Supplementary methods

Intracerebroventricular injection

Mice were anesthetized with an injection (ip.) of ketamine (100 mg/kg)/xylazine (10 mg/kg) and positioned on a stereotaxic apparatus (Kopf Instruments, Tujunga, CA, USA). A 23-gauge stainless steel guide cannula was implanted into the right lateral ventricle (coordinates: 0.3 mm posterior, 1.0 mm lateral, and 2.5 mm ventral to bregma) and fixed to the skull using stainless steel screws and dental cement. Drug delivery was performed using a 26-gauge stainless steel needle (Plastics One, Roanoke, VA, USA) at 0.2 μL/min, with a total volume of 2 μL.

Electrophysiological recordings

For electrophysiological recordings, brain slices were transferred to a recording chamber, where they were continuously perfused with oxygenated ACSF at a flow rate of 3 ml/min. Synaptic responses were evoked by constant current pulses (0.1 ms, 0.05 Hz) from a stimulator (SEN-3301, Nihon Kohden, Japan). The signals were amplified using an Axoclamp 2B amplifier (Axon Instruments, Foster City, CA, USA), digitized at 20 kHz (filtered at 10 kHz) with a Digidata 1200 converter (Axon Instruments), and acquired for analysis. Basal synaptic transmission was assessed by plotting the input/output (I/O) relationship from responses to stimulus intensities ranging from 0.1 to 0.7 mA. The paired-pulse ratio (PPR) was measured using paired stimuli at an intensity eliciting half-maximal EPSP slopes, with inter-pulse intervals (IPIs) of 25 to 100 ms. The PPR was calculated as the slope ratio of the second EPSP to the first. Before LTP induction, slice viability was confirmed by a linear increase in EPSP slope with stimulus intensity and a stable baseline response. A stable 20-min baseline recording was established using the half-maximal stimulus intensity before applying high-frequency stimulation (HFS; 50 pulses, 100 Hz, 30 s). LTP induction was deemed successful if the EPSP slope measured 50–60 min post-HFS exhibited a sustained increase of >20% over baseline. All EPSP slopes were measured in mV/ms between 10% and 90% of the peak response.

Histological Examination

For immunohistochemistry, every fifth free-floating section was treated with 2 M HCl at 37°C for 30 min for antigen retrieval. After neutralization, the sections were blocked with 3% normal goat serum and subsequently incubated overnight at 4°C with primary antibodies: mouse monoclonal anti-BrdU (cat. no. MAB4072, RRID: AB_95024, 1:500, MilliporeSigma, Burlington, MA, USA), rabbit anti-PSD95 (cat. no. 20665-1-AP, RRID: AB_2687961, 1:500), or rabbit anti-synaptophysin (Syn) (cat. no. 17785-

1-AP, RRID: AB_2271365, 1:500) (both from Proteintech Group, Inc., Wuhan, China). Immunoreactivity was visualized using the appropriate Alexa Fluor-conjugated secondary antibodies (F(ab′)2 fragment of goat anti-mouse IgG-A594 (cat. no. A48288, RRID: AB_2896354, 1:500), goat anti-rabbit IgG-A488 (cat. no. A32731, RRID: AB_2633280, 1:500), or donkey anti-rabbit IgG-A594 (cat. no. A21207, RRID: AB_141637, 1:500); all from Thermo Fisher Scientific, Waltham, MA, USA). Finally, nuclei were counterstained with DAPI (cat. no. D9542; Sigma-Aldrich, St. Louis, MO, USA).

For double immunofluorescence staining of BrdU with either NeuN or GFAP, sections were co-incubated with a mouse anti-BrdU antibody and either a rabbit anti-NeuN antibody (cat. no. 26975-1-AP, RRID: AB_2880708, 1:500, Proteintech Group, Inc., Wuhan, China) or a mouse anti-GFAP antibody (cat. no. MAB360, RRID: AB_11212597, 1:500, MilliporeSigma, Burlington, MA, USA). Detection was carried out using corresponding Alexa Fluor-conjugated secondary antibodies (goat anti-mouse IgG-A488 (cat. no. A32723TR, RRID: AB_2866489, 1:500), goat anti-rabbit IgG-A488 (cat. no. A32731, RRID: AB_2633280, 1:500), or F(ab′)2 fragment of goat anti-mouse IgG-A594 (cat. no. A48288, RRID: AB_2896354, 1:500); all from Thermo Fisher Scientific, Waltham, MA, USA). BrdU-positive ($BrdU^+$) cells and $BrdU^+$ cells co-expressing NeuN ($BrdU^+/NeuN^+$) or GFAP ($BrdU^+/GFAP^+$) were visualized using an Olympus BX50 epifluorescence microscope (Olympus, Tokyo, Japan) equipped with an Olympus DP72 CCD digital camera (Olympus Corporation, Tokyo, Japan). Images were acquired using DP Controller software under identical acquisition parameters across all experimental groups. Representative images were obtained using appropriate filter sets for DAPI, FITC (Alexa Fluor 488), and TRITC/Alexa Fluor 594 channels. Images were acquired using 4×, 10×, 20×, and 40× objective lenses depending on the experimental requirement. Quantitative image analysis was performed using ImageJ software (U.S. National Institutes of Health, Bethesda, MD, USA). Quantitative analysis was performed according to established stereological principles to minimize oversampling: only central cell profiles >4 μm within the defined regions were counted, excluding those in the uppermost focal plane. For 1-day-old $BrdU^+$ cells, counting was restricted to the subgranular zone (SGZ, defined as a two-cell-body-wide layer between the GCL and hilus). For 28-day-old populations ($BrdU^+$, $BrdU^+/NeuN^+$, $BrdU^+/GFAP^+$), cells were quantified across the GCL, SGZ, and hilus. From each animal, 12 systematically sampled sections (every fifth section) were analyzed, and the total number of labeled cells in the DG was estimated by multiplying the counts by 5. Fluorescence intensities for PSD95 and Syn in the DG were measured using ImageJ software (U.S. National Institutes of Health, Bethesda, MD, USA).

Golgi-Cox staining

After mice were anesthetized, brains were collected and immersed in a mixed impregnation solution (Solution A and Solution B at a 1:1 ratio) and kept at room temperature in the dark for 2 weeks. The brains were then transferred into Solution C and incubated under the same conditions for an additional 72 h. Coronal sections of 100 μm thickness were prepared using a freezing microtome (Microslicer DTK-1500; Dosaka EM Co., Ltd, Kyoto, Japan) and mounted on gelatin-coated glass slides with Solution C. Following incubation with Solutions D and E, neurons and their dendritic branches marked by Golgi staining in the DG were imaged with a confocal microscope. (LSM 780; Carl Zeiss Microscopy GmbH, Jena, Germany). For each group, 4–6 dendritic segments per neuron were randomly selected, and at least three neurons per mouse were analyzed. Dendritic spine density was analyzed using ImageJ software (U.S. National Institutes of Health).

Western blot analysis

Following anesthesia and decapitation, brains were promptly removed and hippocampal tissues was collected 28 days after the final BrdU injection. Total protein was isolated using a Whole Cell Lysis Assay Kit (cat. no. KGP250; Nanjing KeyGen Biotech Co., Ltd., Nanjing, China) according to the manufacturer's protocol. Protein concentrations were determined with a BCA Protein Assay Kit (Pierce, Thermo Fisher Scientific, Rockford, IL, USA). Equal amounts of protein (20 μg) were separated by SDS–PAGE and transferred onto PVDF membranes. The membranes were blocked in 5% non-fat milk prepared in TBS containing 0.1% Tween 20, and then incubated overnight at 4 °C with primary antibodies presented in Supplementary Table 1 as previously reported. Following washes in TBS/Tween-20, the membranes were treated with HRP-conjugated secondary antibodies. Signals were detected using an ECL Kit (Amersham Biosciences, Piscataway, NJ, USA), and band density was quantified with ImageJ software (U.S. National Institutes of Health). Protein levels in GSK mice were expressed relative to those of control mice. For drug treatment analyses, protein levels in drug-treated GSK mice were compared with their vehicle-treated counterparts, while those in drug-injected mice were normalized to vehicle-injected controls.

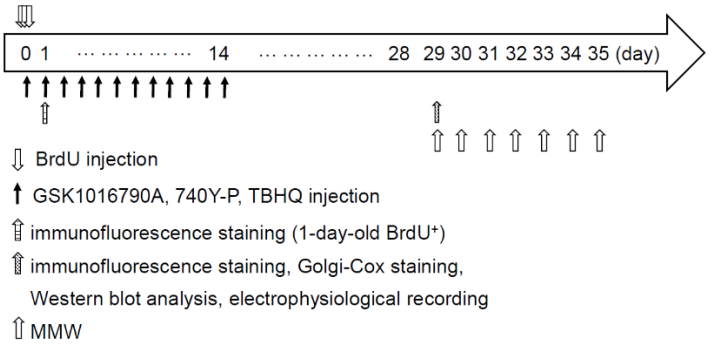
Experimental Animals and Grouping

A total of three hundred and seventy-eight mice were used for this study. All animals were randomly assigned to their respective groups, and detailed allocations are provided in Supplementary Table 4.

Sample size and replicates

For Western blot analyses of animal tissues, nine biological replicates (n = 9 mice per group) were included. For BrdU-related analyses ($BrdU^+$, $BrdU^+/NeuN^+$, $BrdU^+/GFAP^+$), 12 systematically sampled sections (every fifth section) per mouse were analyzed. Cell numbers in the dentate gyrus (DG) were estimated using systematic sampling, and values from individual sections were averaged to generate one biological value per mouse (n = 9 mice per group). For immunofluorescence analyses of PSD95 and Syn, three anatomically matched hippocampal sections per mouse were analyzed, and the mean value per animal was used as a single biological replicate (n = 9 mice per group). For Golgi–Cox staining, 4–6 dendritic segments were randomly selected per neuron, and three neurons per mouse were averaged to obtain one biological value (n = 9 mice per group). For the Morris water maze test, six biological replicates (n = 6 mice per group) were included. For electrophysiological recordings, data were analyzed at the slice level (n = 9 slices per group). Slices were obtained from 6 mice per group, with each mouse contributing 1–2 slices. Biological replication was ensured at the animal level.

Time chart of experimental procedure



GSK1016790A was administered once daily for 14 consecutive days. 740Y-P or TBHQ was injected 30 min before GSK1016790A administration and subsequently injected once daily for 14 days. On the first day of GSK1016790A treatment, BrdU was injected three times at 8-hour intervals. 1-day-old $BrdU^+$ cells and 28-day-old $BrdU^+$ cells were examined on Day 1 and Day 29, respectively. On Day 29, immunofluorescence staining (for quantification of 28-day-old $BrdU^+/NeuN^+$ and $BrdU^+/GFAP^+$ cells, as well as PSD95 and Syn immunofluorescence intensity), Golgi-Cox staining, western blot analysis, and electrophysiological recording were performed. On Days 29–35, MMW was performed.

Supplementary Table 1 Primary and secondary antibodies used in the Western blot analysis

Target	Antibody (catalog no., dilution, source)	Reference
NeuN	cat. no. 26975-1-AP, RRID:AB_2880708, 1:20 000, Proteintech Group, Inc., Wuhan, China	Qi X, Chen X, Luo Q, Liu L, An D, Sha S, Du Y, Wu C, Chen L (2025) TRPV4 blockage inhibits the neurogenesis in the adult hippocampal dentate gyrus following pilocarpine induced status epilepticus. Mol Neurobiol. 62, 3615–3629. https://doi.org/10.1007/s12035-024-04504-x
GAPDH	cat. no. 60004-1-Ig, RRID:AB_2107436, 1:10000, Proteintech Group, Inc., Wuhan, China	
p-Akt	cat. no. 4060, RRID:AB_2315049, 1:2000, Cell Signaling Technology, Inc., Danvers, MA, USA	
Akt	cat. no. 10176-2-AP, RRID:AB_2224574, 1:2000, Proteintech Group, Inc., Wuhan, China	
p-ERK1/2	cat. no. 4370, RRID:AB_2315112, 1:1000, Cell Signaling Technology, Inc., Danvers, MA, USA	
ERK1/2	cat. no. 4695, RRID:AB_390779, 1:1000, Cell Signaling Technology, Inc., Danvers, MA, USA	
p-GSK3β	cat. no. 9336, RRID:AB_331405, 1:2000, Cell Signaling Technology, Inc., Danvers, MA, USA	Krauß D, Moreno-Viedma V, Adachi-Fernandez E, de Sá Fernandes C, Genger JW, Fari O, Blauensteiner B, Kirchhofer D, Bradaric N, Gushchina V, Fotakis G, Mohr T, Abramovich I, Mor I, Holcmann M, Bergthaler A, Haschemi A, Trajanoski Z, Winkler J, Gottlieb E, Sibilia M (2025) EGFR controls transcriptional and metabolic rewiring in KRASG12D colorectal cancer. EMBO Mol Med. 17, 1355–1392. https://doi.org/10.1038/s44321-025-00240-4
GSK3β	cat. no. 9351, RRID:AB_2315225, 1:2000, Cell Signaling Technology, Inc., Danvers, MA, USA	
p-CREB	cat. no. ab32096, RRID:AB_731734, 1:2000, Abcam, Cambridge, UK	Wang C, Shen D, Hu Y, Chen J, Liu J, Huang Y, Yu X, Chu H, Zhang C, Yin L, Liu Y, Ma H (2023) Selective targeting of class I HDAC reduces microglial inflammation in the entorhinal cortex of young APP/PS1 mice. Int J Mol Sci. 24, 4805. https://doi.org/10.3390/ijms24054805

CREB	cat. no. 9197, RRID:AB_331277, 1:1000, Cell Signaling Technology, Inc., Danvers, MA, USA	Wei R, Zong F, Dong J, Zhao W, Zhang F, Wang W, Zhao S, Wang Z, Zhang F, Zhang HT (2024) Identification of phosphodiesterase-7A (PDE7A) as a novel target for reducing ethanol consumption in mice. Int J Neuropsychopharmacol. 27, pyae032. https://doi.org/10.1093/ijnp/pyae032
p-MEK	cat. no. 9154, RRID:AB_2138017, 1:1000, Cell Signaling Technology, Inc., Danvers, MA, USA	Sun K, Sun Y, Jia Y, Duan X, Ma Z, Zhang X, Wang L, Zhu Y, Gao Y, Basang W (2023) MicroRNA miR-212-5p regulates the MEK/ERK signaling pathway by targeting A-Raf proto-oncogene serine/threonine-protein kinase (ARAF) to regulate cowshed PM2.5-induced NR8383 apoptosis. Toxics 11, 981. https://doi.org/10.3390/toxics11120981
MEK	cat. no. ab178876, RRID:AB_2891005, 1:2000, Abcam, Cambridge, UK	Luo M, Li L, Ding M, Niu Y, Xu X, Shi X, Shan N, Qiu Z, Piao F, Zhang C (2023) Long-term potentiation and depression regulatory microRNAs were highlighted in bisphenol A induced learning and memory impairment by microRNA sequencing and bioinformatics analysis. PLoS One 18, e0279029. https://doi.org/10.1371/journal.pone.0279029
Ras	cat. no. ab52939, RRID:AB_2121042, 1:5000, Abcam, Cambridge, UK	Li J, Liu B, Wu H, Zhang S, Liang Z, Guo S, Jiang H, Song Y, Lei X, Gao Y, Cheng P, Li D, Wang J, Liu Y, Wang D, Zhan N, Xu J, Wang L, Xiao G, Yang L, Pei G (2023) Sensory nerves directly promote osteoclastogenesis by secreting peptidyl-prolyl cis-trans isomerase D (Cyp40). Bone Res. 11, 64. https://doi.org/10.1038/s41413-023-00300-w
p-Raf1	cat. no. 9422, RRID:AB_390808, 1:1000, Cell Signaling Technology, Inc., Danvers, MA, USA	Mao Y, Liu P, Wei J, Xie Y, Zheng Q, Hu X, Yao J, Meng W (2024) Exosomes derived from umbilical cord mesenchymal stem cell promote hair regrowth in C57BL6 mice through upregulation of the RAS/ERK signaling pathway. J Transl Int Med. 12, 478–494. https://doi.org/10.1515/jtim-2024-0012
Raf1	cat. no. 9427, RRID:AB_2067317, 1:1000, Cell Signaling Technology, Inc., Danvers, MA, USA	
TrkB	cat. no. 13129-1-AP, RRID:AB_2155156, 1:5000, Proteintech Group, Inc.,	You M, Gu W, Li M, Qiu Z, Li S, Jiang Z, Yao D, Xu Y, Wang Y (2018) Perinatal

