



A nomenclature for ligand-gated ion channels

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ARTICLE INFO

Article history:

Received 30 May 2008

Received in revised form 17 June 2008

Accepted 18 June 2008

Keywords:

Ligand-gated ion channels

Nomenclature

ABSTRACT

The ligand-gated ion channels that participate in fast synaptic transmission comprise the nicotinic acetylcholine, 5-hydroxytryptamine₃ (5-HT₃), γ -aminobutyric acid_A (GABA_A), glycine, ionotropic glutamate and P2X receptor families. A consistent and systematic nomenclature for the individual subunits that comprise these receptors and the receptors that result from their co-assembly is highly desirable. There is also a need to develop criteria that aid in deciding which of the vast number of heteromeric combinations of subunits that can be assembled in heterologous expression systems *in vitro*, are known, or likely, to exist as functional receptors *in vivo*. The aim of this short article is to summarize the progress being made by the nomenclature committee of IUPHAR (NC-IUPHAR) in formulating recommendations that attempt to address these issues.

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1. Introduction

The heteromeric nature of most ligand-gated ion channels (Fig. 1), with their accessory proteins, and the multiple proteins involved in receptor trafficking and responses to receptor activation pose multiple challenges to the definition of their pharmacology. Furthermore, the receptors must be well characterized for definition of their functional roles in normal brain and in disease states and for new drug discovery. To this end the journal *Neuropharmacology* and The International Union of Basic and Clinical Pharmacology (IUPHAR) have joined forces in this Special Issue to address the nomenclature, the structures, the pharmacology, the roles, and therapeutic opportunities of ligand-gated ion channels (LGICs) that are activated by neurotransmitters (Fig. 1).

2. NC-IUPHAR

The International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) is a body that issues guidelines for receptor and ion channel classification. It addresses the main issues in pharmacology today, classifying the major receptor and ion channel systems in the human genome and depositing the data on a freely available web site (<http://www.iuphar-db.org>). NC-IUPHAR has >50 subcommittees with expert scientists freely giving up their time in order to

facilitate the interface between the discovery of new sequences from the Human Genome Project and the designation of the derived proteins as functional receptors and ion channels.

Furthermore, the multitude of factors between a published genomic sequence and an assigned receptor function in a given tissue (epigenetics, alternative splicing, messenger RNA editing, polymorphisms, the combinatorial nature of subunit association) ensures that there are multiple drug targets. The practical implications of the new pharmacology are immense, particularly for drug discovery where the magnitude of the variables affecting drug response is only now becoming fully appreciated. NC-IUPHAR needs input from motivated scientists interested in receptors, so if you are interested please contact us! NC-IUPHAR works in co-ordination with the Human Genome Organisation (HUGO) Gene Nomenclature Committee (HGNC).

The goals of NC-IUPHAR include: (i) establishing, as far as possible, an overall consistent classification and nomenclature for the LGICs; and (ii) developing a subunit list (with template information for a database). Table 1 presents such a list of the genes encoding LGIC subunits that are expressed in humans. Thus, certain subunits, such as the nicotinic acetylcholine receptor $\alpha 8$ subunit (Schoeper et al., 1990) that has not been identified in the mammalian brain, and the glycine receptor $\alpha 4$ subunit (Matzenbach et al., 1994), which is likely to be a pseudogene in man, are not listed. Similarly, the avian GABA_A receptor $\beta 4$ and $\gamma 4$ subunits, which may have evolved into the mammalian GABA_A receptor θ and ε subunits, respectively, are not tabulated (Simon et al., 2004). At this point in time we also do not consider intracellular ion channels such as the inositol trisphosphate (IP₃) or ryanodine receptors that

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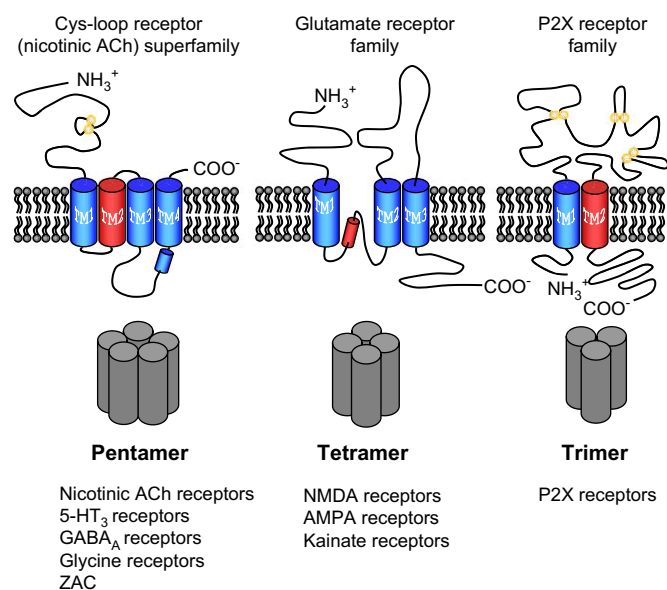


