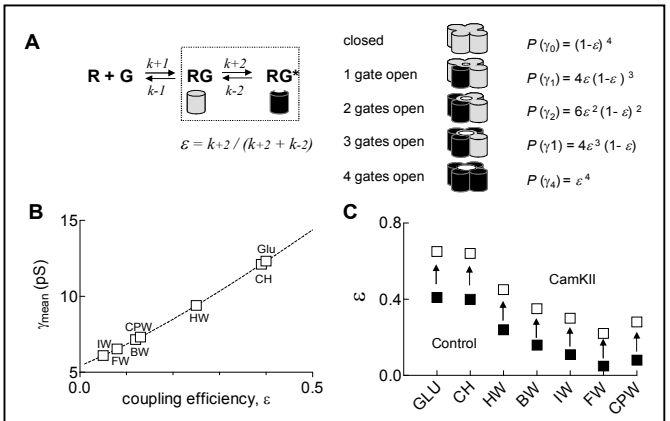
Control of glutamate receptor ion channel function by phosphorylation

Posttranslational regulation of receptor function is widespread in the central nervous system, and represents an important means by which cells regulate receptor function and localization. Numerous studies have identified sites for tyrosine, threonine, and serine phosphorylation of native glutamate receptors. We have studied regulation of the GluA1 subunit of AMPA receptor function by serine/threonine kinases and phosphatases for over a decade. The GluA1 subunit occupies a unique role among AMPA receptor subunits in that its localization and function is regulated in cellular models of plasticity. Our lab is evaluating the four intracellular serine/threonine residues within the C-terminal that are known as phosphorylation sites. Ongoing experiments assess the functional effects on receptor gating and trafficking of each site in the dephosphorylated and phosphorylated state. In addition, we are working with models of intracellular structure, and using site-directed mutagenesis to test the involvement of the GluA1 C-terminal domain in functional regulation by serine/threonine phosphorylation. This work involves a combination of electrophysiological, biochemical, and imaging approaches to understand how regulation of this subunit by phosphorylation and dephosphorylation at different intracellular residues affects receptor activation. Information gained from this approach will provide new insight into the mechanism by which intracellular signaling pathways that engage serine/threonine kinases (such as CaMKII and various PKC isoforms) can influence receptor activation to alter synaptic strength.



(A) Model of independent subunit-activation, and **(B)** the relationship between independent subunit gating and conductance for a range of partial agonists. **(C)** CamKII acting at GluA1 Ser831 enhances coupling between agonist binding and subunit activation independent of partial agonist efficacy.