Molecular mechanisms for agonist selectivity in inhibitory Cys-loop ligand-gated ion channels

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Cys-loop ligand-gated ion channels constitute one of two major superfamilies of receptors mediating rapid chemical synaptic transmission in the central nervous system. Mammalian members of the superfamily include cation selective channels that are receptors for excitatory neurotransmitters, acetylcholine and serotonin, and anion selective channels that are receptors for inhibitory neurotransmitters, GABA and glycine. Structural information for snail acetylcholine binding proteins (AChBP), and nicotinic acetylcholine receptors provided a clear picture of the acetylcholine-binding site, including a conserved box of aromatic resides that form cation-pi bonds with bound agonists. From AChBP-based homology models, we proposed (Cromer *et al.*, 2002) that the 3-dimensional position of one of the aromatic box residues is replaced with an acidic residue in inhibitory receptors for GABA ($GABA_{A/C}R$) and glycine (GlyR). Further that this residue forms a charge-charge interaction with the primary amine group of bound agonists and is important for selectivity for primary amine agonists, such as GABA and glycine, over bulkier quaternary amines, such as acetylcholine.

We now present evidence in support of this hypothesis, particularly using the homopentameric Rho1 GABA receptor ($GABA_CR$) as a model for the broader family of inhibitory Cys-loop LGICs. We also present evidence for a series salt-bridge and hydrogen bond interactions in the agonist-binding site of inhibitory Cys-loop LGICs that are determinants of selectivity between agonists of different size, such as glycine *versus* GABA. These results are consistent with our initial hypothesis and provide a more detailed understanding of agonist-receptor interactions in inhibitory Cys-loop ligand-gated ion channels.

Cromer, B.A., Morton, C.J. & Parker, M W. (2002). Anxiety over $GABA_A$ receptor structure relieved by AChBP. *Trends in Biochemical Science* **27**, 280-7.