Novel mechanism of age-dependent pathologic tau accumulations in type 2 diabetes

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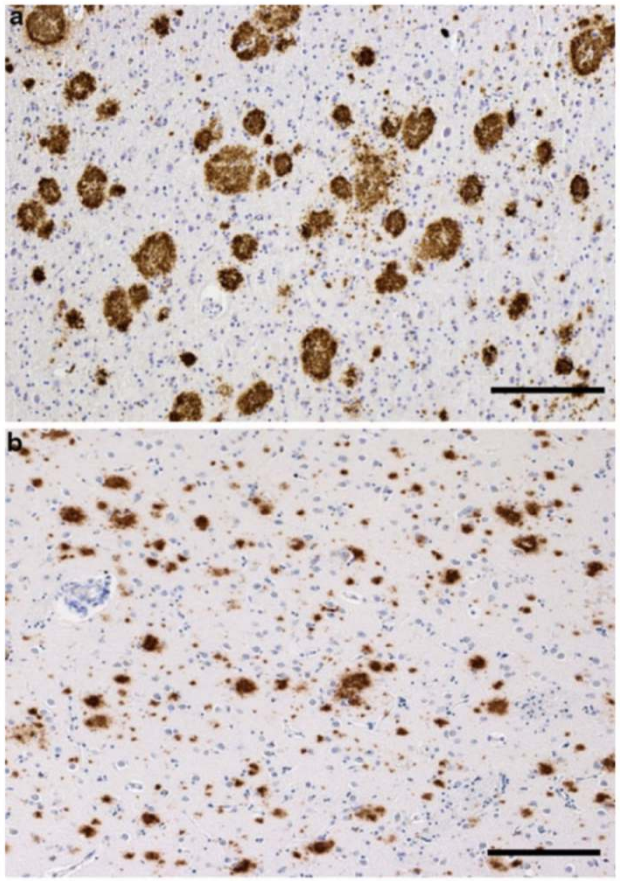
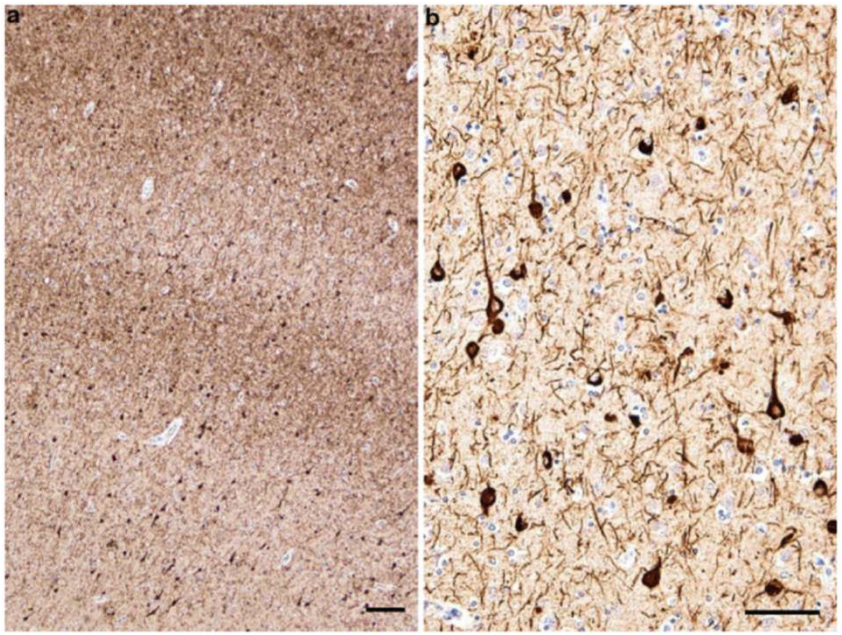
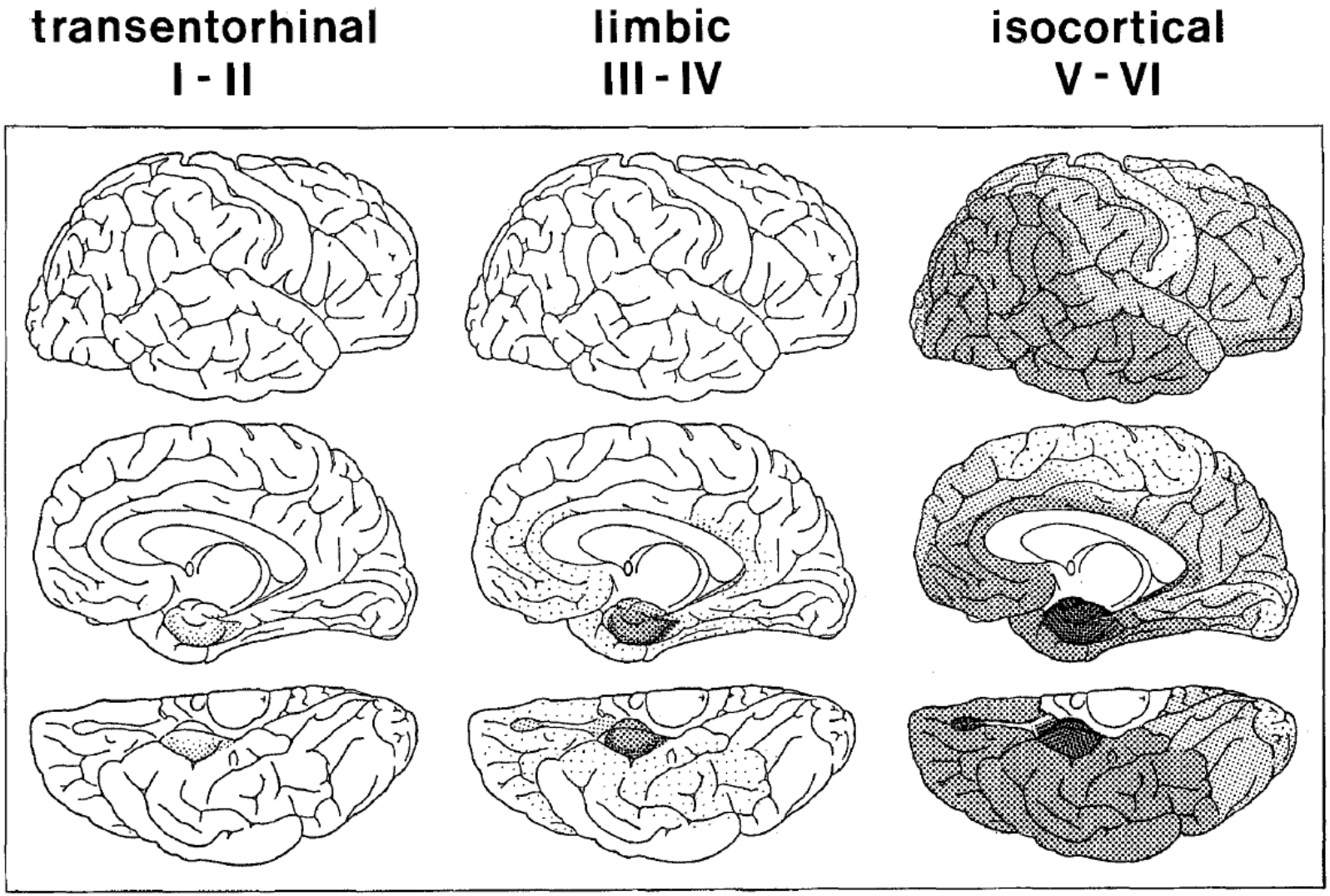
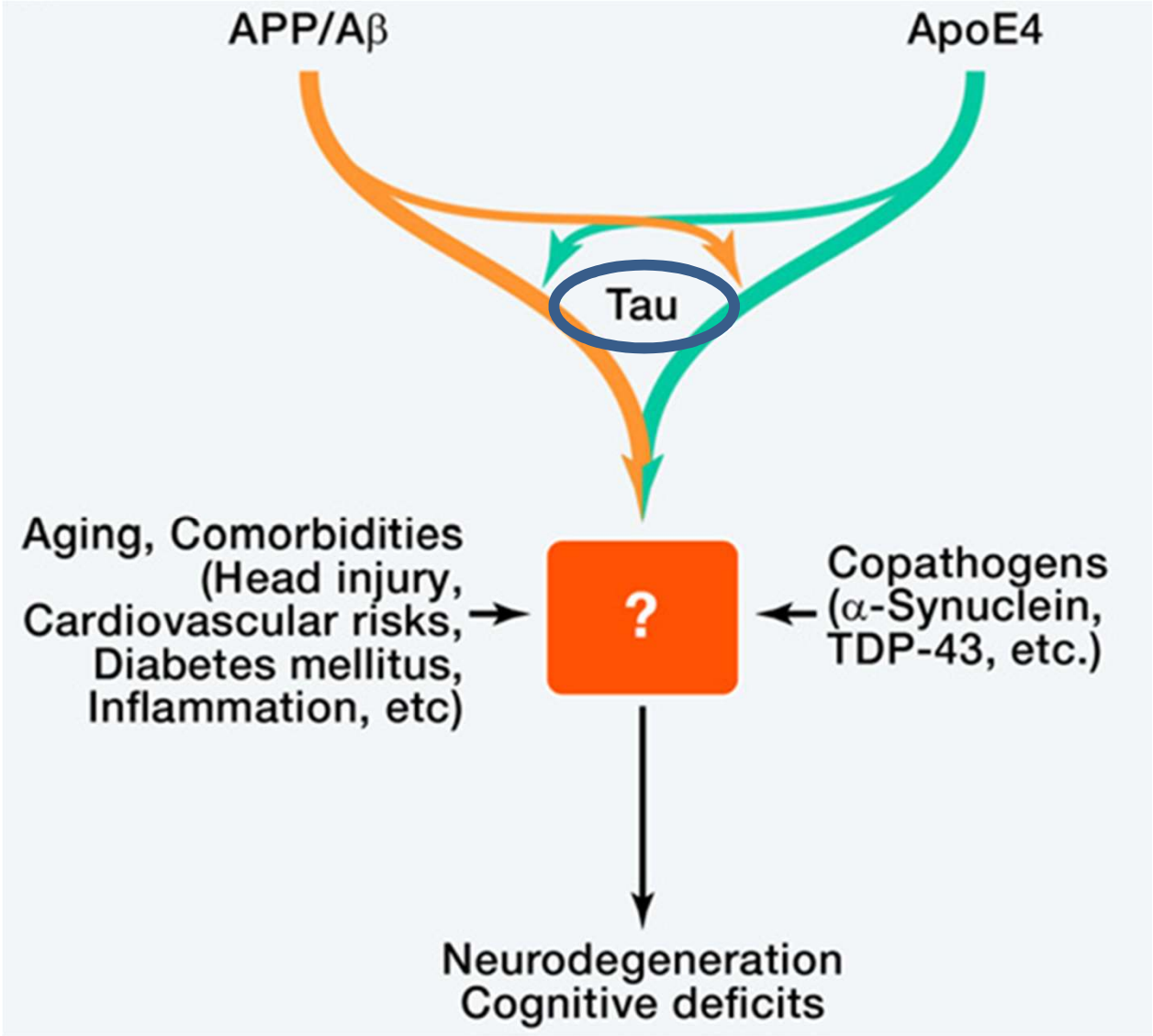