Fig. 1. Schematic representation of the three structural categories of ligand-gated ion channel subunit. The pentameric Cys-loop receptor superfamily comprises the nicotinic acetylcholine (ACh) receptors, 5-hydroxytryptamine₃ (5-HT₃) and a zinc-activated channel that form anion selective ion channels and the γ -aminobutyric acid_A and strychnine-sensitive glycine receptors that conduct anions. The tetrameric ionotropic glutamate receptors are subdivided into *N*-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptor subfamilies. The highly schematic topography of each receptor category indicates the locations of the extracellular and intracellular termini, the number of transmembrane spans (large colored cylinders), and cysteine residues participating in disulphide bond formation (yellow circles). Red cylinders indicate α -helical regions participating in ion conduction/selectivity.

are gated by ligands. Other classes of cell surface ion channel that are activated, or modulated, by ligands, such as the cyclic nucleotide regulated ion channels and numerous members of the transient receptor potential family have been the subject of previous NC-IUPHAR recommendations (Clapham et al., 2005; Hofmann et al., 2005).

In recommending a consistent nomenclature for LGIC subunits, it is appropriate to reflect upon the acceptance, or otherwise, of previous NC-IUPHAR recommendations and current practice in the literature. Lukas et al. (1999) in an interim NC-IUPHAR statement on the nomenclature of nicotinic acetylcholine receptor subunits stated that 'the 16 nACh receptor subunits identified to date are defined using a Greek letter sometimes followed by an Arabic numeral (neither a subscript nor superscripted)'. A survey of the literature indicates this formalism to be widely employed. By contrast, in an extensive and still valuable review of the classification of GABA_A receptors, Barnard et al. (1998) indicated that Greek subunit letters should be followed by a subscripted Arabic numeral, where appropriate. However, a representative search of the literature subsequent to that publication indicates no consistent usage of subscripts even, in some instances, between contributions emanating from the same laboratory. A similar situation is apparent for the strychnine-sensitive glycine receptors, upon which NC-IUPHAR have yet to issue guidance. By contrast, subscripted numbers and letters are almost universally used to denote the 5-HT₃ and P2X receptor subunits (e.g. 5-HT_{3A}; P2X₃) in accordance with previous NC-IUPHAR guidelines (Hoyer et al., 1994; Khakh et al., 2001).

A revised nomenclature of the ionotropic glutamate receptors subunits triggered NC-IUPHAR to reconsider the naming of LGIC subunits in general, but in particular with regard to the use of subscripts. Each of the LGIC subcommittees were consulted in an attempt to reach an overall consensus. Various reasons were

elaborated for the continued use (largely historical), or not (consistency across receptor families, reserving subscript to specify receptor stoichiometry, difficulties in database searches, formatting issues) of subscript notation. After considerable deliberation the NC-IUPHAR Committee sets out the following which is a recommendation for implementation:

1. The use of subscript may be retained specifically for the receptor names GABA_A and 5-HT₃. For historical reasons this would be difficult, if not impossible, to change.
2. Subunits within a receptor should not be denoted by subscripts.
3. Stoichiometry, where known, should be indicated by placing the subunit in parenthesis and indicating the number of subunits by use of a subscripted number following the close of the parenthesis (where the number of subunits is greater than one). This is already a formal recommendation of the NC-IUPHAR nicotinic acetylcholine receptor subcommittee (Lukas et al., 1999). However, stoichiometry should not be indicated unnecessarily.
4. Subunits should be listed in alphabetical, or numerical, sequence without punctuation between subunits. An exception arises in the case of subunit types denoted by a numeral (e.g. P2X₂; P2X₃), where a solidus should be placed between the subunits as previously recommended when describing receptors of unspecified stoichiometry (Khakh et al., 2001).

