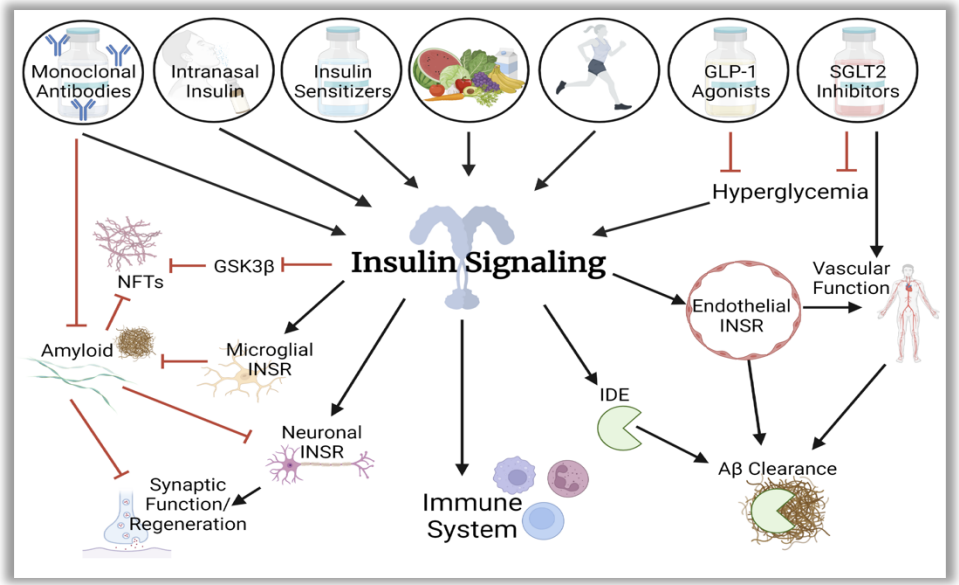
Insulin dysregulation and chronic conditions of aging: Implications for treatment of AD and ADRD



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Disclosures

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- Alzheimer's Association Part the Cloud program (Aptar Pharamaceutical provided intranasal delivery devices at no cost; no input into study design or analyses)
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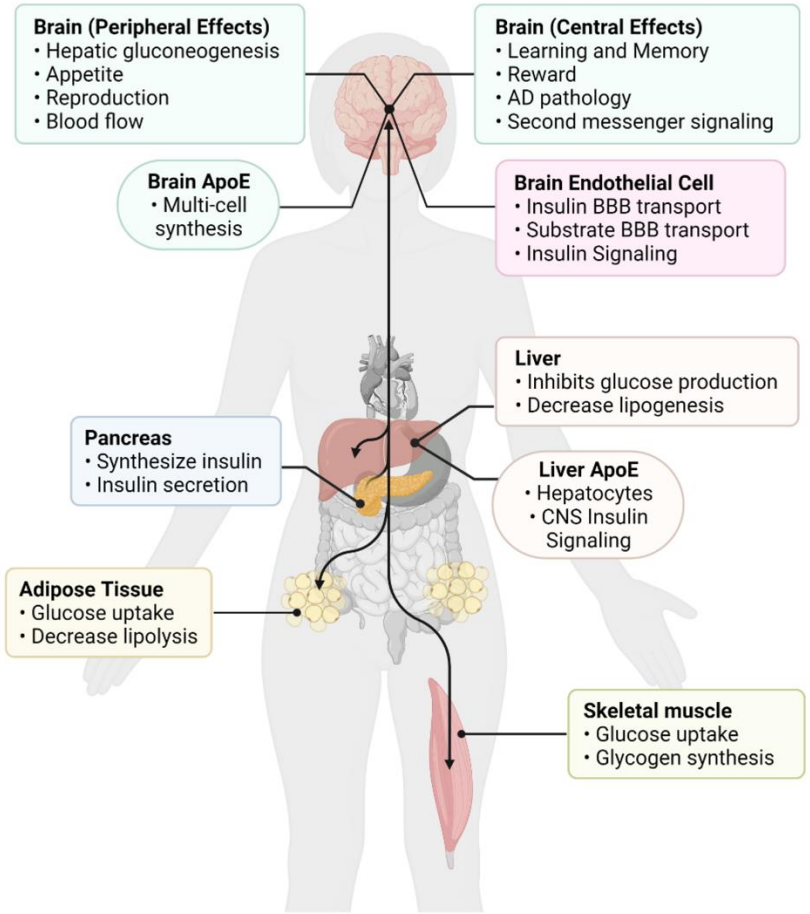
Other disclosures:

- I am a Scientific Advisory Board member for the Belfer Neurodegeneration Consortium.
- My content will include reference to commercial products; however, generic and alternative products will be discussed whenever possible.
- I will be discussing investigational products and their ongoing trials.