a
b

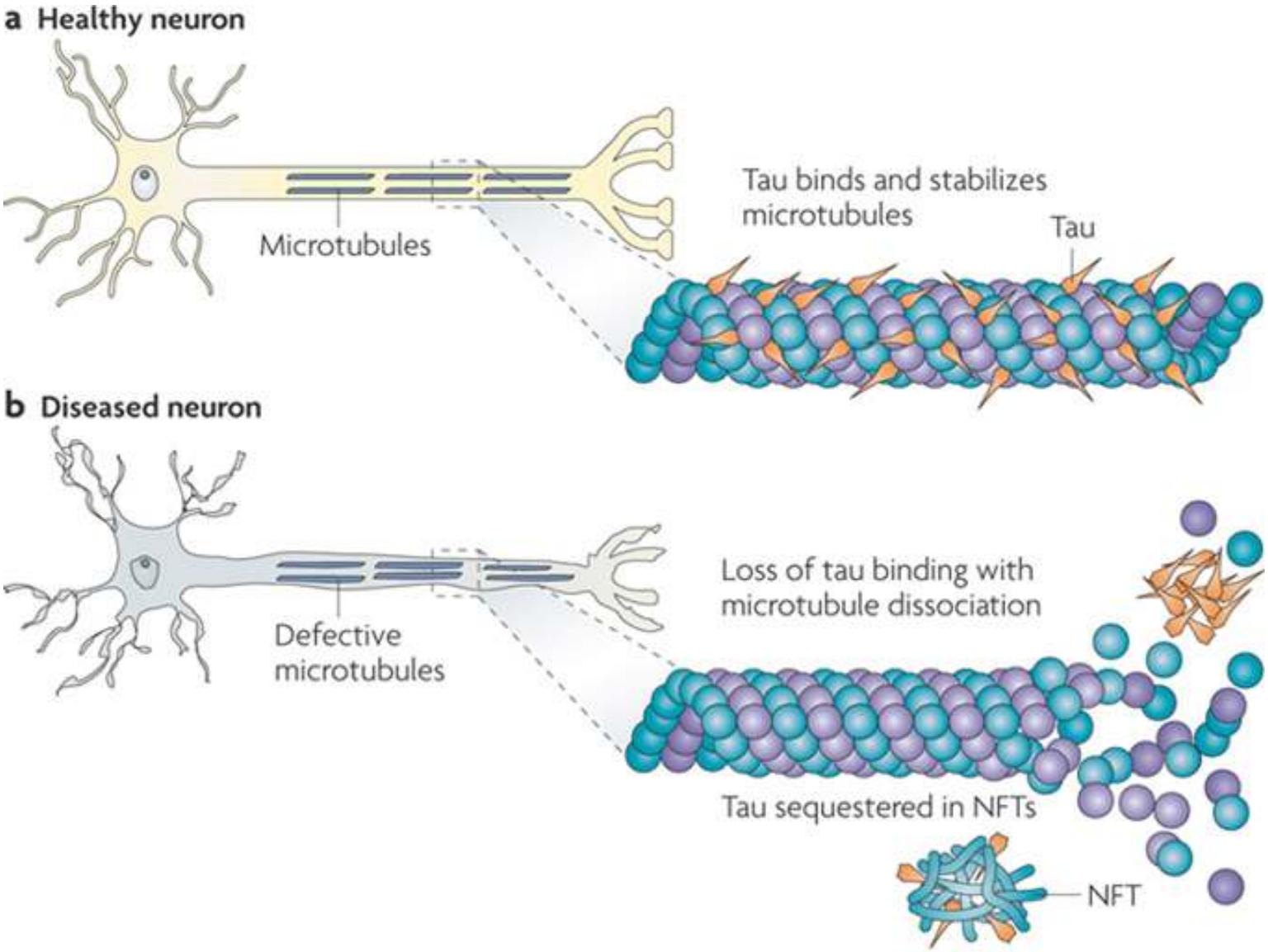

a
b


transentorhinal
I - II
limbic
III - IV
isocortical
V - VI


APP/Aβ
ApoE4
Tau
Aging, Comorbidities
(Head injury,
Cardiovascular risks,
Diabetes mellitus,
Inflammation, etc)
?
Copathogens
(α-Synuclein,
TDP-43, etc.)
Neurodegeneration
Cognitive deficits

Mechanism of gain of toxicity of tau in AD

- Tau phosphorylation
- Tau ubiquitination
- Tau conformational changes
- PHF formation



Brunden et al., 2010

Background

- Type 2 diabetes mellitus (T2DM) increases the risk of Alzheimer's disease (AD) by 1.4–4.3 times

- Various mechanisms are shared by both diseases

Table 2 The correlations of HOMA-IR with neuropsychological and neuroimaging data

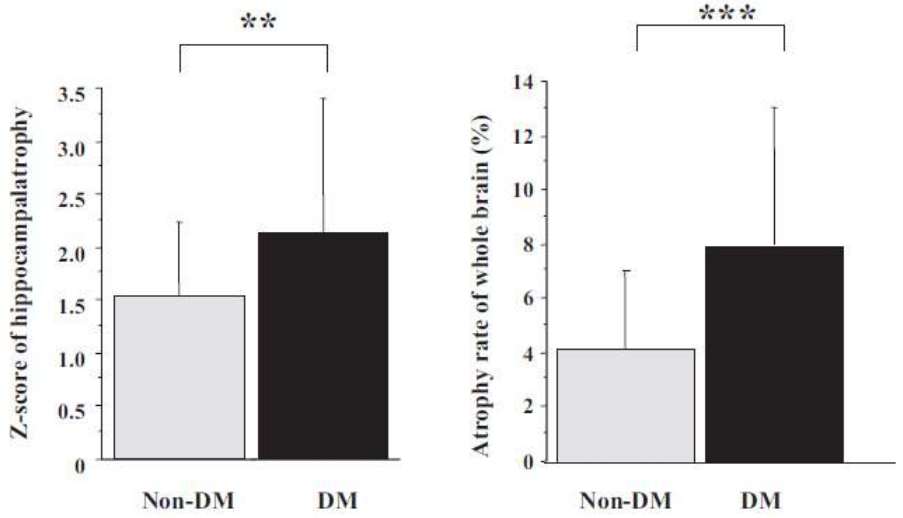
	Mean ± SD	Correlations
NP tests		
K-MMSE	23.5 ± 3.9	$r = -0.053$, $p = 0.630$
K-BNT	−0.9 ± 1.7	$r = 0.102$, $p = 0.354$
RCF T-copy	−1.0 ± 2.9	$r = -0.147$, $p = 0.181$
SVLT-I	−1.1 ± 1.0	$\mathbf{r = -0.244}$, $\mathbf{p = 0.026}$*
SVLT-D	−1.2 ± 1.3	$r = -0.152$, $p = 0.165$
RCFT-I	−1.1 ± 1.0	$r = -0.106$, $p = 0.338$
RCFT-D	−1.1 ± 1.0	$r = -0.150$, $p = 0.174$
COWAT	−0.6 ± 0.9	$\mathbf{r = -0.270}$, $\mathbf{p = 0.013}$*
Digit span	0.1 ± 1.1	$r = -0.080$, $p = 0.479$
Neuroimaging		
Lt H vol (mL)	3624 ± 1036	$r = -0.097$, $p = 0.564$
Rt H vol (mL)	3565 ± 1404	$r = -0.119$, $p = 0.476$

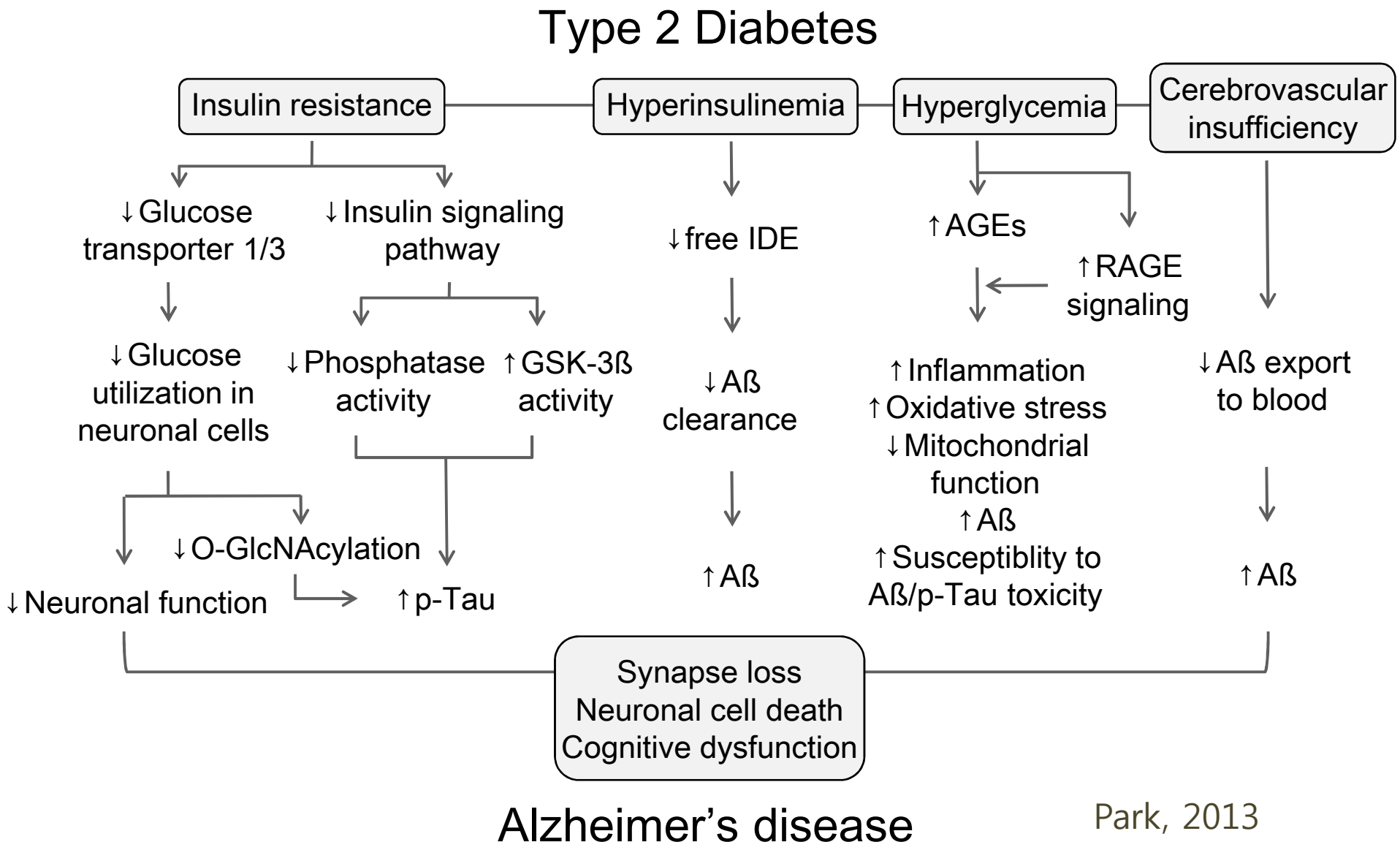
Kim et al., 2014

- Association of cognitive dysfunction with hippocampal atrophy in elderly patients with T2DM (Hayashi, et al., 2011)

Table 1 – Comparison of non-diabetic subjects and patients with type 2 diabetes.

