

**Supplementary Figure 1. Mouse body weight and survival during *in vivo* study.** Mice maintained body weight and all mice survived through the study. Untreated, non-genetic carriers (NCAR-Veh), untreated, genetic careers (Hemi-Veh), mabuterol-treated, genetic carriers (Hemi-Maburterol) are represented by blue, red, green, and purple data curves.



**Supplementary Figure 2. Activity chamber time shows no significant differences through the study.** We measured the distance moved (upper left), vertical counts (upper right), vertical time (lower left), and total duration of activity (lower right) across the duration of the study and observed no statistically significant differences. Untreated, non-genetic carriers (NCAR-Veh), untreated, genetic careers (Hemi-Veh), mabuterol-treated, genetic carriers (Hemi-Maburterol) are represented by blue, red, green, and purple data curves.





**Supplementary Figure 3. Y-maze FA shows no difference across treatment groups**. We measured duration of time in novel and familiar arms at 4 weeks (upper left) and 7 weeks (lower left), total duration of time spent in novel and each familiar arms at 4 weeks (upper middle) and 7 weeks (lower middle), and total duration spent in novel arms and either familiar arm at 4 weeks (upper right) and 7 weeks (lower right). Untreated, non-genetic carriers (NCAR-Veh), untreated, genetic careers (Hemi-Veh), mabuterol-treated, genetic carriers (Hemi-Maburterol) are represented by blue, red, green, and purple data curves.

**Chart

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**Supplementary Figure 4. Protein level changes varied across treatment group.** Protein level changes and their significance were assess for propranolol-treated mice compared to vehicle treated (**A**,**B**) and vehicle-treated compared to non-carrier mice (**C**,**D**). Blue and red bars indicate down- and up- regulated proteins respectively.

**Chart, bar chart

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**Supplementary Figure 5. ELISA measured cytokine differences across treatment groups.** We measured changes in cytokine levels using ELISA comparing 5xFAD carrier to non-carriers (**A**) and comparing propranolol-treated to untreated mice (**B**).

