THIS IS YOUR BRAIN ON DIABETES
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I HAVE NO FINANCIAL CONFLICTS OF INTEREST
OBJECTIVES

• Understand the changes in brain imaging seen in diabetes
• Describe diabetes mediated causes of cognitive decline
• Describe the impact of hypoglycemia and hyperglycemia on brain function
• Understand the potential role of insulin in Alzheimer’s disease pathogenesis and treatment
Dual Epidemics

- Type 2 diabetes doubles your risk for AD\(^3\)
- Even in the non-diabetic range, fasting glucose correlates with brain volume loss\(^2\)
- A1c correlates with cognitive decline across the non-diabetic and diabetic range\(^3\)
- Higher BMI is associated with worse cognition and cognitive decline over time\(^3\)

1 Ahtiluoto, Neurology, 2010
2 Cherbuin, Neurology, 2012
3 Zheng, Diabetologia, 2018
4 Cournot, Neurology, 2006

Type 1 Diabetes Causes Increased Cognitive Impairment in Middle Age

N=201, average age 68

Chaytor, J Diabetes Complications 2018

N=97 with Diabetes
N=138 controls
Average age 49

Nunley, Diabetes Care 2015

Possible Causes of Cognitive Dysfunction in Diabetes

Metabolic Syndrome

Modified from Strachan MTL. Diabetes, obesity and metabolism 2009
Areas of atrophy in diabetes

- Atrophy pattern, not cerebrovascular lesions, correlated with memory impairment.
- The atrophy pattern is similar to preclinical Alzheimer's disease.

Possible Causes of Cognitive Dysfunction in Diabetes

- Hypertension
- Dyslipidemia
- Genetic predisposition
- Macrovascular disease
- Advanced glycation end-products
- Hyperglycemia
- Medications
- Depression
- Recurrent hypoglycemia

Diabetes

Modified from Strachan MRI; Diabetes, obesity and metabolism 2009

MRI 150 patients with diabetes and 363 without diabetes

Macrovascular disease-Stroke

Read, Diabetic Medicine 2015
Studies Linking Microvascular Complications with Outcomes in the Brain

Possible Causes of Cognitive Dysfunction in Diabetes

Hypoglycemia

- Worse cognition in Type 1 diabetes in later life correlated with
  - Recent severe hypoglycemic event
  - Hypoglycemic unawareness
  - Not a prospective study

- Type 2 diabetes
  - Evidence of more frequent hypoglycemia in those with cognitive impairment.
  - Frequent severe hypoglycemia speeds progression of cognitive impairment.
  - Prospective studies do not suggest that severe hypoglycemia is the cause of the cognitive impairment.
Possible Causes of Cognitive Dysfunction in Diabetes

- Possible Causes
  - Diabetes
  - Hypertension
  - Dyslipidemia
  - Genetic predisposition
  - Microvascular disease
  - Advanced glycation end-products
  - Hypoglycemia
  - Medications
  - Amyloid deposition

Multiple Possible Pathways Connecting Diabetes and Alzheimer's Disease

- Multiple Possible Pathways
  - Hyperinsulinemia
  - Type 2 Diabetes
  - Initial injury/Damage
  - Loss of insulin receptor
  - Slows insulin access to the brain

Loss of Insulin Receptor Slows Insulin Access to the Brain

- Loss of insulin receptor
  - Slows insulin access
  - Brain regions: hypothalamus, hippocampus, frontal cortex, olfactory bulb.
The Cholesterol Biosynthesis Pathway Is Suppressed in Brain of Insulin Deficient Diabetic Mice

Decreasing Brain Cholesterol Impairs Neuronal Activity

Decreasing Brain Cholesterol Impairs Memory
Simvastatin Increases Amyloid Beta Induced Cell Death

Fukuda, Ferris and Kahn, J Biol Chem 2015

Statins- Don’t Worry, We Aren’t Making Things Worse

Wannamaker, Clin Cardiol 2015
Type 3 Diabetes??

- What is it?
  - Insulin and IGF1 resistance in the brain in Alzheimer’s disease
- Is it real?
  - Remains controversial
- Why should I care?
  - Is likely relevant to both Alzheimer’s disease and Type 2 diabetes

Insulin is Not Required for Glucose Transport into the Brain and Yet....

Insulin and IGF-1 Binding Correlates with AD Progression
Non-diabetic Alzheimer’s Brains Fail to Respond Normally to Insulin and IGF-1

Talbot, JCI 2012

Intranasal Insulin Improves Plaques and Behavior in an AD Mouse Model

Mao, Aging Cell 2016

Intranasal Insulin- There May be Improvement in Some Patients

Patients with mild cognitive impairment or AD were given 20 IU (low) or 40 IU (high) of intranasal insulin detemir once daily for 21 days.

Those with the greatest insulin resistance also benefited the most.

Claxton, J Alz Dz 2015
### SNIFF Trial- Study of Nasal Insulin to Fight Forgetfulness

- 12 month, placebo controlled study of intranasal insulin
- Fully recruited and should finish collecting data in December of this year
- 240 patients enrolled
- Outcomes are brain atrophy, cognitive function and biomarkers

### What is the Therapeutic Target of Intranasal Insulin?

![Diagram showing the therapeutic target of intranasal insulin](image)

Blazquez, Front Endo, 2015

### Summary

- Both Type 1 and Type 2 diabetes impact cognition, probably through different mechanisms.
- Insulin may play an important role in the development of Alzheimer’s disease, in both the Type 2 diabetes population and the non-diabetes population.