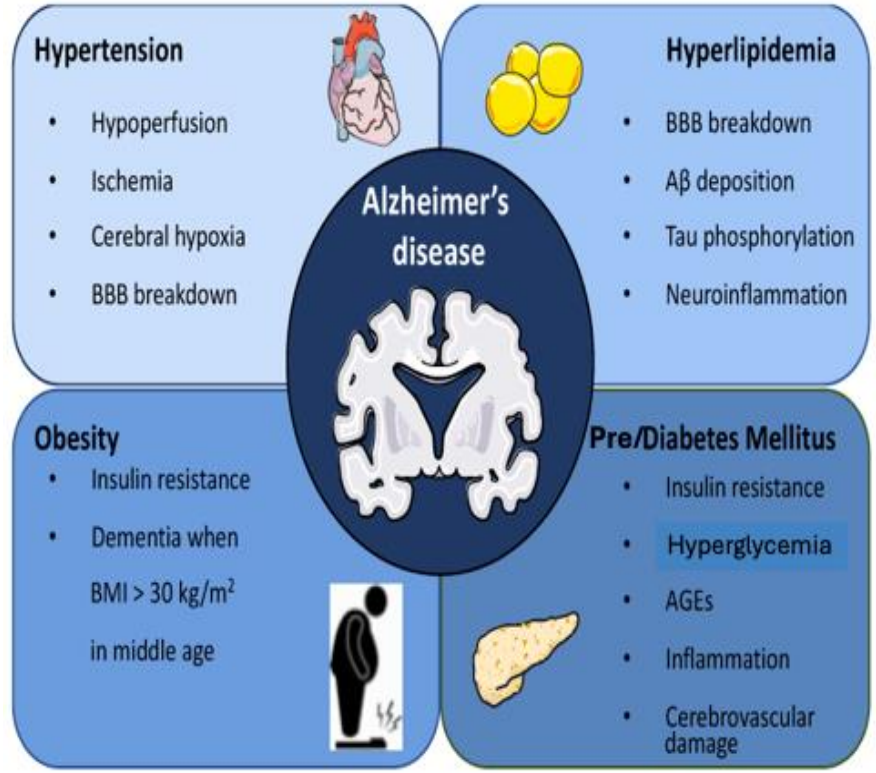
Insulin: Master regulator of metabolism, immune function and aging in periphery and brain

- Insulin/IGF ancient signaling pathway
- Evolutionarily conserved in all species
- Essential for body & brain
- Preserved insulin sensitivity strongest predictor of longevity and delayed aging



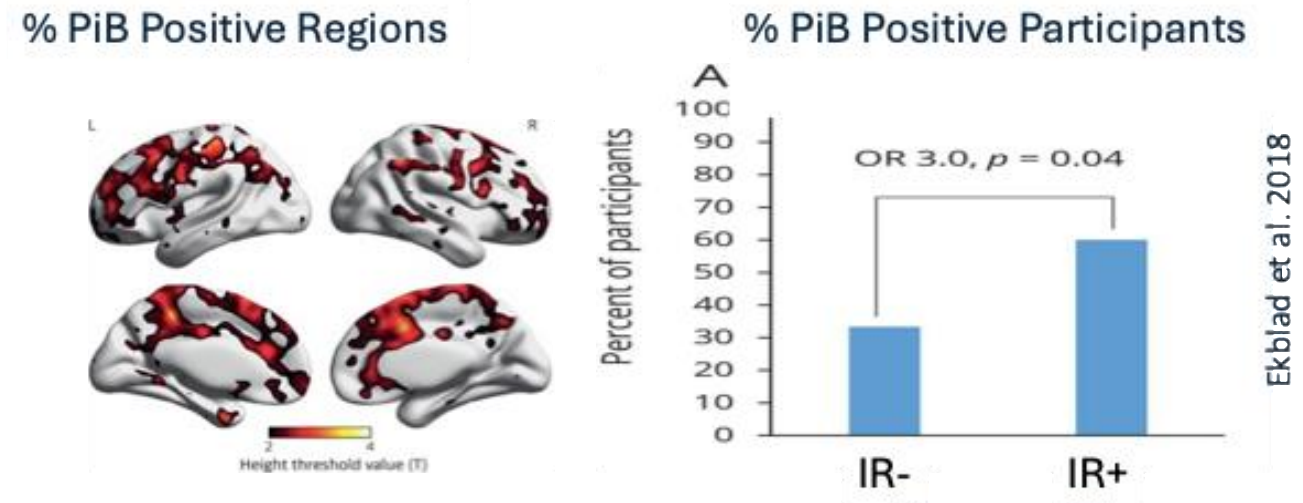
Rhea et al. 2022

Common conditions associated with insulin dysregulation that increase risk of AD/ADRD



