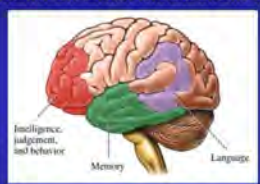
Is Alzheimer's Disease Type 3 Diabetes?

Effects of Insulin on Brain Metabolism and Function



Cardiometabolic Conference
October 24, 2014

C. Ronald Kahn, MD

Joslin Diabetes Center | Harvard Medical School

Disclosures – C. Ronald Kahn, MD

In the past 3 years, have received grant funding from:

- Eli Lilly Foundation
- Sanofi

I currently serve on the SAB or consulted for:

- Catabasis
- CohBar
- Merck
- Antriabio
- Third Rock Ventures

I am a Founder and serve on the SAB of Ember Therapeutics

Outline of Presentation

- Epidemiology of diabetes and Alzheimer's disease and other CNS disorders
- Insulin action action in the brain
- Effect of insulin resistance of brain function
- Potential use of anti-diabetic medications in Alzheimer's disease and dementia

Population Studies on Association of Diabetes and Alzheimer's Disease

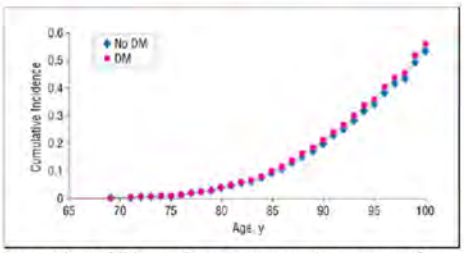
	N	Follow up	Association of DM
Rotterdam Study, 2000	6330	2 years	Double risk of AD
Rochester Study, 2001	1455	15 years	37% increased risk of AD in women; double risk in men
Religous Order Study 2004-2006	824	6 Years	65% increased risk of AD
Eric, Arch Neurol 2008	2457	8 years	1.4-1.8 increased risk of AD
Allen, Eur J Pharmacol, 2004	Review		DM associated with either accelerated cognitive decline or an ↑incidence of dementia in 8 of 9 studies
Yaffe, Diabetes Care, 2009	2977		HbA1c inversely correlated with progressive dementia

Potential Relationship Between Diabetes and Alzheimer's Disease

- Prospective 9 year study of 824 nuns and priests
- Individuals with type 2 diabetes had a 65% increased risk of developing Alzheimer's disease
- Alzheimer's patients with diabetes showed a 44% faster decline in some perceptual functions than non-diabetics with Alzheimer's disease

Arvanitakis, et al, Arch Neurol. , May 2004

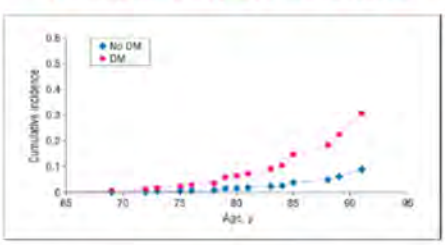
Diabetes Mellitus and Risk of Alzheimer's Disease Framingham Study: All Subjects



Cumulative incidence of Alzheimer disease in entire sample: comparison of groups with and without diabetes mellitus (DM), adjusted for age and sex

Arch Neurol. 2006;63:1551-1555

Diabetes Mellitus and Risk of Alzheimer's Disease Framingham Study: Low Risk Subjects



Cumulative incidence of Alzheimer disease in low-risk group: comparison of persons with and without diabetes mellitus (DM), adjusted for age and sex.

Arch Neurol. 2006;63:1551-1555

Low-risk subjects = plasma homocysteine level less than the top quartile or no *APOE* ε4 gene

Biological Support for Asssociation Between Diabetes and AD

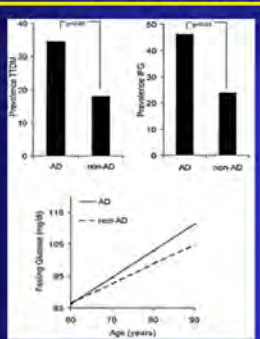
Brain amyloid

Islet amyloid

"Similar" pathological features in islet and brain

- Amyloid derived from amyloid beta protein in the brain in Alzheimer disease
- Islet amyloid derived from islet amyloid polypeptide in the pancreas in type 2 diabetes.

