Emerging structural explanations of ionotropic glutamate receptor function

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ABSTRACT High-resolution studies of ionotropic glutamate receptor (iGluR) extracellular domains are beginning to bridge the gap between structure and function. Crystal structures have defined the ligand binding pocket well beyond what was suggested by mutational analysis and homology models alone, providing initial suggestions about the mechanisms of channel gating and desensitization. NMR-derived backbone dynamics and molecular dynamics simulations have added further insights into the role of protein dynamics in receptor function. As a whole, the current knowledge of iGluR structure in conjunction with new advances in the understanding of K⁺ channels provides a vastly improved understanding of iGluR function. This review focuses on structural and dynamic studies of the extracellular ligand binding domain of iGluRs and the pore region of K⁺ channels that have contributed to mechanistic insights into the processes of iGluR gating and desensitization.—McFeeters, R. L., Oswald, R. E. Emerging structural explanations of ionotropic glutamate receptor function. FASEB J. 18, 428–438 (2004)

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BACKGROUND

In the past two decades, studies of ionotropic glutamate receptors (iGluRs) have progressed from pharmacological characterization using partially specific drugs and toxins (22) to characterization of atomic resolution structures (1–3, 7, 9, 23–26). With such advances, iGluRs now comprise one of the best-characterized families of ligand-gated ion channels. Once thought simply to mediate fast synaptic transmission, many new functional roles have been found for these adaptable receptor ion channels. Within the central nervous system (CNS), iGluRs are known to participate in synaptogenesis, neuronal pathfinding, neuronal viability underlying onset of several neurodegenerative diseases, and regulation of synaptic efficacy, which forms the basis of learning and memory (27). More recently, the functional realm of iGluRs has been found to extend well outside the CNS to include roles in insulin secretion, bone resorption, cardiac pacemaking, as well as involvement in taste and tactile sensation (28–35). iGluRs were originally suggested to be constructed from bacterial precursors (36, 37). This has since been supported by the presence of iGluRs in plants (38) and the discovery of an iGluR predecessor in bacteria (39).

To date, almost 20 different iGluR subunits have been cloned from higher vertebrates. Based on agonist preference, they can be pharmacologically categorized into those that form receptors that are activated by the synthetic agonist N-methyl-D-aspartate (NMDA) and those that do not. Receptors formed from subunits not activated by NMDA are further categorized by their affinity for the synthetic agonist α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) vs. the naturally occurring neurotoxin kainate (22). Despite unique functional properties and varying degrees of sequence identity (between 20 and 70%; ref 40), the major structural features are conserved in all known iGluR subunits.

iGluRs are integral membrane proteins that assemble as heteromeric or homomeric receptors from subunits within their respective families. Most evidence indicates that, similar to K⁺ channels, four subunits are present per receptor (41–45). The physiologically relevant subunit stoichiometries that constitute functional receptors in vivo are not completely understood, although the presence of certain subunits (e.g., GluR2) in a given receptor are known to alter functional properties, including channel conductance, ion selectivity, and desensitization (22). Thus, the multimeric nature of iGluRs allows them to be tremendously diverse and adaptable, accounting for their presence in a broad range of biological processes. Post-transcriptional and post-translational modifications impart additional diversity and adaptability (46–48). Since iGluRs are such an evolutionarily old signaling family that contributes to many cellular processes, a thorough understanding of the structure of these receptors is important for exploiting their therapeutic potential.

The large size of iGluR subunits (>900 residues) presents several barriers to high-resolution studies of individual subunits and intact receptors. With advances in X-ray crystallography, proteins of this size can be studied; however, no successful crystallization effort for intact membrane-bound iGluR subunits has been re-
ported. Electron microscopic studies are also hampered because, unlike nicotinic acetylcholine receptors (49), no naturally occurring source of well-ordered 2-dimensional crystalline protein arrays is known. Recently, Madden and collaborators (45) have estimated the molecular dimensions of homomeric GluR2 channels to be $11 \times 14 \times 17$ nm using single particle image analysis. While embedding in micelles and selective segmental isotope labeling could allow for NMR structural studies, the size of the complex and the lack of an efficient expression system for the intact receptor present formidable hurdles.

