Diabetes and Alzheimer’s disease: Animal model study

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Suggested Common Pathogenesis

- Insulin deficiency
- Insulin resistance
- Impaired glucose metabolism
- AGEs and oxidative stress
- ↑FFA → inflammation and oxidative stress
- Hypercholesterolemia → ↑caveolae and lipid rafts
Studies using DM model

- **Type I DM**
  - STZ injection model: ip, icv
  - Spontaneous T1DM model
    - BB/Wor rat
- **Type II DM**
  - Spontaneous T2DM model
    - db/db mouse, BBZDR/Wor rat
- **Insulin signaling genetic model**
  - IDE KO
  - Irs2 KO
  - Neuron-specific IR KO
Studies using AD model

- **APP mutation model**
  - TG2576 mouse (APP K670N/M671L) taking high lipid diet
  - TG2576 mouse injected STZ (i.c.v.)

- **Tau mutation model**
  - pR5 (p301L) taking STZ (i.p.)

- **Cross mating**
  - APP23 - ob/ob (leptin deficient) mouse
  - APP23 – NSY (polygenic T2DM) mouse
T1DM, STZ systemic injection

- ↓ Insulin
- ↑ tau phosphorylation
- ↑ Aβ production: controversial
  - + Spatial learning,
  - ↓ hippocampal LTP

Recovered by insulin
STZ intraventricular injection

STZ act to GLUT2 in the brain, small and heterogenous

- → IR, IGF-1R
- ↓ pPI-3K, pERK-1, pGSK-3β
- ↓ GLUT-3, Glucose metabolism
- ↓ O-GlcNAcylation

- ↑ p-tau, ↑ p-NF, ↓ MT binding activity
- NF degeneration
- Aβ production: ↑ conglo-red+ aggregates in the capillaries
- ↓ Spatial learning
T1DM, spontaneous

BB/Wor rat

- Progressive impaired cognitive function
- Insulin, IGF-1 action, neuronal apoptosis

Reversed by insulinomimetic C-peptide
T2DM, spontaneous

**BBDZR/Wor**, diminished GLUT2 transporters, obesity and insulin resistance

- Neuronal loss, gliosis, \( \downarrow \) synaptophysin, \( \uparrow \) dystrophic neurites
- Normal IR-\( \beta \) but \( \downarrow \) IGF-1R\( \beta \) and \( \downarrow \) p-Akt
- \( \uparrow \) p-tau, \( \uparrow \) APP, \( \uparrow \) \( \beta \)-secretase, \( \uparrow \) A\( \beta \)

**Db/db mouse**, point mutation in *leptin* gene

- \( \uparrow \) Tau cleavage
- \( \uparrow \) p-tau at S199/202, T231, Ser396, more than ip STZ injected mouse
T2DM

- Normal insulin, IR
- Impaired insulin signaling, Obese

- ↑ tau phosphorylation >> T1DM
- ↑ tau cleavage, only in T2DM
- ↑ Aβ production

Neuronal loss, gliosis, ↓ synaptophysin, ↑ dystrophic neurites

Recovered by?
Insulin deficiency

+ effect of insulin
  - Memory
  - Regulate synapse, trophic factor
  - Improve cognition
  - Intranasal insulin trial

- effect of insulin
  - Hyperinsulinemia → ↑Aβ42 & Inflm cytokines
  - IDE deficiency → ↓Aβ42 clearance

Optimal dosage!
Insulin resistance

Insulin → Insulin R

Ras → Shc → PI3 kinase

PI3 kinase → p85, p110

PI3 kinase → PDK1

PDK1 → Akt

Akt → PKC

Akt → GSK3

Akt → FOXO

Akt → TSC-2
Impaired glucose metabolism

(Liu et al., 2009 Brain)
AGEs and others

- AGEs and oxidative stress
- ↑FFA → inflammation and oxidative stress
- Hypercholesterolemia → ↑caveolae and lipid rafts
Insulin signaling animal model

IDE-/-

- Hyperinsulinemia and Glucose intolerance
- \( \downarrow \) A\( \beta \) degradation
- \( \uparrow \) Cerebral accumulation of endogenous A\( \beta \)
Irs2-/-
- ↑ tau phosphorylation at Ser202 → ↑ cytoplasmic deposits → but not resulting in cell death ...? Significance

Tg2576/Irs2-/-, Rather
- ↓ Amyloid deposit
- Behavioral improvement on fear memory
- ↑ tau phosphorylation at 396/404, 235, 231, but not at Ser199/202/Thr205
NIRKO mice

- ↓↓↓↓ PI-3K, p-Akt, GSK3β
- ↑ tau phosphorylation at Thr231 but not at Ser202
- No change in neuronal survival and memory on MWZ, open field test, and PET

Additional mechanism should be present!
in APP mutation model

TG2576 fed high fat diet

- Greater insulin level and obesity
- ↓Tyr P-IR, p-PI3K, p-Akt, IDE

- 2x ↑Aβ40 & 42, ↑γ-secretase
- ↓p-GSKα and β, correlate with γ-CTF

- Water maze spatial learning
TG2576 injected STZ icv

- ↓ Spatial cognition
- ↑ cerebral aggregated Aβ fragments
- ↑ total tau and ↓ p-tau fraction
- No marked necrotic and apoptotic changes
- Linear negative correlation
  - between Aβ42 and cognition,
  - between GSK-3α/β and aggregated Aβ
in Tau mutation model

P301L tau mutation, STZ injection

- ↑ tau phosphorylation, ↑ soluble tau
- Aggregation and NFT formation

- But no behavior evidence
in 3xTg-AD mouse

STZ exposure

- ↑ Soluble Aβ
- ↑ APP
- Reversed by long-acting analogue exendin-4 (Ex-4) = GLP-1 receptor stimulator
Cross mating

- APP23 (APPsw mutant)-ob/ob
  - Greater Hyperglycemia, Hyperinsulinemia, Glucose intolerance, Hyperlipidemia, ↓pAkt
  - Only faint amyloid plaques in Ent both in APP or APP-ob/ob at 12M
  - dense amyloid deposits in small arteries,
  - RAGE in blood vessels, ↑infl molecules
  - ↓brain volume, Early learning deficit
Takeda et al., PNAS 2010
Treatment evidence

- In 6M TgCRND8 (double APP mutation)→ leptin treatment for 8 weeks
  - ↓ Aβ40, ↓ amyloid burden, ↓ C99-CTF, ↓ β-secretase activity
  - ↓ p-tau
  - ↑ Cognitive function in object recognition and fear conditioning
Rosiglitazone for 4 months in 13M old J20 APP mutation mouse

- ↑ Aβ clearance, ↓ Aβ aggregation, ↓ Aβ oligomer
- ↓ Neuropil threat
- ↓ proinflammatory markers
- ↑ Object recognition and spatial memory
SUMMARY

- Multiple factors are involved in linking DM and AD, not solitary one
  - Insulin deficiency
  - Insulin resistance, Impaired glucose metabolism
  - AGEs, ↑FFA, inflammation and oxidative stress, Hypercholesterolemia
- What is the significance of ↑pTau?
- Evidence of effect of DM on Aβ is weak
- Can AD itself sufficiently result in T2DM?
- Can T2DM itself sufficiently result in AD?
- At least, AD and DM aggravate each other
  → modulation both at the same time will be beneficial
Thank you for your attention!