	Wuhan, China	exposure to nonylphenol impairs dendritic outgrowth of cerebellar Purkinje cells in progeny. Chemosphere 211, 758–766. https://doi.org/10.1016/j.chemosphere.2018.08.007
BDNF	cat. no. ab108319, RRID:AB_10862052, 1:2000, Abcam, Cambridge, UK	Cook AA, Leung TCS, Rice M, Nachman M, Zadigue-Dube É, Watt AJ (2023) Endosomal dysfunction contributes to cerebellar deficits in spinocerebellar ataxia type 6. eLife 12, RP90510. https://doi.org/10.7554/eLife.90510
p-mTOR	cat. no. ab109268, RRID:AB_10888105, 1:1000, Abcam, Cambridge, UK	Li Z, Du Y (2023) CST3 alleviates bilirubin-induced neurocytes' damage by promoting autophagy. Transl Neurosci. 14, 20220314. https://doi.org/10.1515/tnsci-2022-0314
mTOR	cat. no. ab32028, RRID:AB_881283, 1:1000, Abcam, Cambridge, UK	
NR2B	cat. no. ab254356, RRID:AB_2895296, 1:1000, Abcam, Cambridge, UK	Song X, Cui Z, He J, Yang T, Sun X (2021) κ opioid receptor agonist U50488H inhibits pyroptosis through NLRP3 via the Ca2+/CaMKII/CREB signaling pathway and improves synaptic plasticity in APP/PS1 mice. Mol Med Rep. 24, 529. https://doi.org/10.3892/mmr.2021.12168
NR2A	cat. no. ab169873, RRID:AB_2895295, 1:1000, Abcam, Cambridge, UK	Ge J, Xue Z, Shu S, Yu L, Qin R, Tao W, Liu P, Dong X, Lan Z, Bao X, Ye L, Xu Y, Zhu X (2023) MiR-431 attenuates synaptic plasticity and memory deficits in APPswe/PS1dE9 mice. JCI Insight. 8, e166270. https://doi.org/10.1172/jci.insight.166270
NR1	cat. no. AF6406, RRID:AB_2835236, 1:2000, Affinity Biosciences, Inc., Changzhou, China	Yang J, Jiang Q, Yu X, Xu T, Wang Y, Deng J, Liu Y, Chen Y (2020) STK24 modulates excitatory synaptic transmission in epileptic hippocampal neurons. CNS Neurosci Ther. 26, 851–861. https://doi.org/10.1111/cns.13391
p-PI3K	cat. no. AF3242, RRID:AB_2834668, 1:2000, Affinity Biosciences, Inc., Changzhou, China	Xi X, Liu N, Wang Q, Chu Y, Yin Z, Ding Y, Lu Y (2019) ACT001, a novel PAI-1 inhibitor, exerts synergistic effects in combination with cisplatin by inhibiting PI3K/AKT pathway in glioma. Cell Death Dis. 10, 757. https://doi.org/10.1038/s41419-019-1986-2
PI3K	cat. no. AF6242, RRID:AB_2835106, 1:2000, Affinity Biosciences, Inc., Changzhou, China	

PSD95	cat. no. 20665-1-AP, RRID:AB_2687961, 1:2000, Proteintech Group, Inc., Wuhan, China	Li X, Zhang J, Li D, He C, He K, Xue T, Wan L, Zhang C, Liu Q (2021) Astrocytic ApoE reprograms neuronal cholesterol metabolism and histone-acetylation-mediated memory. Neuron 109, 957–970.e8. https://doi.org/10.1016/j.neuron.2021.01.005
Syn	cat. no. 17785-1-AP, RRID:AB_2271365, 1:40 000, Proteintech Group, Inc., Wuhan, China	
HRP-conjugated goat anti-rabbit IgG	cat. no. BL003A, RRID:AB_2827666, 1: 10000, Biosharp Biotechnology Co., Ltd., Hefei, Anhui, China	Qi X, Chen X, Luo Q, Liu L, An D, Sha S, Du Y, Wu C, Chen L (2025) TRPV4 blockage inhibits the neurogenesis in the adult hippocampal dentate gyrus following pilocarpine induced status epilepticus. Mol Neurobiol. 62, 3615–3629. https://doi.org/10.1007/s12035-024-04504-x
HRP-conjugated goat anti-mouse IgG	cat. no. BL001A, RRID:AB_2827665, 1: 10000, Biosharp Biotechnology Co., Ltd., Hefei, Anhui, China	

Supplementary Table 2

Tests for normality and variance homogeneity

Figure	experimental group	Sample size (*n*)	Mean ± SD.	Shapiro-Wilk test		Levene's Test		Median	Interquartile ranges	Independent samples *t*-test			Mann-Whitney U test	
				Statistics	*P* value	*F* value	*P* value		25%~75%	*t* value	*P* value	df	Z value	*P* value
1A	control	9	2345.00 ± 401.10	0.95	0.76	2.15	0.30			0.94	0.36	16		
	GSK	9	2122.00 ± 588.60	0.97	0.94									
1B	control	9	1778.00 ± 229.70	0.95	0.64	2.61	0.20			3.02	0.008	16		
	GSK	9	1339.00 ± 371.20	0.98	0.95									
1C-ii	control	9		0.78	0.01	2.06	0.33	1277.00	1120.00 ~ 1448.00				-2.69	0.006
	GSK	9		0.97	0.91			894.00	730.50 ~ 1148.00					
1D-ii	control	9	395.60 ± 62.80	0.93	0.50	3.42	0.10			0.14	0.89	16		
	GSK	9	389.10 ±116.10	0.90	0.25									
1E-ii-SGZ	control	9		0.78	0.01	3.06	0.13	59.86	54.44 ~ 64.30				-2.61	0.008
	GSK	9		0.90	0.27			69.90	66.91 ~ 77.64					
1E-ii-Gi	control	9		0.87	0.11	5.10	0.03	12.89	10.04 ~ 16.37				-0.53	0.6219
	GSK	9		0.96	0.85			11.62	10.55 ~ 12.63					
1E-ii-Gm	control	9	10.50 ± 2.07	0.99	0.99	2.26	0.27			1.69	0.11	16		
	GSK	9	8.39 ± 3.12	0.92	0.36									
1E-ii-Go	control	9		0.93	0.52	1.00	0.99	15.65	11.56 ~ 16.90				-3.13	<0.001
	GSK	9		0.76	0.008			8.01	6.59 ~ 9.53					
1F-46kDa	control	9		0.95	0.66	5.58	0.03	98.90	97.10 ~ 104.6				-3.58	<0.001
	GSK	9		0.90	0.25			72.67	54.20 ~ 80.25					
1F-48kDa	control	9	100.00 ± 4.71	0.96	0.75	1.80	0.42			10.77	<0.001	16		
	GSK	9	71.66 ± 6.33	0.93	0.49									
2B-0.1mA	control	9		0.77	0.008	2.30	0.15	0.0102	0.0098 ~ 0.0106				-1.63	0.11
	GSK	9		0.54	<0.001			0.0097	0.0091 ~ 0.0102					
2B-0.2mA	control	9	0.22 ± 0.10	0.97	0.87	3.19	0.09			0.14	0.89	16		
	GSK	9	0.22 ± 0.04	0.98	0.98									

2B-0.3mA	control	9	0.61 ± 0.07	0.94	0.56	4.76	0.04	0.61	0.54~0.69				-2.25	0.02
	GSK	9	0.56 ± 0.03	0.95	0.70			0.54	0.51~0.56					
2B-0.4mA	control	9		0.97	0.93	0.48	0.50			5.15	<0.001	16		
	GSK	9		0.85	0.08									
2B-0.5mA	control	9	0.94 ± 0.07	0.95	0.72	0.11	0.74			5.03	<0.001	16		
	GSK	9	0.75 ± 0.08	0.95	0.71									
2B-0.6mA	control	9	1.28 ± 0.10	0.92	0.40	2.03	0.17			6.18	<0.001	16		
	GSK	9	1.03 ± 0.11	0.93	0.47									
2B-0.7mA	control	9	1.57 ± 0.10	0.94	0.53	0.32	0.58			6.07	<0.001	16		
	GSK	9	1.24 ± 0.12	0.94	0.55									
2C-25ms	control	9		0.85	0.07	8.27	0.01	1.11	1.03~1.12				-2.61	0.008
	GSK	9		0.94	0.64			1.25	1.11~1.34					
2C-50ms	control	9	1.16 ± 0.12	0.88	0.16	1.05	0.95			2.28	0.036	16		
	GSK	9	1.28 ± 0.11	0.90	0.27									
2C-75ms	control	9		0.83	0.04	1.67	0.49	1.12	1.10~1.35				-2.78	0.005
	GSK	9		0.96	0.82			1.45	1.23~1.51					
2C-100ms	control	9		0.95	0.64	1.48	0.59	1.47	1.41~1.56				-3.31	<0.001
	GSK	9		0.81	0.03			1.99	1.74~2.08					
2E-55min	control	9	300.80 ± 15.09	0.98	0.94	1.32	0.70			15.12	<0.001	16		
	GSK	9	184.90 ± 17.35	0.94	0.55									
2E-60min	control	9	304.80 ± 21.38	0.96	0.79	3.14	0.13			14.80	<0.001	16		
	GSK	9	183.70 ± 12.07	0.95	0.74									
2F	control	9		0.95	0.70	5.72	0.02	302.2	283.30~317.00				−3.58	<0.001
	Ro-1uM	9		0.97	0.89			166.9	163.90~172.10					
	control	9		0.95	0.70	5.25	0.03	302.2	283.30~317.00				−3.58	<0.001
	Ro-3uM	9		0.90	0.26			106.1	95.63~110.2					
	control	9	301.50 ± 17.68	0.95	0.70	1.06	0.93			24.04	<0.001	16		
	Ro-6uM	9	104.10 ± 17.15	0.93	0.46									
2H-NR1	control	9	100.0 ± 4.40	0.92	0.38	3.94	0.07			9.42	<0.001	16		
	GSK	9	69.31 ± 8.73	0.93	0.53									
2H-NR2A	control	9		0.81	0.02	1.06	0.94	105.30	90.45~107.00				-3.58	<0.001

	GSK	9		0.91	0.30			74.20	65.12~79.37					
2H-NR2B	control	9	100.0 ± 7.24	0.91	0.33	1.55	0.55			7.70	<0.001	16		
	GSK	9	70.36 ± 9.00	0.94	0.60									
2I-ii	control	9	46.05 ± 8.66	0.98	0.95	1.17	0.83			3.01	0.008	16		
	GSK	9	33.27 ± 9.34	0.93	0.47									
2J-PSD95	control	9	100.0 ± 5.95	0.94	0.55	2.97	0.14			7.71	<0.001	16		
	GSK	9	69.56 ± 10.24	0.87	0.13									
2J-Syn	control	9		0.74	0.005	3.36	0.11	96.73	95.41~102.60				-3.58	<0.001
	GSK	9		0.95	0.71			61.37	52.32~75.61					
3A-Ras	control	9		0.90	0.28	5.75	0.02	100.50	97.51~104.80				-3.49	<0.001
	GSK	9		0.87	0.11			76.50	52.71~82.20					
3A-p-Raf1	control	9		0.93	0.50	28.52	<0.001	98.83	97.49~102.50				-3.58	<0.001
	GSK	9		0.78	0.01			80.39	66.42~84.34					
3B-p-MEK	control	9		0.87	0.14	6.55	0.02	98.67	97.31~102.5				-3.58	<0.001
	GSK	9		0.96	0.74			67.70	58.70~75.05					
3B-p-ERK1	control	9		0.86	0.09	4.66	0.04	97.63	96.70~104.20				-3.58	<0.001
	GSK	9		0.95	0.68			70.31	63.03~78.36					
3B-p-ERK2	control	9		0.90	0.28	10.32	0.003	98.72	96.33~103.30				-3.58	<0.001
	GSK	9		0.93	0.45			64.26	50.12~68.16					
3C-p-PI3K (55KDa)	control	9	100.00 ± 7.42	0.97	0.93	1.73	0.45			1.24	0.23	16		
	GSK	9	94.92 ± 9.78	0.97	0.90									
3C-p-PI3K (85KDa)	control	9	100.00 ± 5.94	0.96	0.76	1.55	0.55			8.51	<0.001	16		
	GSK	9	73.06 ± 7.40	0.94	0.57									
3C-p-Akt	control	9	100.00 ± 5.02	0.91	0.29	3.33	0.11			9.94	<0.001	16		
	GSK	9	65.40 ± 9.16	0.86	0.11									
3E-p-GSK3β	control	9	100.00 ± 5.56	0.94	0.64	2.19	0.29			9.04	<0.001	16		
	GSK	9	70.07 ± 8.23	0.93	0.53									
3D-p-mTOR	control	9		0.96	0.77	4.89	0.04	100.50	97.41~102.90				-3.58	<0.001
	GSK	9		0.95	0.67			70.95	62.64~77.57					
3D-p-CREB	control	9	100.00 ± 8.20	0.91	0.31	4.19	0.06			9.50	<0.001	16		
	GSK	9	71.10 ± 4.00	0.97	0.93									
3E-p-ERK1	GSK+vehicle	9		0.94	0.60	9.18	0.005	98.40	95.29~104.60				-3.58	<0.001

	GSK+TBHQ	9		0.93	0.46			149.20	140.10~157.50					
3E-p-ERK2	GSK+vehicle	9		0.92	0.39	8.47	0.007	98.95	96.62~103.60				-3.58	<0.001
	GSK+TBHQ	9		0.90	0.23			132.30	128.70~150.40					
3E-p-CREB	GSK+vehicle	9	100.00 ± 4.95	0.96	0.84	3.60	0.09			9.28	<0.001	16		
	GSK+TBHQ	9	132.80 ± 9.38	0.95	0.70									
3F-p-Akt	GSK+vehicle	9		0.92	0.38	9.57	0.004	101.70	97.28~103.30				-3.58	<0.001
	GSK+740Y-P	9		0.87	0.12			152.80	150.40~166.10					
3F-p-GSK3β	GSK+vehicle	9		0.94	0.54	9.33	0.005	100.20	96.86~103.40				-3.58	<0.001
	GSK+740Y-P	9		0.94	0.55			169.90	160.70~181.30					
3F-p-mTOR	GSK+vehicle	9		0.83	0.05	23.60	<0.001	101.10	97.00 ~ 102.50				-3.58	<0.001
	GSK+740Y-P	9		0.84	0.05			140.00	134.30 ~ 149.20					
3F-p-CREB	GSK+vehicle	9		0.91	0.29	14.24	0.0011	101.10	96.81~102.50				-3.58	<0.001
	GSK+740Y-P	9		0.95	0.72			140.10	132.80~153.60					
4A-BrdU$^+$	GSK+vehicle	9	1391.00 ± 118.10	0.91	0.33	1.51	0.57			7.23	<0.001	16		
	GSK+TBHQ	9	1842.00 ± 145.30	0.97	0.89									
4A-BrdU$^+$/NeuN$^+$	GSK+vehicle	9	925.30 ± 63.14	0.98	0.98	3.77	0.08			6.78	<0.001	16		
	GSK+TBHQ	9	1237.00 ± 122.60	0.94	0.62									
4A-BrdU$^+$/GFAP$^+$	GSK+vehicle	9	385.30 ± 38.51	0.95	0.71	3.72	0.08			4.16	<0.001	16		
	GSK+TBHQ	9	501.30 ± 74.32	0.87	0.12									
4B-BrdU$^+$	GSK+vehicle	9	1402.00 ± 247.20	0.91	0.32	3.77	0.08			5.01	0.001	16		
	GSK+740Y-P	9	2303.00 ± 480.00	0.88	0.16									
4B-BrdU$^+$/NeuN$^+$	GSK+vehicle	9	925.70 ± 211.80	0.92	0.43	1.14	0.86			5.71	<0.001	16		
	GSK+740Y-P	9	1515.00 ± 225.90	0.98	0.98									
4B-BrdU$^+$/GFAP$^+$	GSK+vehicle	9	402.60 ± 97.38	0.91	0.31	1.83	0.41			3.65	0.002	16		
	GSK+740Y-P	9	550.10 ± 72.08	0.92	0.42									
4C-SGZ	GSK+vehicle	9	69.53 ± 3.77	0.98	0.94	2.03	0.34			0.47	0.64	16		
	GSK+TBHQ	9	70.56 ± 5.37	0.95	0.69									
4C-Gi	GSK+vehicle	9	11.93 ± 1.90	0.97	0.92	3.26	0.11			0.17	0.87	16		
	GSK+TBHQ	9	11.71 ± 3.44	0.98	0.99									
4C-Gm	GSK+vehicle	9	8.64 ± 2.67	0.94	0.54	2.11	0.31			0.34	0.74	16		
	GSK+TBHQ	9	9.01 ± 1.84	0.95	0.65									
4C-Go	GSK+vehicle	9	9.90 ± 2.68	0.98	0.96	1.29	0.73					16		

