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Abstract:

Enigmatic orphan glutamate delta receptors (GluD) are one of the four classes of the ionotropic glutamate receptors (iGluRs) that play key roles in synaptic transmission and plasticity. While members of other iGluR families viz AMPA, NMDA, and kainate receptors are gated by glutamate, the GluD receptors neither bind glutamate nor evoke ligand-induced currents upon binding of glycine and D-Ser. Thus, the GluD receptors were considered to function as structural proteins that facilitate the formation, maturation, and maintenance of synapses in the hippocampus and cerebellum. Recent work has revealed that GluD receptors have extensive crosstalk with metabotropic glutamate receptors (mGlus) and are also gated by their activation. The latest development of a novel optopharamcological tool and the cryoEM structures of GluD receptors would help define the molecular and chemical basis of the GluD receptor's role in synaptic physiology.

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1. Introduction

Almost two decades after the excitatory amino acids first emerged as neurotransmitters in the vertebrate central nervous system, the three major subtypes of ionotropic glutamate receptors (iGluRs) were named *N*-methyl-D-aspartate (NMDA), quisqualate, and kainate in the seminal review by Watkins and Evans in 1981(Watkins and Evans, 1981). Quisqualate receptors were later named α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Honoré et al., 1982). Delta receptors were, however, identified a decade later by low stringency hybridization screening using GluA1-GluA4 as probes on mouse forebrain library and named as Delta1 (Yamazaki et al., 1992) and Delta2 (Lomeli et al., 1993) owing to their low but significant sequence similarity of ~17-28 % to other iGluR subfamilies. Despite similarities in sequence and structural topologies, glutamate, AMPA, and kainate did not bind to the Delta1 or Delta2 or evoked whole-cell currents from HEK293 cells expressing homomeric Delta1 or Delta2 receptors, attracting the label "orphan" (Lomeli et al., 1993). This discovery, however, necessitated the addition of the fourth class into the iGluR family resulting in NMDA, AMPA, kainate, and Delta receptors as is known today. While initial studies reported expression of delta receptors (GluD1 and GluD2) in the inner ear (Gao et al., 2007), hippocampus (Gao et al., 2007; Tao et al., 2018), and cerebellum (Araki et al., 1993), respectively, recent work has revealed much broader expression in several regions of the brain (Hepp et al., 2015; Jakobs et al., 2007; Konno et al., 2014; Nakamoto et al., 2020). GluD receptors mediate numerous behavioral and neurocognitive functions, insights into which primarily came from genetic and knockdown studies. Mice defective in the GluD2 receptors were ataxic and had defective Parallel Fiber (PF) - Purkinje cell (PC) synapse formation and cerebellar long term depression (LTD) (Kashiwabuchi et al., 1995; Kurihara et al., 1997). In addition, single-nucleotide polymorphism and copy number variation studies have linked GluD1 with autism, schizophrenia, bipolar disorder, aberrant social and cognitive behavior, and major depression (Benamer et al., 2018; Liu et al., 2020; Yadav et al., 2013, 2012; Yuzaki and Aricescu, 2017). Similarly, de novo and inherited mutations in GluD2 have been associated with cerebellar symptoms, retarded speech, and cognitive impairment (Maier et al., 2014; Utine et al., 2013; Yuzaki and Aricescu, 2017).

GluD receptor function in synapse formation, maturation, and maintenance are primarily attributed to their role in mediating trans-synaptic, tripartite complex formation with cerebellin and neurexin

at PF-PC synapses by GluD2 (Cheng et al., 2016; Elegheert et al., 2016; Matsuda et al., 2010; Uemura et al., 2010) and at parallel fiber (PF)–molecular interneuron (MLI) synapses (Konno et al., 2014), hippocampal synapses (Tao et al., 2018) and cortex (Fossati et al., 2019) by GluD1.

The mechanisms underlying ionotropic functions of the GluD receptor are, however, much less clear. Extensive electrophysiological assays on the Lurcher mutant (Lc) and chimeric receptors generated by transplantation of LBD from AMPA and kainate receptors to GluDs had identified the presence of functional ion channels (Kakegawa et al., 2011; Naur et al., 2007; Orth et al., 2013; Schmid et al., 2009; Schmid and Hollmann, 2008; Wollmuth et al., 2000). Notably, the GluD2 Lc mutant has been instrumental in demonstrating the binding of D-ser and glycine. Both amino acids cause a reduction of GluD2 Lc ion current (Naur et al., 2007). Recent studies have shed light on the role of group I metabotropic glutamate receptors (mGlu1/5) and adrenergic receptors in triggering the opening of GluD pore (Ady et al., 2014; Benamer et al., 2018; Dadak et al., 2017; Gantz et al., 2020; Lemoine et al., 2020). Alike the Lc mutant, this current is reduced by D-ser and by NASPM, a blocker of GluD2 Lc, and was absent upon expression of dead pore mutant or in the absence of GluD1/2 (Ady et al., 2014; Benamer et al., 2018; Gantz et al., 2020). The recent development of an optogenetic pharmacological tool holds promise to probe further the elusive ionotropic contribution of GluD receptors to synaptic physiology (Lemoine et al., 2020).

Structural insights in GluD receptors first came from the crystal structures of ligand-binding binding domain (LBD) of GluD2 in apo and D-Ser bound states (Naur et al., 2007). Subsequently, structures of the amino-terminal domain (ATD) of GluD1 and GluD2 (Elegheert et al., 2016) and extracellular domain (ATD-LBD) of GluD2 receptor (Cheng et al., 2016) gave initial insights into the structure and function of GluD receptors. These studies showed that the LBD cleft could not accommodate glutamate like GluN1 and shares structural similarities with other iGluRs (Kristensen et al., 2016; Naur et al., 2007). Recent structures of the full-length GluD1 (Burada et al., 2020b) and GluD2 (Burada et al., 2020c) revealed a novel architecture distinct from other iGluR families (Burada et al., 2020a).

In this review, we summarize the insights gained from the structures of the isolated extracellular domains of GluD receptors and the recently determined cryoEM structures of full-length receptors. In addition, we review the latest developments in the understanding of the crosstalk between metabotropic glutamate receptors and GluD receptors and their role in synaptic physiology.

2. Amino-terminal domains in Delta receptor function and stability

Amino-terminal domain (ATD) is the largest sub-domain of the iGluRs with an average of 400 amino acids, nearly one-third of the full-length receptor. They play a crucial role in tetrameric assembly by mediating inter-subunit interactions (Clayton et al., 2009; Jin et al., 2009; Kumar et al., 2009; Kumar and Mayer, 2010) and receptor trafficking (Qiu et al., 2009). GluD-ATDs perform many functions, including maintenance of the receptor's tetrameric assembly (Burada et al., 2020b, 2020a); mediating interactions with the soluble cerebellin from presynaptic neurons, and neurexin from the presynaptic membrane for the formation of a trans-synaptic complex (Elegheert et al., 2016; Tao et al., 2018; Yuzaki, 2004; Yuzaki and Aricescu, 2017) essential for the proper apposition of the pre and postsynaptic neurons (Cheng et al., 2016; Yamashita et al., 2013; Yuzaki and Aricescu, 2017). Besides, ATD was found to be important for potentiating fast excitatory synaptic transmission *via* GluD1 (Tao et al., 2018). Indeed, expression of GluD1 without ATD or GluD1 with GluA1 ATD or GluA1 alone failed to increase excitatory transmission, whereas chimeric GluA1 with GluD1 ATD could still carry out the functions of wild type GluD1 (Tao et al., 2018). Moreover, the ATD mediates ATD-LBD coupling, which has been shown to be important for GluD gating (Elegheert et al., 2016). Tinkering with the ATD-LBD linker by adding a glycan wedge impaired the inhibition of Lurcher currents requiring ~ 1.5 times more D-Ser than the wild type Lurcher mutant, highlighting the role of ATD-LBD coupling in the gating of GluD receptors (Elegheert et al., 2016; Naur et al., 2007).

The monomers of GluD family receptor ATDs have conserved bilobed (R1 and R2) architecture (Elegheert et al., 2016). Interestingly, unlike other iGluRs, the cleft between the two lobes is occupied by a 12 amino acid long cleft loop that extends from the R1 to R2 lobe and is stabilized by a disulfide bridge, unique to GluDs (Elegheert et al., 2016). Posterior to the cleft loop, another loop harbors an N-glycan and is stabilized by another GluD-specific disulfide bridge (Cheng et al., 2016; Elegheert et al., 2016) (**Fig. 1a**). This loop is well-extended and could be a hub for interacting sites of other proteins. Apart from these differences, a GluD-exclusive helix is also present and is hypothesized to be involved in ATD-LBD intra subunit interactions (Cheng et al., 2016; Elegheert et al., 2016). These three exclusive structural components might play a role in the unique functionality and architecture of the GluD family of receptors.

