Insulin Dysregulation and Alzheimer's Disease: Novel Mechanisms and Therapeutic Implications

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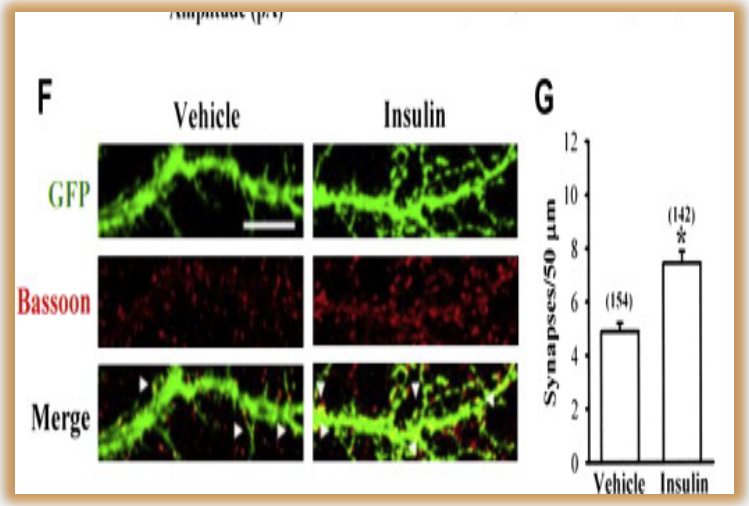
No Disclosures

Overview

- Role of insulin in normal brain function and cognition
- Insulin dysregulation increases risk for pathological brain aging: cognitive impairment, AD & other neurodegenerative diseases
- Potential mechanisms of increased risk
- Metabolism-based approaches to treatment and prevention: Western, Mediterranean and ketogenic diets

Insulin's Multi-faceted Role in Normal Brain

- **Dense receptor distributions in hippocampus, entorhinal cortex, frontal cortex, choroid plexus** [Apelt et al. 2001]
- **Insulin readily crosses the BBB**
  - Transport reduced with chronic hyperinsulinemia, obesity
  - Transport modulated by systemic inflammation [Banks et al. 2014]
- **Insulin production within brain** [Molnar et al. 2014]
  - GABA-ergic neurogliaform cells provide insulin in cortical microcircuits
  - Modulate memory consolidation, slow wave sleep, tonic neuronal excitability
- **Insulin modulates GLUT4/glucose uptake in HC, promotes dendritic spine & synapse formation via PI3K/Akt/MTOR pathways, and modulates memory** [Lee et al. 2011]