Biochemical studies from several laboratories established the transmembrane topology of iGluR subunits (50–52), which led to the recognition they are modular proteins (53) made up of four domains, three of which are homologous to bacterial proteins (Fig. 1). Each of the four iGluR domains within any given subunit has unique properties contributing to the overall function of the protein. The amino-terminal domain shows sequence homology to the bacterial leucine/isoleucine/valine binding protein (37). It influences receptor desensitization and contains the binding site for many modulators of NMDA receptors (54, 55). For non-NMDA receptors, it contributes to receptor assembly and surface expression (41, 56–59). To date, no high-resolution structure for this domain has been reported. The intracellular carboxyl-terminal domain is the most divergent region of iGluR subunits without homology to bacterial proteins, ranging in size from ~40 to ~600 residues. Functionally, this domain is involved in cytoskeletal interactions, subunit trafficking, and modulation of channel conductance and contains a variety of sites for post-transcriptional/post-translational modifications (60–64). Unfortunately, little information on the structures of the carboxyl-terminal domains is available. In the case of GluR2 and GluR3 subunits, the isolated and relatively short carboxyl-terminal domains are unstructured in solution (R. L. McFeeters and R. E. Oswald, unpublished results), but a peptide derived from the NMDA-R1 carboxyl-terminal domain does adopt a stable structure when bound to calmodulin in the presence of $\text{Ca}^{2+}$ (J. Kweon and R. E. Oswald, unpublished results). The iGluR pore domain shows a high degree of sequence homology to $K^+$ channel pores, although inverted with respect to the membrane (53). This domain has proved extremely difficult to study since it is very hydrophobic and embedded in the membrane; at least a portion of M2 (Fig. 1) in isolation from an NMDA subunit has been characterized using solid-state NMR (65). As discussed below, the expanding knowledge of structural correlates of function for the $K^+$ channel pore provides important insights into the gating of iGluR channels.

Most iGluR structural efforts have focused on the extracellular ligand binding domain (henceforth referred to as S1S2) since understanding iGluR/ligand interactions paves the way for potential therapeutic treatments for many diseases such as amyotrophic lateral sclerosis, epilepsy, stroke, Rasmussen's encephalitis, Alzheimer's, Parkinson's, and Huntington's diseases, diabetes, osteoporosis, and cardiac arrhythmias (22, 40). Before the availability of high-resolution structures, homology models were developed based on sequence similarity to bacterial amino acid binding proteins (10, 11, 13, 66, 67). These models successfully predicted both the bi-lobed structure of the glutamate binding domain and lobe closure upon agonist binding (68). Based on the modular topology of each subunit and homology of the agonist binding domains to bacterial amino acid binding proteins, the S1S2 domain of GluR4 was excised from the full-length subunit by Keinanen and collaborators (69) to generate soluble constructs amenable to high-resolution study. The analogous domain was subsequently prepared from several other iGluR subunits (9, 70, 71). Remarkably, the pharmacological properties of these S1S2 domains remain nearly identical to those observed for full-length subunits in wild-type receptors, suggesting that the structure of the isolated domain is similar to that of the intact protein (70, 72). Recently, Jayaraman and collaborators demonstrated that the UV spectrum of the iGluR antagonist CNQX bound to the S1S2 domain of GluR4 and to the intact homomeric GluR4 receptor.

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**Figure 1.** Modular structure of iGluRs illustrating the transmembrane topology, the two extracellular domains, and the carboxyl-terminal domain. Flip/flop refers to an alternatively spliced segment that plays a role in desensitization. S1 refers to the sequence between the amino-terminal domain and M1; S2 refers to the sequence between M3 and M4. Lobe 1 is the structural unit attached to the amino-terminal domain, and Lobe 2 is the structural unit that links to M1 and M3. Note that segments of S1 and S2 are found in both Lobes 1 and 2.
were identical (73), further indicating conserved structural integrity of the ligand binding pocket in the isolated S1S2 domain.

RECENT RESULTS

Although originally expressed in insect cells (74), the ability to overexpress Glur2 S1S2 in Escherichia coli, denature, and refold it into a fully functional, monomeric, soluble protein (71) has allowed for determination of the crystal structure (1) and characterization of backbone dynamics by NMR spectroscopy (15). The original structure of the GluR2 S1S2 domain bound to kainate reported by Gouaux and collaborators (1) confirmed the bi-lobed structure predicted by homology modeling (11). Contrary to an earlier view that one lobe was derived from the amino-terminal segment before M1 and the second lobe was derived from the loop between M3 and M4, the crystal structure showed two interlobe crossings, indicating that both sequences contributed to both lobes (Fig. 1 and Fig. 2). Furthermore, the artificial linker introduced as a substitute for M1-M3 was found to be unstructured (1). This is consistent with the location of the linker on the surface of the protein and its lack of influence on pharmacological properties (ref 2; Fig. 2).