Two GluD ATD monomers form 2-fold symmetric dimers similar to that observed in AMPA and kainate receptors (**Fig. 1b**). The dimers form with high affinity (nanomolar) as observed in other iGluRs and pack tightly with more interacting surface area when compared to other iGluRs (Burada et al., 2020b, 2020c; Cheng et al., 2016; Elegheert et al., 2016). The buried surface area (Krissinel and Henrick, 2007) for the ATD dimer interface in GluD1 (5KC9) and GluD2 (5KC8) is ~1601 $Å^2$ and ~1588 $Å^2$, respectively, which is slightly higher than ~1490 $Å^2$ for GluK2 (3H6G), and ~1152 $Å^2$ for GluA2 (6U5S). Further, ATD domains mediate the dimer-of-dimer interactions that contribute to iGluR assembly as tetramers. Usually, R2 lobes of proximal subunits are involved in tetramer formation at the ATD layer. The GluD1 receptor structure revealed a much lesser buried surface ~28$Å^2$ when compared to ~300 $Å^2$ interaction interface in AMPA, kainate receptors. The crystal structures of isolated GluD2 ATD fused with Cbln1 assembled as N-shaped tetrameric arrangement in unit cells as observed in GluA2 and kainate receptors (Elegheert et al., 2016). However, in the full-length cryo-EM structures of GluD receptors (Burada et al., 2020b, 2020c) and the crystal structures of the extracellular domain of the GluD2 receptor, it was not observed (Cheng et al., 2016). In addition, unlike kainate and AMPA receptors where the two ATD dimer pairs are tilted at the dimer-of-dimer interface owing to a domain-swapped organization, the GluD1 ATD dimer pairs are arranged almost in the same plane. Due to this arrangement, a line connecting the center of masses (COMs) of the lower R2 lobes of subunits A and B makes a reflex angle of ~200° with COM of subunit D (from the BD dimer pair) (**Fig. 2 a-b**). However, in the case of AMPA (GluA2) and kainate (GluK3) receptors the R2 COMs of subunits A, B and D subtend an obtuse angle of ~120° (**Fig. 2 c-d**) owing to the tilt.

3. Insights from high-resolution structures of GluD receptor ligand-binding domains

LBDs undergo conformational changes on agonist binding and transduce the generated strain towards ATD and TM domains, resulting in ion channel opening in NMDA, AMPA, and KA receptors. LBDs are highly conserved with sequence identities of ~48% across the iGluR subfamilies and ~61% between GluD1 and GluD2 subunits (Burada et al., 2020a; Traynelis et al., 2010). The first structure of an isolated domain of the GluD family was GluD2-LBD (Naur et al., 2007) and to date, only three crystal structures of isolated LBDs of GluD2 (Kristensen et al., 2016; Naur et al., 2007) have been reported. The LBD structures revealed structural features similar to other iGluRs having a venus flytrap-like architecture with two subdomains, D1 and D2 (Armstrong

and Gouaux, 2000; Furukawa and Gouaux, 2003; Mayer, 2005; Veran et al., 2012). In addition, the apo form of the GluD2 LBD that crystallized as a dimer with calcium sitting at the dimer interface, possibly contributing to its stability, pointed towards a conserved mechanism of coupling at the LBD layer (Hansen et al., 2009; Naur et al., 2007). The apo structure also gave insights into the binding pocket of the LBD domain. The LBD pocket of GluD2 is similar to GluN1 and cannot accommodate glutamate. Further, amino acids Val687 and Trp741 in GluD that corresponds to Val689 and Trp731 in GluN1 create a hydrophobic environment that hinders the binding of glutamate (Furukawa and Gouaux, 2003). On the other hand, the LBD of GluD2 bound to D-Ser and 7-CKA (7-chloro Kynurenic acid) crystallized as a monomer (Kristensen et al., 2016; Naur et al., 2007) and, by comparison with apo structure, gave insights into LBD domain movements. The degree of cleft closure varied between the apo, D-Ser, and 7-CKA bound structures (**Fig 3**). The apo state was most relaxed having an extended cleft with a 29.9º angle compared to D-Ser bound form that induced a closed cleft conformation. LBD clam-shell in the 7-CKA bound state showed an intermediate cleft closure of ~19.5º (Kristensen et al., 2016; Naur et al., 2007). Structural studies of AMPA, KA, and NMDA LBDs have shown that agonist induces maximum cleft closure, while an antagonist on binding brings relatively small cleft closure compared to the apo conformation of the domain (Kristensen et al., 2016; Pohlsgaard et al., 2011; Yu et al., 2018). Thus the D-Ser bound GluD2 LBD resembles the agonist-induced cleft closure, whereas the 7-CKA resembles an antagonist-induced cleft closure (Kristensen et al., 2016). This is consistent with the lower inhibition of Lurcher currents by 7-CKA compared to D-Ser (Kristensen et al., 2016). D-Ser induces complete cleft closure, which pulls the LBD-TM linkers with sufficient energy for closing the constitutively conducting pore. While D-Ser binds with much lower affinity to GluD2 LBD (Naur et al., 2007), attributed to the hinge region connecting the two lobes (Tapken et al., 2017); recent computations of the conformational free energy landscapes remarkably revealed that D-Ser binding exhibited a significantly higher conformational free energy of agonist binding in comparison to GluA2, GluK2, GluN1, GluN2A and GluN3A LBDs (Chin et al., 2020). This is consistent with D-Ser-induced LTD (long-term depression) by GluD receptors that require the transmission of the signal from LBD to CTD. However, why the D-Ser binding is unable to gate the GluD receptors is still not understood as insufficient force generation on agonist binding may not the reason for the inactivity of GluD receptors and requires further exploration. The key could

be the ATD-LBD and LBD-TM linkers that have been shown to significantly influence the receptor's functions (Elegheert et al., 2016).

4. The unique arrangement of subunits in GluD receptor tetramer

All the iGluR full-length structures for AMPA, NMDA, and kainate receptors solved to date either *via* X-ray crystallography (Lee et al., 2014; Sobolevsky et al., 2009) or cryoEM structures of recombinantly expressed receptors (Kumari et al., 2019; Meyerson et al., 2014; Romero-Hernandez et al., 2016; Twomey et al., 2017; Zhu et al., 2016) or isolated from native source **(Yu et al., 2021; Zhao et al., 2019)** showed a conserved domain architecture. The extracellular domains are arranged as 2-fold symmetric dimers with a 4-fold symmetric pore domain. A hallmark of the full-length structures has been domain crossover at the ATD and LBD layer between the proximal and distal subunits such that the dimer partners at the ATD and LBD layers are swapped (**Fig. 4 a**). However, the full-length structures of both GluD1 (**Fig. 4 b**) and GluD2 (**Fig. 4 c**) showed a lack of domain swapping at the LBD layer (Burada et al., 2020b, 2020c). Thus, GluDs maintain the same subunit partners at both the ATD and LBD layers. In the GluD1 receptor, the two-fold symmetry at the extracellular domain and 4-fold symmetry at the pore domains is, however, conserved. Also, the tetrameric dimer-of-dimer interface at the ATD layer was observed in "compact" conformation and confirmed by cysteine crosslinking experiments (Burada et al., 2020b). The lack of crossover imparts increased conformational freedom to the two extracellular dimer arms allowing the receptor to adopt an extended or splayed conformation whereby the tetrameric ATD dimer-of-dimer interface is disrupted (Burada et al., 2020b). While disrupted ATD dimer-of-dimer interface has been observed previously in AMPA (Nakagawa et al., 2005; Dürr et al., 2014; Meyerson et al., 2014; Zhao et al., 2019), and NMDA receptors (Jalali-Yazdi et al., 2018; Zhu et al., 2016), the non-swapped architecture is unique to GluD receptors. It seems likely that the extensive interactions at the ATD, LBD layer and ATD-LBD interface coupled with short ATD-LBD linkers contribute to the unique non-swapped architecture of GluD receptors. Due to the limited resolution of both the GluD1 and GluD2 structures, the ATD-LBD and LBD-TM linkers could not be modeled. However, non-crossover in GluD receptors would have an effect on the conformations of the linkers and the order in which the TM domains are arranged (**Fig. 5**). Relevant to this, a non-swapped-like arrangement of LBD domains was observed recently in a study on the ATD-deleted NMDA receptors where a fraction of the receptor population adopted

