

Supplementary Figures

Figure S1: Related to figure 1

Figure S1

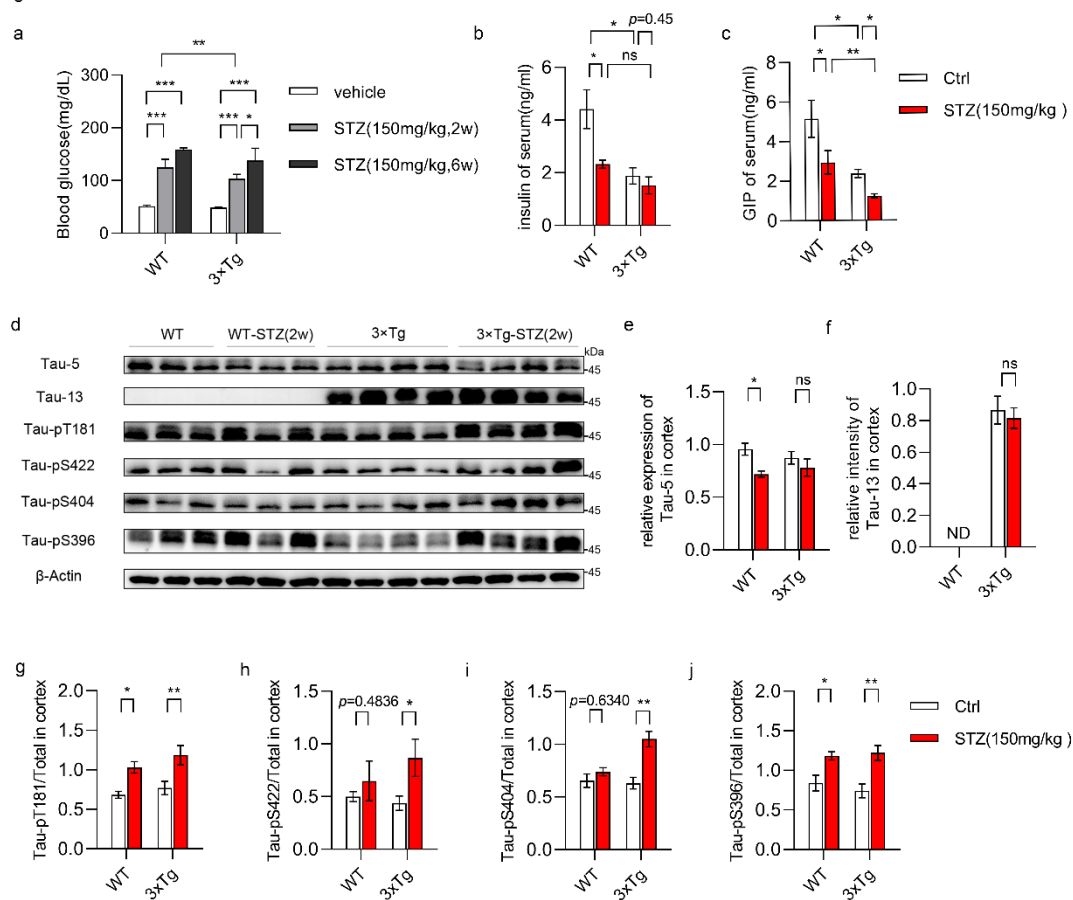


Figure S1 STZ injection induced tau phosphorylation in 3xTg AD mice

a, The fasting blood glucose levels of WT and 3xTg AD model mice at 4 months of age were measured (WT, $n=14$. 3x Tg AD, $n=18$), and then these mice were subjected to STZ treatment, thereafter, the fasting blood glucose were measured at 2 w (WT, $n=8$. 3x Tg AD, $n=11$) as well as at 6 w (WT, $n=6$. 3x Tg AD, $n=7$) after STZ injection, respectively. The results are shown as the mean \pm s.e.m., * $P<0.05$, ** $P<0.01$, *** $P<0.001$ by two-way ANOVA with Tukey's test.

b-c, The levels of insulin (**b**) and GIP (**c**) in non-fasting serum of WT mice ($n=3$) and 3xTg AD model mice ($n=6$) that were injected with STZ (150 mg/kg) for 2 w, compared with that of WT mice ($n=4$) and 3xTg AD model mice ($n=7$) which were injected with PBS. The results are shown as the mean \pm s.e.m., * $P<0.05$, ** $P<0.01$, by two-way ANOVA with Tukey's test.