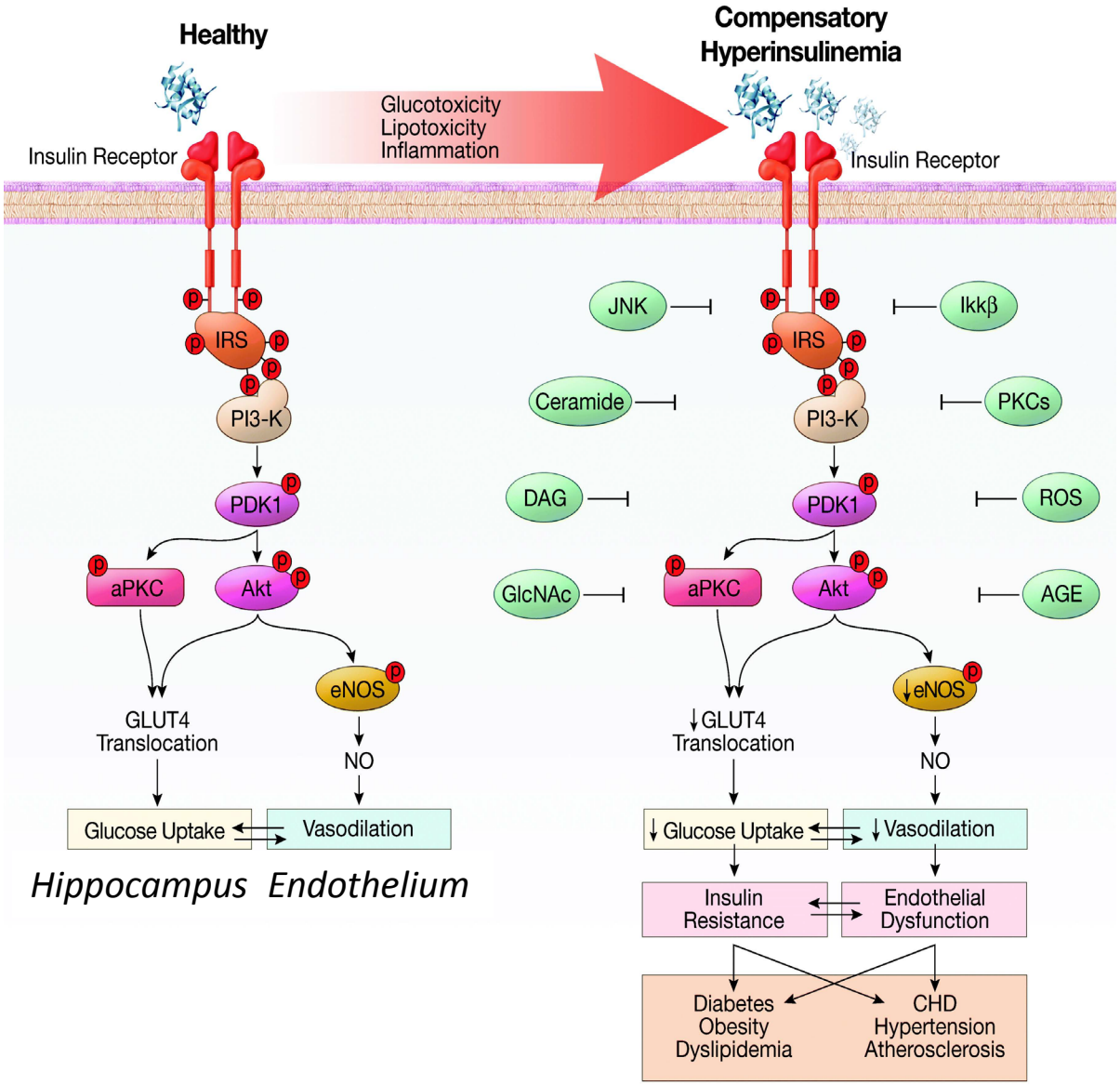
Lee et al. 2011

Insulin Resistance and AD

- **Insulin resistance**
  - **Tissue-specific inability of insulin to activate normal signaling pathways**
  - **Conditions associated with insulin resistance (prediabetes, T2D, HTN, CVD) are AD risk factors** [Ott et al. 1999; Luchsinger et al. 2004]
  - **Caused by poor diet, physical inactivity, obesity, sleep disruption, stress, genetic vulnerability**
  - **Associated with high peripheral insulin and reduced BBB transport of insulin**
  - **Peripheral index: Homeostatic Method of Assessing Insulin Resistance (HOMA-IR)**
  - **Molecular signature: Serine phosphorylation of IRS-1**

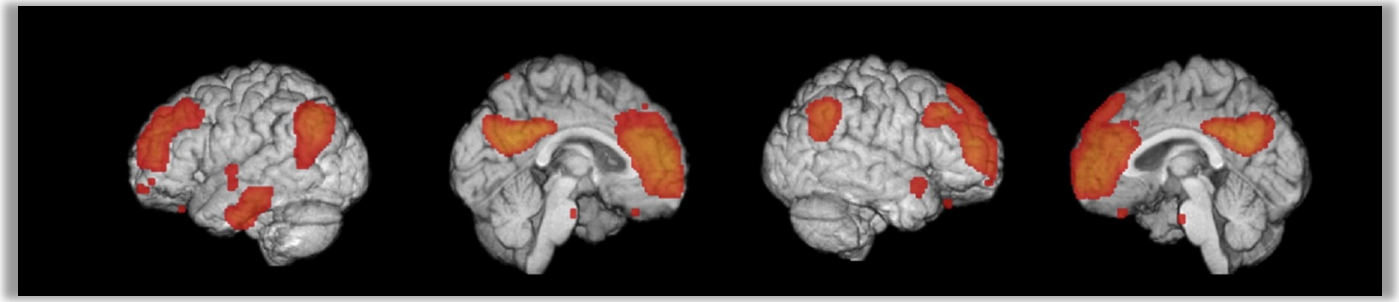
Insulin Resistance and AD: Pathological Links

- Reduced cerebral glucose metabolism
- Vascular dysfunction, inflammation, dyslipidemia
- Aβ, tau dysregulation
- Synapse loss, atrophy

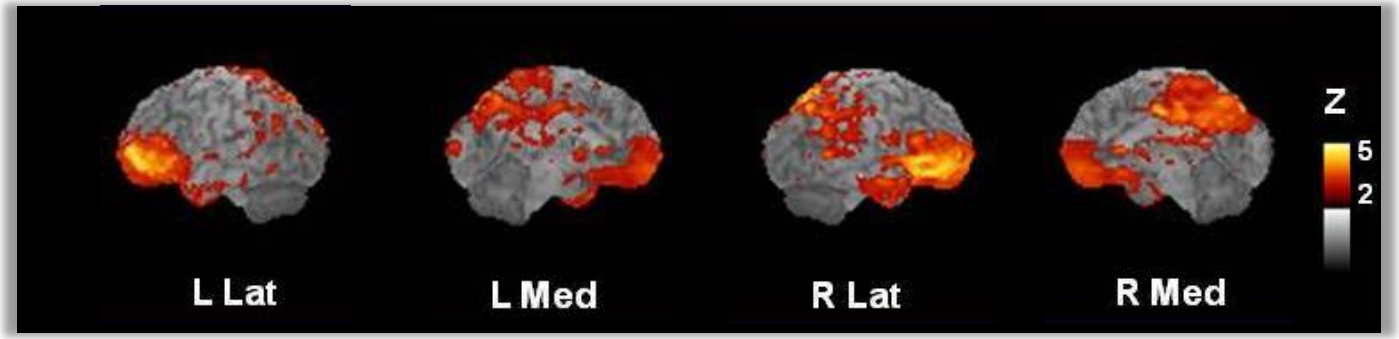


Pathological Links: Insulin Resistance is Associated with AD-Like Cerebral Hypometabolism in Middle-Aged Adults

