Agonist selectivity of neuronal glycine receptors

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Glycine and GABA are the two primary inhibitory neurotransmitters, glycine in the spinal cord, and GABA in the brain. The glycine receptor (GlyR) and the GABA receptor ($GABA_{A/C}R$) are chloride selective ligand-gated ion channels within the pentameric, or Cys-loop, superfamily. They are closely related in sequence and all evidence suggests they have very similar structures. Despite the apparent structural similarity, these two receptors are highly selective for their respective agonists, which differ only in the length of their carbon backbone. Unpublished research in our laboratory has recently identified a salt bridge network in the $GABA_A$ receptor to be important in ligand size-selectivity. Consistent with this role, the residues in this network are not conserved in GlyR.

Based on molecular modelling techniques, we hypothesized that K200 in loop C of the GlyR may have a similar role in ligand selectivity. This was tested using two-electrode voltage-clamp electrophysiology of *Xenopus laevis* oocytes expressing the human α1 GlyR. Contrary to our hypothesis, we found that while a K200A mutation affected agonist sensitivity, it did not affect relative selectivity based on agonist size. A F159Y mutation in the GlyR ligand-binding pocket was earlier shown to have a dramatic effect on size-selectivity (Schmieden *et al.*, 1993). Again based on molecular modelling, we hypothesized that this effect was due to a hydrogen bond between the tyrosine and S129 in the adjacent subunit. Consistent with our hypothesis, removing the possibility of this hydrogen bond with a S129A mutation, the effect of F159Y on size-selectivity was abolished.

Schmieden V, Kuhse J, Betz H. (1993) Mutation of glycine receptor subunit creates beta-alanine receptor responsive to GABA. *Science* **262,** 256-8.