d, Immunoblot and quantifications of the protein levels of total tau and the phosphorylation levels of tau.

e-j, total tau (tau-5) (**e**), human tau (tau-13) (**f**), phosphorylated tau-pT181 (**g**), tau-pS422 (**h**), tau-pS404 (**i**), tau-pS396 (**j**) in the lysates of cortex from WT mice injected with PBS ($n=3$), or STZ ($n=3$) for 2 w, as well as 3xTg AD model mice injected with PBS ($n=4$), or STZ ($n=4$) for 2 w. The results are shown as the mean \pm s.e.m., * $P<0.05$, ** $P<0.01$, by two-tailed unpaired student's t -test (**e-j**).

Figure S2: Related to figure 2

Figure S2

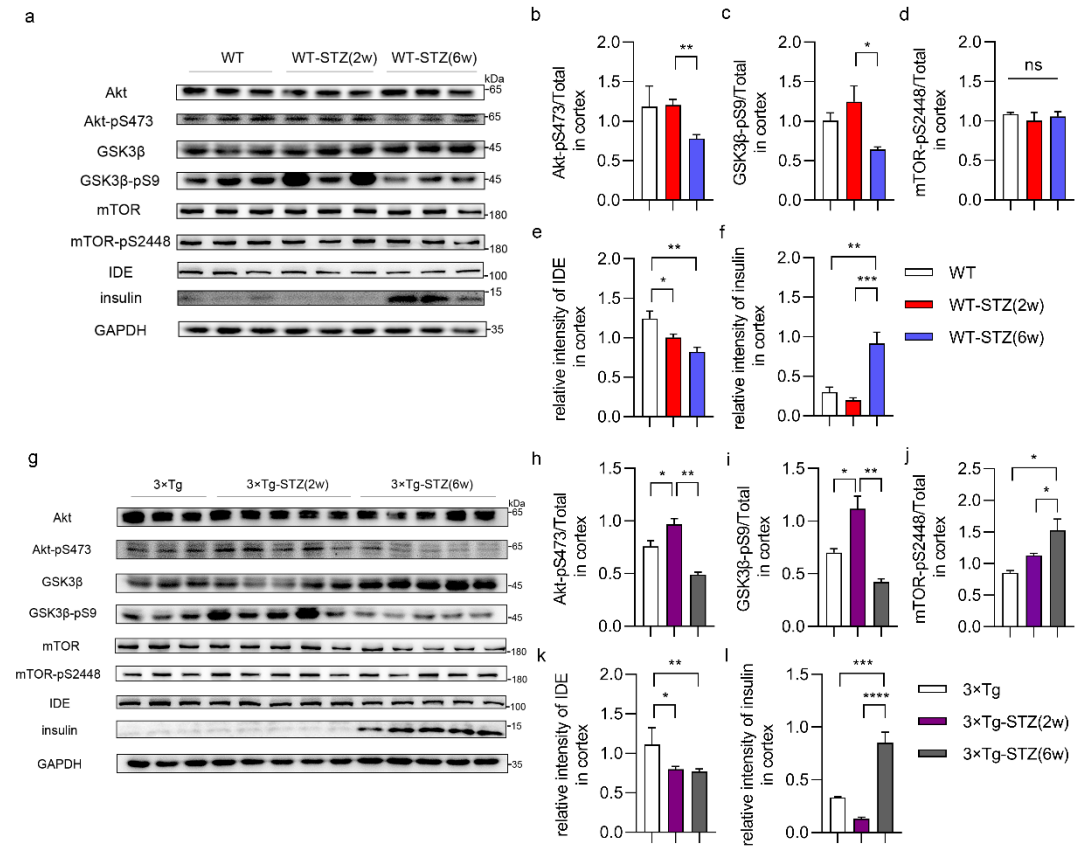


Figure S2 Prolonged hyperglycemia induced insulin resistance in brain

a, WT mice injected with STZ for 2 w (n=3), and 6 w (n=3), respectively, the lysates of cortex were isolated and subjected for immunoblot analysis compared with that of WT mice (n=3) injected with PBS for 2 w.

