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

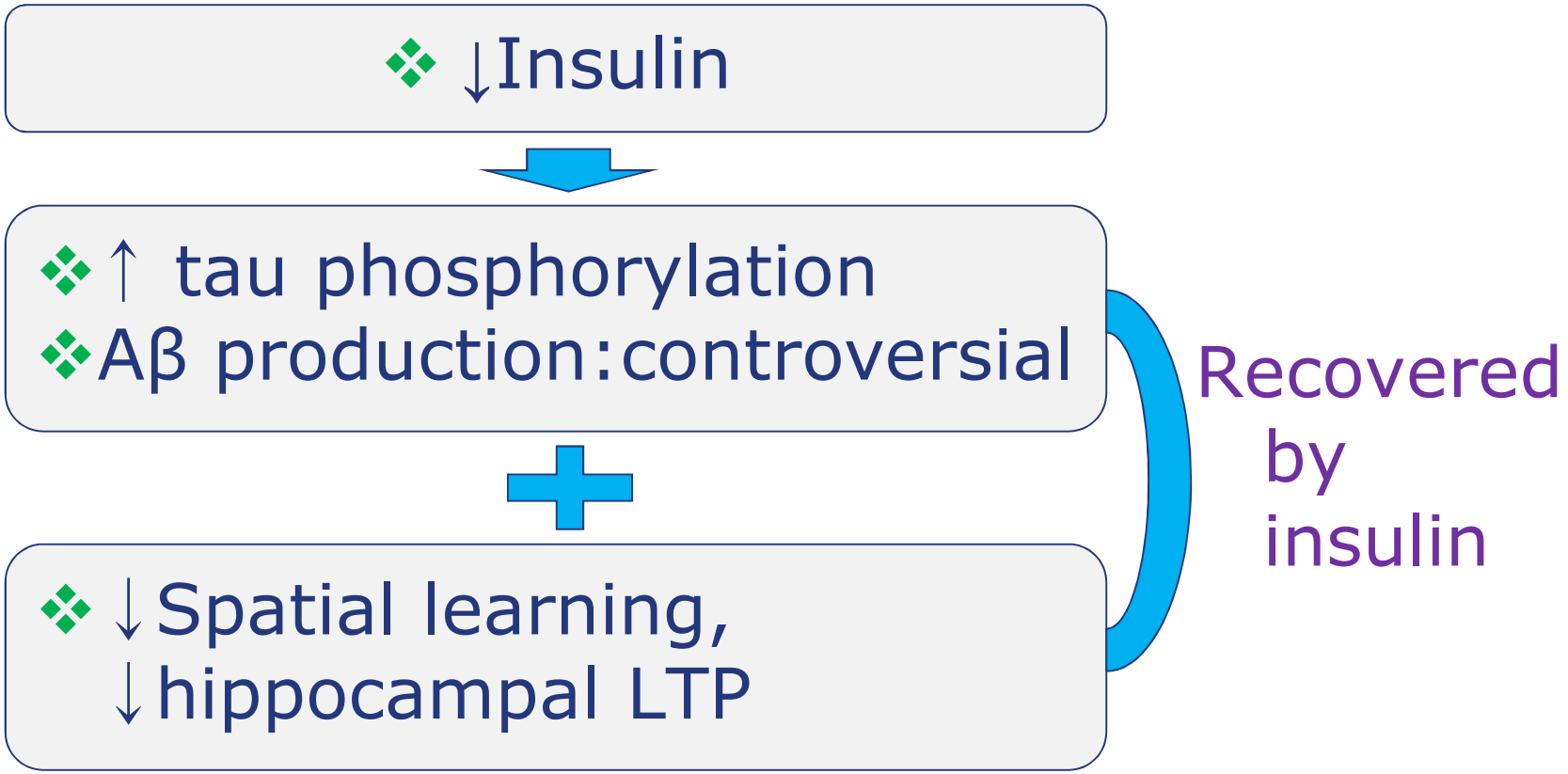
Studies using DM model

- 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



●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:? ↑congo-red+ aggregates in the capillaries

- ↓Spatial learning

●T1DM, spontaneous

BB/Wor rat

- ❖Progressive impaired cognitive function
- ❖Insulin, IGF-1 action, neuronal apotosis

Reversed by insulinomimetic C-peptide

●T2DM, spontaneous

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

- Neuronal loss, gliosis, ↓synaptophysin, ↑dystrophic neurites
- Normal IR-β but ↓IGF-1Rβ and ↓p-Akt
- ↑p-tau,↑APP, ↑β-secretase, ↑Aβ

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

- ↑Tau cleavage
- ↑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 ?