	Non-diabetic subjects	Patients with type 2 diabetes	*p*
N	53	61	
Age (years)	74 ± 5	74 ± 7	0.62
Sex (M/F)	25/28	34/27	0.36
Height (cm)	156.3 ± 9.9	154.4 ± 8.4	0.29
Weight (kg)	57.3 ± 11.3	55.2 ± 9.8	0.28
BMI (kg/m^2)	23.3 ± 3.3	23.2 ± 4.0	0.80
FPG (mg/dl)	96 ± 10	160 ± 46	<0.01
HbA1c (%)	5.7 ± 0.3	9.5 ± 2.1	<0.01




Type 2 Diabetes
Insulin resistance
Hyperinsulinemia
Hyperglycemia
Cerebrovascular insufficiency
↓Glucose transporter 1/3
↓Insulin signaling pathway
↓free IDE
↑AGEs
↑RAGE signaling
↓Glucose utilization in neuronal cells
↓Phosphatase activity
↑GSK-3ß activity
↓Aß clearance
↑Inflammation
↑Oxidative stress
↓Mitochondrial function
↑Aß
↑Susceptiblity to Aß/p-Tau toxicity
↓Aß export to blood
↓O-GlcNAcylation
↓Neuronal function
↑p-Tau
↑Aß
↑Aß
Synapse loss
Neuronal cell death
Cognitive dysfunction
Alzheimer's disease

Park, 2013

Table 1. Animal studies using the diabetes mellitus (DM) models in the literature

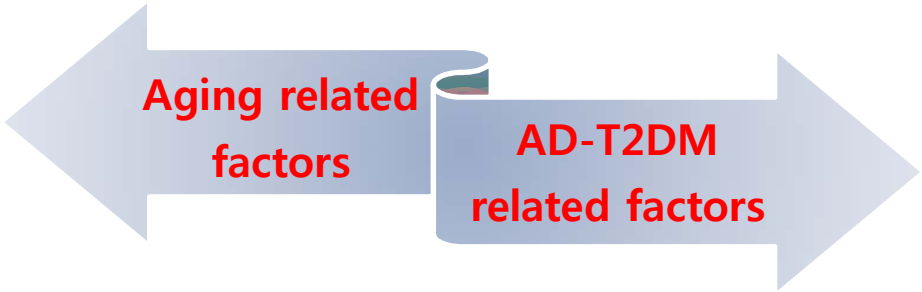
DM models	AD-related pathologic changes	Behavior changes
STZ-injection models		
STZ systemic injection to C57BL/6J, JAX mice [14]	↑ p-Tau at S199/202 & T231, No tau cleavage Less prominent tau pathology than T2DM models (db/db mice), which were compared at the same time	ND
STZ systemic injection to Swiss Webster mice [16]	↑ p-Tau at T231 ↑ Aβ, but similar level of APP & CTF ♣ Partial reversal of these changes by insulin	Impaired learning on Barnes circular-maze task
STZ systemic injection to C57BL/6NJcl mice [15]	↑ p-Tau at S199, S396, S404 ⇒↓Tau binding to microtubules p-Tau expression is limited to the neuropil & axons, No difference in APP, CTF, & Aβ levels ♣ Prevention of tau pathology by insulin	ND
STZ systemic injection to Wistar rats [20]	↑AGEs-RAGE complexes ⇒ ↑BACE1 (both protein & mRNA) through ↑NF-kB	ND
STZ i.c.v. injection to Wistar rats [19]	↑ p-Tau at S199, T212, S396 in the cerebrum, but not at S202, T205, S214, S217, S262, S422 ↑ Phosphorylation of neurofilaments ↓ Microtubule-binding activity of tau ↑ Neurofibrillary degeneration	ND
STZ i.c.v. injection to Wistar rats [18]	↑ Congo-red-positive aggregates in the brain capillaries, suggesting Aβ peptide-like aggregates	↓Memory function on Morris water-maze test
STZ i.c.v. (3rd ventricle) injection into Wistar rat [21]	↓ Phosphorylation of CREB ↓ Akt, ↓IDE, ↑Aβ in hippocampus	↓ Performances on Morris water-maze test
Spontaneous DM models		
BBZDR/Wor rats (T2DM) compared with BB/Wor (T1DM) [22]	Neuronal loss in both, but worse in BBZDR/Wor Gliosis in both, but more in BBZDR/Wor ↓ Synaptophysin stain ↑ Dystrophic neurites, but worse in BBZDR/Wor ↑ APP, β-secretase, Aβ, but more in BBZDR/Wor ↑ p-Tau in both, but more in BBZDR/Wor ♣ Prevention by insulinomimetic C-peptide	ND
db/db mice (T2DM) compared with STZ-injection model [14]	↑Tau cleavage in db/db ↑ More prominent p-Tau at more sites, S199/202, T231, & Ser396 in db/db	ND
Otsuka Long-Evans Tokushima Fatty (OLETF) rats [23]	↑3R Tau isoform with alteration of splicing factors, ↑Total Tau, ↑p-tau, ↑Tau cleavage, ↑Tau aggregates, ↓Synaptophysin	ND
Genetically engineered models targeting insulin signaling		
Neuron-specific insulin receptor KO mice [26]	Complete loss of activation of PI-3K and Akt ↓ p-Akt & p-GSK3β ↑ p-Tau at T231 but not at S202 No neurofibrillary tangles No alteration in neuronal proliferation/survival	No memory impairments No change in brain glucose metabolism on PET
IRS-2-deletion mice [28]	↓ Neuronal proliferation only during development by 50%, but no increase in apoptosis ↑p-Tau at S202 in cytoplasmic deposits	ND

♣, Therapeutic trials; Aβ, amyloid β protein; AD, Alzheimer's disease; APP, amyloid precursor

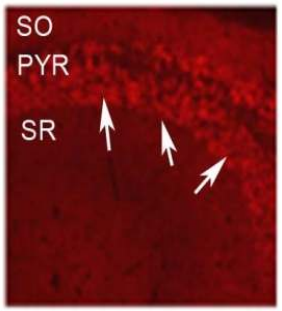
Park, 2013

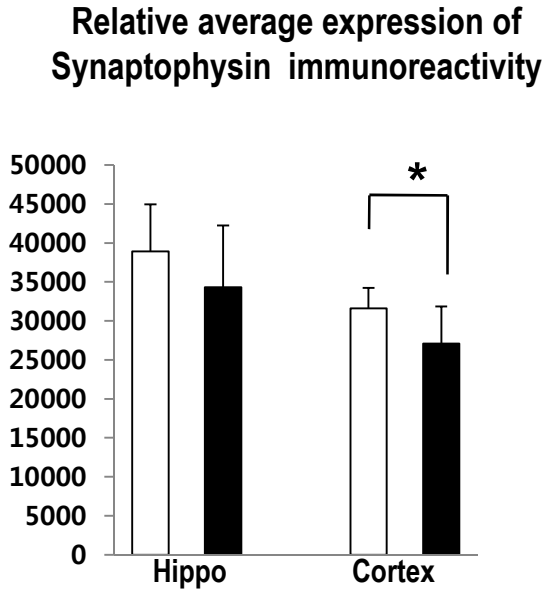
Objectives

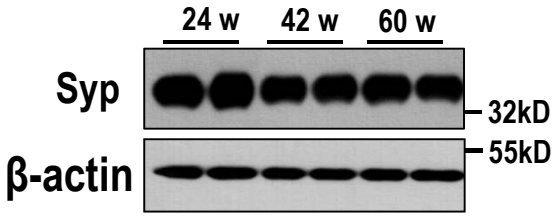
- Aging increases both T2DM and AD

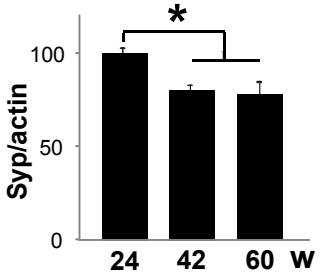


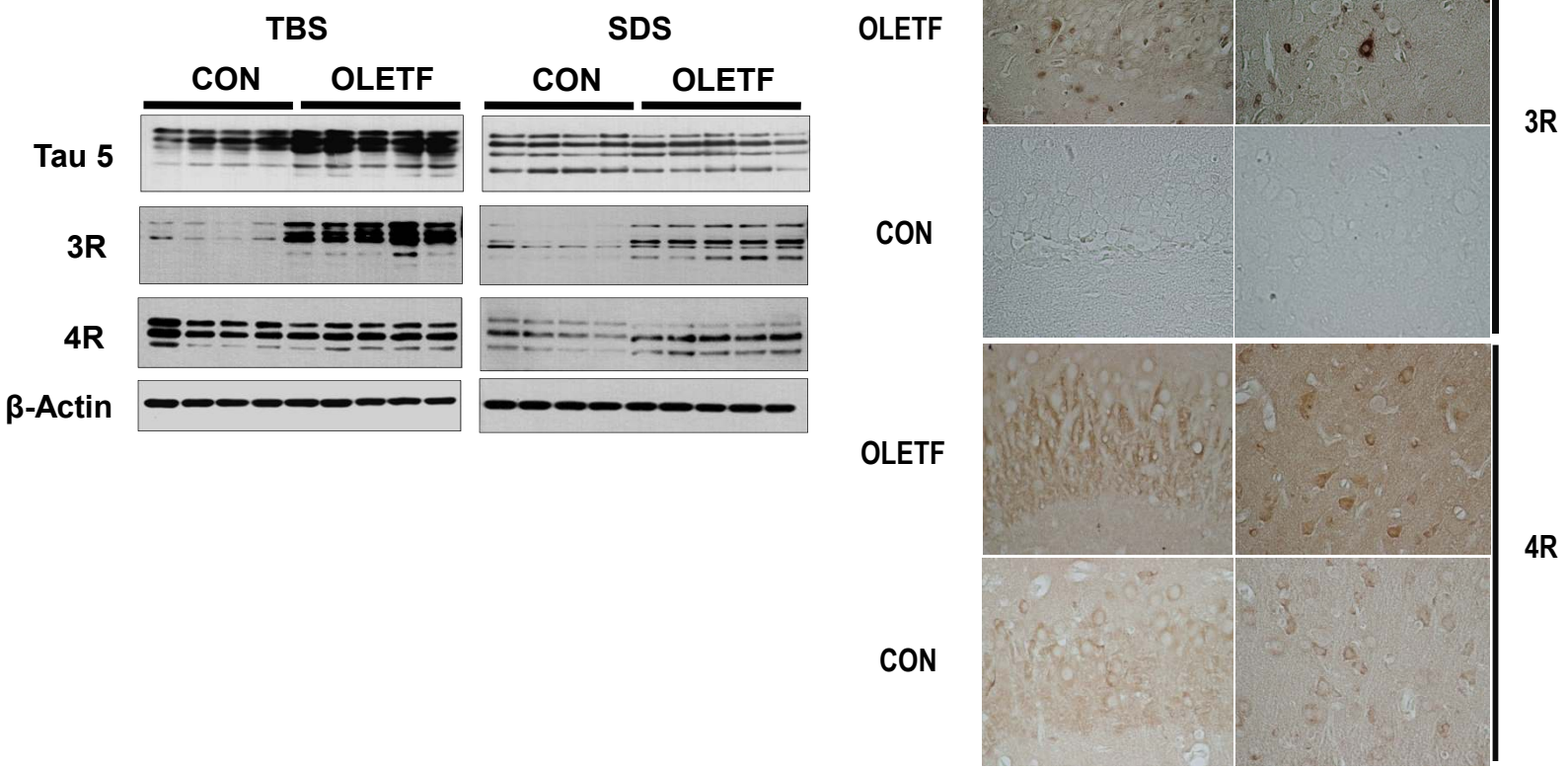
- Does T2DM increases AD pathology with aging?
- What is the most susceptible pathologic substrate?
- What mechanisms do play a main role?
- Age-dependent AD pathology can be a therapeutic target for AD?


