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## A nomenclature for ligand-gated ion channels

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### Abstract

The ligand-gated ion channels that participate in fast synaptic transmission comprise the nicotinic acetylcholine, 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>),  $\gamma$ -aminobutyric acid<sub>A</sub> (GABA<sub>A</sub>), 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.

### Keywords

Ligand-gated ion channels; Nomenclature

## 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

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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 coordination 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 (Schoepfer 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<sub>A</sub> receptor  $\beta 4$  and  $\gamma 4$  subunits, which may have evolved into the mammalian GABA<sub>A</sub> receptor  $\theta$  and  $\epsilon$  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 (IP<sub>3</sub>) or ryanodine receptors that 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 subscripted 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<sub>A</sub> 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-HT<sub>3</sub> and P2X receptor subunits (e.g. 5-HT<sub>3A</sub>; P2X<sub>3</sub>) 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<sub>A</sub> and 5-HT<sub>3</sub>. 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 subunits types denoted by a numeral (e.g. P2X<sub>2</sub>; P2X<sub>3</sub>), 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,<sup>1</sup> 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 ζ1 (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<sub>A1</sub>, GLU<sub>A2</sub>, GLU<sub>A3</sub> and GLU<sub>A4</sub> (Table 3). The decision to omit "R" conformed to the NC-IUPHAR general recommendation that it is preferable not to label 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

<sup>1</sup>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.

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<sup>+</sup> and Ca<sup>2+</sup> channels (Catterall et al., 2005; Goldstein et al., 2005; Gutman et al., 2005; Kubo et al., 2005; Wei et al., 2005).

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<sub>A</sub> 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.

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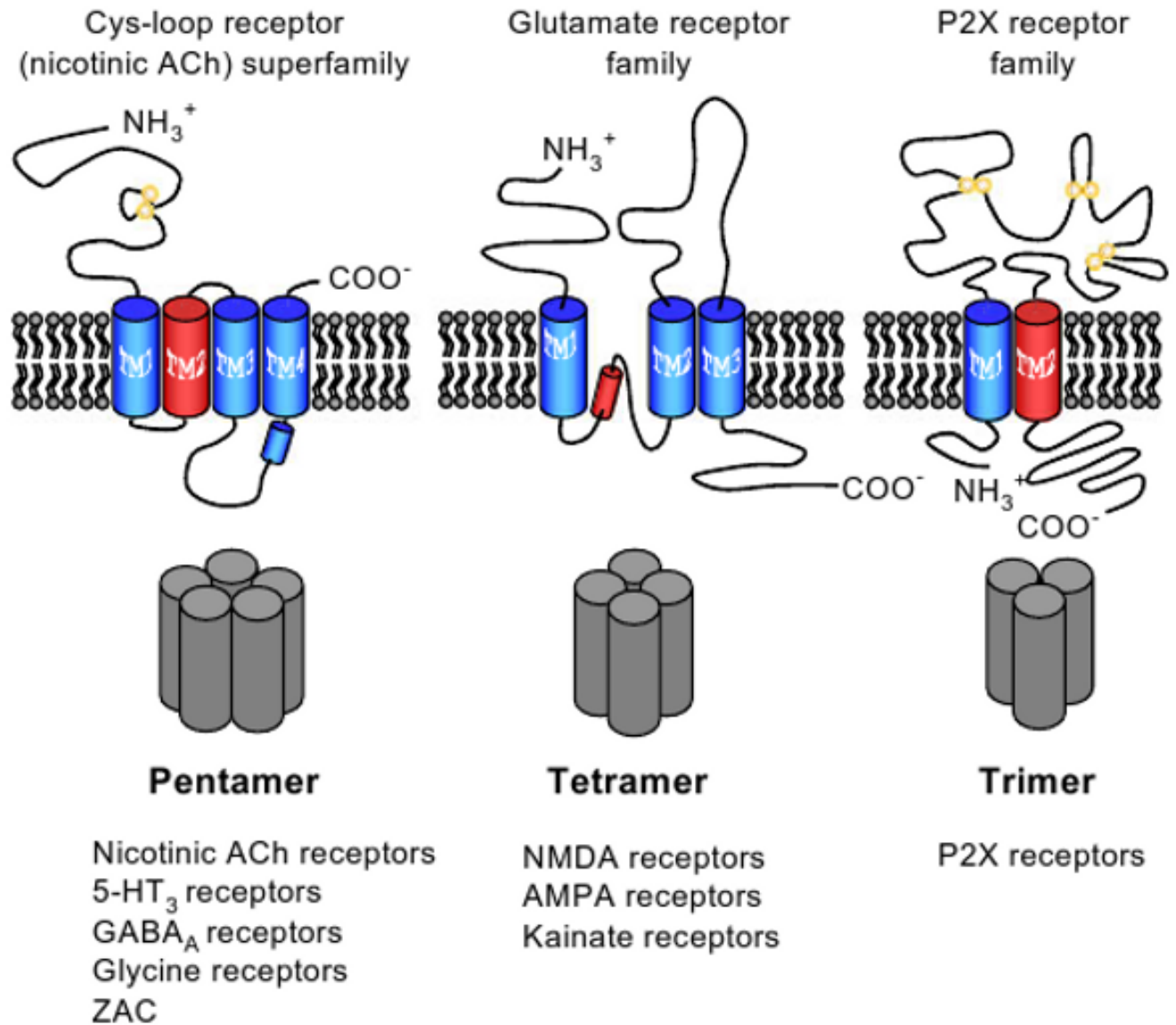
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**Fig. 1.**

