of beta amyloid degradation

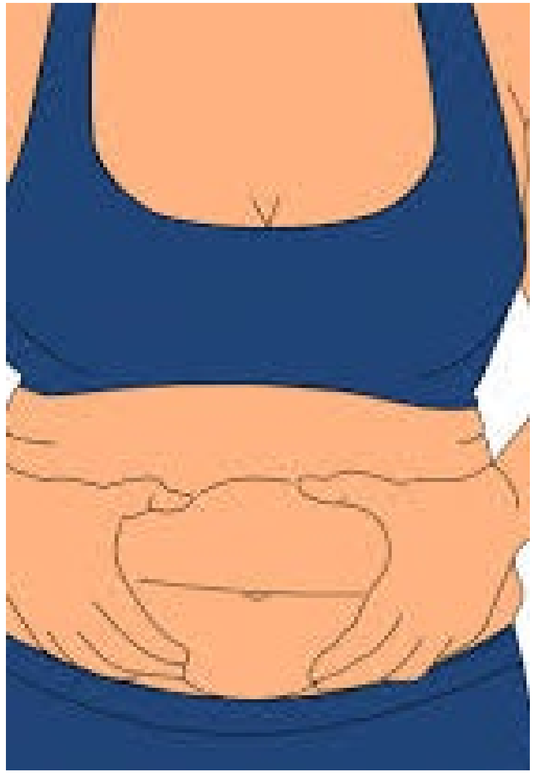


DIABETES & AD?

- Central insulin receptors are clustered in learning and memory areas of the brain (hippocampus, frontal cortex)

- Accumulation of beta amyloid interferes with insulin mediated neuron growth, synapse formation and neurotransmitter production

Obesity & Dementia



- Obesity in middle age (40-60 yo) is linked to increased risk of Alzheimer's disease
- Belly fat, rather than body mass index (BMI), provides a more important indication that weight loss may help to prevent dementia because central fat is an inflammatory tissue.
- Metabolic syndrome, which includes obesity, high blood pressure, high blood cholesterol, and diabetes, confers increased risk of AD. Metabolic syndrome has become increasingly common and now affects an estimated 47 million adults in the United States.

Sleep Disturbance & Dementia

Obstructive Sleep Apnea results in intermittent decreased oxygen caused by the collapse of airways at night.

OSA is linked to increased neuroinflammation, vascular disease, Amyloid burden as well as impaired mitochondrial function.

Positive airway pressure therapy and adherence lowered the incidence of Alzheimer's disease and dementia not otherwise specified (53,000 Medicare Beneficiaries). There was also a trend for reduction of mild cognitive impairment.

Resource Links

Exercise and Neuroinflammation in Health and Disease - NCBI
https://www.ncbi.nlm.nih.gov › articles › PMC6905205

Mitochondrial function - Exp Gerontol. 2017 Apr; 90: 1–13.
Published online 2017 Jan 18. doi: 10.1016/j.exger.2017.01.013

Vascular Health - ninds.nih.gov/current-research/focus-disorders/alzheimers-disease-and-related-dementias/focus-vascular-contributions-cognitive-impairment-and-dementia-vcid

Questions?

THANK YOU

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LOUISIANA DEPARTMENT OF HEALTH