Supplementary figures and legends

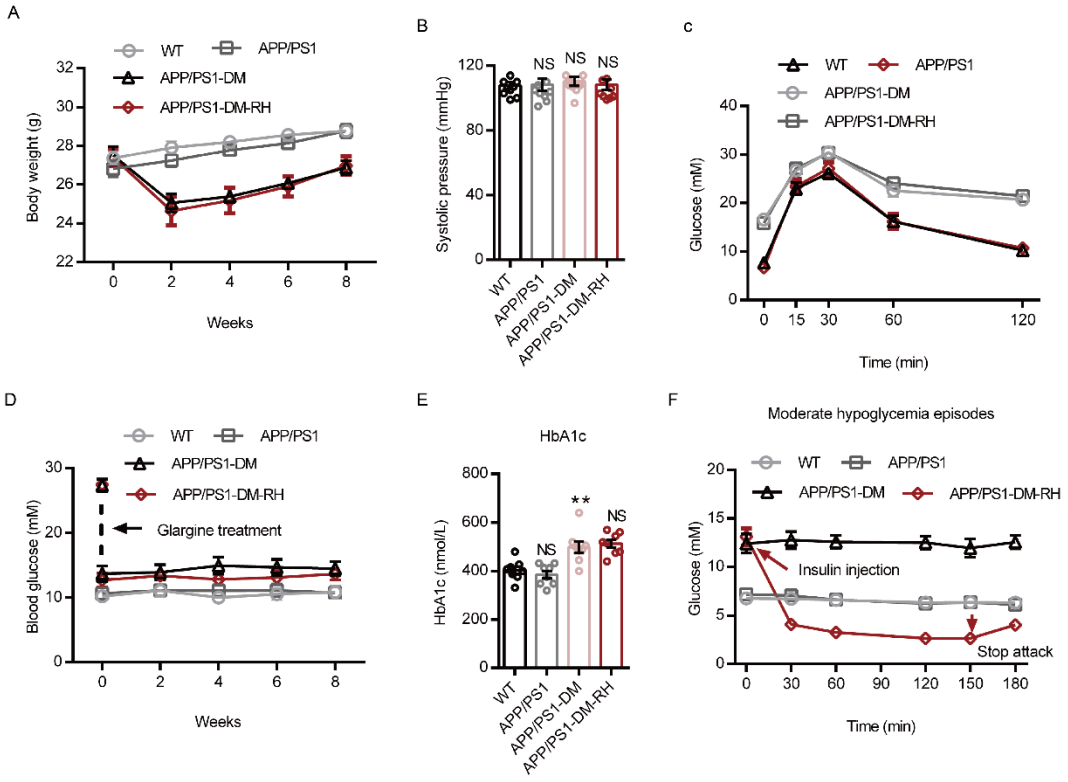


Figure S1, Related to Figure 1. The metabolic effects of RH. (A) Changes of body weight (n=10). **(B)** Blood pressure after completing RH treatment (n=10). **(C)** Intraperitoneal Glucose Tolerance Test (IPGTT) in mice after completing RH treatment (n=6). **(D)** The random blood glucose among 8 weeks of RH treatment (n=10). Glargine treatment, diabetic mice received glargine once a day. **(E)** The HbA1c in serum of mice (n=8 for each group). **(F)** Changes of blood glucose during a moderate hypoglycemia episode induced by insulin injection (n=10).The data are expressed as the mean ± SEM. Statistical significance was assessed using a one-way ANOVA (panel B and E) or two-way ANOVA (panel A, C and D) followed by Dunnett's multiple comparisons test. $^{***}P<0.001$, APP/PS1-DM VS APP/PS1; WT VS APP/PS1, APP/PS1-DM-RH VS APP/PS1-DM, no significant difference (NS).

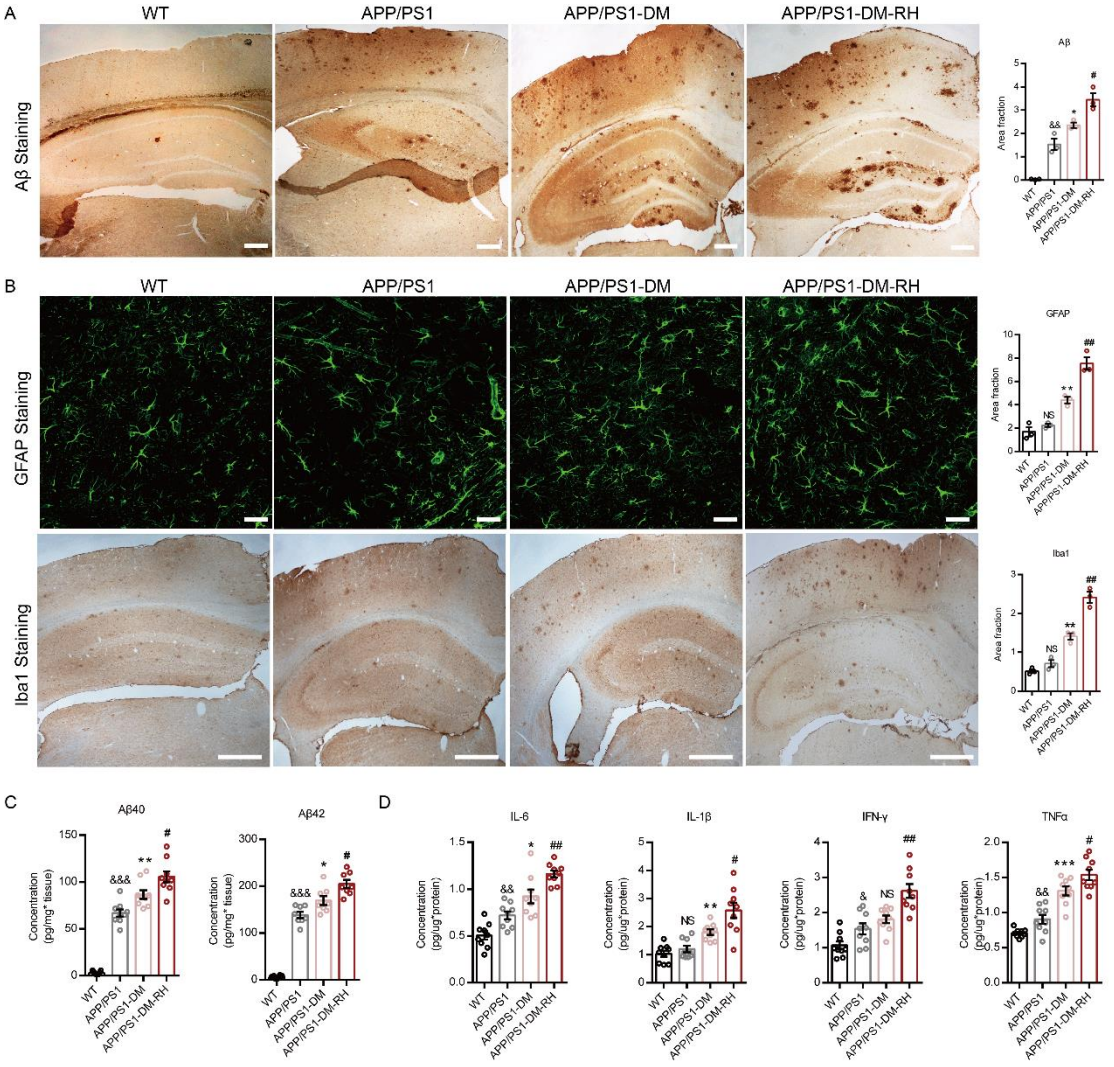


Figure S2, Related to Figure 2. AD-type pathology in hippocampus. (A) Immunohistochemical staining for Aβ deposition in hippocampus. Quantitation is shown on the right (n=3 mice for each group). **(B)** Immunofluorescent staining for GFAP (astrocyte marker, *top*) and immunohistochemical staining for Iba1 (microglia marker, *bottom*). Quantitation is shown on the right (n=3 mice for each group). **(C)** ELISA of Aβ40 and Aβ42 concentration in hippocampal homogenates (n=9 mice for each group). **(D)** Quantification of IL-6, IL-1β, IFN-γ and TNF-α by ELISA in hippocampal homogenates (n=9 mice for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's T test (panel A-C) one-way ANOVA followed by Dunnett's multiple comparisons test (panel D). $^{\&}P<0.05$ and $^{\&\&}P<0.05$, WT VS APP/PS1; $^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.01$, APP/PS1-DM VS APP/PS1; $^{\#}P<0.05$ and $^{\#\#}P<0.01$, APP/PS1-DM-RH VS APP/PS1-DM; NS, no significant difference.

