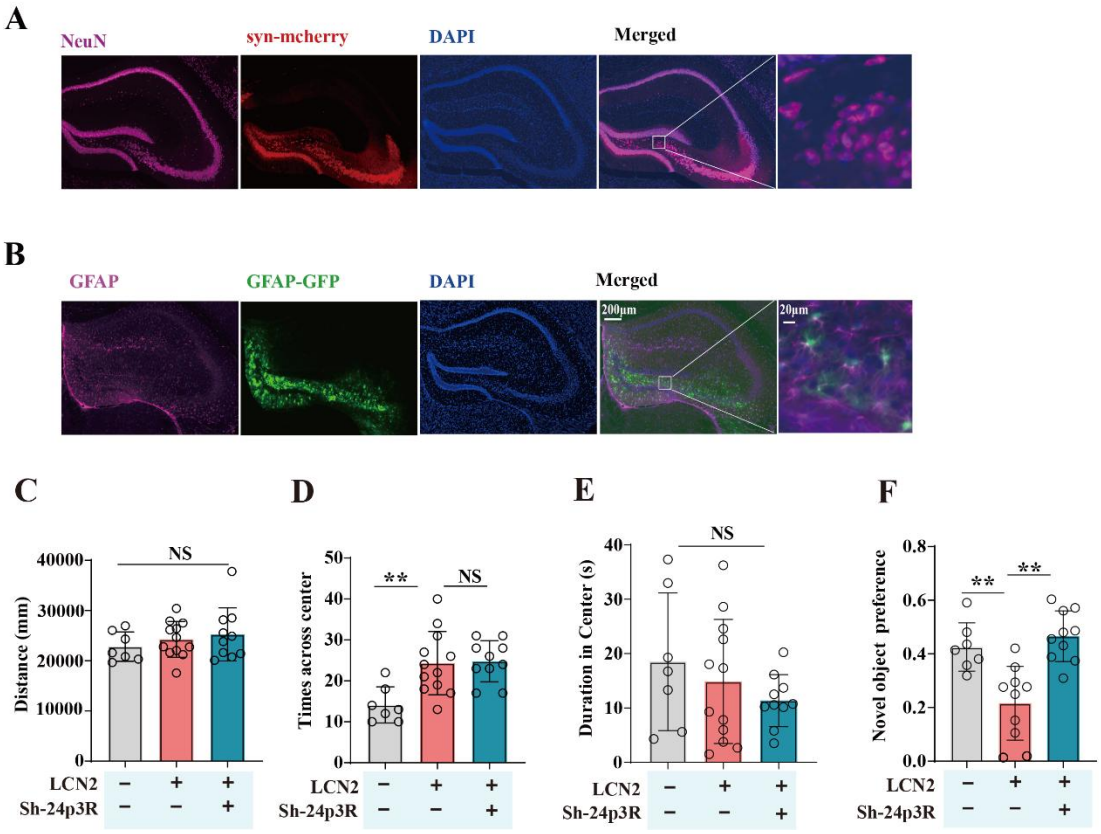
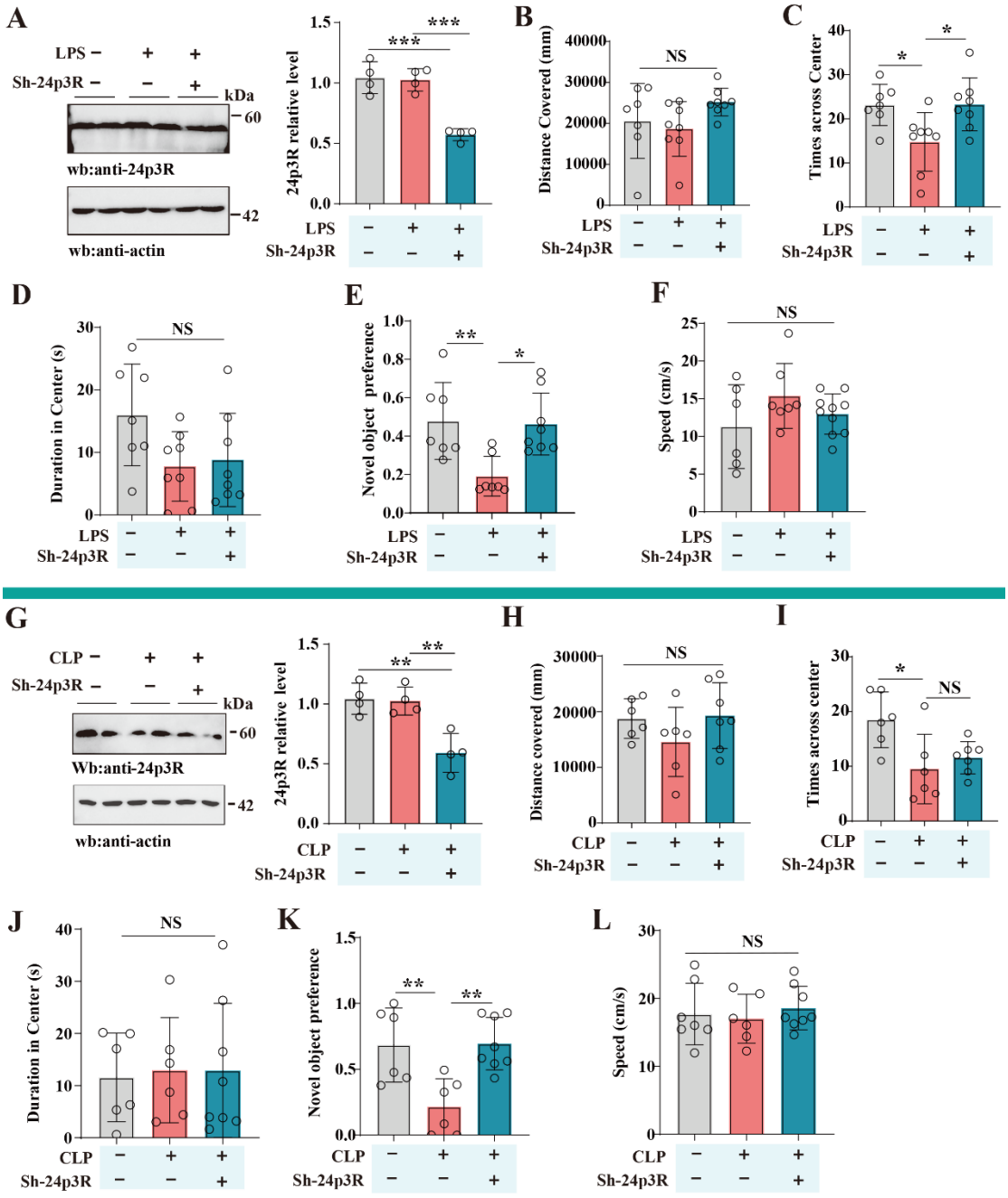


