Fig. S1. Calcium signaling pathway in response to granisetron treatment with the IPA molecule activity predictor. Red and green symbols indicate proteins up- and down-regulation in granisetron treated mice, respectively. Orange and blue nodes indicate predictions of to be activated or inhibited in granisetron treated mice, respectively. The color intensity is proportional to the degree of fold change. Edges between the nodes are colored orange when leading to the activation of downstream proteins, blue when inhibiting downstream proteins. Yellow edges indicate that the states of downstream genes are inconsistent with the prediction based on previous findings.

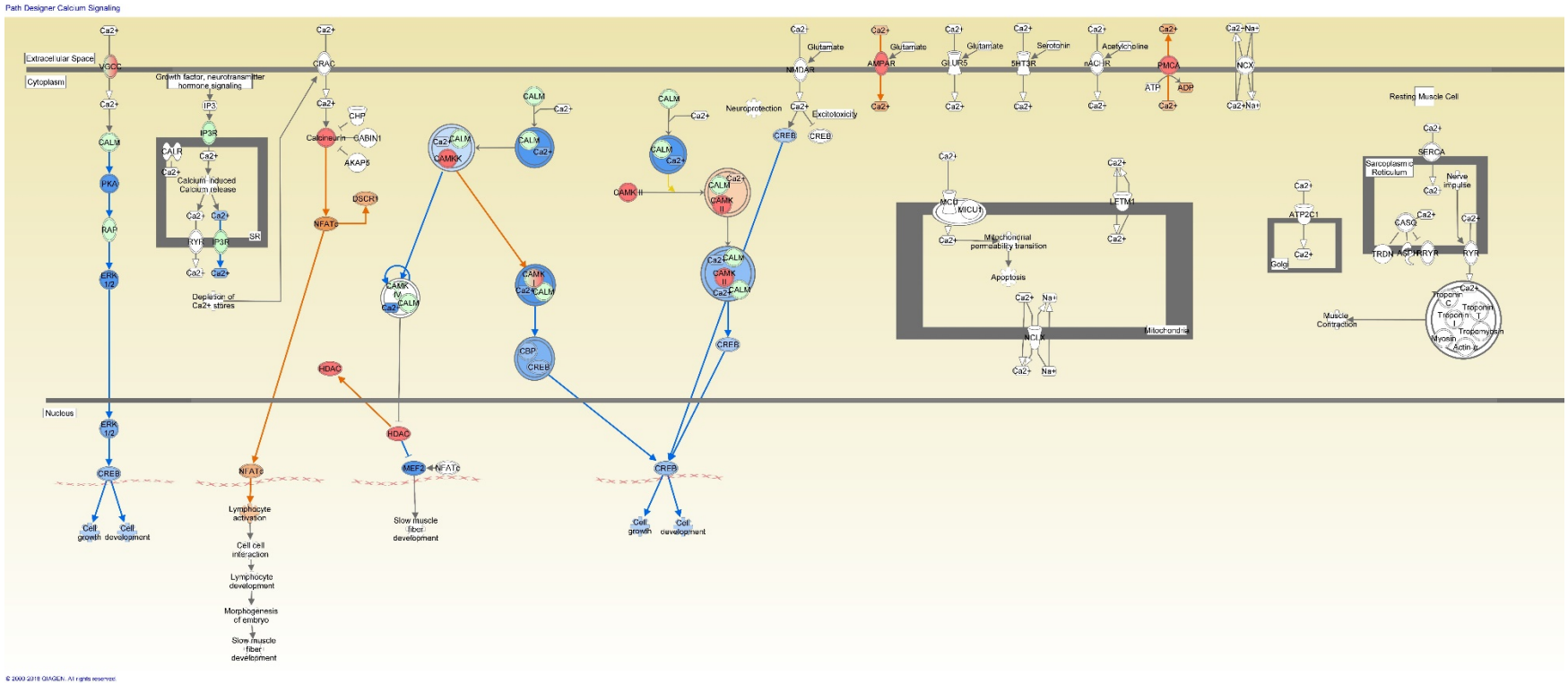

Fig. S2. Granisetron restored Ca^{2+} homeostasis by modulating CREB pathway in the brains of C57Bl/6J aged mice. Data are presented as mean±SEM of 5 mice in each group. Statistical analysis was determined by Student's t-test. *P<0.05 and **P<0.01 versus control group.

