The role of the counter ion in determining the anion-cation permeability ratio in glycine receptor channels of different size

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We investigated the permeation of the counter ions Na^+, Li^+ and Cs^+ relative to the predominantly permeant Cl^- anions in both homomeric α1 wild type (WT) and mutant glycine receptor (GlyR) channels. The mutant GlyR channel with a proline deletion (P-2′Δ) had a larger minimum pore diameter and smaller anion-cation permeability. We transiently expressed both channels in HEK 293 cells and recorded whole-cell currents in response to the application of glycine, using standard patch-clamp techniques at 20°C. Relative anion-cation permeabilities in three different salt solutions (LiCl, NaCl and CsCl) were determined from dilution potential experiments by measuring the shifts in zero current reversal potentials, when the salt concentration in the external solution was decreased to ~50% and ~25%. Permeability ratios were determined from the shifts in reversal potential plotted against salt activity gradient using the Goldman-Hodgkin-Katz equation. In WT GlyR channels, where the pore diameter is ~0.54 nm (Rundström *et al.*, 1994), $P_{Cl}/P_{Cs} = 5.1 \pm 0.5$, $P_{Cl}/P_{Na} = 14 \pm 1$ and $P_{Cl}/P_{Li} = 35 \pm 6$. However, in the larger mutant P-2′Δ GlyR, where the pore diameter is ~0.69 nm (Lee *et al.*, 2003), $P_{Cl}/P_{Cs} = 1.9 \pm 0.1$, $P_{Cl}/P_{Na} = 3.5 \pm 0.2$ and $P_{Cl}/P_{Li} = 6.8 \pm 0.5$. Since, in terms of atomic radius, $Cs^+ > Na^+ > Li^+$, with Li^+ having the greatest magnitude of hydration energy (and largest hydration shell) and Cs^+ the smallest, this clearly indicates that counter ion hydration energies play a significant role in anion-cation permeability ratios, with the relative effect being greater in the smaller diameter channel.

Lee DJ, Keramidas A, Moorhouse AJ, Schofield PR & Barry PH (2003) *Neuroscience Letters*, **351**: 196-200.

Rundström N, Schmieden V, Betz H, Bormann J, and Langosch D (1994) *Proceedings of the National Academy of Science USA*, **91**: 8950-8954.