Increased Prevalence of T2D and IGT in Patients with Alzheimer's Disease

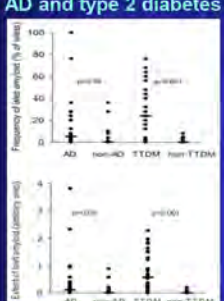


- Olmstead County Study
- The prevalence of diabetes and IFG is significantly greater in the AD patients (n=100) compared to the controls (n=138)
- AD group has a greater increase of FPG with aging compared to controls (diabetic subjects excluded)

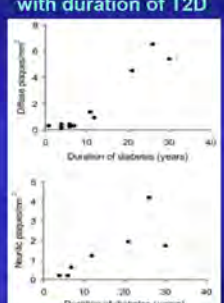
Janson et al, Diabetes, 2004

The Olmsted County Pathological Study

Increased islet amyloid in AD and type 2 diabetes

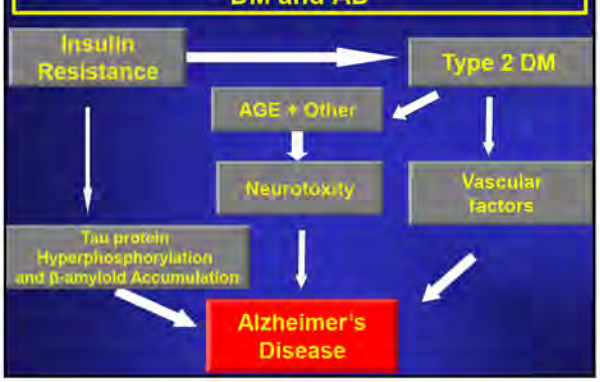


Placque density correlates with duration of T2D



Janson et al, Diabetes, 2004

A Model of the Interaction between Type 2 DM and AD



Other CNS Complications of Diabetes

- **Non-Alzheimer's Cognitive Dysfunction** (T1DM & T2DM)
  - Northam et al. *Diabetes Care* **24**:1541-1546, 2001
  - Brands et al. *Diabetes Care* **28**:726-735, 2005
  - Cukierman et al. *Diabetologia* **48**:2460-2469, 2005
  - Jacobson et al. *Diabetologia* 54:245-55, 2011
- **Higher prevalence of Depression** (T1DM & T2DM)
  - Anderson et al. *Diabetes Care* **24**:1069-1078, 2001
  - Ali et al. *Diabet Med* **23**:1165-1173, 2006
  - Hill Golden et al. *JAMA* **299**:2751-2759, 2008
- **Higher prevalence of Eating Disorders** (T1DM)
  - Daneman et al. *Horm Res* **50** Suppl 1:79-86, 1998
  - Mannucci et al. *J Endocrinol Invest* **28**:417-419, 2005
- **Abnormalities in brain imaging** (T1DM & T2DM)
  - van Harten et al. *Diabetes Care* **29**:2539-2548, 2006
  - Biessels et al. *Lancet Neurol* **7**:184-190, 2008
  - Musen, et al, Diabetes, 2012

Insulin Action in Brain

- The classical idea that CNS is insulin-insensitive and that insulin is unable to cross the blood–brain barrier (BBB) is wrong.
- Accumulating evidence shows that insulin can reach physiological levels in brain and exert short-term signaling and long-term neuronal trophic effects.
- Insulin present in adult CNS originates primarily from pancreatic β-cells and enters the CSF through areas outside the blood brain barrier as well as being transported into the brain by the cerebrospinal fluid (CSF) and crossing the BBB via a carrier-mediated, saturable process.

Links Between Alzheimer's and Diabetes

- Decreased insulin levels and IR expression in AD brain
- Inverse correlation between AD Braak stage and levels of insulin, IGF-1 and −2 and their receptors
- Decreased insulin clearance and increased amyloid-β (Aβ) levels in AD patients
- T2D-associated hyperinsulinemia has been also shown to increase Aβ peptide accumulation (a pathological hallmark of AD), due to the competition between insulin and Aβ for insulin degrading enzyme (IDE, a major Aβ-degrading enzyme) and its subsequent inhibition.
- AD model mice submitted to high fat diet-induced insulin resistance, as well as the non-obese T2D Goto-Kakizaki (GK) show increased Aβ accumulation and decreased IDE levels.
- Similar results were described for AD patients with brain insulin resistance.