Structure and dynamics of the ligand binding site

The ligand binding pocket is located between the two lobes and can be thought of as comprising two components. The portion that binds the equivalent of the backbone portion of glutamate (the α substituents) is relatively fixed and varies little between structures with different ligands bound (2). In contrast, the portion that binds the equivalent of the side chain of glutamate (the γ substituents) varies considerably between structures with different bound ligands. In the glutamate-bound structure (Fig. 3), the α-carboxyl forms essential interactions with the side chain guanidinium of R485 and the main chain NH group of T480. Mutation of the equivalent of R485 has been shown to abolish agonist-induced channel opening in GluR4 and NMDA subunits and agonist binding to the chick kainate binding protein (66, 75, 76). S654 and P478 are also involved in important interactions with the α substituents that are conserved among agonists (2). This portion of the binding site shows little local motion in NMR dynamics experiments (15). Thus, it appears that this region of the binding site (subsites A and B; Fig. 3) functions with a lock-and-key mechanism.

The structure of the binding site in contact with the γ substituents differs with different ligands bound. In the case of glutamate and kainate, the γ binding site is formed by S654, T655, L650, and L703 (subsites D and E), with the interaction occurring through the backbone of each residue, except for T655, whose side chain hydroxyl is involved. In contrast to residues involved in the α site, NMR dynamics experiments have shown that all four of these residues interacting with γ substituents display backbone motion on the μs-ms time scale (15). In the case of AMPA, the D subsite is occupied by water, and subsites G and F are occupied by the 5-methyl group and isoxazole nitrogen (P478, Y405, E705, and M708; ref 2). M708 undergoes a rotamer change in binding AMPA relative to the binding of kainate and glutamate (2) and, likewise, is a relatively mobile component (measured using NMR dynamics experiments) of the binding pocket (15). Differences in the structure of the binding site with different ligands bound and the relatively mobile nature of this portion of the binding site may suggest that the ligands bind with an induced fit mechanism. Thus, the binding site can be viewed as having two structurally and dynamically distinct portions: the relatively fixed portion of the binding site for the α substituents and the more dynamic portion for the γ substituents.

Lobe closure

As suggested by the original homology modeling studies (11, 13, 66, 67) and demonstrated experimentally with the subsequent X-ray crystal structures (1, 2), the
bilobed ligand binding domain closes upon agonist binding. The unbound apo-state exhibited the widest opening between lobes and the antagonist DNQX showed only a small 3° change in lobe orientation relative to the apo form. The partial agonist kainate and the full agonist glutamate showed approximate closures of 12° and 20°, respectively. In short, the extent of lobe separation decreased in the order of apo > DNQX > kainate > glutamate ≈ AMPA (2). These observations led to the lobe closure hypothesis in which the degree of lobe closure is directly related to the extent of receptor activation and desensitization (3). More specifically, in the crystal, S1S2 forms a dimer and the movement of Lobe 2 relative to a fixed dimer interface between two copies of Lobe 1 is thought to produce the torque needed for channel opening (4). In addition to the crystal structures, lobe closure has been observed in solution based on scattering studies. While original solution scattering studies indicated no reduction in the radius of gyration for S1S2 (77), more recent studies have detected changes in the radius of gyration that are consistent with the overall shape of the apo- and agonist-bound crystal structures (D. R. Madden, personal communication).