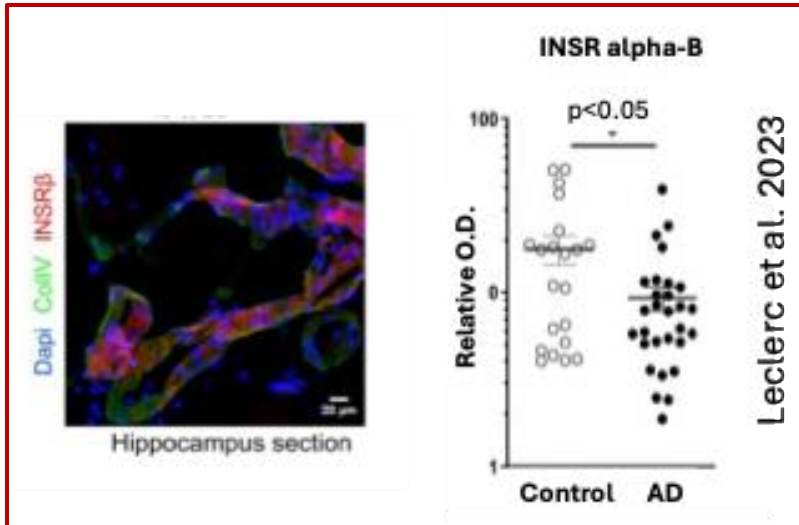
Adapted from Ezkurdia et al. 2023

Links between insulin, Aβ, tau and vascular pathologies



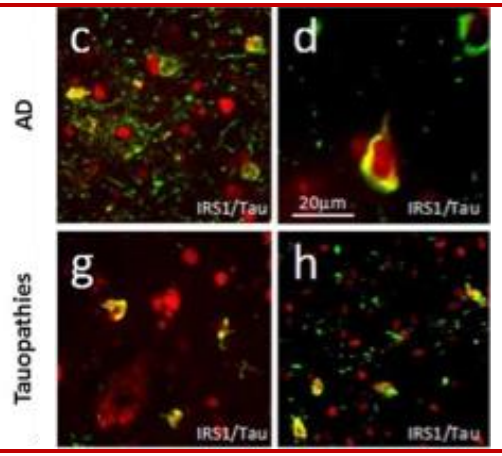
Ekblad et al. 2018

Midlife insulin resistance predicts Aβ positivity and burden 15 years later



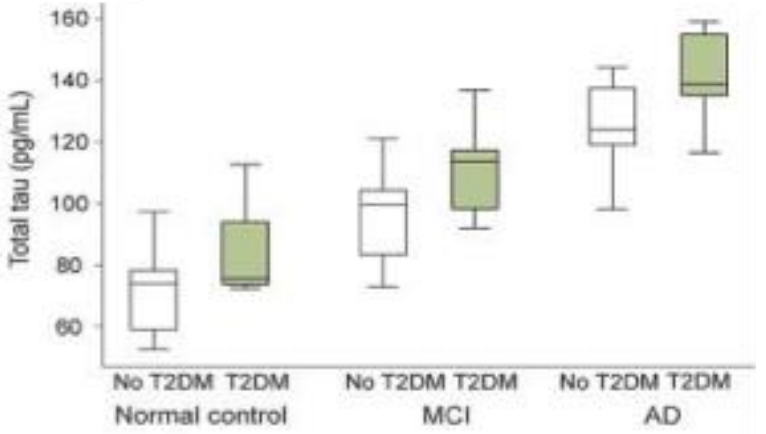
Leclerc et al. 2023

Reduced INSRs in AD cerebral vessels



Insulin resistance markers co-localize with tangles in AD and other tauopathies

