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Review

Progress toward advanced understanding of metabotropic glutamate receptors: structure, signaling and therapeutic indications

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ABSTRACT

The metabotropic glutamate (mGlu) receptors are a group of Class C Seven transmembrane spanning/G protein coupled receptors (7TMRs/GPCRs). These receptors are activated by glutamate, one of the standard amino acids and the major excitatory neurotransmitter. By activating G protein-dependent and non G protein-dependent signaling pathways, mGlus modulate glutamatergic transmission in both the periphery and throughout the central nervous system. Since the discovery of the first mGlu receptor, especially the last decade, a great deal of progress has been made in understanding the signaling, structure, pharmacological manipulation and therapeutic indications of the 8 mGlu members.

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1. Introduction

Glutamate is not only one of the 23 proteinogenic amino acids, but it is also the major excitatory neurotransmitter in the central nervous system (CNS). The glutamate receptors can be divided into two classes: the ionotropic glutamate receptors and the metabotropic glutamate receptors. While the ionotropic glutamate receptors (AMPA receptors, NMDA receptors and kainate receptors) mediate fast responses elicited by glutamate, the metabotropic glutamate (mGlu) receptors provide a mechanism by which glutamate can transduce environmental cues and modulate synaptic transmission via second messenger signaling pathways. Because of their widespread distribution, especially in the CNS, pharmacological manipulation of mGlus may represent ideal therapeutic interventions for a wide range of neurological and psychiatric disorders (Reviewed in [76,156]).

2. Classification of mGlus

The 7 Transmembrane Spanning Receptors/G Protein Coupled Receptors (7TMRs/GPCRs) account for 4% of the entire protein-coding genome [20] but represent the targets of approximately 40–50% of medicinal drugs on the market [226]. The core function of 7TMRs is to serve as a transducer of signals from the extracellular environment to the intracellular signaling machinery. The 7TMR superfamily can be classified into several classes: the Class A 7TMRs (or Rhodopsin-like receptors) account for almost 85% of the GPCR genes, the Class B 7TMRs (or secretin-like receptors) include 15 receptors and are regulated by peptide hormones, and the Class C 7TMRs, which are characterized by a large extracellular N-terminal domain and contain 22 distinct receptors. The Adhesion, Frizzled, Taste type-2 and other unclassified receptors comprise the rest of the superfamily [20].

The mGlus belong to the Class C 7TMRs; this class also encompasses calcium sensing receptors, the $GABA_B$ receptor, taste receptors and other orphan Class C receptors. Since the cloning of rat $mGlu_1$ in 1991, 8 mGlu subtypes have been cloned thus far, named $mGlu_1$ through $mGlu_8$. Within the family, the eight mGlu subtypes can be further classified into three groups, with an intragroup sequence homology of about 70% and an intergroup sequence homology of about 45% (reviewed in [37]). The classification of mGlu receptors are summarized in Table 1: the group I mGlus include $mGlu_1$ and $mGlu_5$, the group II includes $mGlu_2$ and $mGlu_3$, whereas $mGlu_{4,\ 6,\ 7\ and\ 8}$ comprise the group III mGlus. While the group I mGlus are coupled to G_q, the group II and group III are coupled to $G_{i/o}$ G proteins.

3. Structure of mGlus

3.1. General structural features of mGlus

As members of the Class C 7TMRs, the mGlus are characterized by a large N-terminal domain, commonly referred to as the Venus Flytrap

Table 1
Classification, G protein coupling, splice variants and selective ligands for mGlu subtypes.

Classification	G protein coupling	Receptor subtypes	Splice variants	Selective ligands
Group I	$G_{q/11}$	$mGlu_1$	$mGlu_{1a\text{-}h,}$	LY367385 (orthosteric agonist)
			$mGlu_{1g393}$	Bay 36–7620 (NAM)
			$mGlu_{1g620}$	Ro 67–7476 (PAM)
			Taste $mGlu_1$	Ro 67–4853 (PAM)
				VU71 (PAM)
		$mGlu_5$	$mGlu_{5a,b}$	CHPG (orthosteric agonist)
				MPEP (NAM)
				MTEP (NAM)
				CDPPB (PAM)
				CPPHA (PAM)
				VU0365396 (SAM)
Group II	$G_{i/o}$	$mGlu_2$	$mGlu_2$	LY487379 (PAM)
				BINA (PAM)
		$mGlu_3$	GRM3Δ2	ML337 (NAM)
			GRM3 Δ 4	
			GRM3 Δ 2 Δ 3	
Group III	$G_{i/o}$	$mGlu_4$	$mGlu_{4a,b}$	LSP1-2111 (orthosteric agonist)
			Taste $mGlu_4$	LSP4-2022 (orthosteric agonist)
				PHCCC (PAM)
				VU0155041(PAM)
				VU0364770 (PAM)
				ADX88178 (PAM)
				Lu AF21934 (PAM)
		$mGlu_6$	$mGlu_{6a\text{-}c}$	
		$mGlu_7$	$mGlu_{7a\text{-}e}$	AMN 082 (allosteric agonist)
				MMPIP (NAM)
				ADX71743 (NAM)
		$mGlu_8$	$mGlu_{8a\text{-}c}$	(S)-3,4-DCPG (orthosteric agonist)
				AZ12216052 (PAM)