The crystal structures predict a rigid body movement of the two lobes in the apo form vs. various agonists, partial agonists and antagonists (2, 3, 23). However, spectroscopic studies in solution suggest that the differences between the various forms of S1S2 may be more complex. Fluorescence and isothermal titration calorimetry measurements have shown that the binding reaction for S1S2 from GluR4 with glutamate is driven primarily by a favorable enthalpy change (78). A kinetic analysis showed that agonist binding involved an initial rapid association, followed by a slower conformation change that stabilized the complex, termed “docking followed by locking” (79). Specifically, residues Y451 and E403 were shown to participate in docking whereas E706 was shown to play a critical role in locking (79). In addition, infrared spectroscopy showed that the ligand charge distribution adapted to optimize binding, partially offsetting the unfavorable interaction of the electronegative ligand moieties with the electronegative functional groups in the binding pocket (80, 81). Changes in vibrational spectra also showed a significant increase in β-sheet content and simultaneous increase in α-helical and turn content upon the binding of both full and partial agonists (80, 82). Furthermore, NMR dynamics showed considerable mobility for the β-sheet core of Lobe 2 and residues in helix-F, all of which contribute to the binding pocket (15). Thus, the core of Lobe 2, helix-F, and the surrounding turns display interesting dynamics and changes in transient structure upon agonist binding. These results are consistent with the inability to determine high-quality electron density for the antagonist DNQX-bound crystal structures of S1S2 (2). Themobile nature of the Lobe 2 core combined with the varied interactions of residues with the γ substituents of various agonists in the binding pocket presumably induces conformational changes that could influence channel gating.

**UNANSWERED QUESTIONS**

X-ray structures provide a precise view of the binding site and core secondary structure of S1S2 in the crystalline state. In instances where crystal packing forces or the low temperature at which data were collected can alter the structure, caution must be exercised in inter-
preparing such results. This especially holds true for bilobed proteins, in which the orientation of the two lobes is particularly susceptible to crystal packing artifacts. For example, NMR measurements of residual dipolar couplings in solution have revealed that maltodextrin binding protein bound to β-cyclodextrin exhibits a lobe closure that differs by ~10° from that found in the crystal structure (83). Likewise, differences between the crystal and solution structures of T4 lysozyme (84) and calmodulin (85) have been reported. The nonphysiological conditions in which crystal structures are determined warrants consideration when inferring function from structure.

Because of the efforts to relate the degree of S1S2 lobe closure to the function of the intact glutamate receptor (2, 3, 23), an accurate measure for the degree of lobe closure for a particular agonist is crucial. In a number of cases (e.g., glutamate- and AMPA-bound forms of S1S2; ref 2), essentially identical degrees of lobe closure for different copies of the protein within the asymmetric unit (where differences in crystal packing may also be present) suggest that the measurement of lobe closure may be free of crystal packing artifacts. However, this may not be the case for the apo form, in which different copies with the asymmetric unit vary by as much as 4° (2). The kainate-bound form of S1S2 crystallizes as a monomer (1), so that crystal-packing artifacts cannot be assessed. Furthermore, crystallization of S1S2 from GluR0 in the absence of ligand resulted in a conformational state only slightly more open (by ~1.1°) than the glutamate-bound form (4). For the NMRA NR1 S1S2 domain, the partial agonist n-cycloserine exhibits a degree of lobe closure similar to the full agonist, glycine (9). Thus, although the degree of lobe closure may be affected by influences in the crystal state, the two lobes likely favor a fully closed state upon full agonist binding and a less open state upon partial agonist binding.

To relate lobe closure to the function of glutamate receptors, Gouaux, Mayer, and collaborators have presented a remarkable series of studies that demonstrate that the degree of lobe closure of the S1S2 crystal induced by binding different full and partial agonists is correlated to activation of the intact homomeric GluR2 induced by binding different full and partial agonists is that the degree of lobe closure of the S1S2 crystal state upon full agonist binding and a less open state upon partial agonist binding.

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agonist), channels exhibit considerably more rapid opening and closings during a burst of channel openings than in the presence of full agonists, and the resolution of these kinetic processes can be limited by the bandwidth of the recording. Rapid closures faster than the bandwidth of the recording can lead to a decrease in the measured channel conductance, so that some of the decrease in channel conductance may be attributable to changes in channel kinetics. In an integrated current measurement, the smaller response of kainate vs. full agonists is likely a combination of rapid channel closures and a decreased conductance. More recently, Jin et al. (92) made a heroic effort to relate the single channel properties of homomeric GluR2 activated by glutamate and various partial agonists (5-substituted willardines) to lobe closure. Although a small number of channels were observed and the data were necessarily filtered heavily (possibly distorting the actual channel amplitude due to the rapid kinetics), the authors concluded that several single channel amplitudes could be observed and that glutamate (the full agonist) produced relatively more larger amplitude events than the partial agonists. Although the structural interpretation remains elusive, several possibilities exist. One is that in the intact receptor, several stable degrees of lobe closure can be produced and that glutamate tends to stabilize the greater degree of lobe closure relative to partial agonists, with the degree of lobe closure determining the amplitude of a particular channel event. This may be similar to the ligand binding domain from metabotropic glutamate receptor mGluR1, which exhibits a mixture of open and closed conformations in the presence of glutamate (93). Several lines of experimental evidence from bacterial amino acid binding proteins indicate that the open and closed conformations are in rapid equilibrium such that in solution at least four molecular species exist. These species correspond to open and closed conformations, both with and without ligand bound (94, 95). Alternatively, lobe closure may be only one of several factors (such as internal dynamics in Lobe 2) that determine the differences in current due to activation by partial and full agonists.

