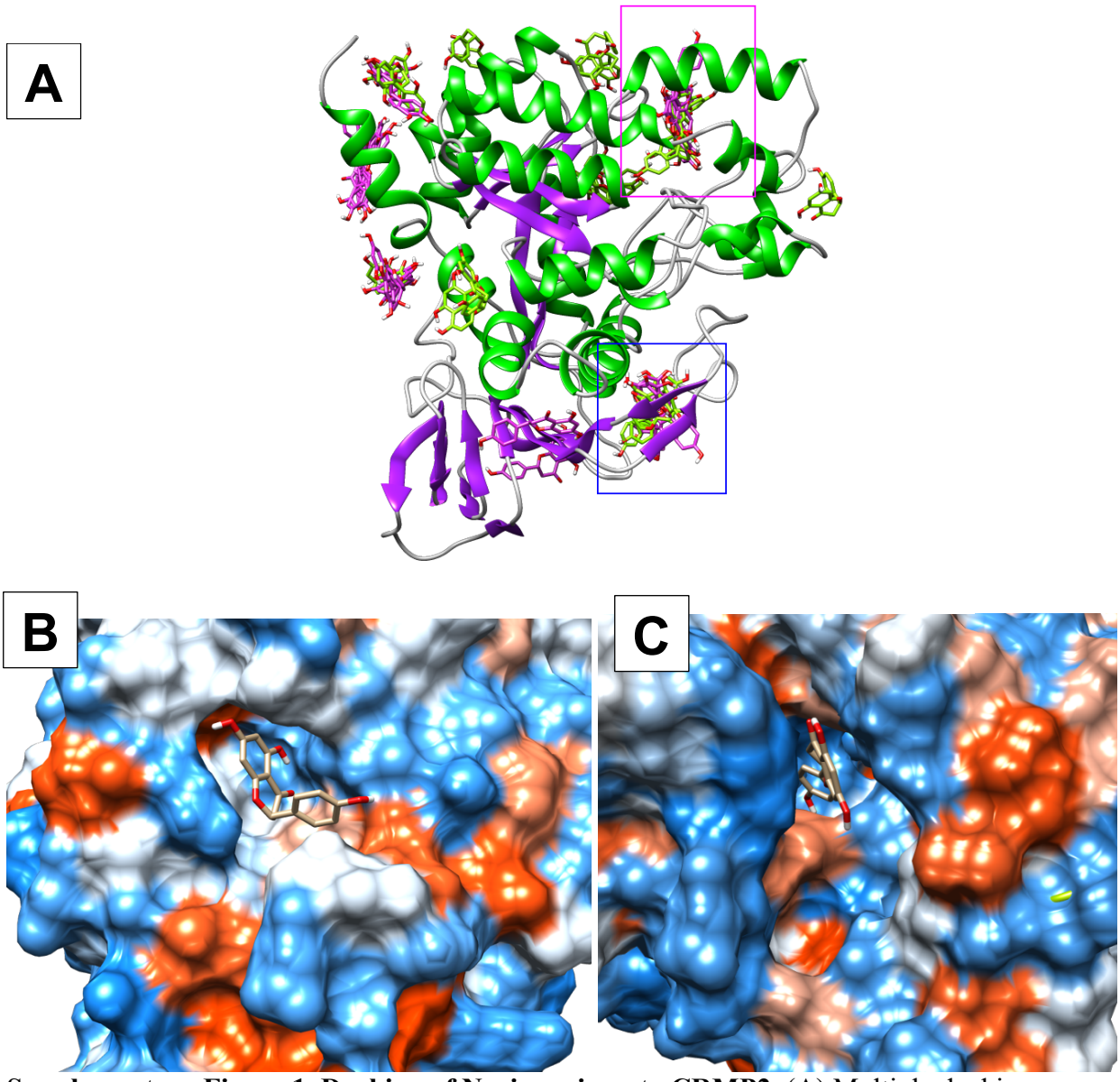
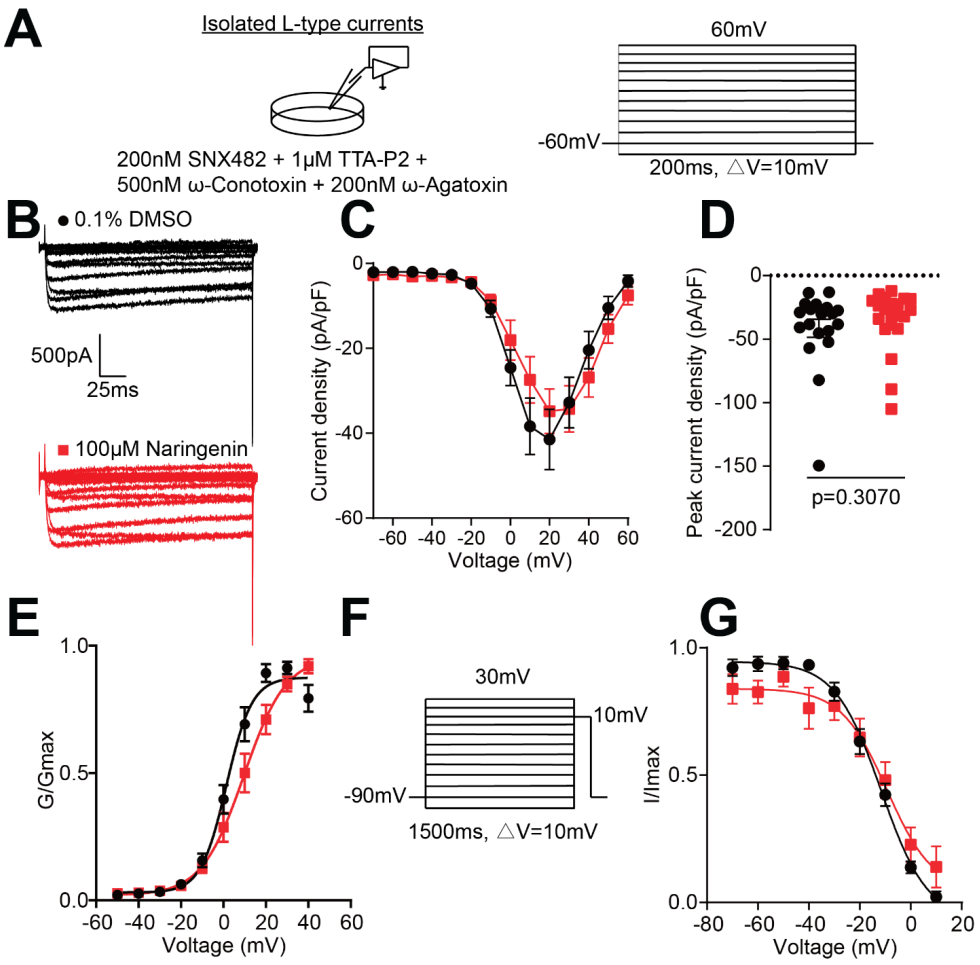
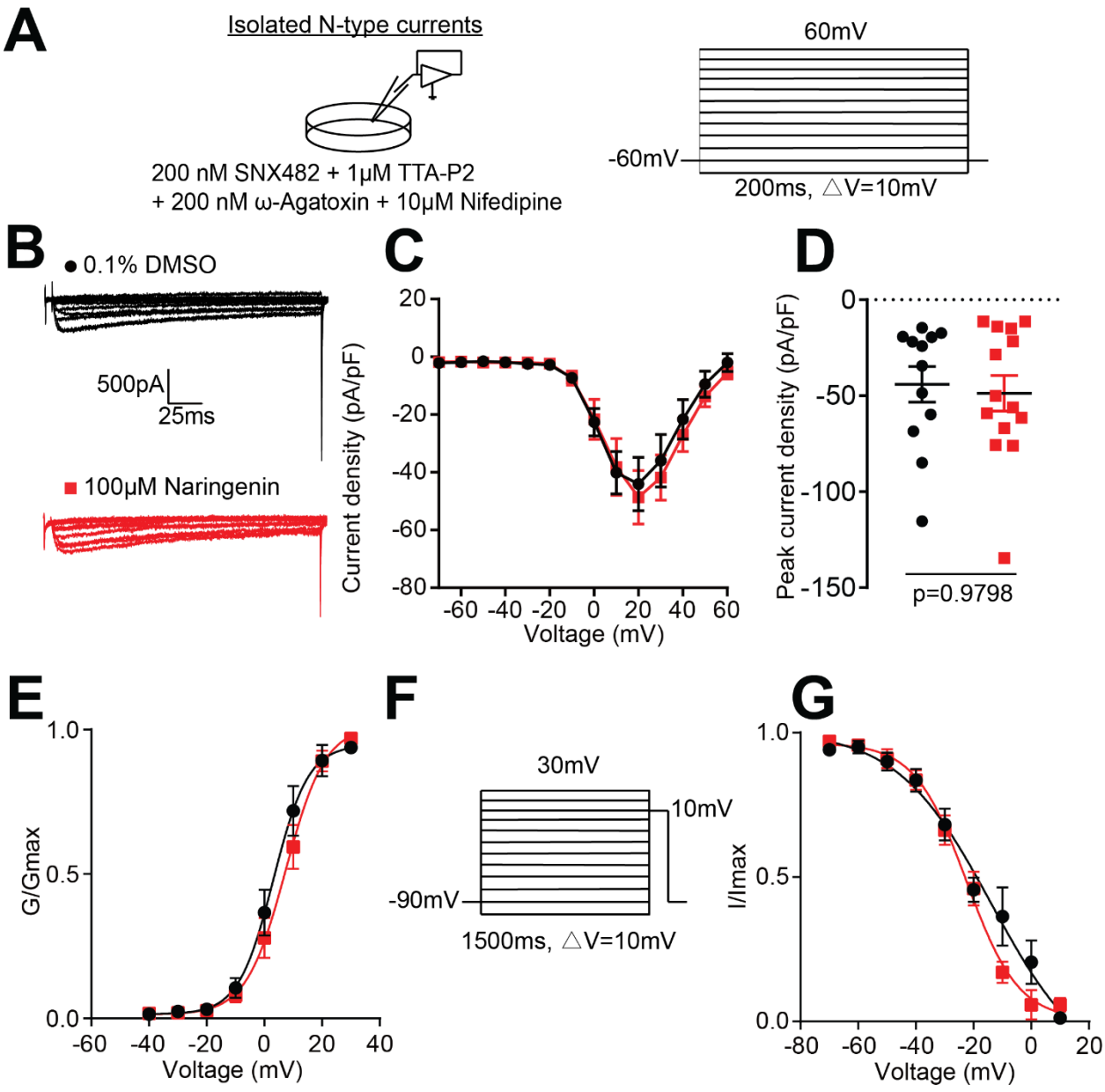


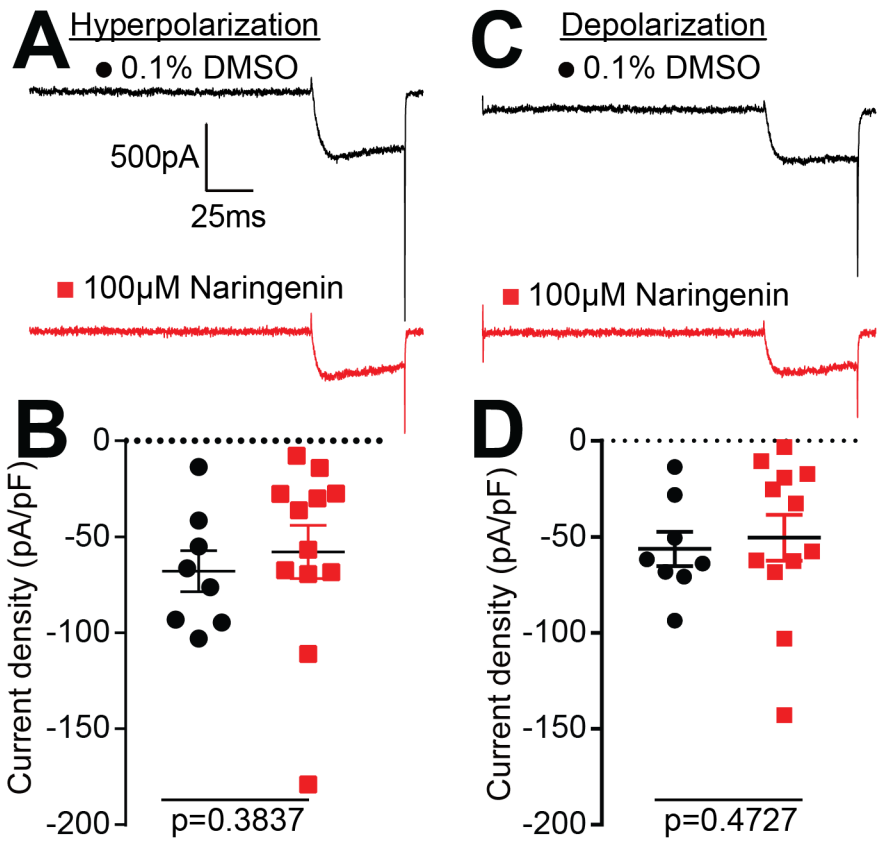
Supplementary Figure 1. Docking of Naringenin onto CRMP2. (**A**) Multiple docking poses of both Naringenin enantiomers on the CRMP-2. Naringenin is rendered as a capped stick in green (S-enantiomer) and magenta (R-enantiomer). (**B**) Naringenin in Lacosamide site. Hydrophobic character of the cavity is mapped onto the protein surface. White-gray – neutral, blue or orange are positively or negatively charged areas. (**C**) Naringenin in DHPase active site. Hydrophobic character of the cavity is mapped onto the protein surface. White-gray – neutral, blue or orange are positively or negatively charged areas.



