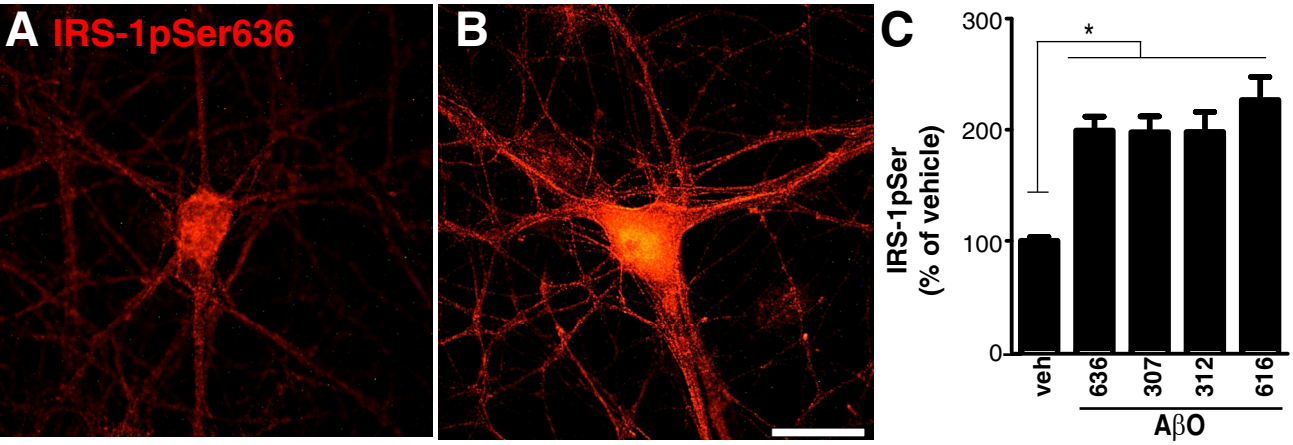
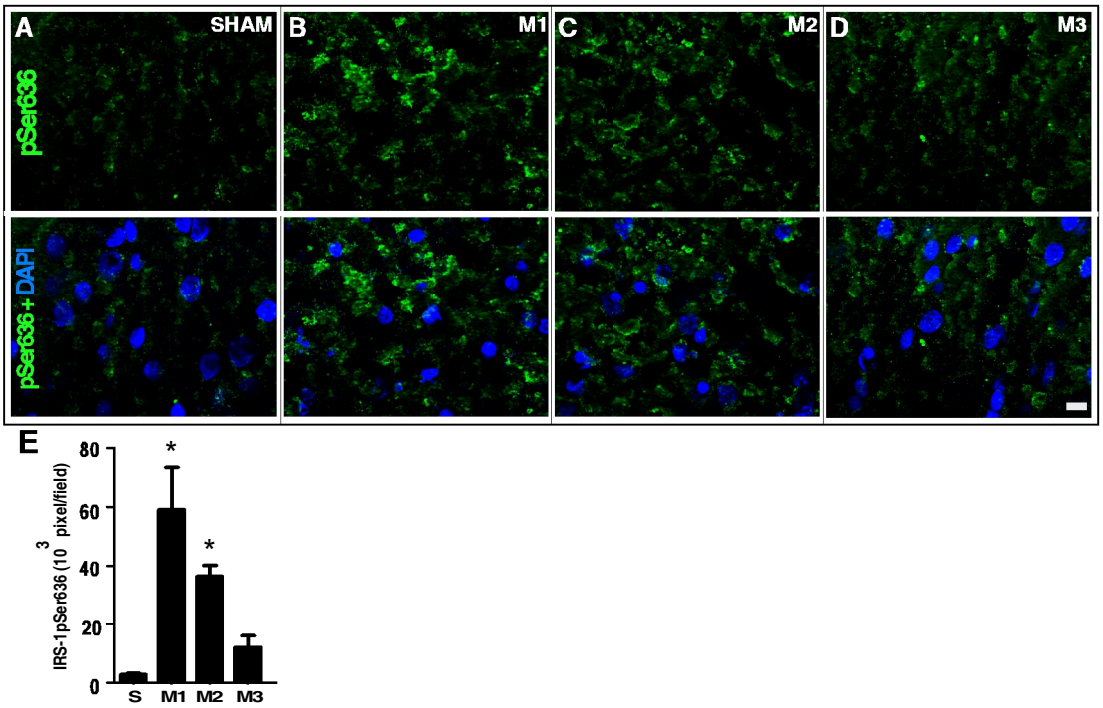
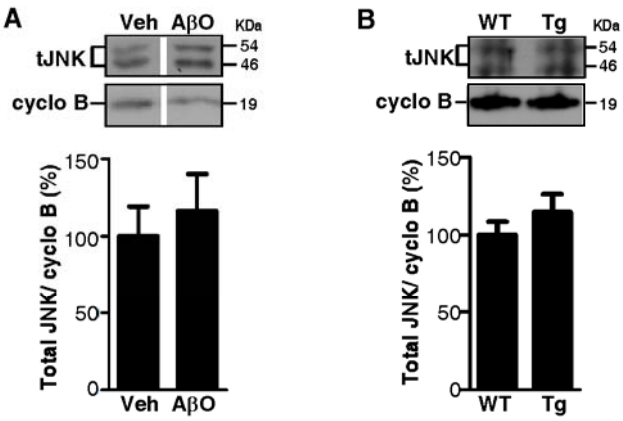
Supplemental Figure 1. Immunohistochemical specificity of Cell Signaling antibody CS2388 to IRS-1pS$^{636/639}$ demonstrated in the hippocampus of AD cases. The antibody reveals the phosphospecific antigen in the cytoplasm of neurons (**A**). Immunoreactivity was blocked by preadsorption of the antibody with a 5X molar excess of the phosphorylated immunogen (**B**). No appreciable inhibition of immunoreactivity was seen, however, after preadsorption of the antibody with a 5X molar excess of non-phosphorylated IRS-1 amino acid sequence 631-646 (Abcam ab41777) (**C**). Identical results were obtained on five AD cases.