**PROSPECTS AND PREDICTIONS**

**Channel gating**

Proteins are dynamic, having motion on multiple time scales. This is especially true for the GluR2 S1S2 domain (15). With the difficulty in interpreting electron density for Lobe 2 with certain ligands bound and the large variations in B factors (which show strong correlations with data from NMR experiments), even crystallography suggests significant internal motion. The B factors (which represent a variation in atomic position in the crystal) in Lobe 2 are greater for the kainate-bound than for the apo or DNQX-bound forms. Moreover, the B factors are greatest when bound to glutamate (2). Molecular dynamics simulations show a decrease in domain mobility for full agonists that is greater than for partial agonists (16). In addition, NMR-derived backbone dynamics has determined significant backbone mobility for residues throughout the Lobe 2 core (15). With the small energy required for gating (less than the 40 kJ/mol provided by agonist binding), internal motions of Lobe 2 may have a significant effect on channel gating. This is especially true since the pore lies between two of the mobile β-sheets constituting the Lobe 2 core (Fig. 4).

Closure of the S1S2 lobes as a result of agonist binding almost certainly provides the energy required for channel opening. Movement of the lobes could be rigidly coupled to the channel gate such that lobe closure induces a radially outward force that alters the conformation of the helix formed gate, opening the channel. However, the complexity of iGluR channel gating suggests that other more subtle structural and dynamic features are also important. The Lurcher mutation at the end of the third transmembrane segment, just preceding Lobe 2, drastically alters gating for β2 receptors (96) such that these channels open spontaneously. Similarly, a mutation in the pre-M1 region linked to Lobe 1 in NR2 alters gating of NMDA receptors (54). One explanation of these results is that

[Figure 4. The β-core of Lobe 2, showing the linkage to M1 and color-coded according to the NMR backbone dynamics. β-Sheets are depicted as ribbons whereas the bound glutamate ligand is shown in a space filling perspective. All coordinates were taken from the crystal structure (1Hj), and S1S2 side chains were left out for clarity (1, 2). Color coding indicates motion measured by NMR spectroscopy (15). The color coding is the same as in Fig. 3.]
the lobes can close spontaneously without agonist (opening the channel), and the mutations in M1 or M3 increase the probability of this spontaneous lobe closure. Alternatively, channel gating may not strictly depend on movement of the lobes and may occur in the absence of lobe closure.

Substantial evidence supports the latter possibility. The β-sheet core of Lobe 2 was shown to have considerable mobility on the μs to ms time scale (15), and the β-sheet content was shown to increase upon agonist binding (80, 82). Since the pore is directly tied to the ligand binding domain through two β-strands that are part of the Lobe 2 core, this region is likely to be involved in channel gating. Subtle conformational and dynamic changes in Lobe 2 (caused by ligand binding and domain closure) would then account for some of the complexities associated with gating. As shown in Fig. 4, M1 is directly tied to β-8 and M3 is directly tied to β-9 via helix-E of the Lobe 2 core. M3 has been implicated as a transduction element, coupling ligand binding to channel gating (87). As such, closure of the S1S2 lobes facilitates conversion from the closed to an open state, but may not be the direct conformational cause of such a transition. Rather, lobe closure could greatly increase the probability that the channel would enter an open conformation and could be thought of as a switch that induces gating by promoting the conformational changes necessary to allow the channel to enter an open state. Further, the role of S1S2 would be predominantly agonist recognition and differentiation, with movement of the lobes determining the single channel conductance and setting limits on the overall timing and duration of channel opening (Fig. 5). Rapid openings and closings within a burst would then be determined by the internal dynamics of Lobe 2, which are apparent both from the B factors in crystallography (2) and by NMR spectroscopy (15).