AD Pattern
Langbaum et al. 2009



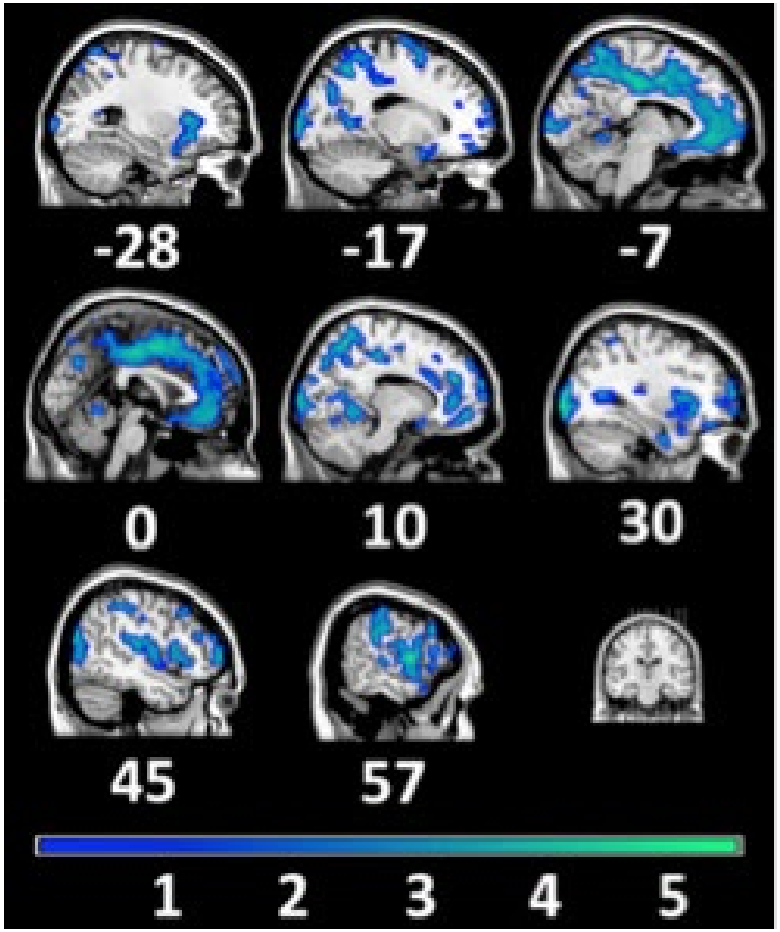
Insulin Resistant Pattern
Baker et al. 2010



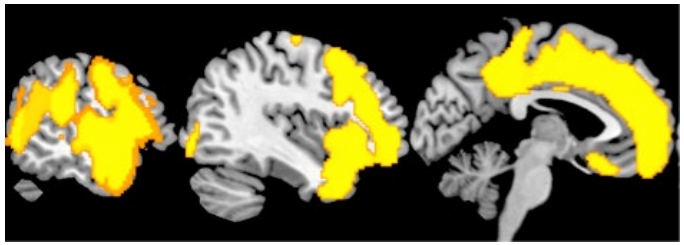
- **Regions in which greater insulin resistance (HOMA-IR) is associated with hypometabolism in cognitively normal insulin-resistant older adults**

Middle-Aged Adults with Insulin Resistance Show Reduced Gray Matter and CBF, Increased Aβ

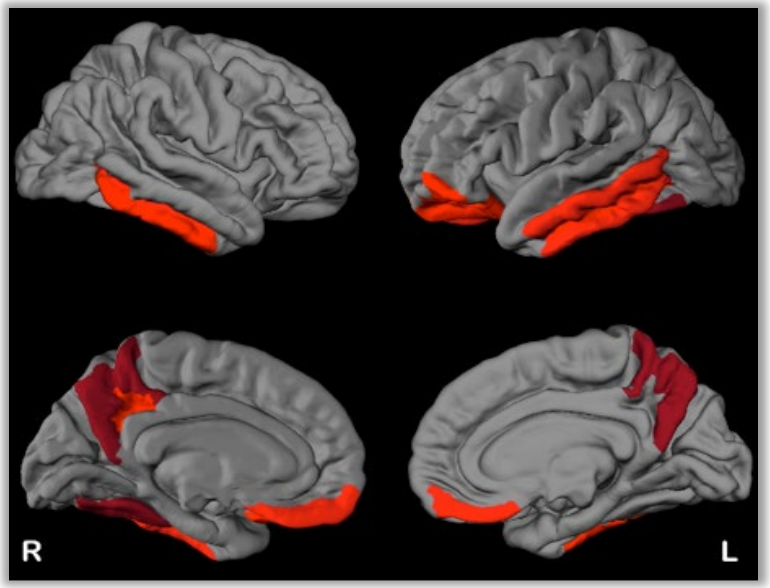
Gray matter reduction over 4 years (n=121) [Willette et al. 2012]



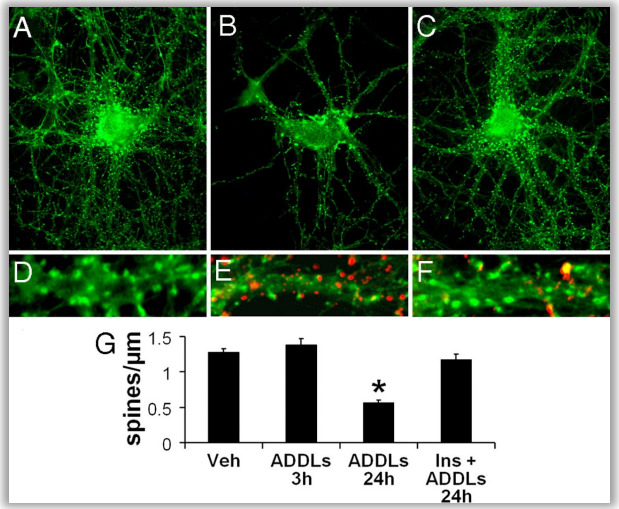
Reduced CBF (pcASL; n=69)
[Birdsill et al. 2014]



Increased Aβ (^{11}C PiB; n=173)
[Willette et al. 2014]