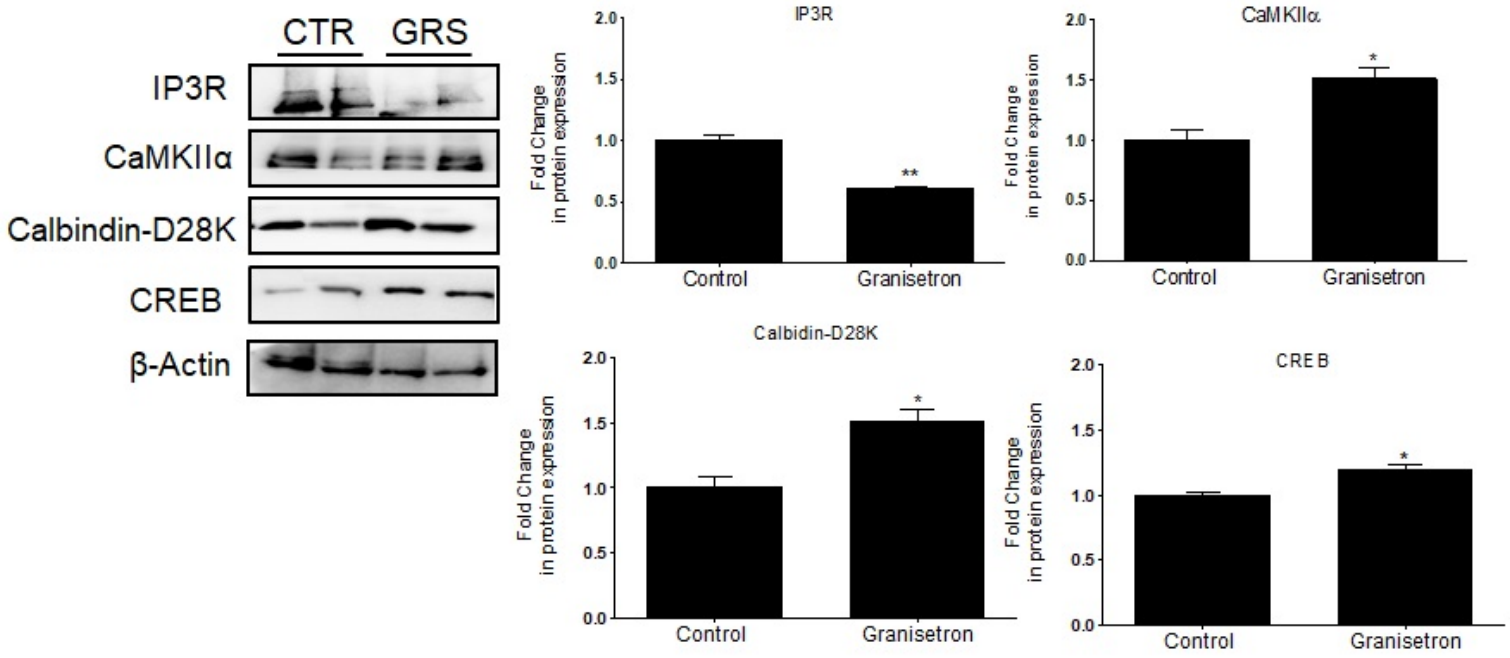

Fig. S3. Individual red and green channels for Panels D and E of Figure 4. These images are representative hippocampus sections stained with Thio-S (green) to detect Aβ plaques load and anti-collagen IV (red) to stain microvessels from control and granisetron treated groups.