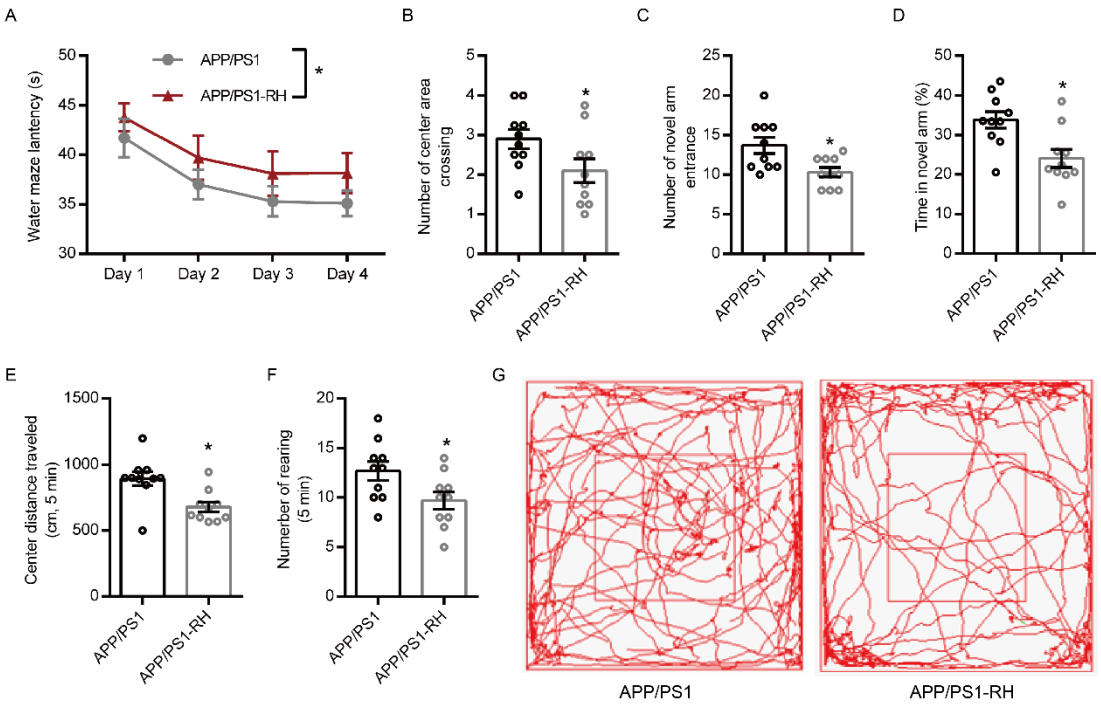


Figure S3, Related to Figure 3. RH impaired the performances of non-diabetic APP/PS1 mice in behavioral tests. (A and B) Morris water-maze test. Escape latency during platform trials (A) and number of center area crossing (B) in probe test. APP/PS1-RH, APP/PS1 mice received 8 weeks of RH treatment. **(C and D)** Novel arm entrance (C) and time spend in the novel arm (D) in Y-maze test. **(E-G)** Distance traveled in center area (E), number of rearing (F), and representative tracing graphs in open field test (G). n=10 for each group. The data are expressed as the mean ± SEM. Statistical significances were assessed using two-way ANOVA (panel A) or unpaired student's T test (panel B-F). $^{*}P<0.05$, $^{**}P<0.01$ versus APP/PS1.

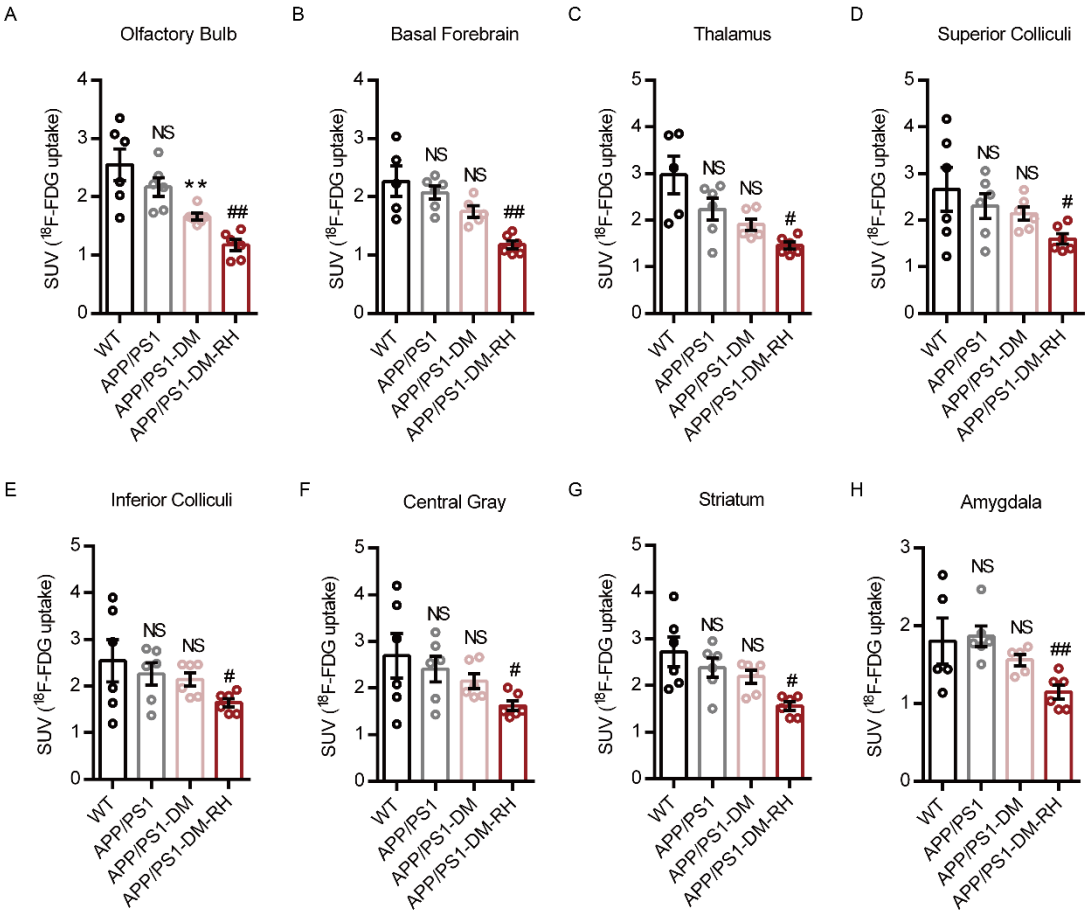


Figure S4, Related to Figure 5. ^{18}F-FDG uptake in brain. (A-H) 18F-FDG uptake in different brain regions measured by PET/CT scanning (n=6 mice for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's T test. $^{**}P<0.01$, APP/PS1-DM VS APP/PS1; $^{\#}P<0.05$ and $^{\#\#}P<0.01$, APP/PS1-DM-RH VS APP/PS1-DM; WT VS APP/PS1, no significant difference (NS).

