Molecular Pharmacology: Molecular determinants of the differential modulation of $Ca_v1.2$ and $Ca_v1.3$ by nifedipine and FPL64176

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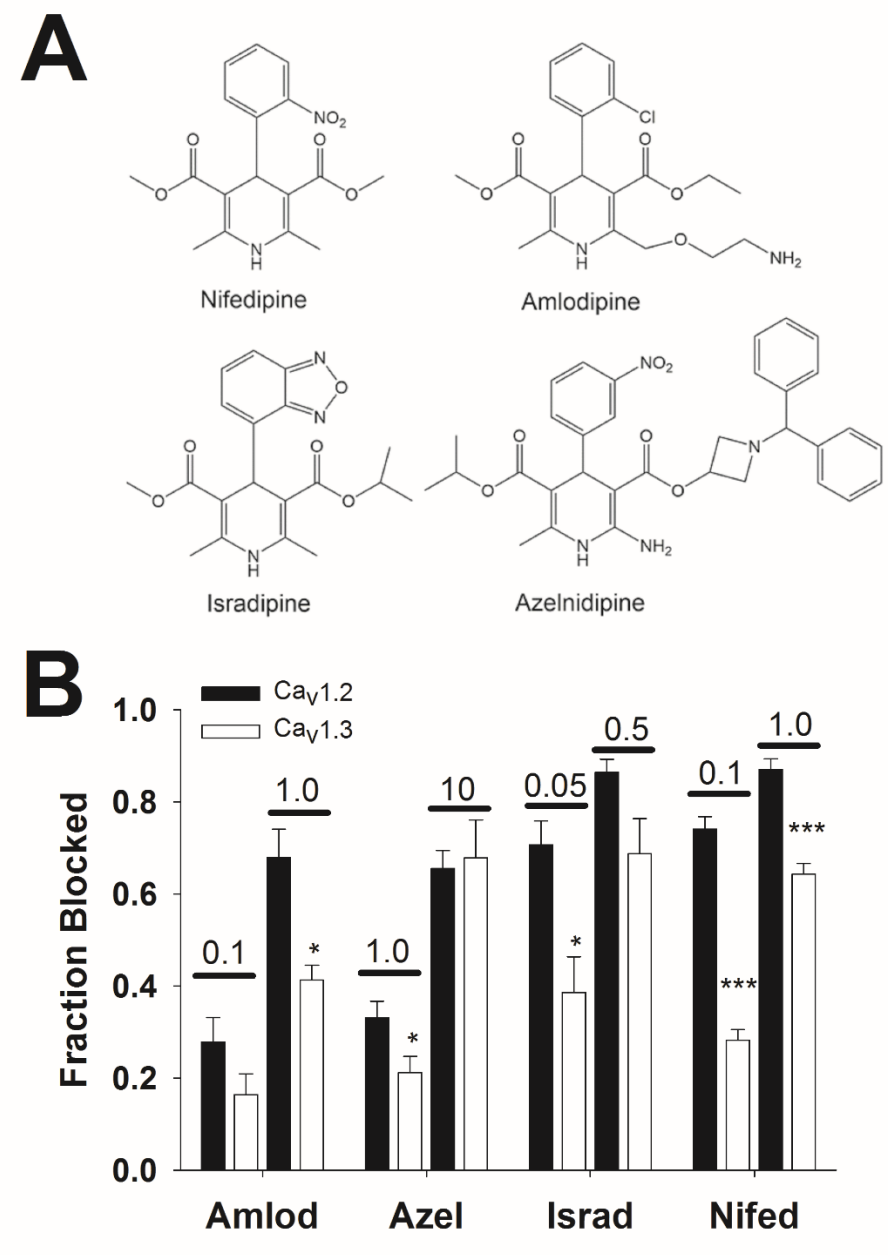

