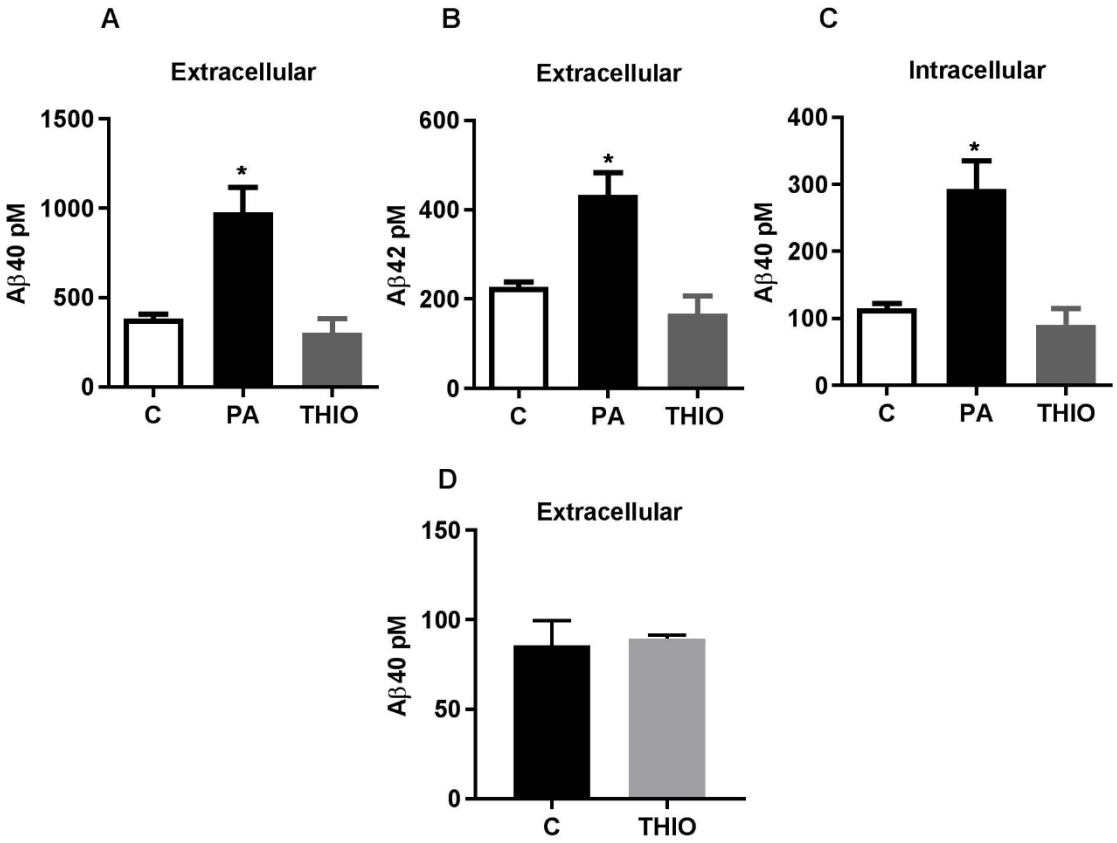
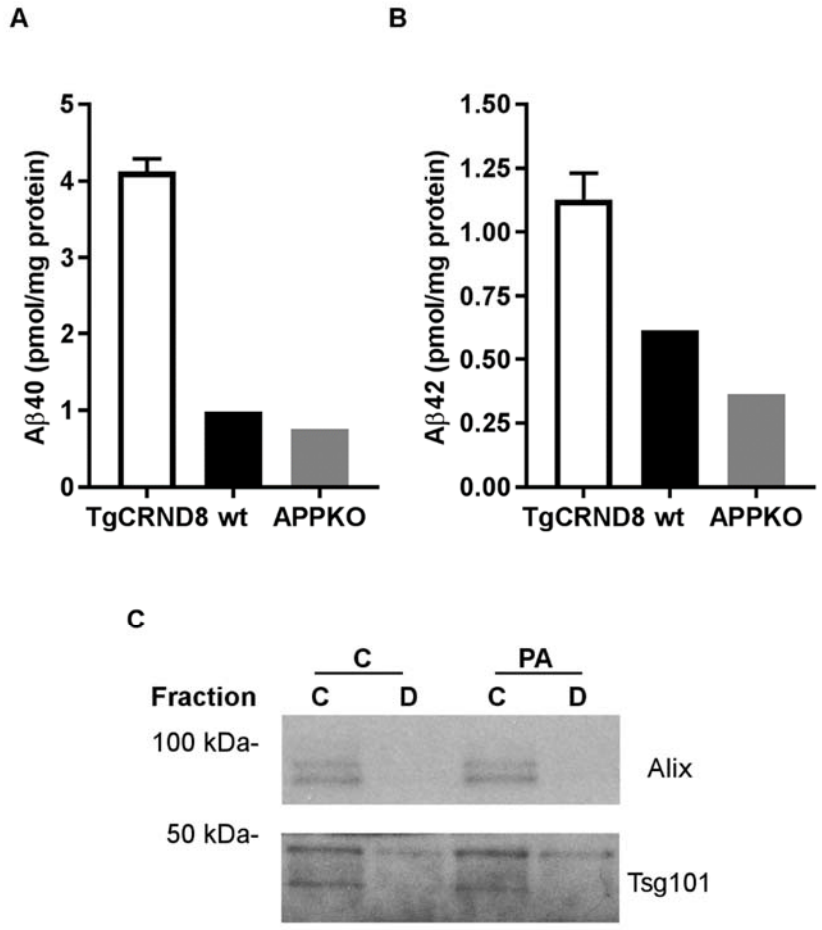
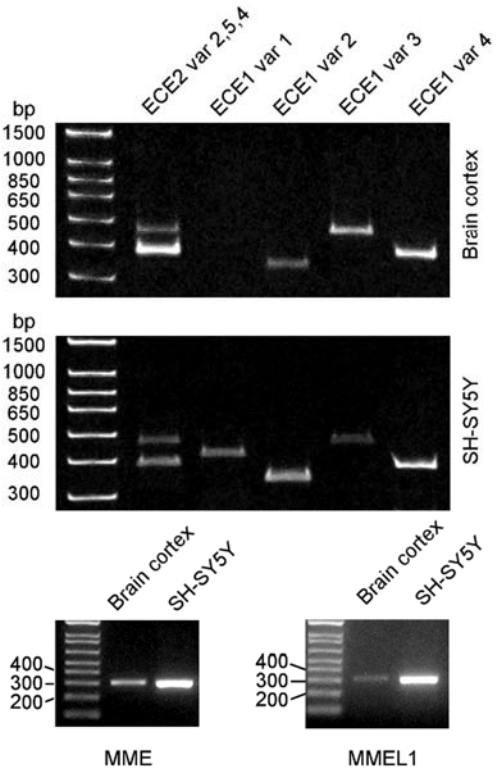