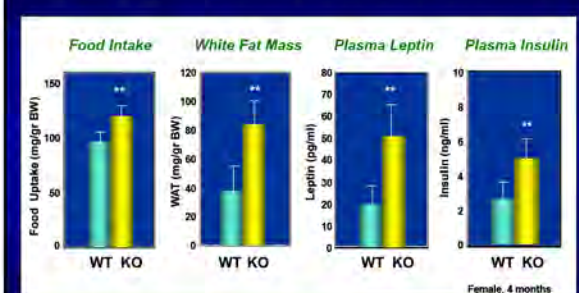
Insulin Signaling in the Brain and Creation of the NIRKO Mice

(Hill, et al 1986)

Bruning, et al. 2002

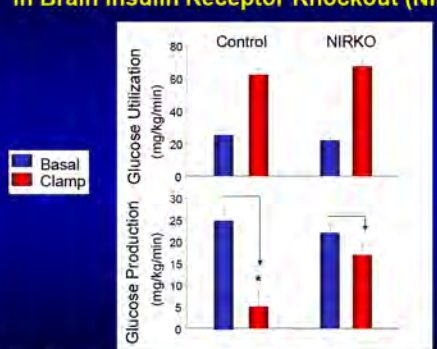
T. Kondo, 2005

NIRKO Mice Exhibit Increased Food Intake, Adipose Mass, Hyperleptinemia and Insulin Resistance



Bruning, 2002

Insulin Fails to Suppress Hepatic Glucose Output in Brain Insulin Receptor Knockout (NIRKO) Mice

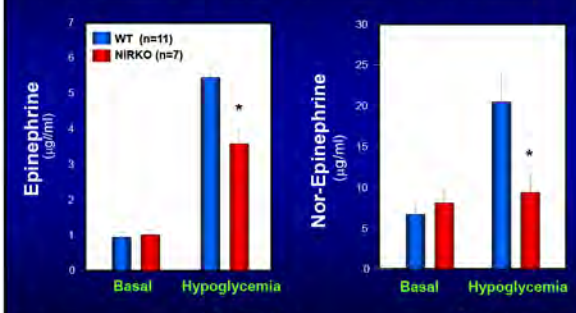


Fisher, et al. 2005

Two Major Classes of Insulin Sensitive Neurons in the Hypothalamus

Koenner, et al. Cell Metab, 2006

Impaired Epinephrine and Norepinephrine Responses to Hypoglycemia in NIRKO Mice



Fisher, 2004

* p<0.01 vs WT

* p<0.05 vs WT

Insulin Actions in the Brain Altered in NIRKO Mice

Insulin Receptors in the Brain

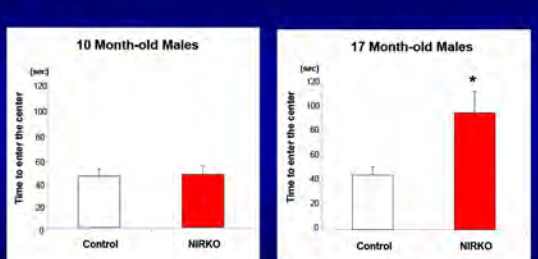
What about mental function: memory, learning, mood, and behavior?

Novelty Suppressed Feeding Test

Mice are fasted for 16 hours, then placed into an open field with a white disc containing food.

Since the mouse is hungry, the longer the mouse takes to go onto the white plate is considered as a sign of anxiety or fear.

NIRKO Mice Develop Abnormal Novelty Suppressed Feeding Test with Age



A. Kleinridders, unpublished

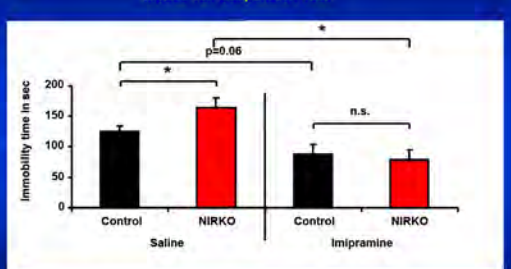
Mouse Tail Suspension Test

A mouse is suspended from its tail and observed for 6 min. The mouse will show alternate periods of agitation and immobility.

The time of immobility is considered as a lack of motivation or depressive behavior.
(Psychopharmacology (Berl). 1985;85(3):367-70.)