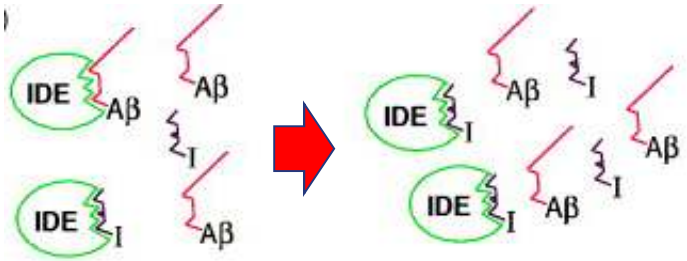
Insulin deficiency

+ effect of insulin

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

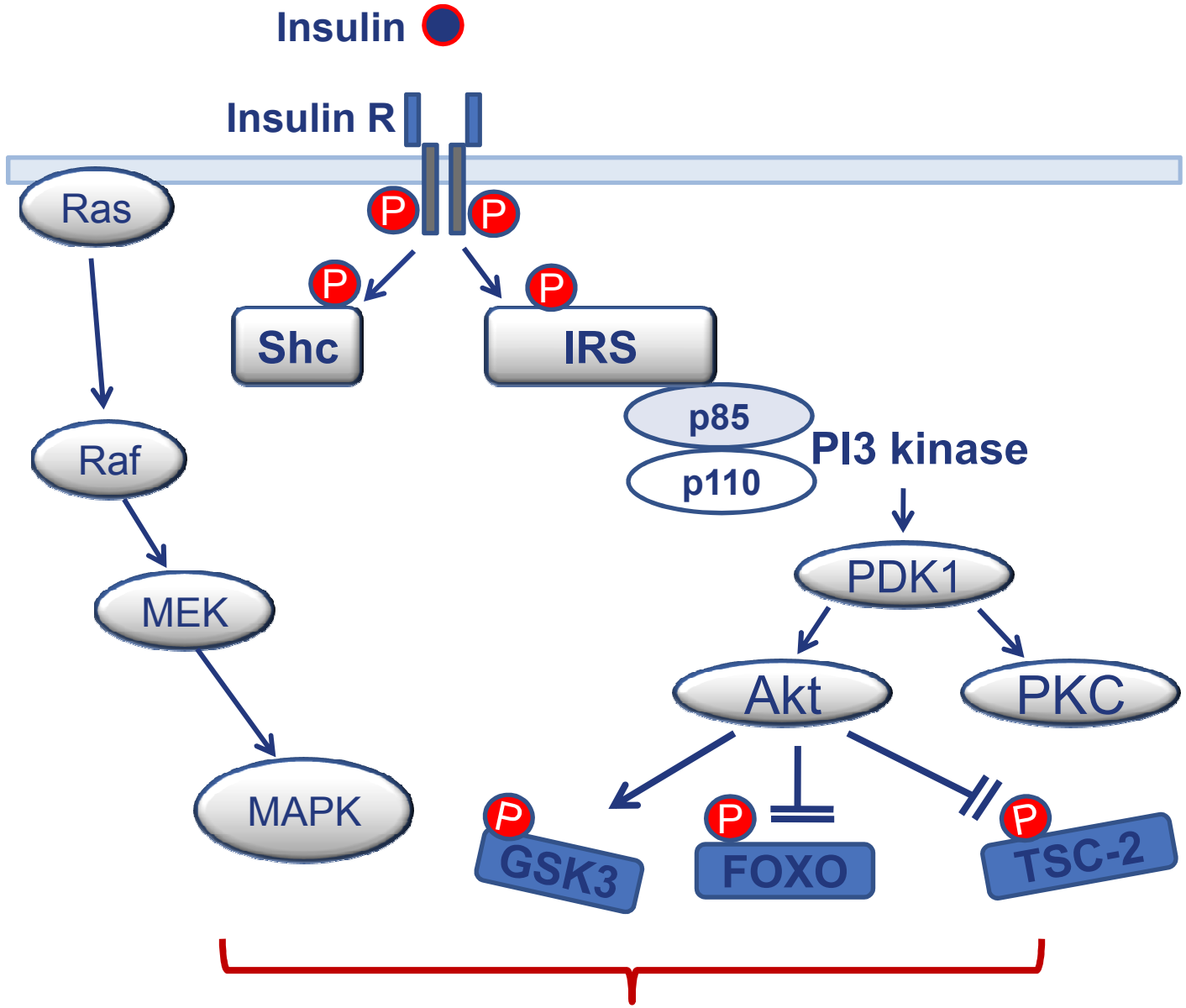
- effect of insulin

