

Dose response analyses were accompanied by calculation of ω^2 , which expresses proportion of variability accounted for in a less-biased way than does η^2 ¹. Fold-change per μM (FC) effect size was calculated as $\frac{x_0 - x_{\max}}{x_0} \div D_{\max}$, where x_0 = outcome at dose = 0 μM , $x_{\max}$ = outcome at dose = 10 μM , and $D_{\max}$ = maximum dose in μM , for mean values at minimum and maximum drug doses for single-treatment studies. Combined rivastigmine $\times$ TAPI tests used a “ ΔFC ” effect size, where FCs were calculated separately for each TAPI dose, and the FC for TAPI = 0 μM was subtracted from the FC for TAPI = 10 μM . Pairwise comparisons of human brain sample assays were accompanied with Hedge’s g effect size ².

- 1 Olejnik, S. & Algina, J. Generalized eta and omega squared statistics: measures of effect size for some common research designs. *Psychol. Methods* **8**, 434-447, doi:10.1037/1082-989X.8.4.434 (2003).
- 2 Hedges, L. V. & Olkin, I. *Statistical Methods for Meta-Analysis*. (Academic Press, 1985).

Table S1. ANOVA and Effect Sizes of Differentiated PC12 Cultures

Single Treatment Assays					
Outcome	Treatment	F	p	ω^2	FC
CTG	Rivastigmine	101.843 (1,22)	<0.001	0.808	0.038
CTG	TAPI	15.666 (1,26)	<0.001	0.344	-0.009
sAPP α	Rivastigmine	101.607 (1,14)	<0.001	0.863	0.211
sAPP β	Rivastigmine	19.347 (1,13)	<0.001	0.550	-0.034
A β 40	Rivastigmine	11.474 (1,14)	0.004	0.396	-0.014

Rivastigmine/TAPI co-Treatment					
CTG	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	55.910 (1,20)	<0.001	0.530	0.008
	TAPI	0.002 (1,20)	0.969	0.000	0.000
	Riva $\times$ TAPI	26.708 (1,20)	<0.001	0.248	-0.010
sAPP α	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	14.644 (1,68)	<0.001	0.129	+0.048
	TAPI	8.769 (1,68)	0.004	0.074	-0.034
	Riva $\times$ TAPI	12.966 (1,68)	<0.001	0.114	-0.036

Table S2. ANOVA and Effect Sizes of PHB Culture APP metabolites

hAPP	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	0.626, (1, 20)	0.438	0.000	0.028
	TAPI	0.764, (1, 20)	0.393	0.000	-0.024
	Riva $\times$ TAPI	1.191, (1, 20)	0.288	0.008	-0.051
sAPPt	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	0.208, (1, 20)	0.654	0.000	0.006
	TAPI	1.417, (1, 20)	0.248	0.014	-0.015
	Riva $\times$ TAPI	6.466, (1, 20)	0.019	0.188	-0.049
sAPP α (WB)	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	11.198, (1, 20)	0.003	0.145	0.138
	TAPI	25.127, (1, 20)	<0.001	0.344	-0.074
	Riva $\times$ TAPI	12.802, (1, 20)	0.002	0.168	-0.175
sAPP α (ELISA)	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	76.483, (1, 20)	<0.001	0.421	0.069
	TAPI	77.262, (1, 20)	<0.001	0.426	-0.039
	Riva $\times$ TAPI	4.474, (1, 20)	0.047	0.019	-0.070
sAPP β	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	33.582, (1, 20)	<0.001	0.469	-0.033
	TAPI	0.262, (1, 20)	0.614	0.000	0.004
	Riva $\times$ TAPI	14.675, (1, 20)	0.001	0.197	0.024
CTF β	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	7.728, (1, 20)	0.012	0.209	-0.031
	TAPI	0.993, (1, 20)	0.331	0.000	0.015
	Riva $\times$ TAPI	2.504, (1, 20)	0.129	0.047	0.014
A β 40	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	24.015, (1, 20)	<0.001	0.406	-0.048
	TAPI	0.439, (1, 20)	0.515	0.000	-0.007
	Riva $\times$ TAPI	11.165, (1, 20)	0.003	0.180	0.048
A β 42	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	19.896, (1, 20)	0.000	0.337	-0.038
	TAPI	2.999, (1, 20)	0.099	0.036	-0.017
	Riva $\times$ TAPI	12.107, (1, 20)	0.002	0.198	0.045
CTG	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	0.400, (1, 20)	0.534	0.000	-0.004
	TAPI	7.955, (1, 20)	0.011	0.231	-0.018
	Riva $\times$ TAPI	0.777, (1, 20)	0.389	0.000	0.009