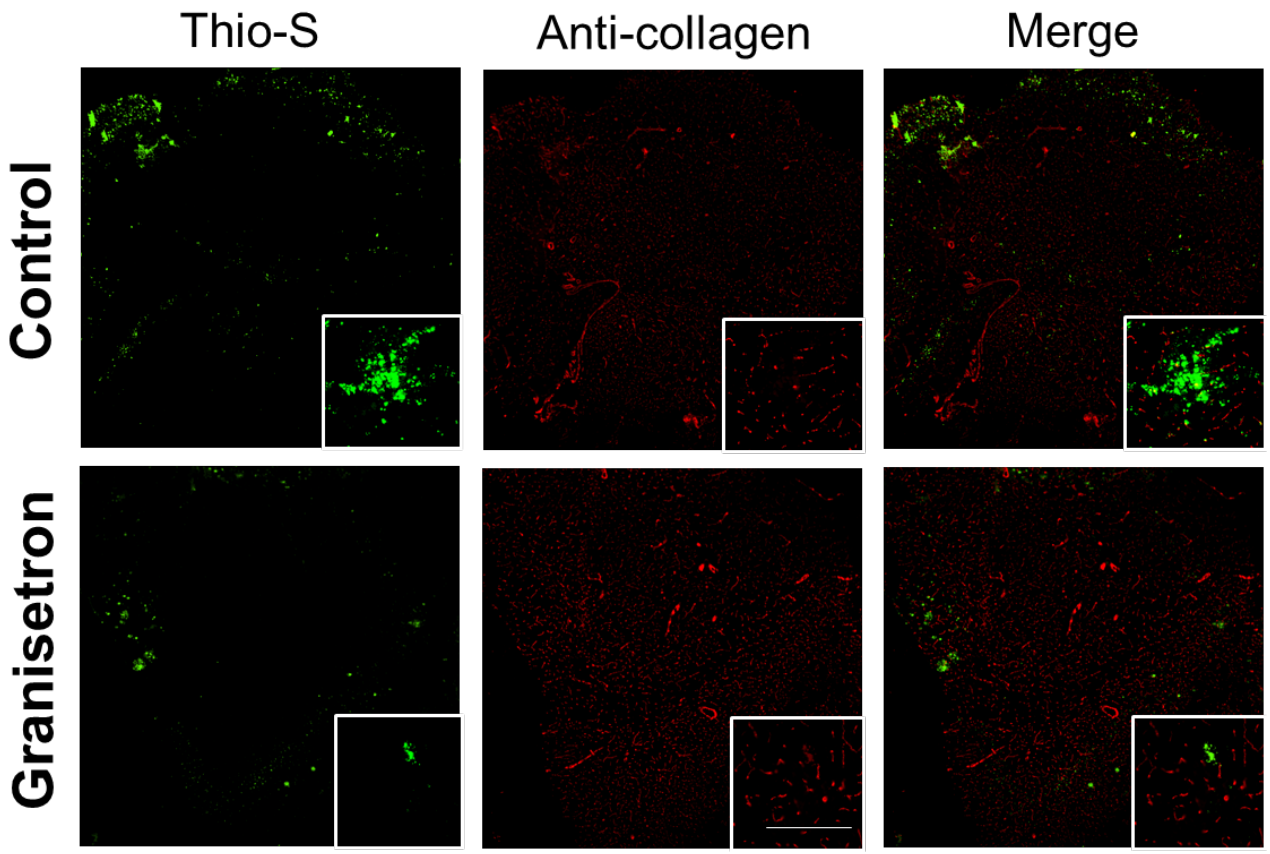

Fig. S4. Individual red and green channels for Panel A of Figure 6. These images are representative brain sections stained with 6E10 (green) antibody to detect Aβ, and anti-GFAP (red) antibody to detect activated astrocytes in control and granisetron treated groups.