SO
PYR
SR
SO
PYR
SR

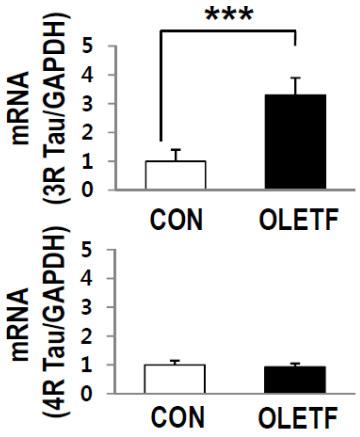

Relative average expression of
Synaptophysin immunoreactivity
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
*
Hippo
Cortex


24 w
42 w
60 w
Syp
β-actin
32kD
55kD

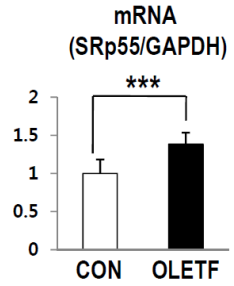

*
100
50
0
Syp/actin
24
42
60
w

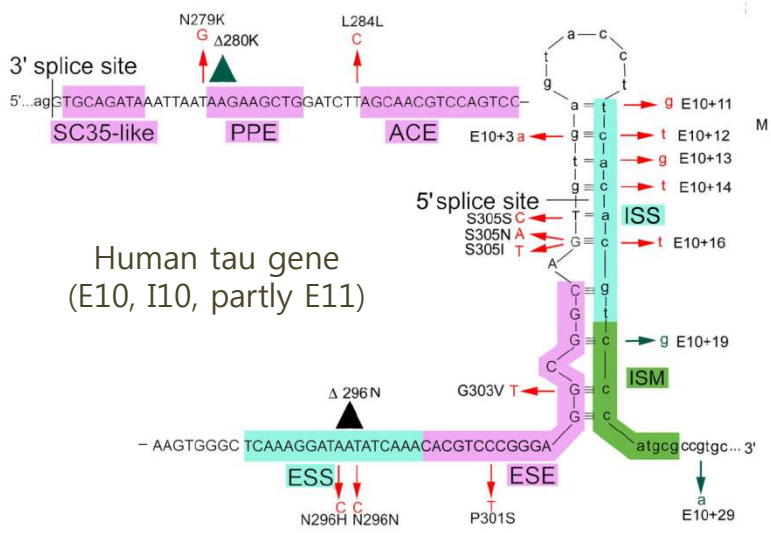


Jung et al., 2011



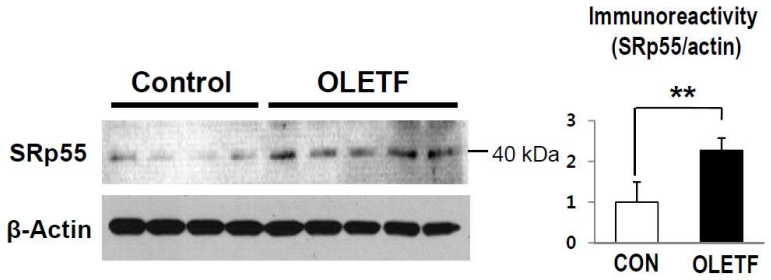
Exclusion effect on exon10 splicing [SR proteins]		
SRp20 (Sfrs3)	F	atc gtg att cct gtc cct tg
NM_001047907.1	R	ttc acc att cga cag ttc ca
9G8 (Sfrs7)	F	cgg tat gga gga gaa acc aa
NM_001039035.1	R	caa tcc tcg aac tgc atc ct
SRp55(Sfrs6)	F	tag tcg ttg cag ttg gca ag
NM_001014185.1	R	taa gag cgc cta tgg ctt gt
Inclusion effect on exon10 splicing [SR proteins]		
SC35(SRp30b)(Sfrs2)	F	cta cag ccg ctc caa gtc tc
NM_001009720.1	R	atg aaa ccg ctc cct ctt ct
Tra2β	F	cgc tcc aag gaa gat tca ag
NM_057119.1	R	aga caa cag ttg ggg tca gg



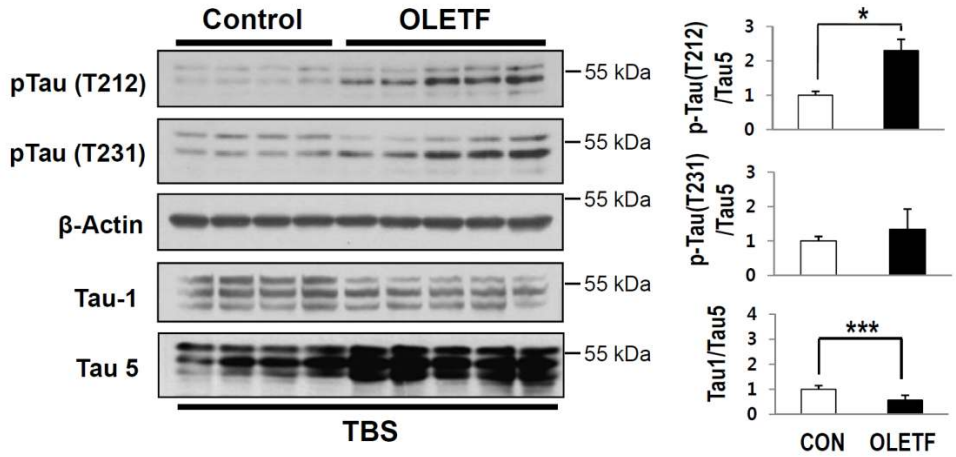


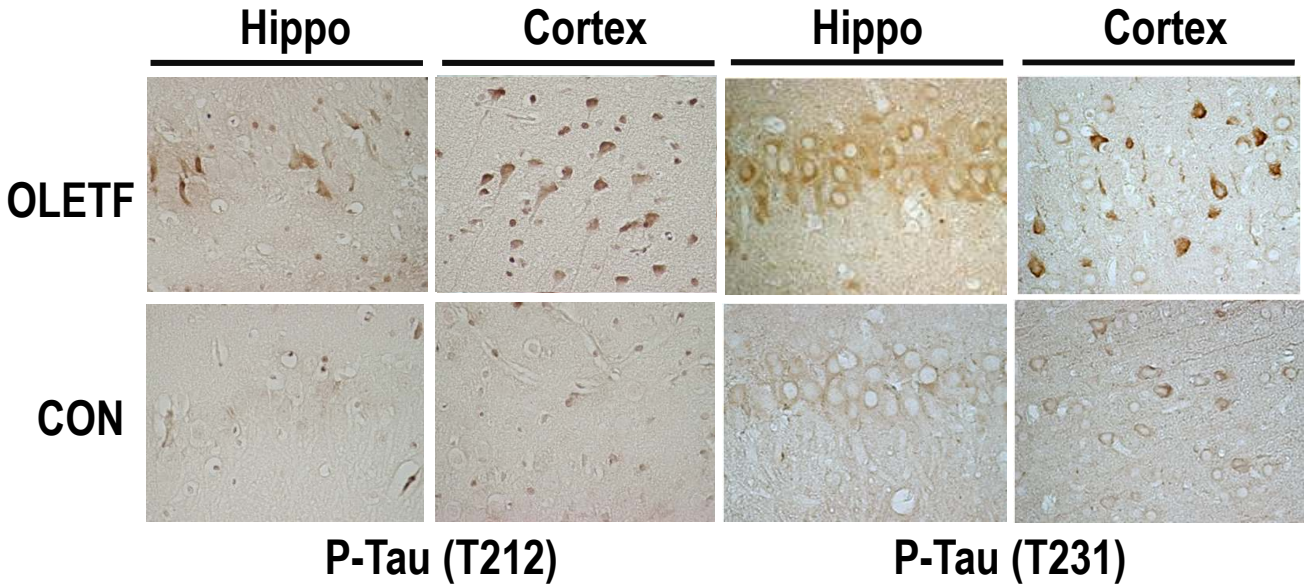
Human tau gene
(E10, I10, partly E11)