Supplemental Figure 1. Differential Block of $Ca_v1.2$ and $Ca_v1.3$ by structurally distinct dihydropyridines- A) Chemical structures of nifedipine, amlodipine, isradipine, and azelnidipine. **B)** Block of $Ca_v1.2$ and $Ca_v1.3$ by two concentrations of each of the dihydropyridine drugs shown in A. Concentrations are given in μM. Note that each drug is significantly more potent in blocking $Ca_v1.2$ compared to $Ca_v1.3$. Amlodipine (1 μM: $P < 0.05$)(N = 4) Azelnidipine (1 μM: $P < 0.05$)(N = 5) Isradipine (50 nM; $P < 0.01$)(N = 5) Nifedipine (100 nM: $P < 0.001$)(N = 4) (1 μM: $P < 0.001$)(N = 4)

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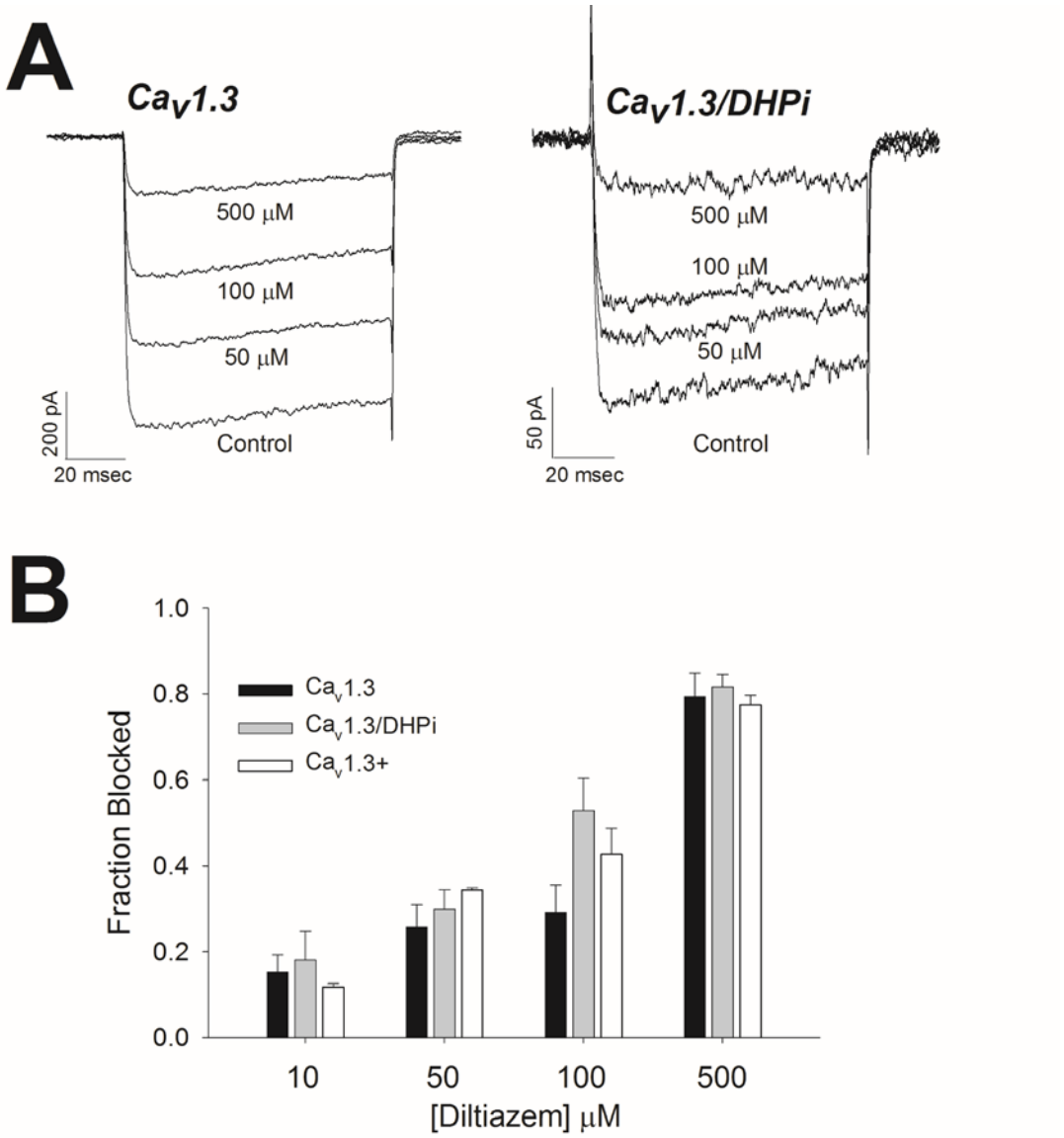