Supplementary Figure 1. Downregulation of Neuronal 24p3R Protects Against Astrocyte-Derived LCN2-induced Cognitive Dysfunction

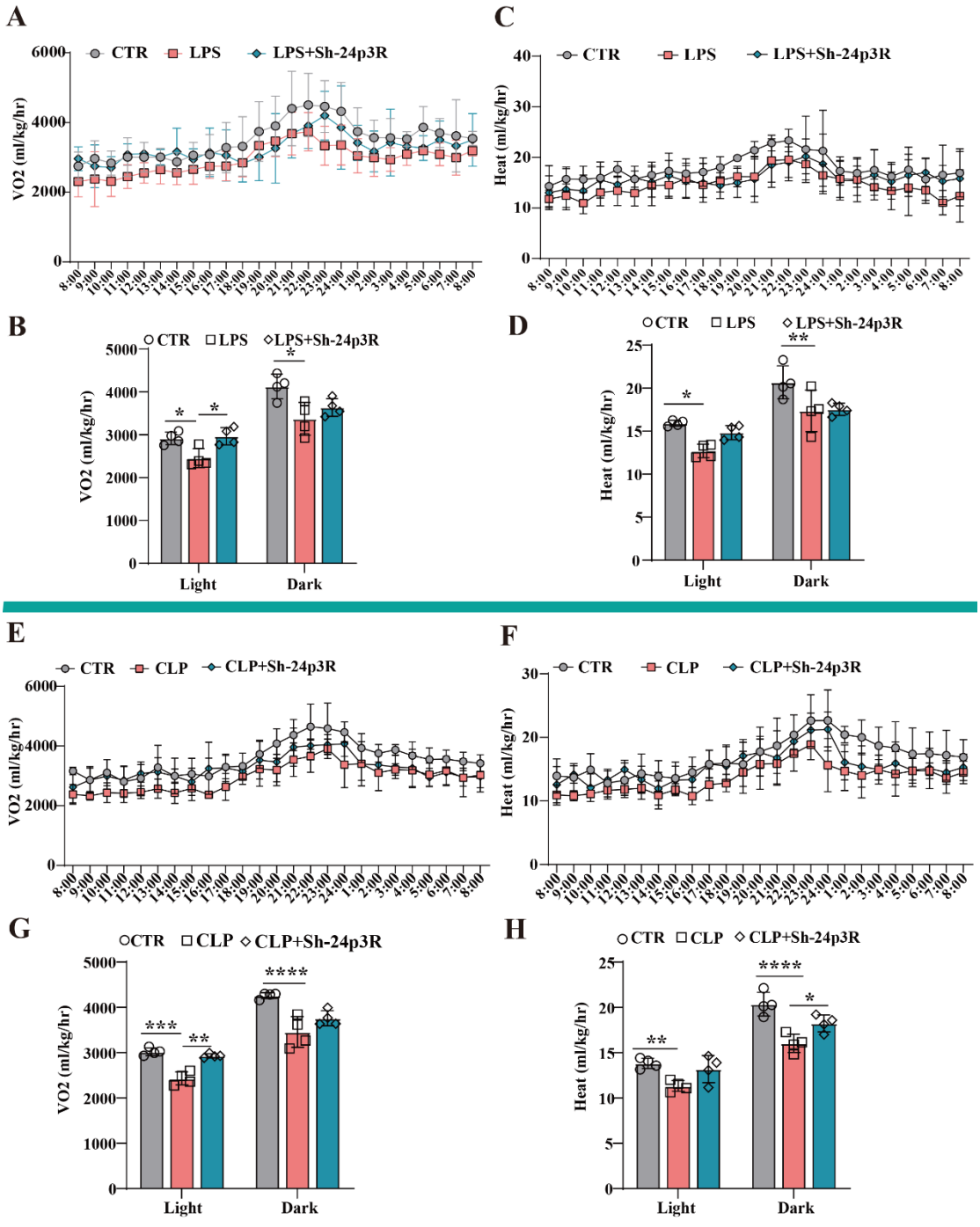
mCherry from the AAV-Syn virus colocalizes exclusively with the neuronal marker NeuN(**A**) and GFP from the AAV-GFAP virus colocalizes specifically with the astrocytic marker GFAP (**B**). The open-field test measured the total distance covered **(C),** times across center **(D)** and duration in center **(E)** in the three groups (n=7–12). **(F)** The novel object recognition test measured the preference for the novel object (n=7–12). Data are presented as Mean ± SD. One-way ANOVA followed by Tukey's multiple comparisons test was used for statistical analysis. **p < 0.01, versus LCN2 group.