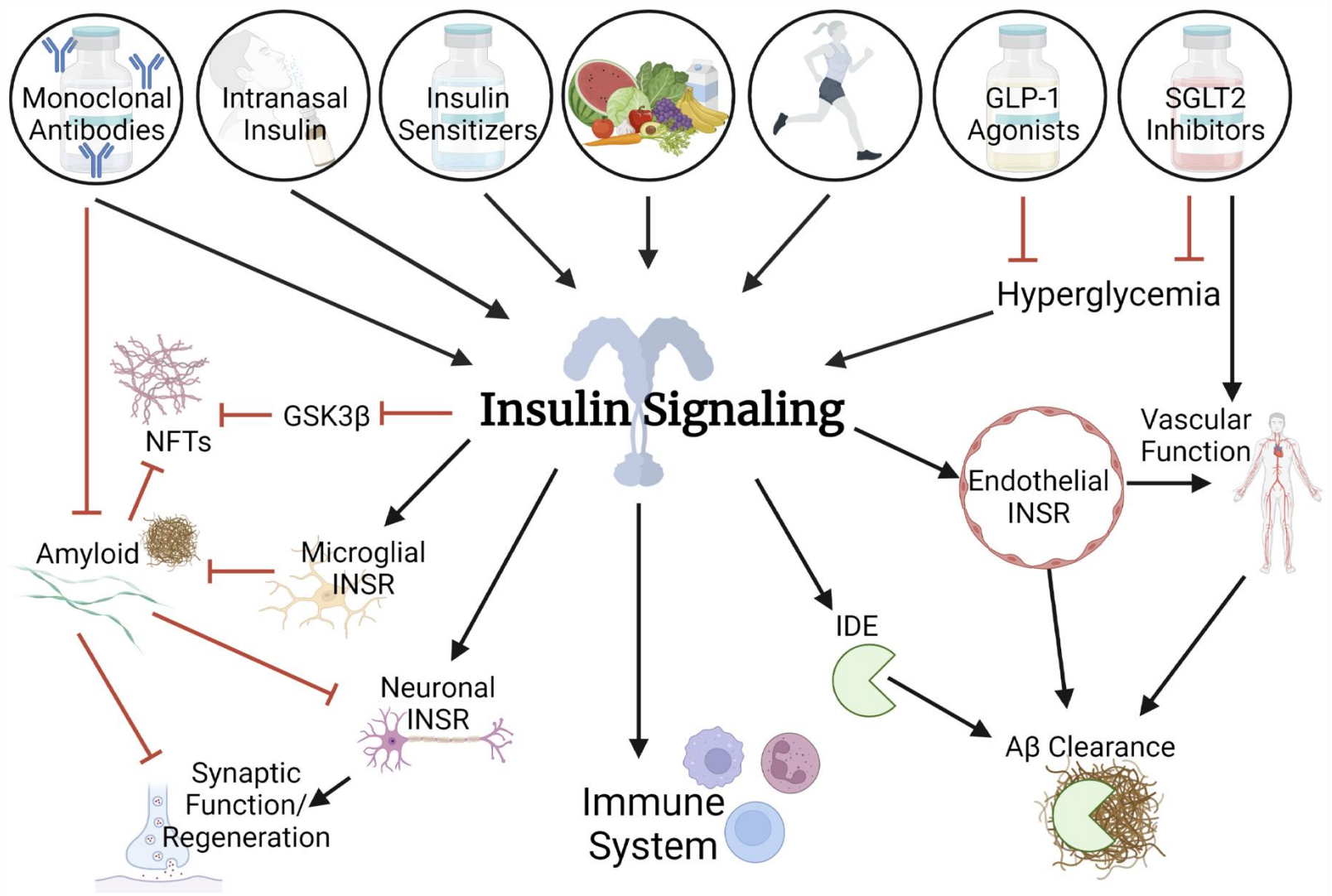
Arnold et al. 2014

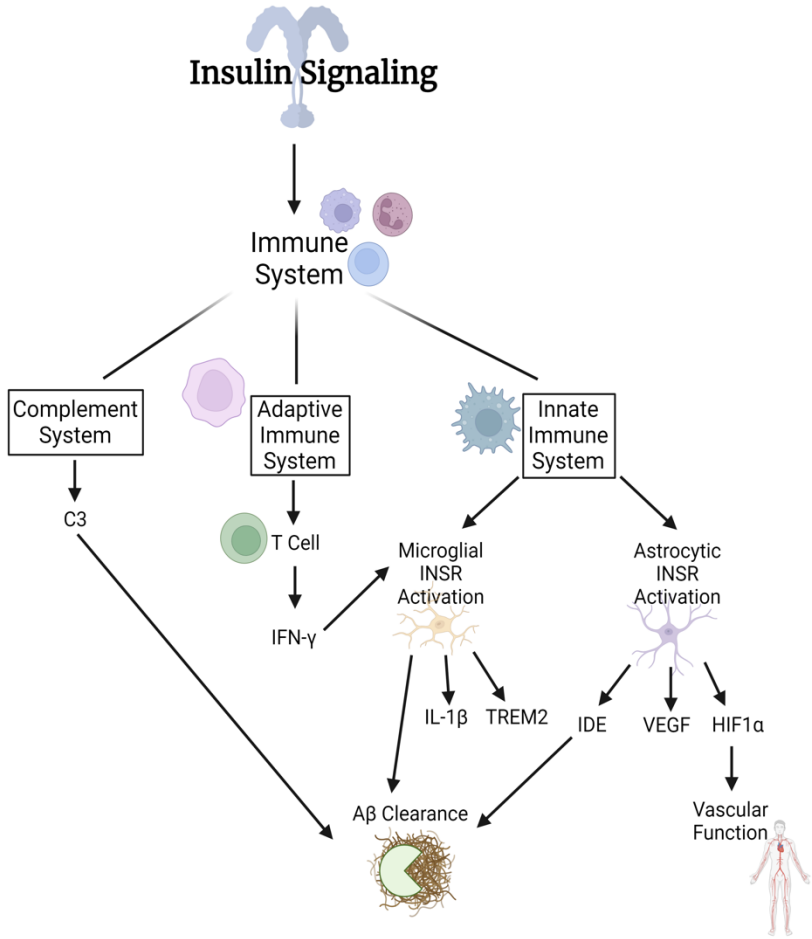


Higher CSF tau inT2DM, independent of Aβ

Moran et al. 2015

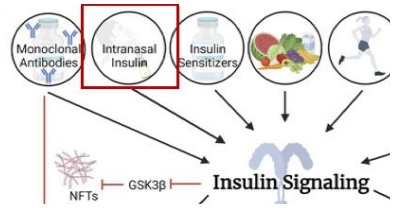
Insulin Signaling Pathways for Design of Repurposed and Combination Therapies for AD





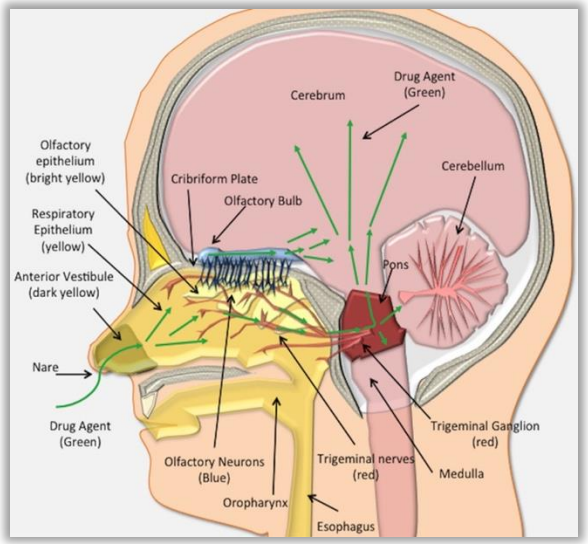
Erichsen & Craft, TRCI, 2023

Therapeutic approaches to correct insulin dysregulation in AD: Intranasal insulin (INI)