Liu et al., 2008

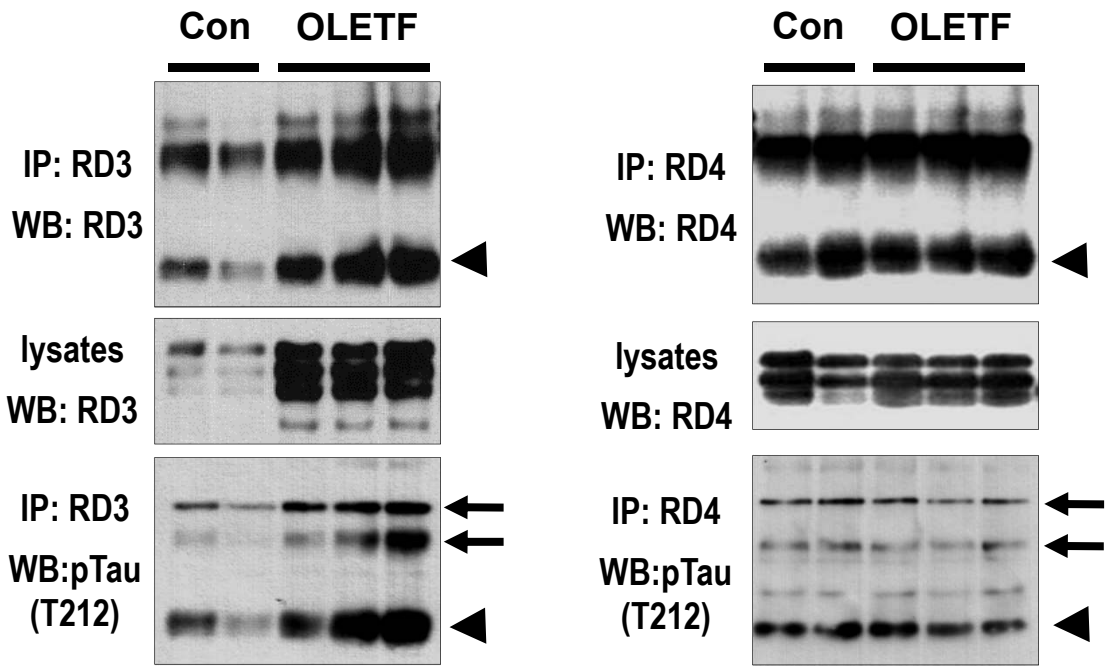


Jung et al., 2011

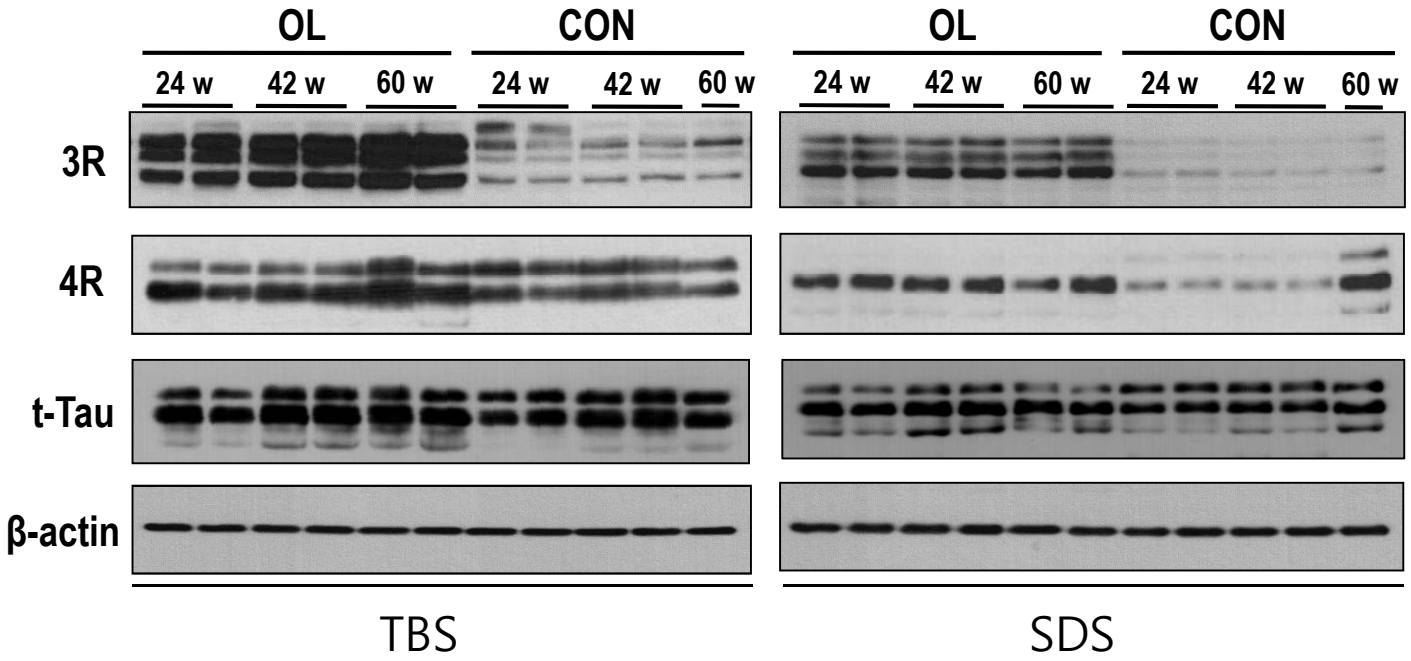




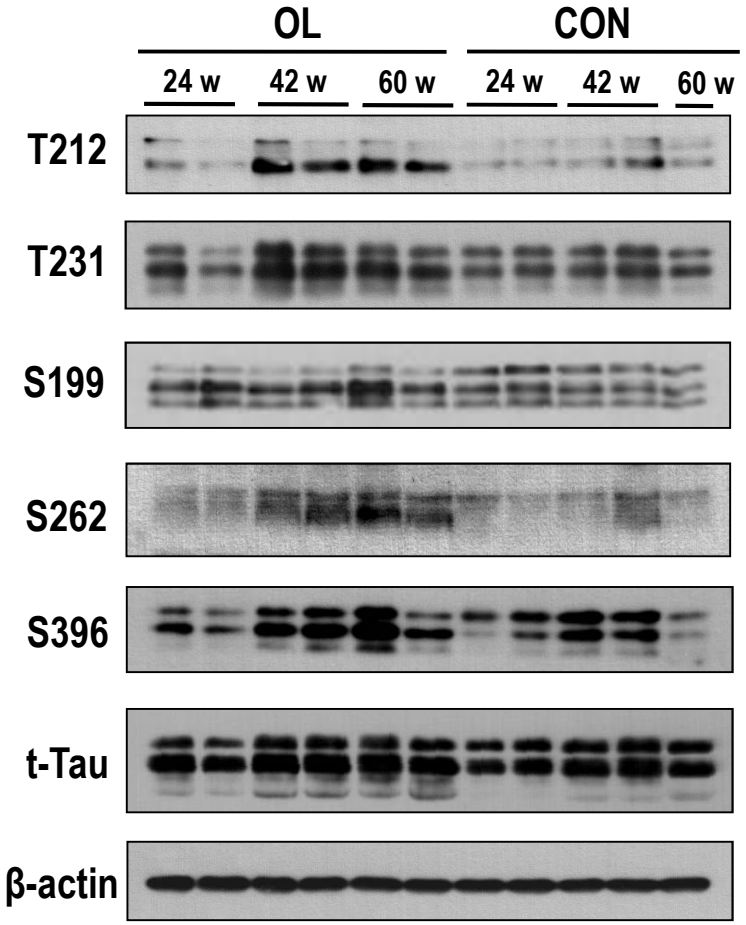
Jung et al., 2011

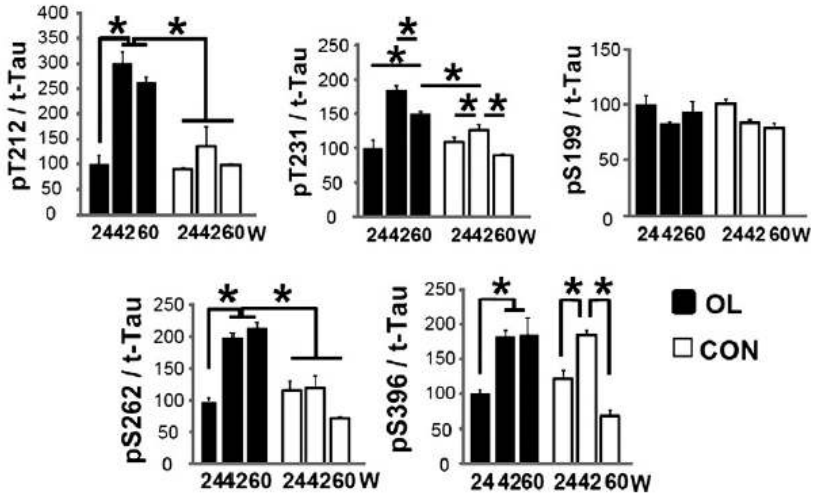


Jung et al., 2011

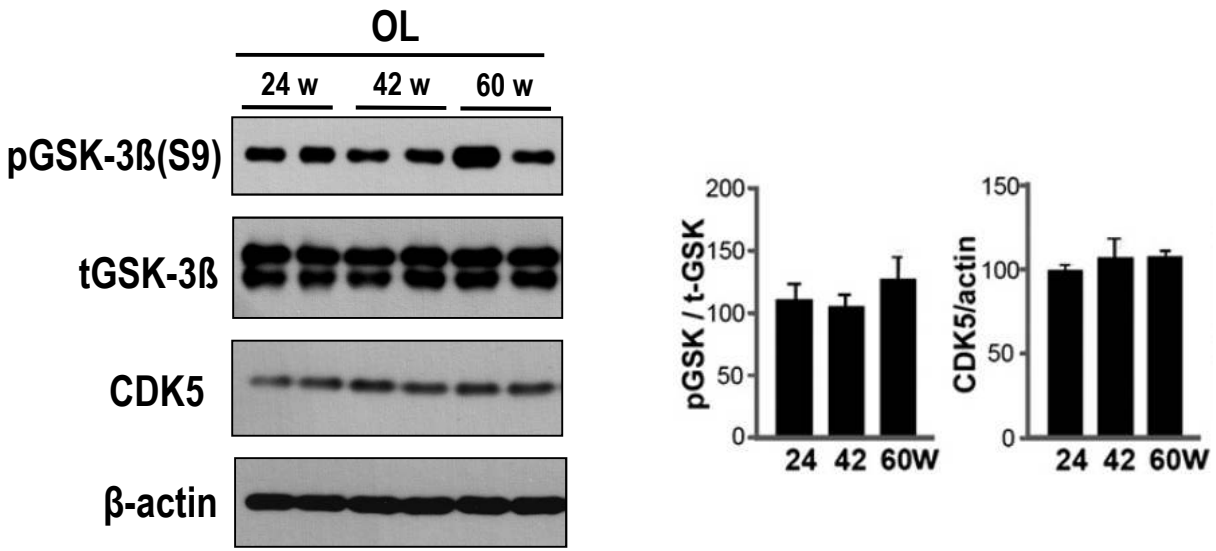


Jung et al., 2011

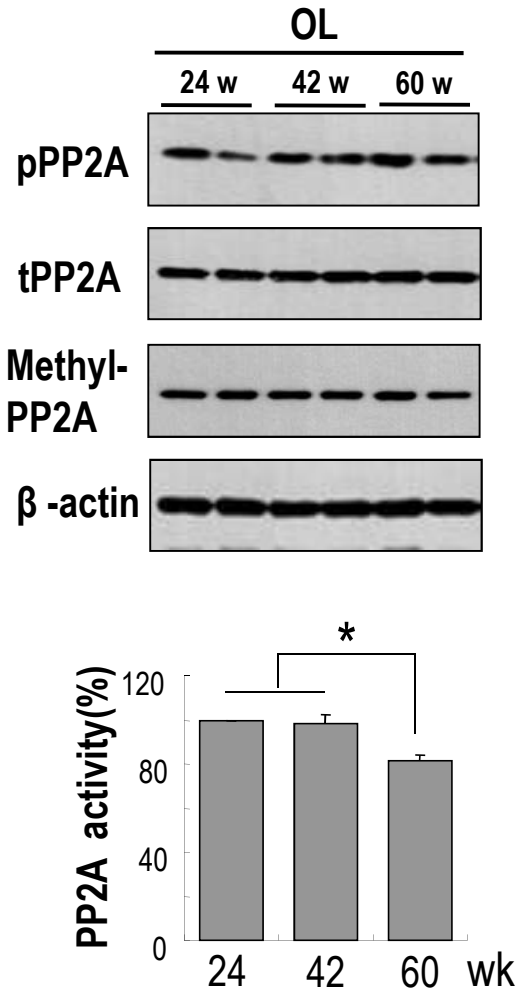


