Supplementary Materials

Tauroursodeoxycholic acid attenuates diet-induced and age-related peripheral endoplasmic reticulum stress and cerebral amyloid pathology in a mouse model of Alzheimer's disease

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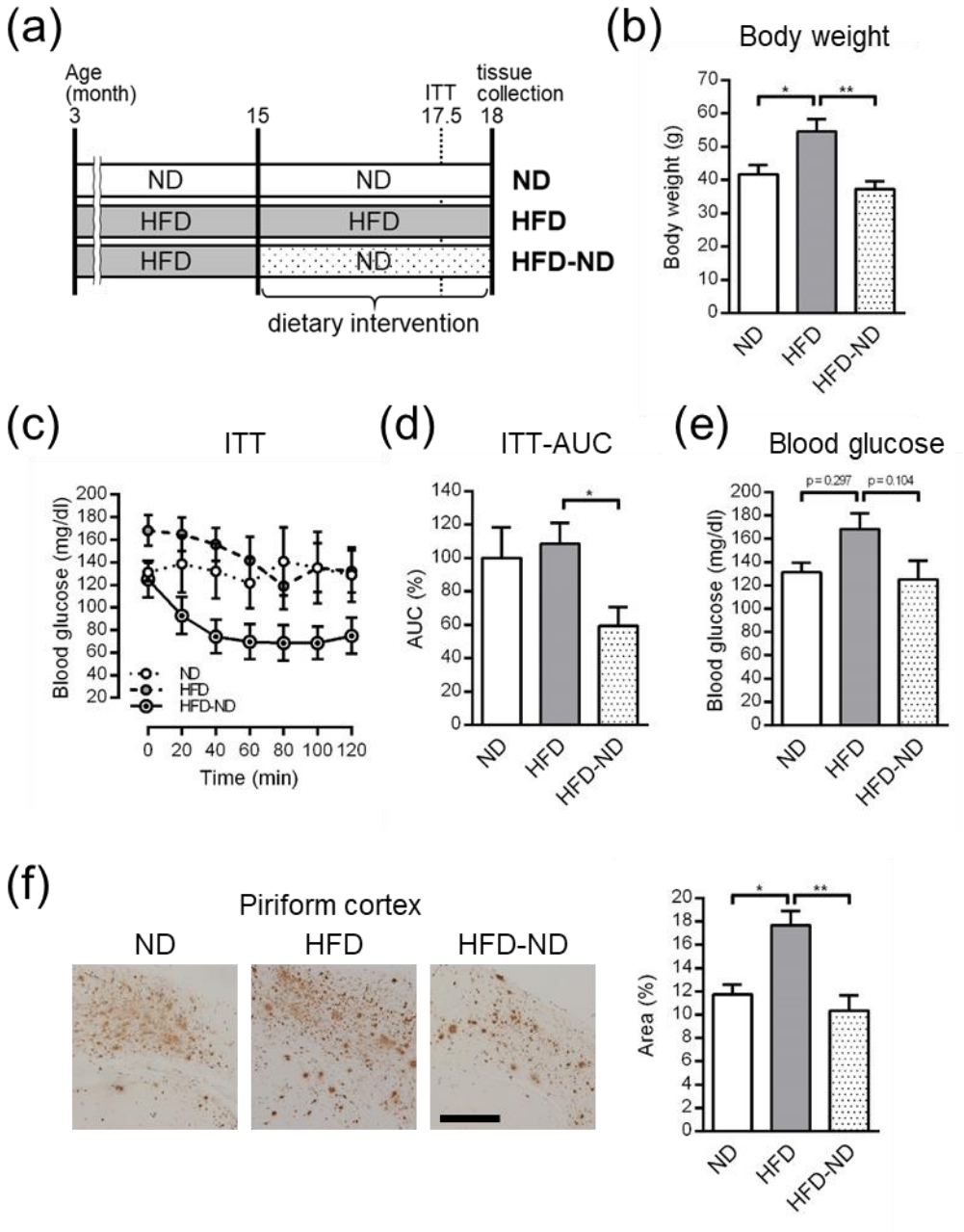

Figure S1. Dietary intervention ameliorated metabolic abnormalities and Aβ pathology in 18-month-old HFD-fed A7-Tg mice

(a) Schematic diagram of the study design. Male A7-Tg mice were fed with ND or HFD from 3 months of age. Half of the HFD-fed mice was switched to ND feeding at 15 months of age (HFD-ND), and brain tissue was collected at 18 months of age. (b) Body weight at 18 months of age. (c-e) Changes in the blood glucose levels (c) and area under the curve (AUC) (d) during ITT at 17.5 months of age, and blood glucose levels before the test (e). (f) Immunohistochemical analyses of brains at 18 months of age using an anti-Aβ (82E1) antibody. Representative images of brain regions including the piriform cortex are shown. The graph represents the percentage of Aβ immunopositive areas. Data are mean ± SEM (ND: n = 4, HFD: n = 7, HFD-ND: n = 7-8). *, $p < 0.05$; **, $p < 0.01$, one-way ANOVA with Tukey's post-hoc test. Scale bar: 500 μm.