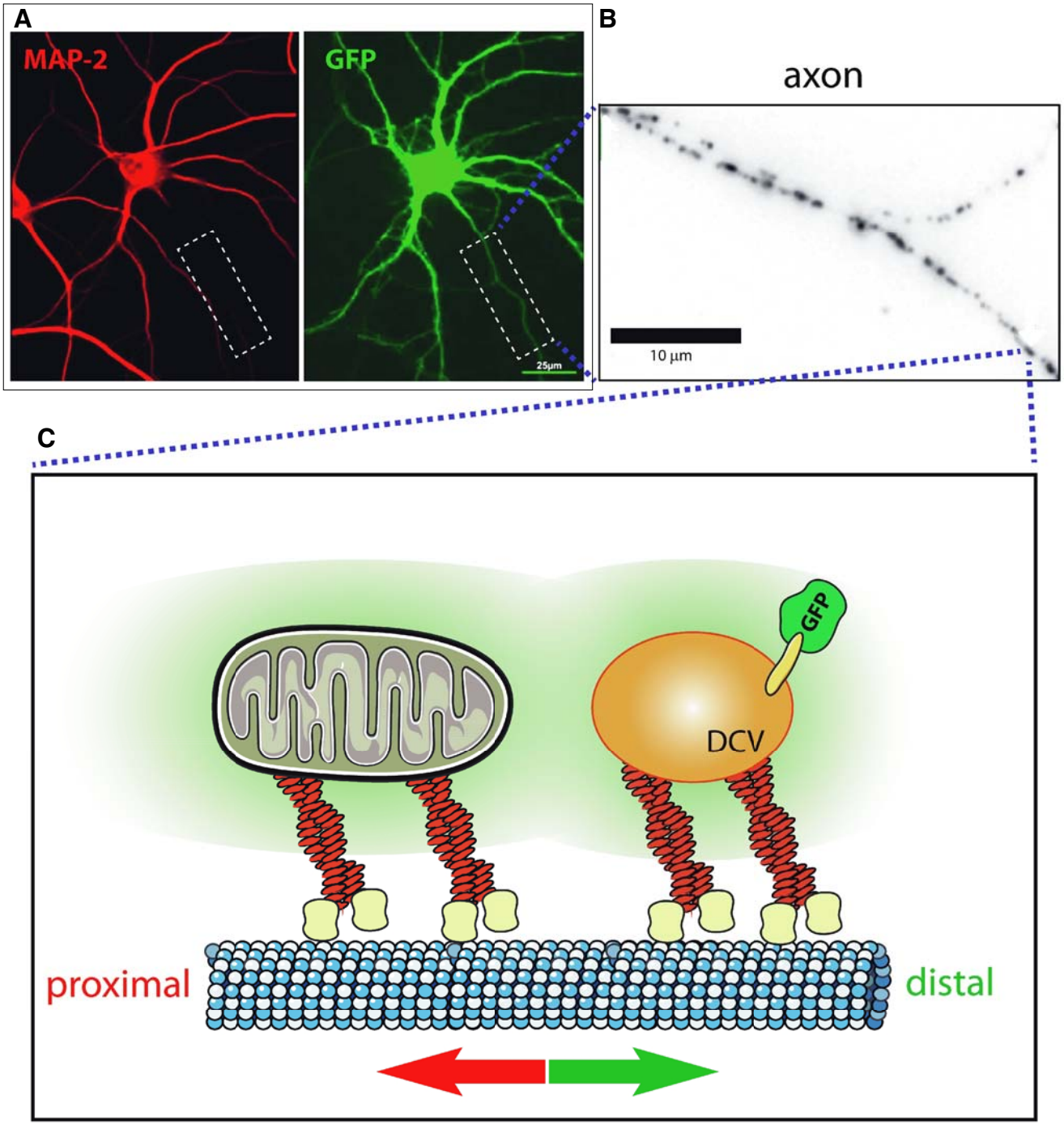
Supplemental Figure 2. Aβ oligomers (AβOs) induce the increase in IRS-1pSer levels in mature hippocampal neurons grown in insulin-free medium. IRS-1pSer^{636} immunolabeling in hippocampal neurons exposed to vehicle (**A**) or 500 nM AβOs (**B**) for 3 h (Scale bars = 20μm). **C**, integrated IRS-1pSer immunofluorescence levels determined from 2 experiments using independent cultures (30 images analyzed/experimental condition/experiment, each experiment carried out in triplicate). * statistically significant differences ($p<0.05$, ANOVA followed by Bonferroni post-hoc test) relative to vehicle-treated cultures.