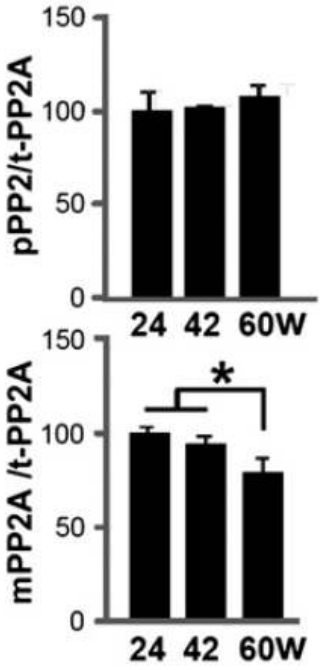


Jung et al., 2013

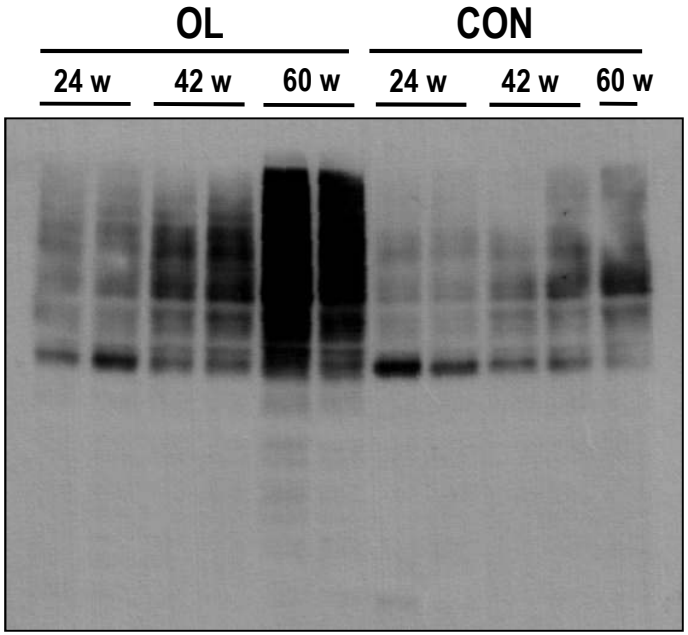


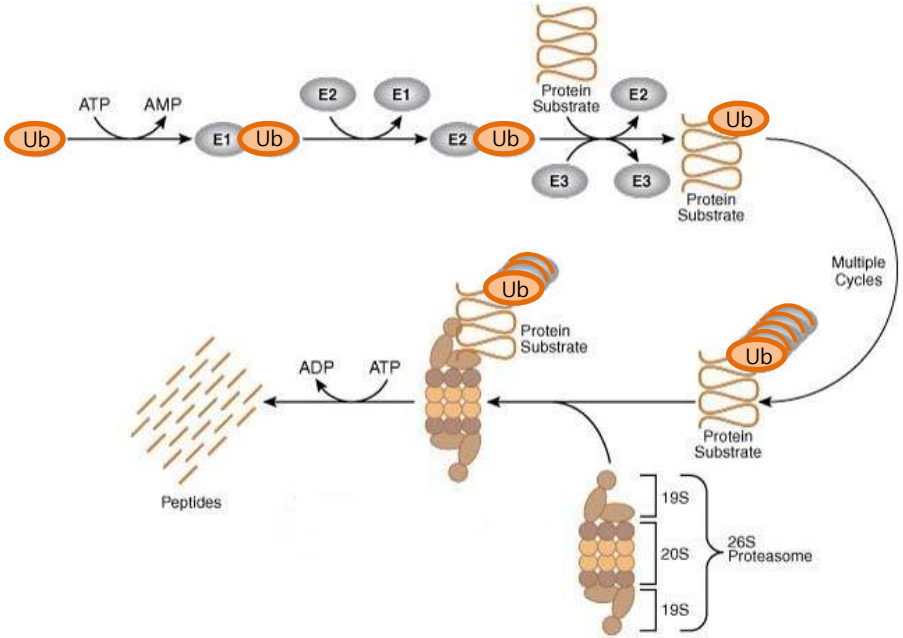
Jung et al., 2013



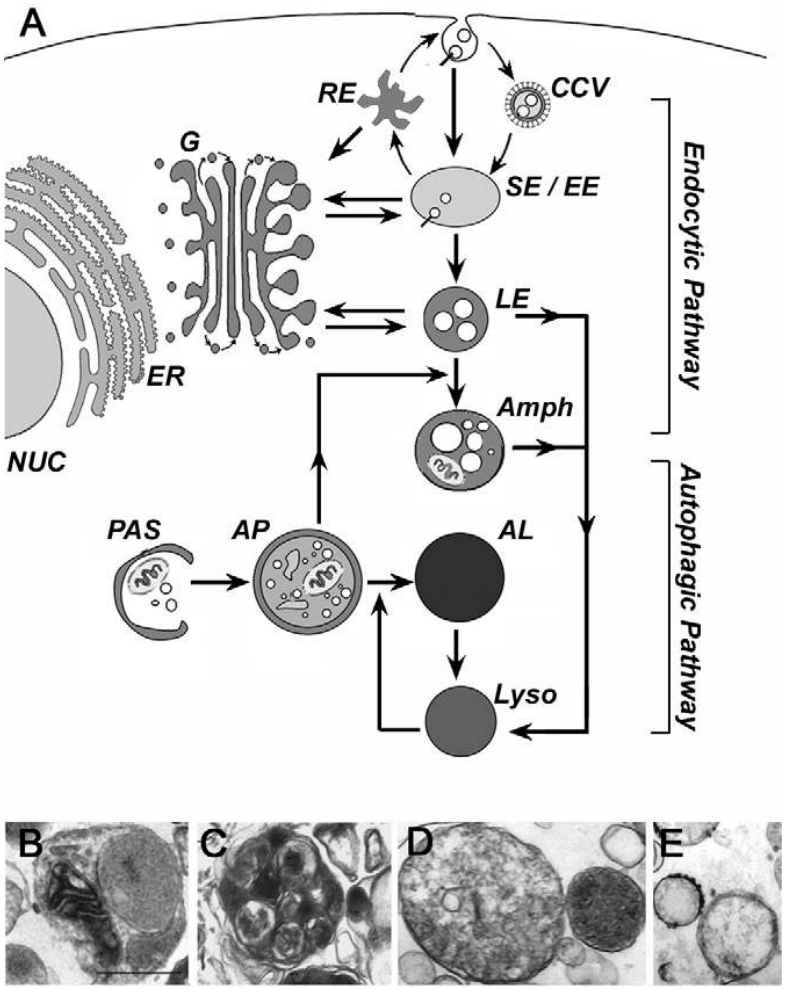


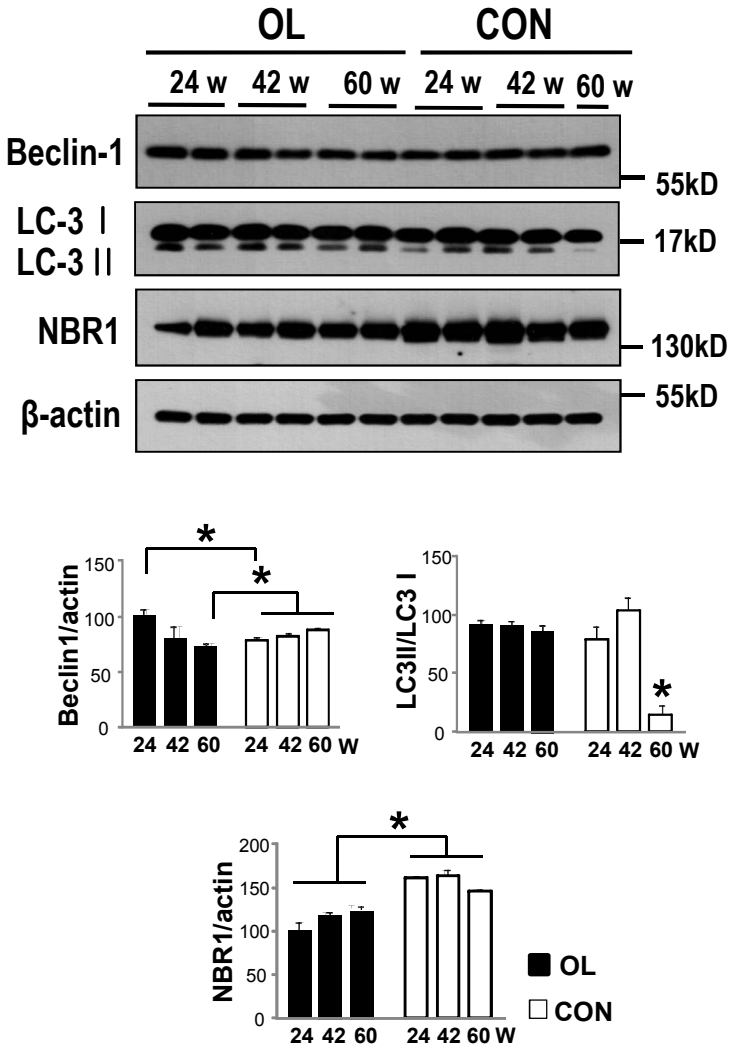
Jung et al., 2013



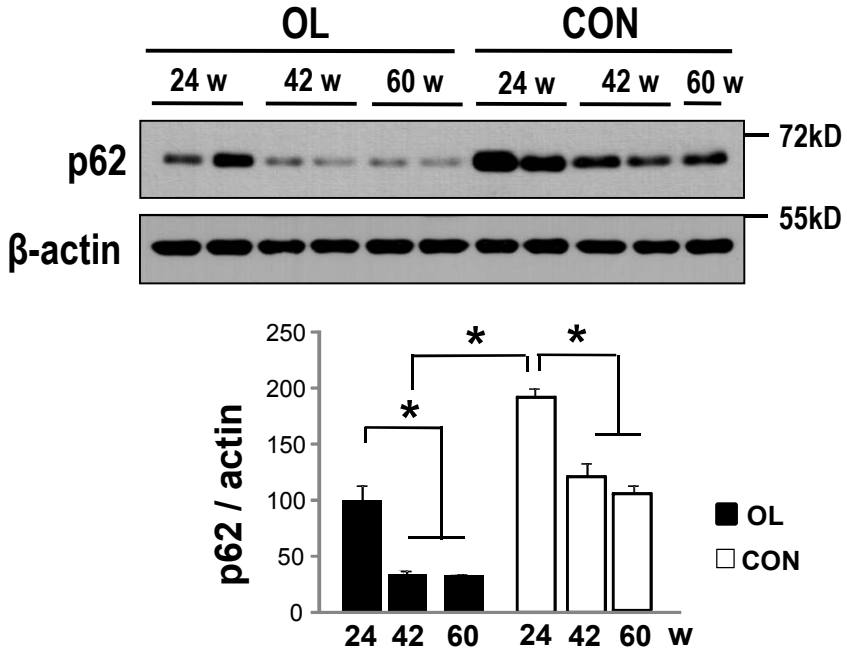


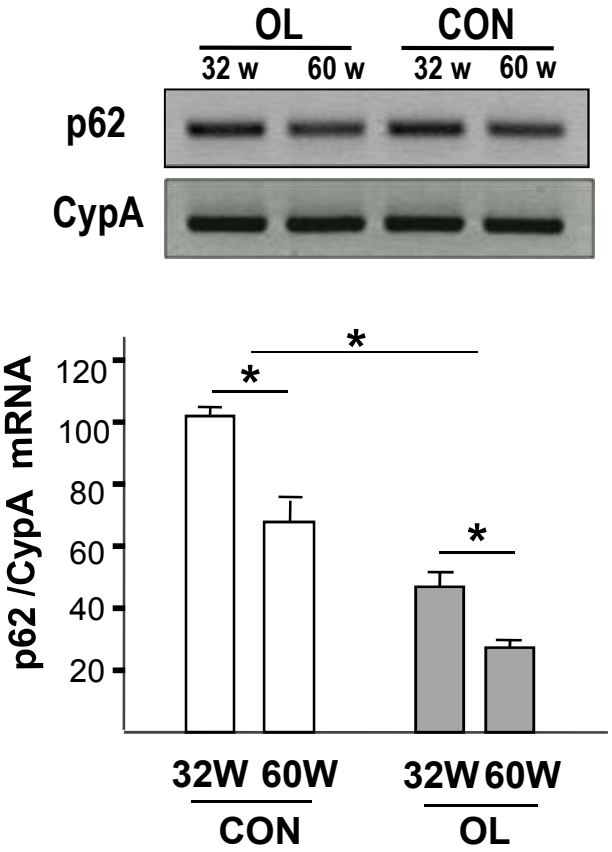
Jung et al., 2013