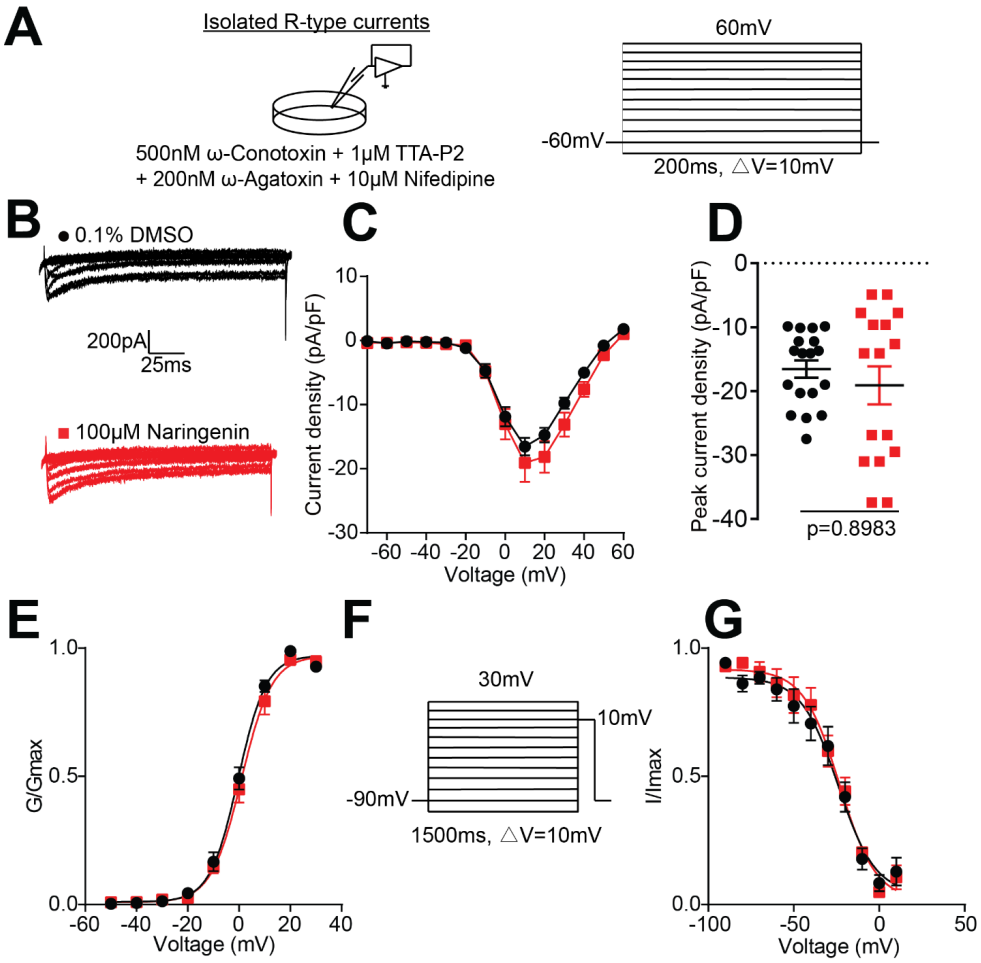
Supplementary Figure2. L-Type (CaV1.x) Ca^{2+} currents in dorsal root ganglion (DRG) sensory neurons are not affected by Naringenin. (**A**) Currents were isolated following the indicated protocol. (**B**) Representative traces of L-Type Ca^{2+} currents from DRG sensory neurons treated with 0.1% DMSO (control) or 100 μM Naringenin. Summary of the normalized (pA/pF) L-Type calcium current density versus voltage relationship (**C**) and peak L-Type Ca^{2+} current density at +20 mV (mean ± SEM) (**D**) from DRG sensory neurons treated as indicated. Boltzmann fits for normalized conductance G/G_{max} voltage relations for voltage dependent activation (**E**) and using the voltage protocol in (**F**), inactivation (**G**) of sensory neurons treated as indicated. $V_{0.5}$ values for activation and inactivation are presented in Table 1. No statistical significance was detected compared with cells treated with 0.1% DMSO ($p>0.05$, Mann-Whitney, n=18-19 cells per condition).