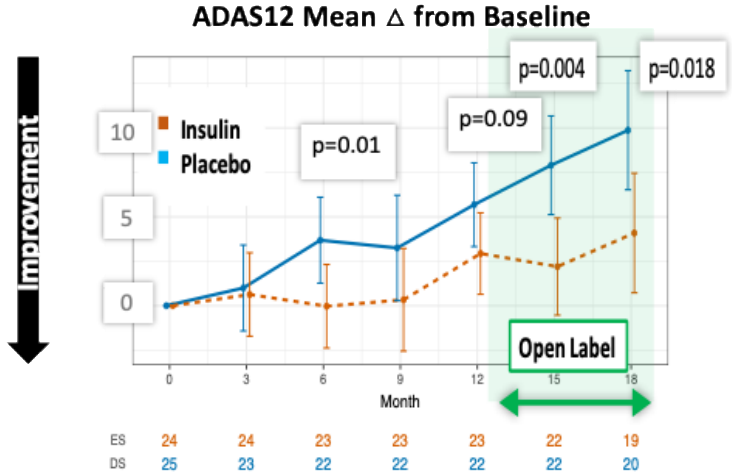


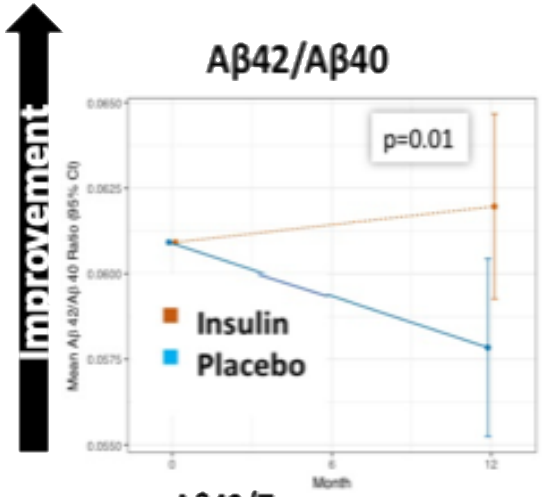
Nose-to-brain pathways

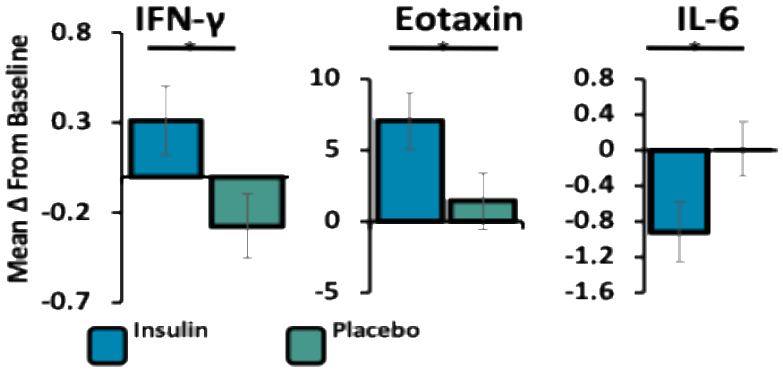
Veronesi et al. 2020

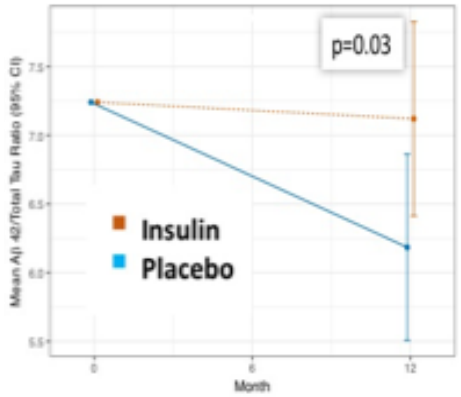


INI treatment improved cognition and CSF AD biomarkers for MCI/early AD [Craft et al. 2020]

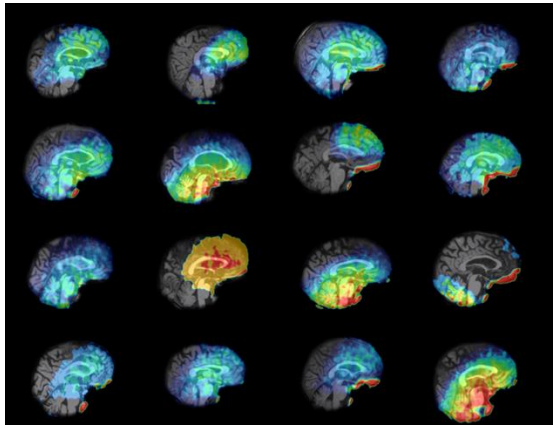






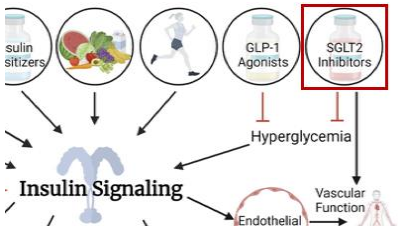