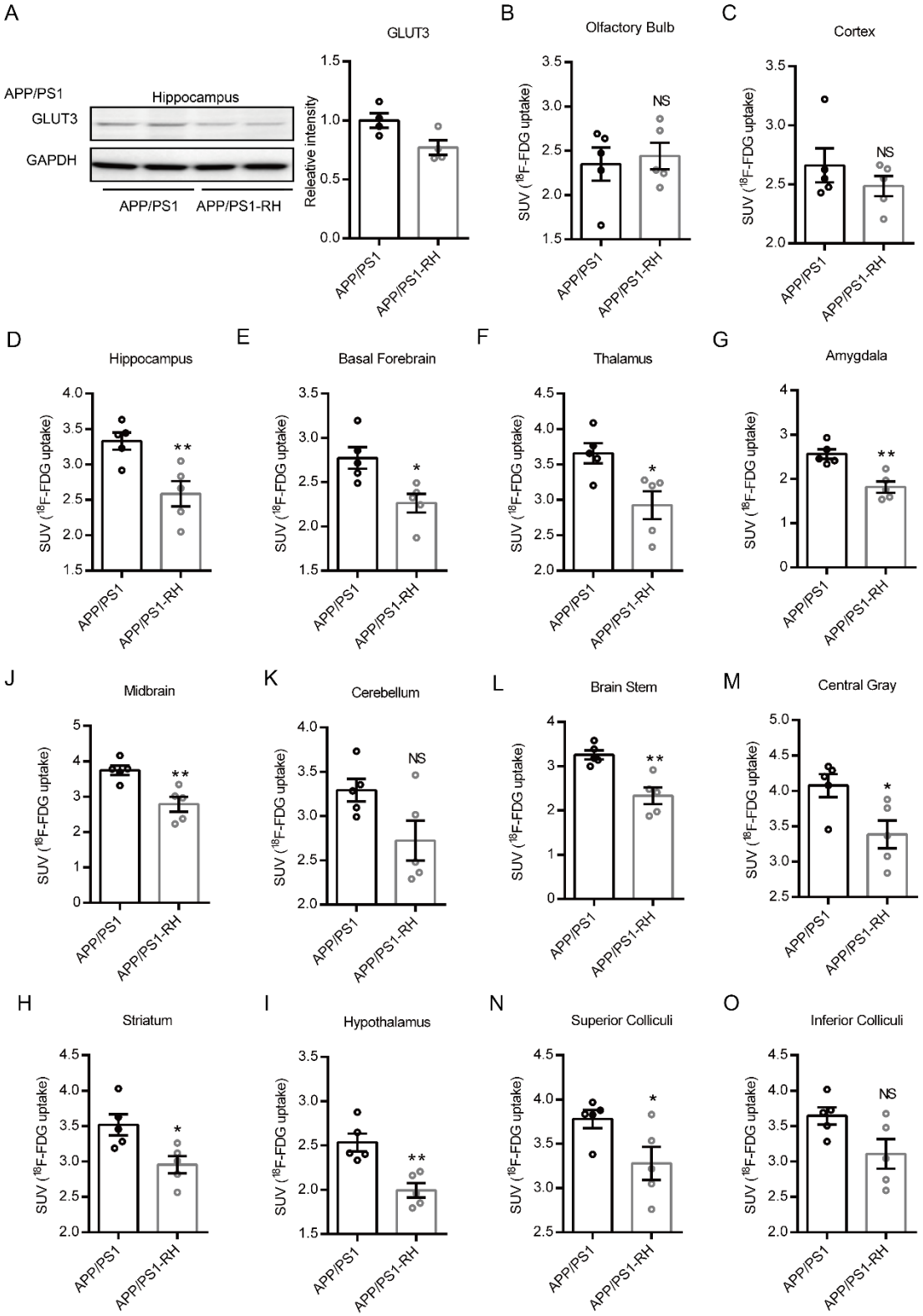


Figure S5, Related to Figure 5. RH reduced hippocampal GLUT3 expression and brain ^{18}F-FDG uptake in non-diabetic APP/PS1 mice. (A) Western-blotting and quantitative data shown the expression of hippocampal GLUT3 (n=4 mice for each group). APP/PS1-RH, APP/PS1 mice received 8 weeks of RH treatment. **(B-O)** The standard uptake value (SUV) of ^{18}F-FDG in brain area (n=5 mice for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's T test. *$P<0.05$,**$P<0.01$; NS, no significant difference (NS).

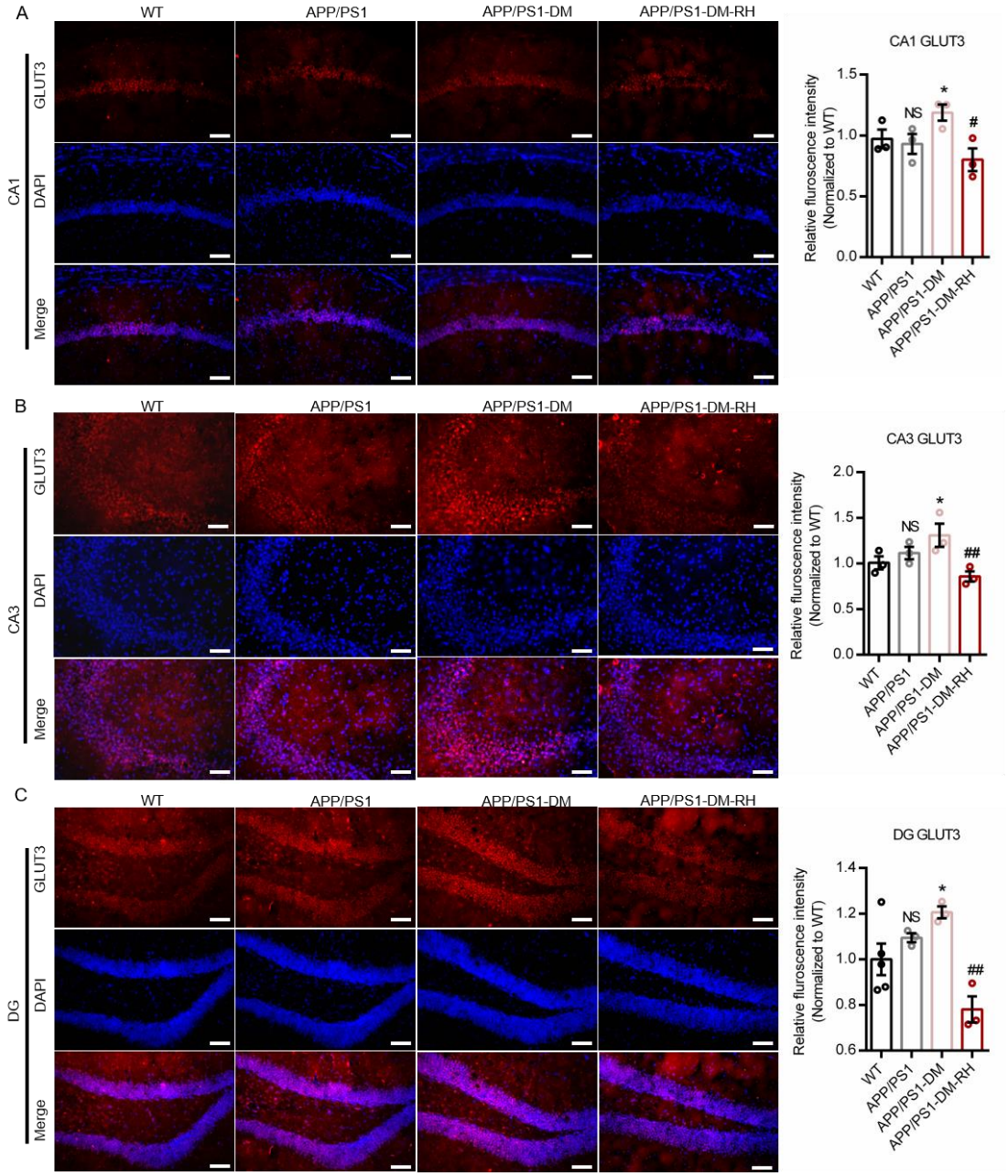


Figure S6, related to Figure 6. GLUT3 expression in hippocampus. (A-C) Representative images of GLUT3 (red) and DAPI (blue) immunostaining in hippocampal area of CA1 (A), CA3 (B) and DG (C) from WT, APP/PS1, APP/PS1-DM, and APP/PS1-DM-RH mice. Scale bar, 100μm. Quantitative results are showed in the right (n=3 mice for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's T test $^{*}P<0.05$, APP/PS1-DM VS APP/PS1; $^{\#}P<0.05$, $^{\#\#}P<0.01$ and $^{\#\#\#}P<0.001$, APP/PS1-DM VS APP/PS1-DM-RH; WT VS APP/PS1, no significant difference (NS).

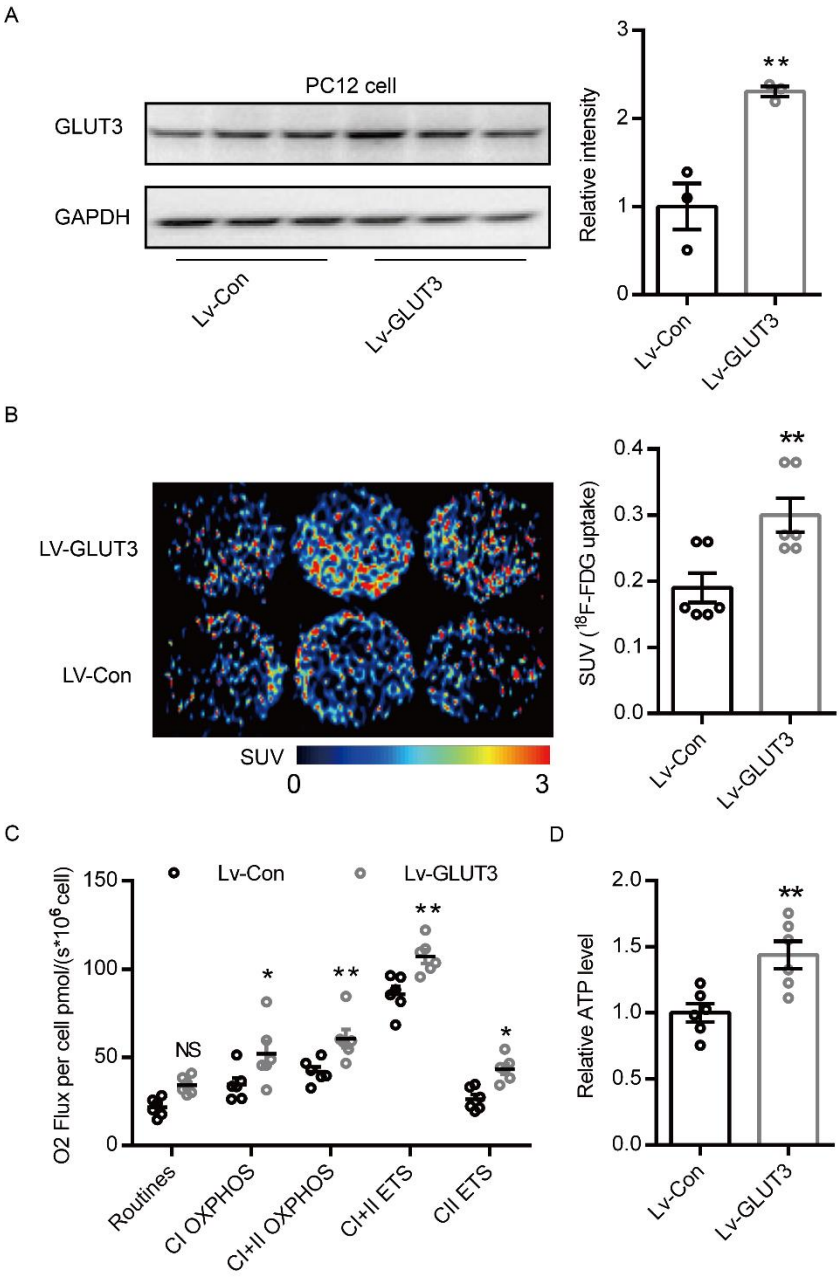


Figure S7, Related to Figure 6. GLUT3 over-expression in PC12 improves mitochondrial function in PC12 cells. (A) Western blotting to assess GLUT3 overexpression in PC12 cells. Lv-Con, PC12 cells infected with empty recombinant lentiviral vector; Lv-GLUT3, PC12 cells infected with GLUT3 recombinant lentiviral vector. **(B)** Representative image and quantitative results show the ^{18}F-FDG uptake in PC12 cells with or without GLUT3 overexpression (n=6 for each group). **(C)** High-resolution respirometry measured the oxygen consumption capacity of mitochondria in PC12 cells (n=6 for each group). **(D)** ATP content in PC12 cells (n=6 for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's t test (panel A,B and D) or two-way ANOVA followed by Sidak's multiple comparisons test (panel C). *$P<0.05$, **$P<0.01$.