Table S3. ANOVA and Effect Sizes of PHB Cultures ADAM-9 and ADAM-10

pro-ADAM-9	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	3.312, (1, 20)	0.084	0.068	0.028
	TAPI	1.818, (1, 20)	0.193	0.024	0.021
	Riva $\times$ TAPI	7.925, (1, 20)	0.011	0.203	-0.057
ADAM-9	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	22.594, (1, 20)	0.000	0.354	0.232
	TAPI	5.577, (1, 20)	0.028	0.075	0.115
	Riva $\times$ TAPI	11.789, (1, 20)	0.003	0.177	-0.237
A9 Maturation	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	31.077, (1, 20)	<0.001	0.442	0.083
	TAPI	8.994, (1, 20)	0.007	0.117	0.045
	Riva $\times$ TAPI	6.993, (1, 20)	0.016	0.088	-0.065
pro-ADAM-10	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	22.117, (1, 20)	0.000	0.376	0.120
	TAPI	4.047, (1, 20)	0.058	0.054	0.051
	Riva $\times$ TAPI	8.949, (1, 20)	0.007	0.142	-0.114
ADAM-10	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	4.166, (1, 20)	0.055	0.019	0.091
	TAPI	141.542, (1, 20)	<0.001	0.842	-0.061
	Riva $\times$ TAPI	0.231, (1, 20)	0.636	0.000	-0.093
A10 Maturation	Effect	F	p	ω^2	FC/ Δ FC
	Rivastigmine	12.909, (1, 20)	0.002	0.163	-0.010
	TAPI	26.698, (1, 20)	<0.001	0.352	-0.057
	Riva $\times$ TAPI	12.425, (1, 20)	0.002	0.156	0.002

Table S4. Pairwise effect sizes (Hedge's *g*), human brain samples

Comparison	sAPPt	sAPP α	sAPP β	sAPP α ratio ^a	sAPP β ratio ^b	A β 40	A β 42	A β 42 ratio ^c
Control vs. AD, no drugs	0.12	1.41	5.23	5.49	5.49	1.75	4.60	2.69
Control vs. Rivastigmine	0.71	0.55	1.82	0.92	0.92	1.59	3.26	1.20
Rivastigmine vs. AD, no drugs	0.75	1.51	3.37	5.17	5.17	0.28	0.95	0.64

^asAPP $\alpha \div (sAPP\alpha + sAPP\beta)$ ^bsAPP $\alpha \div (sAPP\alpha + sAPP\beta)$ ^cA β 42 $\div$ (A β 40 + A β 42)

Table S5. Correlation of β -actin normalized signals, Rivastigmine $\times$ TAPI

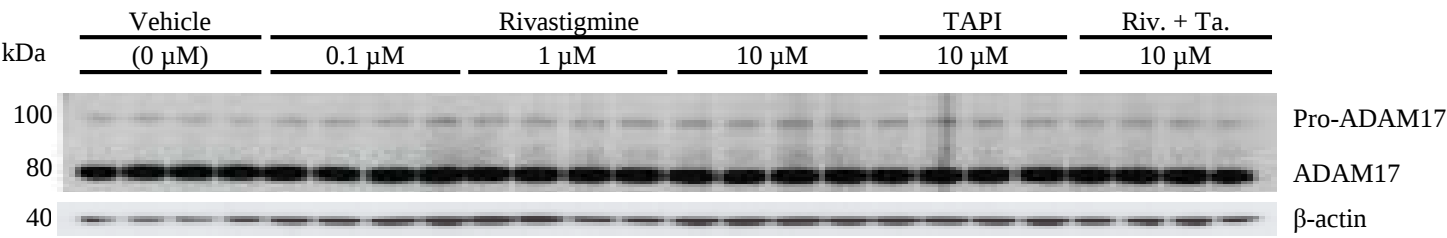
		iAPPt ^{ab}	sAPPt ^b	sAPP α^b	sAPP α^c	sAPP β^c	CTF β^c	A β 40 ^c	A β 42 ^c	ADAM-9		ADAM-10		A17 ^d
										pro ^b	mature ^b	pro ^b	matur ^{be}	pro ^b
sAPPt ^b		0.630												
sAPP α^b		0.466	0.509											
sAPP α^c		0.451	0.510	0.875										
sAPP β^c		-0.242	-0.362	-0.737	-0.687									
CTF β^c		-0.184	-0.238	-0.506	-0.567	0.584								
A β 40 ^c		-0.334	-0.488	-0.637	-0.665	0.777	0.445							
A β 42 ^c		-0.134	-0.223	-0.471	-0.496	0.608	0.350	0.761						
ADAM-9	pro ^b	0.327	0.583	0.363	0.329	-0.490	-0.251	-0.643	-0.377					
	mature ^b	0.437	0.305	0.399	0.400	-0.523	-0.484	-0.584	-0.504	0.595				
ADAM-10	pro ^b	0.220	0.237	0.423	0.332	-0.649	-0.622	-0.579	-0.533	0.424	0.728			
	mature ^b	0.495	0.685	0.834	0.849	-0.747	-0.670	-0.691	-0.452	0.444	0.510	0.550		
ADAM-17	pro ^b	0.284	0.367	0.277	0.252	-0.157	-0.153	-0.436	-0.469	0.674	0.701	0.326	0.294	
	mature ^b	0.169	0.400	0.443	0.435	-0.234	-0.285	-0.374	-0.537	0.380	0.481	0.344	0.421	0.777

^aBoldface indicates significance at adjusted $p \leq 0.05$.