LBD packing similar to that in the GluD1, emphasizing the importance of ATDs in guiding the subunit arrangement of the LBD layer. The well-resolved LBD-TM linkers in this ΔATD NMDA receptor adopted a relaxed conformation, rendering the receptor inactive (Song et al., 2018). Apart from the non-swapped organization of the extracellular domains and the differences in the arrangement of TM domains (**Fig. 5**), the GluD1 structure also revealed a splayed assembly of the TM domains. In contrast to AMPA, kainate, and NMDA receptors, the TM domains appear to be more loosely packed (**Fig. 6**). The distances between the Cα atoms of the M3 helix residues L632 (Top) L622 (middle) and R611 (bottom) are ~13Å, 22Å, and 35Å in GluD1(**Fig. 6 a**), whereas the distances between corresponding residues in GluA2, GluK2, and GluN1/GluN2A are ~15Å, 16Å, 30Å (GluA2), 16Å, 16Å, 30Å (GluK2) and 15Å, 16Å, 28Å (GluN1/GluN2A) respectively (**Fig. 6 b-d**). Thus GluD1 M3 helix is more constricted at the top and splayed towards the bottom. This results in a much wider vestibule in the GluD1 receptor compared to other iGluRs. It's also evident when the distances between M4 helices are analyzed (**Fig. 6**). Whether this TM domain arrangement also translates into requiring more energy to open the pore is an outstanding question. High-resolution structures of GluD receptors where the LBD-TM linkers are resolved coupled with molecular dynamics simulations might be able to provide some answers.

Several other questions remain to be answered, such as the driving force behind the domain swapping and its importance in the receptor's functionality. It could be hypothesized that domain swapping is required for the conductivity of the receptors. However, in the case of GluD receptors, the physiological relevance and implications of the unique non-swapped architecture are unclear and need further investigations. Moreover, biochemical and structural investigations in the emerging area of mGlu and GluD crosstalk and regulation of ionotropic activity of GluD receptors by mGlus (discussed below) are warranted to reveal mechanistic details into physiological functions of GluD receptors.

5. Overlap between mGlu1/5 and GluD1/2 molecular interactors

Both GluD2 and mGlu1 are strongly expressed in Purkinje cells (PC) of the cerebellum (Araki et al., 1993; Baude et al., 1993; Hepp et al., 2015; Kano et al., 1997; Lomeli et al., 1993; Nusser et al., 1994). While mGlu1 is present at both glutamatergic parallel fibers (PF) and climber fibers (CF)-to-PC synapse, GluD2 is only expressed at PF-PC synapses (Baude et al., 1993; Landsend et al., 1997; Nusser et al., 1994). In the cerebellar molecular layer, GluD1 is expressed in GABAergic

interneurons, which also express mGlu1/5 (Hámori et al., 1996; Konno et al., 2014). GluD1 is selectively present at the PF-interneurons glutamatergic synapse (Konno et al., 2014). Similarly, both mGlu1/5 are expressed at glutamatergic synapses in striatal neurons but GluD1 is selectively expressed at synapses expressing type 2 vesicular glutamate transporter (VGluT2, putatively, thalamostriatal synapses) (Liu et al., 2020). These data support the idea that GluD1/2 and mGlu1/5 are present at the same glutamatergic synapses. Biochemical assays further showed that they belong to the same protein complex or are very close to each other. In the cerebellum, GluD2 and mGlu1 have been reported to co-immunoprecipitate (Kato et al., 2012; Uemura et al., 2004). Such protein-protein interaction has also been demonstrated between GluD1 and mGlu1/5, both in a HEK cell heterologous expression system (Benamer et al., 2018) and in native hippocampal tissue (Suryavanshi et al., 2016). Further investigation is required to determine whether the interaction is direct, however, it is noteworthy that several interaction partners of GluD1/2 are also linked to mGlu1 signaling or membrane trafficking. This is the case of protein kinase C gamma, which is part of the canonical signaling cascade of mGlu1/5 (Kato et al., 2012) and of protein interacting with C kinase 1 (PICK1), which is necessary for mGlu1-dependent long term plasticity in PC (Yawata et al., 2006). Similarly, MRCKγ (CDC42-binding protein kinase gamma) and Itpr1 (inositol 1,4,5-triphosphate receptor 1) were detected in GluD2 immunoprecipitates from PC postsynaptic density, indicating that they are not only present at the PF-PC synapse but also participate in the same protein complex as GluD2. These proteins can bind to, respectively, DAG and IP3, which are the metabolites of PIP2 hydrolysis involved in mGlu1/5 signaling (Selimi et al., 2009). Moreover, the alpha isoform of MRCK is found in GluD1 immunoprecipitate (Fossati et al., 2019). Both GluD1 and GluD2 were found to interact with the neuronal isoform of Golgi protein PIST (PDZ domain Protein Interacting Specifically with TC10), also known as CAL (Cystic fibrosis transmembrane conductance regulator (CFTR)-Associated Ligand) (Yue et al., 2002). This protein regulates mGlu5 membrane targeting and mGlu1 activity (Cheng et al., 2010; Zhang et al., 2008). The family of scaffolding proteins Homer and Shank are crucial for regulating mGlu1/5 function. Interestingly, these two proteins were found in the same protein complex as GluD2 in the cerebellum (Selimi et al., 2009; Uemura et al., 2004). Shank1 and Shank2 were shown to interact directly with GluD2 but not with GluD1. The Shank family also comprises a third isoform, Shank3, whose autism-associated mutations alter mGlu1/5 expression and mGlu1/5-dependent synaptic plasticity (Lee et al., 2019). Furthermore, Shank3 loss-of-function in the

ventral tegmental area (VTA) causes a defect in excitatory transmission maturation and impairment of social interaction, which can be rescued by mGlu1 PAM (Bariselli et al., 2016). However, whether Shank3 interacts with GluD1/2 is still unknown (Uemura et al., 2004). The co-expression of mGlu1/5 and GluD1/2 at the same synapse combined with the physical interaction of GluD with mGlu receptors and mGlu-related signaling molecules suggests functional crosstalk between mGlu and GluD receptors signaling. The following sections will provide experimental evidence that GluD receptors regulate mGlu signaling and reciprocally that mGlu activation gate ionotropic function of GluD receptors.

6. mGlu1/5 gate the ion channels of GluD

Activation of mGlu1/5 induces a long-lasting excitation in several brain regions including the neocortex, thalamus, hippocampus, striatum, cerebellum, and midbrain (Batchelor and Garthwaite, 1993; Camiré et al., 2012; Kaneda et al., 2007; Mo et al., 2017; Viaene et al., 2013). Electrical stimulation of PF-PC synapse induced a slow excitatory postsynaptic current (sEPSC) mediated by mGlu1 activation in PC. It has been reported that this current (mGlu1-sEPSC) could be the result of the opening of canonical transient receptor (TRPC) channels (Hartmann et al., 2008; Kim et al., 2003). Similar observations have been made regarding the role of TRPC channels in mGlu1-gated slow excitation in cerebellar interneurons, in the hippocampus, and the midbrain (Bengtson et al., 2004; Kougioumoutzakis et al., 2020; Kubota et al., 2014). However, in PC, although mGlu1-mediated excitation is absent in TRPC3-KO, it seems that the TRPC3 channel accounts for only a fraction of the mGlu1-sEPSC since selective TRPC3 blocker does not abolish the mGlu1-sEPSC (Ady et al., 2014; Kubota et al., 2014). Indeed, in cerebellar PC and midbrain dopaminergic (DA) neurons, it has been shown that this excitation also relies on the opening of the GluD1/2 ion channel (Ady et al., 2014; Benamer et al., 2018). Inward currents elicited either pharmacologically with mGlu1/5 agonist or synaptically by high-frequency electrical stimulation are strongly dampened in loss-of-function GluD1/2 mice or upon expression of GluD1/2 dead-pore mutants. This is reproduced in HEK cells upon coexpression of mGlu1/5 and GluD1/2 (Ady et al., 2014; Benamer et al., 2018). These results indicate that both TRPC and GluD channels contribute to the mGlu1/5-gated current, but their relative contribution still needs to be determined. Interestingly, DA neurons exhibit two types of firing activity, phasing and bursting, the latter being associated with high DA release in target regions. The absence of GluD1 or expression of dead-pore GluD1

