become a weak partial agonist at AMPA receptors. We report that these CNQX-evoked responses actually desensitize. A kinetic analysis of responses in the presence of CNQX suggests that for AMPA receptors with TARPs, but not AMPA receptors alone, CNQX inhibits channel function in part by desensitizing receptors. These data demonstrate three things, first that internal and external polyamine block, previously thought to occur through a common mechanism, are in fact dissociable processes. Second, that TARPs do not significantly reduce the potency of CNQX as an antagonist and third, that TARPs enable CNQX to inhibit AMPARs by both competitive antagonism and by desensitization. As the effects of TARPs and other auxiliary proteins become known, such re-evaluations of pharmacological tools like polyamines and competitive antagonists will be required, particularly as CP-AMPARs are emerging as therapeutic targets.

2708-Pos
Crystal Structure of KA2-Subtype Ionotropic Glutamate Receptor Amino Terminal Domain
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The glutamate receptor ion channels that mediate excitatory synaptic transmission in the mammalian brain have a unique modular architecture distinct from that for other ligand gated ion channels. It took ten years since publication of the first crystal structure of an isolated ligand-binding domain (S1S2) (1) to solve structures of the amino terminal domain (ATD) of GluR6 (2) and GluR2 (3). These structures give insight into the regulation of subtype specific assembly by ATDs. However, structures of ATDs from other subtypes are still unknown. We have now determined high-resolution crystal structures of KA2 ATD in 2 forms at 1.4 Å & 1.6 Å respectively. KA2ATD has a clamshell-like fold similar to GluR6 and GluR2. However, the dimer assembly is significantly different than that for GluR6 & GluR2 where the R1 & R2 domains of both the protomers contribute equally to dimer formation. In KA2, the R2 domains also co-assemble and form close contacts similar to GluR6 & GluR2 ATDs but the R1 domains are separated. This assembly is interesting because the R1 domain has loops that likely specify subtype specific assembly. These loops make no contacts across the dimer interface in KA2 ATD, consistent with obligate co-assembly of KA2 with GluR5-7 for formation of functional ion channels.
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2709-Pos
A Comparative Molecular Dynamics Simulation Study of the Amino Terminal Domain of Ionotropic Glutamate Receptors
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Glutamate receptors account for the vast majority of excitatory neurotransmission in the vertebrate nervous system. The modular architecture of these membrane receptors consists of an extracellular amino terminal domain (ATD) and ligand binding domain (LBD) as well as a transmembrane ion channel. While numerous water soluble constructs of the LBD have been crystallised, high resolution structures of the ATD have been unavailable till very recently. Multiple long (3 x 50 ns) molecular dynamics simulations of five ATD dimer structures - two GluA2 (AMPA) and three GluK2 (kainate) - were performed to evaluate the stability of the structure and the rigidity of the dimer interface. The dimers remained intact throughout the course of all simulations. Overall, these structures appear to undergo very little motion. It is yet unknown whether the ATD is capable of binding a ligand. Simulations of these ligand-free structures suggest two possible regions with increased flexibility that may lead to a potential binding site. Several water molecules are also conserved across the structures as well as the two families. Electrostatic calculations indicate that the "bottom" of the ATD and the "top" of the LBD exposes complementary charge surfaces, which could explain how the two modular regions may interact in the full-length receptor.

2710-Pos
Structurally Variable Regions of the Ligand-Binding Domain of Ionotropic Glutamate Receptors Link Dynamics and Functional Properties
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It has been hypothesized that the behavior of the channel gate is controlled by structural and dynamical events within the bi-lobate ligand binding domain (LBD) of ionotropic glutamate receptors (iGluRs). With the ulterior goal of developing reliable coarse-grained models that would allow probing this hypothesis with μs to ms time-scale simulations, we have characterized the ns time-scale conformational dynamics of the LBD of GluR-2, GluR-6 and NR2A, respectively representing the AMPA, kainate and NMDA receptor class. Each LBD was modeled both using the AMBER SB99 and the GROMOS G43A1 force field. The structural and dynamical properties of the 3 LBDs were obtained from extensive molecular dynamics simulations (at least 3 independents 20 ns run per system and force field). To compare these properties across the three classes of LBD a common structural core was defined based on structural similarity. The results of these computational experiments show that (1) all 3 LBDs possess 2 common rigid body domain motions that modify the degree of twist and hinge bending of the lobes; (2) these motions do not appear to be class specific at this time-scale; instead (3) structural elements outside of the common structural core modulate the conformational space of the core and are responsible for defining class specific dynamics of the LBDs. These structural elements have been implicated previously in the modulation of ligand efficacy and extent of receptor desensitization. Thus, together these observations suggest that these identified structural elements impart class specific dynamics behavior to the LBD of iGluRs and may be responsible for the distinct functional properties of these receptors.

2711-Pos
Theoretical Investigation of Structure and Gating Mechanisms in Glutamate Receptor Ion Channels
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The ionotropic glutamate receptors (iGluRs) are excitatory synaptic transmitters found in the fore-brain. Together with potassium, sodium, and calcium channels they form a tetrameric ligand gated ion channel class of P-loop receptors. The structures of iGluRs are currently not resolved, while functional mechanisms are not well understood. To gain insight into the structure of the iGluR channel region, the KcsA potassium channel pore is used as a working model for its known structural homology with iGluR transmembrane regions. A conserved hydrophobic patch among all P-loop receptors is located along the pore lining M3 helix which spans the lipid-water interface. This patch creates a helical bundle crossing where single residue mutations produce constitutive open channels in mice, suggesting its role in the control of ion conduction. Molecular dynamics simulations and umbrella sampling methods were used to examine the opening of the KcsA M3 bundle crossing starting from the closed KcsA crystal structure (PDB ID: 1k4c). The potential of mean force defining the free energy landscape obtained from the structures of KcsA is then used to abstract the unknown closed and open forms of iGluR transmembrane regions. Assuming the P-loop region comprising the selectivity filter changes little between functional states, energetically defined conformations provide points of refinement for unknown structures of transmembrane regions for proteins such as iGluRs. In order to describe a mechanistic model of iGluR, Ca2+/Mg2+ selectivity is currently under investigation for an NMDA type iGluR. Homology modeling of the transmembrane region based on potassium channels is being used to infer structure; and Ca2+/Mg2+ interactions with organic caging agents are used to parameterize divalent ion selectivity. Understanding how iGluRs control ion conduction together with monovalent versus divalent ion selectivity will aid in describing ion channel structure-function relation.

2712-Pos
Rearrangements at the Heterodimer Interface are Integral to NMDA Receptor Activation
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