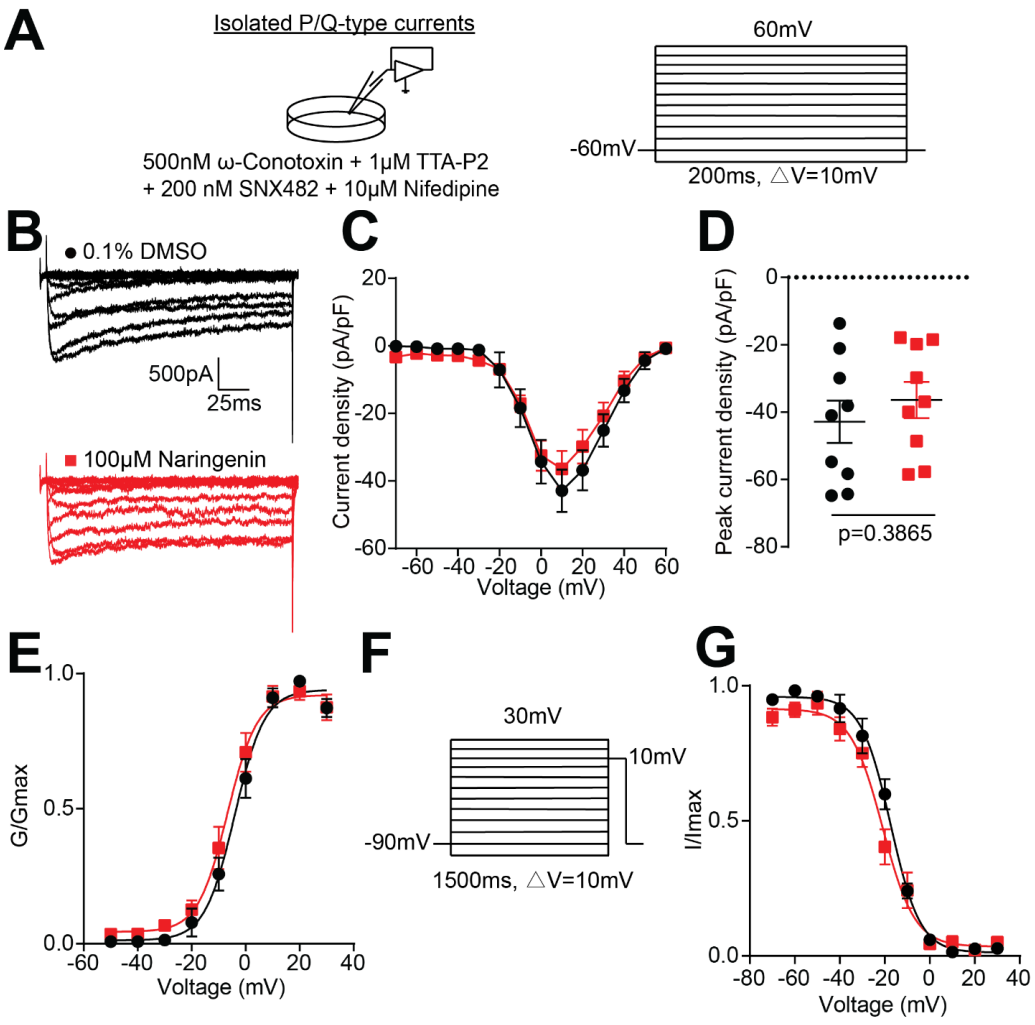
Supplementary Figure 3. Naringenin does not inhibit N-Type Ca^{2+} currents in dorsal root ganglion (DRG) sensory neurons under hyperpolarized and depolarized conditions. Representative traces of DRG neuron treated with 0.1% DMSO (control) or 100 μM Naringenin under hyperpolarized (**A**) and depolarized (**C**) conditions. Peak N-Type Ca^{2+} current density at +10 mV (mean ± SEM) from DRG sensory neurons under hyperpolarized (**B**) and depolarized (**D**) conditions. No statistical significance was observed compared with cells treated with 0.1% DMSO ($p>0.05$ as noted, Mann-Whitney, n=8-12 cells per condition).



