A salt-bridge network determines agonist size selectivity in ρ1 $GABA_C$ receptor

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The homopentameric ρ1 γ-aminobutyric acid receptors ($GABA_C$) are members of the Cys-loop ligand-gated ion channel superfamily. Homology models of these receptors based on recent structural evidence have provided a reasonable view of the receptor structure but precise molecular details and the exact orientation of GABA and other agonists in the binding pocket remains unclear. In this study, we generated a homology model for $GABA_C$ receptor and identified a series of conserved charged residues involved in a salt-bridge network at the (+) side of the GABA binding site. We hypothesized that the network may constrain interaction with agonists and determine agonist size selectivity. In order to test this hypothesis we utilized site-directed mutagenesis in combination with two-electrode voltage clamp recording of recombinant receptors expressed in *Xenopus oocytes*. Several of the mutants tested showed a reduced GABA sensitivity compared to the wild type receptor, whilst at the same time showing an increase in sensitivity to both smaller and larger agonists. Our results are consistent with our hypothesis and demonstrate the functional importance of these conserved charged residues in determining agonist size selectivity of the $GABA_C$ receptor and potentially other related receptors.