Supplemental Figure 2. Block of $Ca_v1.3$, $Ca_v1.3$/DHPi, and $Ca_v1.3$+ by the benzothiazepine diltiazem- A) Example current traces showing dose-dependent block of current conducted by $Ca_v1.3$ and $Ca_v1.3$/DHPi by diltiazem. **B)** Fraction of current blocked by 10, 50, 100, and 500 μM diltiazem in $Ca_v1.3$, $Ca_v1.3$/DHPi, and $Ca_v1.3$+. There was no significant difference in the fraction of current blocked in each of the three channel constructs at any diltiazem concentration (*one-way* ANOVA) (n = 3-7).

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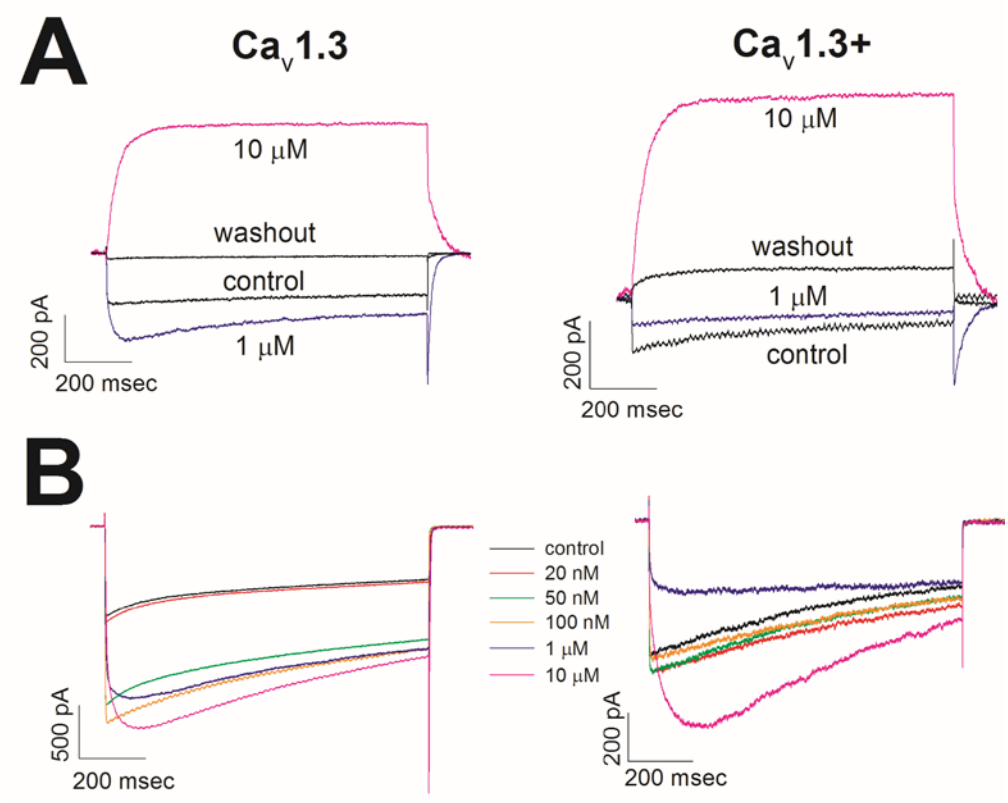

Supplemental Figure 3. Effect of FPL 64176 on current conducted by $Ca_v1.3$ and $Ca_v1.3$+ - A) Example traces of current through $Ca_v1.3$ or $Ca_v1.3$+ elicited with a step to 0 mV from a holding potential of -80 mV using the standard solution set. FPL 64176 at the indicated concentration was applied via extracellular perfusion as described in Materials and Methods. **B)** Example dose response experiments with $Ca_v1.3$+ and FPL 64176 using the NMDG-balanced solution set described in Materials and Methods. Note the increase in current amplitude at 50 and 100 nM FPL, and reduction in current amplitude at 1 μM, even though channel activation is slower than at lower concentrations.