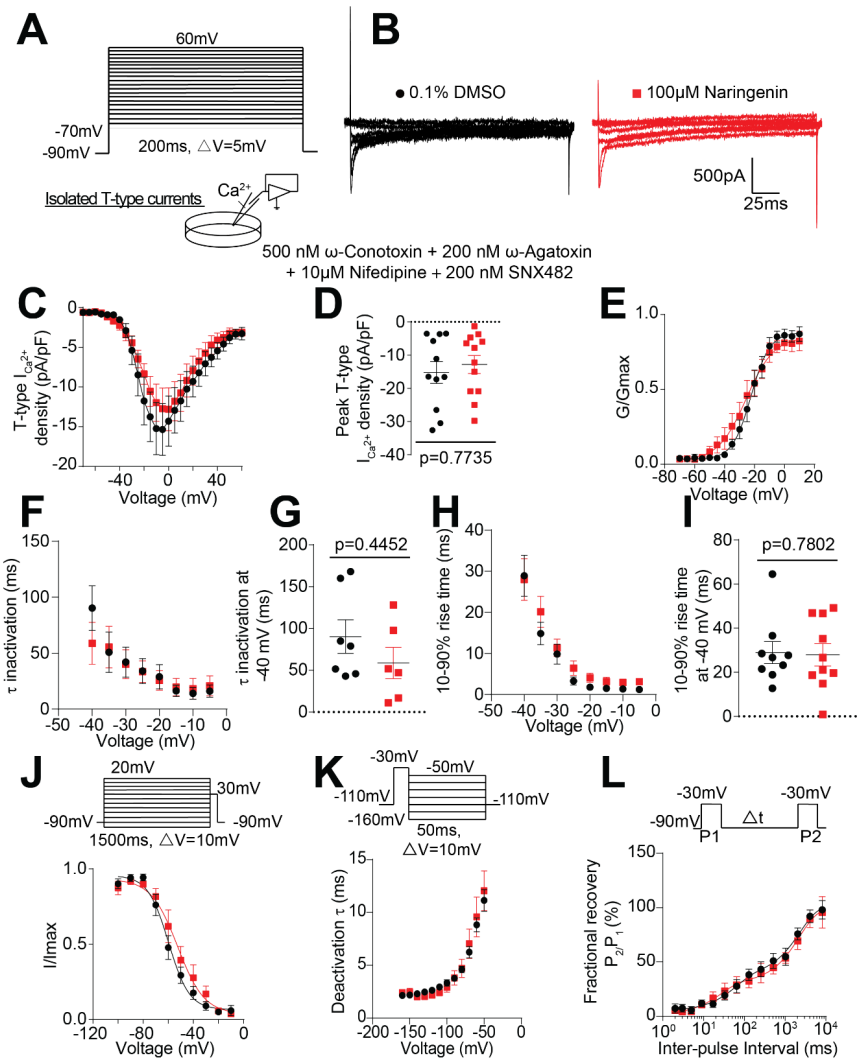
Supplementary Figure 4. N-Type (CaV2.2) Ca^{2+} currents in dorsal root ganglion (DRG) sensory neurons are not affected by Naringenin. (**A**) Currents were isolated following the indicated protocol. (**B**) Representative traces of N-Type Ca^{2+} currents from DRG sensory neurons treated with 0.1% DMSO (control) or 100 μM Naringenin. Summary of the normalized (pA/pF) N-Type calcium current density versus voltage relationship (**C**) and peak N-Type Ca^{2+} current density at +20 mV (mean ± SEM) (**D**) from DRG sensory neurons treated as indicated. Boltzmann fits for normalized conductance G/G_{max} voltage relations for voltage dependent activation (**E**) and using the voltage protocol in (**F**), inactivation (**G**) of sensory neurons treated as indicated. $V_{0.5}$ values for activation and inactivation are presented in Table 1. No statistical significance was detected compared with cells treated with 0.1% DMSO ($p>0.05$, Mann-Whitney, n=12-14 cells per condition).