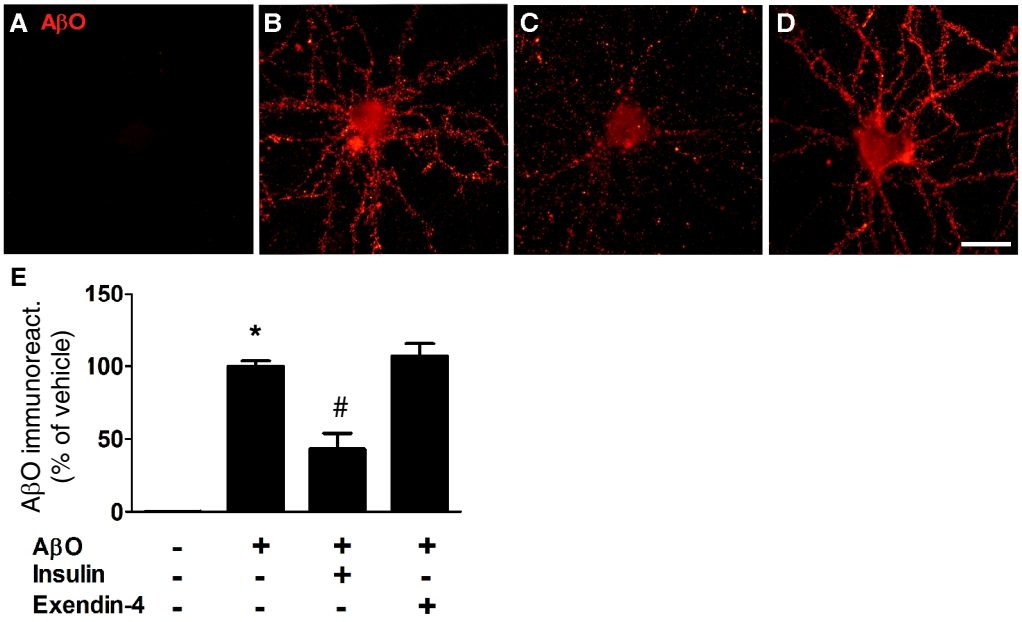
Supplemental Figure 3. Elevated IRS-1pSer^{636} levels in the temporal cortices of cynomolgus monkeys that received intracerebroventricular injections of AβOs. IRS-1pSer^{636} immunoreactivities in the same segments of the temporal cortex from a control (sham-operated) monkey (**A**) and 3 different monkeys that received AβOs injections (**B**-**D**). **E**, IRS-1pSer^{636} immunolabeling density (pixels/field; see "Methods") from 20-30 images acquired from temporal cortices of sham (S) or oligomer-injected monkeys (M1-M3). DAPI staining is in blue. * statistically significant ($p<0.001$ ANOVA followed by Bonferroni post-hoc test) differences relative to the sham-operated monkey.



