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Invited review

# Lessons from crystal structures of kainate receptors

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ABSTRACT

Kainate receptors belong to the family of ionotropic glutamate receptors. These receptors assemble from five subunits (GluK1-5) into tetrameric ion channels. Kainate receptors are located at both pre- and postsynaptic membranes in the central nervous system where they contribute to excitatory synaptic transmission and modulate network excitability by regulating neurotransmitter release. Dysfunction of kainate receptors has been implicated in several neurological disorders such as epilepsy, schizophrenia and depression. Here we provide a review on the current understanding of kainate receptor structure and how they bind agonists, antagonists and ions. The first structure of the ligand-binding domain of the GluK1 subunit was reported in 2005, seven years after publication of the crystal structure of a soluble construct of the ligand-binding domain of the AMPA-type subunit GluA2. Today, a full-length structure has been determined of GluK2 by cryo electron microscopy to 7.6 Å resolution as well as 84 high-resolution crystal structures of N-terminal domains and ligand-binding domains, including agonist and antagonist bound structures, modulatory ions and mutations. However, there are still many unanswered questions and challenges in front of us.

This article is part of the Special Issue entitled 'Ionotropic glutamate receptors'.



**Contents**



*Abbreviations:* AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; iGluRs, ionotropic glutamate receptors; LBDs, ligand-binding domains; NMDA, *N*-methyl-D-aspartate; NTDs, N-terminal domains.

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## 1. Introduction

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system and exerts its fast effects through ionotropic glutamate receptors (iGluRs) by gating of their cationic channels to generate synaptic current essential to brain function. The iGluRs are grouped into four classes based on their sequence similarity and preferred agonist: *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate and delta receptors (Traynelis et al., 2010). It is a characteristic feature of these receptors that they form tetrameric ion channels.

The kainate receptors assemble from five subunits (GluK1-5) whereof GluK1-3 (previously named GluR5-7) can form homomeric and heteromeric receptors (Egebjerg et al., 1991; Schiffer et al., 1997). In contrast, GluK4-5 (previously known as KA-1 and KA-2, respectively) require heteromeric assembly with one of the GluK1-3 subunits to form functional channels (Herb et al., 1992; Werner et al., 1991). GluK1-3 have been termed the low-affinity kainate receptors and GluK4-5 the high-affinity kainate receptors (Fletcher and Lodge, 1996). Unlike AMPA receptors that are found exclusively at postsynaptic sites, kainate receptors are located at both pre- and postsynaptic membranes. Here, they contribute to excitatory synaptic transmission and modulate network excitability by regulating neurotransmitter release (Contractor et al., 2011). Owing to this involvement in neuronal function, dysfunction of kainate receptors have been implicated in several neurological disorders such as epilepsy, schizophrenia, depression and bipolar disorder (Das et al., 2012; Ibrahim et al., 2000; Li et al., 2010; Milanesi et al., 2015; Pickard et al., 2006).

We here present a review of 84 crystal structures of kainate receptor N-terminal domains and ligand-binding domains deposited in the Protein Data Bank (www.pdb.org) as of April 2016. The structures have provided functional insight at the molecular level and revealed the binding modes of several agonists and antagonists as well as cations and anions.

## 2. GluK2 full-length structure

The extracellular part of the receptor is comprised of N-terminal domains (NTDs) that exist as dimers-of-dimers with two-fold symmetry and are proximal to the ligand-binding domains (LBDs) that harbor the binding site for (*S*)-glutamate (Fig. 1A). The LBDs also form dimers-of-dimers but a crossover occurs from the NTD layer to the LBD layer, meaning that different subunits form the NTD and LBD dimers. The ion channel pore located in the membrane is composed of 12 α-helices and four P-entrant loops.

Whereas full-length crystal structures are available of the AMPA receptor GluA2 (Sobolevsky et al., 2009; Chen et al., 2014; Dürr et al., 2014; Yelshanskaya et al., 2014) and the NMDA receptor GluN1/GluN2B (Karakas and Furukawa, 2014; Lee et al., 2014), no full-length crystal structures have been reported of kainate receptors so far. However, an EM structure of a tetrameric full-length GluK2 in complex with the agonist (2*S*,4*R*)-4-methylglutamate has been published where the resolution extends to 7.6 Å (PDB code 4UQQ; Meyerson et al., 2014). Furthermore, single-particle cryoelectron tomography structures were reported by Schauder et al. (2013) showing subunit crossover in the resting state.

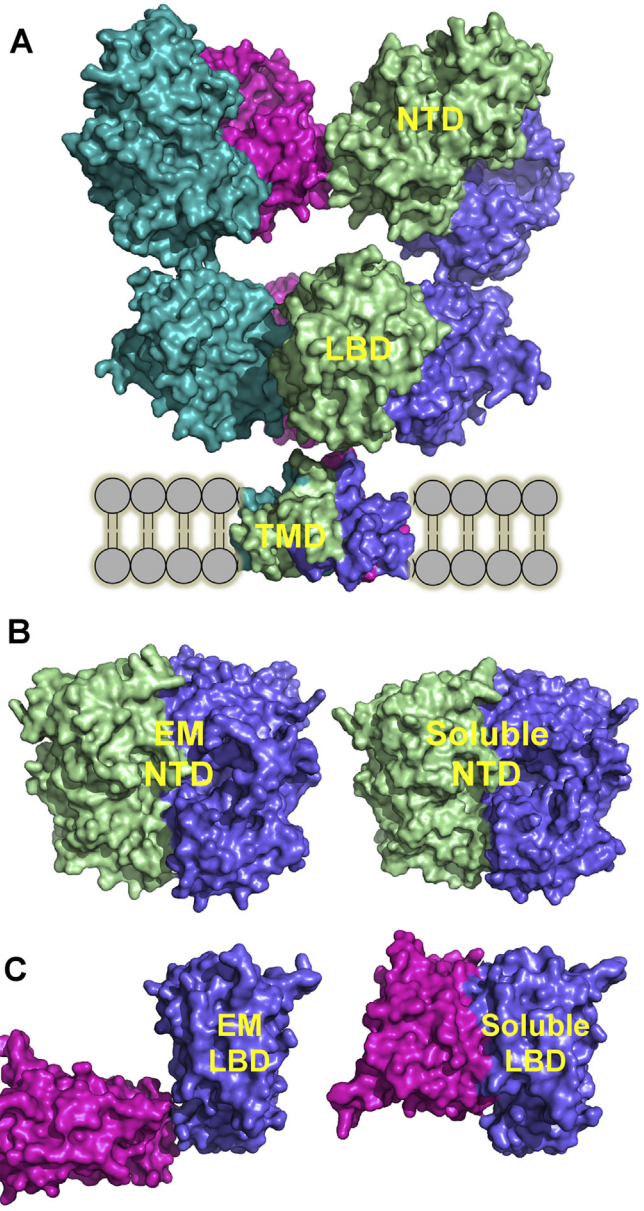


**Fig. 1.** Full-length GluK2 structure determined by EM to 7.6 Å resolution (PDB code 4UQQ). (A) Surface representation of the structure with the four subunits colored differently. (B) The NTD dimer in the desensitized full-length GluK2 is similar to the dimer of a soluble NTD construct (PDB code 3QLT). (C) The LBD dimer is very different in the full-length GluK2 compared to a soluble LBD construct (PDB code 2XXR).