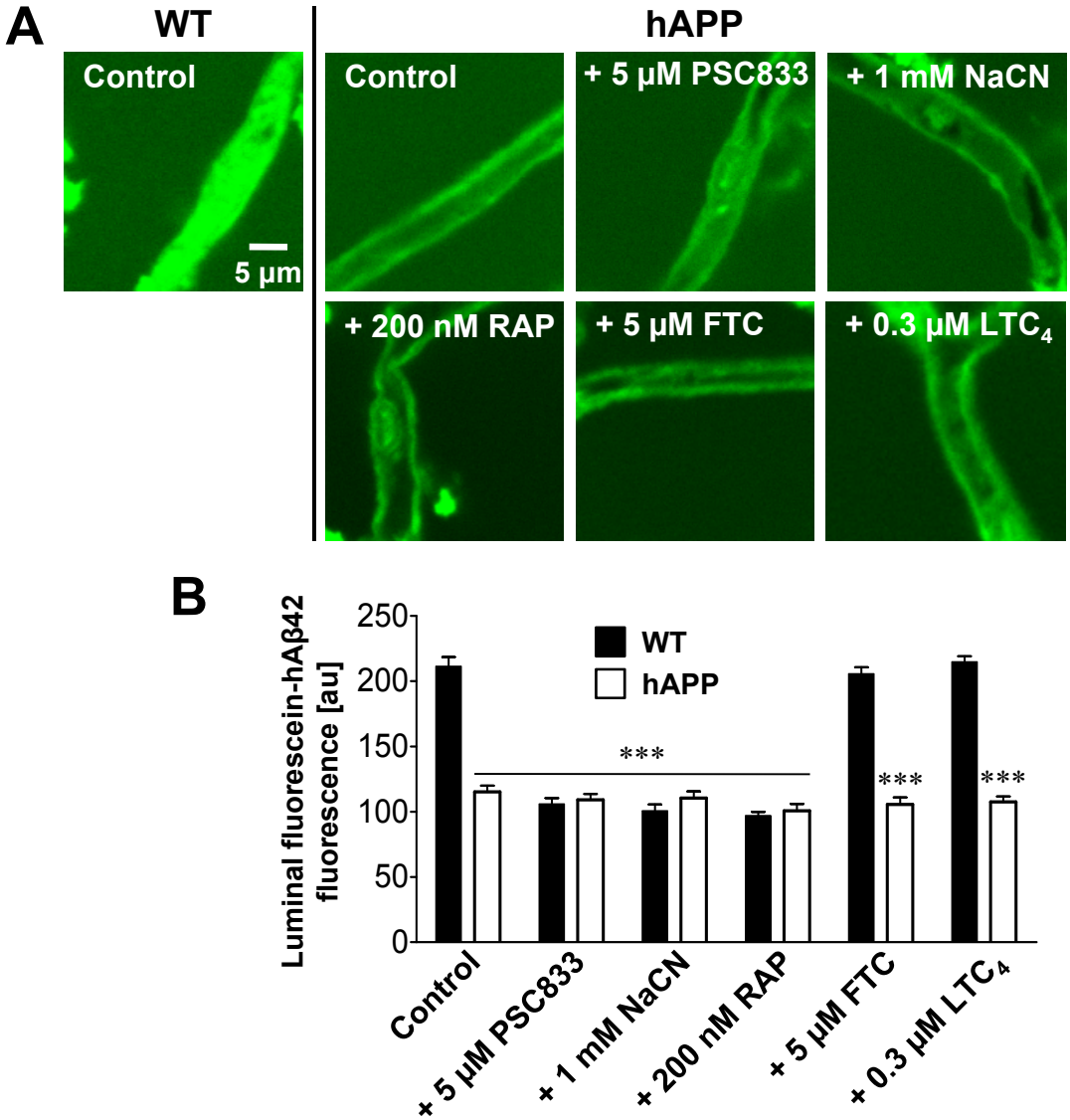
Supplemental Figure 1

Hartz AMS, Miller DS, Bauer B

Restoring Blood-Brain Barrier P-glycoprotein Reduces Brain Aβ in a Mouse Model of Alzheimer's Disease