b-f, Quantifications of the blot were shown as the mean \pm s.e.m. of the ratios of Akt-pS473/Akt (**b**), GSK3β-pS9/GSK3β (**c**), mTOR-pS2448/mTOR (**d**), IDE/GAPDH (**e**), and insulin/GAPDH (**f**). The results are shown as the mean \pm s.e.m., * P <0.05, ** P <0.01, *** P <0.001, by one-way ANOVA with Tukey's test.

g, 3x Tg AD mice were injected with STZ for 2 w (n=5), and 6 w (n=5), respectively, the lysates of cortex were isolated and subjected for immunoblot analysis compared with that of 3x Tg AD mice (n=3) injected with PBS for 2 w (n=3).

h-l, Quantifications the blot were shown as the mean \pm s.e.m. of the ratios of Akt-pS473/Akt (**h**), GSK3β-pS9/GSK3β (**i**), and mTOR-pS2448/mTOR (**j**), IDE/GAPDH (**k**), and insulin/GAPDH (**l**). The results are shown as the mean \pm s.e.m., * P <0.05, ** P <0.01, *** P <0.001, **** P <0.0001 by one-way ANOVA with Tukey's test.

Figure S3: Related to figure 2

Figure S3

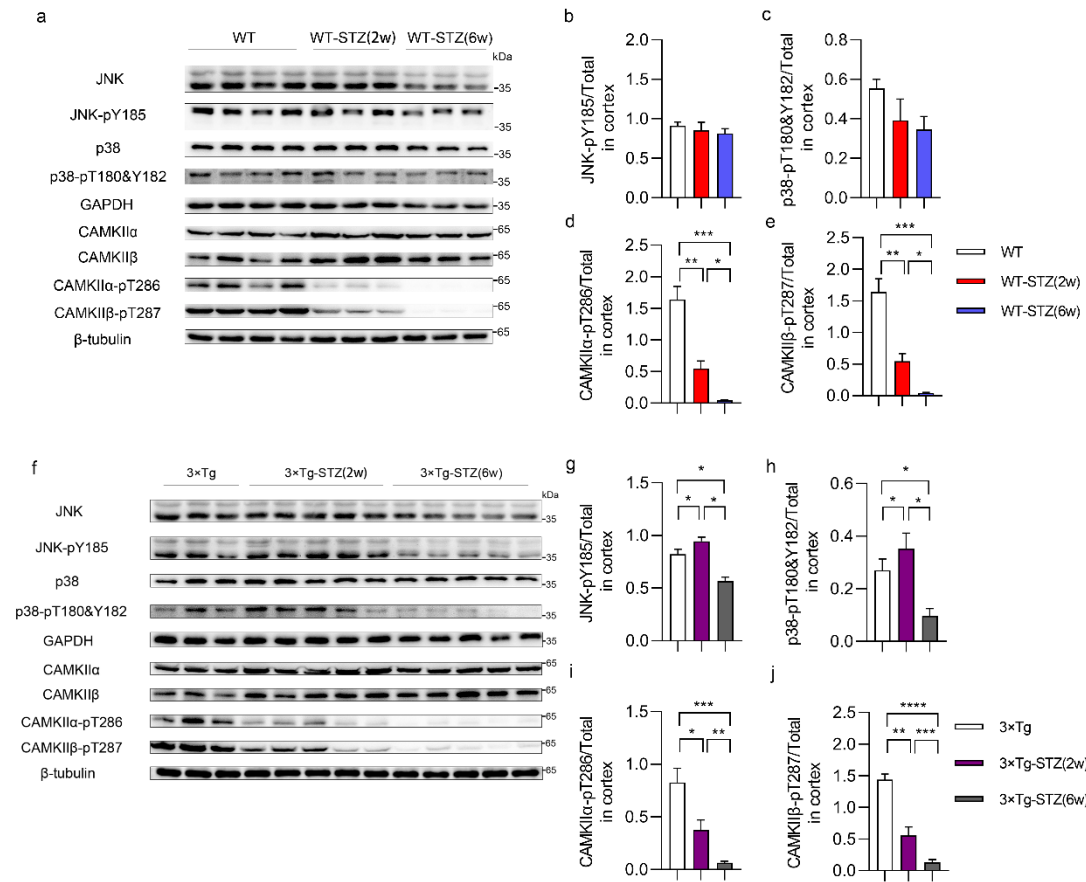


Figure S3 Prolonged hyperglycemia inhibited the phosphorylation of MAPKs and CaMKII