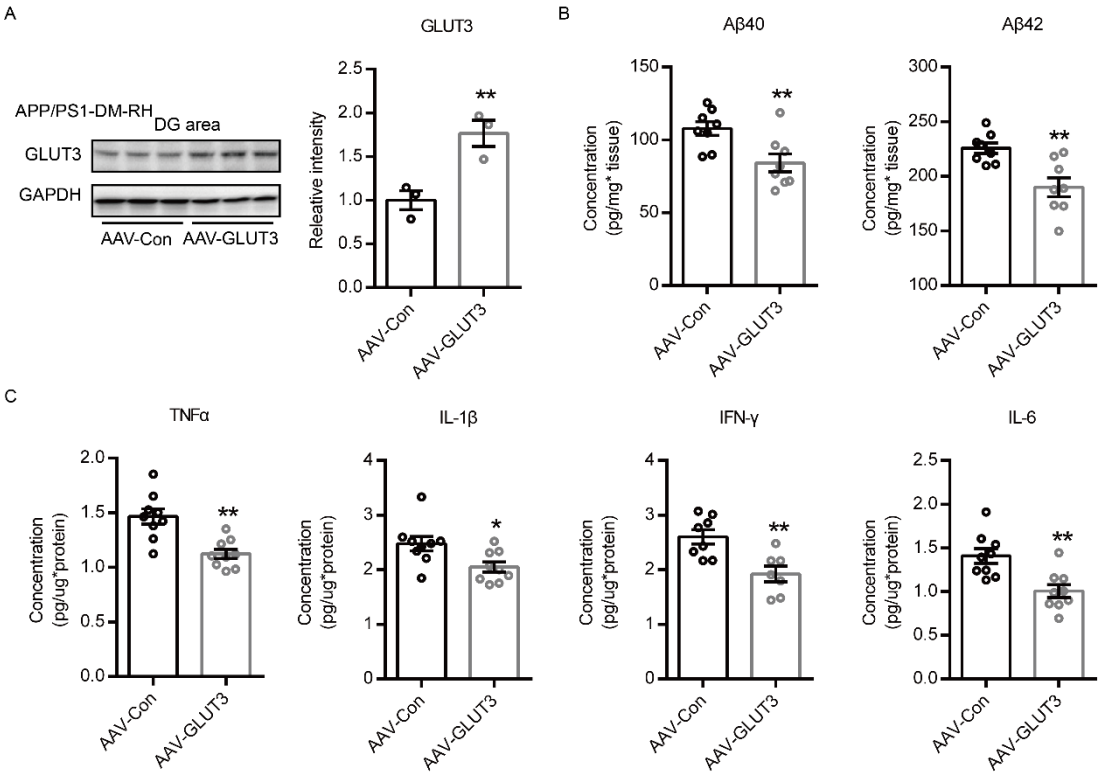


Figure S8, Related to Figure 6. GLUT3 over-expression in DG area of hippocampus improve RH induced AD-type pathologies in APP/PS1-DM-mice. (A) Western blot to assess GLUT3 abundance in DG area of hippocampus and the quantitative data shown in the right (n=3 mice for each group). AAV-Con, APP/PS1-DM-RH mice injected with empty adeno-associated virus in DG area; AAV-GLUT3, APP/PS1-DM-RH mice injected with adeno-associated virus expressing GLUT3 protein in DG area. (**B)** ELSIA to detect Aβ40 and Aβ42 in DG area of hippocampus (n=8 mice for each group). **(C)** Quantification of IL-6, IL-1β, IFN-γ and TNF-α by ELISA in DG area of hippocampus (n=9 mice for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's t test. *$P<0.05$, **$P<0.01$.

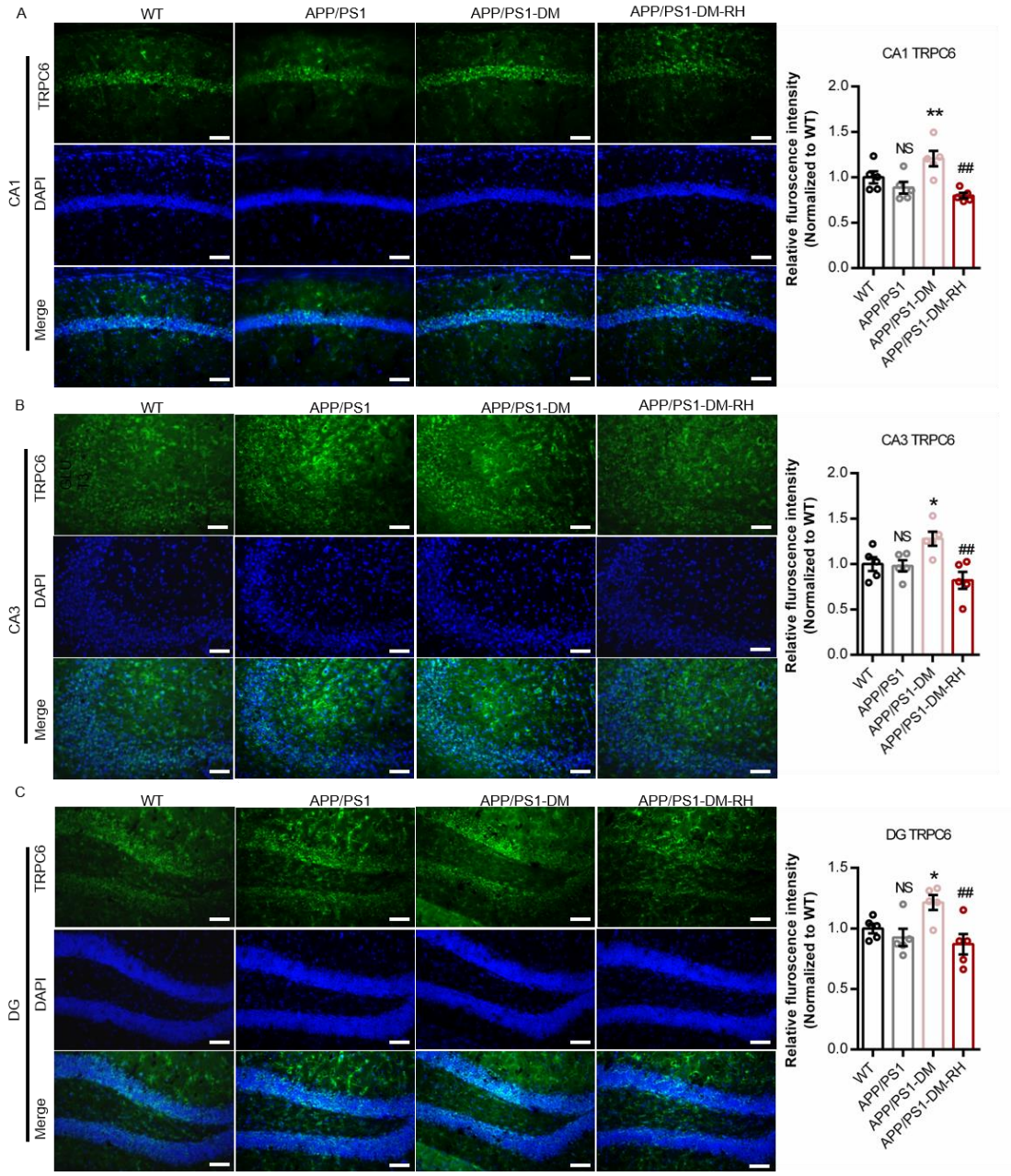


Figure S9, related to Figure 7. TRPC6 expression in hippocampus. (A-C) Representative images of TRPC6 (green) and DAPI (blue) immunostaining in hippocampal area of CA1 (A), CA3 (B) and DG (C) from WT, APP/PS1, APP/PS1-DM, and APP/PS1-DM-RH mice. *Scale bar*, 100μm. Quantitative results are showed in the right (n=5 mice for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's t test. $^{*}P<0.05$, APP/PS1-DM VS APP/PS1; $^{\#\#}P<0.01$, APP/PS1-DM VS APP/PS1-DM-RH; WT VS APP/PS1, no significant difference (NS).