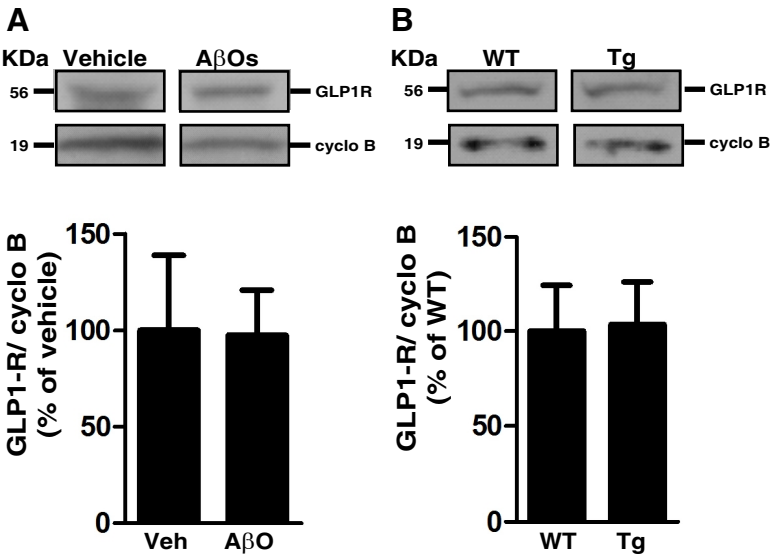
Supplemental Figure 4. Total c-Jun N terminal kinase (JNK) levels in hippocampal cell cultures exposed to AβOs and in the hippocampi of transgenic mice. Immunoblotting for JNK levels in hippocampal neurons exposed to vehicle or 500 nM AβOs for 3 h at 37 °C (**A**) and in hippocampal homogenates from APPSwe,PS1deltaE9 transgenic mice (Tg; n=7) or wild-type mice (WT; n=5) (**B**). Graphs show quantification of JNK levels in cultures (**A**) or in transgenic mice (**B**) normalized by cyclophilin B as a loading control.