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

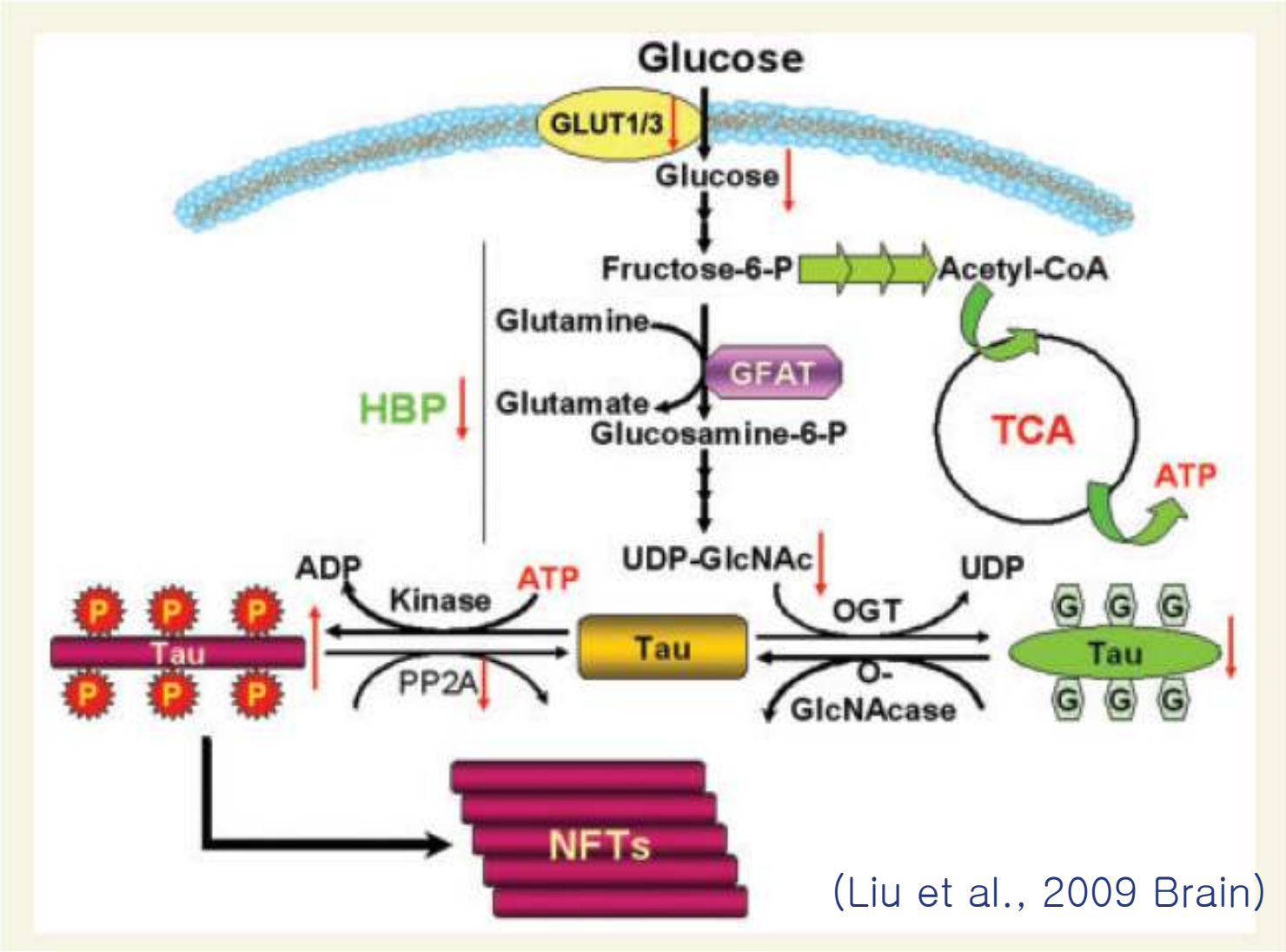


Optimal dosage!

Insulin resistance



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
- ↓ Aβ degradation
- ↑ Cerebral accumulation of endogenous Aβ

