무엇을 먹지 말아야 할까?

오 지 영
건국의대 신경과

What You should not eat for Your Brain

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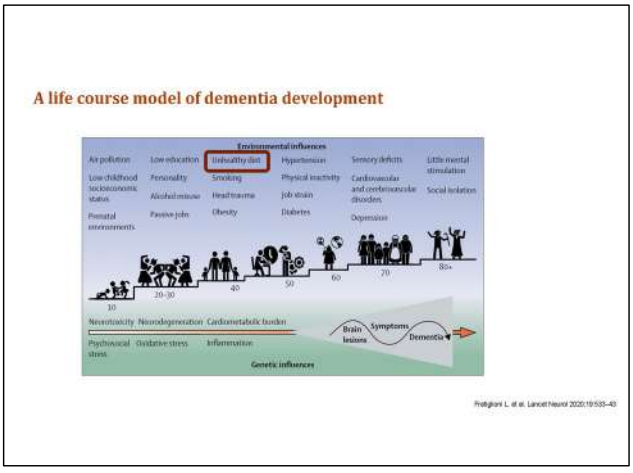
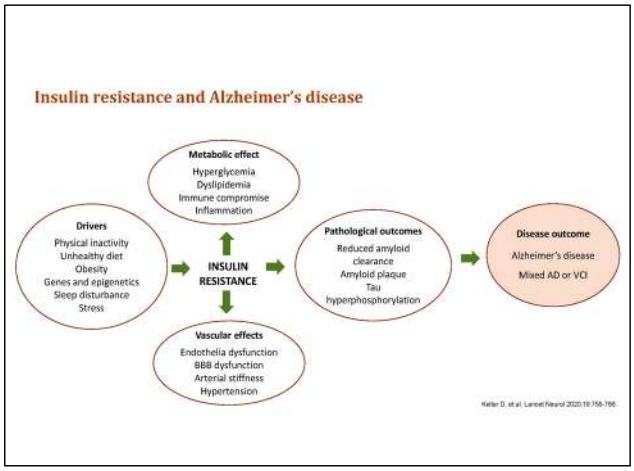
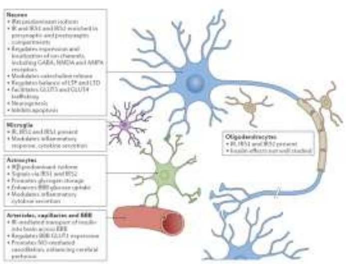




Insulin effects in major cell types of the brain

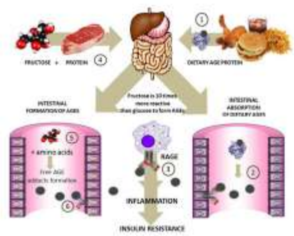


Considerable overlap in the risk factors, comorbidities and putative pathophysiological mechanisms of Alzheimer's disease and related dementias (ADRSs) and T2DM

Brain insulin resistance

Arnold SE, et al. Nat Rev Neurol 2018;14:168-181

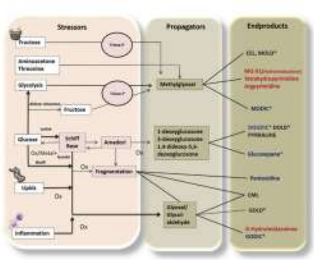
Why AGEs are matter?



- High circulating AGEs levels are associated with insulin resistance.[1]
- AGEs trigger mechanisms eliciting metabolic dysfunction including activation of inflammation, oxidative stress, and impaired mitochondrial oxidative metabolism.[2]
- AGEs directly impact upon the hypothalamic control of energy balance leading to obesity.[2]
- Higher concentration of the circulating AGE is associated with worse cognitive performance in people with and without T2DM.[3]
- Brain is an important target for insulin actions.[4]

[1]Tan KC, et al. Diabetes Metab Res Rev 2011;27:488. [2]Sergi D, et al. Mol Nutr Food Res 2020 (E-pub ahead). [3]Biessels GJ, et al. Lancet Neurol 2020;19:699-710. [4]De Felice FG. J Clin Invest 2013;123:531-539.