NIRKO Mice Have Depressive-like Behavior Which is Reversed by Imipramine

Mouse Tail Suspension Test



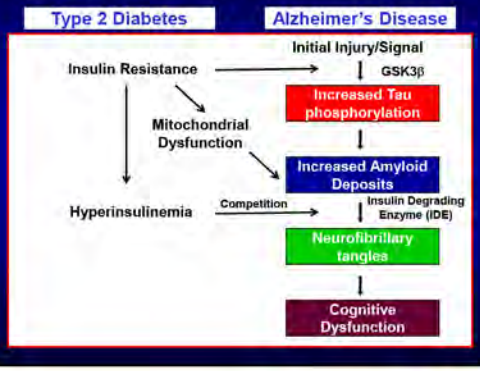
Age:24 month male mice; n=6-8 per group

Mice were injected i.p. 16 mg/kg imipramine 30 min prior to Tail Suspension Test

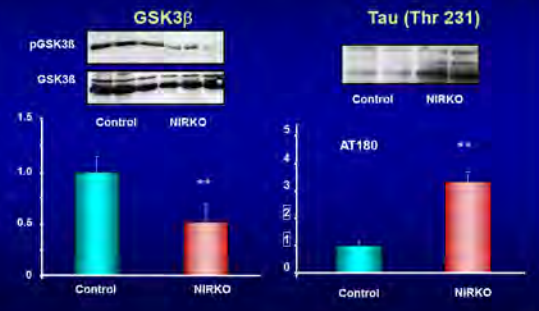
How Does Insulin Action Affect Brain Function?

- Insulin can affect glucose uptake and metabolism, at least in selected regions of the brain
- Insulin can regulate brain mitochondrial metabolism and levels of oxidative stress
- Insulin regulates lipid (cholesterol, triglyceride, and free fatty acid metabolism in the brain
- Insulin may regulate production of neurotransmitters and their receptors in brain.
- Insulin may regulate Tau protein phosphorylation and clearance of amyloid and amyloid precursors in the brain.

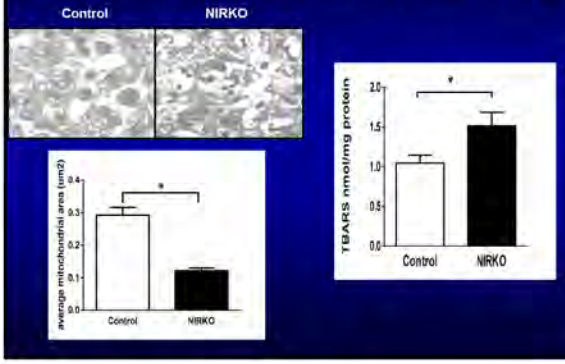
Potential Relationship Between Insulin Signaling and Alzheimer's Disease



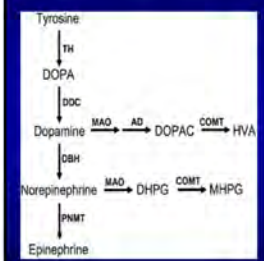
NIRKO Mice Exhibit Decreased GSK3 Phosphorylation & Increased Tau Phosphorylation

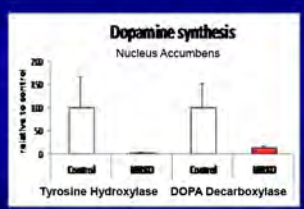


NIRKO Mice Exhibit Altered Mitochondrial Function and Increased Oxidative Stress in Brain



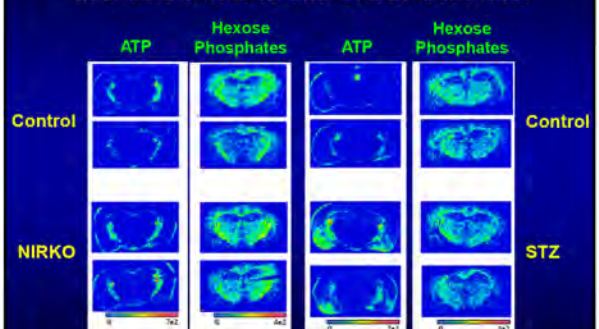
Dopamine Synthesis Enzymes are Decreased in NIRKO Mice





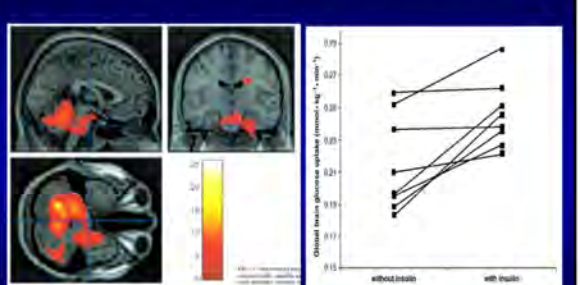
Andre Kleinridders and Emmanuel Pothos

Changes in Hexose Phosphate and ATP Levels in Brains of NIRKO and STZ Diabetic Mice