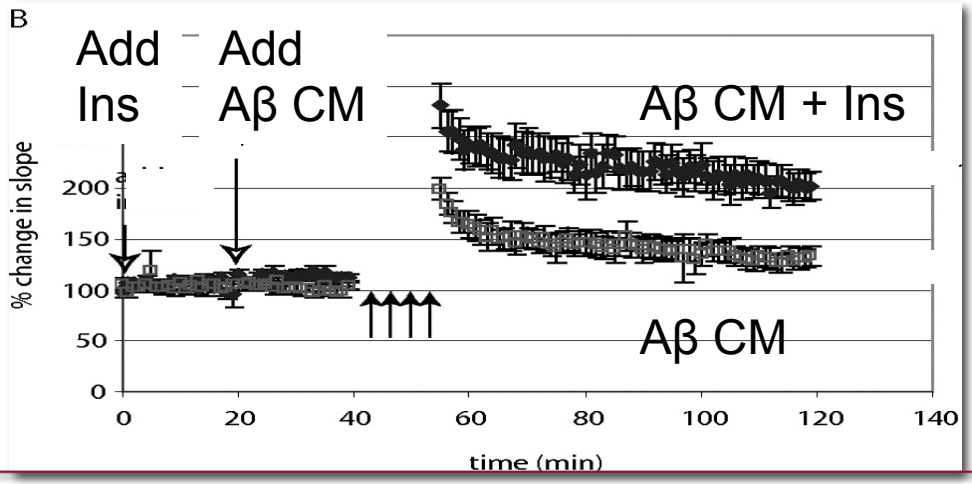
Pathological Links: Insulin, Aβ & Tau Interactions

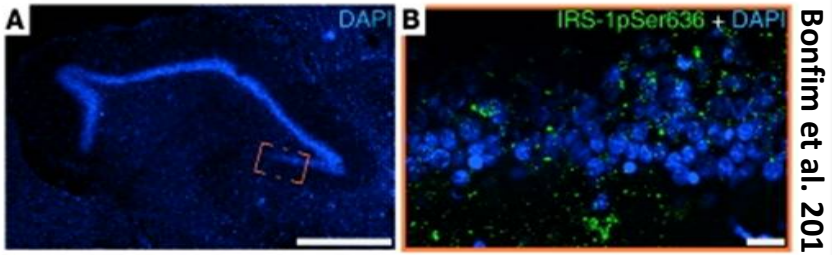


De Felice et al. 2009

- Insulin blocks Aβ-induced synapse loss

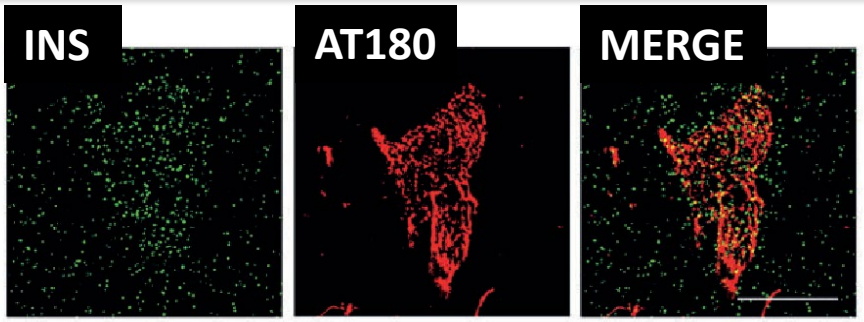
- Inhibitory effect of Aβ-rich CM on hippo LTP rescued with insulin **Townsend et al. 2007**