Examples of the recommended nomenclature are given in Tables 1 and 2.

3. Ionotropic glutamate receptors (iGluRs)

The ionotropic glutamate receptors posed a special case to its subcommittee,¹ due to historical circumstances (see Lodge, submitted for publication). The receptors had been classified by pharmacologists and named after the synthetic agonists AMPA, kainate and NMDA and by the end of the 1980's this terminology was firmly established (Watkins and Jane, 2006). The cloning of the subunits confirmed this pharmacological classification but, of course, added a wealth of complexity by virtue of the identification of the many constituent proteins. Various nomenclatures were introduced by the laboratories that cloned the subunits, so, for example, the same AMPA receptor subunit was called either GluR1 (Boulter et al., 1990), or GluR-A (Keinanen et al., 1990), and the same NMDA receptor subunit NMDAR1 (Moriyoshi et al., 1991), or ζ 1 (Meguro et al., 1992). Table 3 presents the currently recommended subunit nomenclature together with a list of former appellations that should be avoided in the future. The kainate receptor subunits had a more consistent, but illogical, nomenclature starting at GluR5. The challenge was two-fold: to obtain a nomenclature that was logical for the ionotropic GluRs and one that was as consistent as possible with the general principles of the nomenclature for the LGIC superfamilies.

The committee took no time to reach the consensus that the AMPARs subunits should be renamed GluA1, GluA2, GluA3 and GluA4. An interim recommendation (Lodge and Dingledine, 2000) had concluded that these subunits be named GLU_{A1}, GLU_{A2}, GLU_{A3} and GLU_{A4} (Table 3). The decision to omit "R" conformed to the NC-IUPHAR general recommendation that it is preferable not to label

¹ NC-IUPHAR subcommittee membership: Bernhard Bettler, Graham Collingridge (Chair), Ray Dingledine, Stephen F. Heinemann, Michael Hollmann, Juan Lerma, David Lodge, Mark Mayer, Masayoshi Mishina, Christophe Mulle, Shigetada Nakanishi, Richard Olsen, John A. Peters, Peter Seeburg, Michael Spedding, Jeffrey C. Watkins, Robert J. Wenthold.

Table 1
NC-IUPHAR list of ligand-gated ion channel subunits

Receptor family	NC-IUPHAR subunit nomenclature	Human gene name	Human chromosomal location
A. Cys-loop superfamily			
5-HT ₃	5-HT3A	HTR3A	11q23.1
	5-HT3B	HTR3B	11q23.1
	5-HT3C	HTR3C	3q27.1
	5-HT3D	HTR3D	3q27.1
	5-HT3E	HTR3E	3q27.1
Nicotinic ACh	$\alpha 1$	CHRNA1	2q24–q32
	$\alpha 2$	CHRNA2	8p21
	$\alpha 3$	CHRNA3	15q24
	$\alpha 4$	CHRNA4	20q13.2–q13.3
	$\alpha 5$	CHRNA5	15q24
	$\alpha 6$	CHRNA6	8p11.21
	$\alpha 7$	CHRNA7	15q14
	$\alpha 9$	CHRNA9	4p14
	$\alpha 10$	CHRNA10	11p15.5
	$\beta 1$	CHRNB1	17p13.1
	$\beta 2$	CHRNB2	1q21.3
	$\beta 3$	CHRNB3	8p11.2
	$\beta 4$	CHRNB4	15q24
	γ	CHRNA3	2q33–q34
	δ	CHRNA3	2q33–q34
	ϵ	CHRNA3	17p13–p12
GABA _A	$\alpha 1$	GABRA1	5q34–q35
	$\alpha 2$	GABRA2	4p12
	$\alpha 3$	GABRA3	Xq28
	$\alpha 4$	GABRA4	4p12
	$\alpha 5$	GABRA5	15q11.2–q12
	$\alpha 6$	GABRA6	5q34
	$\beta 1$	GABRB1	4p12
	$\beta 2$	GABRB2	5q34
	$\beta 3$	GABRB3	15q11.2–q12
	$\gamma 1$	GABRG1	4p12
	$\gamma 2$	GABRG2	5q31.1–q33.1
	$\gamma 3$	GABRG3	15q12
	δ	GABRD	1p36.3
	ϵ	GABRE	Xq28
	θ	GABRQ	Xq28
	π	GABRP	5q33–q34
	$\rho 1$	GABRR1	6q13–q16.3
	$\rho 2$	GABRR2	6q13–q16.3
	$\rho 3$	GABRR3	3q11.2
Glycine	$\alpha 1$	GLRA1	5q32
	$\alpha 2$	GLRA2	Xp22.1–p21.3
	$\alpha 3$	GLRA3	4q33–q34
	β	GLRB	4q31.3
Zinc-activated	ZAC	ZACN	17q25.3
B. P2X family			
P2X	P2X1	P2RX1	17p13.3
	P2X2	P2RX2	12q24.33
	P2X3	P2RX3	11q12
	P2X4	P2RX4	12q24.32
	P2X5	P2RX5	17p13.3
	P2X6	P2RX6	22q11.21
	P2X7	P2RX7	12q24
C. Ionotropic glutamate family			
AMPA	GluA1	GRIA1	5q31.1
	GluA2	GRIA2	4q32–q33
	GluA3	GRIA3	Xq25–q26
	GluA4	GRIA4	11q22
Kainate	GluK1	GRIK1	21q22.11
	GluK2	GRIK2	6q16.3–q21
	GluK3	GRIK3	1p34–p33
	GluK4	GRIK4	11q22.3
	GluK5	GRIK5	19q13.2
NMDA	GluN1	GRIN1	9q34.3
	GluN2A	GRIN2A	16p13.2
	GluN2B	GRIN2B	12p12
	GluN2C	GRIN2C	17q25
	GluN2D	GRIN2D	19q13.1

