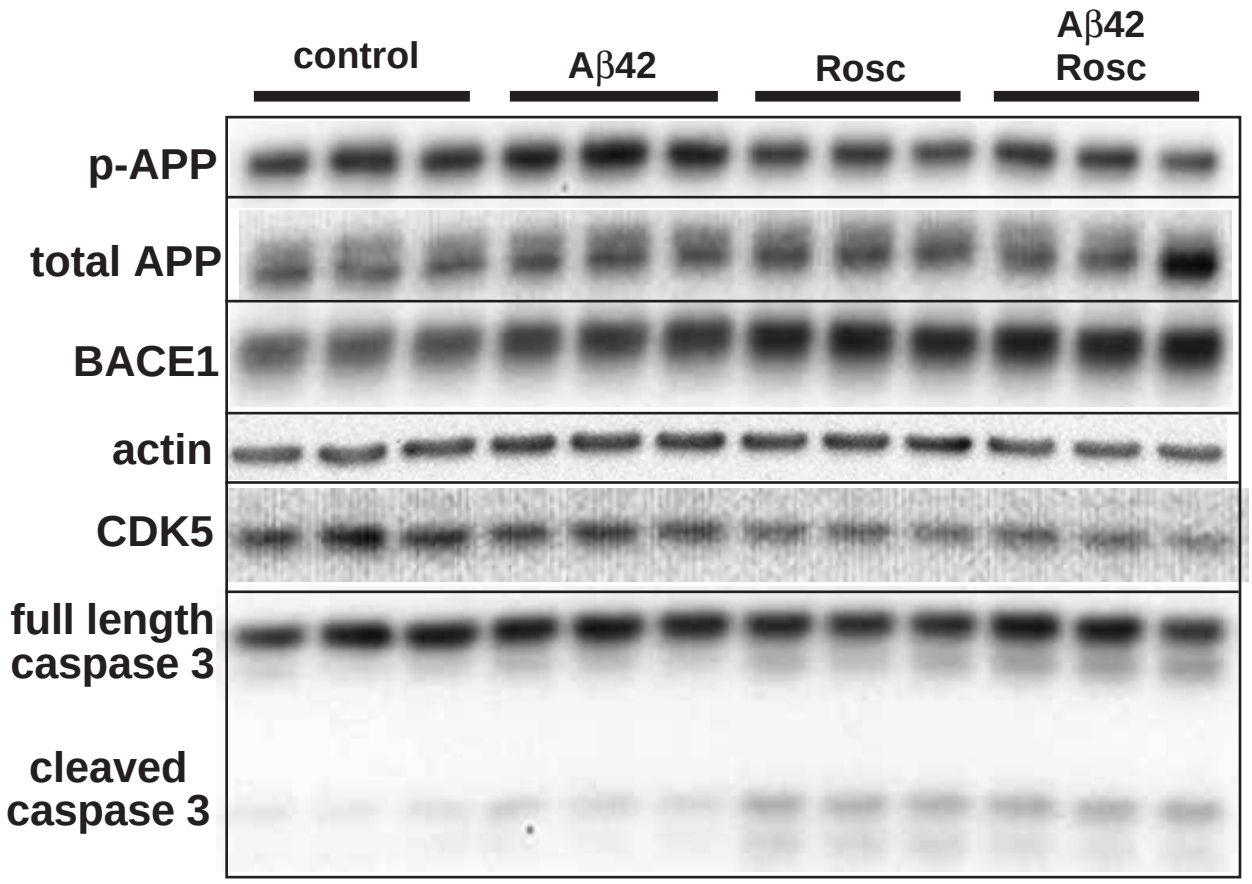
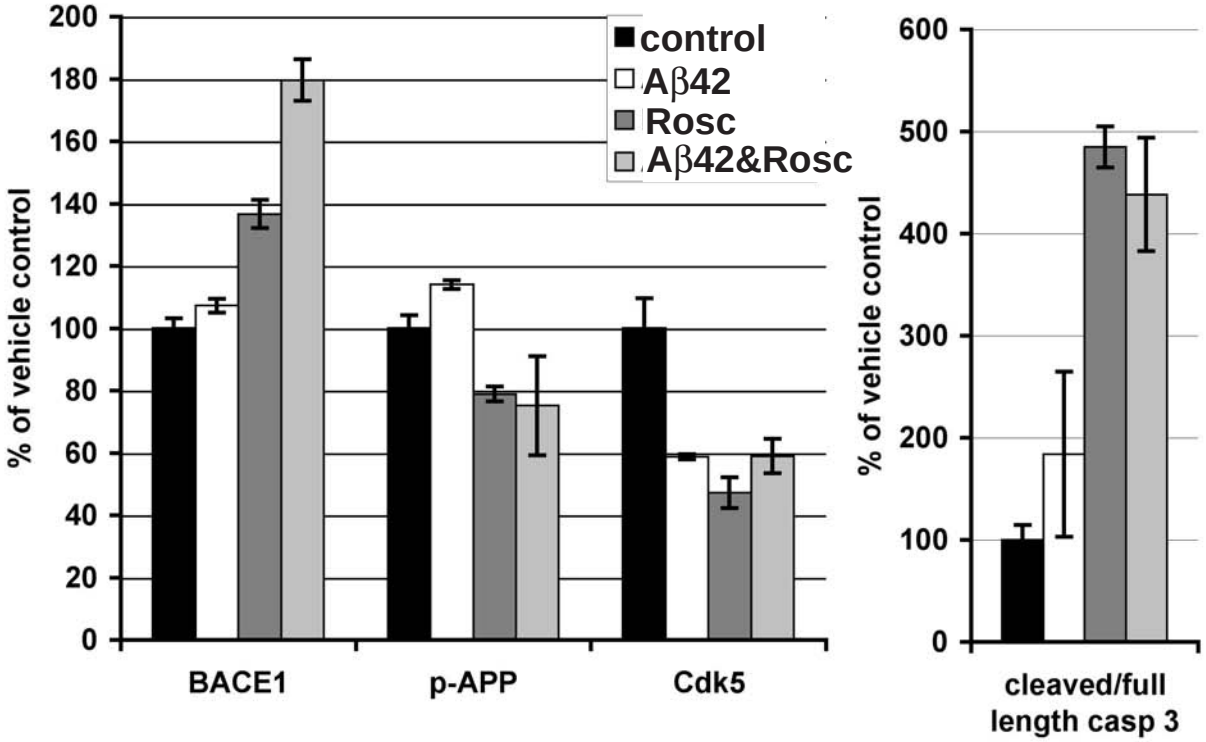
Supplemental Figure 1. Roscovitine alone or in combination with Aβ42 increases BACE1 level in primary neurons. Primary neuron cultures were pre-treated with 10μM roscovitine for 4 hrs and then exposed to 10μM oligomeric Aβ42 for 48hrs. Neurons were lysed in RIPA buffer and samples analyzed by immunoblot (15μg/lane, upper panel). Immunoblot signals were quantified, normalized, and presented as percentage of vehicle control (lower panel). Note that roscovitine treatment alone increased BACE1 level above control. Importantly, roscovitine in combination with Aβ42 caused the most potent elevation of BACE1 level in neurons, suggesting that Cdk5 was not responsible for Aβ42-induced BACE1 elevation. Roscovitine did effectively inhibit Cdk5 activity, as demonstrated by decreased APP Thr 668 phosphorylation. In addition, like CP681301, roscovitine reduced Cdk5 level and increased caspase 3 cleavage compared to control.