Supplementary Figure 1. Pharmacological inhibition of NEP does not elevate Aβ levels in primary neuronal cultures or organotypic slice cultures. (A-C) Three-week old TgCRND8 brain-derived primary neuronal cultures that were responsive to PA treatment did not show any elevation in extracellular Aβ40 or Aβ42 or intracellular Aβ40 after treatment for 48 h with the more selective NEP inhibitor, thiorphan (THIO) at 500 nM, a dose one hundred times higher than the IC50 (~5 nM) for NEP (n=3 for all groups). **(D)** Extracellular Aβ40 was also unchanged in organotypic slice cultures treated with thiorphan (200 nM for 24h, n=3 for all groups).



Supplementary Figure 2. Validation of Aβ40 and Aβ42 measurements and of exosome markers in EVs isolated from TgCRND8 mice. (A-B) To confirm the specificity of exosome-associated Aβ measurements, exosomes were isolated from 2-month-old TgCRND8 mice (n=3), wild-type mice (pooled sample from 3 mice) and APP knockout mice (n=1). The Aβ40 ELISA is human-specific, indicating that signal obtained in exosomes from both wild-type and APP knockout mice represents background. The Aβ42 ELISA is capable of detecting both human and rodent Aβ42. **(C)** Western blotting for exosomes markers confirmed that fraction c (used for ELISA measurements) was enriched in Alix and Tsg101, and that there was no difference between vehicle and PA-treated mice in the level of exosomes in the brain extracellular space.



Supplementary Figure 3. Evaluation of mRNA expression of members of the M13 protease family in SH-SY5Y-APP cells and human temporal cortex. The presence of mRNAs for *ECE1*, *ECE2*, *MME* (coding for NEP), and *MMEL1* (coding for NEP-2) was evaluated by reverse-transcription PCR in SH-SY5Y-APP cells and human brain temporal cortex. Expected product sizes for the primer pair designed to amplify transcripts for all 3 major ECE-2 isoforms are: variant 2 (395 bp), variant 5 (482 bp), and variant 4 (620 bp). *ECE1* transcripts coding for different protein isoforms were amplified in individual reactions with the following expected product sizes: variant 1 (442 bp), variant 2 (355 bp), variant 3 (482 bp) and variant 4 (406 bp). Primers for *MME* (318 bp) and *MMEL1* (309 bp) amplify all known transcripts of each gene.