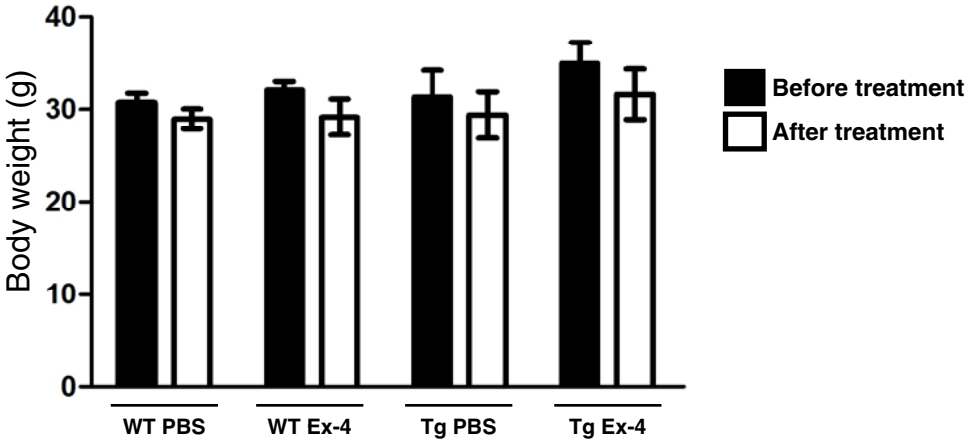
Supplemental Figure 5: Schematic representation of axonal transport experiments: (**A**) Primary hippocampal neurons (prepared as described, 35) were transfected (at 9–12 days in vitro) to express BDNF-mRFP, a dense-core vesicle (DCV) cargo, or mitochondrially-targeted YFP. Cells were allowed to express constructs for 24 h before imaging or immunocytochemistry. Axons and dendrites were initially distinguished based on morphology and confirmed retrospectively by antibody staining against MAP-2, a dendritic cytoskeletal protein. (**B**) Axons were live imaged using a wide-field fluorescent microscope (DMI 6000 B, Leica) as previously described (35). (**C**) Bidirectional axonal transport of BDNF-DCVs or mitochondria. Anterograde and retrograde transport are indicated by green and red arrows, respectively. Pannels **A** and **B** adapted from 73.



Supplemental Figure 6. Exendin-4 does not interfere with AβO binding to neurons. Hippocampal neurons were exposed for 3 h to vehicle (**A**), 500 nM AβOs (**B**), 1 μM insulin + 500 nM AβOs (**C**) or 300 nM exendin-4 + 500 nM AβOs (**D**) and AβO binding was detected using oligomer-specific NU4 antibody. Scale bars = 50 μm. (**E**) Integrated oligomer immunofluorescence determined from 5 experiments using independent cultures (25 images analyzed per experimental condition per experiment). * and #, statistically significant differences relative to vehicle-treated neurons ($p < 0.01$) or AβO-treated neurons ($p < 0.001$), respectively.



Supplemental Figure 7. Glucagon-like peptide 1 receptor (GLP1R) levels in hippocampal cell cultures exposed to AβOs and in the hippocampi of transgenic mice. Immunoblotting for GLP1R levels in hippocampal neurons exposed to vehicle or 500 nM AβOs for 3 h at 37 °C (**A**) and in hippocampal homogenates from APPSwe,PS1deltaE9 transgenic mice (Tg; n=7) or wild-type mice (WT; n=5) (**B**). Graphs show densitomteric quantification of GLP1R levels in cultures (**A**) or in transgenic mice (**B**) normalized by cyclophilin B as a loading control.



Supplemental Figure 8. Lack of effect of 3-week intraperitoneal administration of exendin-4 on body weight of APPSwe,PS1deltaE9 mice. Transgenic mice (n=7) or wild-type mice (n=5) received intraperitoneal exendin-4 (25 nmol/kg bw) or saline (0.9% w/v) injections once-daily for 3 weeks, for the duration of the behavioral experiments. Values are shown as means ± SD.