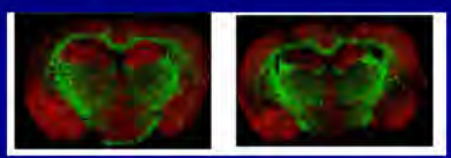
Andre Kleinridders with Michelle Reyzer and Richard Caprioli

Insulin Effect on Brain Glucose Uptake



Bingham, Diabetes, 2002

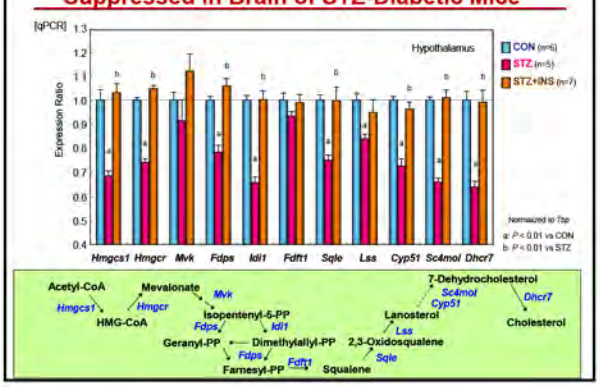
Regional Differences in Brain Metabolism Detected by High Density Mass-Spectroscopy Imaging



Green = Hexose monophosphate
Red = Hexose bisphosphate

Kleinfelders, et al, unpublished

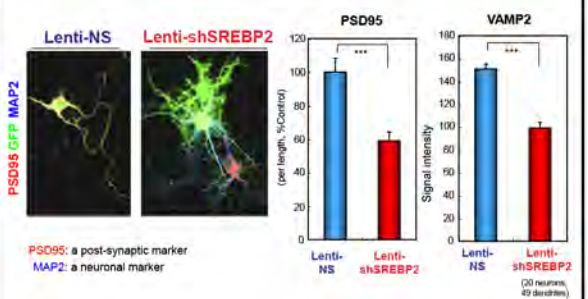
Cholesterol Biosynthesis Pathway Is Suppressed in Brain of STZ-Diabetic Mice



Role of Cholesterol in the Brain

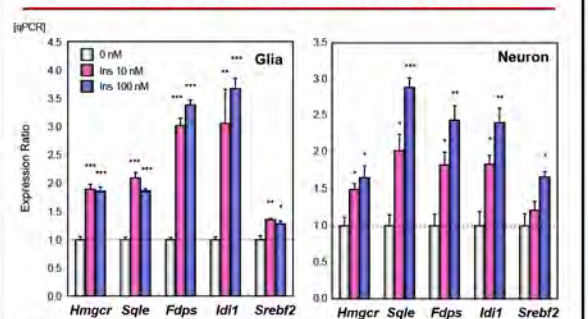
- The brain is the most cholesterol rich organ in the body, accounting for ~25% of cholesterol present in humans
- About 70% of the brain cholesterol is associated with myelin, while the remaining 30% is involved in membrane function
- More than 95% of the cholesterol in the brain occurs through de novo synthesis
- Diseases altered brain cholesterol metabolism include:
  - Nieman Pick Type C
  - Smith-Lemli-Opitz syndrome (*DHCR7* gene)
    - Microcephaly, mental retardation, learning disabilities
  - Alzheimer's disease
    - Genetic risk associated with ApoE ε4 allele
    - SNPs in LRP1 and HMG-CoA reductase

SREBP-2 Knockdown in Neurons Results in Reduced Cholesterol Synthesis and Reduced Synapse and Vesicle Formation



PSD95: a post-synaptic marker
MAP2: a neuronal marker

Insulin Induces Cholesterol Synthesis Genes in Both Glial And Neuronal Cells



19 days in vitro
Serum-deprived
0.5% BSA for 5 hrs
Incubated with insulin for 5 hrs

Improvement in Alzheimer's with Diabetes Treatment Modalities

- Intensive diabetes therapy to control glycemia
- Intranasal Insulin
- GLP-1 analogues

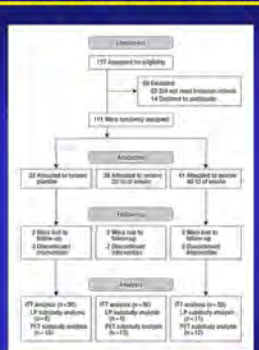
Improvement in Alzheimer's with More Intense Diabetes Treatment