Bonfim et al. 2012

- ICV Aβ causes HC insulin resistance (IRS-1pSer) in non-human primates



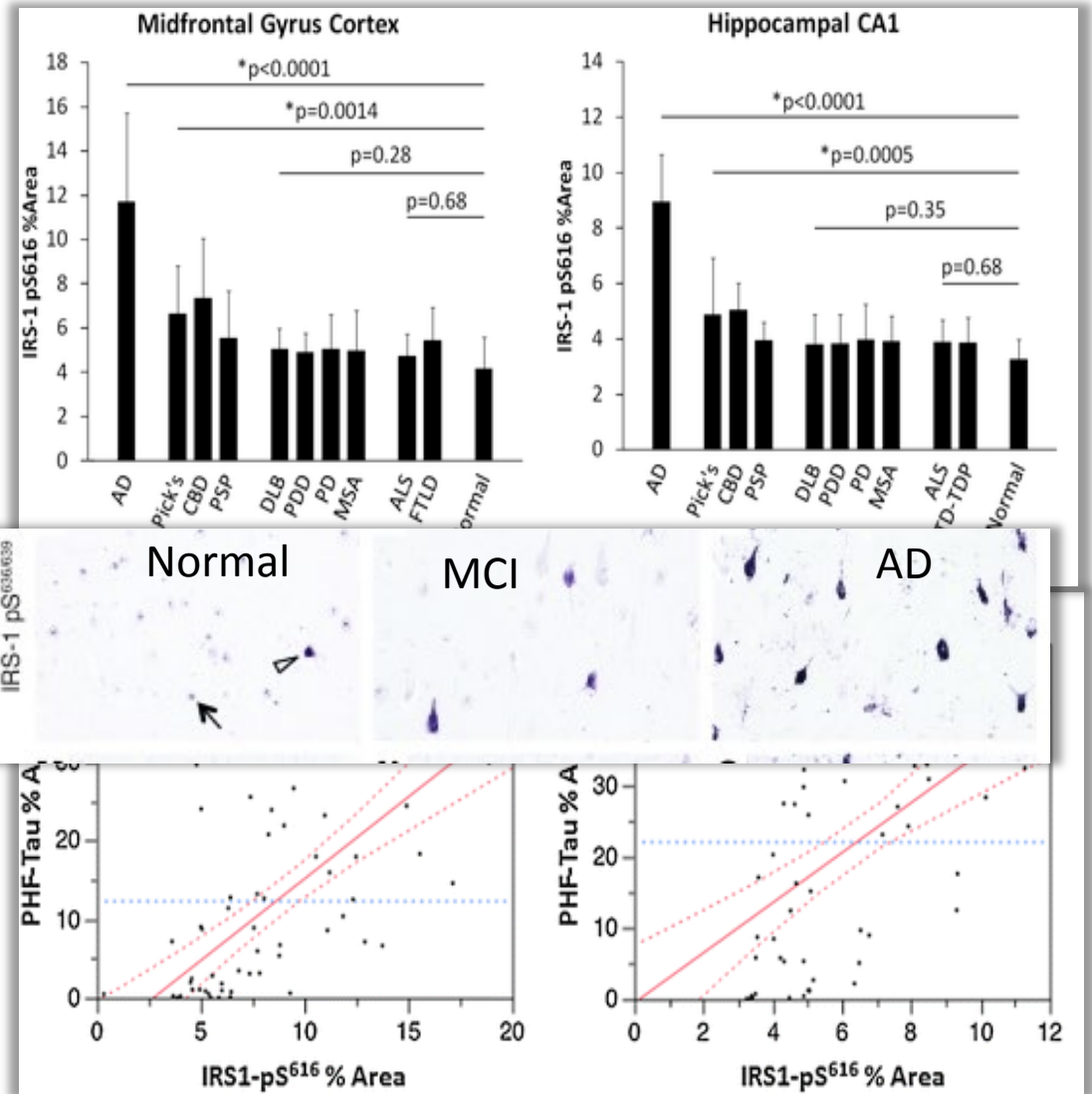
Rodriguez et al. 2017

- Oligomeric insulin aggregates in tau+ neurons, inducing insulin resistance

Brain Insulin Resistance is Increased in AD and Associated with PHF Tau

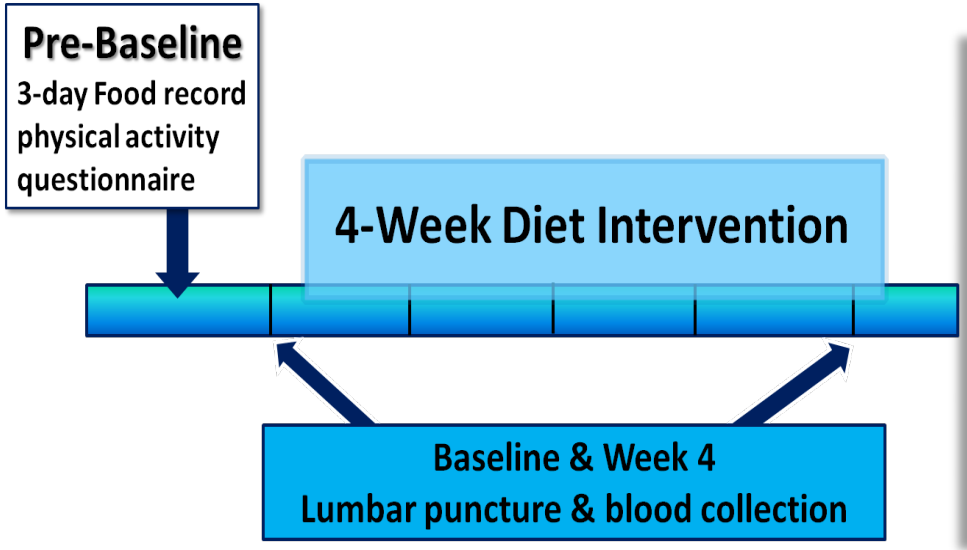
- **Insulin resistance marker IRS-1 pSer+ neurons increased in MCI and AD**
  [Talbot et al. 2013]

- **Increased (IRS-1 pSer) associated with PHF tau in MCI and AD**
  [Yarchoan et al. 2014]



Dietary approaches to preventing or treating brain insulin resistance and AD

Western vs. Healthy Diet Effects on Brain Markers of AD and Insulin Resistance in Middle-Aged Adults



mean (SD)	LOW	HIGH
N	44	43
Age, yrs	55.7 (5.5)	56.9 (4.6)
Educ, yrs	15.2 (2.3)	15.7 (2.2)
BMI kg/m^2	28.9 (2.6)	28.5 (4.5)
MMSE	28.8 (1.1)	29.4 (1.0)

- HIGH diet: 40% fat w/ 25% sat fat, 40% CHO, 20% protein, GI>70, Na>3500 mg
- LOW diet: 40% fat w/ 7% sat fat, GI<55, 40% CHO, 20% protein, Na<1500mg
- All food prepared by metabolic kitchen & delivered to pts 2x/wk
- Eucaloric diet w/normal calorie intake; no weight change
- Exclusions: Statins, T2D, HTN