Desensitization

Termination of the iGluR response can be mediated by the loss of bound agonists (deactivation) or conversion to an unresponsive state (inactivation/desensitization).

Like gating, desensitization is a complex phenomenon with different rates and mechanisms of desensitization are observed for different iGluR subtypes (22). NMDA receptors desensitize slowly via multiple mechanisms whereas AMPA and kainate receptors desensitize much more quickly (22). The complexity of desensitization is illustrated by the many different iGluR regions that play roles in the overall process. For example, the amino-terminal (54, 55), flip/flop (Fig. 1; ref 48), and carboxyl-terminal regions (97) all have different effects on desensitization. Since many regions affect desensitization to differing degrees, multiple processes may contribute to the overall phenomenon. The structure of S1S2 bound to cyclothiazide (a compound known to inhibit desensitization) as well as equilibrium sedimentation studies and crystal structures of several GluR2 S1S2 mutants that affect desensitization suggest that mutations that prevent desensitization promote the dimerization of S1S2 though an interface on Lobe 1 (26). This interface includes the L483Y mutation that blocks desensitization and a portion of the flip/flop alternative splicing segment that affects desensitization. Based on these results, a mechanism of activation and desensitization has been proposed by Gouaux and collaborators (26) whereby activation requires the movement of Lobe 2 relative to the Lobe 1 interface (lobe closure). The dissociation of the Lobe 1-mediated dimer can then uncouple the lobe closure from the channel domains, leading to desensitization. These findings provide one of the first mechanistic accounts of desensitization and represent an important advance in our understanding of this process.

However, like the complexities associated with channel gating, desensitization is likely to be a conglomerate of multiple mechanisms. For example, desensitization by the carboxyl-terminal domain could be mediated through the pore by displacement of the M4 transmembrane helix or through interaction with intracellular proteins that affect pore conformation or the ion conduction pathway. An example of this is Ca2+-mediated inactivation, which is caused by the interaction of calmodulin with the carboxyl-terminal domain of the NMDA NR1 subunit (98). Another

Figure 5. A typical single channel record showing closures within a burst. We postulate that the degree of lobe closure determines single channel conductance and the length of the burst. Closures within the burst may be controlled by the internal dynamics of Lobe 2. This single channel event was recorded from a homomeric GluR3 channel by K. Margot and L. Nowak (91).
possibility supported by protein dynamics studies of the GluR2 S1S2 domain is that the concerted motion of helix-F may allow for agonist dissociation in the lobe-closed state (15). That is, if helix-F were sufficiently mobile, dissociation of the agonist could occur while the lobes are closed, allowing the channel to revert to a closed state due to the lack of $\gamma$ interactions in the binding site. The time for the lobes to reopen and rebind agonist would account for the desensitized refractory period. Further evidence for the role of helix-F in agonist binding and receptor activation has been suggested from mutational analysis (99) and from molecular dynamics (16).

Desensitization provides further evidence for subtle dynamic processes governing channel gating when the “flip” and “flop” splice variants are considered. AMPA receptors carrying the flop splice variants of GluR3 and GluR4 were shown to have desensitization time constants roughly four times faster than those of the flip variants (100). The amino acid sequence difference between AMPA receptor flip and flop shows the greatest divergence directly preceding M4. In the fast desensitizing flop sequence, three consecutive glycines are substituted for a lysine-aspartate-serine sequence. Intuitively, the enhanced flexibility of the additional glycines could allow for less constrained motion, both spatially and temporally. Though speculative, the increased mobility could provide an expedient pathway for the conformational change underlying desensitization.

CONCLUDING REMARKS

In the past 15 years, great advances in understanding the structure of ionotropic glutamate receptors have been made. With such discoveries it has become possible to think about ion channel function on a whole new level of detail. Definition of the ligand binding site and detection of structural mobility in regions that couple the ligand binding domain to the pore provide tentative structural explanations for functional mechanisms. Coupled with the advances in understanding of $K^+$ channel conductance and gating, speculation into the processes of gating and desensitization has become feasible. We propose here the idea that motions and rearrangement within the core of Lobe 2 contribute to the structural changes underlying channel gating and that the degree of S1S2 lobe closure may govern conductance and the time domain of receptor function. Further work in crystallography, spectroscopy, simulations, and functional measurements should provide the basis for a detailed molecular understanding of this essential receptor family and clues for the development of effective therapeutic agents directed toward specific glutamate receptor subtypes.

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