Molecular Pharmacology



Supplemental Figure 1. P-glycoprotein mediates hAβ42 transport in brain capillaries from wild-type mice but such transport is substantially reduced in brain capillaries from hAPP transgenic mice. (**A**) Representative images of brain capillaries isolated from wild-type and hAPP transgenic mice; capillaries were incubated with 5 µM fluorescein-hAβ42 for 1 h alone (control) or with 5 µM fluorescein-hAβ42 plus PSC833 (P-glycoprotein inhibitor), NaCN (metabolic inhibitor), RAP (receptor-associated protein, LRP1 inhibitor), FTC (fumitremorgin C, BCRP inhibitor), or LTC_4 (leukotriene C_4, MRP inhibitor). (**B**) shows luminal fluorescein-hAβ42 fluorescence in brain capillaries after digital image analysis; residual fluorescence is due to non-specific binding (14). Data represent mean ± SEM for 10 capillaries from one preparation (pooled tissue from 10 wild-type and 10 hAPP transgenic mice); shown are arbitrary fluorescence units (scale 0-255). Statistics: ***significantly lower than control, $P<0.001$.

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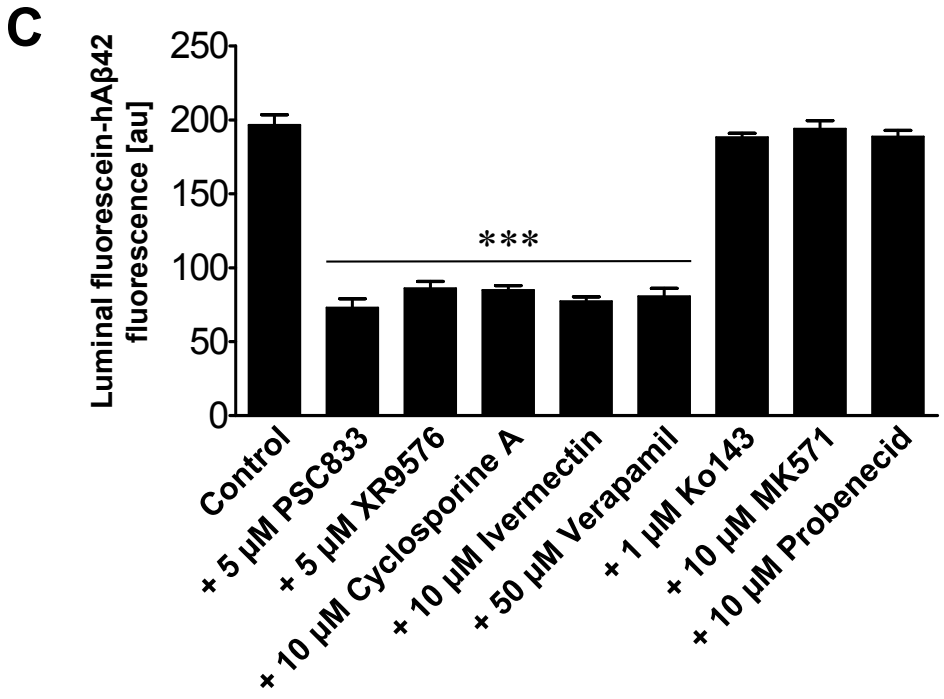

Supplemental Figure 1. P-glycoprotein mediates hAβ42 transport in brain capillaries from wild-type mice. (**C**) shows luminal fluorescein-hAβ42 fluorescence in brain capillaries after inhibition with the P-glycoprotein-specific inhibitors, PSC833 (valspodar), XR9576 (tariquidar), cyclosporine A, ivermectin, and verapamil. Luminal capillary fluorescein-hAβ42 fluorescence was not affected by the BCRP inhibitor, Ko143, and the MRP inhibitors, MK571 and probenecid.

Data represent mean ± SEM for 10 capillaries from one preparation (pooled tissue from 10 wild-type mice); shown are arbitrary fluorescence units (scale 0-255). Statistics: ***significantly lower than control, $P<0.001$.