Supplemental Videos Legends

Supplemental Video 1. Role of JNK in disruption of dense-core vesicle (DCV) transport induced by Aβ oligomers. Hippocampal cultures expressing the DCV cargo BDNF-mRFP were used. Video shows live imaging of DCV transport in representative axons from hippocampal neurons exposed to vehicle, 500 nM oligomers or 10μM SP600125 + 500 nM oligomers for 18 hours. Quantification of DCV transport parameters is shown in Supplemental Table 2.

Supplemental Video 2. Exendin-4 and insulin prevent Aβ oligomer-induced disruption of dense-core vesicle (DCV) transport. Hippocampal cultures expressing the DCV cargo BDNF-mRFP were used. Video shows live imaging of DCV transport in representative axons from cultures exposed to 300 nM exendin-4 + 500 nM oligomers or 1 μM insulin + 500 nM oligomers for 18 hours. Quantification of DCV transport parameters is shown in Supplemental Table 2.

Supplemental Video 3. Exendin-4 blocks Aβ-oligomer-induced disruption of mitochondria transport. Hippocampal cultures expressing mitochondrially-targeted YFP were used. Video shows time-lapse imaging of mitochondria transport in representative axons from cultures exposed to 300 nM exendin-4 + 500 nM oligomers for 18 hours. Quantification of mitochondria transport parameters is shown in Supplemental Table 3.

Supplemental Table 1: Demographic and Autopsy Data on Human Cases

Variable	*NCI*	*AD*
Number of Cases	22	22
*Age (y, mean ± SD)**	71.45 ± 13.44	72.77 ± 11.13
Males/Females	10/12	10/12
*PMI (h, mean ± SD)**	12.43 ± 5.18	10.43 ± 4.24

AD = Alzheimer's Disease Cases, NCI = Non-Cognitively Impaired Cases

*No significant difference between NCI and AD groups

Supplemental Table 2: Quantitative analysis of DCV transport

	DCVs						
	Traffic values					%	
	All events	Anterograde		Retrograde		All events	
Flux (min^{-1})							
Vehicle 18h	10.28 ± 1.49	6.60 ± 1.18		3.67 ± 0.55	#	100.00 ± 14.09	
AβOs 18h	2.55 ± 0.49	1.40 ± 0.29	**	1.15 ± 0.23	**	24.78 ± 4.75	**
AβOs scrambled	8.05 ± 0.55	4.42 ± 0.41	++	3.63 ± 0.44	++	78.29 ± 5.35	++
Insulin + AβOs	10.35 ± 1.39	6.13 ± 0.85	++	4.26 ± 0.81	++	100.64 ± 13.55	++
Exendin + AβOs	8.68 ± 1.29	4.35 ± 0.59	++	4.34 ± 0.85	++	84.43 ± 12.63	++
JNK inhibitor + AβOs	7.23 ± 1.23	3.40 ± 0.80	*/+	3.83 ± 0.54	++	70.35 ± 12.01	++
Velocity (µm/s)							
Vehicle 18h	1.66 ± 0.11	1.66 ± 0.10		1.63 ± 0.12		100.00 ± 6.68	
AβOs 18h	1.32 ± 0.07	1.32 ± 0.08	*	1.34 ± 0.07		79.94 ± 4.15	*
AβOs scrambled	1.68 ± 0.09	1.74 ± 0.07	+	1.59 ± 0.14		101.51 ± 5.72	+
Insulin + AβOs	1.75 ± 0.09	1.82 ± 0.09	++	1.63 ± 0.09	+	105.44 ± 5.19	+
Exendin + AβOs	1.39 ± 0.10	1.37 ± 0.10		1.40 ± 0.11		83.81 ± 6.19	
JNK inhibitor + AβOs	1.96 ± 0.08	1.94 ± 0.09		1.95 ± 0.08	*	118.61 ± 4.73	*
Run length (µm)							
Vehicle 18h	8.45 ± 0.69	9.53 ± 0.83		6.78 ± 0.51		100.00 ± 8.19	
AβOs 18h	5.20 ± 0.33	5.30 ± 0.42	**	4.90 ± 0.39	*	61.56 ± 3.85	**
AβOs scrambled	6.03 ± 0.45	6.52 ± 0.56	*	5.39 ± 0.46		71.32 ± 5.31	*
Insulin + AβOs	7.72 ± 0.61	8.53 ± 0.76	++	6.70 ± 0.56	+	91.37 ± 7.23	++
Exendin + AβOs	7.71 ± 0.76	8.02 ± 0.73	+	7.26 ± 0.94	+	91.19 ± 8.98	+
JNK inhibitor + AβOs	5.13 ± 0.31	5.00 ± 0.42	**	5.06 ± 0.30	*	60.74 ± 3.71	**