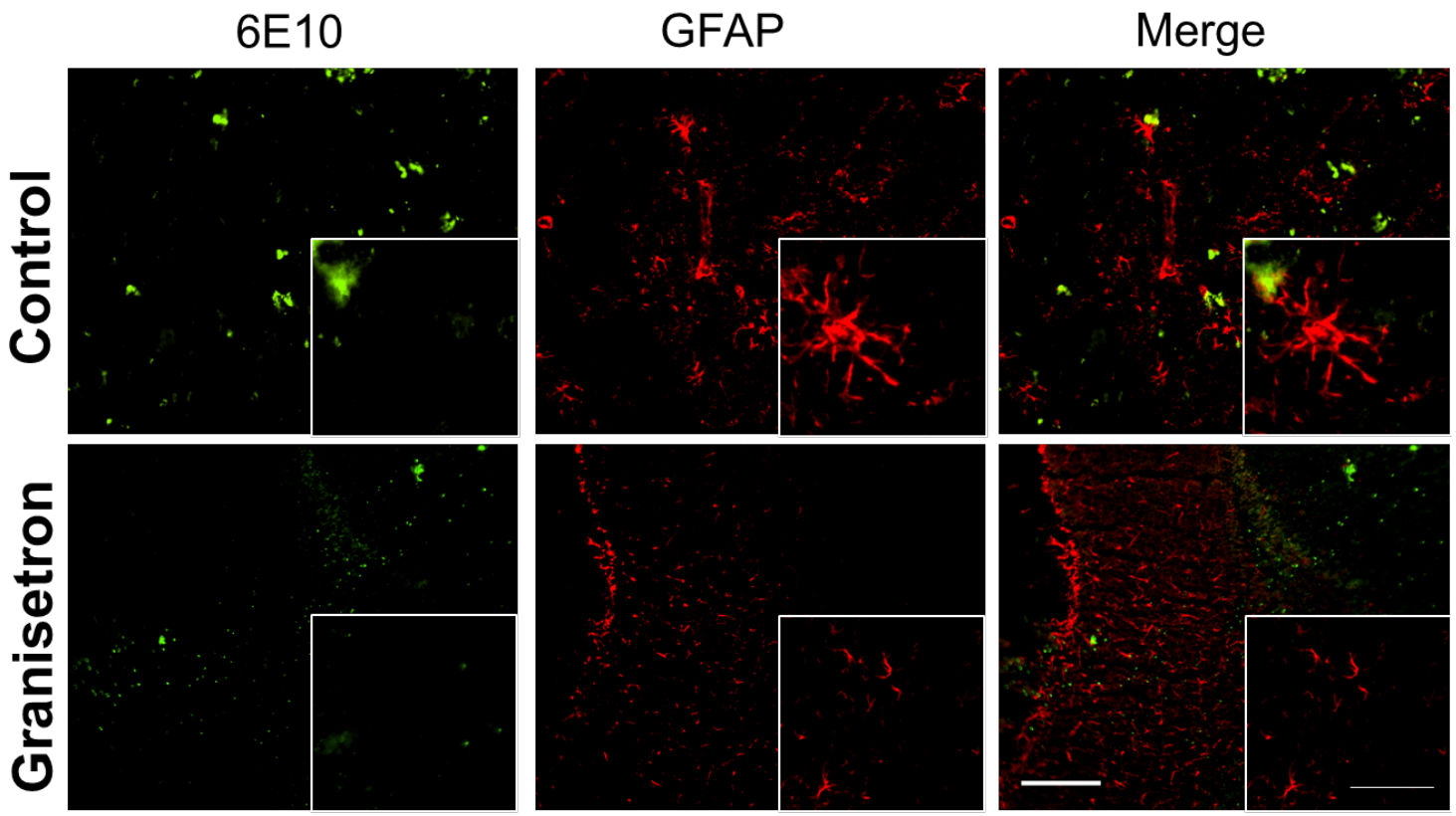

Table S1: A selection of significantly changed proteins in calcium pathway (P<0.05; fold change > 2) for granisetron effect in C57Bl/6J wild-type mice as determined by IPA analysis.