PET [^{68}Gallium]-insulin binding in brain in CN and MCI adults 30 minutes after intranasal delivery [in prep]

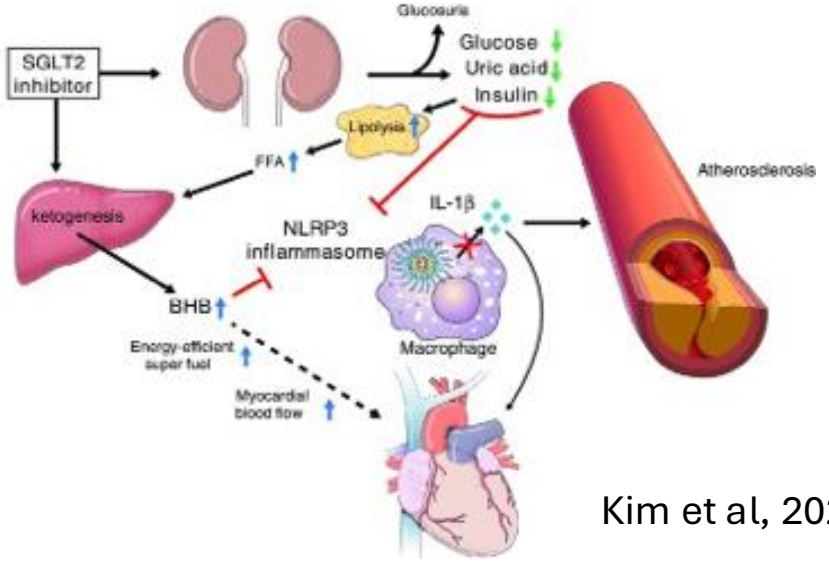


INI moderated immune/inflammatory profile in direction associated with slower clinical progression and compensatory immune response [Kellar et al. 2022]

New approaches to metabolic modulation in MCI/AD: Sodium-glucose Co-transporter 2 Inhibitors