Supplementary Figure 2. Downregulation of Neuronal 24p3R Alleviates Sepsis-associated Cognitive Impairments

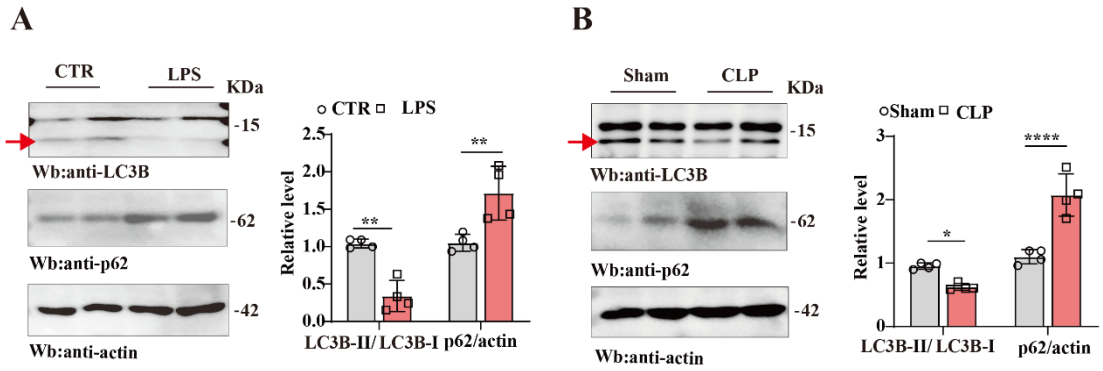
(A) Brain tissues (hippocampus DG region) from Control, LPS, and LPS+Sh-24p3R mice were homogenized, and 24p3R protein levels were detected by immunoblotting (actin as a loading control), and quantitative analysis of 24p3R expression was conducted (n = 4). **(B-D)** The open-field test measured the total distance covered **(B),** times across center **(C),** and duration in center **(D)** in the three groups (n=7–8). **(E)** The novel object recognition test measured the preference (n=7–8). **(F)** The movement speed in the Barnes maze test was recorded. **(G)** Brain tissues (hippocampus DG region) from Control, CLP, and CLP+Sh-24p3R mice were homogenized, and 24p3R protein levels were detected by immunoblotting (actin as a loading control), and quantitative

analysis of 24p3R expression was conducted (n=4). **(H-J)** The open-field test measured the total distance covered **(H)** times across center **(I)** and duration in center **(J)** in the three groups (n = 6–8). **(K)** The novel object recognition test measured the preference, (n=6–8). (**L**) Barnes maze test: speed was recorded in CLP model. Data are presented as Mean ± SD. One-way ANOVA followed by Tukey's multiple comparisons test was used for statistical analysis. *p < 0.05, **p < 0.01, ***p < 0.001, versus sepsis group.



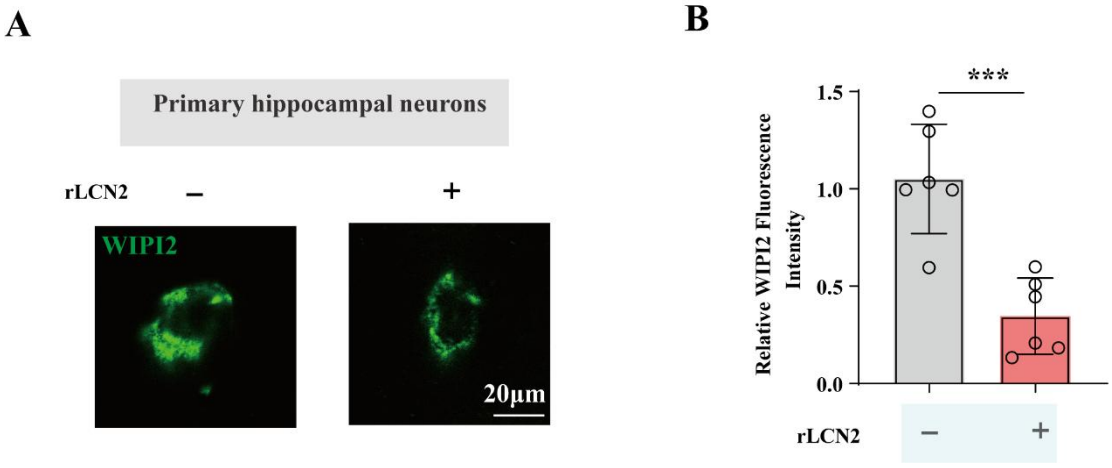
Supplementary Figure 3. Downregulation of Neuronal 24p3R Alleviates Sepsis-induced Energy Metabolism Dysfunction