Supplemental Figure 2. Cycloheximide treatment prevents the Aβ42-induced BACE1 elevation in primary neurons. Primary neuron cultures (7 div) in triplicate were pre-treated with 10μg/ml cycloheximide (CHX) or vehicle (veh) for 2 hrs and then exposed to 10μM oligomeric Aβ42 with or without 10μg/ml cycloheximide for 24hrs. Neurons were lysed in RIPA buffer and samples analyzed by immunoblot for BACE1, p35/25, and tubulin (5μg/lane, upper panel). Immunoblot signals were quantified by phosphorimager, normalized to tubulin signal, and presented as percentage of vehicle control (lower panel). Aβ42 treatment alone increased BACE1 level and induced p25 formation compared to vehicle, as previously observed. Cycloheximide strongly reduced levels of short-lived p35/25, indicating effective inhibition of protein synthesis. In the presence of cycloheximide alone, BACE1 levels were also reduced. Importantly, Aβ42 plus cycloheximide treatment did not elevate BACE1 levels compared to cycloheximide alone, indicating that protein synthesis appears to play a role in Aβ42-induced BACE1 elevation. Error bars = SEM; * = $p \leq 0.05$

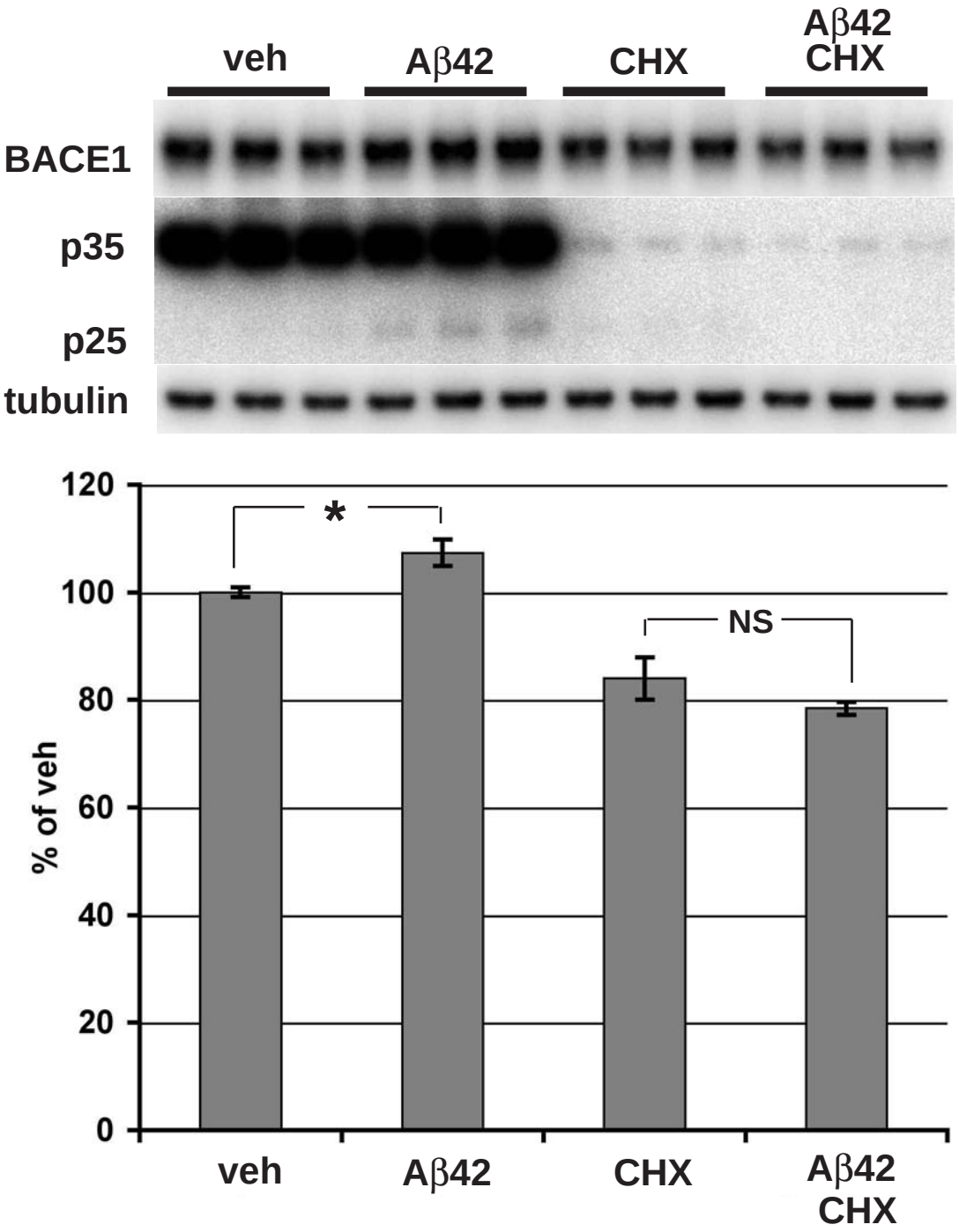
Supplemental Table 1: Data on human brain samples analyzed for BACE1, Cdk5, and p25/p35. "label:" label used in Figure 1A. NCI=non-cognitively impaired (control), AD=Alzheimer's disease. "gender:" F=female, M=male. "years educ": years of formal education. '"last MMSE score": score on last mini-mental states exam administered before death., ≥25 is considered cognitively normal. "days since last MMSE": days elapsed between administration of last MMSE and death. "age": age in years. at death "overall diagnosis" NCI=non-cognitively impaired, AD=Alzheimer's disease. "APOE geno": APOE genotype, E2=APOE2 allele, E3=APOE3 allele, E4=APOE4 allele. "PMI": post-mortem interval in hours:minutes. "Braak Score": Braak Score (1) 1=Stage I, 2=Stage II, 3=Stage III, 4=Stage IV, 5=Stage V, 6=Stage VI, with increasing number indicating increasing extent of tau neurofibrillary tangles. "CERAD diagnosis": Consortium to Establish a Registry for Alzheimer's Disease composite score (2) 4=No AD, 3=Possible AD, 2=Probable AD, 1=Definite AD. "NIA/Reagan Diagnosis" (3) 4=No AD, 3=Low likelihood AD, 2=Intermediate likelihood AD, 1=High likelihood AD.