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-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) and a zinc-activated channel that form cation selective ion channels and the  $\gamma$ -aminobutyric acid<sub>A</sub> and strychnine-sensitive glycine receptors that conduct anions. The tetrameric ionotropic glutamate receptors are subdivided into *N*-methyl-D-aspartate (NMDA),  $\alpha$ -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  $\alpha$ -helical regions participating in ion conduction/selectivity.

**Table 1**

NC-IUPHAR list of ligand-gated ion channel subunits

Receptor family	NC-IUPHAR subunit nomenclature	Human gene name	Human chromosomal location
<i>A. Cys-loop superfamily</i>			
5-HT <sub>3</sub>	5-HT3A	<i>HTR3A</i>	11q23.1
	5-HT3B	<i>HTR3B</i>	11q23.1
	5-HT3C	<i>HTR3C</i>	3q27.1
	5-HT3D	<i>HTR3D</i>	3q27.1
	5-HT3E	<i>HTR3E</i>	3q27.1
Nicotinic ACh	α1	<i>CHRNA1</i>	2q24–q32
	α2	<i>CHRNA2</i>	8p21
	α3	<i>CHRNA3</i>	15q24
	α4	<i>CHRNA4</i>	20q13.2–q13.3
	α5	<i>CHRNA5</i>	15q24
	α6	<i>CHRNA6</i>	8p11.21
	α7	<i>CHRNA7</i>	15q14
	α9	<i>CHRNA9</i>	4p14
	α10	<i>CHRNA10</i>	11p15.5
	β1	<i>CHRNA1</i>	17p13.1
	β2	<i>CHRNA2</i>	1q21.3
	β3	<i>CHRNA3</i>	8p11.2
	β4	<i>CHRNA4</i>	15q24
	γ	<i>CHRNA5</i>	2q33–q34
	δ	<i>CHRNA6</i>	2q33–q34
	ε	<i>CHRNA7</i>	17p13–p12
	GABA <sub>A</sub>	α1	<i>GABRA1</i>
α2		<i>GABRA2</i>	4p12
α3		<i>GABRA3</i>	Xq28
α4		<i>GABRA4</i>	4p12
α5		<i>GABRA5</i>	15q11.2–q12
α6		<i>GABRA6</i>	5q34
β1		<i>GABRB1</i>	4p12
β2		<i>GABRB2</i>	5q34
β3		<i>GABRB3</i>	15q11.2–q12
γ1		<i>GABRG1</i>	4p12
γ2		<i>GABRG2</i>	5q31.1–q33.1
γ3		<i>GABRG3</i>	15q12
δ		<i>GABRD</i>	1p36.3
ε		<i>GABRE</i>	Xq28
θ		<i>GABRQ</i>	Xq28
π		<i>GABRP</i>	5q33–q34
ρ1		<i>GABRR1</i>	6q13–q16.3
ρ2	<i>GABRR2</i>	6q13–q16.3	