Symbol	Entrez Gene Name	Symbol in pathway	Experimental P-value	Experimental Fold Change	Expected	Location	Type
CACNA2D2	calcium voltage-gated channel auxiliary subunit alpha2 delta 2	CaCn	0.00009	-2.46		Plasma Membrane	ion channel
CACNG8	calcium voltage-gated channel auxiliary subunit gamma 8	CaCn	0.0036	2.42		Plasma Membrane	ion channel
CAMK4	calcium/calmodulin dependent protein kinase IV	CAMK IV	0.00012	-2.23	Up	Nucleus	kinase
CAMK2G	calcium/calmodulin dependent protein kinase II gamma	CAMK II	0.0009	2.22	Up	Cytoplasm	kinase
GNA13	G protein subunit-α13	Gα	0.0022	-2.16		Plasma Membrane	enzyme
GNAL	G protein subunit-αL	Gα	0.0017	-2.61		Cytoplasm	enzyme
GNB1	G protein subunit-β1	Gβ	0.00009	2.36		Plasma Membrane	enzyme
GRIA2	glutamate ionotropic receptor AMPA type subunit 2	iGLUR	0.0019	2.19	Up	Plasma Membrane	ion channel
GRID2	glutamate ionotropic receptor δ type subunit 2	iGLUR	0.00009	-5.08	Up	Plasma Membrane	ion channel
ITPR1	inositol 1,4,5-tris-phosphate receptor type 1	IP3R	0.00009	-2.88	Up	Cytoplasm	ion channel
PLCB3	phospholipase C β3	PLC	0.00028	-2.42	Up	Cytoplasm	enzyme
PLCB4	phospholipase C β4	PLC	0.00009	-2.45	Up	Cytoplasm	enzyme
PRKCA	protein kinase C α	PKC	0.0042	2.16	Up	Cytoplasm	kinase
PRKCD	protein kinase C δ	PKC	0.00011	2.25	Up	Cytoplasm	kinase
RPS6KA1	ribosomal protein S6 kinase A1	p90RSK	0.0031	-2.35	Up	Cytoplasm	kinase

Table S2: A selection of significantly changed proteins in CREB pathway (P<0.05; fold change > 2) for granisetron effect in C57Bl/6J wild-type mice as determined by IPA analysis

Symbol	Entrez Gene Name	Symbol in pathway	Experimental P-value	Experimental Fold Change	Expected	Location	Type
ATP2B1	ATPase plasma membrane Ca2+ transporting 1	PMCA	0.0016	2.17	Up	Plasma Membrane	transporter
CACNA2D2	calcium voltage-gated channel auxiliary subunit alpha2delta 2	VGCC	0.00009	-2.46	Up	Plasma Membrane	ion channel
CACNG8	calcium voltage-gated channel auxiliary subunit gamma 8	VGCC	0.0036	2.42	Up	Plasma Membrane	ion channel
CAMK4	calcium/calmodulin dependent protein kinase IV	CAMK IV	0.00012	-2.23	Up	Nucleus	kinase
CAMK2G	calcium/calmodulin dependent protein kinase II gamma	CAMK II	0.0009	2.22	Up	Cytoplasm	kinase
CAMKK1	calcium/calmodulin dependent protein kinase kinase 1	CAMKK	0.00065	2.28	Up	Cytoplasm	kinase
GRIA2	glutamate ionotropic receptor AMPA type subunit 2	AMPAR	0.0019	2.19	Up	Plasma Membrane	ion channel
HDAC6	histone deacetylase 6	HDAC	0.0024	2.19		Nucleus	transcription regulator
ITPR1	inositol 1,4,5-trisphosphate receptor type 1	IP3R	0.00009	-2.88	Up	Cytoplasm	ion channel
PPP3CA	protein phosphatase 3 catalytic subunit α	CALM	0.0059	2.2	Up	Cytoplasm	phosphatase
RAP2B	RAP2B, member of RAS oncogene family	RAP	0.0032	-2.18	Up	Plasma Membrane	enzyme