	GSK+TBHQ	9	8.71 ± 2.36	0.95	0.65					1.00	0.33			
4D-SGZ	GSK+vehicle	9	69.84 ± 5.42	0.96	0.76	2.56	0.20			2.82	0.01	16		
	GSK+740Y-P	9	60.22 ± 8.68	0.95	0.71									
4D-Gi	GSK+vehicle	9	11.61 ± 1.51	0.91	0.30	2.64	0.19			4.72	<0.001	16		
	GSK+740Y-P	9	16.16 ± 2.46	0.96	0.76									
4D-Gm	GSK+vehicle	9	9.14 ± 2.06	0.97	0.93	1.90	0.38			2.88	0.01	16		
	GSK+740Y-P	9	12.50 ± 2.84	0.93	0.50									
4D-Go	GSK+vehicle	9	9.40 ± 3.08	0.89	0.20	1.34	0.68			1.27	0.22	16		
	GSK+740Y-P	9	11.12 ± 2.65	0.85	0.07									
4E-46kDa	GSK+vehicle	9	100.00 ± 7.29	0.86	0.10	2.79	0.17			6.85	<0.001	16		
	GSK+TBHQ	9	132.50 ± 12.19	0.97	0.89									
4E-48kDa	GSK+vehicle	9		0.83	0.04	4.19	0.06	96.07	95.30~106.90				-3.58	<0.001
	GSK+TBHQ	9		0.95	0.67			145.80	128.20~152.60					
4F-46kDa	GSK+vehicle	9	100.00 ± 6.88	0.94	0.64	2.38	0.24			13.56	<0.001	16		
	GSK+740Y-P	9	157.10 ± 10.61	0.96	0.86									
4F-48kDa	GSK+vehicle	9		0.94	0.60	12.55	0.002	100.50	95.68~105.00				-3.58	<0.001
	GSK+740Y-P	9		0.84	0.06			134.30	123.20~140.8					
5A-i-0.1mA	control	9	0.10 ± 0.02	0.92	0.39	1.22	0.78			0.23	0.82	16		
	TBHQ	9	0.10 ± 0.01	0.92	0.36									
5A-i-0.2mA	control	9		0.96	0.83	4.70	0.04	0.167	0.15~0.19				-1.46	0.16
	TBHQ	9		0.97	0.86			0.1538	0.14~0.16					
5A-i-0.3mA	control	9	0.48 ± 0.07	0.96	0.81	1.34	0.69			2.19	0.04	16		
	TBHQ	9	0.55 ± 0.06	0.93	0.53									
5A-i-0.4mA	control	9	0.87 ± 0.06	0.91	0.32	2.20	0.29			5.42	<0.001	16		
	TBHQ	9	0.99 ± 0.04	0.96	0.85									
5A-i-0.5mA	control	9	1.13 ± 0.08	0.93	0.48	1.11	0.88			1.38	0.18	16		
	TBHQ	9	1.18 ± 0.09	0.94	0.63									
5A-i-0.6mA	control	9	1.43 ± 0.11	0.95	0.71	1.01	0.99			0.12	0.90	16		
	TBHQ	9	1.44 ± 0.11	0.97	0.88									
5A-i-0.7mA	control	9	1.49 ± 0.12	0.93	0.48	1.15	0.84			0.69	0.50	16		
	TBHQ	9	1.53 ± 0.13	0.98	0.97									
5A-ii-25ms	control	9	1.07 ± 0.07	0.97	0.90	1.17	0.83					16		

	TBHQ	9	1.19 ± 0.07	0.88	0.17					3.39	0.004			
5A-ii-50ms	control	9	1.14 ± 0.06	0.96	0.86	1.03	0.97			1.31	0.21	16		
	TBHQ	9	1.10 ± 0.06	0.90	0.24									
5A-ii-75ms	control	9	1.25 ± 0.08	0.95	0.67	3.54	0.09			7.41	<0.001	16		
	TBHQ	9	1.01 ± 0.04	0.96	0.80									
5A-ii-100ms	control	9	1.45 ± 0.08	0.93	0.52	1.19	0.81			10.58	<0.001	16		
	TBHQ	9	1.07 ± 0.07	0.95	0.69									
5A-iv-55min	control	9	300.40 ± 20.07	0.93	0.46	2.13	0.31			0.06	0.95	16		
	TBHQ	9	299.90 ± 13.76	0.91	0.32									
5A-iv-60min	control	9	308.00 ± 17.07	0.98	0.98	1.58	0.53			0.58	0.57	16		
	TBHQ	9	303.80 ± 13.58	0.96	0.83									
5B-i-0.1mA	GSK+vehicle	9	0.10 ± 0.006	0.96	0.82	1.90	0.38			1.15	0.27	16		
	GSK+TBHQ	9	0.10 ± 0.004	0.97	0.93									
5B-i-0.2mA	GSK+vehicle	9		0.96	0.84	3.01	0.14	0.16	0.15~0.18				-2.25	0.02
	GSK+TBHQ	9		0.70	0.001			0.15	0.14~0.15					
5B-i-0.3mA	GSK+vehicle	9		0.76	0.007	16.10	<0.001	0.44	0.40~0.52				-2.52	0.01
	GSK+TBHQ	9		0.91	0.30			0.56	0.52~0.58					
5B-i-0.4mA	GSK+vehicle	9	0.86 ± 0.05	0.89	0.22	1.45	0.61			0.65	0.52	16		
	GSK+TBHQ	9	0.88 ± 0.07	0.96	0.76									
5B-i-0.5mA	GSK+vehicle	9	1.04 ± 0.06	0.96	0.79	1.10	0.90			4.85	<0.001	16		
	GSK+TBHQ	9	1.17 ± 0.06	0.93	0.53									
5B-i-0.6mA	GSK+vehicle	9	1.19 ± 0.05	0.93	0.47	2.50	0.21			10.05	<0.001	16		
	GSK+TBHQ	9	1.49 ± 0.08	0.96	0.83									
5B-i-0.7mA	GSK+vehicle	9	1.22 ± 0.03	0.98	0.98	3.84	0.07			13.91	<0.001	16		
	GSK+TBHQ	9	1.58 ± 0.07	0.96	0.85									
5B-ii-25ms	GSK+vehicle	9	1.27 ± 0.06	0.97	0.88	1.95	0.36			0.16	0.87	16		
	GSK+TBHQ	9	1.28 ± 0.09	0.96	0.77									
5B-ii-50ms	GSK+vehicle	9	1.26 ± 0.09	0.93	0.45	2.00	0.35			2.00	0.06	16		
	GSK+TBHQ	9	1.34 ± 0.06	0.94	0.58									
5B-ii-75ms	GSK+vehicle	9	1.44 ± 0.07	0.97	0.86	1.77	0.44			8.73	<0.001	16		
	GSK+TBHQ	9	1.19 ± 0.05	0.84	0.06									
5B-ii-100ms	GSK+vehicle	9	1.82 ± 0.07	0.84	0.06	1.02	0.97					16		

	GSK+TBHQ	9	1.34 ± 0.07	0.89	0.18					14.55	<0.001			
5B-iv-55min	GSK+vehicle	9	184.30 ± 10.41	0.93	0.48	1.74	0.45			15.29	<0.001	16		
	GSK+TBHQ	9	272.10 ± 13.74	0.98	0.97									
5B-iv-60min	GSK+vehicle	9	176.90 ± 21.64	0.84	0.05	2.09	0.32			10.50	<0.001	16		
	GSK+TBHQ	9	269.10 ± 14.97	0.94	0.58									
5C-i-0.1mA	control	9		0.77	0.008	2.01	0.34	0.01	0.0097~0.01				-2.43	0.01
	740Y-P	9		0.94	0.62			0.01	0.011~0.012					
5C-i-0.2mA	control	9		0.97	0.87	6.04	0.02	0.21	0.15~0.28				-1.28	0.13
	740Y-P	9		0.93	0.44			0.16	0.14~0.20					
5C-i-0.3mA	control	9	0.61 ± 0.07	0.94	0.56	2.20	0.28			1.08	0.30	16		
	740Y-P	9	0.58 ± 0.05	0.91	0.33									
5C-i-0.4mA	control	9	0.94 ± 0.06	0.97	0.93	2.29	0.26			6.00	<0.001	16		
	740Y-P	9	1.18 ± 0.10	0.95	0.72									
5C-i-0.5mA	control	9	1.28 ± 0.10	0.95	0.72	1.36	0.67			4.05	<0.001	16		
	740Y-P	9	1.49 ± 0.12	0.91	0.31									
5C-i-0.6mA	control	9	1.58 ± 0.14	0.92	0.40	1.57	0.54			1.36	0.19	16		
	740Y-P	9	1.68 ± 0.18	0.90	0.26									
5C-i-0.7mA	control	9	1.57 ± 0.10	0.93	0.52	2.47	0.22			1.48	0.16	16		
	740Y-P	9	1.67 ± 0.16	0.96	0.82									
5C-ii-25ms	control	9	1.08 ± 0.05	0.85	0.07	3.71	0.08			0.42	0.68	16		
	740Y-P	9	1.09 ± 0.09	0.90	0.24									
5C-ii-50ms	control	9		0.88	0.16	11.27	0.002	1.13	1.06~1.26				-2.07	0.04
	740Y-P	9		0.95	0.75			1.05	1.02~1.09					
5C-ii-75ms	control	9		0.83	0.04	2.35	0.25	1.12	1.10~1.35				-2.25	0.02
	740Y-P	9		0.95	0.73			1.08	1.01~1.12					
5C-ii-100ms	control	9		0.95	0.64	2.23	0.28	1.47	1.41~1.56				-2.69	0.01
	740Y-P	9		0.77	0.01			1.24	1.20~1.29					
5C-iv-55min	control	9	302.50 ± 14.04	0.97	0.93	2.50	0.22			0.48	0.64	16		
	740Y-P	9	306.60 ± 22.19	0.85	0.07									
5C-iv-60min	control	9	305.20 ± 19.95	0.94	0.64	1.07	0.93			0.05	0.96	16		
	740Y-P	9	304.70 ± 20.61	0.92	0.38									
5D-i-0.1mA	GSK+vehicle	9		0.85	0.08	32.47	<0.001	0.1135	0.09~0.12				-0.93	0.39

	GSK+740Y-P	9		0.93	0.54			0.1009	0.098~0.11					
5D-i-0.2mA	GSK+vehicle	9		0.94	0.60	6.93	0.01	0.18	0.17~0.20				-1.99	0.05
	GSK+740Y-P	9		0.91	0.32			0.22	1.18~0.23					
5D-i-0.3mA	GSK+vehicle	9	0.41 ± 0.02	0.88	0.17	2.99	0.14			12.15	<0.001	16		
	GSK+740Y-P	9	0.58 ± 0.04	0.93	0.53									
5D-i-0.4mA	GSK+vehicle	9		0.96	0.83	2.15	0.30	0.75	0.71~0.77				-3.58	<0.001
	GSK+740Y-P	9		0.80	0.02			0.95	0.92~0.97					
5D-i-0.5mA	GSK+vehicle	9		0.86	0.09	4.85	0.04	0.98	0.94~0.98				-3.58	<0.001
	GSK+740Y-P	9		0.97	0.90			1.28	1.21~1.34					
5D-i-0.6mA	GSK+vehicle	9	1.14 ± 0.09	0.92	0.36	1.26	0.75			10.03	<0.001	16		
	GSK+740Y-P	9	1.54 ± 0.08	0.87	0.12									
5D-i-0.7mA	GSK+vehicle	9		0.93	0.46	1.88	0.39	1.20	1.12~1.32				-3.58	<0.001
	GSK+740Y-P	9		0.83	0.05			1.54	1.50~1.65					
5D-ii-25ms	GSK+vehicle	9	1.26 ± 0.10	0.92	0.42	1.49	0.59			0.43	0.67	16		
	GSK+740Y-P	9	1.28 ± 0.12	0.94	0.64									
5D-ii-50ms	GSK+vehicle	9	1.16 ± 0.07	0.91	0.31	1.97	0.36			2.43	0.03	16		
	GSK+740Y-P	9	1.09 ± 0.05	0.95	0.69									
5D-ii-75ms	GSK+vehicle	9	1.60 ± 0.08	0.99	0.99	1.56	0.54			13.22	<0.001	16		
	GSK+740Y-P	9	1.13 ± 0.06	0.92	0.37									
5D-ii-100ms	GSK+vehicle	9		0.91	0.31	6.39	0.02	1.77	1.74~1.85				-3.05	0.001
	GSK+740Y-P	9		0.89	0.22			1.62	1.39~1.65					
5D-iv-55min	GSK+vehicle	9	201.10 ± 21.39	0.92	0.41	1.97	0.36			6.41	<0.001	16		
	GSK+740Y-P	9	279.70 ± 29.98	0.87	0.12									
5D-iv-60min	GSK+vehicle	9	203.40 ± 12.27	0.88	0.15	2.51	0.21			10.86	<0.001	16		
	GSK+740Y-P	9	286.70 ± 19.45	0.98	0.99									
6A	GSK+vehicle	9	36.52 ± 4.99	0.92	0.41	1.23	0.28			6.86	<0.001	16		
	GSK+TBHQ	9	50.78 ± 3.74	0.96	0.84									
6B-PSD95	GSK+vehicle	9	100.00 ± 7.25	0.98	0.94	2.65	0.12			8.80	<0.001	16		
	GSK+TBHQ	9	138.60 ± 11.00	0.93	0.45									
6B-Syn	GSK+vehicle	9		0.93	0.43	4.95	0.04	100.10	96.22~102.1			16	-3.58	<0.001
	GSK+TBHQ	9		0.90	0.24			147.80	137.50~151.90					
6C	GSK+vehicle	9	32.50 ± 4.47	0.94	0.61	1.92	0.18			4.28	<0.001	16		