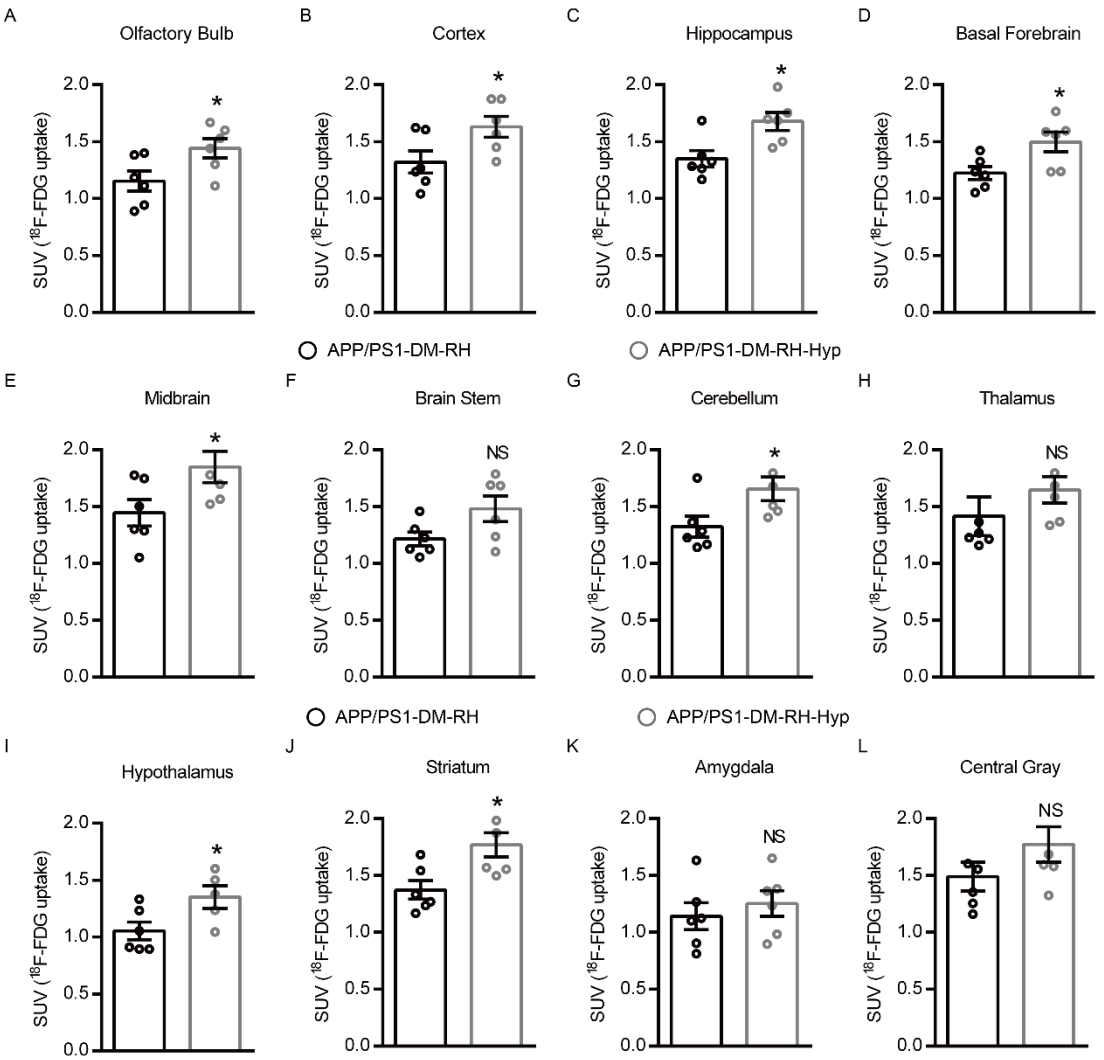


Figure S10, Related to Figure 7. Whole brain ^{18}F-FDG uptake. (A-L) The standard uptake value (SUV) of ^{18}F-FDG in different brain regions measured by ^{18}F-FDG PET/CT scanning (n=6 mice for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's t test. $^{*}P<0.05$ and $^{**}P<0.01$; NS, no significant difference.

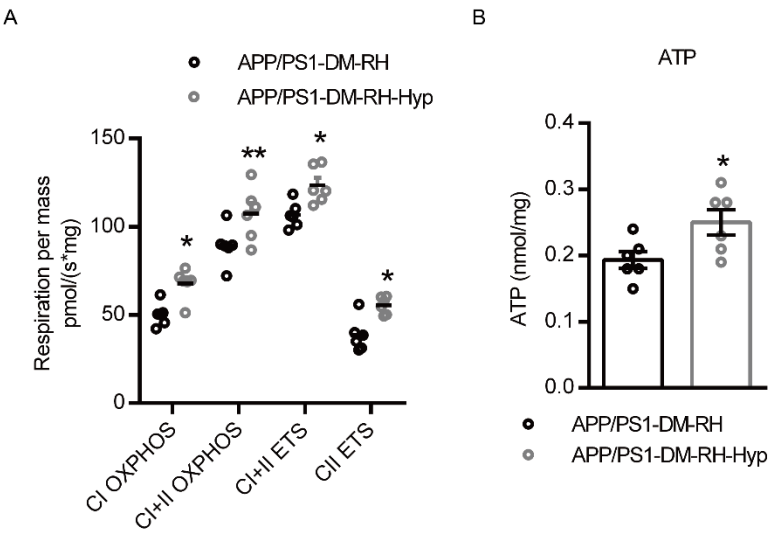


Figure S11, Related to Figure 7. Hyperforin treatment improves mitochondrial function. (A) High-resolution respirometry measured the oxygen consumption capacity of hippocampal mitochondria (n=6 for each group). **(B)** ATP content in hippocampus (n=6 for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's t test (panel B) or two-way ANOVA followed by Sidak's multiple comparisons test (panel A). *$P<0.05$, **$P<0.01$.

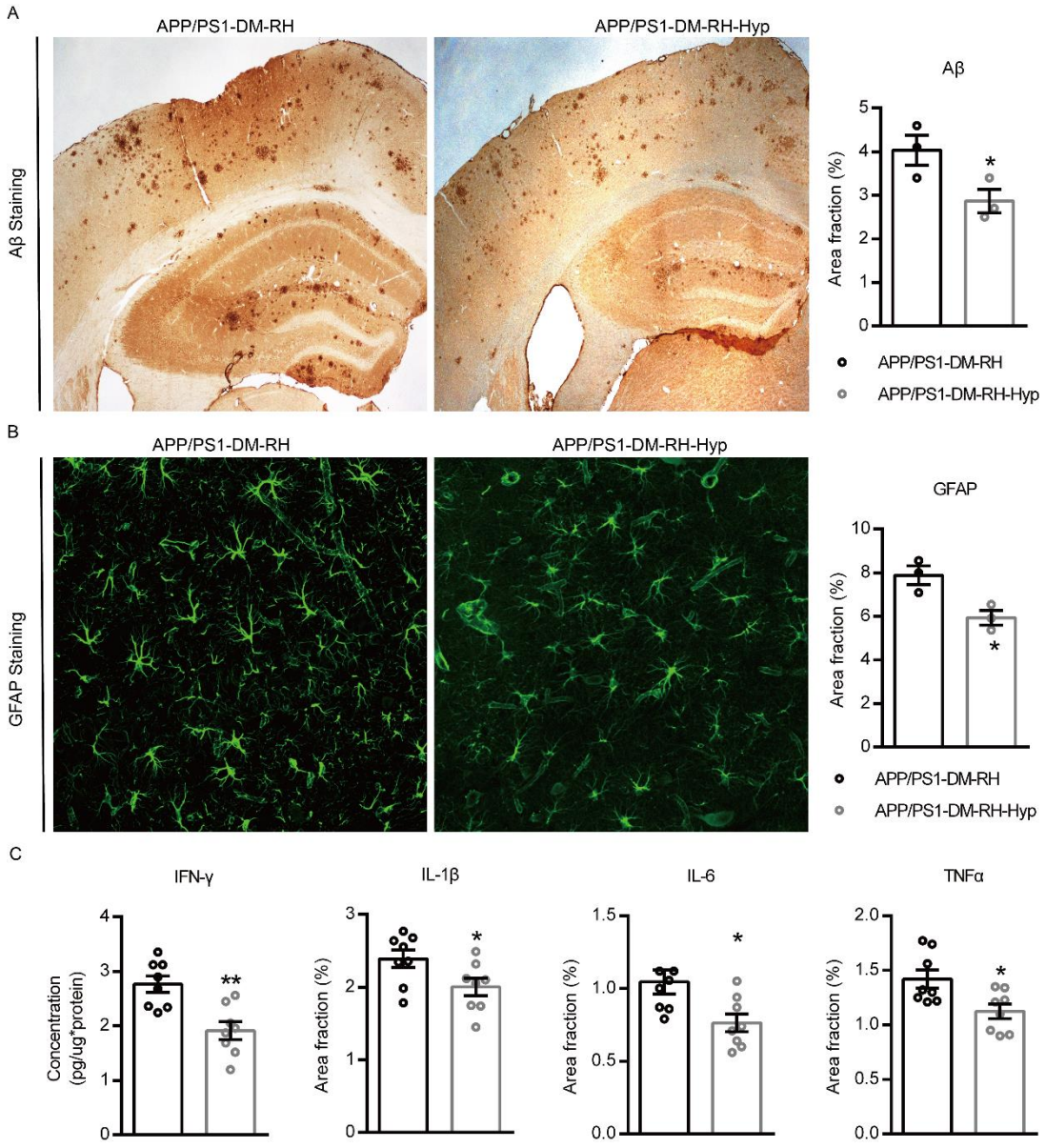


Figure S12, Related to Figure 7. Hyperforin treatment improves AD-type pathologies. (A) Representative images of Aβ immunohistochemistry staining (n=3 mice for each group). Hyp, hyperforin. **(B)** Representative images of GFAP immunofluorescent staining (n=3 mice for each group). **(C)** Quantification of IFN-γ、IL-1β、IL-6 and TNFα by ELISA in hippocampal homogenates (n=8 mice for each group). The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's t test. *$P<0.05$ and **$P<0.01$; NS, no significant difference.