Vehicle n=21 kymographs (21 cells, 3669 vesicles) / AβOs n=25 kymographs (25 cells, 1332 vesicles)

AβOscr. n=10 kymographs (10 cells, 1917 vesicles) / Insulin + AβOs n=14 kymographs (14 cells, 3273 vesicles)

Exendin + AβOs n=15 kymographs (15 cells, 2280 vesicles) / JNK inhibitor + AβOs n=15 kymographs (15 cells, 2336 vesicles)

* p<0.05 when compared with vehicle (from each column)

** p<0.0001 when compared with vehicle (from each column)

+ p<0.05 when compared with AβOs (from each column)

++ p<0.0001 when compared with AβOs (from each column)

# p<0.0001 when compared vehicle anterograde with vehicle retrograde

Supplemental Table 3: Quantitative analysis of mitochondria transport

	Mitochondria						
	Traffic values					%	
	All events	Anterograde		Retrograde		All events	
Flux (min^{-1})							
Vehicle 18h	0.24 ± 0.05	0.10 ± 0.03		0.14 ± 0.03		100.00 ± 21.70	
AβOs 18h	0.06 ± 0.03	0.02 ± 0.01	*	0.04 ± 0.02	*	26.56 ± 11.84	*
Insulin + AβOs	0.24 ± 0.03	0.12 ± 0.02	+	0.12 ± 0.03		100.83 ± 14.51	++
Exendin + AβOs	0.22 ± 0.03	0.11 ± 0.03	+	0.11 ± 0.02	+	93.79 ± 13.94	+
Velocity (μm/s)							
Vehicle 18h	0.42 ± 0.04	0.30 ± 0.04		0.46 ± 0.07		100.00 ± 8.73	
AβOs 18h	0.27 ± 0.07	0.10 ± 0.05	*	0.35 ± 0.10		63.32 ± 18.02	
Insulin + AβOs	0.46 ± 0.05	0.39 ±0.07	+	0.46 ± 0.07		108.89 ± 12.91	
Exendin + AβOs	0.42 ± 0.04	0.34 ± 0.04	+	0.47 ± 0.07		100.32 ± 9.31	
Run length (μm)							
Vehicle 18h	8.26 ± 1.07	5.36 ± 0.89		8.89 ± 1.50		100.00 ± 12.93	
AβOs 18h	3.27 ± 0.98	1.89 ± 0.94	**	2.80 ± 0.95	*	39.60 ± 11.87	*
Insulin + AβOs	6.88 ± 0.79	6.49 ± 1.12	++	5.83 ± 0.98	+	83.31 ± 9.51	+
Exendin + AβOs	9.06 ± 1.06	9.35 ± 2.11	+	8.99 ± 1.90	+	109.70 ± 12.86	+

Vehicle n=15 kymographs (15 cells, 229 vesicles) / AβOs n=15 kymographs (15 cells, 56 vesicles)
Insulin + AβOs n=13 kymographs (13 cells, 275 vesicles) / Exendin + AβOs n=14 kymographs (14 cells, 257 vesicles)

*****p<0.05, when compared with vehicle (from each column)

******p<0.0001, when compared with vehicle (from each column)

\+ p<0.05 when compared with AβOs (from each column)
++ p<0.0001 when compared with AβOs (from each column)