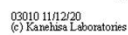
a, WT mice injected with STZ for 2 w (n=3), or 6 w (n=3), respectively, the lysates of cortex were isolated and subjected for immunoblot analysis compared with that of WT mice (n=4) injected with PBS for 2 w.

b-e, Quantifications of the blot were shown as the mean \pm s.e.m. of the ratios of JNK-pY185/JNK (**b**), p38-pT180&182/p38 (**c**), CAMKII α -pT286/CAMKII α (**d**), and CAMKII β -pT287/CAMKII β (**e**). The results are shown as the mean \pm s.e.m., * P <0.05, ** P <0.01, *** P <0.001, by one-way ANOVA with Tukey's test.

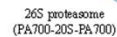
f, 3x Tg AD mice were injected with STZ for 2 w (n=5), or 6 w (n=5), respectively, the lysates of cortex were isolated and subjected for immunoblot analysis compared with that of 3x Tg AD mice (n=3) injected with PBS for 2 w (n=5).

g-j, Quantifications the blot were shown as the mean \pm s.e.m. of the ratios of JNK-pY185/JNK (**g**), p38-pT180&182/p38 (**h**), CAMKII α -pT286/CAMKII α (**i**), and CAMKII β -pT287/CAMKII β (**j**). The results are shown as the mean \pm s.e.m., * P <0.05, ** P <0.01, *** P <0.001, **** P <0.0001 by one-way ANOVA with Tukey's test.

Figure S4
a



PROTEASOME



Bacteria / Archaea	23S	5S		16S
Eukaryotes	25S	5S	5.8S	18S

EF-Tu	S10	L3	L4	L23	L2	S19	L22	S3	L16	L29
	S20e	L3e	L4e	L23Ae	L8e	S15e	L17e	S3e		L35e

S17	L14	L24			L5	S14	S8	L6				L18	S5	L30	L15	SecY
S11e	L23e	L26e	S4e		L11e	S29e	S15Ae	L9e	L32e	L19e		L5e	S2e	L7e	L27Ae	

		IF1				RpoA				
		L36	S13	S11	S4			L17	L13	S9
L34e	L14e		S18e	S14e	S9e	L18e		L13Ae	S16e	

EF-Tu.G

S7	S12
S5e	S23e

L30e

L7A
L7Ae

RpoC.B

L7/L12	L12	L10	L1	L11
L1P1	L1P2	L1P0	L10Ae	L12

EF-Ts IF2 IF3 RF1

L28 L33 L21 L27 FeY,Fh S16 L19 S1 S20 S21 L25

L10e L13e L15e L21e L24e L31e L35Ae L37e L37Ae L39e L40e L41e L44e

339e	30e	30e	317e	317e	324e	327e	320e	327e	32720e	340e	330e	Ln
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PA700 (Lid)

Rpn3	Rpn4	Rpn5	Rpn6	Rpn7
Rpn8	Rpn9	Rpn11	Rpn12	Rpn15

PA28- $\alpha\beta$
(hetero hexamer or heptamer)

PA28 α	PA28 β
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PA28- γ
(homo hexamer)

PA28 γ

PA700 (Base)						PA200
Rpn1	Rpn2	Rpn13				
Rpt1	Rpt2	Rpt6	Rpt4	Rpt5	Rpt3	PA200

Bacterial regulatory subunit (AAA ATPase forming ring-like complex)	Archaeal regulatory subunit (oligomeric complex)
ARC	PAN

Standard proteasome subunits

α_1	α_2	α_3	α_4	α_5	α_6	α_7
β_1	β_2	β_3	β_4	β_5	β_6	β_7

Immunoproteasome subunits

β_{1i} β_{2i} β_{5i}

Thymoproteasome subunits

βSt

Prokaryotic 20S subunits

α
β

Figure S4 human tau arrested the association of the of 26s proteasome and ribosome related proteins with membrane

a-b, KEGG analysis of membrane-associated proteome indicated that the components of ribosome (**a**) and proteasome (**b**) were less abundant in association with membrane in the hippocampus from hTau mice than that from Tau KO mice. The cells with green background indicated the proteins that did not show significant difference in the membrane extract of hippocampus between hTau mice and Tau KO mice. The cells with blue background indicated the proteins that were significant less abundant in association with membrane in the hippocampus between hTau mice and Tau KO mice.

