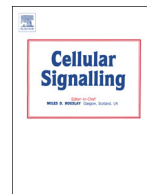




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Review

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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Contents

33	1. Introduction	0
34	2. Classification of mGlu	0
35	3. Structure of mGlu	0
36	3.1. General structural features of mGlu	0
37	3.2. The dimeric complex of mGlu	0
38	4. Alternative splicing of mGlu	0
39	4.1. Signaling of mGlu	0
40	4.1.1. G protein-dependent signaling	0
41	5. G protein-independent signaling	0
42	6. Orthosteric modulation of mGlu	0
43	6.1. Non-selective ligands	0
44	6.2. Orthosteric ligands of group I mGlu	0
45	6.3. Orthosteric ligands of group II mGlu	0
46	6.4. Orthosteric ligands of group III mGlu	0
47	7. Allosteric modulation of mGlu	0
48	7.1. Mechanism and advantages of allosteric modulation	0
49	7.2. Allosteric modulators of group I mGlu	0
50	7.3. Allosteric modulators of group II mGlu	0
51	7.4. Allosteric modulators of group III mGlu	0
52	8. Therapeutic indications of mGlu	0
53	8.1. CNS-related diseases	0
54	8.1.1. Schizophrenia and Alzheimer's disease	0
55	8.1.2. Fragile X syndrome	0

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56	8.1.3.	Anxiety	0
57	8.1.4.	Parkinson's disease	0
58	8.1.5.	Other CNS disorders	0
59	8.2.	Peripheral diseases	0
60	8.2.1.	Pain sensation	0
61	8.2.2.	Congenital stationary night blindness	0
62	9.	Concluding remarks	0
63		Acknowledgement	0
64		References	0

65

66 1. Introduction

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

80 2. Classification of mGlu

81 The 7 Transmembrane Spanning Receptors/G Protein Coupled
82 Receptors (7TMRs/GPCRs) account for 4% of the entire protein-coding
83 genome [20] but represent the targets of approximately 40–50% of
84 medicinal drugs on the market [226]. The core function of 7TMRs is
85 to serve as a transducer of signals from the extracellular environ-
86 ment to the intracellular signaling machinery. The 7TMR superfamily
87 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 mGlu 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 mGlu₁ in 1991,
8 mGlu subtypes have been cloned thus far, named mGlu₁ through
mGlu₈. Within the family, the eight mGlu subtypes can be further classi-
fied 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 mGlu include mGlu₁ and mGlu₅, the group II includes
mGlu₂ and mGlu₃, whereas mGlu₄, 6, 7 and 8 comprise the group III
mGlu. While the group I mGlu are coupled to G_q, the group II and
group III are coupled to G_{i/o}/G proteins.

83 3. Structure of mGlu

84 3.1. General structural features of mGlu

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

t1.1 **Table 1**
t1.2 Classification, G protein coupling, splice variants and selective ligands for mGlu subtypes.

t1.3	Classification	G protein coupling	Receptor subtypes	Splice variants	Selective ligands
t1.4	Group I	G _{q/11}	mGlu ₁	mGlu _{1a-h} ,	LY367385 (orthosteric agonist)
t1.5				mGlu _{1g393}	Bay 36–7620 (NAM)
t1.6				mGlu _{1g620}	Ro 67–7476 (PAM)
t1.7				Taste mGlu ₁	Ro 67–4853 (PAM)
t1.8					VU71 (PAM)
t1.9			mGlu ₅	mGlu _{5a,b}	CHPG (orthosteric agonist)
t1.10					MPEP (NAM)
t1.11					MTEP (NAM)
t1.12					CDPPB (PAM)
t1.13					CPPHA (PAM)
t1.14					VU0365396 (SAM)
t1.15	Group II	G _{i/o}	mGlu ₂	mGlu ₂	LY487379 (PAM)
t1.16			mGlu ₃	GRM3Δ2	BINA (PAM)
t1.17				GRM3 Δ 4	ML337 (NAM)
t1.18				GRM3 Δ 2 Δ 3	
t1.19	Group III	G _{i/o}	mGlu ₄	mGlu _{4a,b}	LSP1-2111 (orthosteric agonist)
t1.20				Taste mGlu ₄	LSP4-2022 (orthosteric agonist)
t1.21					PHCCC (PAM)
t1.22					VU0155041 (PAM)
t1.23					VU0364770 (PAM)
t1.24					ADX88178 (PAM)
t1.25					Lu AF21934 (PAM)
t1.26			mGlu ₆	mGlu _{6a-c}	
t1.27			mGlu ₇	mGlu _{7a-e}	AMN 082 (allosteric agonist)
t1.28					MMPIP (NAM)
t1.29					ADX71743 (NAM)
t1.30					(S)-3,4-DCPG (orthosteric agonist)
t1.31			mGlu ₈	mGlu _{8a-c}	AZ12216052 (PAM)
t1.32					

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