Respiratory energy and general behavior monitoring were tested. **(A)** VO_2 was tested in 24 h of three groups in Control, LPS, and LPS+Sh24p3R groups. **(B)** Quantitative analysis of the VO_2 of Light and Dark (n=4). **(C)** The heat was tested for 24h. **(D)** Quantitative analysis of the heat of Light and Dark (n=4) in Control, LPS, LPS+Sh-24p3R groups. **(E)** VO_2 was tested in 24 h of three groups in Control, CLP, and CLP+Sh24p3R groups. **(G)** Quantitative analysis of the VO_2 of Light and Dark (n = 4). **(F)** The heat was tested for 24 h. **(H)** Quantitative analysis of the heat of Light and Dark (n=4) in Control, CLP, CLP+Sh-24p3R groups. Data are presented as Mean ± SD. One-way ANOVA followed by Tukey's multiple comparisons test was used for statistical analysis. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 versus Model group.



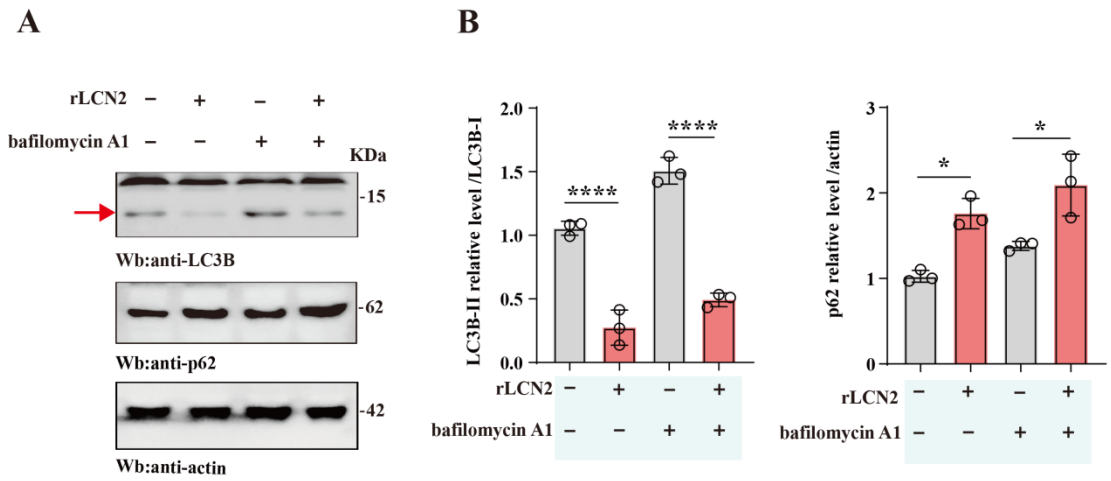
Supplementary Figure 4. Sepsis could impair autophagy in hippocampus

Brain tissues (hippocampus DG region) were homogenized, LC3B and p62 levels were detected by immunoblotting. Quantitative analyses of LC3-II and p62 levels were conducted in LPS model (A) and in CLP model (B) (n = 4). Data are presented as Mean ± SD, two-way ANOVA followed by Sidak's multiple comparisons test was used for statistical analysis. *p < 0.05, **p < 0.01, ****p < 0.0001 versus Model group.