Main known AGEs

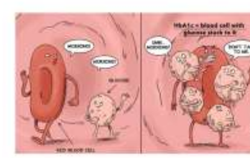


CEL; carboxyethyl lysine
MOLD; Methylglyoxal lysine dimer
MGH1; methylglyoxal-derived hydroimidazolone
MODIC; methylglyoxal dimer imidazolone crosslink
DOGDIC; 3-deoxyglucosone-derived imidazolium crosslink
DOLD; deoxyglucosone lysine dimer
CML; arboxymethyl lysine
GOLD; glyoxal lysine dimer
GODIC; glyoxalderived imidazolium cross-link

Chaudhry J, et al. Cell Metab Rev 2018;8:337-352

Biologically-generated AGEs

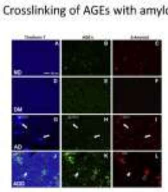
- **Glycated hemoglobin (HbA1c)**
  - Glucose irreversibly attached to hemoglobin at a rate dependent upon the prevailing blood glucose concentration
- **Normal aging process**
  - Long-lived proteins
  - Collagen in the extracellular matrix
  - Crystalins in the eye lens
  - Basement membrane in the kidney
  - Globular albumin into amyloid fibrils

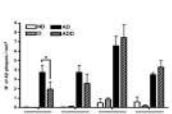


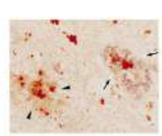
https://aplqure.com/type-2-diabetes/com.medicines.t2diabetes

AGE accumulation is related with AD pathology

- Beta-amyloid is modified by AGEs, and it exacerbates the toxicity of Aβ[1]
- AGEs are present in both neurofibrillatory tangles and senile plaque of the patients with AD[2]
- Receptors for AGE is involved in the transport of amyloid peptide through blood-brain barrier[3]
- Crosslinking of AGEs with amyloid-beta peptide and hyper-phosphorylated tau.[4]



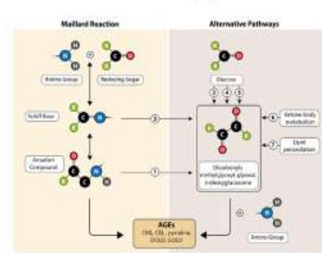




[1]Li XH et al. Cell Death 2013;4:e673. [2]Valente T, et al. Neurobiol Dis 2010;37:67-76. [3]Candela P, et al. J Alzheimers Dis 2010;22:849-859. [4]Sasaki N, et al. Am J Pathol 1998;153:1149-1155.

Exogenous AGEs – by Maillard reaction

Irreversible chemical reaction between reducing sugars and amino acids responsible for the browning of food

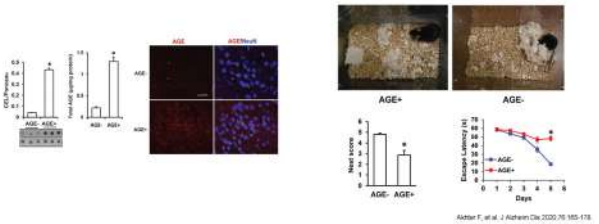


Louis-Camille Maillard

Sergi D, et al. Mol Nutr Food Res 2020 (E-pub ahead)

High dietary AGEs are related with AD

- Dietary AGEs are important source of brain AGE accumulation
- High dietary AGEs impair mitochondrial function and linked to cognitive decline

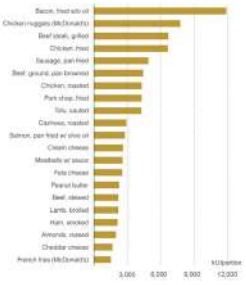


Source of dietary AGEs

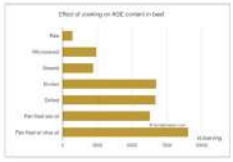
Combination of **refined carbohydrates** and **long-chain saturated fat** is the key.

- Fructose >> glucose (x 7.5)
- Food processing of high temperature for prolonged period of time

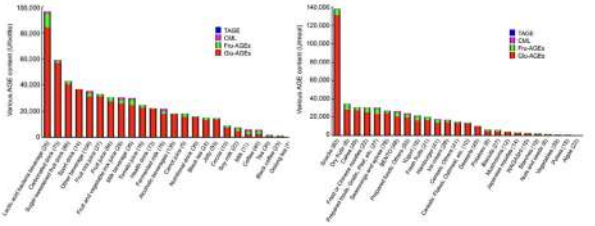
AGEs content in food



- Meats and animal foods are usually the largest dietary AGEs sources, followed by nuts and cheeses.
- Among meats, beef is the highest in AGEs, followed by pork, chicken, and seafood.