**Diagram

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**Supplementary Figure 6. Targeted western blot analysis did not uncover protein level changes in a handful of selected proteins.** We analyzed protein level changes for Akt (**A**), Atg5 (**B**), GluA1 (**C**), Synapsin I (**D**), DAPK1 (**E**), NR2B (**F**), phosoDAPK on serine 308 (“pDAPK”)(**G**), phosphoDAPK normalized to DAPK1 (**H**), PSD95 for the top (**I**), combined (**J**), and bottom (**M**) bands, LC3-I (**K**), and LC3-II (**L**). Except for (**H**), all values are shown normalized to alpha tubulin. Non-carriers, vehicle, mabuterol, and propranolol groups are shown in blue, red, green, and purple respectively.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| GO Term | Description | P-value | FDR q-value | Enrichment | N | B | n | b | Genes |
| GO:0030705 | cytoskeleton-dependent intracellular transport | 6.25E-05 | 9.52E-01 | 11.69 | 15155 | 180 | 36 | 5 | [ARL8A - adp-ribosylation factor-like 8a, ARL8B - adp-ribosylation factor-like 8b, PPFIA2 - protein tyrosine phosphatase, receptor type, f polypeptide (ptprf), interacting protein (liprin), alpha 2, HTT - huntingtin, RAB1A - rab1a, member ras oncogene family] |
| GO:0007030 | Golgi organization | 1.29E-04 | 9.85E-01 | 15.31 | 15155 | 110 | 36 | 4 | [LMAN2 - lectin, mannose-binding 2, HTT - huntingtin, RAB1A - rab1a, member ras oncogene family, ATL3 - atlastin gtpase 3] |
| GO:0071705 | nitrogen compound transport | 1.33E-04 | 6.73E-01 | 3.3 | 15155 | 1529 | 36 | 12 | [ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, S100A13 - s100 calcium binding protein a13, PPFIA2 - protein tyrosine phosphatase, receptor type, f polypeptide (ptprf), interacting protein (liprin), alpha 2, ARL8B - adp-ribosylation factor-like 8b, LMAN2 - lectin, mannose-binding 2, SLC25A42 - solute carrier family 25, member 42, MFF - mitochondrial fission factor, TBC1D17 - tbc1 domain family, member 17, MTX3 - metaxin 3, RAB1A - rab1a, member ras oncogene family, AIP - aryl hydrocarbon receptor interacting protein] |
| GO:0006810 | transport | 2.02E-04 | 7.67E-01 | 2.18 | 15155 | 3667 | 36 | 19 | [CTSL - cathepsin l, S100A13 - s100 calcium binding protein a13, EPN2 - epsin 2, SLC25A42 - solute carrier family 25, member 42, MFF - mitochondrial fission factor, TBC1D17 - tbc1 domain family, member 17, MTX3 - metaxin 3, RAB1A - rab1a, member ras oncogene family, AIP - aryl hydrocarbon receptor interacting protein, RIN1 - ras and rab interactor 1, ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, PPFIA2 - protein tyrosine phosphatase, receptor type, f polypeptide (ptprf), interacting protein (liprin), alpha 2, LMAN2 - lectin, mannose-binding 2, ARL8B - adp-ribosylation factor-like 8b, GABRB3 - gamma-aminobutyric acid (gaba) a receptor, beta 3, TJP2 - tight junction protein 2, HTT - huntingtin, CACNA1B - calcium channel, voltage-dependent, n type, alpha 1b subunit] |
| GO:0015031 | protein transport | 2.97E-04 | 9.04E-01 | 3.58 | 15155 | 1175 | 36 | 10 | [ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, S100A13 - s100 calcium binding protein a13, ARL8B - adp-ribosylation factor-like 8b, LMAN2 - lectin, mannose-binding 2, MFF - mitochondrial fission factor, TBC1D17 - tbc1 domain family, member 17, MTX3 - metaxin 3, RAB1A - rab1a, member ras oncogene family, AIP - aryl hydrocarbon receptor interacting protein] |
| GO:0051234 | establishment of localization | 3.31E-04 | 8.40E-01 | 2.1 | 15155 | 3800 | 36 | 19 | [CTSL - cathepsin l, S100A13 - s100 calcium binding protein a13, EPN2 - epsin 2, SLC25A42 - solute carrier family 25, member 42, MFF - mitochondrial fission factor, TBC1D17 - tbc1 domain family, member 17, MTX3 - metaxin 3, RAB1A - rab1a, member ras oncogene family, AIP - aryl hydrocarbon receptor interacting protein, RIN1 - ras and rab interactor 1, ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, PPFIA2 - protein tyrosine phosphatase, receptor type, f polypeptide (ptprf), interacting protein (liprin), alpha 2, LMAN2 - lectin, mannose-binding 2, ARL8B - adp-ribosylation factor-like 8b, GABRB3 - gamma-aminobutyric acid (gaba) a receptor, beta 3, TJP2 - tight junction protein 2, HTT - huntingtin, CACNA1B - calcium channel, voltage-dependent, n type, alpha 1b subunit] |
| GO:0015833 | peptide transport | 3.47E-04 | 7.55E-01 | 3.51 | 15155 | 1198 | 36 | 10 | [ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, S100A13 - s100 calcium binding protein a13, ARL8B - adp-ribosylation factor-like 8b, LMAN2 - lectin, mannose-binding 2, MFF - mitochondrial fission factor, TBC1D17 - tbc1 domain family, member 17, MTX3 - metaxin 3, RAB1A - rab1a, member ras oncogene family, AIP - aryl hydrocarbon receptor interacting protein] |
| GO:0099111 | microtubule-based transport | 3.83E-04 | 7.29E-01 | 11.53 | 15155 | 146 | 36 | 4 | [ARL8A - adp-ribosylation factor-like 8a, ARL8B - adp-ribosylation factor-like 8b, HTT - huntingtin, RAB1A - rab1a, member ras oncogene family] |
| GO:0010970 | transport along microtubule | 3.83E-04 | 6.48E-01 | 11.53 | 15155 | 146 | 36 | 4 | [ARL8A - adp-ribosylation factor-like 8a, ARL8B - adp-ribosylation factor-like 8b, HTT - huntingtin, RAB1A - rab1a, member ras oncogene family] |
| GO:0042886 | amide transport | 4.32E-04 | 6.57E-01 | 3.42 | 15155 | 1231 | 36 | 10 | [ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, S100A13 - s100 calcium binding protein a13, ARL8B - adp-ribosylation factor-like 8b, LMAN2 - lectin, mannose-binding 2, MFF - mitochondrial fission factor, TBC1D17 - tbc1 domain family, member 17, MTX3 - metaxin 3, RAB1A - rab1a, member ras oncogene family, AIP - aryl hydrocarbon receptor interacting protein] |
| GO:0099518 | vesicle cytoskeletal trafficking | 4.64E-04 | 6.42E-01 | 19.73 | 15155 | 64 | 36 | 3 | [PPFIA2 - protein tyrosine phosphatase, receptor type, f polypeptide (ptprf), interacting protein (liprin), alpha 2, HTT - huntingtin, RAB1A - rab1a, member ras oncogene family] |
| GO:0045184 | establishment of protein localization | 5.04E-04 | 6.39E-01 | 3.35 | 15155 | 1255 | 36 | 10 | [ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, S100A13 - s100 calcium binding protein a13, ARL8B - adp-ribosylation factor-like 8b, LMAN2 - lectin, mannose-binding 2, MFF - mitochondrial fission factor, TBC1D17 - tbc1 domain family, member 17, MTX3 - metaxin 3, RAB1A - rab1a, member ras oncogene family, AIP - aryl hydrocarbon receptor interacting protein] |
| GO:0051179 | localization | 5.33E-04 | 6.24E-01 | 1.96 | 15155 | 4287 | 36 | 20 | [CTSL - cathepsin l, S100A13 - s100 calcium binding protein a13, EPN2 - epsin 2, SLC25A42 - solute carrier family 25, member 42, MFF - mitochondrial fission factor, TBC1D17 - tbc1 domain family, member 17, MTX3 - metaxin 3, RAB1A - rab1a, member ras oncogene family, AIP - aryl hydrocarbon receptor interacting protein, RIN1 - ras and rab interactor 1, ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, PPFIA2 - protein tyrosine phosphatase, receptor type, f polypeptide (ptprf), interacting protein (liprin), alpha 2, LMAN2 - lectin, mannose-binding 2, ARL8B - adp-ribosylation factor-like 8b, GABRB3 - gamma-aminobutyric acid (gaba) a receptor, beta 3, TJP2 - tight junction protein 2, HTT - huntingtin, TM9SF2 - transmembrane 9 superfamily member 2, CACNA1B - calcium channel, voltage-dependent, n type, alpha 1b subunit] |
| GO:0071702 | organic substance transport | 5.93E-04 | 6.44E-01 | 2.82 | 15155 | 1793 | 36 | 12 | [ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, S100A13 - s100 calcium binding protein a13, PPFIA2 - protein tyrosine phosphatase, receptor type, f polypeptide (ptprf), interacting protein (liprin), alpha 2, ARL8B - adp-ribosylation factor-like 8b, LMAN2 - lectin, mannose-binding 2, SLC25A42 - solute carrier family 25, member 42, MFF - mitochondrial fission factor, TBC1D17 - tbc1 domain family, member 17, MTX3 - metaxin 3, RAB1A - rab1a, member ras oncogene family, AIP - aryl hydrocarbon receptor interacting protein] |
| GO:0016192 | vesicle-mediated transport | 8.30E-04 | 8.42E-01 | 2.91 | 15155 | 1592 | 36 | 11 | [CTSL - cathepsin l, RIN1 - ras and rab interactor 1, ARL8A - adp-ribosylation factor-like 8a, EXOC2 - exocyst complex component 2, S100A13 - s100 calcium binding protein a13, EPN2 - epsin 2, ARL8B - adp-ribosylation factor-like 8b, LMAN2 - lectin, mannose-binding 2, TBC1D17 - tbc1 domain family, member 17, HTT - huntingtin, RAB1A - rab1a, member ras oncogene family] |
| GO:0006890 | retrograde vesicle-mediated transport, Golgi to ER | 9.93E-04 | 9.44E-01 | 15.22 | 15155 | 83 | 36 | 3 | [LMAN2 - lectin, mannose-binding 2, HTT - huntingtin, RAB1A - rab1a, member ras oncogene family] |