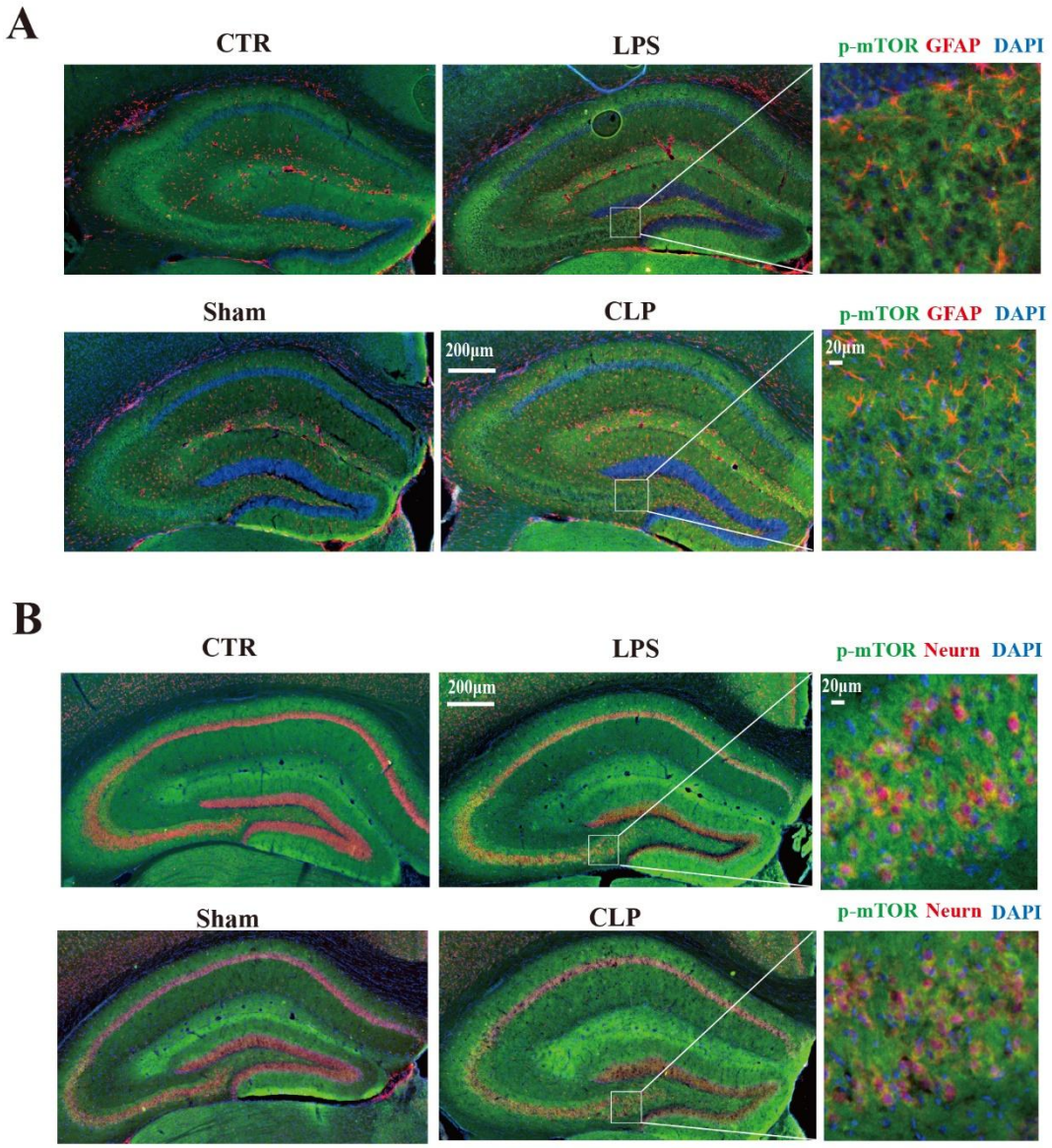
Supplementary Figure 5. LCN2 Inhibits the Initiation of Neuronal Autophagy

Primary neurons were treated with rLCN2. The WIPI2 antibody was used to measure initiation of neuronal autophagy (scale bar, 20μm)，(A), WIPI2 relative fluorescence intensity in primary neurons (n=6), (B). Data is presented as Mean ± SD. One-way ANOVA followed by Tukey's multiple comparisons was used for statistical analysis. ***p < 0.001 versus Model group.



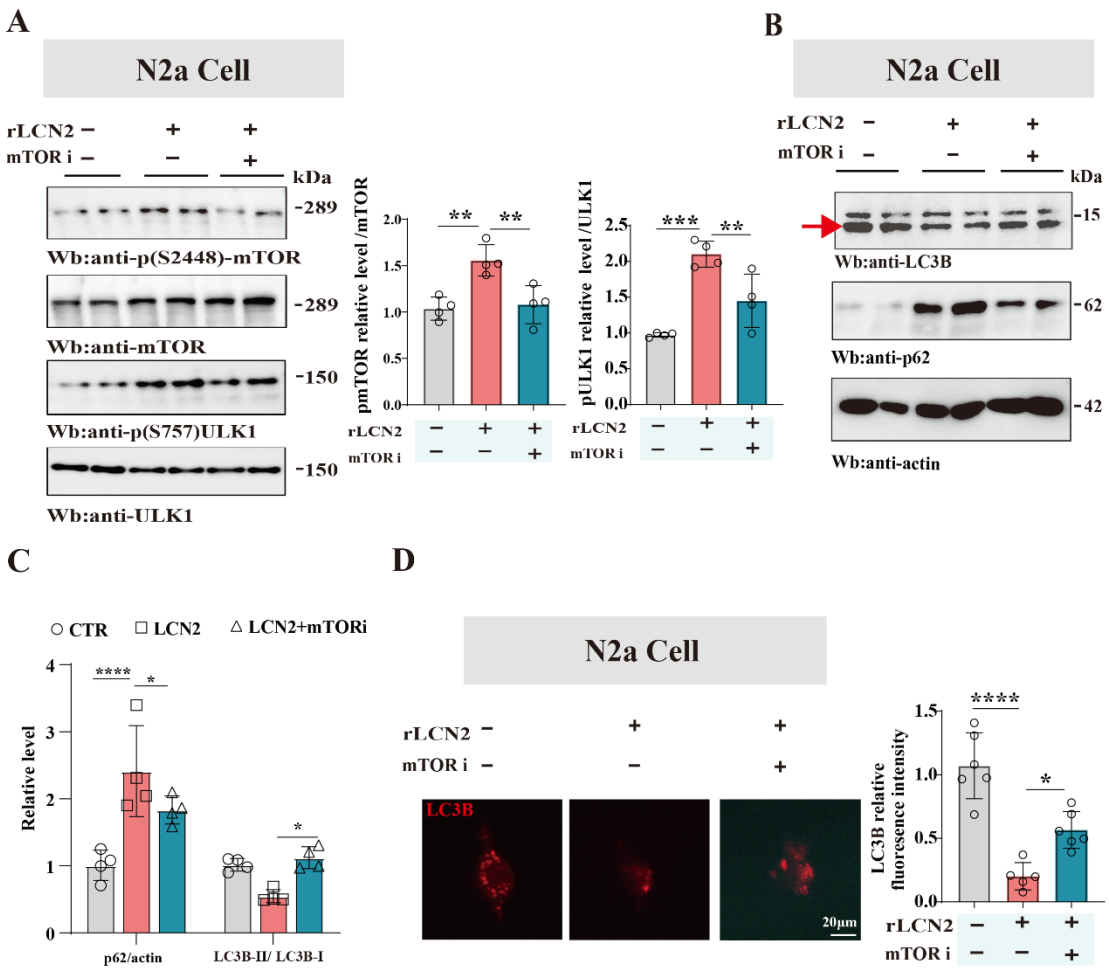
Supplementary Figure 6. LCN2 Impairs Initiation of Neuronal Autophagy