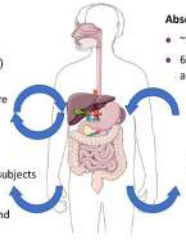
Average total AGEs in beverage and food



The fate of consumed AGEs

Circulation in the blood stream

- Up to 2/3 consumed AGEs: free (?), protein-bound (?) or metabolized (?)
- In DM patients higher AGE half-lifes depending on severity of renal failure



Absorption

- ~30% of consumed AGEs
- 60-80% of consumed pyrraline and pentosidine

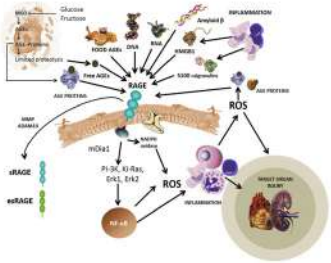
Urinary excretion

- 1/3 of consumed AGEs in healthy subjects
- <5% in DM patients
- 60% of free vs. 2% of peptide-bound pentosidine

Fecal excretion

- ?% excretion of unabsorbed AGEs
- ?% microbial degradation and metabolism

RAGE signal is a key pathway for inflammation

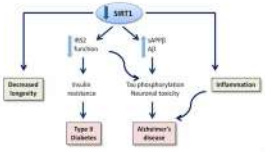


RAGE (receptor for AGE)

- Immunoglobulin superfamily of pattern recognition receptors
- mRAGE
  - ✓ Surface receptor
  - ✓ Present in the peripheral immune cells, mimcroglia, endothelial cells, and neurons
  - ✓ Transport beta-amyloid into neurons
- sRAGE, esRAGE
  - ✓ No capacity to elicit intracellular signal transduction

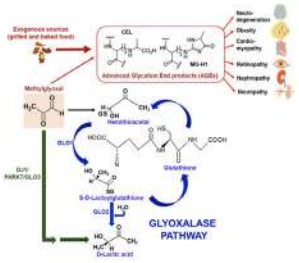
AGE also binds to other receptors

- Role of AGE homeostasis
- **AGER1**
  - ✓ Upregulated by AGE and increase uptake and removal of AGE
  - ✓ Counteract AGE-induced oxidative stress
  - ✓ Inhibit the activation of NF-κB by promoting a sirtuin 1-dependent deacetylation and suppression of NF-κB
- High level of AGEs damage the protective mechanism leading to a downregulation of both AGER1 and sirtuin 1



Lovestone S, et al. PNAS 2014;111:4703-4704

Detoxification of AGEs is possible, but

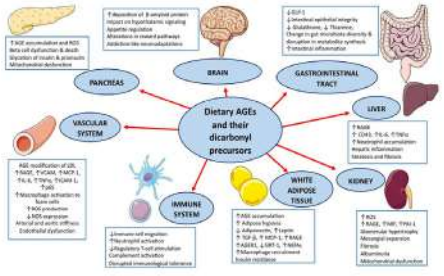


Glyoxalase pathway

- Convert glyoxal and methylglyoxal to lactic acid and glycolic acid
- Pivotal role in maintaining dicarbonyl homeostasis and preventing the formation of AGEs.
- Upregulated in the patients with DM
- Scavenging capacity is overridden by an increase in dicarbonyl formation.

Chaudry J, et al. Cell Metab Rev 2018;8:557-562

AGEs irreversibly accumulate in the body

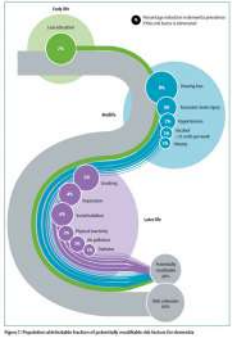


What and Why we should not eat for our brain?

Alcohol

What is a unit of alcohol?

The Lancet Commissions



Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

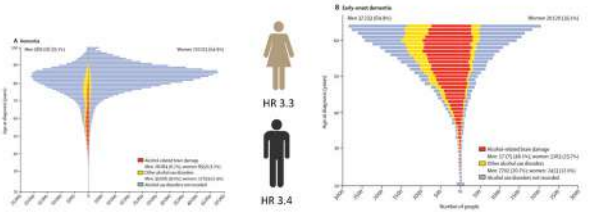
***NEW* modifiable risk factors for dementia**

- Excessive alcohol consumption
- Head injury
- Air pollution

Livingston G, et al. Lancet 2020;396:413-446

Heavy drinking is associated with dementia

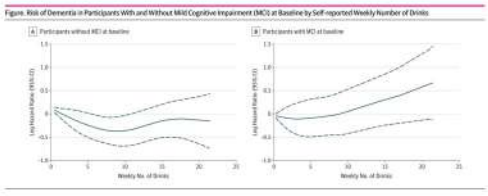
A nationwide retrospective cohort of all adult (≥20 years) patients admitted to hospital in metropolitan France between 2008 and 2013 (n=31,624,156).



Schwarzinger M. et al. Lancet Public Health 2018;3:e124-132.

Drinking pattern is also important

Prospective cohort study of 3069 participants enrolled in the Ginkgo Evaluation of Memory Study (GEMS)



N=2,548

Koch M. et al. JAMA Netw Open 2019;4:e1910019.