Ketogenic Diet as a Therapeutic Tool

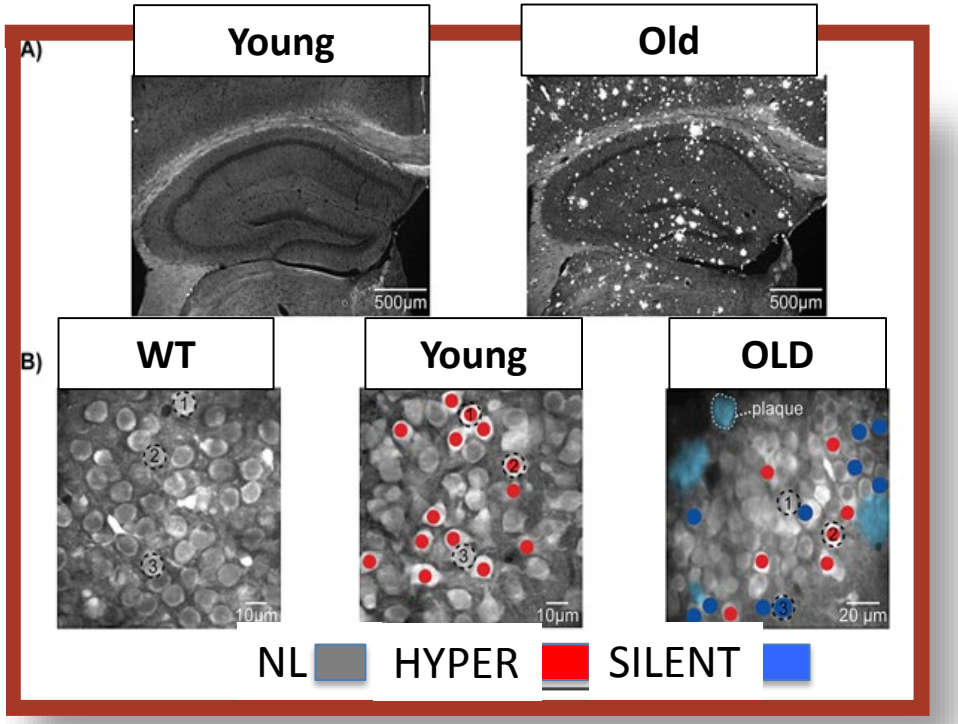
- Developed in the 1920s at Mayo for refractory epilepsy; 70% success rate
- Very low carbohydrate, adequate protein, and high fat diet that mimics the effects of a fasted state, improves insulin sensitivity, decreases seizure frequency
- Modified Mediterranean KD (MMKD): slightly higher CHO consumption allowed (<10%), emphasis on healthy fats (~65%), proteins (~25%); better compliance and nutritional profile
- Increases plasma and CNS ketone bodies (KB): beta-hydroxybutyrate (BHB), acetoacetate (AcAc), and acetone, which serve as preferred alternate fuel for brain

Rationale for Use in AD

- Glucose hypometabolism in AD years prior to symptom onset; ketone provide alternative energy substrate

- Neuronal hyperexcitability in early stages of AD, linked to increased soluble Aβ and GABA/glutamate imbalance, may promote Aβ production and deposition [Stargardt et al. 2014; Bushe & Konnerth, 2015]

- KD inhibits hyperexcitability via increased production of GABA [Dahlin et al. 2005; Roy et al. 2015]

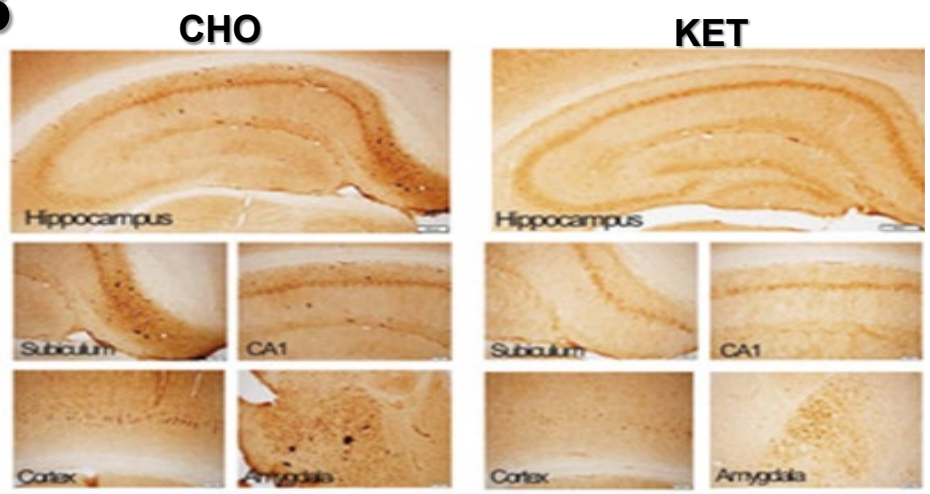


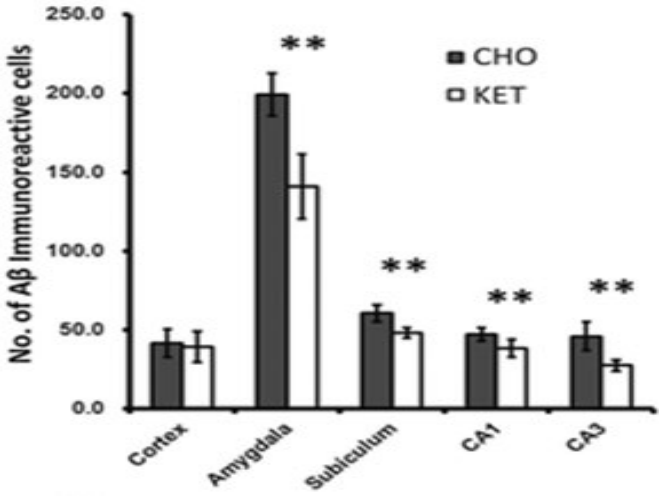
[Busche & Konnerth, 2015]

- Reduced impact of Aβ on mitochondria and neurons due to neuroprotective effect of ketones

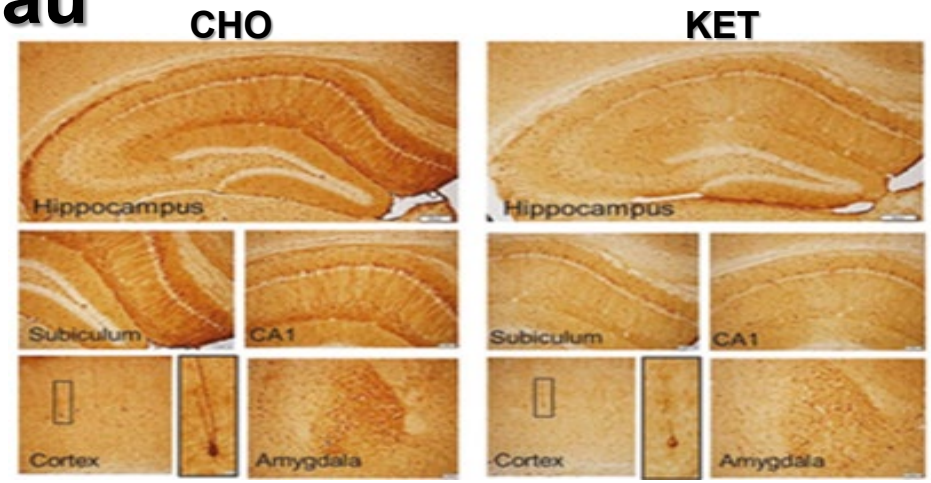
Pre-clinical Studies: KD reduced Aβ and pTau, improved memory in 3xTgAD mice