Supplemental Figure 2

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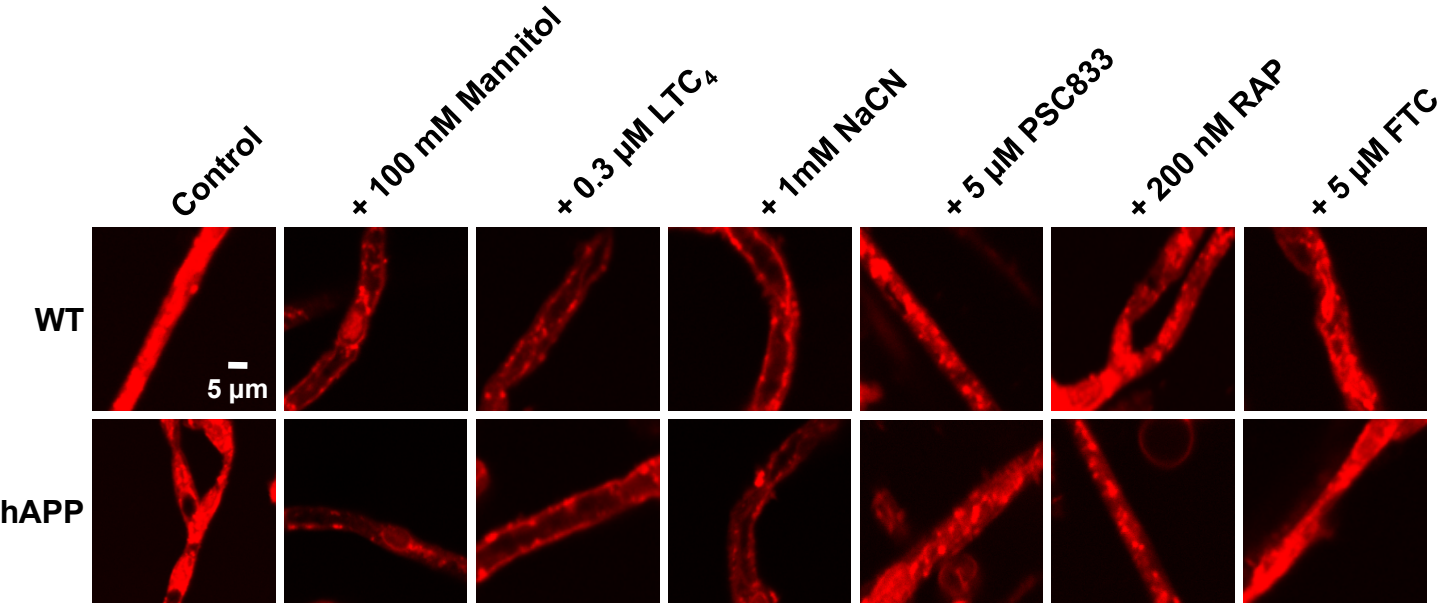
Molecular Pharmacology



Supplemental Figure 2. Concentrative transport of sulforhodamine 101 into the brain capillary luminal space. Representative images of brain capillaries isolated from wild-type and hAPP mice; capillaries were incubated with 2 μM sulforhodamine 101 for 1 h alone (control) or with 2 μM sulforhodamine 101 plus mannitol (osmotic tight junction disruptor), LTC4 (MRP inhibitor), NaCN (metabolic inhibitor), PSC833 (P-glycoprotein inhibitor), RAP (LRP1 inhibitor), or FTC (BCRP inhibitor). Note that sulforhodamine 101 is transported by Mrp2, another ATP-driven efflux pump (15). Consistent with this, concentrative transport of sulforhodamine 101 into the luminal space was reduced by mannitol, LTC4, and NaCN, but remained unaltered by inhibitors of other transporters (PSC833, RAP, FTC). Unaltered luminal accumulation of sulforhodamine 101 in control capillaries from hAPP mice indicates that reduced transport of NBD-CSA and fluorescein-hAβ42 found in brain capillaries from hAPP mice was not due to disruption of tight junctions, but rather to reduced P-glycoprotein-mediated transport.

