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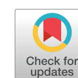
Review article

Glutamate heteroreceptor complexes in the brain



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ABSTRACT

The existence of mGluR, NMDAR, AMPAR and putative KAR heteroreceptor complexes in synaptic and extrasynaptic regions of brain glutamate synapses represents a major integrative mechanism. Our aim in the current article is to analyze if the formation of the different types glutamate hetereceptor complexes involves the contribution of triplet amino acid homologies (protriplets) in a postulated receptor interface based on the triplet puzzle theory. Seven main sets (lists) of receptor pairs in databases were used containing various sets (lists) of human receptor heteromers and nonheteromers obtained from the available scientific publications including the publically available GPCR-hetnet database. Brain mGluR1-mGluR5 and mGluR2-mGluR4 isoreceptor complexes were demonstrated with a predominant extrasynaptic localization at a post- and prejunctional localization. The existence of putative mGluR4-mGluR7 heteroreceptor complexes in the basal ganglia is proposed. Metabotropic glutamate receptor subtypes also participated in the formation of a large number of heteroreceptor complexes like mGluR1-A1R, mGluR5-A2AR, mGluR5-D2R and D2R-A2AR-mGluR5, located in relation to glutamate synapses, especially in the basal ganglia. A putative mGluR1-GABAB1/2 heterocomplex may also exist. NMDAR heteroreceptor complexes were also demonstrated as a fundamental integrative mechanism in the glutamate synapse and its extrasynaptic membranes. It represented fundamental work on inter alia NMDAR-mGluR5, NMDAR-D1R and NMDAR-D2R heteroreceptor complexes involving both antagonistic and facilitatory allosteric receptor–receptor interactions. As to AMPA receptors, a heterocomplex was found for the interaction between IFNgR1 and the AMPAR mediated *via* the subunit GluA1 which may be of relevance for neuroinflammation. AMPAR-D2R heteroreceptor complexes were also demonstrated. Besides glutamate heteroreceptor complexes and their allosteric receptor–receptor interactions, a significant mechanism for the functional crosstalk can also be phosphorylation and/or reorganization of adapter proteins with dynamic binding to the two receptors modulating the allosteric receptor mechanism.

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Introduction

The concept of allosteric receptor–receptor interactions in G protein-coupled receptor (GPCR) homo- and heteroreceptor complexes of the central nervous system (CNS) gave a new biological principle to understanding brain integration and neuropsychopharmacology [1–8]. Allosteric receptor–receptor interactions, accomplished through receptor oligomerization, led to novel receptor dynamics during which the receptor protomers change their recognition, pharmacology, signaling and trafficking and novel allosteric binding sites can develop, see also [6,9–11].

However, no reviews was focused on all the glutamate heteroreceptor complexes and how to understand why some were formed and not others in the glutamate synapses and their extrasynaptic regions. These receptor complexes are present on the glutamate nerve terminals and the dendritic spines on which the glutamate synapse is located (Fig. 1). Thus, there is a gap in our knowledge to understand why certain mGluR, NMDAR, and AMPAR heteroreceptor complexes can form heteromers while others fail to do so (see www.gpcr-hetnet.com [7,12–14]). Our perspective is that the formation of glutamate receptor heteromers is linked to the existence of triplet amino acid homologies (protriplets) in a putative receptor interface domain [15,16]. Using a mathematical approach, this triplet puzzle theory states that these protriplets represent one general molecular mechanism to help develop heteroreceptor complexes and their receptor–receptor interactions by guiding them towards each other [15–17]. We have tested this theory in the current review on glutamate heteroreceptor complexes.

The receptor interface

In the glutamate homo- and heteroreceptor complexes the allosteric communication between the two protomers takes place *via* the receptor interface, which therefore plays a key role in mediating the receptor–receptor interaction [18–20]. Therefore, there is a significant body of work that has focused on identifying key residues of importance for GPCR heteroreceptor complex interface interactions. Several models of GPCR homodimerization have been proposed and some receptor domains have also been identified to be involved in this phenomenon [21,22]. While disulphide bonds in the N-terminal domain play a key role in the homodimerization of certain GPCRs belonging to family C (e.g. mGlu5, mGlu1a and Ca^{2+}-sensing receptors) [13,23], the C-terminal tail plays a role of another receptor of this family, namely the GABAB receptor [24]. It drives the heterodimerization of the GABAB1R and the GABAB2R by means of “coiled-coil” interactions.

On the other hand, in a model of the rhodopsin dimer/oligomer the intradimeric contact was proposed to be located within the transmembrane helix IV and transmembrane helix-V (TM4 and TM5, respectively) [25]. In this model, which is based on images obtained by means of atomic force microscopy, rhodopsin homodimers might also interact to form higher-order oligomers by means of interdimeric and row–row contacts. Furthermore, the transmembrane helix-1 (TM1) and helix 8 of the β2-adrenergic receptor was proposed to participate in the homodimerization of this receptor [26]. These results agree with the studies demonstrating that the interface of the dopamine D2 receptor homodimer takes place within the TM4 [21,22,27]. The participation of TM4 in the oligomer interface was also demonstrated within other receptor dimers like serotonin 5-HT2C receptor homodimer [28], the serotonin 5-HT4 receptor homodimer [29], the chemokine CCR5 receptor homodimer [30], and the 5-HT2A/metabotropic glutamate receptor 2 heterodimer [31].

Overall, it is now well accepted and demonstrated that transmembrane helices participate in class A, B and C GPCR dimerization [12]. The interaction interfaces are formed by lipid-exposed surfaces within the transmembrane helical-bundle of each individual protomer. Thus, alterations in the receptor hydrophobic core, particularly residues containing the ligand-binding site, predictably may affect the receptor conformation and oligomerization.

Accordingly, two levels of interaction could be considered within the GPCR oligomer interface: the transmembrane helices and the intra- and extracellular domains. Rather than being exclusive they operate in a coordinated manner for the oligomer stabilization and function. Indeed, a class A receptor intracellular interaction interface was also described [32–35]. A high energy strength double arginine-phosphate electrostatic interaction was e.g., found in the receptor interface of the A2A-D2 heteromer [19,32,36]. It possesses a covalent-like stability as demonstrated with mass spectrometry, site directed mutagenesis and BRET [19,32,36].

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