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Title: Structural insights into the ligand binding domain of GluD1 and GluD2 receptors

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Running title: Structure of the LBD of GluD1/GluD2

Abbreviations:

LBD: ligand binding domain

Keywords: GluD, ligand binding domain, protein structure, receptor biology, molecular dynamics

Conflicts of Interest : None

Abstract:

GluD1 and GluD2 subunits (also known as delta 1 and 2) are the members of the delta family of ionotropic glutamate receptors. They are particularly puzzling, since they are unable to bind glutamate, but rather bind glycine and D-serine via their classical ligand binding domain (LBD). While GluD2 has been the subject of intensive research over the past decades, it is only recently that GluD1 received similar interest and very few studies compare the properties of these two membrane proteins. In their research article included in this issue Magdalena Masternak and colleagues resolved the 3D structure of the GluD1 LBD, compared its D-serine sensitivity with that of GluD2 and identified critical residues involved in the dynamics of the LBD.

Introduction:

When GluD1 and GluD2 subunits were cloned in the nineties [1, 2], they were classified as ionotropic subunits by sequence homology to the AMPA, NMDA and kainate receptors [3]. At this time, the absence of glutamate binding strongly dampened any investigation on their role in synaptic transmission. Most of the studies focused on GluD2 since the discovery of its preferential expression in cerebellum and of its major role in motor learning. GluD2 appeared to be critical for synaptic plasticity and synaptogenesis in an ion channel-independent manner [4]. More recently, studies confirmed that GluD1 and GluD2 comprise a functional ion pore, but the mode of activation is largely discussed [5-8]. In all scenarios, D-serine binding was found to regulate both ionotropic and non-ionotropic functions of GluDs [9]. D-serine also binds GluN1 and GluN3 subunits of NMDA receptors but acts as a channel-opening agonist[3]. The finding that GluD1 is more broadly expressed in the brain than was initially thought raised the question of the relative function in brain circuits of GluD1 and GluD2, which exhibit strong sequence homology and roughly complementary expression patterns [10, 11]. GluD2 has been associated with formation of excitatory synapses while GluD1 has been linked to formation of both excitatory and inhibitory synapses [9]. The 3D structure of the ligand binding domain (LBD) of GluD2 was solved many years ago by Traynelis' lab [12], which demonstrated the D-serine/Glycine binding to GluD2, whereas structural data concerning GluD1 are sparse [13].

Structural insights into the LBD of GluD1

In their study [14], Masternak and colleagues succeeded in solving the 3D structure of the LBD of GluD1 (GluD1-LBD). They could establish the organisation of residues known to interact with D-serine. They showed that residues forming the binding pocket are conserved between GluD1- and GluD2-LBD, suggesting that GluD1-LBD is able to bind the same ligands as GluD2. Interestingly, they further showed that D-serine exhibits a fivefold higher affinity for GluD1-LBD compared to GluD2-LBD and that binding occurs via the formation of additional, favourable, non-covalent bonds rather than by solvent release as it is the case for GluD2-LBD. Nonetheless, GluDs affinity remains in the hundreds of micromolar range, far higher that of GluN1 subunits (micromolar range). This is attributed to the high flexibility of the hinge region linking the two lobes that form the LBD of GluDs.

They next investigated the effect of D-serine binding on GluD current using *Lurcher* mutants. These variants exhibit spontaneous current and have been used for a long time as a proxy to explore the pharmacology of GluDs. The authors pointed that the A654T mutation classically used in GluD2 study also induced a spontaneous current when inserted in GluD1, but that the presence of a glutamate amino acid at position 822 was critical. Surprisingly, they observed that 1mM D-serine has almost no effect on GluD1 *Lurcher* current while it causes an important reduction of GluD2 *Lurcher* current. Along the same line, NASPM, a classical blocker of GluD2 *Lurcher* mutant, was found poorly effective on the GluD1 *Lurcher* current, as shown previously [15].

In order to evaluate whether this difference of D-serine sensitivity was linked to a difference in D-serine ability to induce full interlobe closure of GluD1-LBD, they performed molecular simulation of GluD1 and GluD2-LBD in apo- and D-serine bound states. They first noticed that Pro725 in GluD1, which is part of the interlobe contact, is not preserved in GluD2 (Ser725) and is critical for the interlobe dynamics. Indeed, the Ser725 to proline mutation in D-serine-bound GluD2-LBD causes an increase of the flexibility of the interlobe domain. Conversely, the Pro725Ser substitution in GluD1 favours a more closed conformation of the interlobe domain of D-serine-bound LBD.

Concluding remarks

This study by Magdalena Masternak *et al.* raises the question of the relative functional properties of GluD1 and GluD2 and structural data suggest they may operate differentially. Further investigation on the effect of D-serine on the GluD activation mechanism and its impact on synaptic transmission is necessary. However, pharmacological tools to manipulate GluD functions such as NASPM and D-serine are not specific for GluDs. NASPM is also a blocker of calcium permeable AMPA receptor. D-serine is a well-known co-agonist of NMDA receptors. The knowledge of the GluD1- and GluD2-LBD structures will be a strong asset in the identification and the design of new ligands that are specific of GluD, i.e., that bind GluD subunits but leave intact NMDA receptors. Approaches based on high throughput virtual screening may identify such GluD ligands that will help understand the role of D-serine binding in GluD function.

Author Contributions:

LT and RH contributed to the writing of the manuscript

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