No data on tight diabetes control in Alzheimer's patients, but effects of intensive glucose lowering on brain structure and function was examined in people with type 2 diabetes in the ACCORD MIND Study

- 2,977 participants (aged 55–80 y) with T2DM, high HbA1c (7.0-7.9%) and a high risk of cardiovascular events
- Two measures of effects of Rx on the brain at 0, 20 and 40 months in :
  - Total brain volume (TBV) by MRI – brain structure (614 pts)
  - Digit Symbol Substitution Test (DSST) - cognition
- No significant difference in mean 20 or 40-month DSST scores, but intensive group tended to have a lower rate of decline over time.
- Intensive-treatment group had a smaller decline in Brain Volume than the standard-treatment group (-13 vs. -17.7, p=0·0007)

Lancet Neurology, 2011

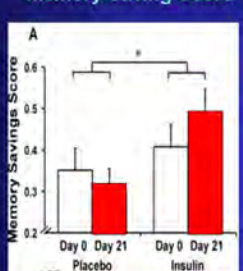
Improvement in Alzheimer's with Nasal Insulin



Reger, Neurology, 2008

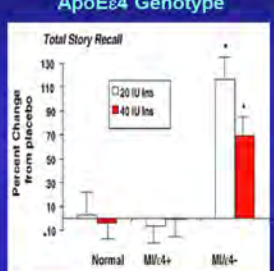
Improvement in Alzheimer's with Nasal Insulin

Memory Saving Score



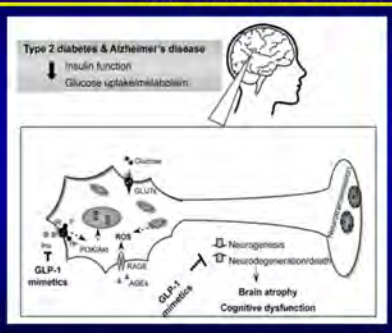
Reger, Neurology, 2008

Improvement Depends on ApoEε4 Genotype



Reger, Neurobiol. Aging, 2006

Potential for GLP-1 Analogues in Alzheimer's with Diabetes Treatment



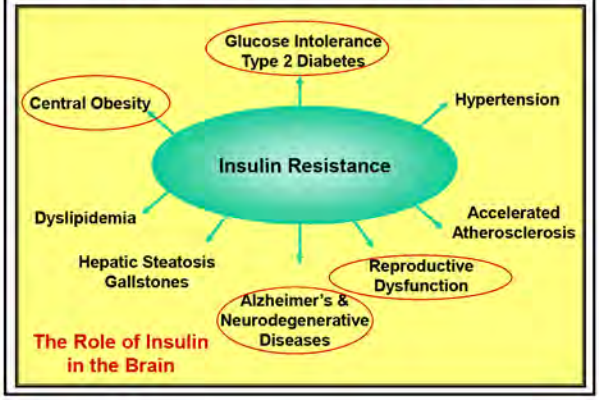
Two clinical trials of Liraglutide are registered on ClinicalTrials.gov, both in Europe

Duarte, BBA, 2013

Potential of GLP-1 Analogues in Alzheimer's Disease

- The GLP-1 receptor is expressed on some neuronal populations (Li., 2009).
- GLP-1R knock-out mice show impaired of memory formation (Abbas, 2009).
- GLP-1R stimulation has been shown to have some neural protection, enhance synaptic plasticity and memory formation, promote LTP (Abbas et al., 2009), stimulate neuronal proliferation (Belsham et al., 2009), induce the differentiation of neural stem cells (Isacson et al., 2011) and produce neurite outgrowth (Luciani et al., 2010; Salcedo et al., 2012).
- The GLP-1 analogue Exendin-4 has been shown to partially reverse the impaired insulin signaling in hippocampal cultures of AD model animals and improved cognition in AD Tg mice.
- Administration of the GLP-1 analogue Liraglutide to APP/PS1 mice for 8 weeks resulted in the prevention of memory impairments and a significant decrease in β-amyloid deposition (McClean et al., 2011).
- These suggest that stimulation of GLP-1 receptors (GLP1Rs) may represent a new approach to prevent treat AD (Bomfimet al., 2012).

Insulin Resistance and the Metabolic Syndrome



The Kahn Lab: Recent Past & Present

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