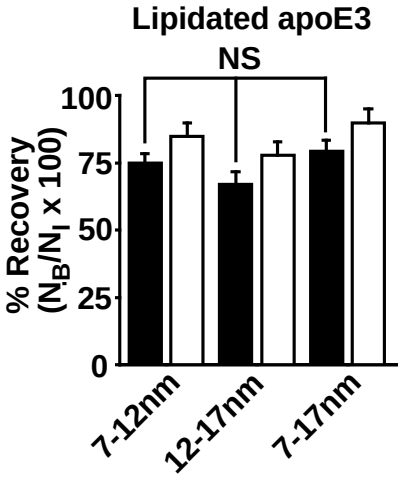


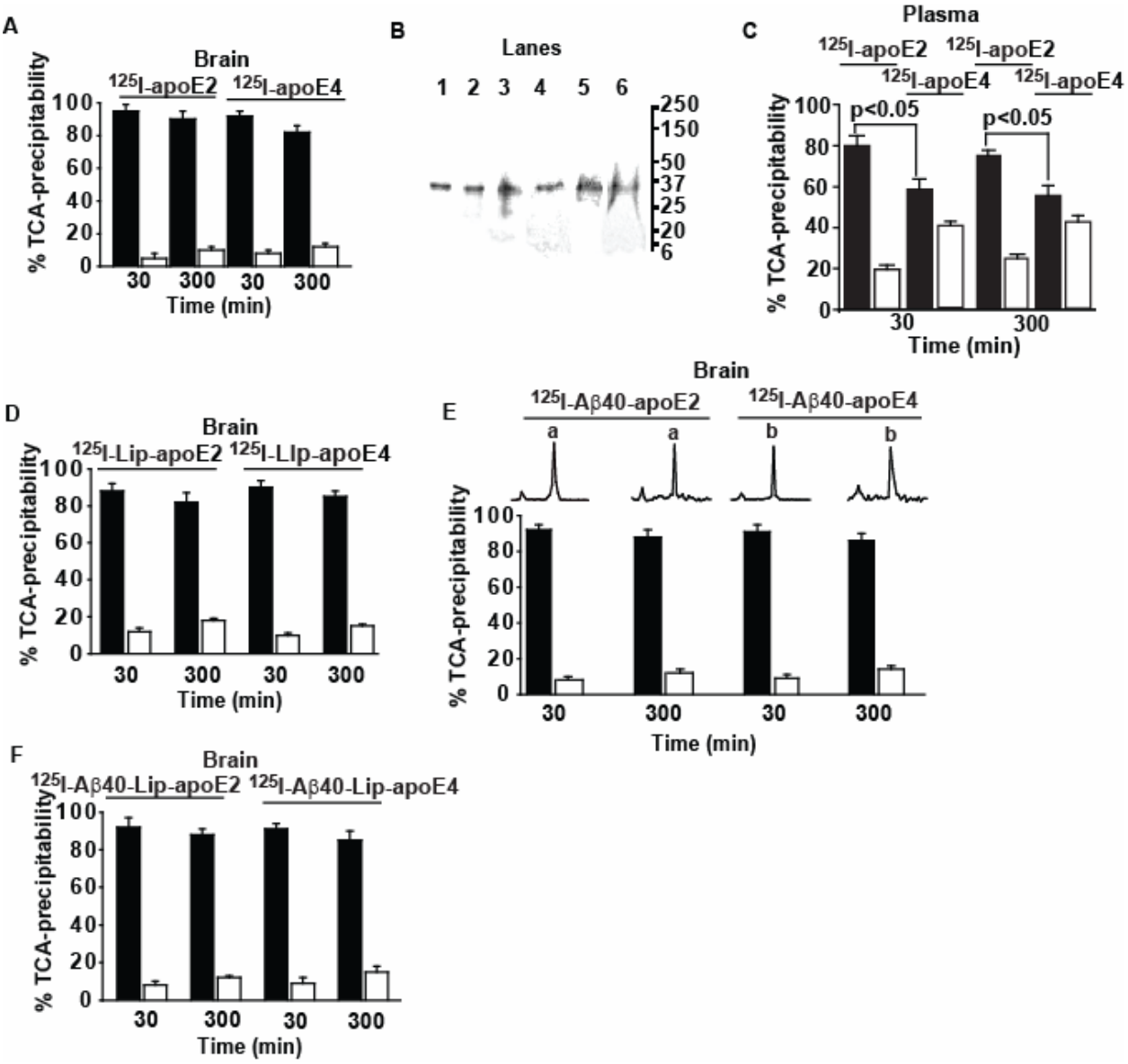
Supplemental Figure 1

Clearance from the mouse brain interstitial fluid (ISF) of different size astrocyte-secreted lipidated apoE3 particles ranging from 7 to 17 nm. Brain recovery of ^{125}I-labeled lip-apoE3 particles (40 nM, TCA-precipitable ^{125}I-radioactivity) was determined using eq. 1 (see Methods). Particles ranging from 7-12, 12-17 and 7-17 nm (solid bars) were microinfused into brain ISF simultaneously with ^{14}C-inulin (clear bars). Recovery was determined within 90 min of the ISF microinfusion of the tracers mixture. Values are mean $\pm$ SEM, n = 3 mice per group.

Parameters	^{125}I-apoE2 kx10^3 (min^{-1})	^{125}I-apoE2 t^1/2 (min)	^{125}I-apoE3 kx10^3 (min^{-1})	^{125}I-apoE3 t^1/2 (min)	^{125}I-apoE4 kx10^3 (min^{-1})	^{125}I-apoE4 t^1/2 (min)	^{125}I-lip apoE2 kx10^3 (min^{-1})	^{125}I-lip apoE2 t^1/2 (min)	^{125}I-lip apoE3 kx10^3 (min^{-1})	^{125}I-lip apoE3 t^1/2 (min)	^{125}I-lip apoE4 kx10^3 (min^{-1})	^{125}I-lip apoE4 t^1/2 (min)	^{14}C-inulin kx10^3 (min^{-1})	^{14}C-inulin t^1/2 (min)