Supplemental Figure 3

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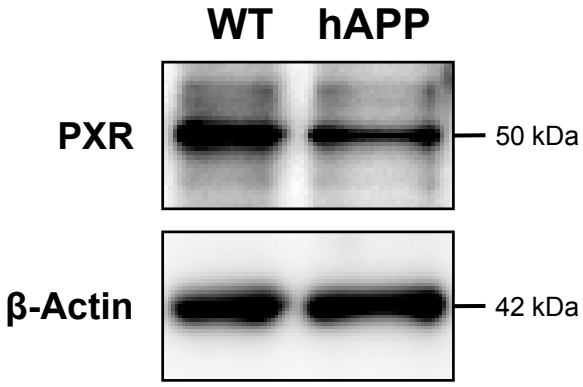
Molecular Pharmacology



Supplemental Figure 3. Western blot of the ligand-activated nuclear receptor, pregnane X receptor (PXR) in brain capillaries from wild-type and hAPP transgenic mice; β-actin was used as protein loading control.

Supplemental Figure 4

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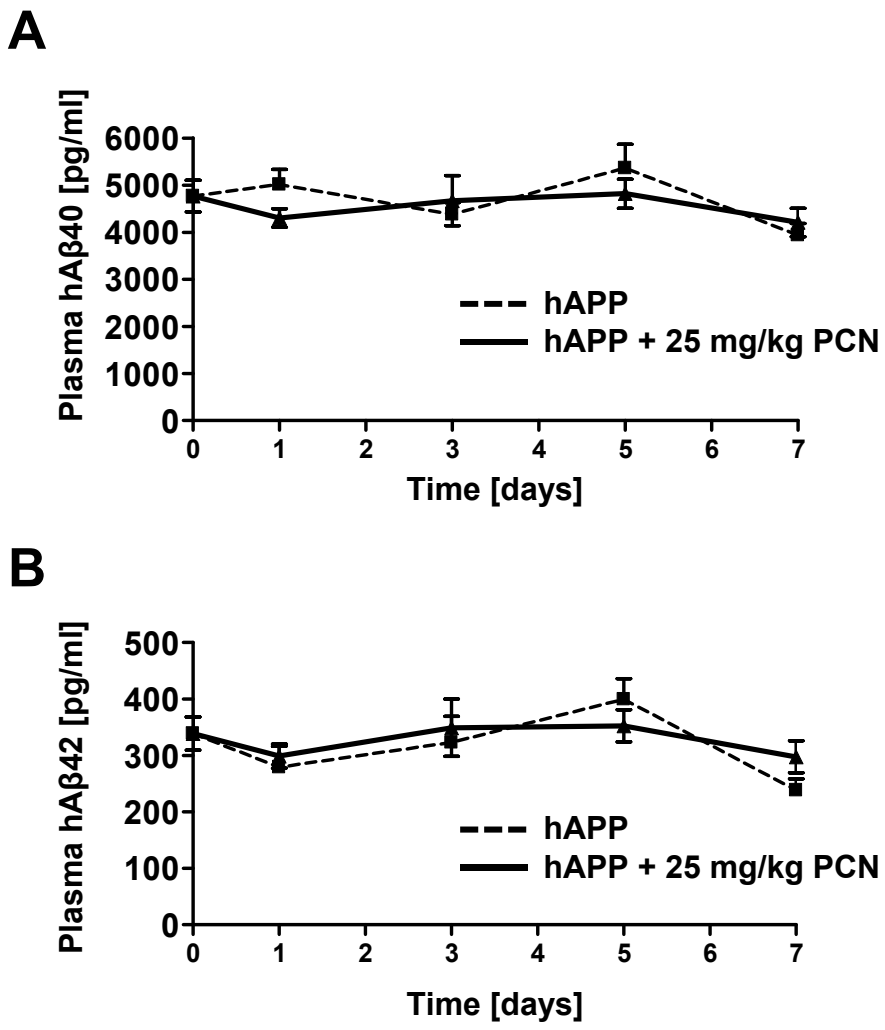
Molecular Pharmacology



Supplemental Figure 4. ELISA analysis of (**A**) hAβ40 and (**B**) hAβ42 in plasma from vehicle- and PCN-treated hAPP mice. At time point 0 days, n = 14 animals for each group, at time points 1, 3, and 5 days, n = 7-8, at time point 7 days, n = 15-19. Data are mean ± SEM. Over the entire time course no statistically significant differences in hAβ40 and hAβ42 plasma levels were observed between hAPP and PCN-treated hAPP mice.