Is the cysteine-loop involved in the gating mecahism of the $GABA_A$ receptor?

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The $GABA_A$ receptor is largely responsible for fast inhibitory action in the mammalian brain. It is a member of the ligand-gated ion channel superfamily which includes nicotinic acetylcholine receptors, serotonin ($5HT_3$) and glycine receptors. These receptors are characterized by a 15 residue cysteine-loop present in their extracellular domain and located at the transmembrane domain interface. It has been proposed that because of its location and conserved nature this loop may be involved in the mechanism that links ligand-binding in the extracellular domain to channel-gating in the transmembrane domain. The $GABA_A$ receptor is modulated by a large number of drugs including anaesthetics, benzodiazepines and barbiturates. If the cysteine-loop is involved in the gating mechanism then mutations in this loop may alter how these drugs modulate the $GABA_A$ receptor.

Preliminary data from our laboratory show that $GABA_A$ receptors containing an alanine rather than a proline residue at the 9' position (P9'A) in the cysteine-loop of either the α or β subunits have a reduced whole cell current response to GABA and modulation by drugs including diazepam is altered. Modulation of the $GABA_A$ receptor by diazepam requires the presence of a γ subunit. Work is currently being undertaken to see how the same substitution (P9'A) made in the γ subunit's cysteine-loop affects its channel activity and its modulation by diazepam and other drugs.