Tauroursodeoxycholic acid (TUDCA), an endogenous bile acid, is a potent anti-apoptotic agent in neuronal cells exposed to amyloid-beta (Abeta). In addition, we have also shown that TUDCA strongly downregulates connective tissue growth factor (CTGF) in hepatocytes. CTGF is a ligand for the low-density lipoprotein-related protein (LRP) receptor, thought to increase gamma-secretase activity in its release of Abeta42. Our hypothesis is that TUDCA reduces Abeta toxicity by interfering with its accumulation. SH-SY5Y cells were pretreated with 100 µM TUDCA for 12 h, and then incubated with either 10 µM Abeta40 or Abeta42 for 1-24 h. Abeta exposure resulted in increased levels of apoptosis, which correlated with Abeta entry into the cell as assessed by confocal microscopy. TUDCA pretreatment markedly reduced apoptosis, ApoE mRNA, and intracellular Abeta. In vivo, APP/PS1 male mice were fed a diet containing TUDCA for a period of 6 months, and tested at 8 months of age on several behavior tasks measuring memory. TUDCA rescued different memory types in transgenic mice compared to control transgenic mice. No differences were observed in control and TUDCA-treated wild-type mice. Furthermore, immunohistochemistry studies and thioflavin assays showed a reduction of Abeta plaque number in hippocampus and cortex in brains of transgenic mice treated with TUDCA compared to control transgenic mice. Further, GFAP staining was reduced in TUDCA-fed transgenic mice, suggesting that inflammation is also modulated by TUDCA. Characterization of the exact mechanism involved in TUDCA inhibition of Abeta accumulation is likely to provide new perspectives for modulation of Abeta-induced toxicity.