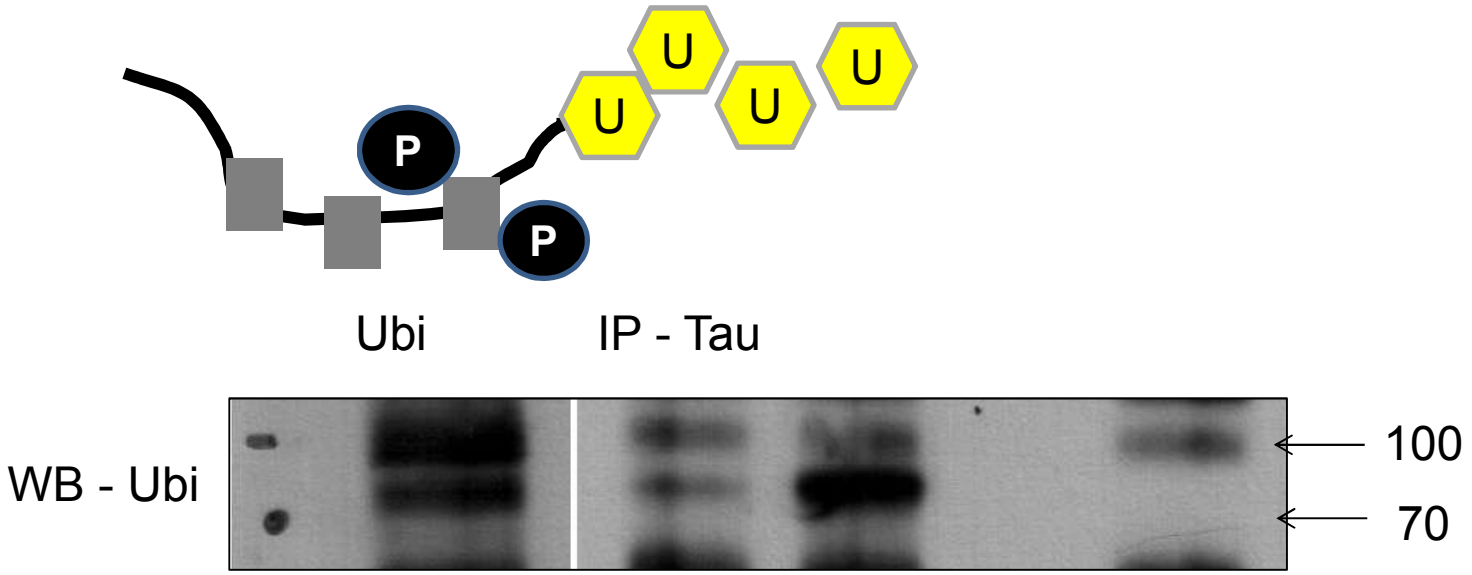




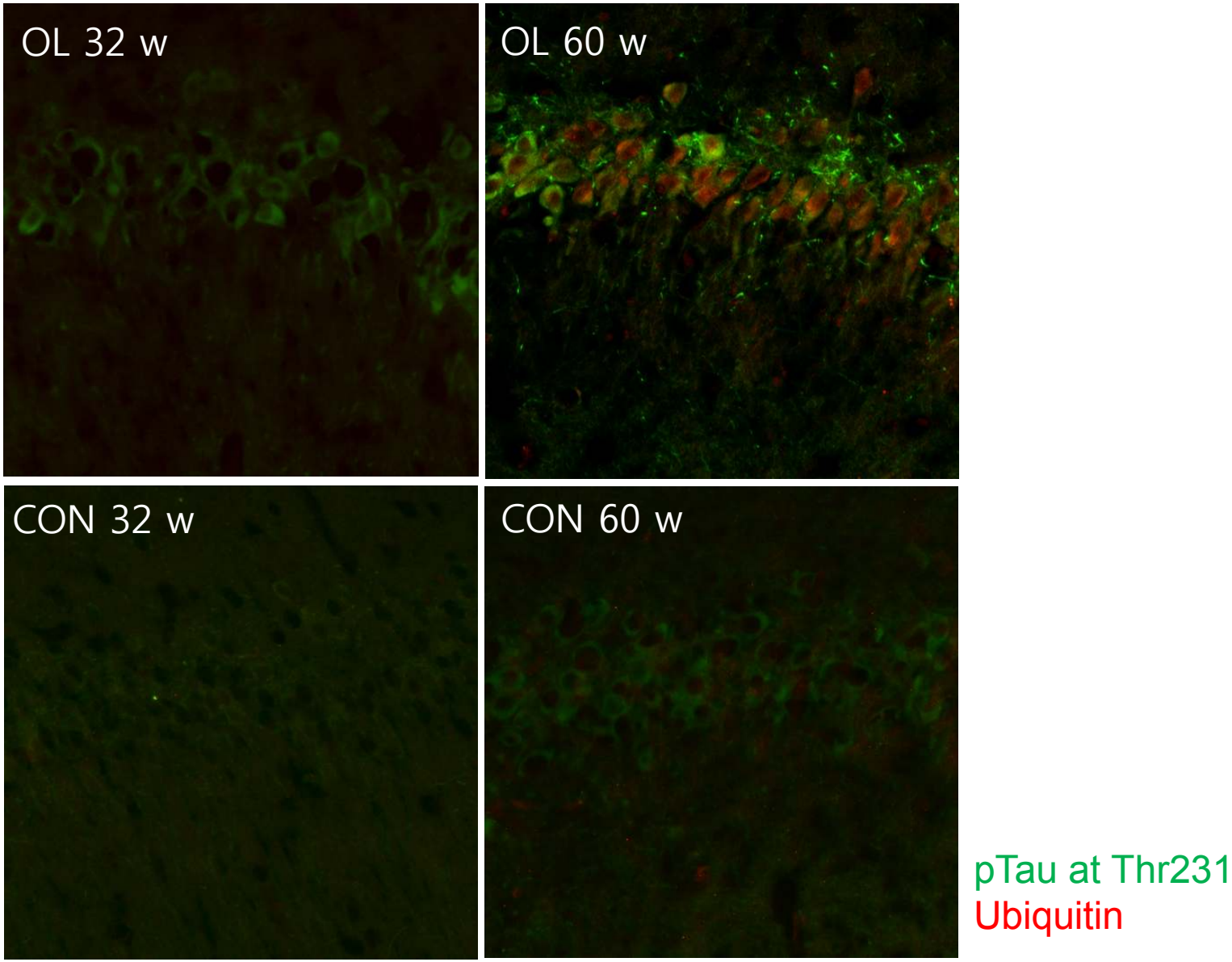
Jung et al., 2013

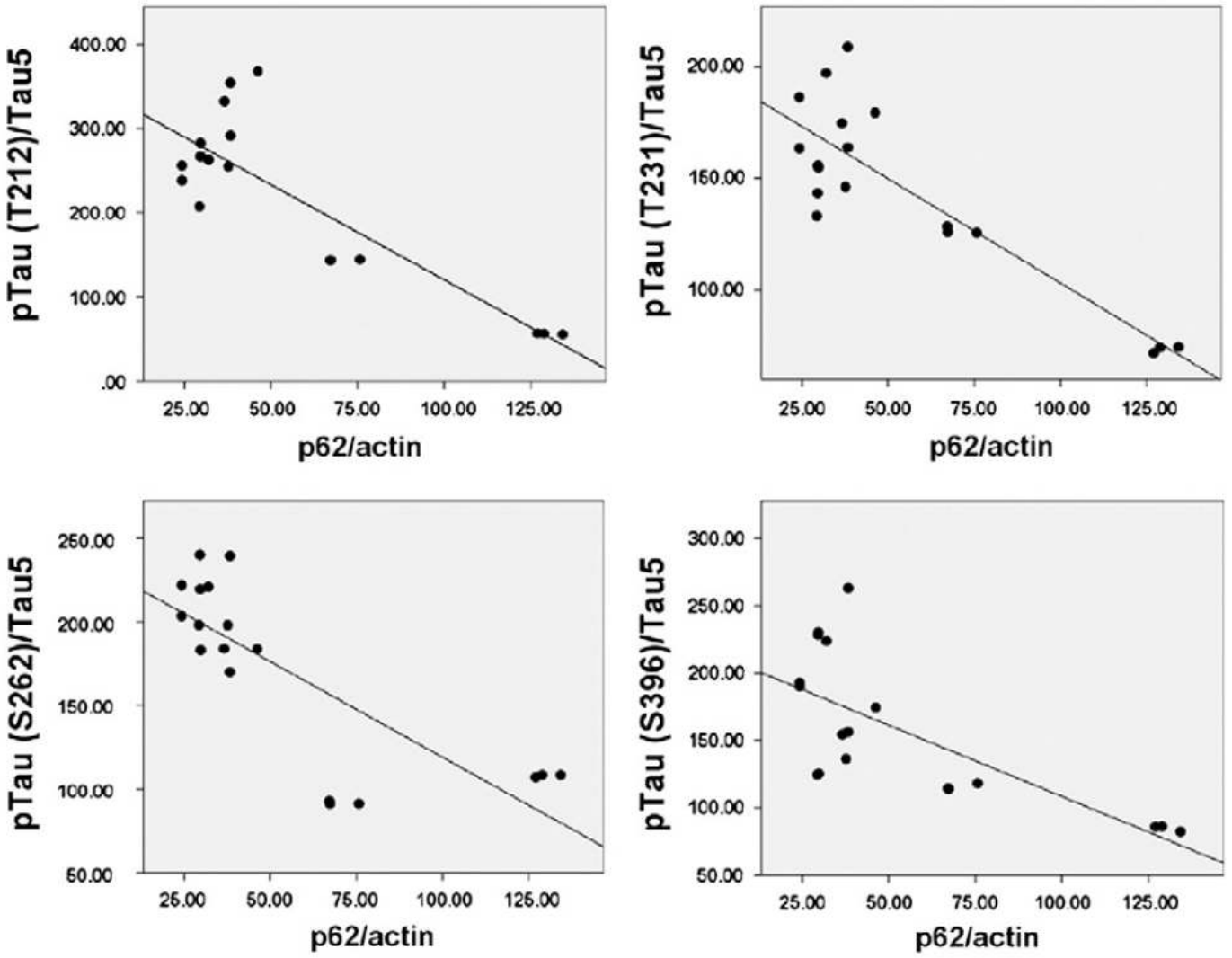

OL
CON
24 w
42 w
60 w
24 w
42 w
60 w
p62
β-actin
72kD
55kD
p62 / actin
250
200
150
100
50
0
24 42 60 24 42 60 w
OL
CON


OL
CON
32 w
60 w
32 w
60 w
p62
CypA
p62 /CypA mRNA
120
100
80
60
40
20
32W 60W
CON
32W 60W
OL