Table 1 (continued)

Receptor family	NC-IUPHAR subunit nomenclature	Human gene name	Human chromosomal location
'Orphan' (GluD)	GluN3A	GRIN3A	9q31.1
	GluN3B	GRIN3B	19p13.3
	GluD1	GRID1	10q22
	GluD2	GRID2	4q22

Note, the entries in this table do not attempt to address the multiple subunits that frequently arise from a single gene as a consequence of alternative splicing and editing of RNA transcripts.

a subunit as a receptor, given that many of these subunits do not form functional receptors when expressed alone. The new nomenclature adopted the same general principle but made two changes. First, it was agreed to adopt Glu, the three letter amino acid code for glutamate, rather than GLU, to identify the neurotransmitter. Secondly it was agreed to drop the use of subscripts (for the reasons set out above). This new nomenclature has two important attributes: first, it harmoniously combines the two commonly used nomenclatures (e.g. GluR1 and GluRA become GluA1). Second the protein name can be instantly derived from the gene name by the conversion to two letters: "RI" becoming "lu": Thus *GRIA1* translates to GluA1, *GRIA2* translates to GluA2, etc. (Table 1). There was a discussion whether, indeed, the two names should be identical but the general consensus was that this could be confusing.

The NMDA receptor was similarly non-contentious and adopted the same pattern: NR1 becoming GluN1, NR2A becoming GluN2A and so forth (Table 3). Once again, the protein name mirrors the gene name, with just the two letter code difference (i.e., *GRIN1* translates to GluN1, *GRIN2A* translates to GluN2A).

The problem with the kainate receptors is that the first subunit cloned was named GluR5 (Bettler et al., 1990) and this name has been widely adopted in the field (Table 3). Clearly, however, there are no functional reasons for considering the kainate receptor subunits as a continuum of the AMPAR subunits. Despite some structural and pharmacological similarities there is no evidence that the two receptor families co-assemble. Several solutions were put forward by the subcommittee, each with its own merits. After considerable deliberation, however, it was decided to take the radical step to rename the subunits as follows: GluK1, GluK2, GluK3, GluK4 and GluK5 to replace the names GluR5, GluR6, GluR7, KA-1 and KA-2, respectively (Table 3). This again has the virtue that the protein names mirror the gene names, which are *GRIK1*, *GRIK2*, *GRIK3*, *GRIK4*, *GRIK5*, respectively (Table 1). Of course, the committee realizes that there will be a period of adjustment whilst the users equate GluK1 with GluR5, etc., but our brains are highly plastic and so such adjustment should not pose a great difficulty. Indeed, the precedent has already been set by the voltage-gated ion channel community who readily embraced a new more logical nomenclature for K⁺ and Ca²⁺ channels (Catterall et al., 2005; Goldstein et al., 2005; Gutman et al., 2005; Kubo et al., 2005; Wei et al., 2005).