Supplementary Figure 5. R-Type (CaV2.3) Ca^{2+} currents in dorsal root ganglion (DRG) sensory neurons are not affected by Naringenin. (**A**) Currents were isolated following the indicated protocol. (**B**) Representative traces of R-Type Ca^{2+} currents from DRG sensory neurons treated with 0.1% DMSO (control) or 100 μM Naringenin. Summary of the normalized (pA/pF) R-Type calcium current density versus voltage relationship (**C**) and peak R-Type Ca^{2+} current density at +20 mV (mean ± SEM) (**D**) from DRG sensory neurons treated as indicated. Boltzmann fits for normalized conductance G/G_{max} voltage relations for voltage dependent activation (**E**) and using the voltage protocol in (**F**), inactivation (**G**) of sensory neurons treated as indicated. $V_{0.5}$ values for activation and inactivation are presented in Table 1. No statistical significance was detected compared with cells treated with 0.1% DMSO ($p>0.05$, Mann-Whitney, n=16-18 cells per condition).



Supplementary Figure 6. P/Q-Type (CaV2.1) Ca^{2+} currents in dorsal root ganglion (DRG) sensory neurons are not affected by Naringenin. (**A**) Currents were isolated following the indicated protocol. (**B**) Representative traces of P/Q-Type Ca^{2+} currents from DRG sensory neurons treated with 0.1% DMSO (control) or 100 μM Naringenin. Summary of the normalized (pA/pF) P/Q-Type calcium current density versus voltage relationship (**C**) and peak P/Q-Type Ca^{2+} current density at +20 mV (mean ± SEM) (**D**) from DRG sensory neurons treated as indicated. Boltzmann fits for normalized conductance G/G_{max} voltage relations for voltage dependent activation (**E**) and using the voltage protocol in (**F**), inactivation (**G**) of sensory neurons treated as indicated. $V_{0.5}$ values for activation and inactivation are presented in Table 1. No statistical significance was detected compared with cells treated with 0.1% DMSO ($p>0.05$, Mann-Whitney, n=9 cells per condition).



Supplementary Figure 7. Naringenin does not affect T-Type Ca^{2+} currents in dorsal root ganglion (DRG) sensory neurons. (**A**) Representative family of traces of T-Type Ca^{2+} currents from DRG sensory neurons treated with 0.1% DMSO (control) or 100 μM Naringenin. Voltage protocol used to evoke the currents is shown above the traces. Summary of the normalized (pA/pF) T-Type calcium current density versus voltage relationship (**B**) and peak T-Type Ca^{2+} current density at -10 mV (mean ± SEM) (**C**) from DRG sensory neurons treated as indicated. Inactivation τ (single-exponential fit of decaying portion of the current waveforms using a single-exponential equation: $y = A_1 \times e^{(-x/\tau 1)} + y_0$, where A_1 is the amplitude, τ_1 is the decay constant, and y_0 is the offset; **D**) and time-dependent activation (10-90% rise time; **E**) from I-V curves in DRG cells shown in **B** over the range of test potentials from –40 to–10 mV. Boltzmann fits for normalized conductance G/G_{max} voltage relations for voltage dependent activation (**F**) and inactivation (**G**) of sensory neurons treated as indicated. $V_{0.5}$ values for activation and inactivation are presented in **Table 1**. (**H**) Deactivating tail currents in DMSO or 100 μM Naringenin were fit with a single-exponential function. The resulting τ values are plotted. (**I**) Recovery from inactivation in both DMSO and 100 μM Naringenin groups. Data are averaged and fitted by double exponential association ($p>0.05$, Mann-Whitney, n=9-10 cells per condition).