	GSK+740Y-P	9	43.66 ± 6.41	0.95	0.73									
6D-PSD95	GSK+vehicle	9	100.00 ± 6.63	0.94	0.54	4.25	0.06			9.90	<0.001	16		
	GSK+740Y-P	9	150.10 ± 13.67	0.93	0.46									
6D-Syn	GSK+vehicle	9		0.85	0.07	17.37	<0.001	99.19	98.02~103.00				-3.58	<0.001
	GSK+740Y-P	9		0.89	0.18			155.80	128.30~164.70					
7A-velocity	control	6	0.19 ±0.03	0.96	0.82	0.04	0.85			0.81	0.44	10		
	GSK	6	0.17 ±0.03	0.93	0.56									
7A-platform crossing	control	6	13.00 ±3.90	0.95	0.72	3.38	0.10			2.51	0.03	10		
	GSK	6	8.67 ±1.63	0.92	0.51									
7A-time in platform	control	6	33.78 ±2.23	0.98	0.95	1.40	0.21			3.89	0.003	10		
	GSK	6	25.67 ±4.59	0.94	0.64									
7A-ecscape latency-Day 1	control	6		0.70	0.006	2.86	0.12	59.59	53.71~60.00	-0.56	0.59	10		
	GSK	6		0.75	0.02			59.57	57.16~60.00					
7A-ecscape latency-Day 2	control	6		0.89	0.32	9.33	0.01	41.79	39.45~51.73	-1.51	0.16		-1.28	0.24
	GSK	6		0.97	0.91			49.34	47.78~50.44					
7A-ecscape latency-Day 3	control	6	37.14±3.55	0.93	0.56	0.05	0.82			-4.70	0.001	10		
	GSK	6	46.30±3.20	0.95	0.76									
7A-ecscape latency-Day 4	control	6		0.88	0.27	5.56	0.04	30.13	27.84~37.46	-5.67	<0.001		-2.88	0.002
	GSK	6		0.98	0.92			45.67	43.85~47.21					
7A-ecscape latency-Day 5	control	6	24.75±3.35	0.88	0.28	0.02	0.89			-6.24	<0.001	10		
	GSK	6	39.55±4.74	0.91	0.41									
7B-velocity	control	6	0.18±0.008	0.97	0.91	1.56	0.24			-0.50	0.63	10		
	TBHQ	6	0.19±0.02	0.97	0.86									
	GSK+vehicle	6	0.18±0.01	0.95	0.76	0.68	0.43			-0.80	0.44	10		
	GSK+TBHQ	6	0.18±0.02	0.91	0.42									
7B-platform crossing	control	6	14.00±2.97	0.89	0.34	0.80	0.39			0.67	0.52	10		
	TBHQ	6	13.00±2.10	0.89	0.32									
	GSK+vehicle	6	8.00±1.677	0.88	0.25	0.10	0.76			-3.67	0.004	10		
	GSK+TBHQ	6	11.83±1.947	0.91	0.45									
7B-time in platform	control	6	32.65±2.27	0.95	0.75	0.94	0.36			0.04	0.97	10		
	TBHQ	6	32.59±1.98	0.83	0.10									
	GSK+vehicle	6	25.04±1.20	0.91	0.44	0.60	0.46					10		

	GSK+TBHQ	6	29.98±2.54	0.93	0.60					-4.31	0.002			
7B-ecscape latency-Day 1	control	6		0.76	0.03	0.37	0.56	58.91	55.35~60.00				-0.17	0.94
	TBHQ	6		0.63	0.001			59.32	57.64~60.00					
	GSK+vehicle	6		0.71	0.008	0.005	0.95	59.36	56.07~60.00				-0.66	0.59
	GSK+TBHQ	6		0.91	0.46			56.74	54.24~60.00					
7B-ecscape latency-Day 2	control	6	44.61±5.40	0.93	0.54	0.76	0.40			0.98	0.35	10		
	TBHQ	6	41.92±4.02	0.84	0.13									
	GSK+vehicle	6	49.35±5.17	0.93	0.57	0.005	0.94			2.47	0.03	10		
	GSK+TBHQ	6	42.08±5.02	0.97	0.92									
7B-ecscape latency-Day 3	control	6	37.31±4.61	0.96	0.81	0.002	0.96			0.35	0.73	10		
	TBHQ	6	36.41±4.19	0.97	0.90									
	GSK+vehicle	6	44.29±3.04	0.96	0.82	0.008	0.93			2.73	0.02	10		
	GSK+TBHQ	6	39.18±3.44	0.93	0.58									
7B-ecscape latency-Day 4	control	6	31.08±4.70	0.87	0.22	0.03	0.87			0.49	0.63	10		
	TBHQ	6	29.67±5.21	0.89	0.31									
	GSK+vehicle	6	43.81±4.35	0.91	0.46	0.009	0.92			2.59	0.03	10		
	GSK+TBHQ	6	36.88±4.92	0.95	0.74									
7B-ecscape latency-Day 5	control	6	24.55±4.38	0.98	0.96	0.56	0.47			0.57	0.58	10		
	TBHQ	6	23.29±3.21	0.90	0.38									
	GSK+vehicle	6	39.70±3.96	0.98	0.96	0.01	0.92			4.87	0.001	10		
	GSK+TBHQ	6	28.20±4.22	0.95	0.74									
7C-velocity	control	6	0.19±0.02	0.96	0.82	0.84	0.38			0.61	0.56	10		
	740Y-P	6	0.18±0.01	0.80	0.06									
	GSK+vehicle	6	0.17±0.01	0.97	0.88	0.02	0.89			-0.51	0.62	10		
	GSK+740Y-P	6	0.18±0.01	0.82	0.09									
7C-platform crossing	control	6	13.00±3.90	0.95	0.72	0.59	0.46			-0.76	0.47	10		
	740Y-P	6	14.50±2.88	0.97	0.91									
	GSK+vehicle	6	7.17±2.14	0.89	0.33	0.33	0.58			-4.24	0.002	10		
	GSK+740Y-P	6	12.17±1.94	0.91	0.45									
7C-time in platform	control	6	33.78±2.23	0.98	0.95	0.45	0.52			1.35	0.21	10		
	740Y-P	6	32.20±1.78	0.90	0.36									
	GSK+vehicle	6	24.80±1.66	0.97	0.86	1.95	0.19					10		

	GSK+740Y-P	6	30.40±3.09	0.94	0.63					-3.92	0.005			
7C-ecscape latency-Day 1	control	6		0.71	0.01	0.67	0.43	59.59	53.71~60.00				-0.09	0.94
	740Y-P	6		0.74	0.02			59.55	56.18~60.00					
	GSK+vehicle	6		0.72	0.01	0.86	0.38	59.77	56.41~60.00				-0.83	0.49
	GSK+740Y-P	6		0.93	0.56			56.73	53.15~60.00					
7C-ecscape latency-Day 2	control	6	44.63±7.26	0.89	0.32	3.32	0.10			0.12	0.91	10		
	740Y-P	6	44.23±3.76	0.97	0.91									
	GSK+vehicle	6	49.40±5.12	0.91	0.43	0.01	0.92			2.44	0.04	10		
	GSK+740Y-P	6	43.11±3.68	0.93	0.55									
7C-ecscape latency-Day 3	control	6	37.14±3.55	0.93	0.56	2.12	0.18			0.10	0.92	10		
	740Y-P	6	36.97±2.08	0.98	0.95									
	GSK+vehicle	6	45.48±4.60	0.99	1.00	0.02	0.88			2.49	0.03	10		
	GSK+740Y-P	6	38.81±4.70	0.94	0.68									
7C-ecscape latency-Day 4	control	6	32.10±5.48	0.88	0.27	4.54	0.06			-0.19	0.86	10		
	740Y-P	6	32.55±2.39	0.96	0.85									
	GSK+vehicle	6	44.82±4.74	0.93	0.58	0.44	0.52			3.70	0.004	10		
	GSK+740Y-P	6	35.44±4.02	0.97	0.88									
7C-ecscape latency-Day 5	control	6	24.75±3.35	0.88	0.28	0.16	0.70			-0.46	0.66	10		
	740Y-P	6	25.62±3.25	0.96	0.79									
	GSK+vehicle	6	39.78±3.67	0.99	0.99	0.32	0.59			5.59	<0.001	10		
	GSK+740Y-P	6	27.11±4.16	0.97	0.89									

Supplementary Table 3

Tests for normality and variance homogeneity

Supplementary Figure	Experimental group	Sample size (*n*)	Mean ± SD.	Shapiro-Wilk test		Levene's Test		Interquartile ranges		Independent samples *t*-test			Mann-Whitney U test	
				Statistics	*P* value	*F* value	*P* value	Median	25%~75%	*t* value	*P* value	df	*Z* value	*P* value
2B-PSD95	control	9	100.0 ± 6.41	0.85	0.07	1.90	0.38			9.94	<0.001	16		
	GSK	9	63.84 ± 8.84	0.97	0.92									
2B-Syn	control	9	100.0 ± 5.20	0.96	0.76	2.93	0.15			9.84	<0.001	16		
	GSK	9	66.18 ± 8.91	0.89	0.21									
4A-p-ERK1	control	9		0.94	0.56	3.99	0.07	101.90	95.67~104.50				-2.69	0.006
	TBHQ	9		0.95	0.66			113.60	102.60~121.80					
4A-p-ERK2	control	9	99.99 ± 5.66	0.95	0.66	2.01	0.34			3.58	0.002	16		
	TBHQ	9	111.70 ± 8.01	0.93	0.52									
4A-p-CREB	control	9	100.00 ± 8.25	0.84	0.06	1.06	0.93			3.04	0.007	16		
	TBHQ	9	112.00 ± 8.51	0.98	0.97									
4B-p-Akt	control	9	100.00 ± 4.46	0.93	0.45	2.05	0.33			5.09	0.0001	16		
	740Y-P	9	113.20 ± 6.39	0.92	0.38									
4B-p-GSK3β	control	9	100.00 ± 5.67	0.95	0.74	1.09	0.90			5.16	<0.0001	16		
	740Y-P	9	113.50 ± 5.42	0.91	0.30									
4B-p-mTOR	control	9	100.00 ± 6.47	0.89	0.20	2.31	0.26			3.82	0.001	16		
	740Y-P	9	115.00 ± 9.83	0.98	0.94									
4B-p-CREB	control	9		0.82	0.04	1.52	0.57	96.97	94.12~105.80				-2.96	0.002
	740Y-P	9		0.87	0.13			111.50	110.10~119.50					
5A-BrdU$^+$	control	9	1700.00 ± 291.60	0.95	0.65	2.99	0.14			3.51	0.003	16		
	TBHQ	9	2094.00 ± 168.50	0.90	0.27									
5A-BrdU$^+$/NeuN$^+$	control	9		0.92	0.38	1.38	0.66	1338.00	115.00~1506.00				-2.96	0.002
	TBHQ	9		0.82	0.03			1787.00	1580.00~1815.00					
5A-BrdU$^+$/GFAP$^+$	control	9		0.90	0.25	19.74	<0.001	404.00	390.00~417.00				-2.78	0.004
	TBHQ	9		0.62	0.0002			526.00	501.00~586.00					
5B-BrdU$^+$	control	9		0.95	0.64	1.28	0.73	1820.00	1547.00~1968.00				-2.52	0.01

	740Y-P	9		0.82	0.03			2050.00	2003.00~2190.00					
5B-BrdU$^+$/NeuN$^+$	control	9		0.78	0.01	1.35	0.68	1277.00	1120.00~1448.00				-2.61	0.008
	740Y-P	9		0.77	0.01			1790.00	1625.00~1853.00					
5B-BrdU$^+$/GFAP$^+$	control	9	395.60 ± 62.80	0.93	0.50	1.62	0.51			1.30	0.21	16		
	740Y-P	9	439.80 ± 79.91	0.95	0.73									
5C-SGZ	control	9		0.92	0.42	3.40	0.10	60.57	55.90~66.32				2.96	0.002
	TBHQ	9		0.79	0.02			53.80	52.71~54.48					
5C-Gi	control	9	14.85 ± 1.67	0.93	0.53	1.14	0.86			2.02	0.06	16		
	TBHQ	9	13.15 ± 1.78	0.94	0.60									
5C-Gm	control	9	10.28 ± 3.85	0.95	0.66	2.53	0.21			2.19	0.04	16		
	TBHQ	9	13.61 ± 2.42	0.94	0.54									
5C-Go	control	9		0.88	0.17	6.69	0.01	15.64	9.77~18.02				-2.52	0.01
	TBHQ	9		0.98	0.96			19.50	17.66~20.67					
5D-SGZ	control	9		0.78	0.01	12.42	0.002	59.86	54.44~64.30				1.81	0.08
	740Y-P	9		0.93	0.46			56.44	53.49~57.92					
5D-Gi	control	9	12.89 ± 3.11	0.86	0.11	2.46	0.22			3.39	0.004	16		
	740Y-P	9	17.05 ± 1.98	0.86	0.09									
5D-Gm	control	9		0.99	0.99	1.18	0.82	10.33	9.12~11.93				-3.13	<0.001
	740Y-P	9		0.80	0.02			13.82	13.56~16.45					
5D-Go	control	9	14.59 ± 3.10	0.93	0.53	1.69	0.47			1.68	0.11	16		
	740Y-P	9	12.41 ± 2.38	0.91	0.29									
5E-46kDa	control	9		0.89	0.22	4.91	0.04	99.44	92.50~106.20				-2.08	0.04
	TBHQ	9		0.94	0.56			117.90	98.19~124.90					
5E-48kDa	control	9		0.99	0.99	15.08	0.001	100.50	97.62~102.10				-2.69	0.006
	TBHQ	9		0.96	0.79			112.00	105.00~120.40					
5F-46kDa	control	9	100.00 ± 6.13	0.91	0.30	3.32	0.11			1.55	0.14	16		
	740Y-P	9	106.60 ± 11.17	0.91	0.29									
5F-48kDa	control	9		0.87	0.13	8.33	0.007	99.79	95.28~102.20				-0.97	0.35
	740Y-P	9		0.87	0.11			101.90	97.21~118.50					
7A	control	9	48.51±6.61	0.90	0.24	3.36	0.11			0.63	0.54	16		
	TBHQ	9	50.09±3.61	0.89	0.18									
7B-i-PSD95	control	9	100.00±4.77	0.88	0.14	2.4	0.23			1.60	0.13	16		

	TBHQ	9	104.70±7.39	0.90	0.24									
7B-i-Syn	control	9		0.92	0.42	8.68	0.01	100.80	98.52~101.50				-3.58	<0.001
	TBHQ	9		0.89	0.20			112.13	106.99~114.61					
7C-PSD95	control	9	100.00±9.26	0.86	0.09	1.39	0.65			3.53	0.003	16		
	TBHQ	9	116.9±10.94	0.96	0.84									
7C-Syn	control	9	100.00±5.35	0.98	0.96	2.16	0.30			4.62	<0.001	16		
	TBHQ	9	114.60±7.86	0.99	0.99									
7D	control	9	46.61±7.03	0.95	0.70	2.93	0.15			1.21	0.24	16		
	740Y-P	9	49.90±4.11	0.91	0.34									
7E-i-PSD95	control	9		0.92	0.36	6.74	0.02	99.73	97.17~101.70				-1.63	0.11
	740Y-P	9		0.94	0.61			105.90	98.37~110.80					
7E-i-Syn	control	9	100.00±7.87	0.90	0.26	1.74	0.45			1.79	0.09	16		
	740Y-P	9	107.80±10.40	0.98	0.98									
7F-PSD95	control	9	100.00±4.91	0.95	0.64	2.24	0.28			6.74	<0.001	16		
	740Y-P	9	119.90±7.35	0.94	0.63									
7F-Syn	control	9	100.00±4.67	0.94	0.61	1.20	0.80			6.35	<0.001	16		
	740Y-P	9	114.70±5.12	0.90	0.23									
8B-ii-PSD95	GSK+vehicle	9	100.00 ± 5.76	0.98	0.95	3.57	0.09			7.14	<0.001	16		
	GSK+TBHQ	9	129.30 ± 10.89	0.94	0.55									
8B-ii-Syn	GSK+vehicle	9		0.82	0.03	0.42	0.53	98.18	92.45~108.20				-3.58	<0.001
	GSK+TBHQ	9		0.96	0.78			148.90	137.20~157.50					
8C-ii-PSD95	GSK+vehicle	9	100.00 ± 14.95	0.95	0.69	3.11	0.10			4.04	<0.001	16		
	GSK+740Y-P	9	138.90 ± 24.65	0.86	0.10									
8C-ii-Syn	GSK+vehicle	9		0.94	0.53	8.75	0.006	97.13	95.51~105.50				-3.58	<0.001
	GSK+740Y-P	9		0.89	0.19			148.00	139.10~162.30					
9-BNDF	control	9		0.83	0.05	5.58	0.03	100.70	96.96~103.80				-3.58	<0.001
	GSK	9		0.93	0.45			60.71	50.71~67.86					
9-TrkB	control	9		0.69	0.001	4.16	0.06	98.47	94.00~100.60				-1.63	0.11
	GSK	9		0.78	0.01			104.70	98.45~108.00					