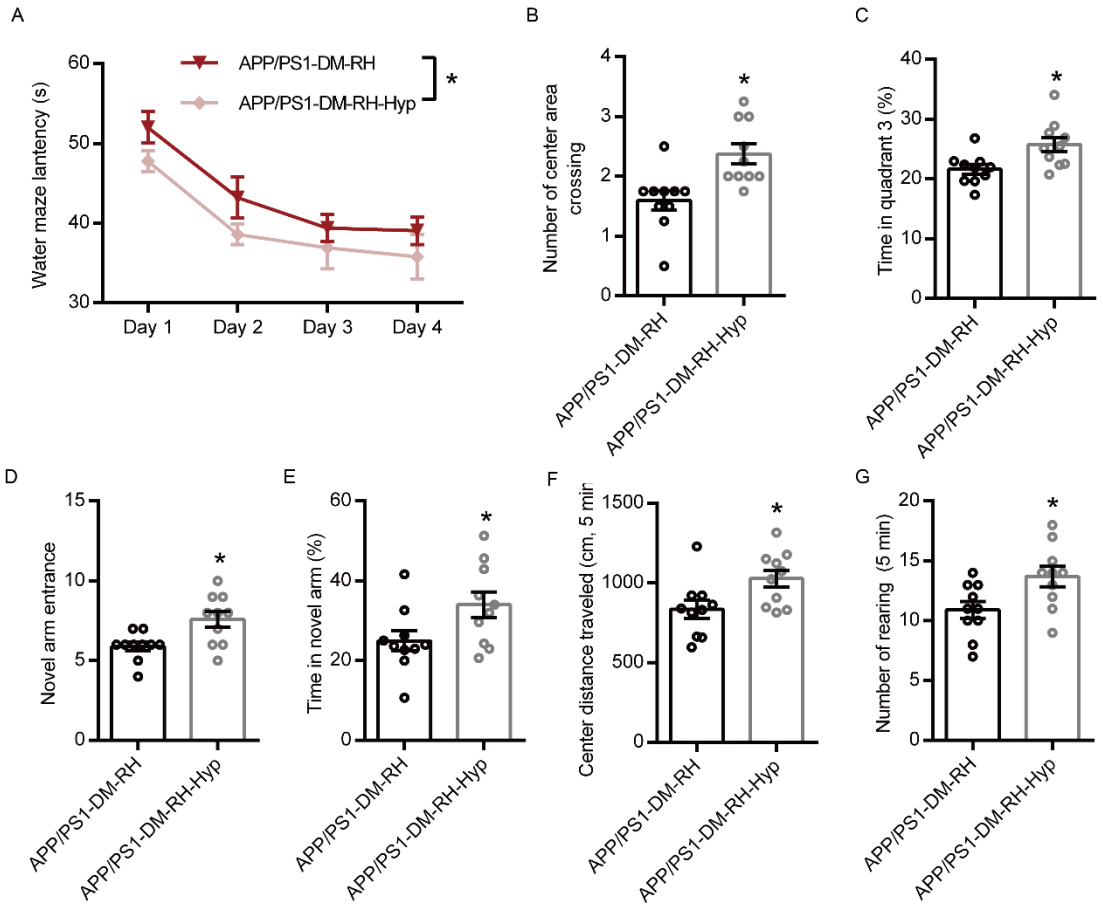


Figure S13, Related to Figure 7. The performances of mice treated with hyperforin in behavioral tests. (A-C) Escape latency during platform trials (A), number of center area crossing (B) and time spend in quadrant 3 o (Q3, C) in probe test. **(D and E)** Novel arm entrance (D) and time spend in the novel arm (E) in Y-maze test. **(F-G)** Distance traveled in center region (F) and number of rearing (G). Hyp, hyperforin, a TRPC6 agonist. n=10 mice for each group. The data are expressed as the mean ± SEM. Statistical significances were assessed using two-way ANOVA followed (panel A) or unpaired student's t test (panel B-G). $^{*}P<0.05$.

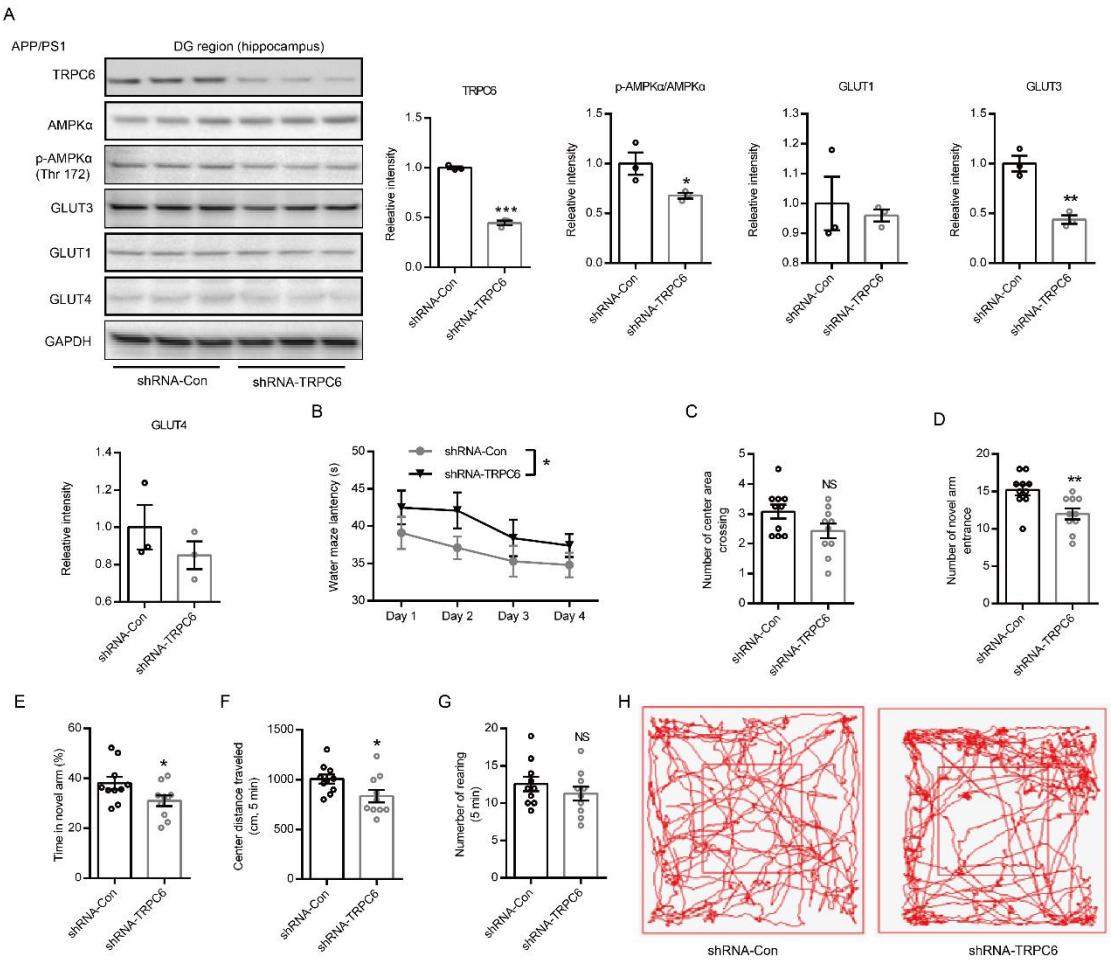


Figure S14, Related to Figure 7. TRPC6 down-regulation with shRNA. (A) Western-blot show the expression of TRPC6, AMPKα，p-AMPKα (Thr172)，GLUT3，GLUT1 and GLUT4 in DG hippocampal region. Quantitative data are shown on the right (n=3). shRNA-Con, APP/PS1 mice were bilaterally injected with empty AAV2/9 virus into DG area of hippocampus; shRNA-TRPC6, APP/PS1 mice were bilaterally injected with AAV2/9 virus expressing mouse shRNA (TRPC6) into DG area of hippocampus. **(B and C)** Escape latency during platform trials (B), number of center area crossing (C) in Morris water-maze test. **(D and E)** Number of novel arm entrance (D) and time spend in the novel arm (E) in Y-maze test. **(F-H)** Distance traveled in center region (F), number of rearing (G) and representative tracing graphs in open field test. n=10 mice for each group. The data are expressed as the mean ± SEM. Statistical significances were assessed using two-way ANOVA followed (panel B) or unpaired student's t test (panel A, C-G). $^{*}P<0.05$, $^{**}P<0.01$.