(A) Primary neurons were treated with rLCN2 in the presence or absence of bafilomycin A1 (Baf A1,100 nM, 6h). **(B)** LC3B and p62 levels were detected by immunoblotting, and quantitative analysis of LC3-II and p62 levels were conducted. (n=3). Data is presented as Mean±SD. One-way ANOVA followed by Tukey's multiple comparisons was used for statistical analysis. *p < 0.05, ****p < 0.0001 versus Model group.



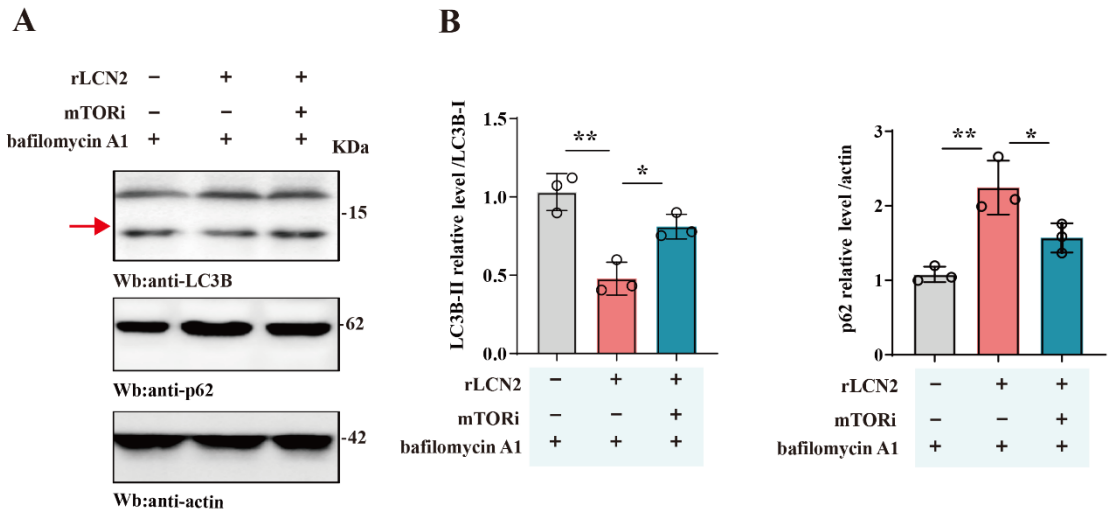
Supplementary Figure 7. mTORC1 Signaling in Septic Mice Predominantly Colocalizes with NeuN

Immunostaining was used to test the phosphorylated-mTOR(Ser2448) in septic mice colocalizes predominantly with the neuronal marker GFAP (**A**) and the astrocytic marker NeuN (scale bar, 200μm) (**B**).