Total Efflux	14.6 [b] ±1.2	47.5 [b] ±3.9	14.3 [b] ±1.2	48.5 [b] ±3.5	9.7[a,b] ±0.7	71.4[a,b] ±5.0	8.4 ±0.7	82.5 ±6.6	6.4 ±0.4	108.3 ±7.6	5.1 [c] ±0.4	135.9[c] ±10.0	2.7 [d] ±0.2	256.7 [d] ±20.2
Transport via BBB	11.9 [b] ±0.9	8.2 [b] ±4.8	11.6 [b] ±0.9	59.7 [b] ±4.8	7.0 [a,b] ±0.5	99.0 [a,b] ±7.2	5.7 ±0.5	121.6 ±8.5	4.1 ±0.3	169.1 ±13.1	3.4 [c] ±0.2	203.8 [c] ±24.1	None	
Transport via ISF Flow	2.7 ±0.2	256.7 ±20.2	2.7 ±0.2	256.7 ±20.2	2.7 ±0.2	256.7 ±20.2	2.7 ±0.2	256.7 ±20.2	2.7 ±0.2	256.7 ±20.2	2.7 ±0.2	256.7 ±20.2	2.7 ±0.2	256.7 ±20.2
Retention in Brain	15.8 [b] ±3.1	43.9 [b] ±3.5	21.0 [b] ±1.7	33.3 [b] ±3.5	30.8 [a,b] ±2.1	22.5 [a,b] ±1.4	35.8 ±1.1	19.4 ±2.4	53.3 ±1.9	16.4 ±2.3	71.2[c] ±3.1	9.7 [c] ±1.7	None	

Values are mean ± SEM from 11 to 24 data points per isoform. [a]P <0.05 for lipid poor apoE4 vs. respective lipid poor apoE3 or apoE2. [b]P <0.05 lipid poor vs. lipidated respective apoE isoform. [c]P <0.05 for lipidated apoE4 vs. lipidated apoE2. [d]P <0.05 inulin vs. each poor or lipidated apoE isoform.