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*

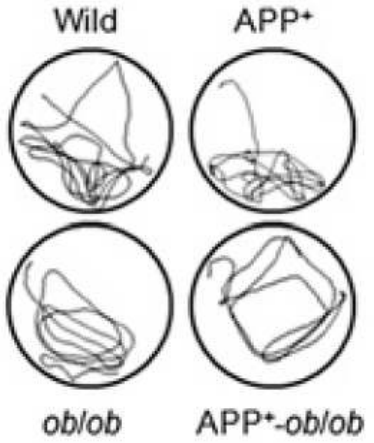
in 3xTg-AD mouse

STZ exposure

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

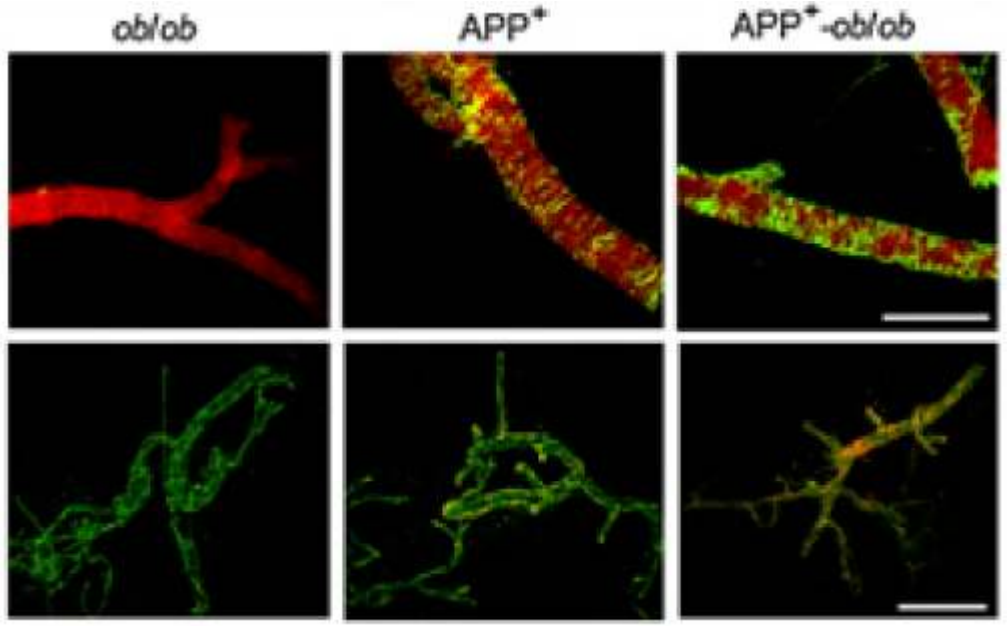
●Cross mating

- ❖ 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

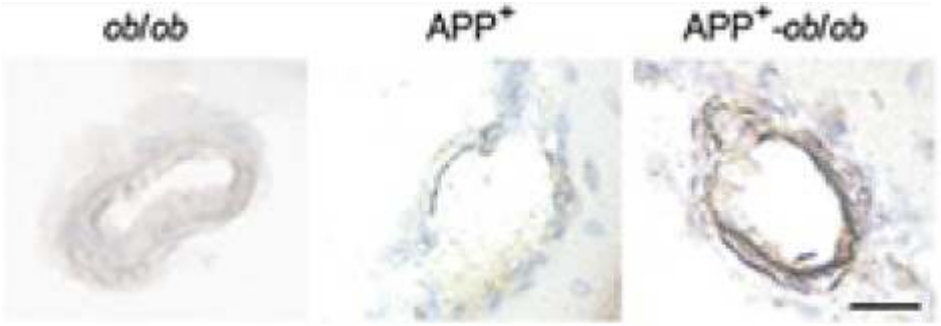


SMA/
Aβ

CD31/
Aβ



RAGE



Takeda et al., PNAS 2010

●Treatment evidence

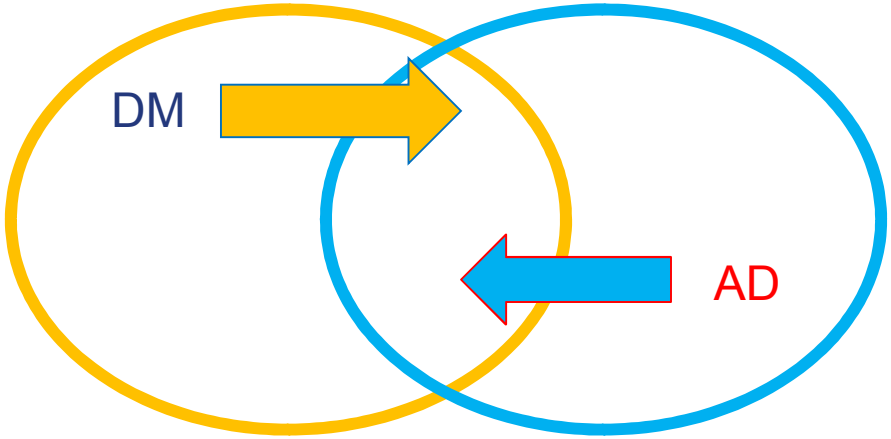
- In 6M TgCRND8 (double APP mutation)→ leptin treatment for 8 weeks
  - ↓ Aβ40, ↓ amyloid burden, ↓ C99-CTF, ↓ β-secretase activity
  - ↓ p-tau
  - ↑Cognitive function in object recognition and fear conditioning

- 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!