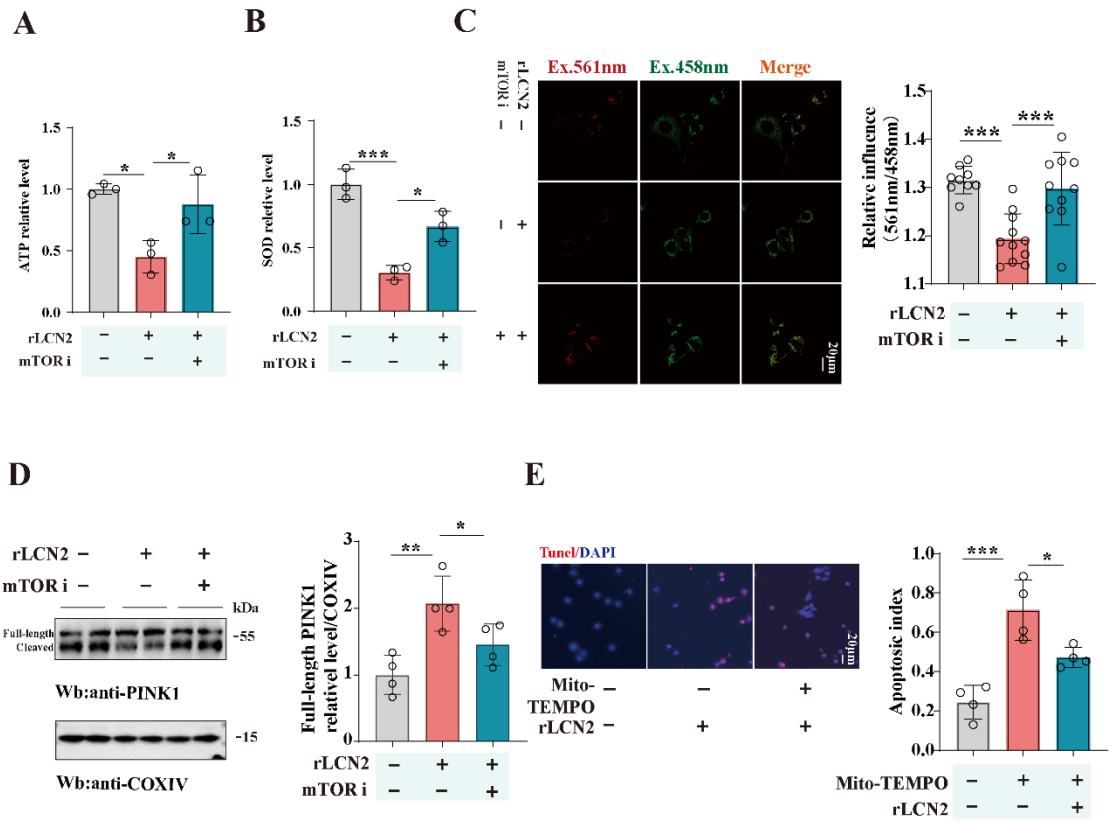
Supplementary Figure 8. mTOR Inhibition Attenuates LCN2-Induced Suppression of Autophagy in N2a Cell

(A) N2a cells were treated with rLCN2 with or without mTOR inhibitor rapamycin. N2a cells were homogenized, and p(ser2448)-mTOR/mTOR p(ser757)-ULK1/ULK1 were detected by immunoblotting; actin was used as a loading control. Quantitative analysis of p-mTOR/mTOR, p-ULK1/ULK1 relative levels were conducted (n=4). **(B)** LC3B, P62 were detected by immunoblotting. **(C)** Quantitative analysis of LC3B, P62 relative levels were conducted (n=4). **(D)** The LC3B antibody was used to measure autophagy (scale bar, 20μm), LC3B relative fluorescence intensity in N2a cell (n=5–6). Data are presented as Mean ± SD. One-way ANOVA followed by Tukey's multiple comparisons test was used for statistical analysis. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 versus LCN2 group.



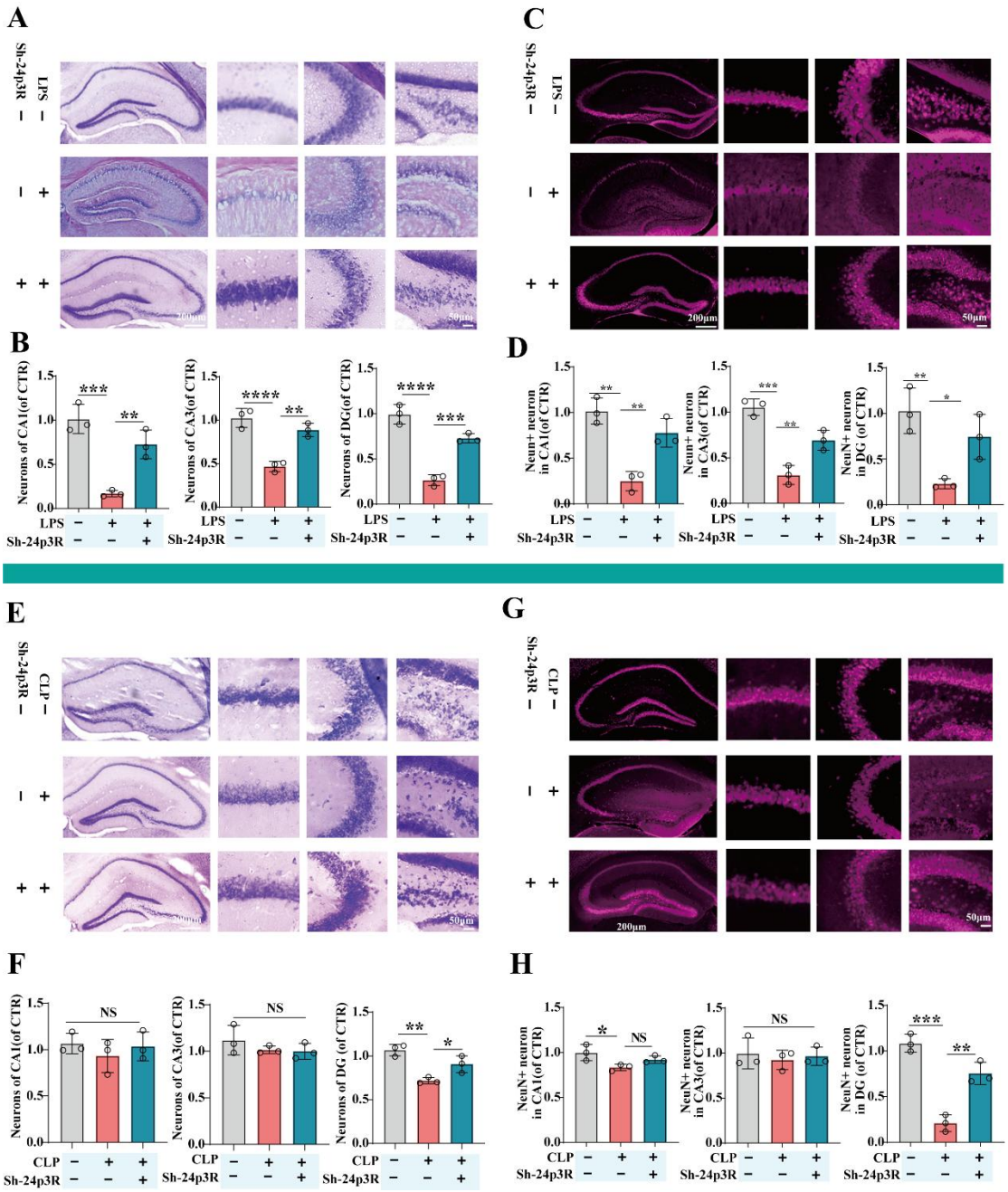
Supplementary Figure 9. mTOR Inhibition Alleviates Autophagic Flux Suppressed by LCN2.