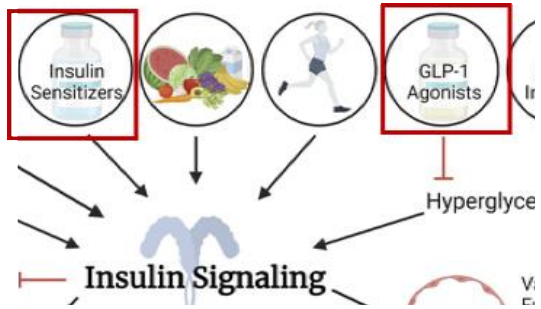
- SGLT2is new treatment for T2D
  - Reduces sodium and glucose uptake in kidney
  - Improves vascular function, hyperglycemia, insulin resistance, inflammation, dyslipidemia, bioenergetics
- In 57,000 adults with T2D, SGLT2is reduced dementia risk more than other treatments [Wium-Andersen et 2019]



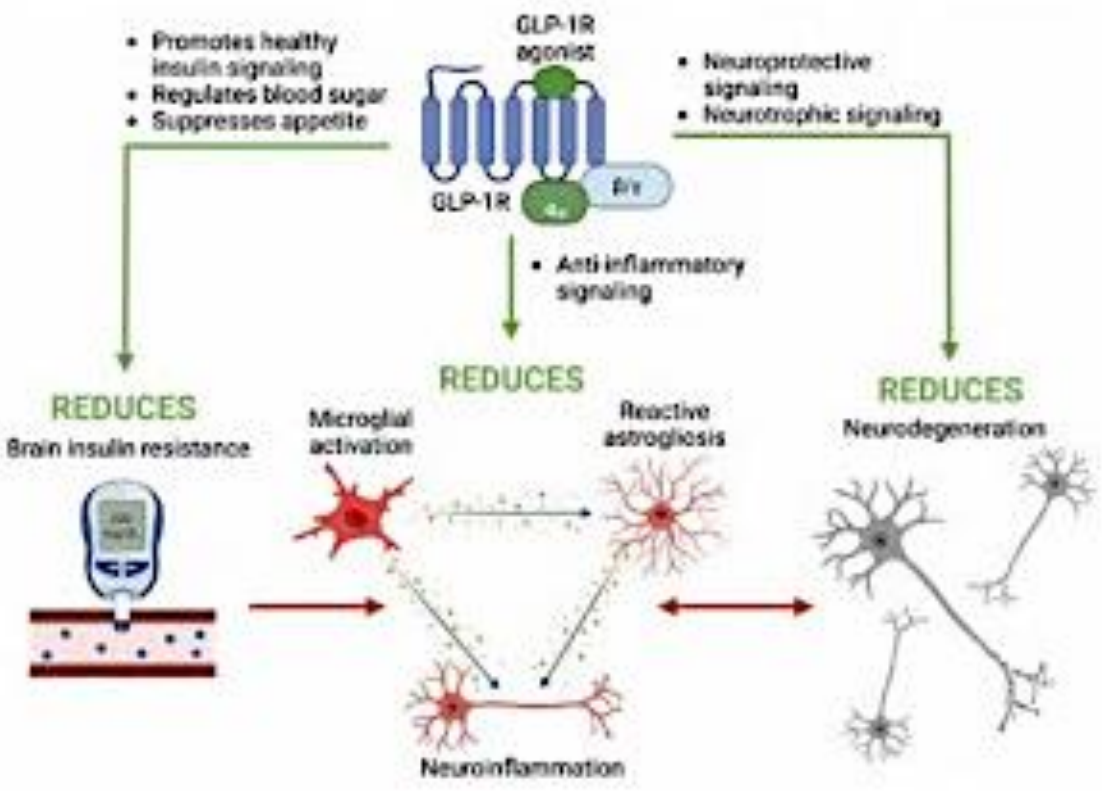
Kim et al, 2020

- Recently concluded Phase II 4-week pilot study of empagliflozin with and without intranasal insulin in MCI and AD (NCT05081219, Craft, PI)
  - Empagliflozin was safe
  - Multiple effects on immune function and inflammation
  - Analyses ongoing

Other metabolic enhancers in MCI/AD: GLP1 receptor agonists and metformin

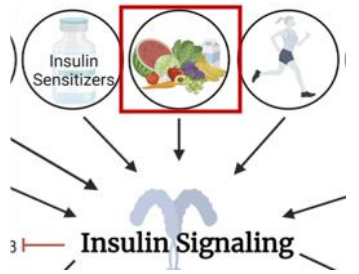


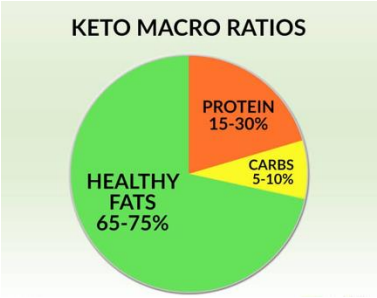
- GLP1 receptors in neurons and glia in hypothalamus, hippocampus, striatum, temporal cortex; highest expression in subcortical areas
  [Reich & Hoscher, Frontiers in Neuroscience, 2022]
- GLP1-Ras have varying BBB penetration; liraglutide and semaglutide poor, exenatide inconsistent
- Benefit cognition in T2DM in trials [Monney et al, Diabetes & Metabolism, 2023]
- No cognitive benefit with liraglutide and exenatide in non-diabetic MCI/AD to date
- Ongoing trial combining intranasal insulin and oral semaglutide (Beeri, PI)
- Two Phase III semaglutide trials (evoke/ evoke+, Novo Nordisk) to report in 2025