1. Braak, H., Braak, E., and Bohl, J. (1993) Staging of Alzheimer-like cortical destruction. *Eur Neurol* **33**, 403-408
2. Mirra, S. S. (1997) The CERAD neuropathology protocol and consensus recommendations for the postmortem diagnosis of Alzheimer's disease: a commentary. *Neurobiol Aging* **18**, S91-94
3. (1997) Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. *Neurobiol Aging* **18**, S1-2





Supplementary figure 1



Supplementary figure 2

label	gender	years educ	last MMSE score	days since last MMSE	age	overall diagnosis	APOE geno	PMI	Braak Score	CERAD diagnosis	NIA/Reagan Diagnosis
NCI 1	F	14	'29/30'	22	95.9	NCI	E2E3	6:25	2	4	3
NCI 2	F	12	'27/30'	166	88.5	NCI	E2E2	5:30	3	4	3
NCI 3	F	13	'26/30'	130	86.6	NCI	E3E3	3:15	4	2	2
NCI 4	F	15	'29/30'	218	85.1	NCI	E2E3	6:45	3	4	3
NCI 5	F	13	'30/30'	220	92.1	NCI	E3E3	4:45	4	2	2
NCI 6	F	15	'28/30'	296	87.7	NCI	E2E4	14:45	1	4	3
NCI 7	M	15	'30/30'	28	81.7	NCI	E3E3	7:10	2	4	3
NCI 8	F	17	'30/30'	180	86.2	NCI	E3E3	3:37	1	4	3
NCI 9	F	14	'29/30'	82	86.7	NCI	E2E3	6:30	2	4	3
NCI 10	F	14	'26/30'	332	92.8	NCI	E3E4	3:20	3	1	2
AD 11	M	16	'13/30'	189	79.5	AD	E3E4	3:37	5	1	1
AD 12	F	16	'22/30'	376	89.6	AD	E3E3	4:05	3	2	2
AD 13	F	16	'1 /30'	30	93.3	AD	E2E3	6:25	4	2	2
AD 14	F	13	'9 /30'	200	87.0	AD	E3E4	5:55	5	1	1
AD 15	F	12	'12/30'	121	91.2	AD	E3E4	5:50	5	2	2
AD 16	F	19	'19/30'	75	86.3	AD	E3E4	6:25	4	1	2
NCI 17	M	16	'28/30'	191	72.9	NCI	E2E3	4:40	1	4	3
NCI 18	M	12	'28/30'	363	78.6	NCI	N/A	7:55	1	4	3
NCI 19	F	7	'28/30'	309	89.1	NCI	N/A	10:10	4	2	2
AD 20	F	12	'6 /30'	829	94.4	AD	E3E3	11:55	6	1	1
AD 21	F	9	'0 /30'	205	92.9	AD	E3E4	6:05	5	1	1
AD 22	M	6	'5 /30'	136	N/A	AD	E3E3	N/A	5	1	1

Supplemental Table 1