(A) Primary neurons were treated with rLCN2 and mTORi in the presence of bafilomycin A1 (Baf A1,100 nM, 6h). **(B)** LC3B and p62 levels were detected by immunoblotting, and quantitative analysis of LC3B-II and p62 levels were conducted. (n=3). Data is presented as Mean ± SD. One-way ANOVA followed by Tukey's multiple comparisons was used for statistical analysis. *$p < 0.05$, **$p < 0.01$ versus Model group.



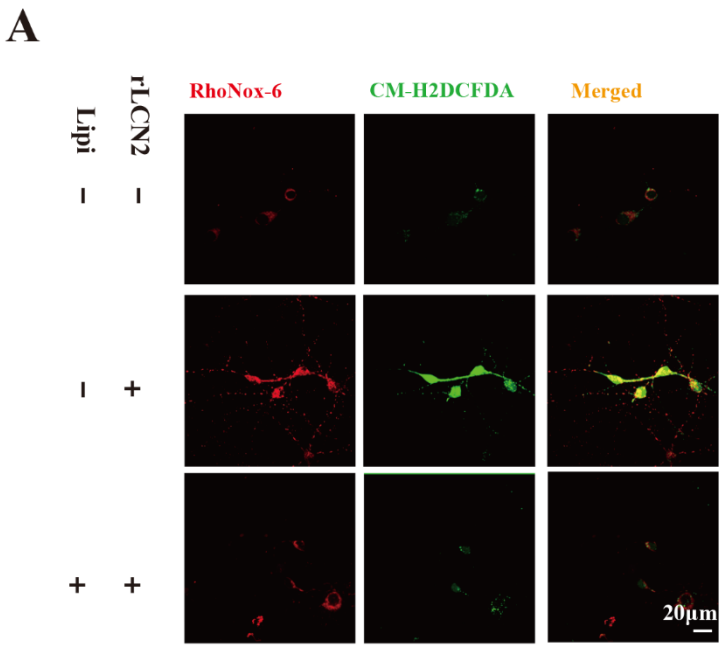
Supplementary Figure 10. mTOR Inhibition Alleviates LCN2-Induced Neuronal Damage

The ATP production **(A)** and the total SOD activity **(B)** were tested in the hippocampus of three groups (n = 3). **(C)** Confocal microscopy images of primary neurons in Control, LCN2, and LCN2+Sh-24p3R groups with mito-Keima,Scale bar, 20μm **(C). (D)** PINK1 protein levels were detected by immunoblotting. Both full-length (~63–66 kDa) and cleaved (~52–55 kDa) forms of PINK1 are shown. Quantitative analysis of the full-length PINK1 levels was performed (n = 4). **(E)** Primary neurons were treated with the mitochondrial antioxidant Mito-TEMPO in the presence of LCN2, and TUNEL staining was performed to assess neuronal apoptosis.. Data is presented as Mean ± SD. One-way ANOVA followed by Tukey's multiple comparisons was used for statistical analysis. *p < 0.05, **p < 0.01, ***p < 0.001 versus LCN2 group.



Supplementary Figure 11. Downregulation of Neuronal 24p3R Improves Sepsis-induced Neuronal Loss

(A, E) Representative images of Nissl's staining of brain slices. **(B, F)** Quantitative analysis of neuronal numbers in the CA1, CA3, DG regions (n=3). **(C, G)** Representative images of NeuN staining of brain slices. **(D, H)** Quantitative analysis of NeuN+ number of CA1, CA3, DG regions (n=3). One-way ANOVA followed by Tukey's multiple comparisons was used for the three groups. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, versus sepsis group.



Supplementary Figure 12. Neuronal Loss Involves Ferroptotic Cell Death

Primary neurons were treated with LCN2 in the presence or absence of Liproxstatin-1 (22 nM; MCE, HY-12726), dual staining with RhoNox-6 (for Fe^{2+} detection) and CM-H2DCFDA (for ROS detection) was performed **(A)**.