- Metformin trial underway [NCT04098666; Luchsinger, PI]

Lifestyle interventions have potent effects on insulin signaling and metabolism: Ketogenic diet

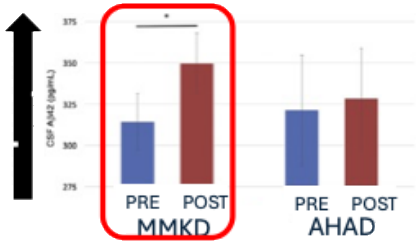




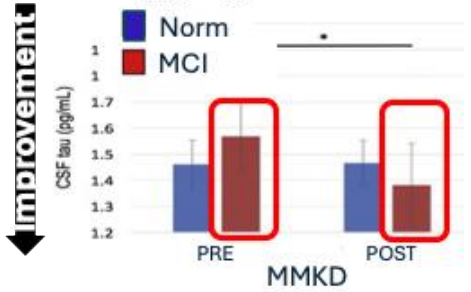
- Very low carbohydrate, adequate protein, and high fat diet that mimics fasting, decreases seizure frequency in epilepsy by 70%
- Modified Mediterranean KD (MMKD): emphasis on healthy fats & proteins, slightly higher carbs

- Increases plasma and CNS ketones
  - Serve as alternate fuel for brain to correct AD bioenergetic deficits
  - Neuroprotective effects via reducing oxidative stress
  - Corrects neuronal and GABA/glutamate imbalance
  - Pilot-6 week Phase II trial of MKKD vs AHAD [Neth et al. 2020] showed:

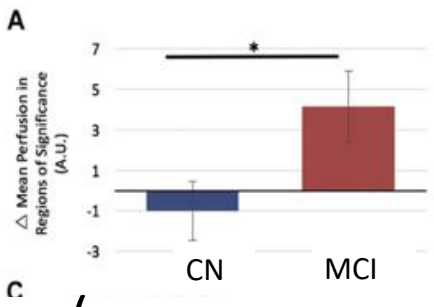
CSF Aβ42



CSF Total Tau

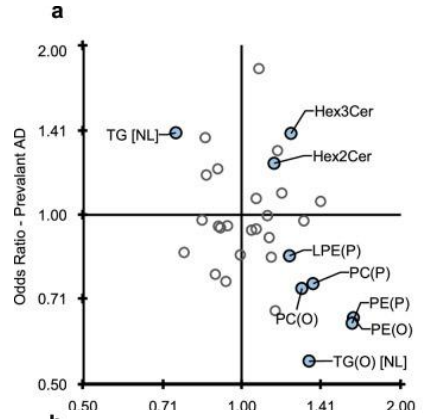


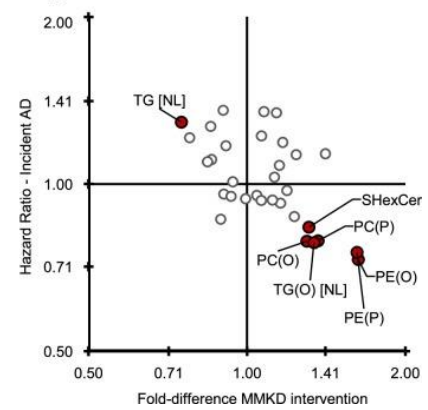
Global Perfusion



- Two larger Phase IIB trials reporting soon (NCT03472664 , Craft, PI; NCT03860792, Swerdlow, PI)

Reversed AD lipid signature derived from AIBL and ADNI





[Neth, Huynh et al. 2025; U19 Gut Microbiome, Kaddurah-Daouk, PI]

Parting thoughts: The future is now!

- Most chronic conditions of aging that increase AD risk are associated with peripheral and CNS insulin dysregulation
- Interventions that restore CNS insulin signaling, metabolism and immune function are available now, and are ideal candidates for repurposed and/or combination therapy approaches to prevent and treat AD

Collaborators

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Tenure-track faculty positions in ADRD available at Wake Forest School of Medicine
Contact suzcraft@wakehealth.edu
https://emis.fa.us2.oraclecloud.com/hcmUI/CandidateExperience/en/sites/CX_1001/job/93546/?utm_medium=jobshare&utm_source=External+Job+Share

Alzheimer's Association

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