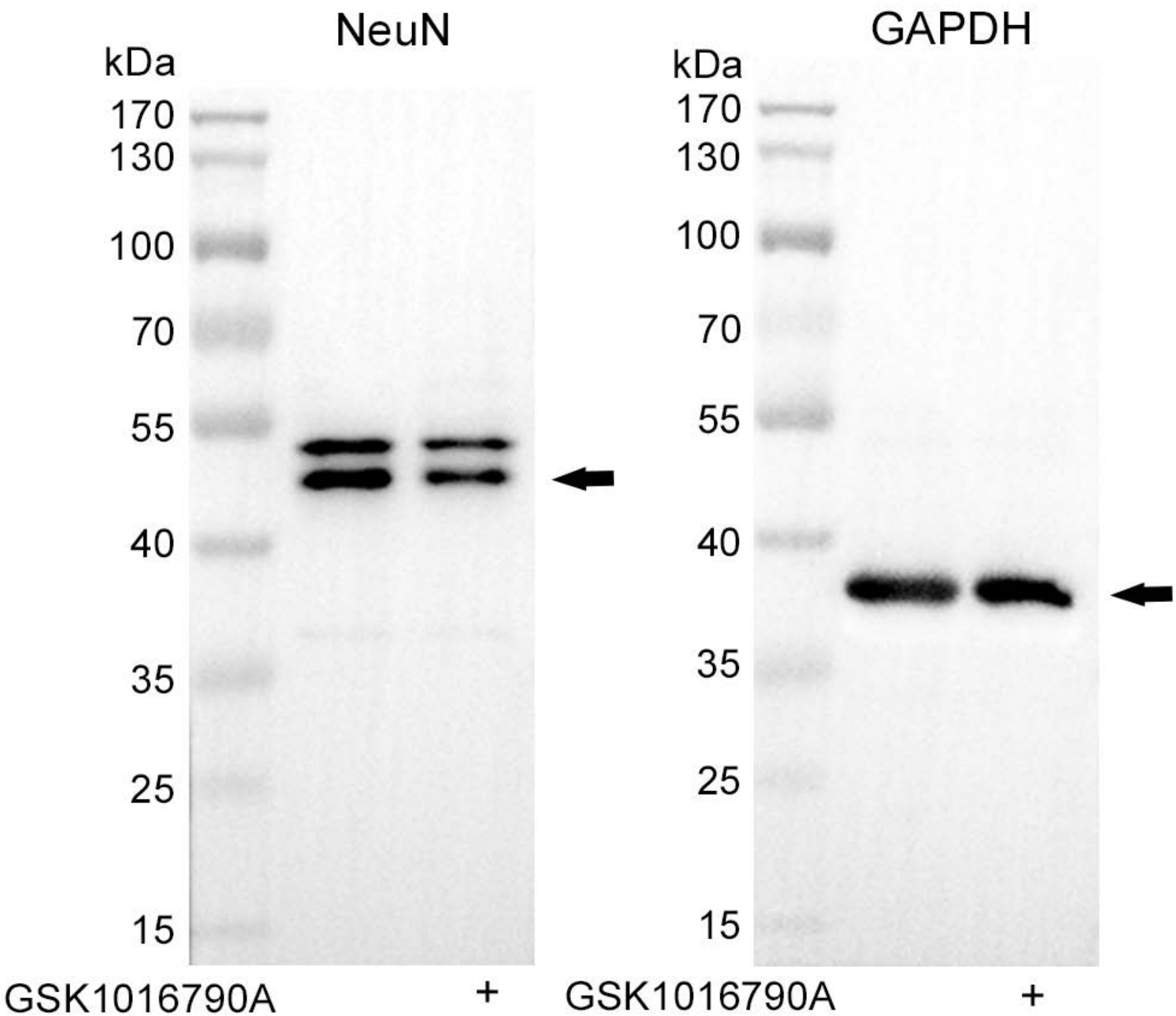
Supplementary Table 4

Experimental grouping

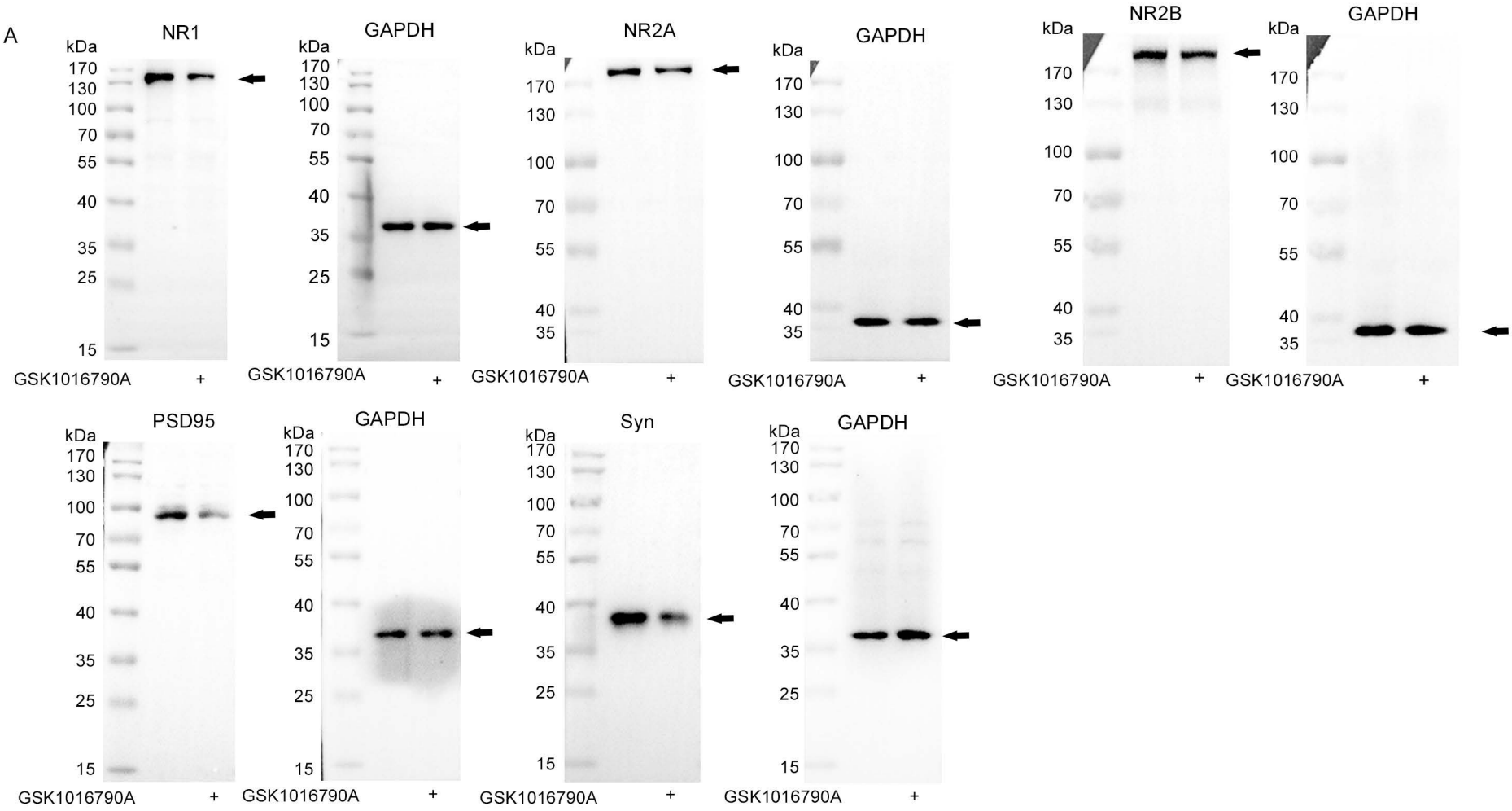
Total mice (*n*)	Group (*n*)	Treatment	Mortality (*n*)	Surviving mice (*n*)	Subgroup					
					Western blot (*n*)	1-day-old BrdU staining (*n*)	28-day-old BrdU, BrdU/NeuN, BrdU/GFAP staining (*n*)	Golgi-Cox staining (*n*)	Electrophysiological recording (*n*)	MMW (*n*)
379	control (50)	vehicle (icv.)	2	48	9	9	9	9	6	6
	GSK (50)	GSK1016790A (icv.)	2	48	9	9	9	9	6	6
	740 Y-P (41)	740 Y-P (icv.)	2	39	9	0	9	9	6	6
	vehicle-treated GSK (40)	GSK+vehicle (icv.)	1	39	9	0	9	9	6	6
	740 Y-P-treated GSK (41)	GSK+740 Y-P (icv.)	2	39	9	0	9	9	6	6
	Control (39)	vehicle (ip.)	0	39	9	0	9	9	6	6
	TBHQ (39)	TBHQ (ip.)	0	39	9	0	9	9	6	6
	vehicle-treated GSK (39)	GSK+vehicle (ip.)	0	39	9	0	9	9	6	6
	TBHQ-treated GSK (40)	GSK+vehicle (ip.)	1	39	9	0	9	9	6	6