mutant specifically in DA neurons results in the absence of bursting activity (Benamer et al., 2018). These data provide the first evidence of the physiological opening of the GluD1/2 ion channel. Previous characterizations of the GluD ion channel were solely based on the analysis of GluD point mutants called Lurcher (Wollmuth et al., 2000; Yadav et al., 2011; Zuo et al., 1997). For example, the mutation A654C in GluD1 or A654T in GluD2 make the ion channel constitutively open. These mutants were used to identify some molecules inhibiting ion flow such as 1-Naphthyl acetyl spermine (NASPM), pentamidine, 7-chloro kynurenic acid (7-CKA), D-Ser/glycine (Hansen et al., 2009; Kohda et al., 2000; Kristensen et al., 2016; Naur et al., 2007; Williams et al., 2003). Although these ligands can reduce mGlu1/5- dependent excitation (Ady et al., 2014; Benamer et al., 2018), they are not specific to GluD subunits since NASPM also antagonizes calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and 7-CKA, D-Ser, and glycine also bind NMDA receptors (Traynelis et al., 2010). To circumvent this issue of selectivity, an optopharmacological approach has been implemented to regulate the ion flow of the GluD2 subunit specifically. This approach consists of incorporating a cysteine mutation in the cavity located above the putative ion channel pore for site-specific conjugation with a photoswitchable ligand (PTL (Mondoloni et al., 2019, 2019; Paoletti et al., 2019). In this new subunit called LiGluD2 (GluD2 I677C), the PTL, called MAGu, adopts two different configurations upon light excitation at 380 and 535 nm, and can rapidly and reversibly inhibit GluD2 ion flow (Lemoine et al., 2020) (**Fig. 7**). This photo-inhibitable GluD2 subunit effectively regulates mGlu-gated GluD2 inward current, thereby confirming that mGlu signaling triggers the opening of the GluD2 ion channel (Lemoine et al., 2020). Such modulation of iGluR ion flow by mGlu1/5 activation has also been reported for NMDA receptors and involves the Pyk2/Src-family kinase pathway and tyrosine phosphorylation of GluN2 subunits (Heidinger et al., 2002). However, in the case of GluD1/2, mGlu1/5 signaling seems the only way for glutamate to trigger the opening of the GluD ion channel since glutamate does not bind GluD directly. The molecular mechanism linking mGlu1/5 activation and pore opening of GluD is still under investigation but, in the case of GluD2, it has been reported in HEK cells and PC that it requires activation of the Gq/PLC/PKC canonical pathway (Dadak et al., 2017) (**Fig. 8**). However, the mechanism of the mGlu1-sEPSC is still a matter of debate since previous reports provide conflicting evidence. Several studies in PC indicate that the mGlu1-sEPSC is G-protein-dependent but insensitive to PKC and PLC inhibitors (Canepari et al., 2004, 2001; Canepari and Ogden, 2003; Hartmann et al.,

2004; Nelson and Glitsch, 2012), which is surprising since TRPC currents require PLC activity and production of diacylglycerol (DAG) (Ramsey et al., 2006). The mGlu1-sEPSC in PC further appears to be dependent on the balance between tyrosine kinase and tyrosine phosphatase. In PC, tyrosine kinase inhibitors and more specifically Src kinase inhibitors potentiate the mGlu1-sEPSC (Auger and Ogden, 2010; Canepari and Ogden, 2003), while tyrosine phosphatase inhibitors cause a reduction of the mGlu1-sEPSC amplitude (Canepari and Ogden, 2003). This is in stark contrast with what is observed in other cell types or brain structures where the mGlu1-sEPSC has been described. In DA neurons and hippocampal neurons, the regulation by the balance tyrosine kinase-phosphatase is the opposite of what is observed in PC (Heuss et al., 1999; Tozzi et al., 2001). In cerebellar interneurons of the molecular layer, inhibition of Src kinase leads to the reduction of the mGlu1-mediated excitation in contrast with what is observed in PC (Kubota et al., 2014).

Regarding the mechanism of GluD channel opening, it is unclear whether GluD2 phosphorylation by PKC is the triggering event. While PKC activity is necessary for the process of mGlu1-induced GluD2 opening, direct stimulation of PKC activity failed to mimic the effect of pharmacological activation of mGlu1 (Dadak et al., 2017). Regardless of the target of PKC, the Gq/PLC/PKC signaling pathway seems important for the opening of the GluD ion channel. Recently, the modulation of GluD1 ion function upon activation of Gq-coupled α1-adrenergic receptors (α1-AR) in serotonergic dorsal raphe neurons has been reported (Gantz et al., 2020). GluD1 ion channels appear to regulate the excitability of these neurons and underlie the slow excitatory current observed upon high-frequency stimulation of noradrenergic fibers. Furthermore, this slow excitation is reduced in the presence of NASPM and D-Ser/glycine and absent after the targeted deletion of GluD1 (Gantz et al., 2020). Noteworthy, the loss of GluD1, specifically in dorsal raphe neurons, causes increased anxiety in mice (Gantz et al., 2020). Interestingly, it has been demonstrated in the same neurons that activation of Gq protein-coupled histamine H1 and orexin OX2 receptors also produces an excitatory response that is occluded by the α1-AR-dependent response (Brown et al., 2002). Whether the GluD1 channel is a common effector of these receptors, and possibly of yet, other Gq coupled receptors remains to be elucidated as well as the underlying mechanisms.

7. GluD regulate mGlu signaling

Group I mGlu activation drives several intracellular signaling pathways, including Gq/PLC/PKC, AkT/mTOR, MAPK/ERK cascades, and regulates trafficking of ionotropic glutamate receptors and local translation (Niswender and Conn, 2010). Among multiple functions, mGlu signaling is crucial for regulating synaptic transmission *via* its role in long-term depression (mGlu-LTD (Bellone et al., 2008; Gladding et al., 2009; Lüscher and Huber, 2010). The mGlu-LTD at parallel fiber to PC synapse has been the subject of intense investigation as it is believed to underlie motor learning, and GluD2 has been shown to be instrumental in the gating and expression of cerebellar mGlu-LTD (Kashiwabuchi et al., 1995; Yuzaki and Aricescu, 2017). Upon LTD induction and mGlu1 activation, PKC phosphorylates GluA2 subunits, which results in the internalization of GluA2-containing AMPA receptors and reduction of EPSC amplitude. The C-terminal end of GluD2 binds the tyrosine phosphatase PTPMEG, which regulates the phosphorylation state of GluA2 and its propensity to be internalized upon PKC phosphorylation (Hironaka et al., 2000; Kohda et al., 2013). Interestingly, the ion function of GluD2 is not necessary for mGlu-LTD since LTD is absent in GluD2-KO mice but is restored upon re-expression of the dead pore GluD2 mutant (Kakegawa et al., 2007; Kohda et al., 2007). Furthermore, it has been reported that the binding of D-Ser to GluD2 LBD induces a conformational change and produces a GluD2-dependent LTD at immature PF to PC synapses (Kakegawa et al., 2011). Not only this, D-Ser-dependent LTD occludes the regular mGlu-dependent LTD at the same synapse, but also, GluD2 mutant mice lacking D-Ser binding exhibit impaired LTD and motor dyscoordination during development (Kakegawa et al., 2011), suggesting that GluD2-dependent and mGlu-dependent LTD share common molecular mechanisms.

Regarding a similar role of GluD1 in LTD, several forms of postsynaptic mGlu1/5-LTD have been described in brain regions where GluD1 predominates over GluD2 (Hepp et al., 2015) such as the striatum, VTA, and hippocampus. They rely on the presence of calcium-permeable AMPA receptors, on the trafficking of GluA2 containing receptors, and regulation of local translation as the postsynaptic mechanism of LTD expression (Bellone et al., 2008; Gladding et al., 2009; Lüscher and Huber, 2010). However, the role of GluD1 is still unclear. For example, in the striatum, agonist-mediated activation of mGlu1/5 or D-Ser application in the presence of NMDA receptor antagonist induces a decrease of EPSC amplitude without a change in release probability, suggesting a postsynaptic origin of the LTD. However, this LTD persists after the selective loss of GluD1 in the striatum (Liu et al., 2020). Nonetheless, GluD1 appears to regulate mGlu1/5

signaling in the hippocampus, as shown by (Suryavanshi et al., 2016). This study showed that the interaction of mGlu5 with Homer was abnormal in GluD1-KO mice. In the same mutant mice, the basal levels of phosphorylated mTOR and Akt were higher, and no increase was observed upon application of the mGlu5 agonist DHPG. They observed higher basal protein translation and an absence of DHPG-induced increase in protein synthesis. In accordance with the role of mGlu5-mediated mTOR signaling in synaptic plasticity, DHPG-induced internalization of surface AMPA receptor subunits was impaired in GluD1 knockout mice.