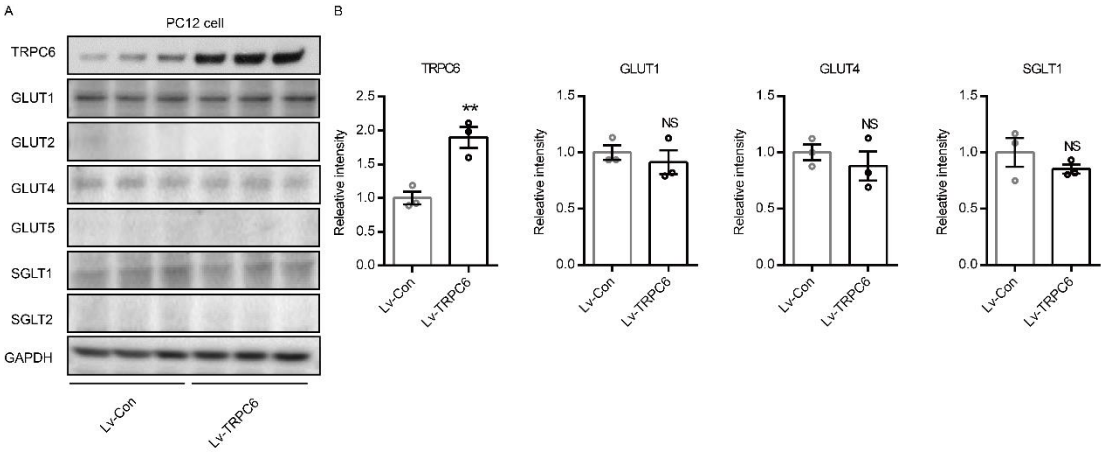
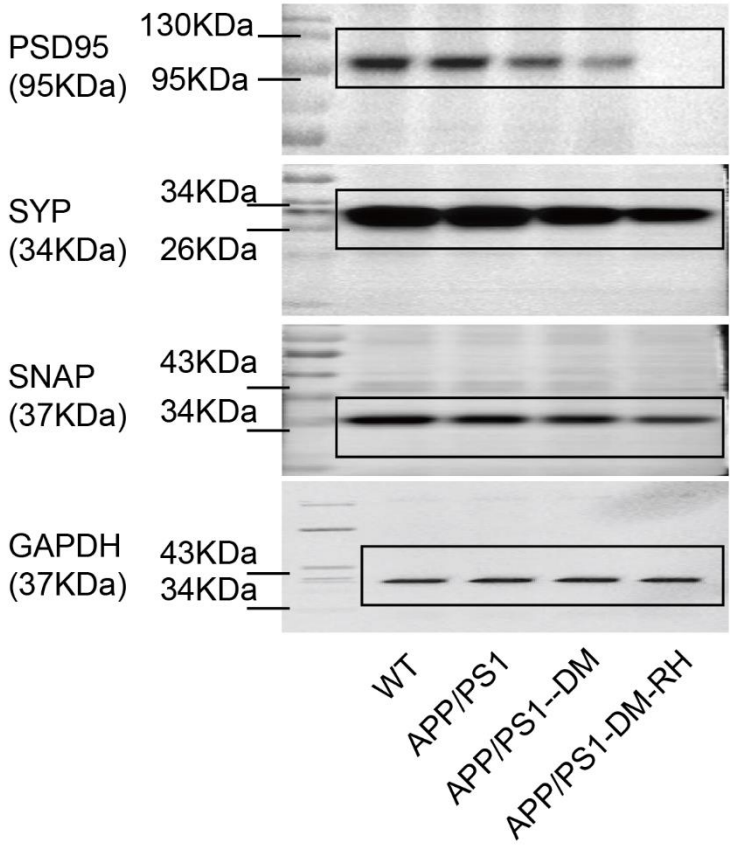


Figure S15, Related to Figure 7. GLUTs and SGLT1/2 expression. (A and B) Western blot and quantitation for TRPC6, GLUT1, GLUT2, GLUT4, GLUT5, SGLT1 and SGLT2 expression in PC12 cells. Lv-Con, the recombinant lentiviral vector; Lv-TRPC6, the recombinant lentiviral vector with TRPC6 over-expression. The data are expressed as the mean ± SEM. Statistical significance was assessed using unpaired student's t test. *$P<0.05$; NS, no significant difference.

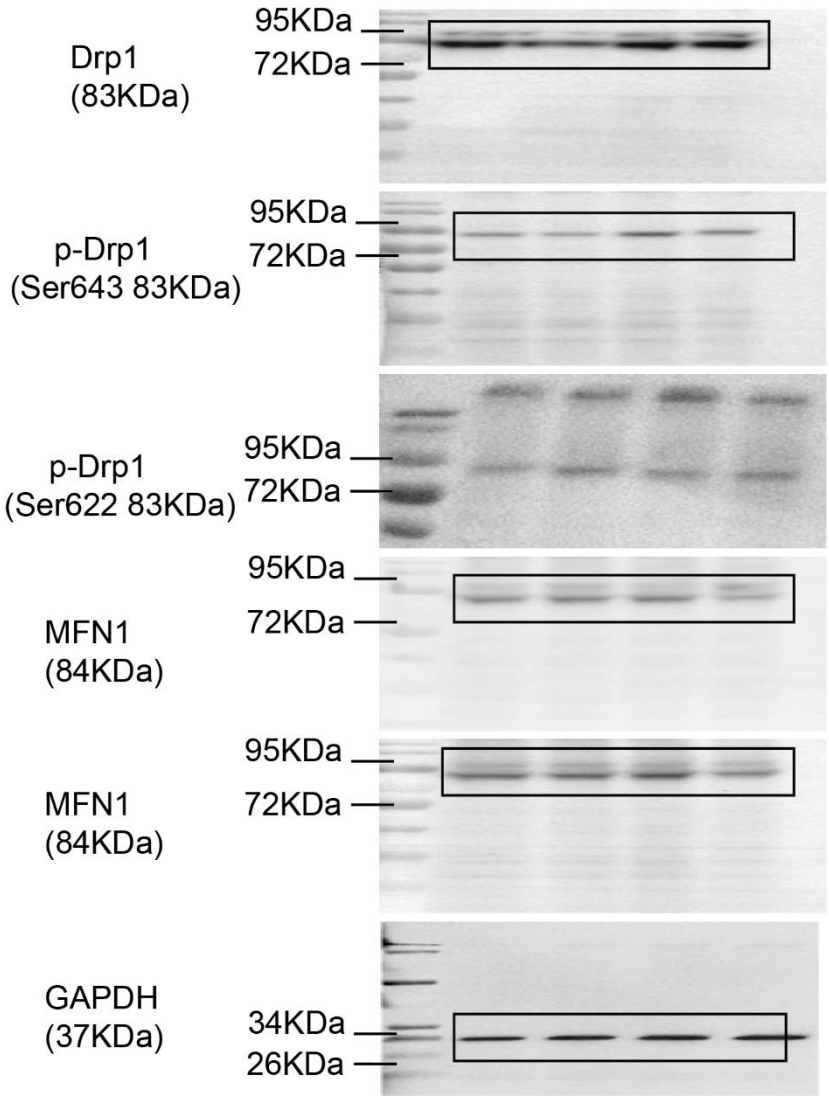
Full unedited gel for Figure 2B

Figure 2B



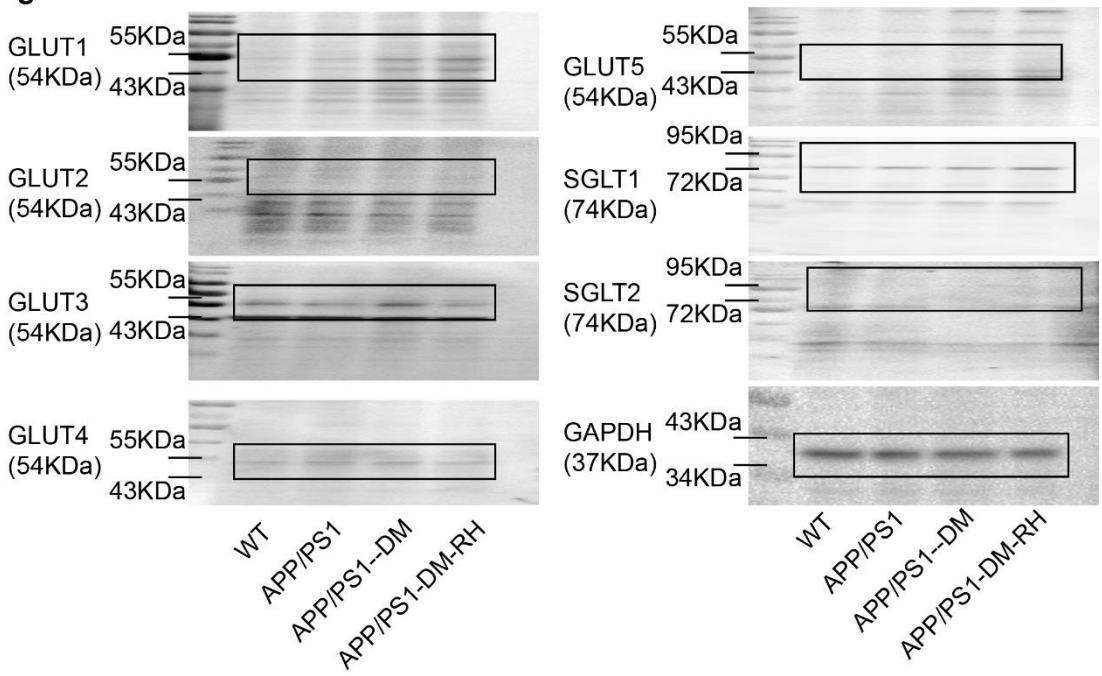
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Figure 4C