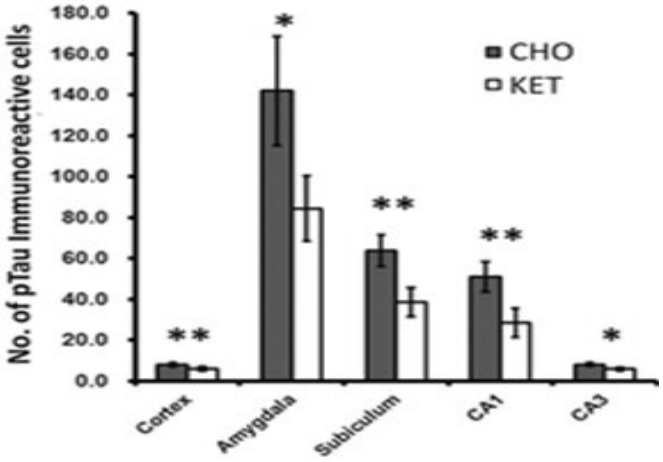
Aβ





p-Tau

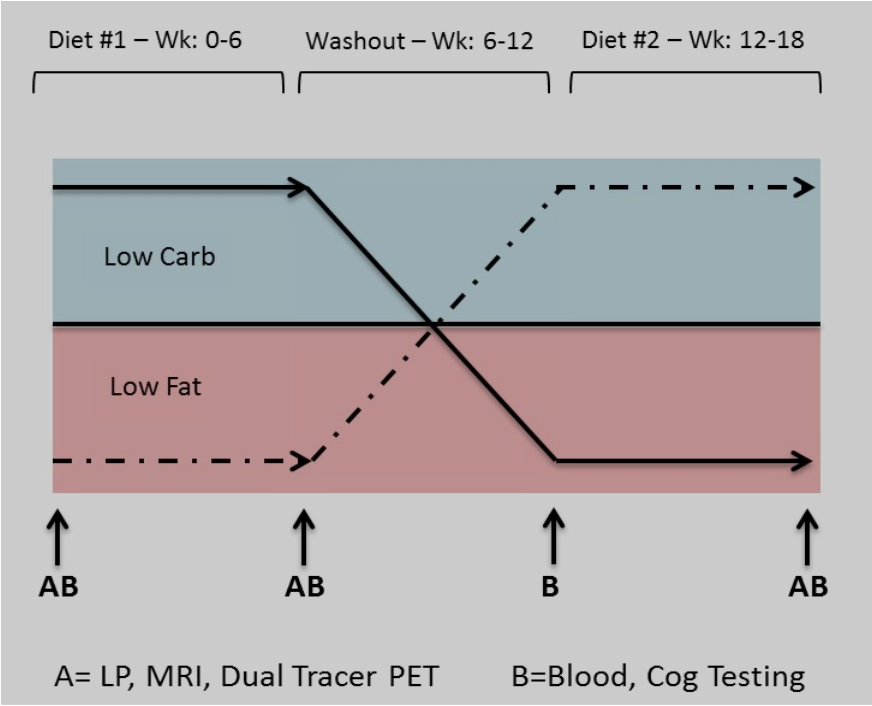




[Kashiwaya et al. 2013]

MMKD vs. AHAD in MCI: Pilot Study Design

- Randomized cross-over comparison of 6-week MMKD (<10% CHO, 65% fat, 25% protein) vs. low fat American Heart Assn Diet (AHAD; 60% CHO, 20% fat, 20% protein) in adults with MCI and/or subjective memory complaints



- Food prepared at home
- Weekly RD contact to design menus, assess compliance with capillary ketone measurement, food log review
- Primary outcome: CSF AD biomarkers
- Secondary outcomes: Delayed memory (story recall, FCSRT), dual tracer ^{11}C-acetoacetate/^{18}F FDG PET, ASL MRI

MMKD Recipes

RECIPE NAME/DETAILS	RECIPE NUMBER	CARBS (GRAMS)	FAT (GRAMS)
Baked Sea Bass with Steamed Squash	LD1	3.5	43
Basil Chicken Packet	LD2	4.5	38
Beef, Bean & Walnut Stir-Fry	LD3	4	40
Beef Tenderloin Steak with Blue Cheese Topping and Green Beans*	LD4	4.5	41
Broiled Dijon Beef Patty with Celery Salad (Recipe: **S6**)	LD5	4.5	60
Broiled Fish Parmesan with Steamed Broccoli	LD6	4	46
Broiled Salmon with Herb Mustard & Steamed Asparagus	LD7	4.5	61
Chef Salad	LD8	4	40
Chicken with Artichokes and Olives	LD9	5	35
Chicken & Asparagus Parmesan	LD10	4.5	52
Chicken & Mushrooms	LD11	5	36
Chicken with Rosemary Butter Sauce and Roasted Broccoli*	LD12	3.5	50
Chicken and Salad	LD13	4.5	40
Chicken with Spaghetti Squash and Asparagus	LD14	5	50
Cilantro-Lime Chicken with Broccoli and Tomato	LD15	4	43
Cod with Tomato	LD16	4.5	23
Curried Chicken Salad	LD17	4	43