These data clearly point to a bidirectional interaction between mGlu1/5 and GluD1/2 signaling. Several studies have reported interaction between GPCR and iGluRs, especially between mGlu5 and other iGluRs such as NMDA receptors (Reiner and Levitz, 2018). Using bioluminescence resonance energy transfer (BRET), a dynamic interaction between the C-terminal end of mGlu5 and GluN1/2B receptors has been reported that results in G protein-independent bidirectional inhibition (Moutin et al., 2012; Perroy et al., 2008). The existence of such direct interaction between mGlu1/5 and GluD1/2 is still unclear and deserves further investigation.

8. Conclusions

In the nineties, ionotropic glutamate receptors were essentially viewed as a ligand-gated ion channel whose function was to convey chemical transmission from one neuron to another. However, over the past years, the idea emerged that they fulfill much more complex functions at the synapse. GluD subfamily is an excellent example since they not only demonstrate ionotropic function but are crucial for synaptogenesis, synaptic plasticity and also regulate metabotropic intracellular signaling. Based on studies of GluDs, ionotropic glutamate receptors start to be considered more than just ligand-gated channels. Recent structural and functional insights have profoundly changed our understanding of the GluD receptors and their role in synaptic physiology. Knowing that, it is not surprising that mutations in the gene encoding for GluD receptors are associated with several neurological disorders. But the molecular link between GluD and its synaptic partners are still unclear and deserves a lot of attention. Several genetic and pharmacological tools have been developed to tackle the different functions of GluDs, and they will be instrumental in the understanding of GluD in neuronal brain circuitry. The crosstalk between GluD and metabotropic glutamate receptor and other GPCR seems to be unique to GluD

receptors, and further investigation is required to better understand the mechanism linking these two receptor families and to apprehend how this relationship shapes synaptic transmission.

Acknowledgments

This work was supported by the Wellcome Trust DBT India Alliance fellowship (grant number IA/I/13/2/501023) awarded to JK and by the French Agency for Research (ANR-16-CE16-0014-01) to LT. APB thanks ICMR, New Delhi, India, for the senior research fellowship (3/1/3/JRF-2014/HRD). RV thanks the Department of Biotechnology, New Delhi, India for a Research Associate fellowship. LT thanks the fondation Lejeune for its support (grants #1693 and 1959).

Author contributions

The manuscript was conceptualized, designed, and written by APB, RV, BL, LT, and JK. All authors reviewed and approved the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

Figure Legends

Figure 1. Unique structural features of GluD Amino-terminal domains (ATD). Panel (a) Superimposition of GluD1 (orange) and GluD2 (green) ATD monomers (a) and dimers (b) are shown, highlighting the structural similarities between the two GluD subtypes. The unique loops and the extra helix found in GluD ATDs are shown. Panels c and d respectively show the superimposition of GluD1 ATD monomers and dimers with that of GluA2 ATD. Key differences between the GluA2 and GluD ATDs are highlighted.

Figure 2. The arrangement of ATDs in the context of receptor tetramer. Panel (a) shows the COMs (spheres) for the R1 and R2 domains mapped onto the GluD1-ATD tetramer (6KSS). Panels (b-e) show the distances and the angles subtended between the COMs of GluD1, GluA2, GluK3, and GluN1/N2B ATD domains. The distances, angles are shown along with the PDB IDs of the coordinates.

Figure 3. GluD Ligand-binding domains undergo ligand-induced conformational changes. A superposition of the crystal structures of GluD2 LBD on the S1 lobe in apo, D-Ser, and 7-CKA bound state is shown. The degree of cleft closure with respect to the D-Ser bound state is shown, highlighting the ligand-induced conformational changes in GluD-LBD. GluD2 in the apo state (2V3T), or complexed with D-Ser (2V3U), 7-CKA (5CC2), and LBD from the ATD-LBD ectodomain structure (5L2E) are shown.

Figure 4. Full-length GluD receptors reveal a distinct architecture. (a) CryoEM structure of homomeric GluA2 (PDB ID: 5KBV) in complex with antagonist shows domain swapping at the LBD layer. Panel (b) and (d) show cryoEM structures of the homomeric GluD1 (PDB ID: 6KSS) and GluD2 (PDB ID: 6LU9) receptors, respectively in the presence of 7-CKA and calcium ions, highlight a non-swapped arrangement of the domains. The four subunits of receptor tetramer are colored uniquely subunit A (orange), subunit B (green), subunit C (yellow), and subunit D (cyan). The TM domains were not resolved in the GluD2 structures and hence are not shown and are depicted by a disc.

Figure 5. Non-swapped architecture is unique to GluD receptors. Shown are the domain arrangement in GluD1, GluD2, GluA2, GluK2, GluN1/GluN2B, and GluN1/GluN2A (super splayed) receptors. Views from the extracellular side (top views) are shown for the ATD, LBD,

and TM domains, highlighting the subunit arrangement. The four receptor subunits are colored uniquely with matching schematic depiction below each layer. All the conformations of AMPA, KA, and NMDA receptors show domain crossover between the ATD and LBD layers, unlike that in GluD1 and GluD2 receptors. Also highlighted is the unique arrangement of the TM domains in GluD receptors compared to other iGluRs.

Figure 6. Assembly at the TM domains. The packing of helices of GluD1 TMD is more compact at the top and expanded towards the cytosolic side when compared with other iGluRs. Distances between residues L632 (top), L622 (middle), and R611 (bottom) of the M3 helices of subunits B and D of GluD1 (a) and the corresponding residues in GluA2 (b), GluK2 (c), and GluN1/GluN2A (d) are shown. Similarly, the distances between M4 helices of subunits C and D are shown in the left panel. Note that due to domain swapping in GluD1 receptors, the position of the TM domains for subunits C and D are interchanged with respect to other iGluRs shown.

Figure 7. GluD receptor activation by mGlu. A schematic of GluD receptor activation by Gq-PLC-PKC is depicted. Also shown are the potential sites for direct interaction between mGlu and GluD receptors. The mGlu5 cryoEM structures in apo (PDB ID: 6N52) and active (PDB ID: 6N51) state and GluD1 receptor (PDB ID: 6KSS) are depicted in a lipid bilayer. Apo mGlu1/5 on the binding of agonist glutamate switches to an active state, leading to a cascade of cytosolic events that might trigger the opening of the GluD pore. Another tantalizing possibility is GluD receptors' activation by direct physical interaction between the mGlu and GluD receptors. However, this poorly understood aspect of mGlu-GluD interactions is highlighted by question marks.

Figure 8. Principle of photoswitchable GluD subunit (a). Approach to block ion channel of GluD2 as described in Lemoine et al. 2020. GluD2 is genetically modified to incorporate a cysteine residue (yellow ball) at the entrance to the pore, which serves as a handle for the covalent attachment of a synthetic, photoswitchable tethered ligand called MAGu. Under green light (525 nm), MAGu adopts an elongated state and places its cationic head group in the lumen, resulting in ion channel blockade. Under violet light (380 nm), MAGu switches to a twisted, shorter form and unblocks the channel. (b) Molecular modeling of GluD2 structure (orange and green) showing the ion channel (grey) in presence of MAGu (with courtesy of Antoine Taly -Université de Paris, UPR 9080, Laboratoire de Biochimie Théorique)