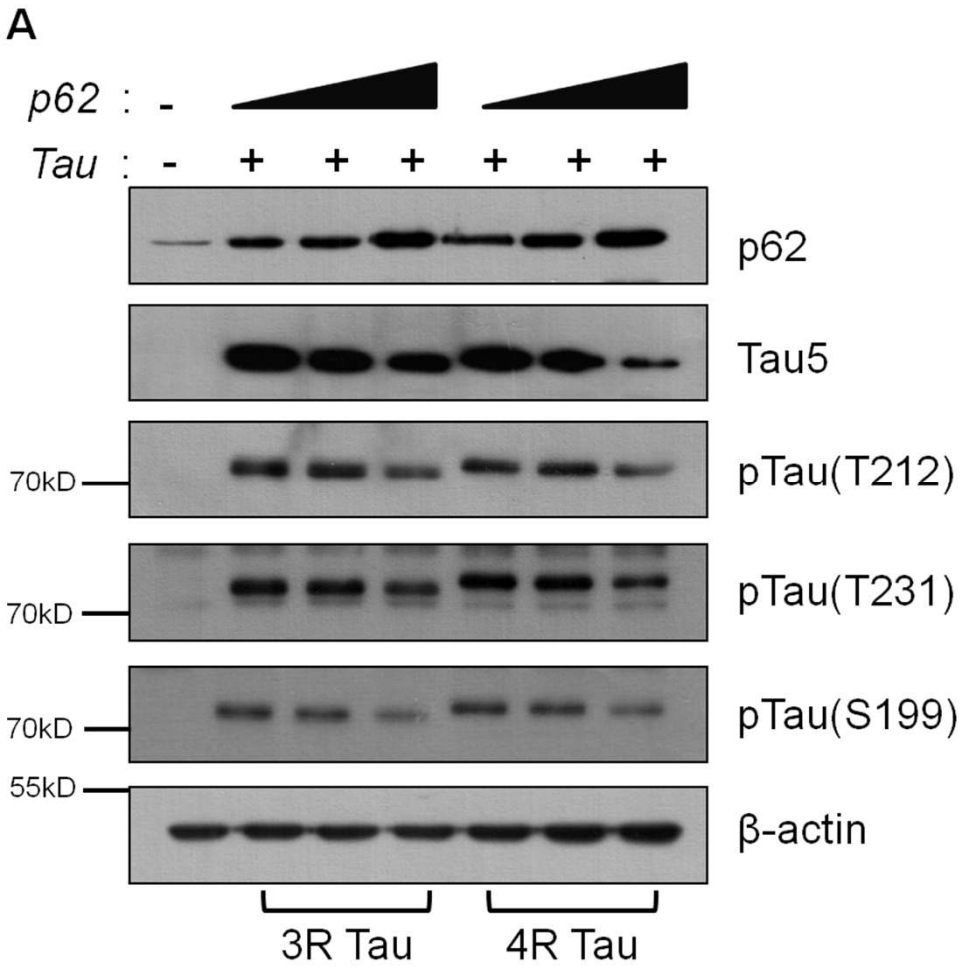


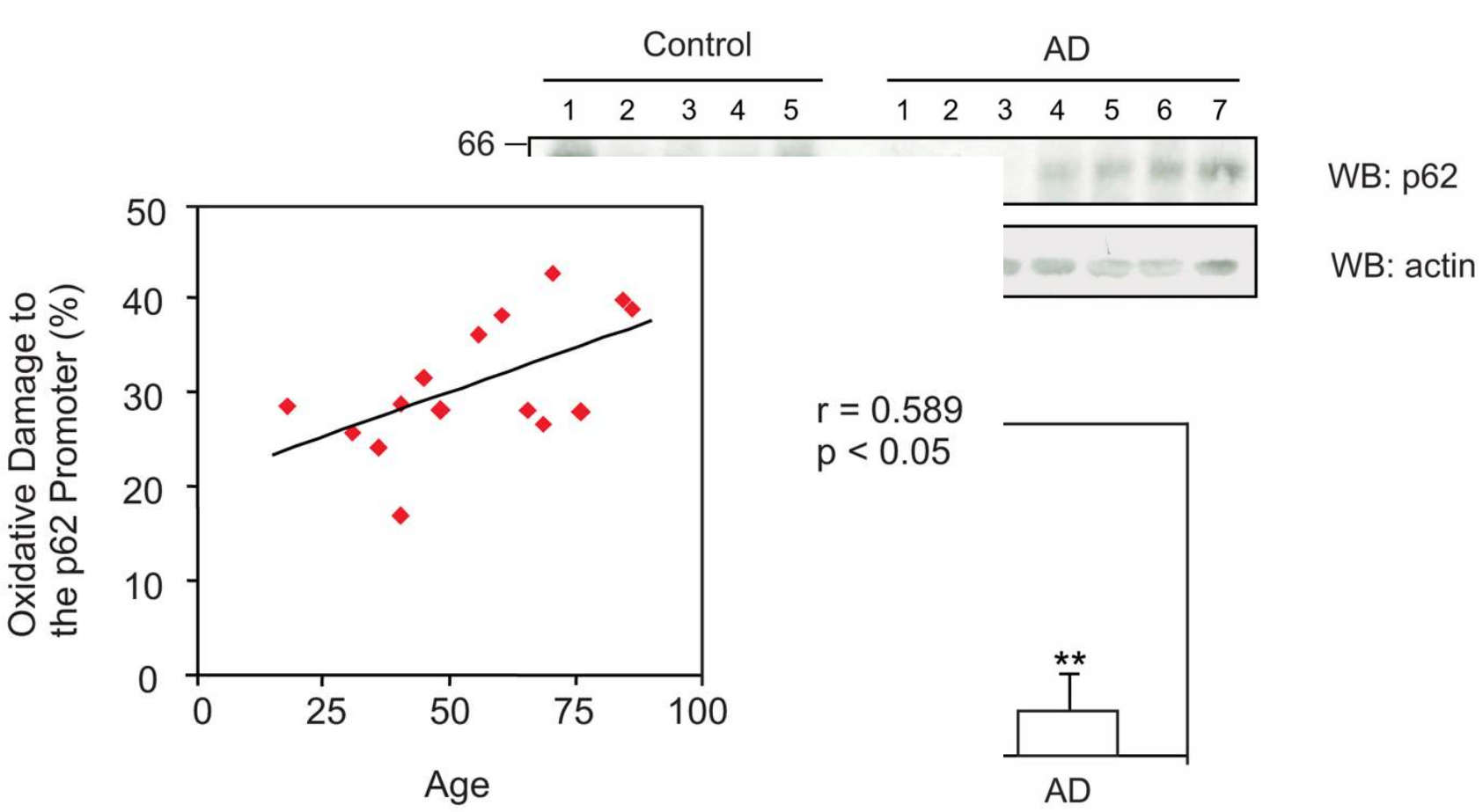
Jung et al., 2013


OL 32 w
OL 60 w
CON 32 w
CON 60 w
pTau at Thr231
Ubiquitin



Jung et al., 2013


A
p62 : -
Tau : - + + + + + +
p62
Tau5
70kD
pTau(T212)
70kD
pTau(T231)
70kD
pTau(S199)
55kD
β-actin
3R Tau
4R Tau



Du Y et al., Free Radic Biol Med 2009

Mature-onset obesity and insulin resistance in mice deficient in the signaling adapter p62

(Cell Metabolism 2006)

Angelina Rodriguez,[1] Angeles Durán,[1] Mohammed Selloum,[4] Marie-France Champy,[4] Francisco J. Diez-Guerra,[1] Juana María Flores,[2] Manuel Serrano,[3] Johan Auwerx,[4] María T. Diaz-Meco,[1,5] and Jorge Moscat[1,5,*]

Sequestosome 1/p62, a Scaffolding Protein, Is a Newly Identified Partner of IRS-1 Protein*

Received for publication, November 10, 2011, and in revised form, June 22, 2012 Published, JBC Papers in Press, July 3, 2012, DOI 10.1074/jbc.M111.322404

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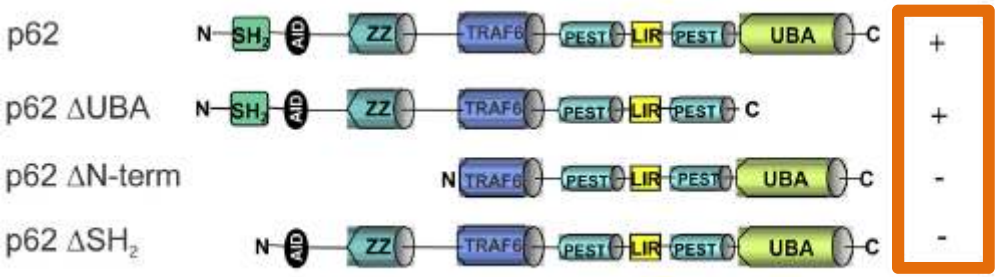
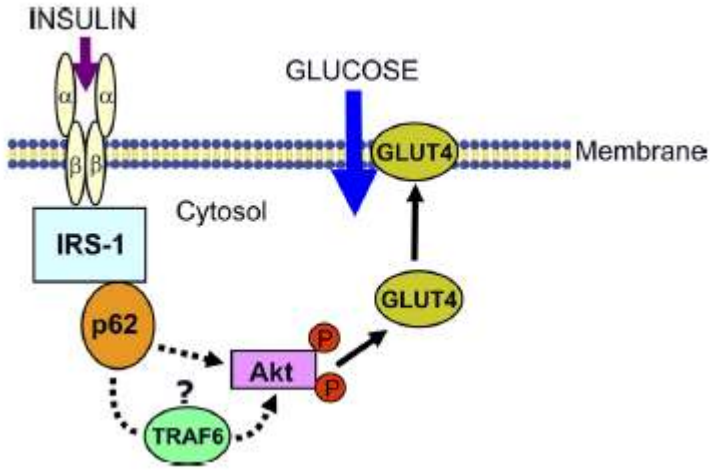
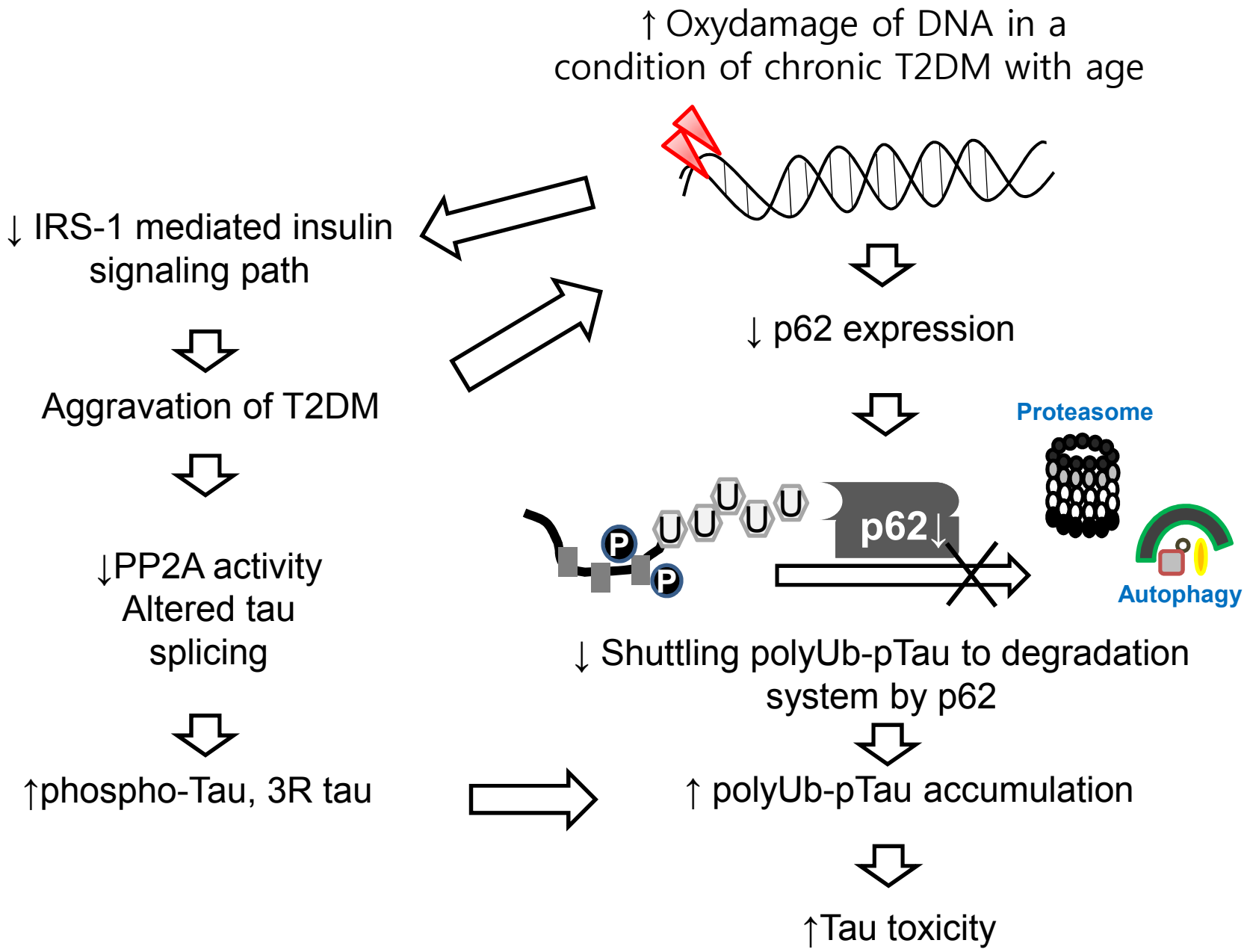


Interaction with IRS-1




↑ Oxydamage of DNA in a condition of chronic T2DM with age
↓ IRS-1 mediated insulin signaling path
↓ p62 expression
Aggravation of T2DM
Proteasome
↓PP2A activity Altered tau splicing
p62↓
Autophagy
↓ Shuttling polyUb-pTau to degradation system by p62
↑phospho-Tau, 3R tau
↑ polyUb-pTau accumulation
↑Tau toxicity

Summary

- Tau pathology is the most characteristic changes in chronic T2DM
- ↑3R isoforms & ↑phospho-tau
- With age, ↑Tau toxicity
  - Changes in splicing factors
  - Impaired phosphatase activity, PP2A
  - Decreased p62 transcription and expression
  - Decreased clearance of toxic tau proteins

감사합니다.