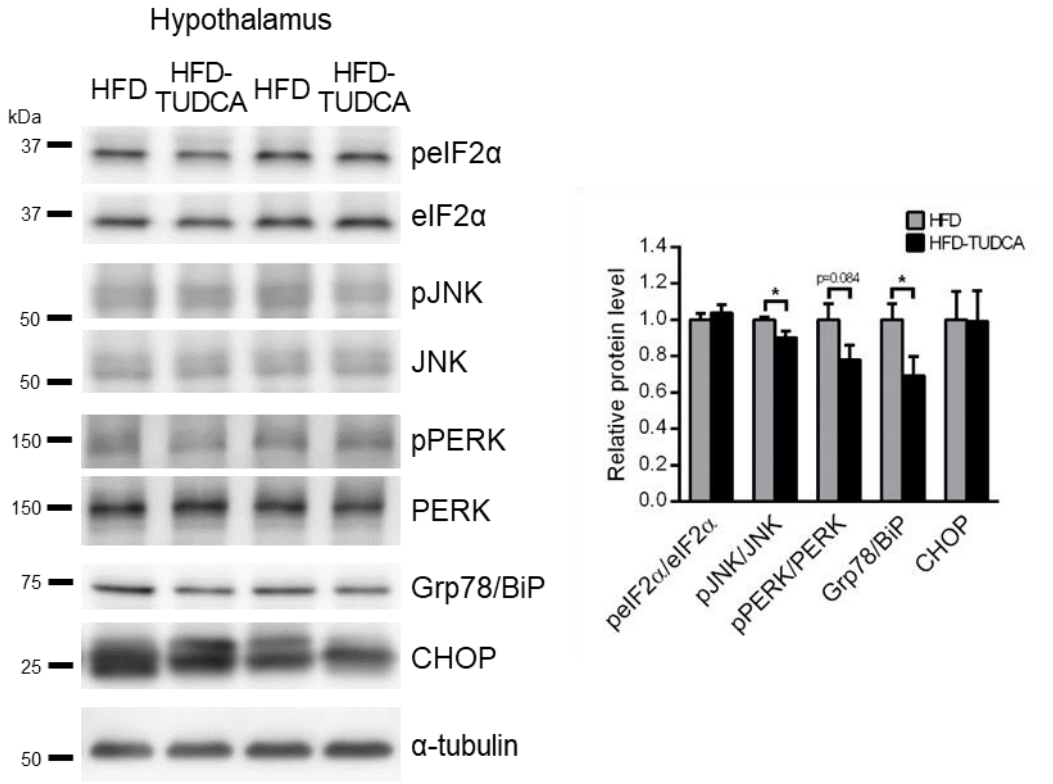

Figure S2. Intracerebroventricular administration of TUDCA decreased hypothalamic ER stress in HFD-fed A7-Tg mice (related to Figure 3)

Immunoblot analyses of peIF2α, eIF2α, pJNK, JNK, pPERK, PERK, Grp78/BiP, CHOP, and α-tubulin in the RIPA-soluble fractions of hypothalamus of 9-month-old HFD-fed A7-Tg mice (left panels). The right panel shows the results of densitometry. The levels of peIF2α, pJNK, pPERK were normalized to total eIF2α, JNK, and PERK, respectively; those of Grp78/BiP and CHOP were normalized to α-tubulin. Data are mean ± SEM (HFD: n = 8, HFD-TUDCA: n = 9). *, $p < 0.05$, unpaired t-test.