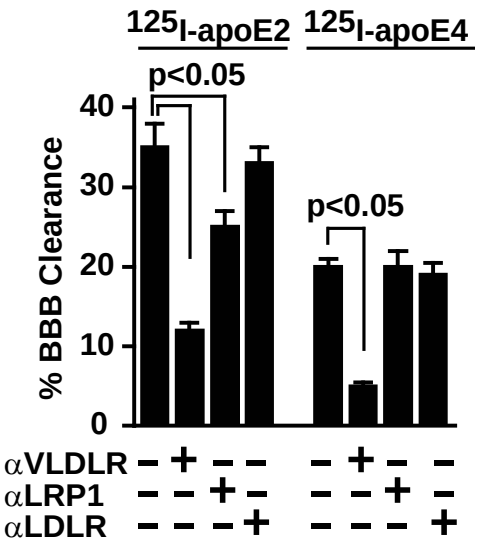
Supplemental Table 1 Clearance rates (kx10^3) and half-time (t^1/$_2$) for ^{125}I-apoE lipid poor and lipidated isoforms and ^{14}C-inulin.



Supplemental Figure 2

Minimal degradation of lipid-poor and lipidated apoE2 and apoE4 in brain interstitial fluid (ISF) compared to plasma after an ISF microinfusion. (**A**) TCA-precipitable (solid bar) and non-precipitable (open bar) ^{125}I-radioactivity in brain tissue supernatants determined at 30 and 300 min of microinfusion of 40 nM ^{125}I-labeled apoE2 and apoE4 into brain ISF. (**B**) SDS-PAGE analysis of brain tissue supernatant [PBS extraction at the focal microinjection site, as described (16)] at 30 min and 300 min after microinfusion of 40 nM ^{125}I-labeled apoE4 (lanes 3

and 4) or apoE2 (lanes 5 and 6). Lanes 1 and 2 are samples of ^{125}I-labeled apoE4 and apoE2 solutions prior to brain ISF microinfusion. **(C)** TCA-precipitable (solid bar) and non-precipitable (open bar) ^{125}I-radioactivity determined in plasma at 30 and 300 min of microinfusion of 40 nM ^{125}I-labeled apoE2 and apoE4 into brain ISF. Values are mean $\pm$ SEM. n = 3 mice per group. **(D)** TCA-precipitable (solid bar) and non-precipitable (open bar) ^{125}I-radioactivity in brain tissue supernatants determined at 30 and 300 min of microinfusion of 40 nM ^{125}I-labeled lipidated apoE2 and apoE4 into brain ISF. **(E)** TCA-precipitable (solid bar) and non-precipitable (open bar) ^{125}I-radioactivity in brain tissue supernatants determined at 30 and 300 min of microinfusion of 40 nM ^{125}I-Aβ40-apoE2 and ^{125}I-Aβ40-apoE4 into brain ISF. ^{125}I-Aβ40-apoE2 and ^{125}I-Aβ40-apoE4 (HPLC analysis, for methods see reference 37) in brain homogenates 30 and 300 min after microinfusion of the complexes into brain ISF (insets above bars) showing the major peak representing ^{125}I-Aβ40-apoE2 (a) and ^{125}I-Aβ40-apoE4 (b). **(F)** TCA-precipitable (solid bar) and non-precipitable (open bar) ^{125}I-radioactivity in brain tissue supernatants determined at 30 and 300 min of microinfusion of 40 nM ^{125}I-Aβ40-lip-apoE2 and ^{125}I-Aβ40-lip-apoE4 complexes into brain ISF. Values are mean $\pm$ SEM. n = 3 mice per group.



Supplemental Figure 3

Isoform specific clearance of lipid-poor apoE across the mouse BBB. ^{125}I-labeled apoE2 and apoE4 efflux at the BBB was determined as in Figure 2D in the absence and presence of receptor specific blocking antibodies to VLDLR, LRP1 and LDLR. ^{125}I-labeled apoE-Aβ complexes (40 nM) and the reference tracer ^{14}C-inulin were simultaneously microinfused into brain ISF and clearance determined at 90 min. Values are mean $\pm$ SEM, n = 3 mice per group.