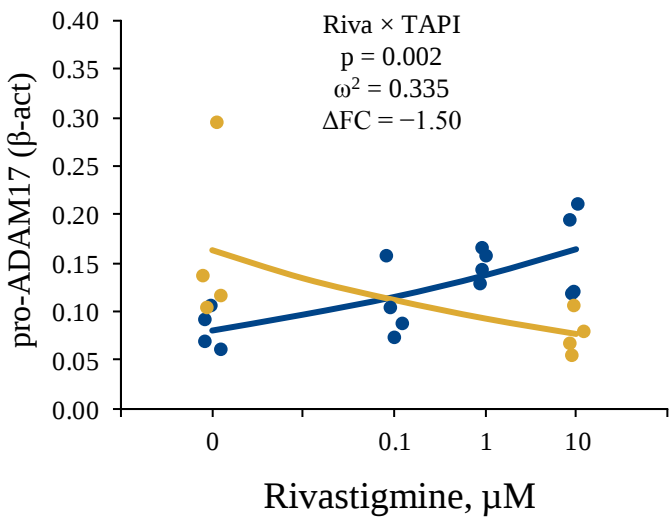
^bMeasured by semi-quantitative western blot.

^cMeasured by ELISA

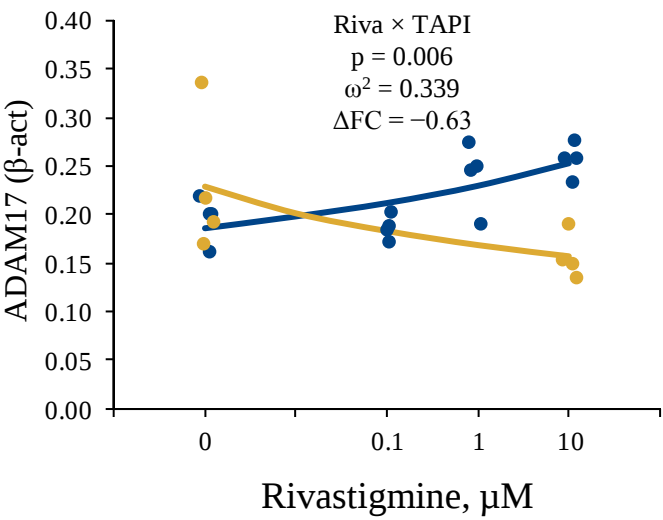
A. Western Blotting



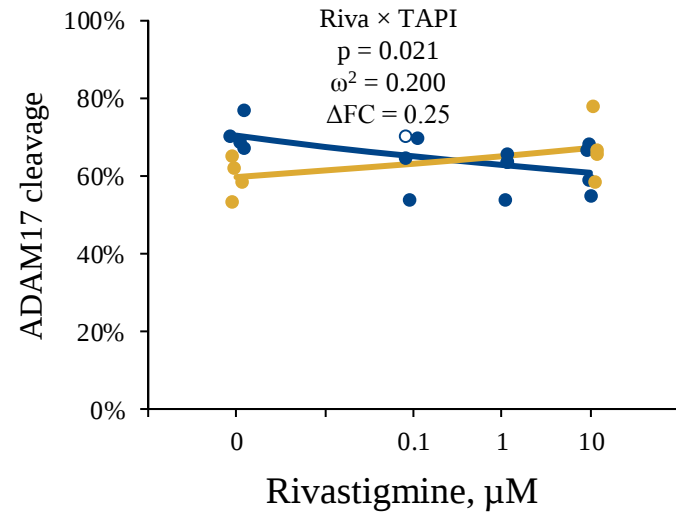
B. pro-ADAM17



C. ADAM17



D. ADAM17 cleavage



Supplemental Figure S1. Changes induced by rivastigmine and TAPI in levels of different pro- and mature ADAM-17 and ADAM-17 processing in human cultures, interaction effects. Primary human brain (PHB) cultures were co-treated with rivastigmine and TAPI as described in the text. Figure shows effects of rivastigmine or TAPI alone. Western immunoblotting was carried out on cell lysates to evaluate alterations of pro- and mature ADAM-17 by rivastigmine treatment and TAPI treatment. Reported statistics are vs. log(dose + 1). A) Western blotting showing different proteins. B) pro-ADAM-17. C) mature ADAM-17. D) ADAM-17 processing, measured as $\text{mature} \div (\text{mature} + \text{proprotein})$.