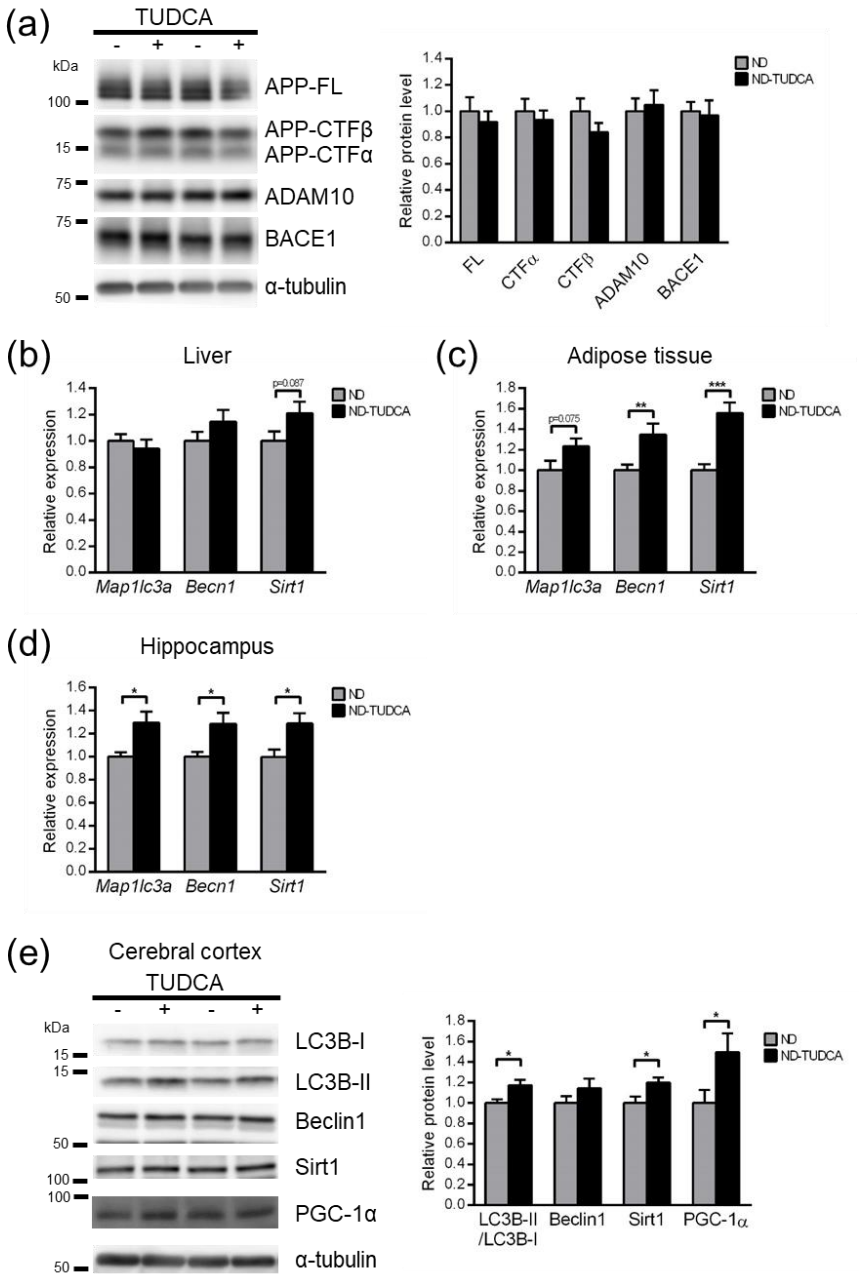

Figure S3. Peripheral administration of TUDCA increased gene and protein expression of autophagy-related molecules and Sirt1 in 15-month-old A7-Tg mice (related to Figures 4 and 5)

(a) Immunoblot analyses of full-length APP (APP FL), APP-CTFα, APP-CTFβ, ADAM10, BACE1, and α-tubulin in the RIPA-soluble fractions of cerebral cortex. The right graph shows the results of densitometry. The amount of protein was expressed as a relative value to the ND group. (b-d) Quantitative RT-PCR analysis of *Map1lc3a*, *Becn1*, and *Sirt1* mRNA expression in the liver (b), adipose tissue (c), and hippocampus (d) of 15-month-old A7-Tg mice in the two experimental groups indicated in Figure 4a (ND, and ND-TUDCA). (e) Immunoblot analyses of LC3B-I, LC3B-II, beclin1, Sirt1, PGC-1α, and α-tubulin in the RIPA-soluble fractions of cerebral cortex (left panels). The levels of LC3B-II were normalized to LC3B-I, and the levels of beclin1, Sirt1, and PGC-1α were normalized to α-tubulin (right panel). Data are mean ± SEM (ND: n = 8, ND-TUDCA: n = 7). *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$, unpaired t-test.