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Figure 1

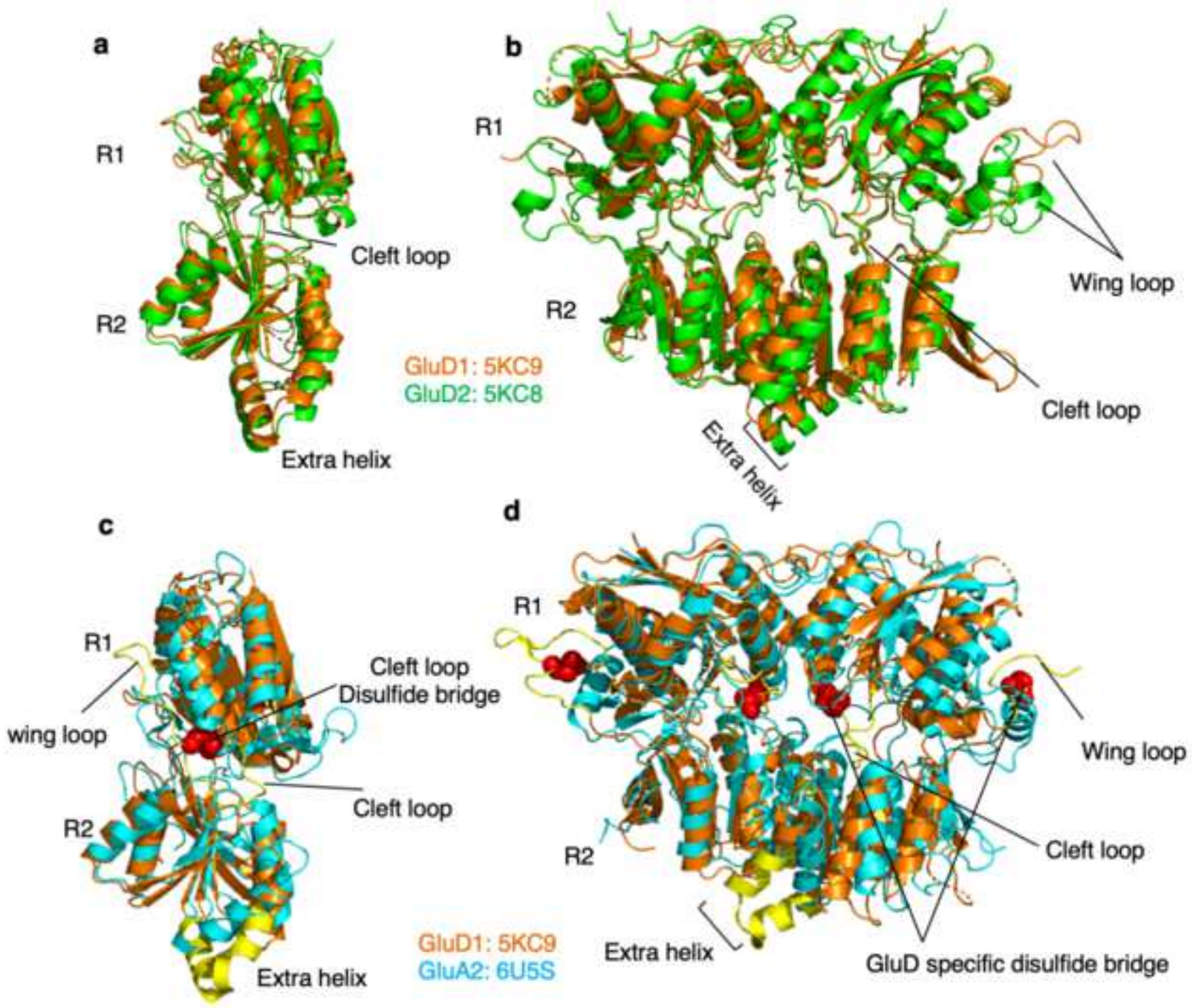

Figure 2

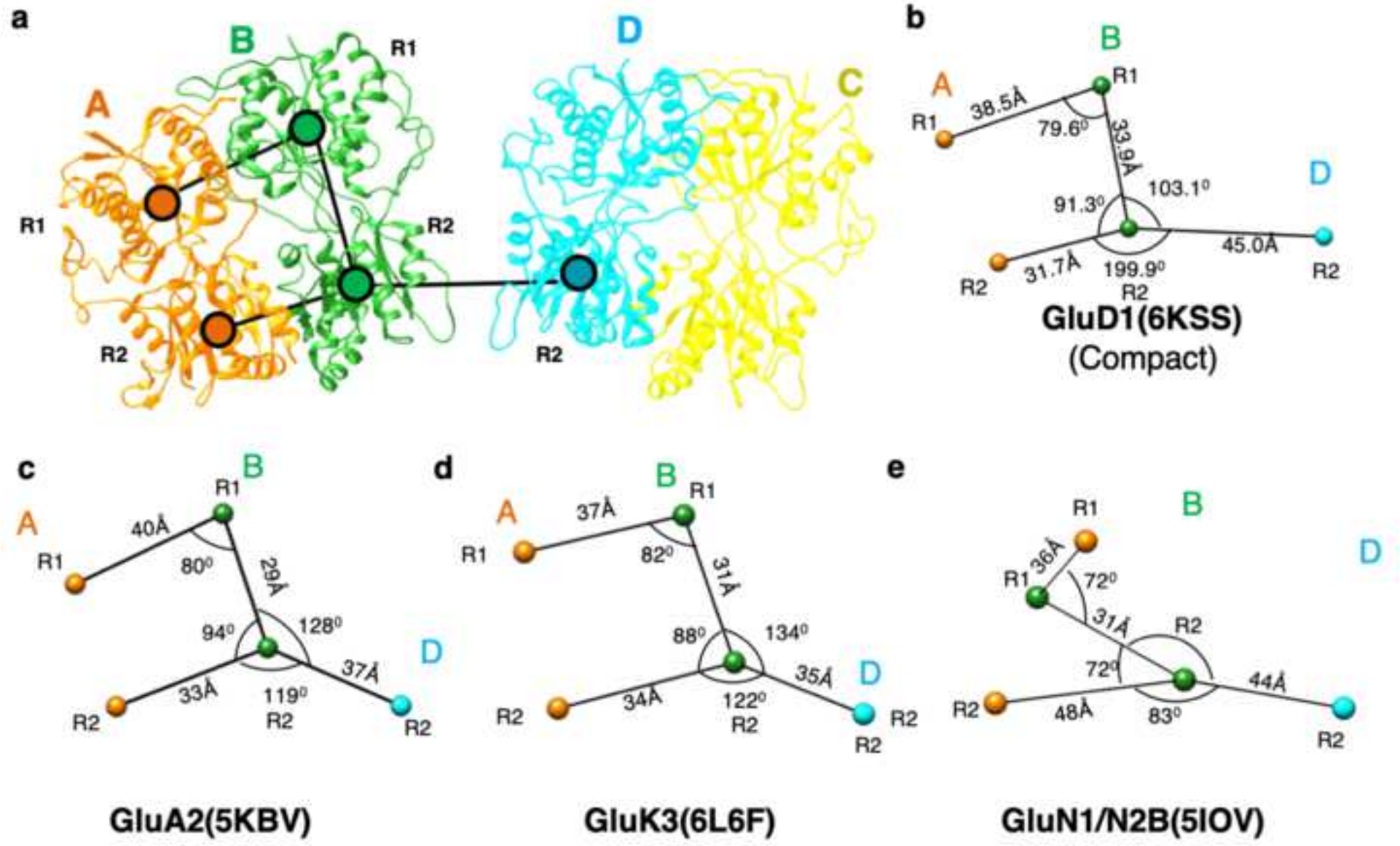

