Fig. S1. GSK3β activation induced tau hyperphosphorylation in hippocampus.

We verified the GSK3β-mediated tau hyperphosphorylation by using C57BL/6 mouse brain tissue. In order to confirm tau hyperphosphorylation, the C57BL/6 mouse brain tissues, hippocampus, cortex, and cerebellum homogenates in 5x Buffer, 1 mM ATP and GSK3β

were incubated at 37°C water bath for 30 min, 1 hr, 2 hr and 4 hr. Hyperphosphorylation of tau was determined by western blot analysis. This result indicates that GSK3β-induced tau hyperphosphorylation and hyperphosphorylated tau was significant, especially in hippocampus at 30 min. –: absence of GSK3β, +: presence of GSK3β.

Fig. S2. Inhibitory effect of morin on the GSK3β-mediated tau phosphorylation was confirmed by *ex vivo* experiment in the presence of phosphatase inhibitors.
Elevated tau phosphorylation was observed in the tissue homogenate without adding exogenous GSK3β catalytic domain in the presence of phosphatase inhibitors. The additional tau hyperphosphorylation was achieved by the exogenously added GSK3β. Morin (100 μM and 500 μM) and LiCl (50 mM) were effective to block the additional tau hyperphosphorylation induced by exogenously added GSK3β. –: absence of GSK3β, +: presence of GSK3β.

Fig. S3. Morin effectively decreases the levels of intraneuronal Aβ in 3×Tg-AD mice.
Intracellular Aβ formation is one of the earliest neuropathological phenotypes described thus far in 3×Tg-AD mice. (A) Aβ staining was mostly observed in the hippocampus and amygdala in 8-month-old 3×Tg-AD mice, and morin treatment dramatically decreased intraneuronal Aβ formation in CA1, CA3, and amygdala regions. Note that extracellular Aβ was not seen in 8-month-old 3×Tg-AD mice. (B) Quantitative analysis of the number of Aβ-immunoreactive neurons in the CA1 and CA3 of hippocampus. The values are reported as the mean ± S.E.M (n=4 mice/group). * $p<0.01$ compared to 3×Tg-AD-Control (ANOVA with Fisher's PLSD procedure). (C) Double-labeled IHC was performed with Aβ antibody 6E10 (green) and microglia marker, Iba-1 (red). Note that microglia activation and/or proliferation were not evident in3×Tg-AD mice compared to WT mice. Scale bar = 100 μm.