n: number of mice

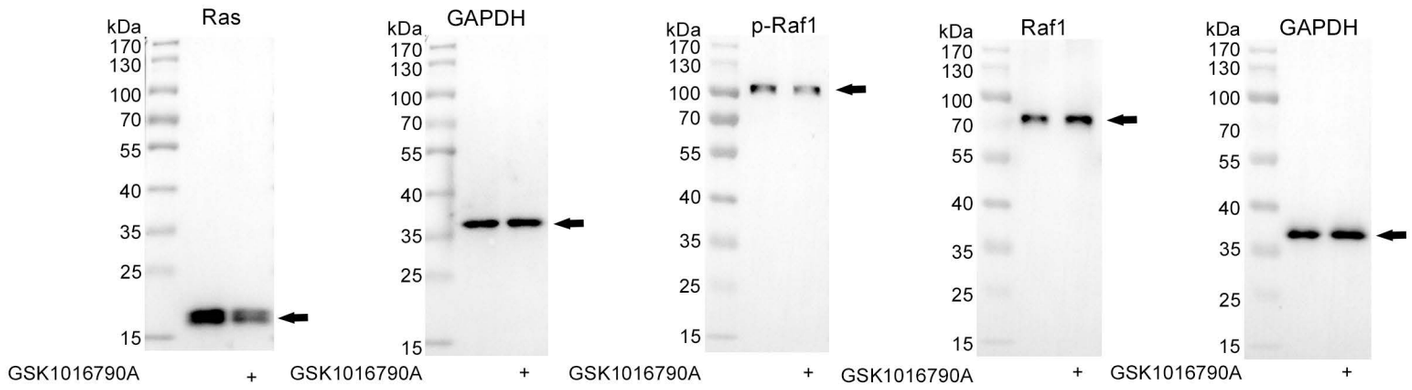
Supplementary Figure 1

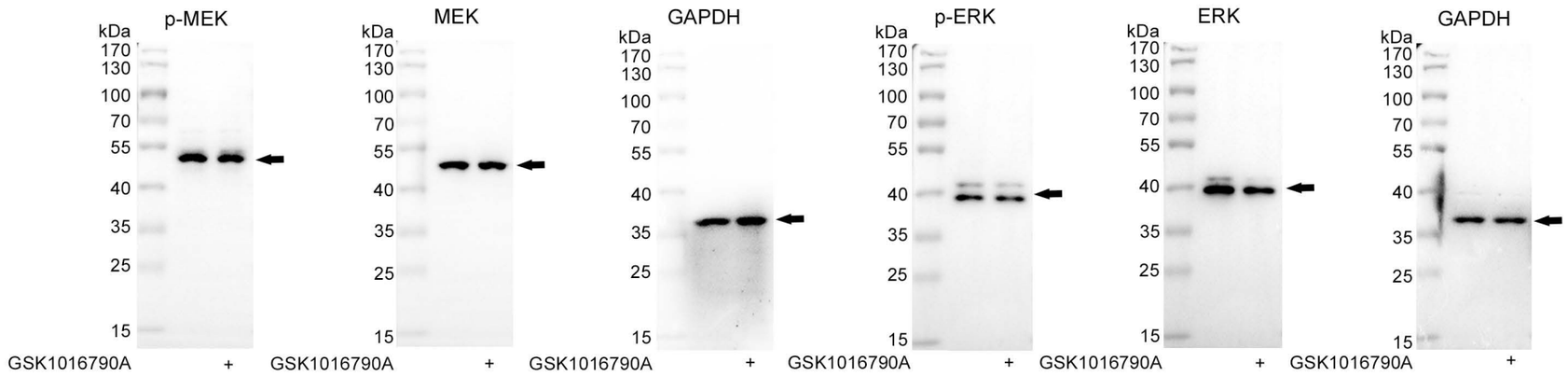


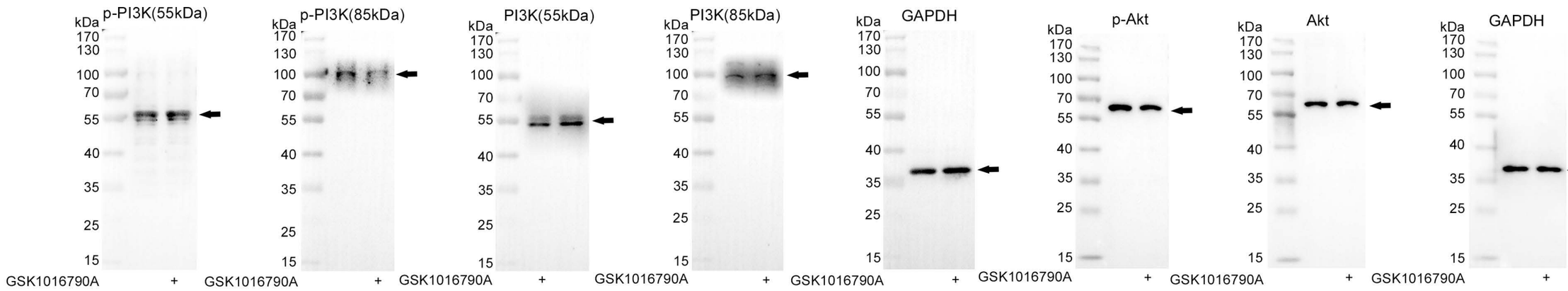
Supplementary Figure 2

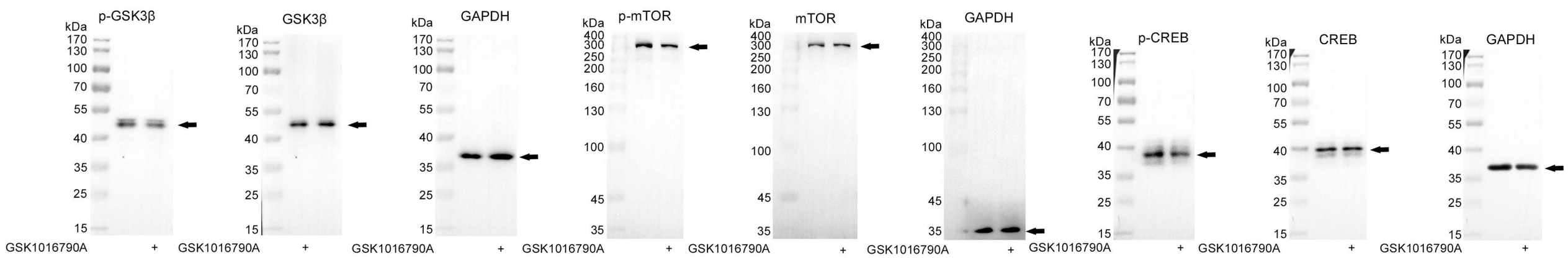


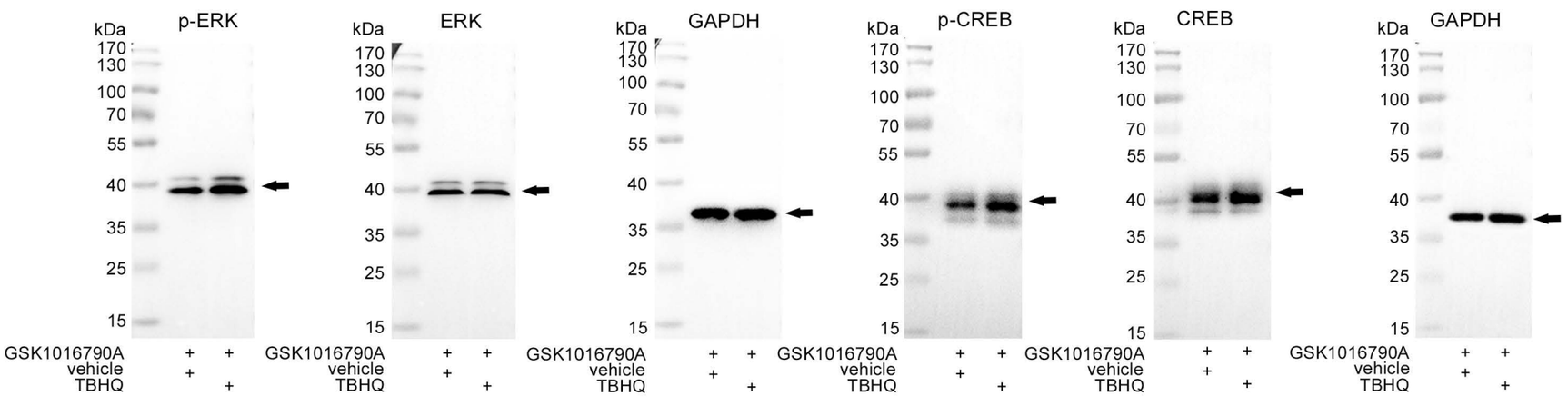
Supplementary Figure 3

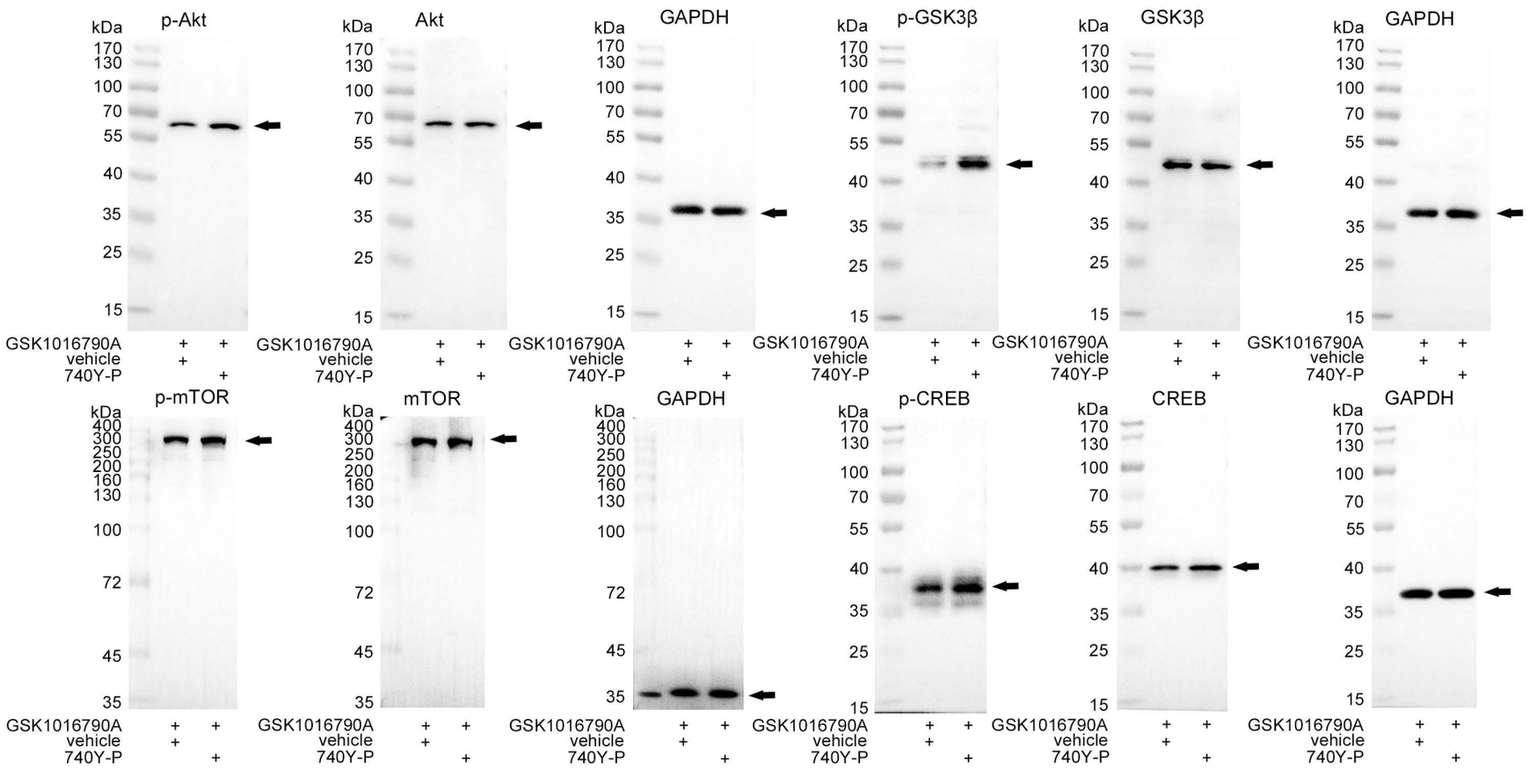




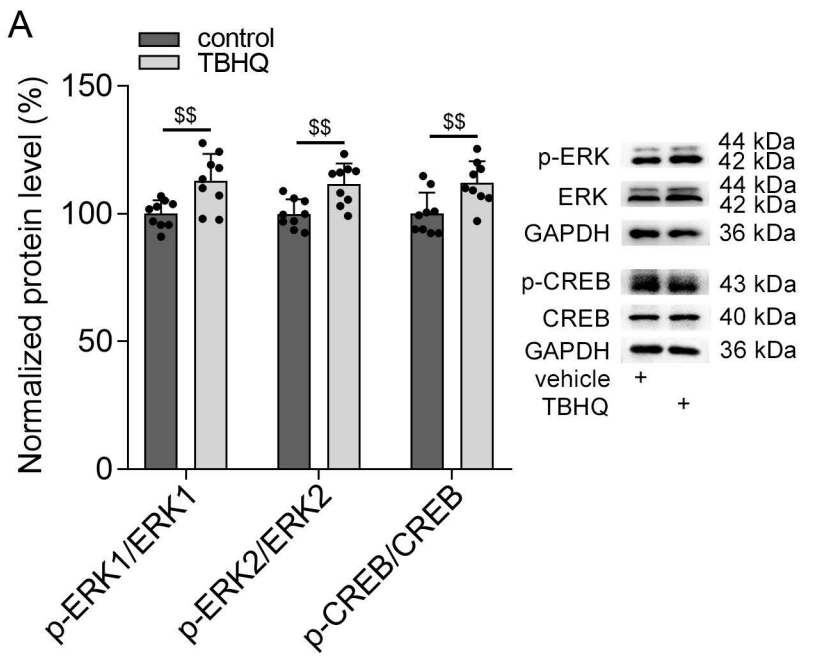


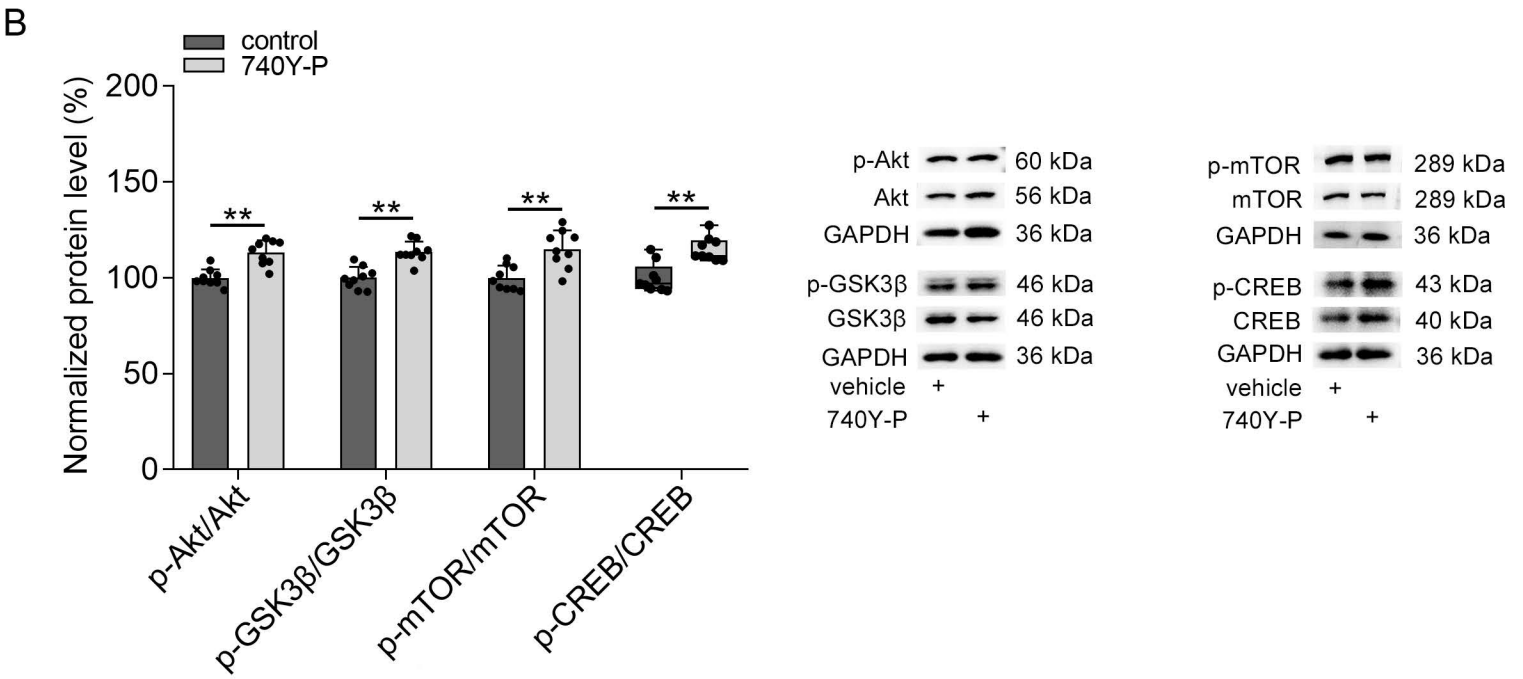


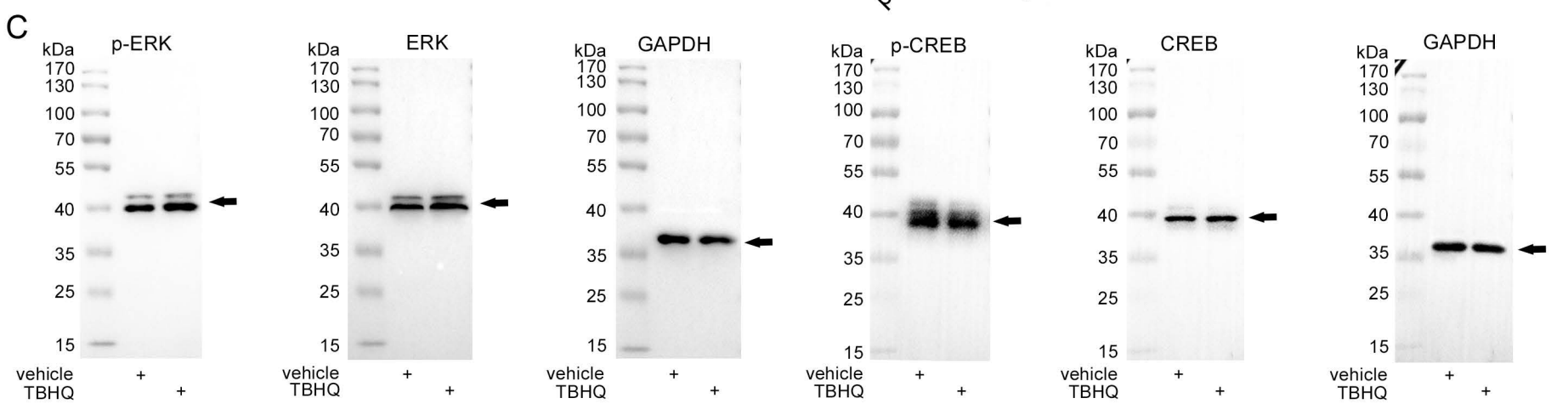


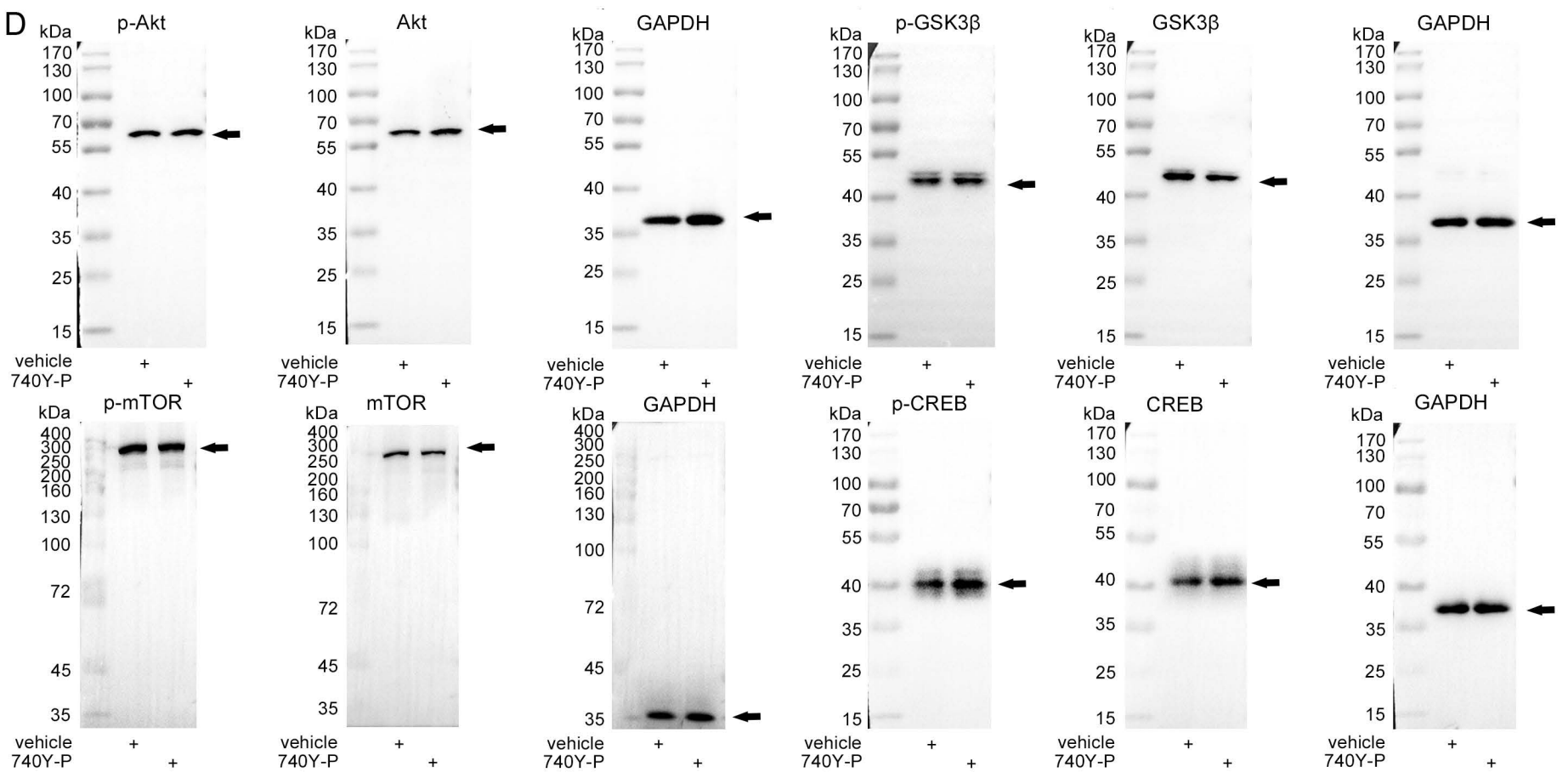


Supplementary Figure 4

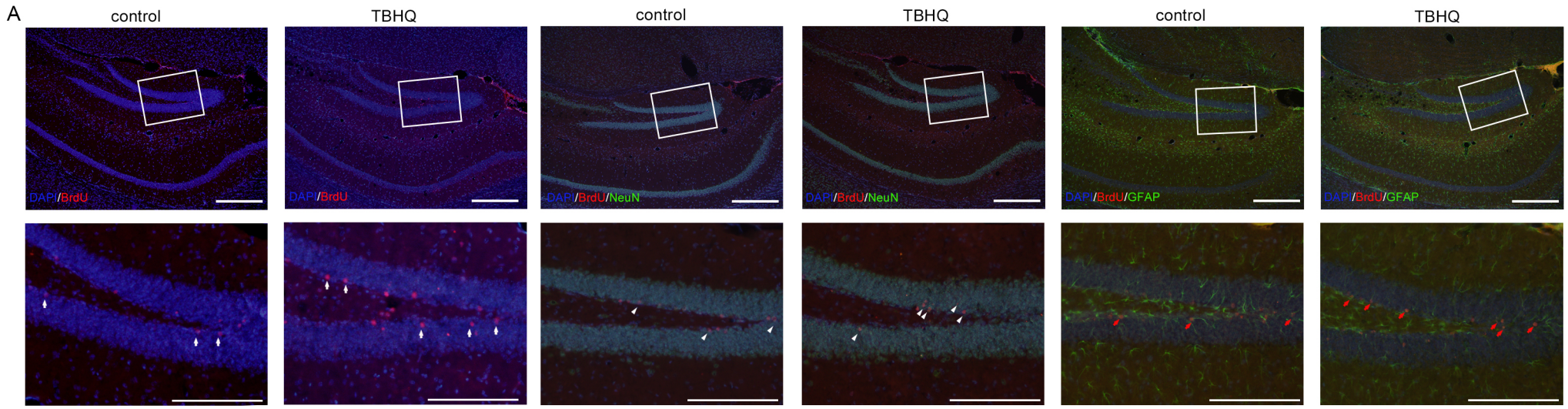


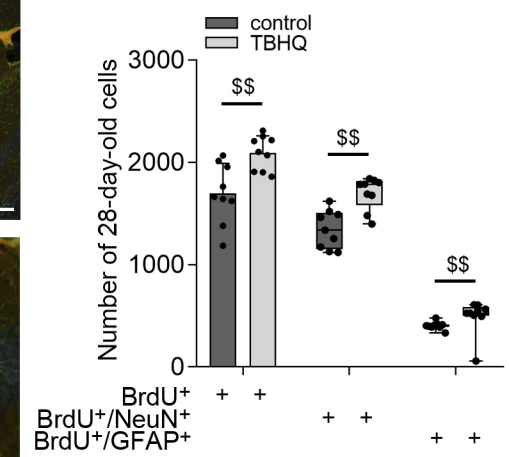


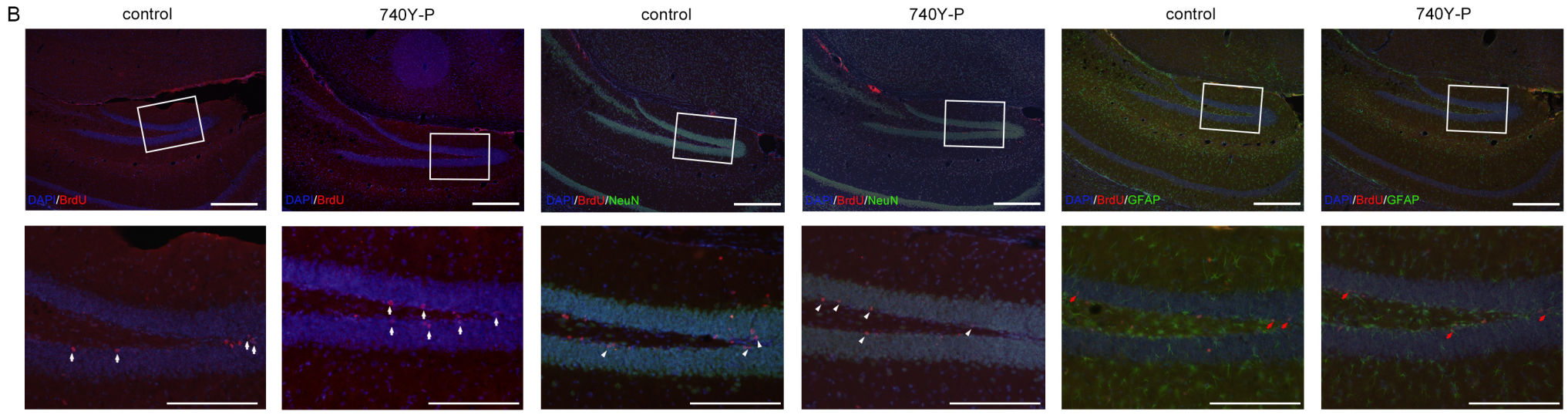


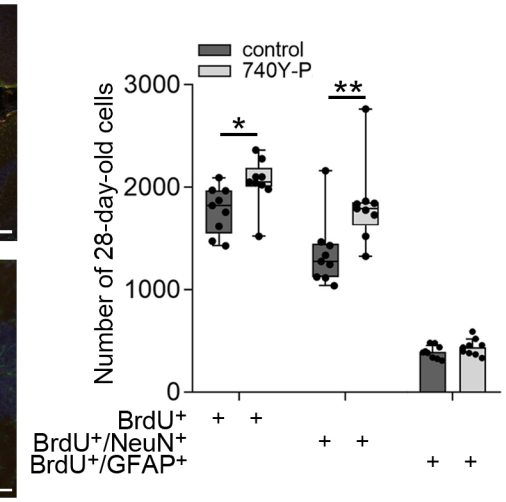


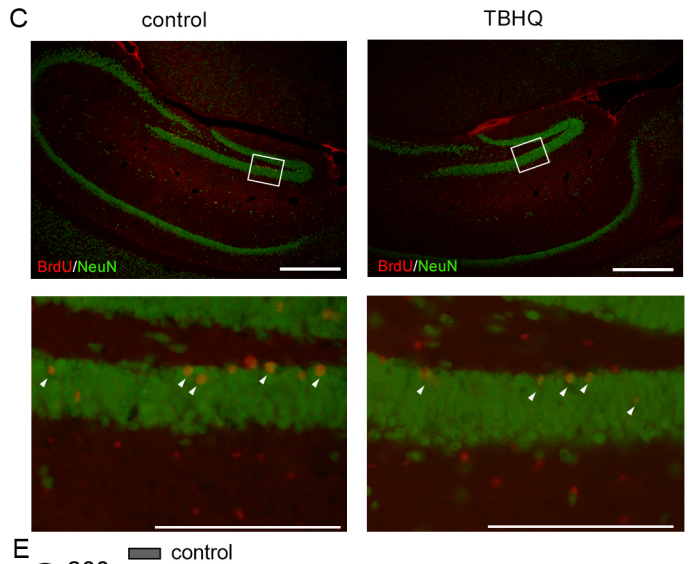
Supplementary Figure 5

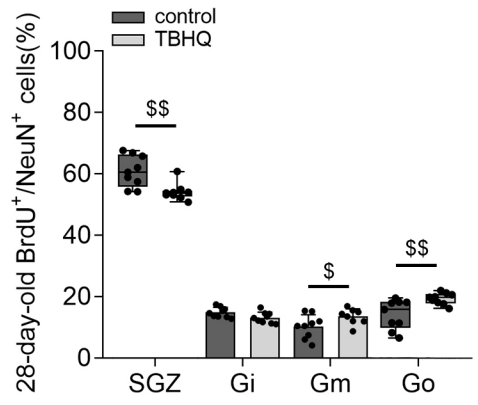


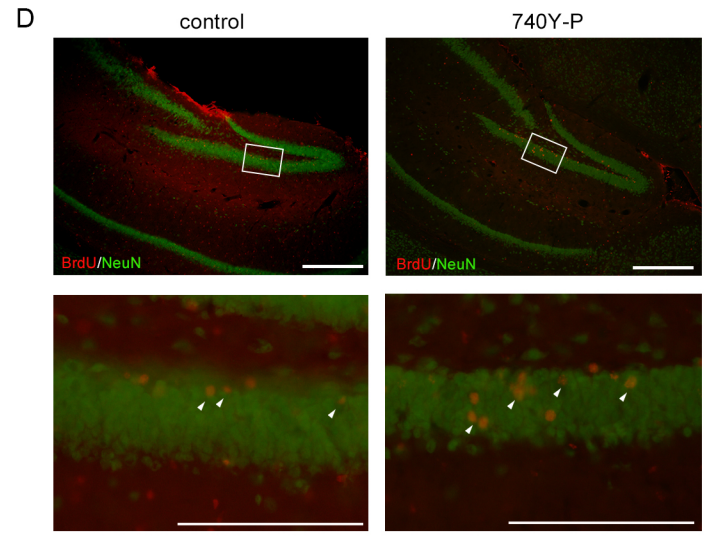


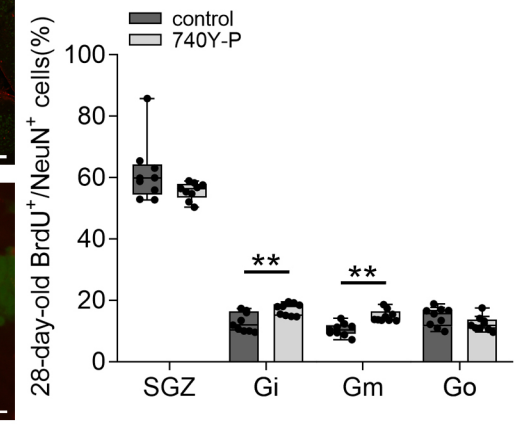


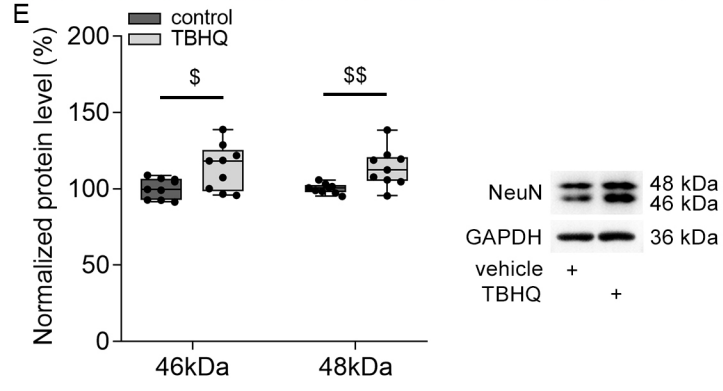


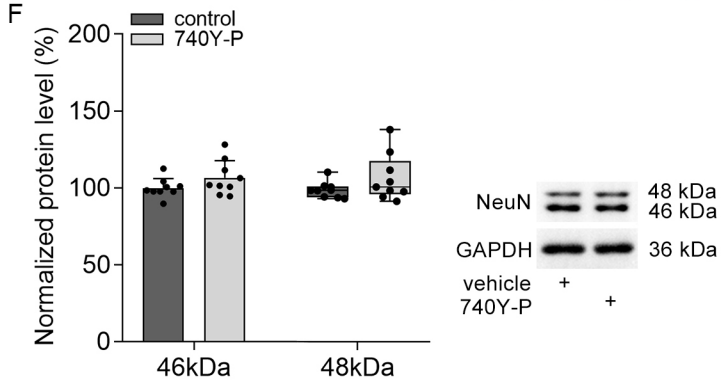




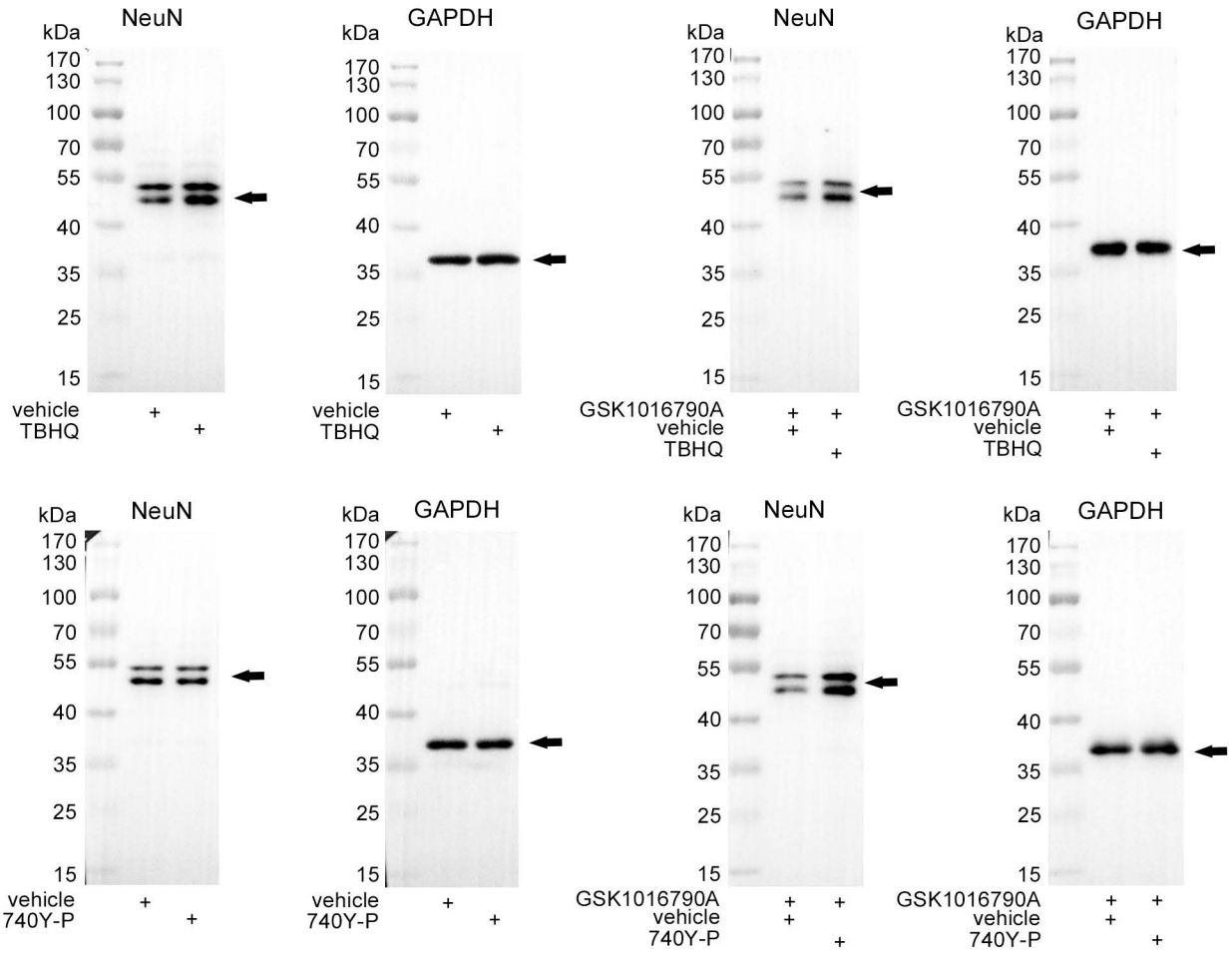




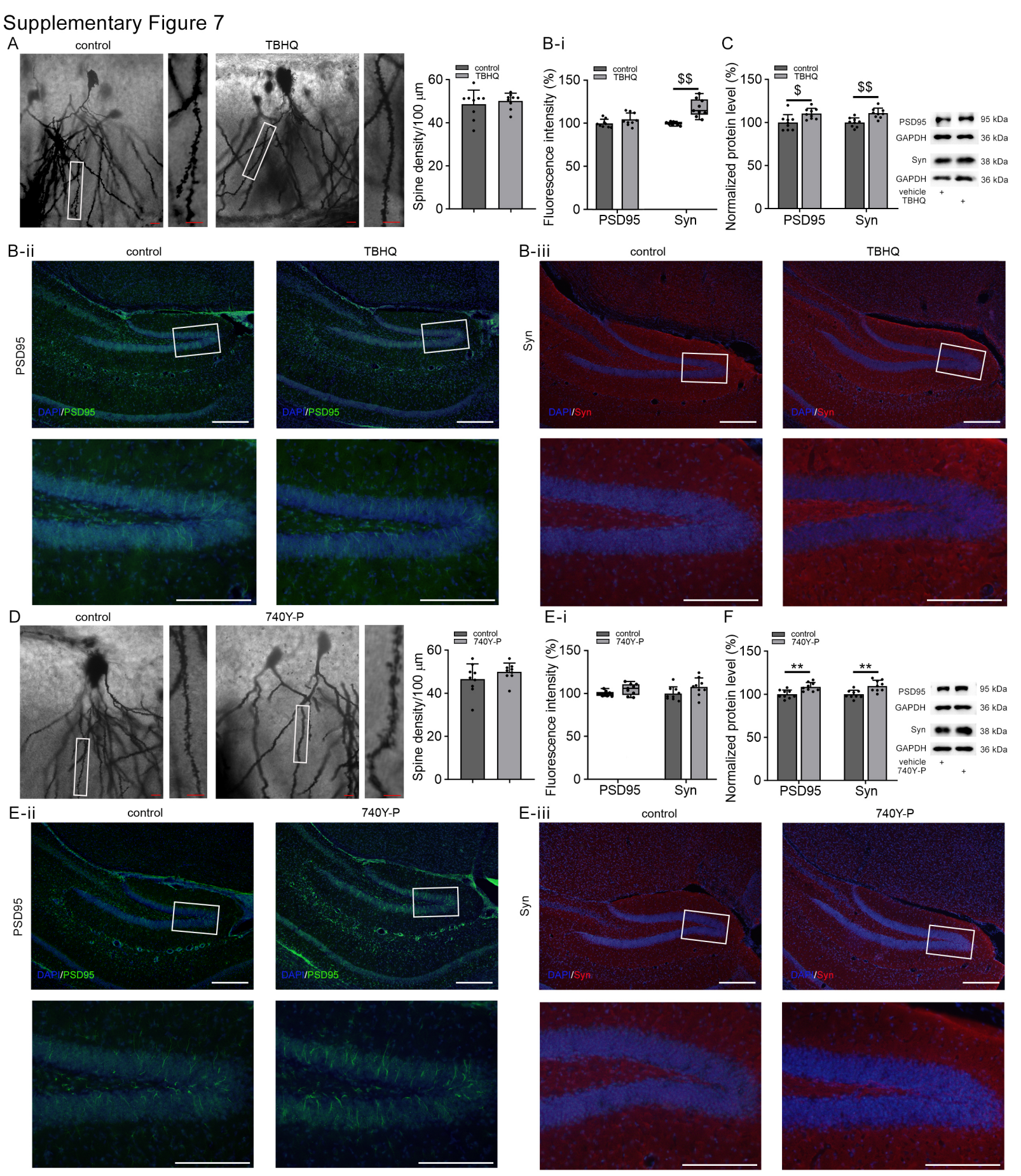




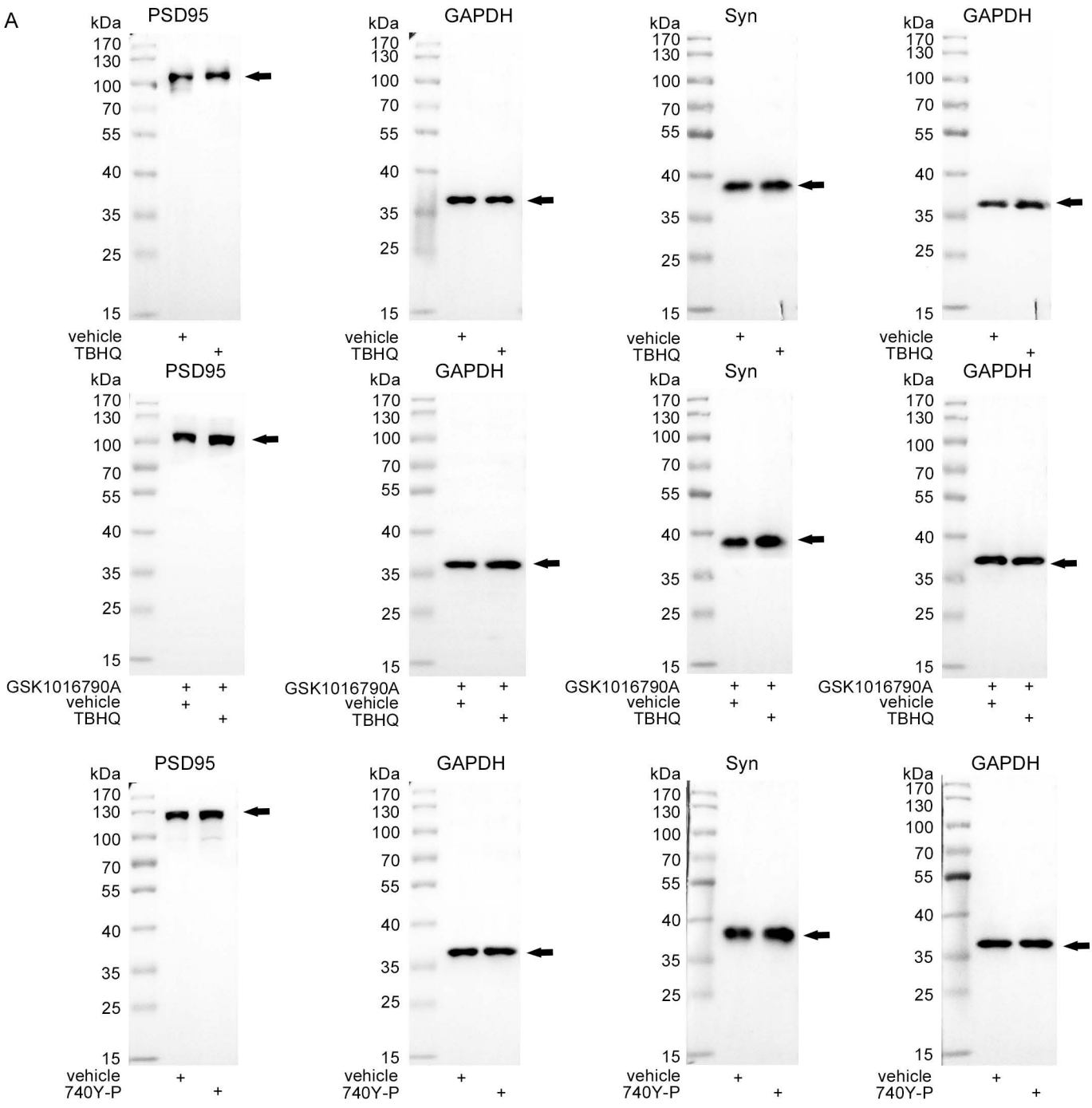
Supplementary Figure 6



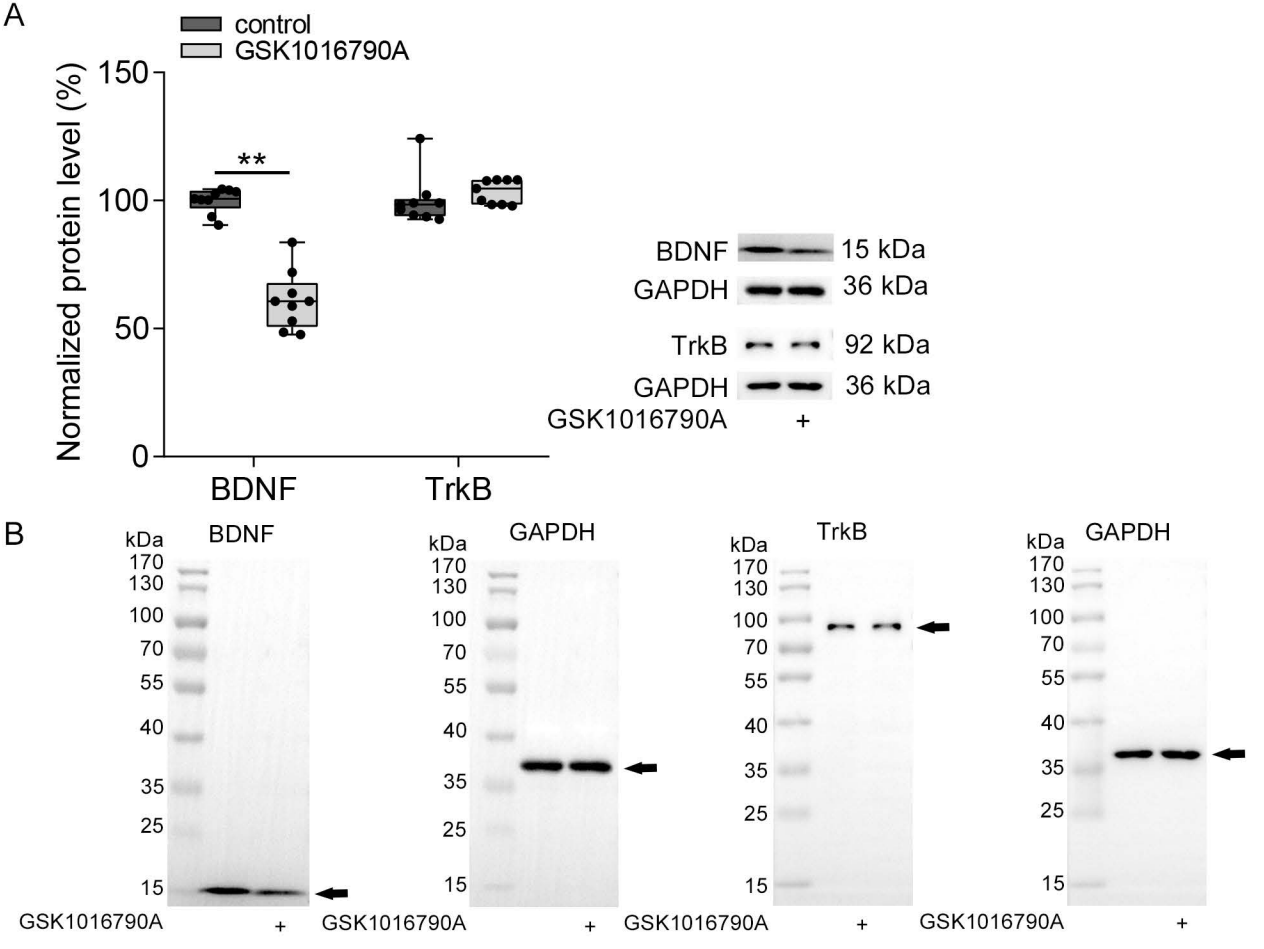
Supplementary Figure 7



Supplementary Figure 8



Supplementary Figure 9



Supplementary Figure legends

Supplementary Fig. 1 Uncropped membrane western blot image with complete molecular weight markers used in the experiments presented in Figure 1

Supplementary Fig. 2 Effect of TRPV4 activation on the expression of NMDAR subunits, PSD95, and Syn in the hippocampus

A. Uncropped membrane western blot image with complete molecular weight markers used in the experiments presented in Figure 2. **B.** The fluorescence intensity of PSD95 and Syn in the DG in the control and GSK mice. $n = 9$ mice per group. Scale bar = 100 μm. 10× objective for the top row, and 20× objective for the bottom row. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control.