Table 2
NC-IUPHAR recommendations on receptor nomenclature

Receptor with unspecified stoichiometry	Receptor with specified stoichiometry
Nicotinic ACh $\alpha 4\beta 2$	Nicotinic ACh($\alpha 4$) ₂ ($\beta 2$) ₃
5-HT ₃ AB	5-HT ₃ (A) ₂ (B) ₃
GABA _A $\alpha 1\beta 2\gamma 2$	GABA _A ($\alpha 1$) ₂ ($\beta 2$) ₂ $\gamma 2$
Gly $\alpha 1\beta$	Gly($\alpha 1$) ₂ (β) ₃
GluA1A2	Glu(A1) ₂ (A2) ₂
P2X _{2/3}	P2X(2) ₂ 3

Stoichiometry should not be indicated unnecessarily.

Table 3

NC-IUPHAR recommended and previous nomenclature of ionotropic glutamate receptor subunits

NC-IUPHAR subunit nomenclature	Previous nomenclatures
GluA1	GLU _{A1} , GluR1, GluRA, GluR-A, GluR-K1, HBGR1
GluA2	GLU _{A2} , GluR2, GluRB, GluR-B, GluR-K2, HBGR2
GluA3	GLU _{A3} , GluR3, GluRC, GluR-C, GluR-K3
GluA4	GLU _{A4} , GluR4, GluRD, GluR-D
GluK1	GLU _{K5} , GluR5, GluR-5, EAA3
GluK2	GLU _{K6} , GluR6, GluR-6, EAA4
GluK3	GLU _{K7} , GluR7, GluR-7, EAA5
GluK4	GLU _{K1} , KA1, KA-1, EAA1
GluK5	GLU _{K2} , KA2, KA-2, EAA2
GluN1	GLU _{N1} , NMDA-R1, NR1, GluR ξ 1
GluN2A	GLU _{N2A} , NMDA-R2A, NR2A, GluR ϵ 1
GluN2B	GLU _{N2B} , NMDA-R2B, NR2B, hNR3, GluR ϵ 2
GluN2C	GLU _{N2C} , NMDA-R2C, NR2C, GluR ϵ 3
GluN2D	GLU _{N2D} , NMDA-R2D, NR2D, GluR ϵ 4
GluN3A	GLU _{N3A} , NMDA-R3A, NMDAR-L, chi-1
GluN3B	GLU _{N3B} , NMDA-R3B
GluD1	GluR δ 1
GluD2	GluR δ 2

Greek symbols in NMDA receptor subunit names were applied to the mouse orthologue only.

There are, of course, challenges ahead. In particular is the need that the community embraces the new nomenclature. Whether the subcommittee has reached the correct recommendation remains to be seen, but what is clear is that a consistent and logical nomenclature that is widely adopted is urgently required. There is also the need to establish a consistent nomenclature for the alternative splice variants and for the edited states of the subunits.

4. Criteria for identifying native receptors

We have suggested criteria for selecting receptor subtype heteromer candidates for inclusion on a native receptor list that is currently under development by the LGIC subcommittees of NC-IUPHAR. These criteria include two categories for recombinant receptors: showing that a given combination of subunits is expressed as a pentamer (Cys-loop family), tetramer (ionotropic glutamate receptors), or trimer (P2X receptors) (see Fig. 1) and that it has unique biophysical and/or pharmacological properties. There are three criteria for native receptors: (i) evidence for co-localization of subunits; (ii) physical evidence for subunit–subunit type interactions; and (iii) demonstration of specific function. The mechanism for selection involves a subcommittee of NC-IUPHAR who evaluate the quality of the evidence that receptor subtype candidates meet the criteria for inclusion on the receptor list. Our tentative selections utilize the new principle of three categories of receptors (Olsen and Sieghart, in press):

- identified;
- existence with high probability;
- tentative.

The same review includes a working receptor list for GABA_A receptors, with 26 total entries. We continue the use of a wild card nomenclature (see, for example, Lukas et al., 1999), when a subunit is not clearly identified.

5. Concluding remarks

Now that we know that there are virtually no more LGICs to be discovered in the human genome, we hope that the proposed nomenclature will be used for all mammalian species for a very long time.

Acknowledgements

We thank the Chairs and members of all the LGIC subcommittees of NC-IUPHAR for their work in developing a receptor nomenclature and database.

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