1-14 unit per week is safe

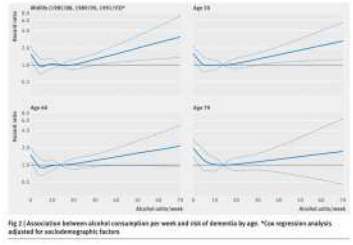


Fig 2 | Association between alcohol consumption per week and risk of dementia by age. *Cox regression analysis adjusted for sociodemographic factors

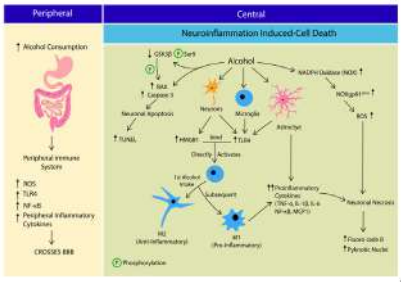
Whitehall II cohort study

9,087 participants aged 35-55 years at study inception with 23 year follow-up

- Abstinence in midlife was associated with a higher risk of dementia (HR 1.47, 95% CI 1.15 to 1.89) compared with consumption of 1-14 units/week.
- Among those drinking >14 units/week, a 7 unit increase in alcohol consumption was associated with a 17% (95% CI 4% to 32%) increase in risk of dementia.

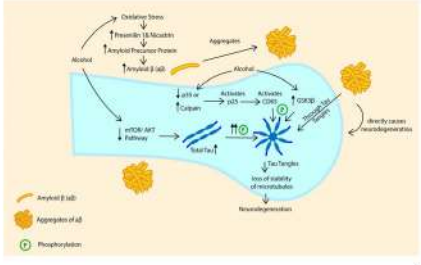
Sabia S. et al. BMJ 2018;362:k2927.

Neuroimmune signaling plays a key role



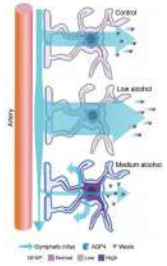
Kamal H. et al. Front Cell Neurosci. 2020;14:282.

Potential association between alcohol and AD

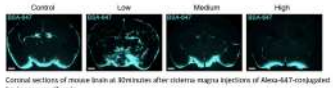


Kamal H. et al. Front Cell Neurosci. 2020;14:282.

Why low chronic dose of alcohol is protective?



- Increase in glymphatic function combined with the reduction of glial fibrillary acidic protein expression.[1]
- Synapse damage induced by amyloid-β and α-synuclein may be counteracted by low concentration of alcohol in animal model.[2]



Coronal sections of mouse brain at 30minutes after cisterna magna injections of Alexa-647-conjugated bovine serum albumin

[1]Lundgaard I. et al. Sci Rep 2015;5:2246. [2]Bate C. et al. Neuropharmacol 2011;61:1406-1412.

Benefits from red wine for prevention of AD

Resverastol

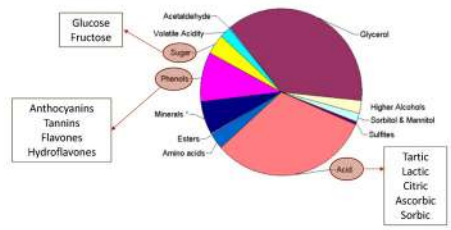
- Protection against ethanol-induced neurotoxicity
- Interruption of the amyloid cascade acting as an antioxidant and anti-inflammatory agent
- Activation of sirtuin-1

Quercetin

- Reduces low-density lipoprotein, IL-1β, and CRP
- Increase the resistance of neuron to oxidative stress and excitotoxicity
- Inhibits Aβ toxicity
- Sirtuin-1 agonist

Reale M, et al. Nutrient 2020;12:206

But, wine is alcohol



Reale M, et al. Nutrient 2020;12:206

Non-modifiable protective factors

- Genetics (i.e. *APOE ε2*)

Modifiable protective factors

- Educational attainment
- Mediterranean diet
- Moderate alcohol intake (?)
- Physical exercise
- Intellectual and social activities

Non-modifiable risk factors

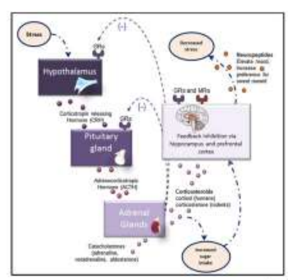
- Genetics (i.e. *APOE ε4*)
- Aging

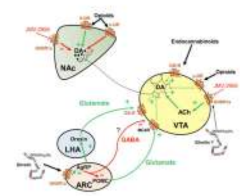
Modifiable risk factors

- Hypertension
- Diabetes mellitus
- Obesity
- **Western style diet**
- **Excessive alcohol consumption**
- Smoking

Serrano-Pozo A, et al. J Alzheim Dis 2018;67:795-819.

Sugar addiction





Jacques A et al. Neurosci Biobehav Rev 2019;103:178-199. Masaadi OA, et al. Neuropharmacol 2019;148:131-138.