Supplementary Fig. 3 Uncropped membrane western blot image with complete molecular weight markers used in the experiments presented in Figure 3

Supplementary Fig. 4 Effects of ERK1/2 pathway and PI3K activation on ERK–CREB and Akt–GSK3β–mTOR–CREB signaling pathways in the hippocampus of control mice

A. The hippocampal protein levels of p-ERK1, p-ERK2 and p-CREB in control and TBHQ (an ERK1/2 pathway activator)-treated mice. **B.** The hippocampal protein levels of p-Akt, p-GSK3β, p-mTOR and p-CREB in control and 740 Y-P (a PI3K agonist)-treated mice (Supplementary Table 3). **C and D.** Uncropped membrane western blot image with complete molecular weight markers used in the experiments presented in A (C) and B (D). In panels A and B, $n = 9$ mice per group. $^{\$\$}P < 0.01$ *vs.* control (ip.), $^{**}P < 0.01$ *vs.* control (icv.)

Supplementary Fig. 5 Effects of ERK1/2 and PI3K activation on the survival and migration of newborn neurons in the DG of GSK mice

A and B. 28-day-old $BrdU^{+}$ cells, 28-day-old $BrdU^{+}/NeuN^{+}$, and 28-day-old

$BrdU^+/GFAP^+$ cells in the DG of control, TBHQ-treated (A), and 740Y-P-treated mice (B). **C and D.** 28-day-old $BrdU^+/NeuN^+$ cells in the SGZ, Gi, Gm and Go of GCL in control, TBHQ-treated (C), and 740Y-P-treated mice (D). **E and F.** The hippocampal protein levels of NeuN in control, TBHQ-treated (E), and 740Y-P-treated mice (F) mice. In panels A–F, n = 9 mice per group. White arrow: 28-day-old $BrdU^+$ cells; white triangle: 28-day-old $BrdU^+/NeuN^+$ cells; red arrow: 28-day-old $BrdU^+/GFAP^+$ cells. Scale bar = 100 μm. 10× objective for the top row in A, B, C and D; 20× objective for the bottom row in A, B, C and D. $^{\$}P < 0.05$, $^{\$\$}P < 0.01$ vs. control (ip.); $^{*}P < 0.05$, $^{**}P<0.01$ vs. control (icv.)