Figure 3

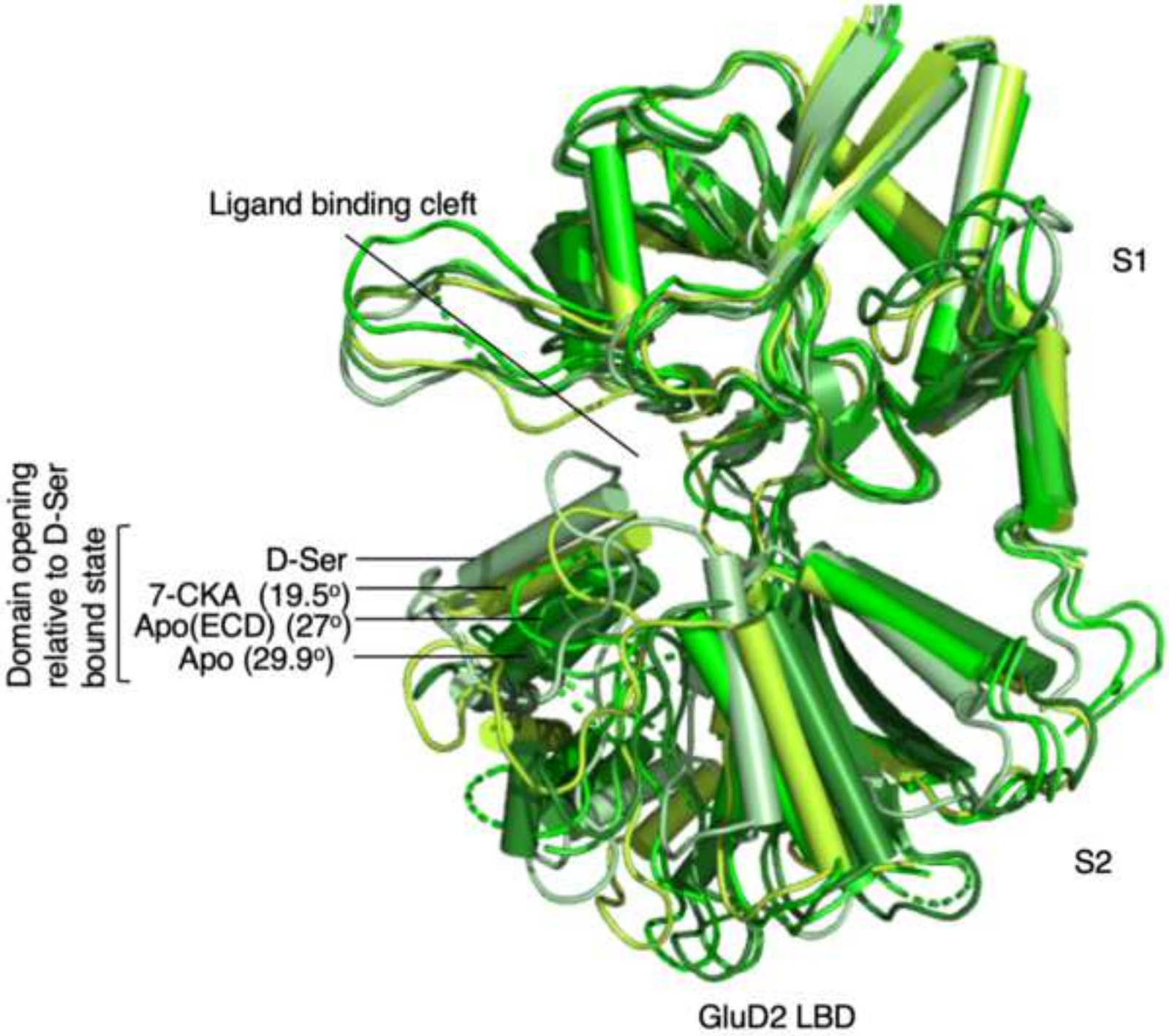

Figure 4

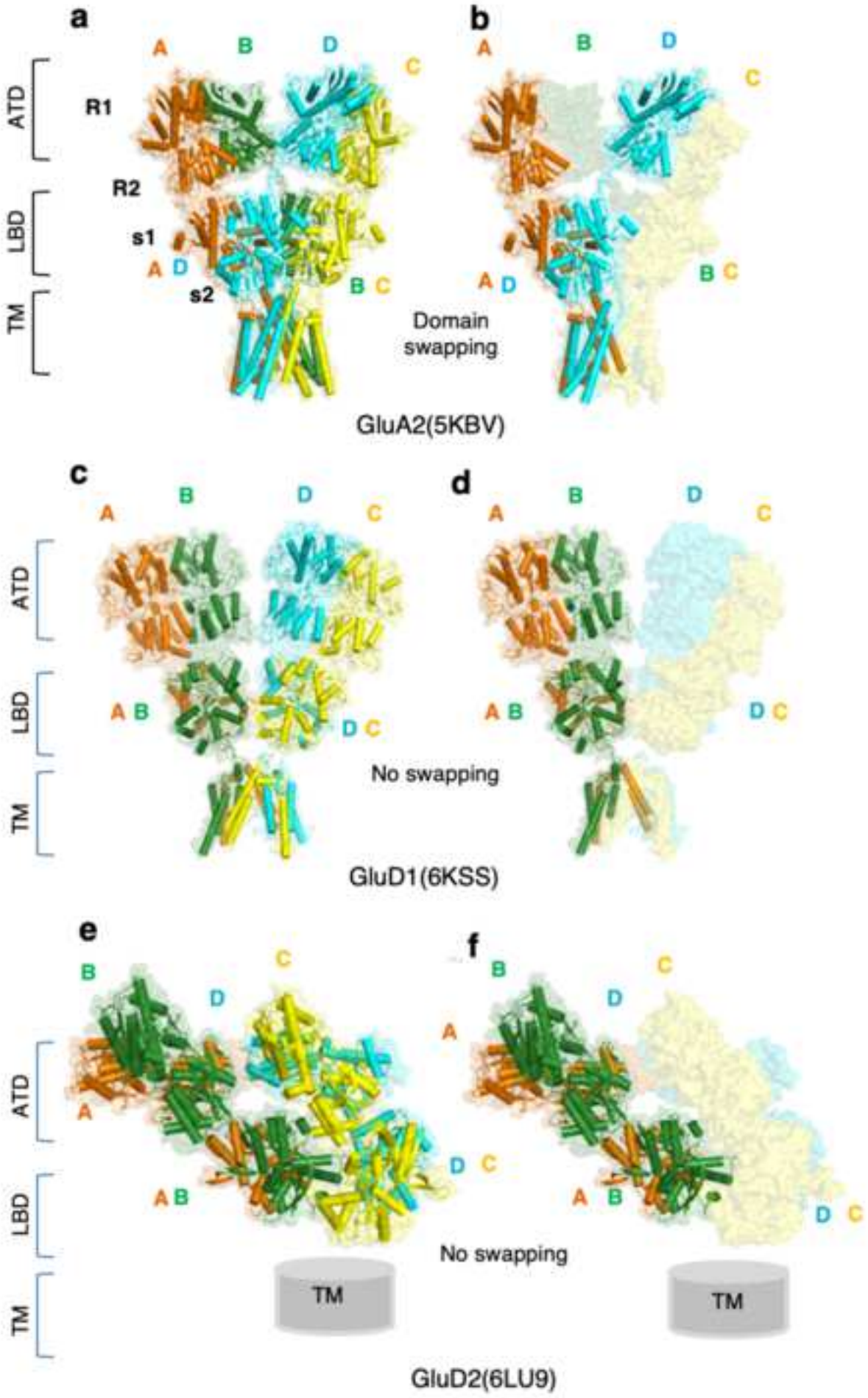

Figure 5