Demographics

- Participants (n=18) with aMCI (n=12; NIA-Alzheimer Assn), or subjective memory complaints (n=6; ADNI Cognitive Change>16)
- Exclusions: anti-diabetic medications, statins, CNS-active drugs, anti-cholinergics, fish/coconut oil

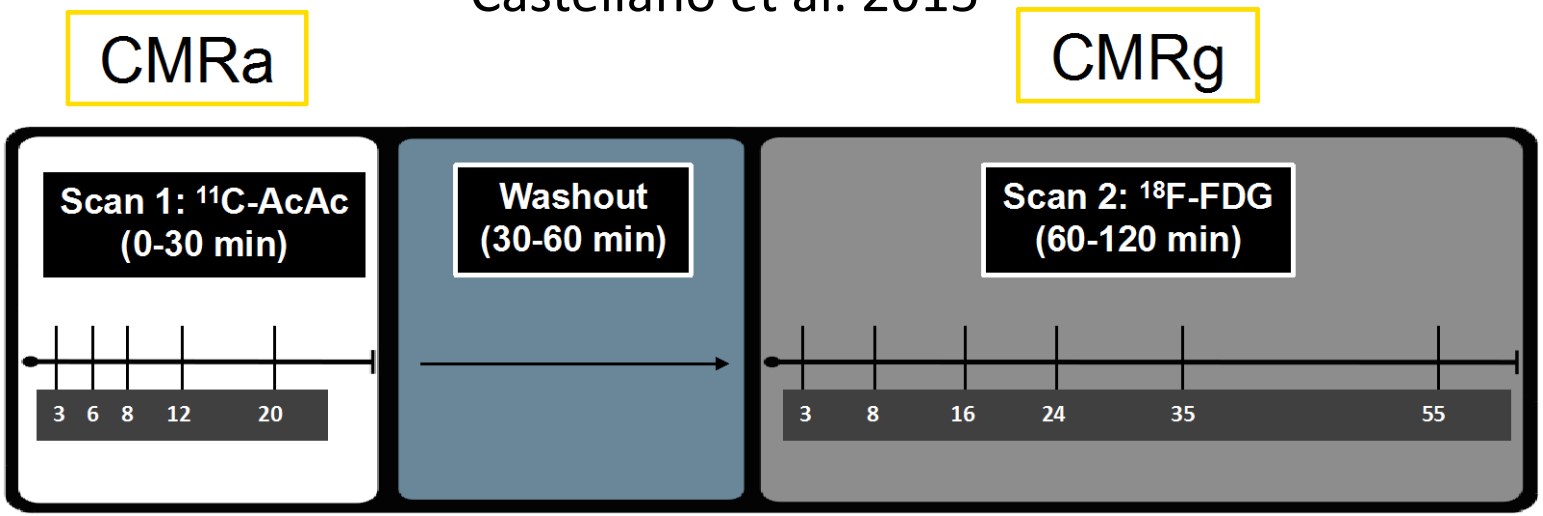
n	18
Sex (M/F)	6 / 12
E4 +/-	6 / 12
Age (yr)	63.1 (4.6)
Education (yr)	15.8 (2.7)
MMSE	29.0 (0.9)
A1C	6.2 (1.7)
BMI	30.1 (6.2)

Effects on Lipid and Glucose Metabolism

	Δ MMKD	Δ AHAD
Ketone (mmol/L)	0.7 ± 0.5	-0.0 ± 0.2
Total Chol (mg/dL)	5.9 ± 58.4	-18.0 ± 26.8
LDL (mg/dL)	13.1 ± 48.2	-10.0 ± 19.4
HDL (mg/dL)	7.4 ± 16.8	-6.9 ± 14.4
Trigly (mg/dL)	-27.3 ± 59.1	-2.2 ± 29.3
Glucose (mg/dL)	-5.9 ± 9.8	-6.4 ± 5.6
HOMA-IR	-0.7 ± 0.2	0.5 ± 0.2
Weight (lb)	-4.2 ± 5.3	-2.8 ± 5.8

Dual Tracer PET Methods

Castellano et al. 2015



- Imaging with ^{11}C-AcAc conducted first with acquisition frames of 12x10 sec, 8x30 sec, and 1x4 min (total scan 10 min), followed by a 50-min wash-out
- FDG imaging then conducted using the time frames 12x10 sec, 8x30 sec, 6x4 min, and 3x10 min (total scan 60 min)
- Plasma radioactivity counted in a gamma counter cross-calibrated with PET scanner
- PET images preprocessed and co-registered to each participant's MR, parametric images of CMRg and CMRa produced for each participant (PMOD 3.5), quantified using an arterial input function
- Calculated activity corrected using the radioactivity of the plasma samples
- Lumped constant set to 0.89 for CMRg, and to 1.0 for CMRa
- CMRg and CMRa expressed as mmol/100 g/min using the graphical Patlak model
- CMRa corrected for loss of 5.9% of the dose of ^{11}C-AcAc that is catabolized to $^{11}CO_2$

Overall Summary & Conclusions

- **Growing evidence from basic science/rodent models demonstrate:**
  - Insulin's role in synaptic function/viability, vascular function, amyloid/tau regulation
  - Central insulin dysregulation in AD mice and human AD brain
- **Diet is a powerful modulater of cerebral perfusion, cognition and CSF biomarkers**
- **Further work needed to validate results, elucidate responder characteristics and underlying mechanisms**
- **Metabolic interventions may be a valuable tool in the AD therapeutic portfolio**

Collaborators

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POST-DOCTORAL AND FACULTY POSITIONS AVAILABLE!