Figure S5: Related to figure 7 (next page)

Figure S5 human tau augment the membrane-association of the peroxisome components and fatty acid degradation enzyme

a-b, KEGG analysis membrane-associated proteome indicated that the components of peroxisome (**a**) and the enzymes that are involved in fatty acid degrading (**b**) were more abundant in association with membrane in the hippocampus from hTau mice than that from Tau KO mice. Significantly different proteins were indicated with red. The cells with green background indicated the proteins that did not show significant difference in the membrane extract of hippocampus between hTau mice and Tau KO mice. The cells with red background indicated the proteins that were significant more abundant in association with membrane in the hippocampus between hTau mice and Tau KO mice.

6.2.1.3: acyl-CoA synthetase long-chain family member 1,

1.3.8.7: acyl-Coenzyme A dehydrogenase,

1.3.8.8: acyl-Coenzyme A dehydrogenase,

2.3.1.16: acetyl-Coenzyme A acyltransferase 1A,

1.2.1.3: aldehyde dehydrogenase family 7, member A1.

a

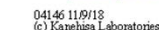


Figure S6: Related to figure 7

Figure S6

a

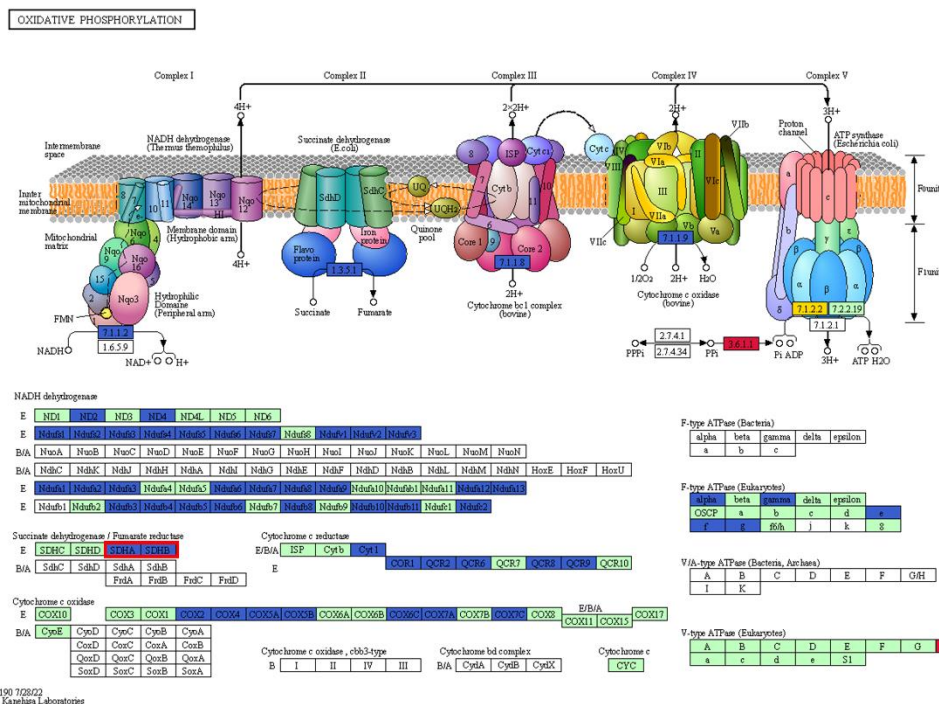


Figure S6 tau knockout resulted in dysregulation of the oxidative phosphorylation related protein locating on membrane under acute hyperglycemia conditions

KEGG analysis of membrane-associated proteome indicated that upon STZ treatment, more oxidative related proteins, including SDHA and SDHB were less abundant in association with membrane the hippocampus from hTau mice than that from Tau KO mice. The cells with white background indicated the proteins that were not detected by TMT-MS. The cells with green background indicated the proteins that did not show significant difference in the membrane extract of hippocampus between hTau mice and Tau KO mice. The cells with blue background indicated the proteins that were significant less abundant in association with membrane in the hippocampus between hTau mice and Tau KO mice. The cells with red background indicated the proteins that were significant more abundant in association with membrane in the hippocampus of hTau mice compared with Tau KO mice.