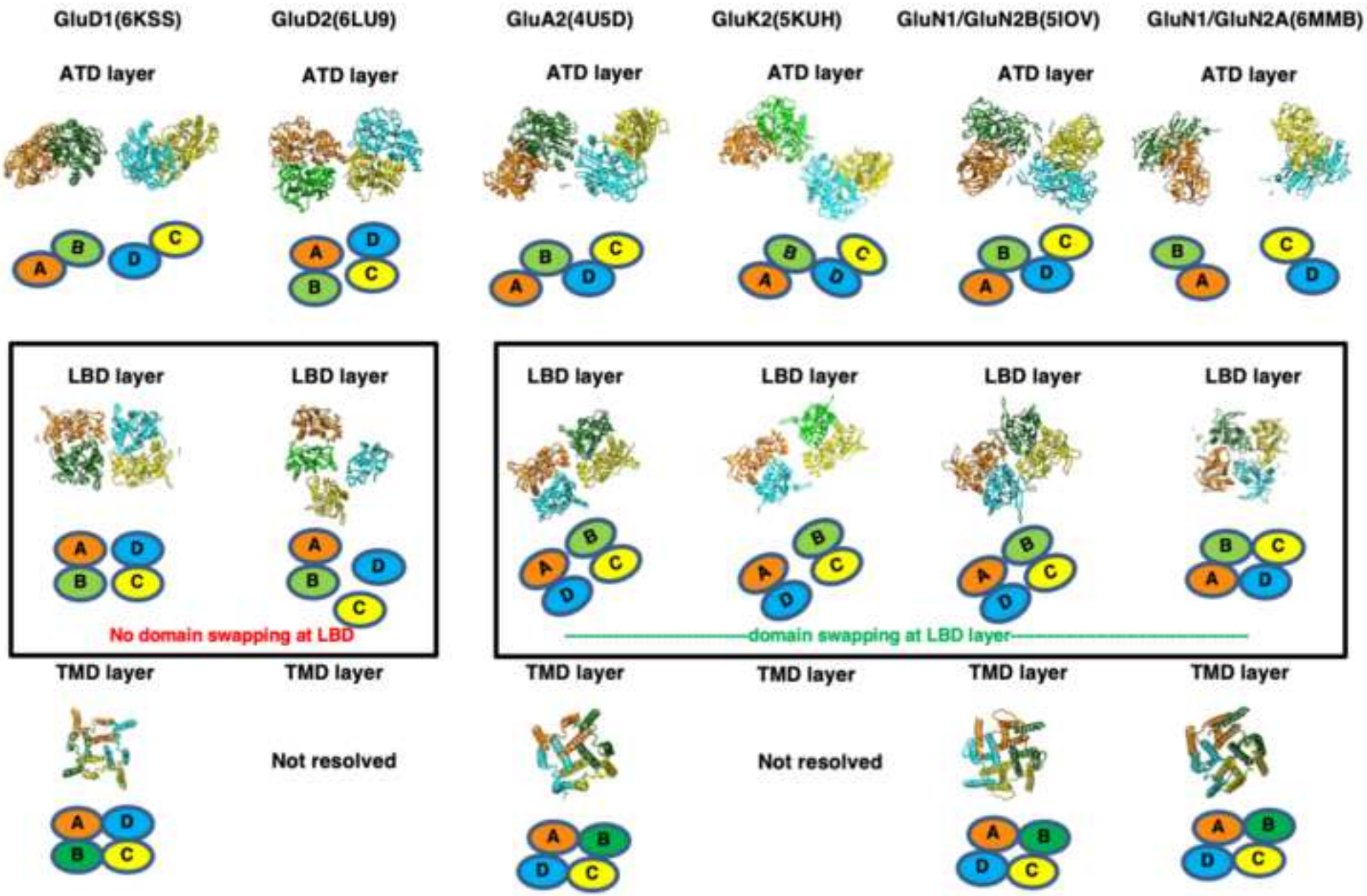

Figure 6

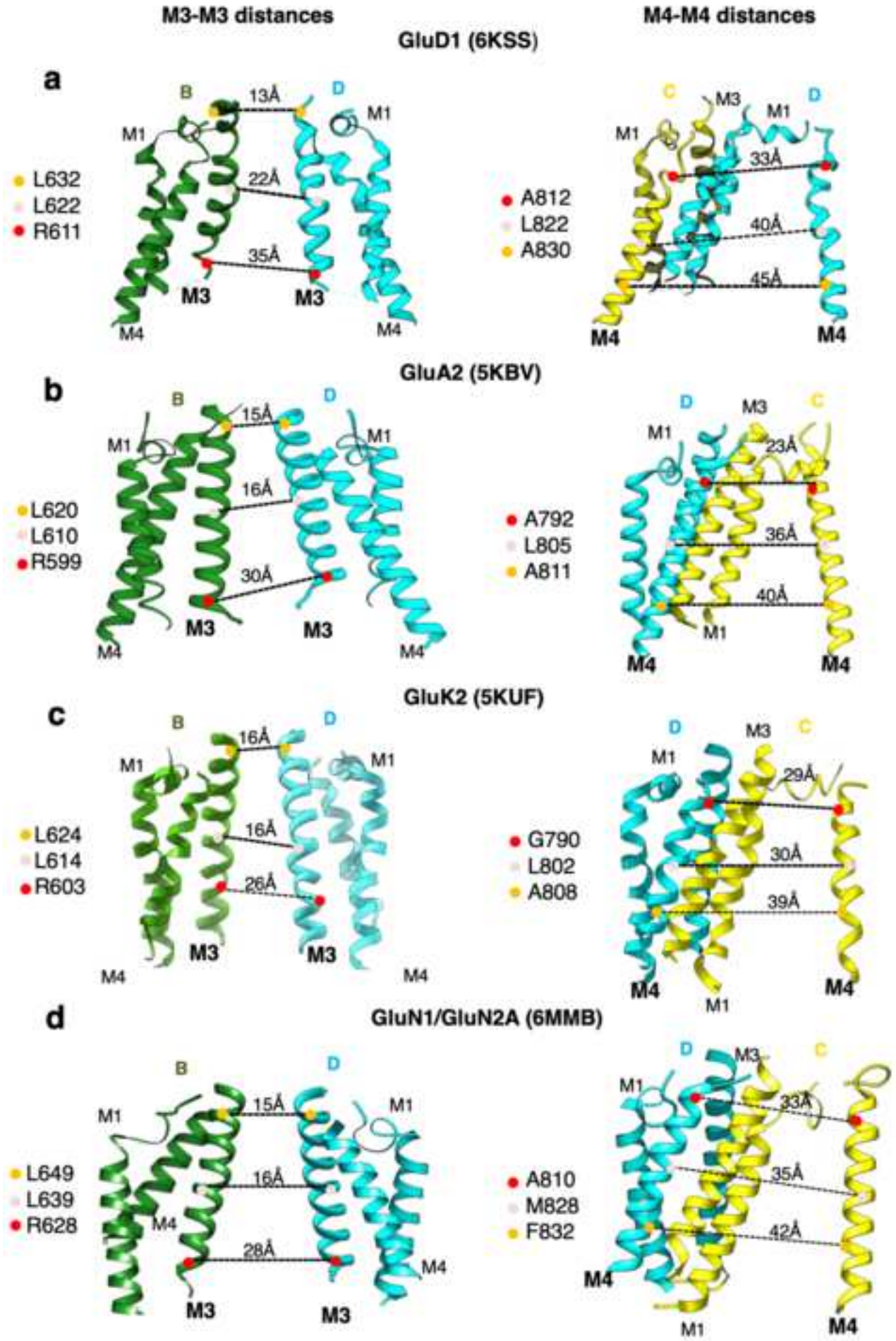

Figure 7

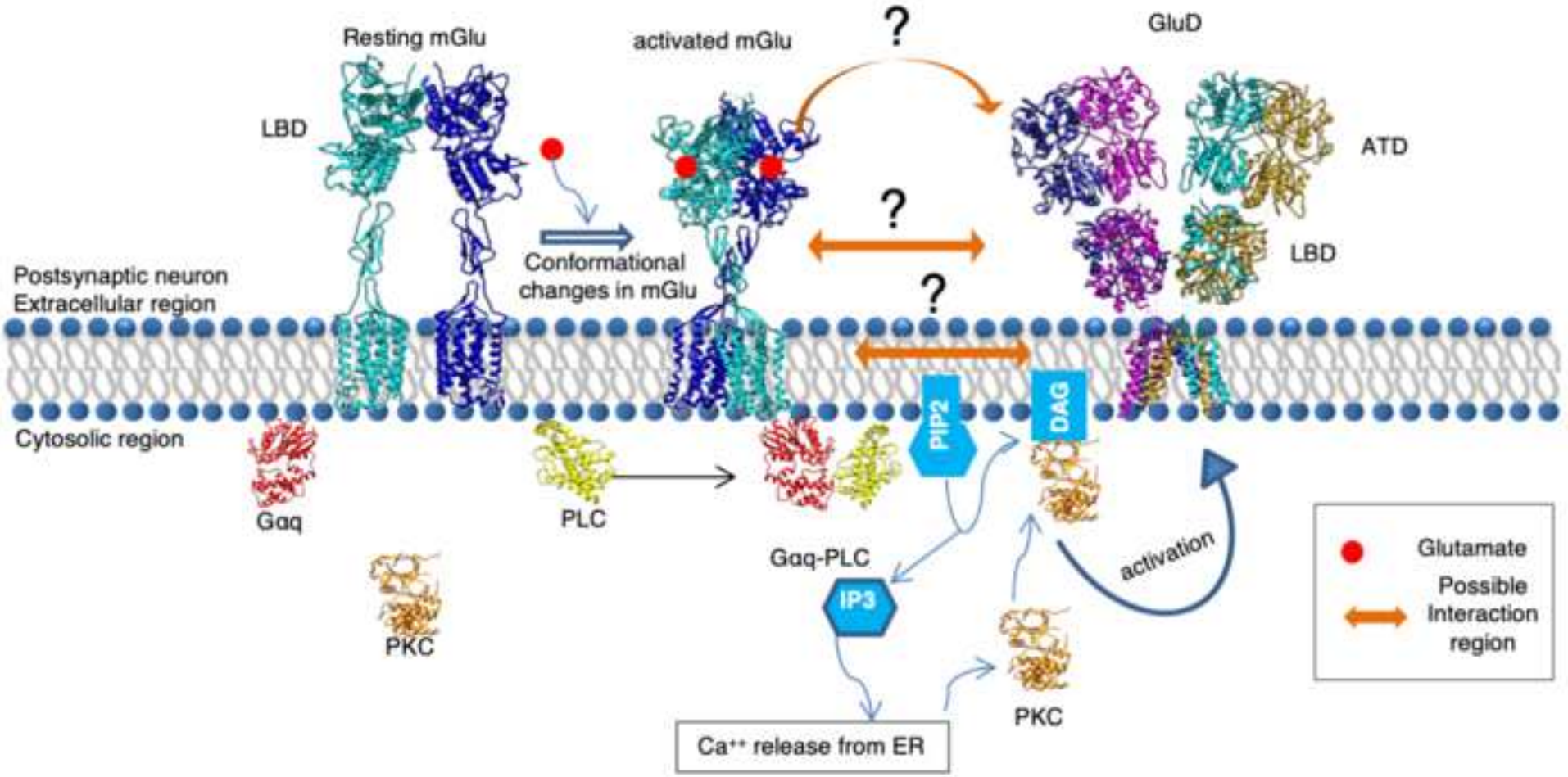

Figure 8