Supplementary Fig. 6 Uncropped membrane western blot image with complete molecular weight markers used in the experiments presented in Supplementary Figure 5

Supplementary Fig. 7 Effects of ERK1/2 and PI3K activation on the synaptic function in the hippocampal DG region of control mice

A and D. The dendritic spine density in the DG of control, TBHQ-treated (A), and 740 Y-P-treated mice (D). Scale bar = 20 μm. Images of A and D were acquired using a ×20 objective or a ×40 objective for enlargement. **B and E.** The fluorescence intensity of PSD95 and Syn in the DG of control, TBHQ-treated (B), and 740 Y-P-treated mice (E). Scale bar = 100 μm. 10× objective for the top row, and 20× objective for the bottom row in B and E. **C and F.** The hippocampal protein levels of PSD95 and Syn in control, TBHQ-treated (C), and 740 Y-P-treated mice (F). In panels A–F, n = 9 mice per group. $^{\$\$}P < 0.01$ vs. control (ip.), $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control (icv.)

Supplementary Fig. 8 Effects of ERK and PI3K activation on the synaptic protein expression in the hippocampus of GSK mice

A. Uncropped membrane western blot image with complete molecular weight markers

used in the experiments presented in Figure 6 and Supplementary Figure 7. **B and C.** The fluorescence intensity of PSD95 and Syn in the DG of vehicle-treated, TBHQ-treated (B), and 740Y-P-treated GSK mice (C). $n = 9$ mice per group. Scale bar = 100 μm. 10× objective for the top row, and 20× objective for the bottom row in B and C. ^^$P < 0.01$ vs. GSK1016790A + vehicle (ip.), $^{\#\#}P < 0.01$ vs. GSK1016790A + vehicle (icv.)

Supplementary Fig. 9 Effect of TRPV4 activation on the hippocampal protein levels of BDNF and TrkB

A. The hippocampal protein levels of BDNF and TrkB in control and GSK mice. **B.** Uncropped membrane western blot image with complete molecular weight markers used in the experiments presented in A. $n = 9$ mice per group, **$P < 0.01$ vs. control