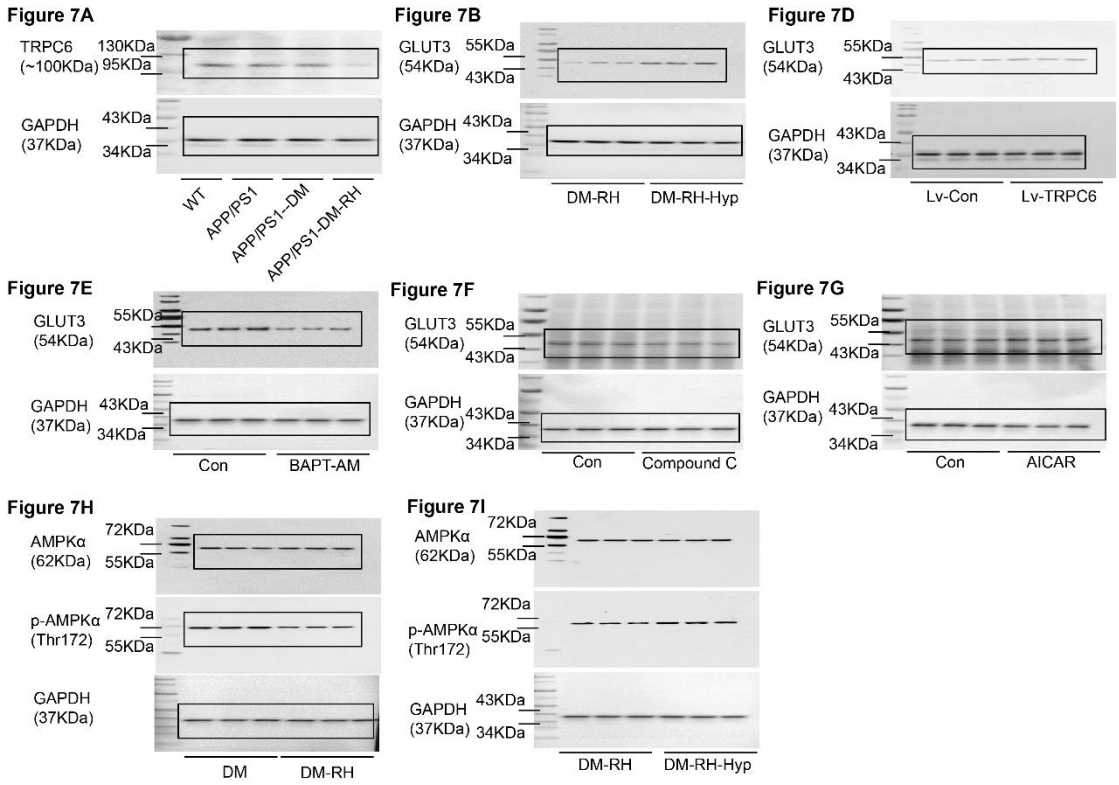


Full unedited gel for Figure 5C

Figure 5C

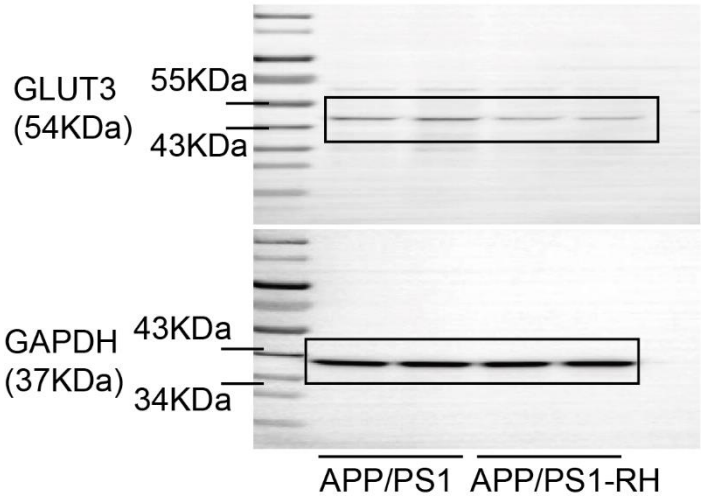


Full unedited gel for Figure 7



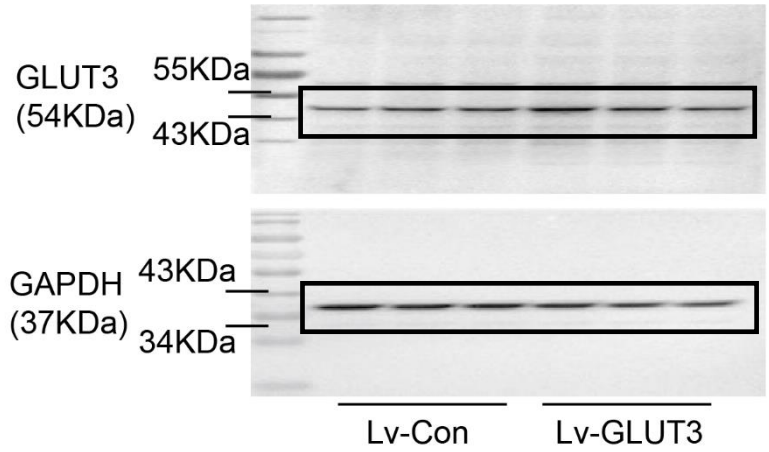
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Figure S5A



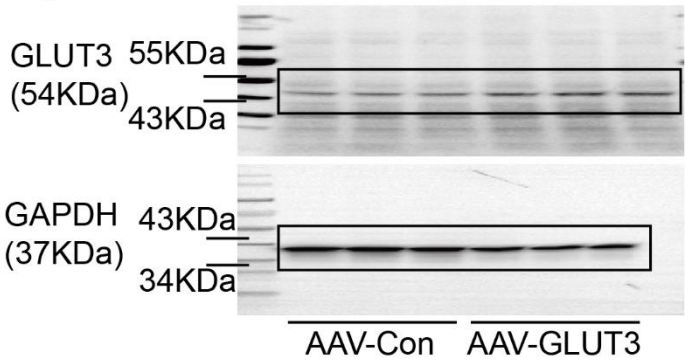
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Figure S7A



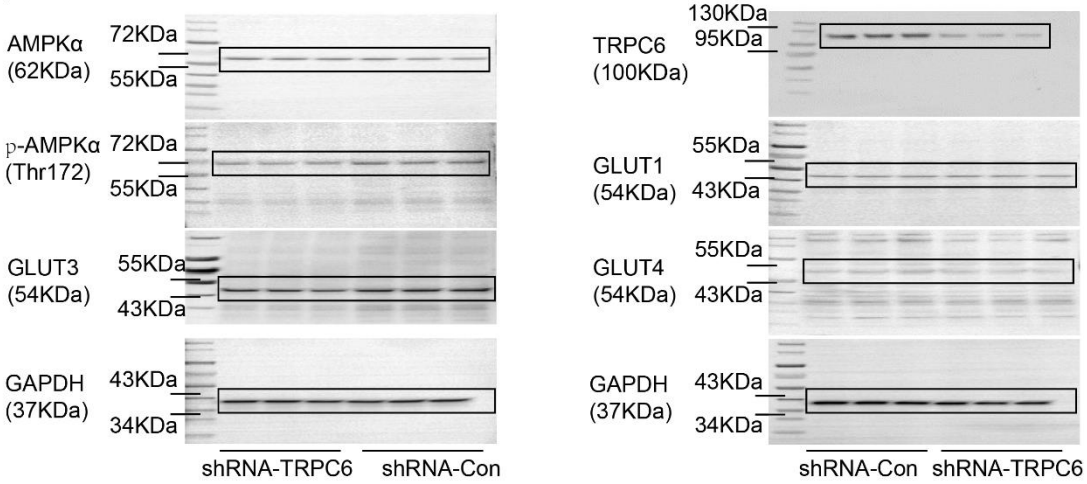
Full unedited gel for Figure S8

Figure S8



Full unedited gel for Figure S14

Figure S14



Full unedited gel for Figure S15

Figure S15

