Charged residues involved in $GABA_C$ receptor agonist selectivity

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The homopentameric ρ1 γ-aminobutyric acid receptor ($GABA_C$) is a member of the Cys loop ligand-gated receptor family and closely related to the heteropentameric $GABA_A$ receptors. The GABA binding sites are at the intersubunit interfaces of the N-terminal extracellular domains. Homology modeling of these receptors, based on recent structural information, has 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 have used homology modeling to identify a series of conserved charged residues at the GABA-binding site that we hypothesized may be important for agonist sensitivity and selectivity. To test this hypothesis we used 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 sensitivity to GABA compared to the wild type receptor, whilst at the same time showing an increase in sensitivity to other agonists. This altered agonist selectivity was particularly sensitive to the size or length of the ligand. Our results are consistent with our hypothesis and demonstrate the functional importance of these conserved charged residues in determining agonist selectivity of the $GABA_C$ receptor and potentially other related receptors.