**Supplementary Table 1. GO enrichment of propranolol regulated proteins.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Antibody** | **Brand / Reference #** | **Molecular Weight (kDa)** | **Species / Concentration / Treatment** | **Conclusions** |
| Akt | Cell Signaling / 2920 | 60 | M / 1:2000 / N | No change due to genotype or treatment. |
| Atg5 | Cell Signaling / 12994 | 55 | R / 1:1000 / N | No change due to genotype or treatment. |
| DAPK1 | Cell Signaling / 3008 | 160 | Rb / 1:1000 / N | Possible elevation of DAPK with Propranolol. |
| pDAPK  (Ser308) | Sigma / D4941 | 160 | M / 1:1000 / B | Possible decrease in pDAPK with Propranolol. |
| GluA1 | Cell Signaling / 13185 | 100 | Rb / 1:1000 / B | No change due to genotype or treatment. |
| LC3B | Novus / NB100-2220 | 15 | Rb / 1:500 / B | Elevation of LC3-I and LC3-II in Hemi mice, reduced for LC3-I is reduced with mabuterol. |
| NR2B | Invitrogen / MA1-2014 | 166 | M / 1:1000 / N HRP | No change due to genotype or treatment. |
| PSD95 | Cell Signaling / 2507 | 95 | Rb / 1:1000 / B | No change due to genotype or treatment. |
| Synapsin I | Cell Signaling / 5297 | 77 | Rb / 1:1000 / B | No change due to genotype or treatment. |
| pSynapsin I  (Ser62, Ser67) | Millipore / AB9848 | 78 | Rb / 1:1000 / B | Elevation of pSynapsin I in Hemi mice. |
| Synaptophysin | Millipore / MAB329-C | 38 | M / 1:1000 / B | No change due to genotype or treatment. |
| Tubulin | Sigma / T5168 | 55 | M / 1:1000 | Used for normalization |

**Supplementary Table 2. Western blot summary.**