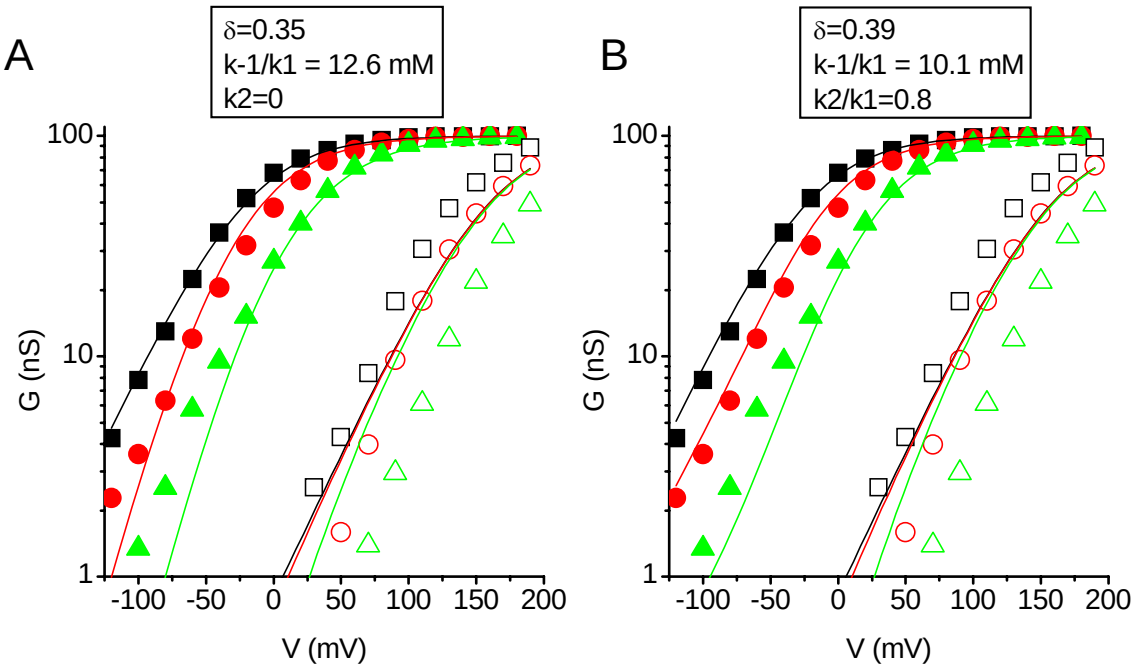

Supplementary Figure 1. Shown are activation curves obtained in the absence (open symbols) and presence of 100 µM menthol (filled symbols), and with 0 mM (black squares), 2 mM (red circles) or 20 mM (green triangles) extracellular Ca^{2+} (data reproduced from Fig. 2D). We investigated the possibility that Ca^{2+} inhibits the channel in a voltage-dependent manner, by binding to a site at a distance δ in the electrical field. The probability that the channel pore is in the unblocked block state is given by:

$$P_{unblock} = \frac{1}{1+\frac{[Ca^{2+}]_e k_1}{k_{-1}+k_2}},$$

where k_1 and k_{-1} represent the rates of Ca^{2+} binding from and Ca^{2+} unbinding to the extracellular solution, whereas k_2 is the rate of Ca^{2+} unbinding towards the intracellular solution. It is assumed that the Ca^{2+} concentration of the intracellular solution is 0. The voltage dependence of the three rate constants is given by:

$$k_1 = k_{10} e^{\frac{-z\delta FV}{2RT}}$$

$$k_{-1} = k_{-10} e^{\frac{z\delta FV}{2RT}}$$

$$k_2 = k_{20} e^{\frac{-z(1-\delta)FV}{2RT}}$$

where k_{10}, k_{-10}, k_{20} represent the rates at 0 mV, z the valence of the blocking ion (i.e. +2 in the case of Ca^{2+}), F the Faraday constant, R the gas constant and T the absolute temperature. Activation curves were fitted by the product of a Boltzmann function and the above function for $P_{unblock}$:

$$G(V) = \frac{G_{max}}{1+\exp(-\frac{(V-V_{1/2})}{s})} \times \frac{1}{1+\frac{[Ca^{2+}]_e k_1}{k_{-1}+k_2}},$$

Panels (**A**) and (**B**) represent the best global fit to the data, where in (**A**) we assumed that Ca^{2+} ions do not pass the channel (i.e. $k_2 = 0$), whereas in (**B**) Ca^{2+} permeation was allowed. $V_{1/2}$ was assumed to be independent of Ca^{2+}, but sensitive to menthol. Clearly, the fits deviate largely from the experimental data.