Receptor family	NC-IUPHAR subunit nomenclature	Human gene name	Human chromosomal location
	$\rho 3$	<i>GABRR3</i>	3q11.2
Glycine	$\alpha 1$	<i>GLRA1</i>	5q32
	$\alpha 2$	<i>GLRA2</i>	Xp22.1–p21.3
	$\alpha 3$	<i>GLRA3</i>	4q33–q34
	$\beta$	<i>GLRB</i>	4q31.3
Zinc-activated	ZAC	<i>ZACN</i>	17q25.3
<i>B. P2X family</i>			
P2X	P2X1	<i>P2RX1</i>	17p13.3
	P2X2	<i>P2RX2</i>	12q24.33
	P2X3	<i>P2RX3</i>	11q12
	P2X4	<i>P2RX4</i>	12q24.32
	P2X5	<i>P2RX5</i>	17p13.3
	P2X6	<i>P2RX6</i>	22q11.21
	P2X7	<i>P2RX7</i>	12q24
<i>C. Ionotropic glutamate family</i>			
AMPA	GluA1	<i>GRIA1</i>	5q31.1
	GluA2	<i>GRIA2</i>	4q32–q33
	GluA3	<i>GRIA3</i>	Xq25–q26
	GluA4	<i>GRIA4</i>	11q22
Kainate	GluK1	<i>GRIK1</i>	21q22.11
	GluK2	<i>GRIK2</i>	6q16.3–q21
	GluK3	<i>GRIK3</i>	1p34–p33
	GluK4	<i>GRIK4</i>	11q22.3
	GluK5	<i>GRIK5</i>	19q13.2
NMDA	GluN1	<i>GRIN1</i>	9q34.3
	GluN2A	<i>GRIN2A</i>	16p13.2
	GluN2B	<i>GRIN2B</i>	12p12
	GluN2C	<i>GRIN2C</i>	17q25
	GluN2D	<i>GRIN2D</i>	19q13.1
	GluN3A	<i>GRIN3A</i>	9q31.1
	GluN3B	<i>GRIN3B</i>	19p13.3
'Orphan' (GluD)	GluD1	<i>GRID1</i>	10q22
	GluD2	<i>GRID2</i>	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.

**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) <sub>2</sub> ( $\beta$ 2) <sub>3</sub>
5-HT <sub>3</sub> AB	5-HT <sub>3</sub> (A) <sub>2</sub> (B) <sub>3</sub>
GABA <sub>A</sub> $\alpha$ 1 $\beta$ 2 $\gamma$ 2	GABA <sub>A</sub> ( $\alpha$ 1) <sub>2</sub> ( $\beta$ 2) <sub>2</sub> $\gamma$ 2
Gly $\alpha$ 1 $\beta$	Gly( $\alpha$ 1) <sub>2</sub> ( $\beta$ ) <sub>3</sub>
GluA1A2	Glu(A1) <sub>2</sub> (A2) <sub>2</sub>
P2X <sub>2/3</sub>	P2X(2) <sub>2</sub> 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 <sub>A1</sub> , GluR1, GluRA, GluR-A, GluR-K1, HBGR1
GluA2	GLU <sub>A2</sub> , GluR2, GluRB, GluR-B, GluR-K2, HBGR2
GluA3	GLU <sub>A3</sub> , GluR3, GluRC, GluR-C, GluR-K3
GluA4	GLU <sub>A4</sub> , GluR4, GluRD, GluR-D
GluK1	GLU <sub>K5</sub> , GluR5, GluR-5, EAA3
GluK2	GLU <sub>K6</sub> , GluR6, GluR-6, EAA4
GluK3	GLU <sub>K7</sub> , GluR7, GluR-7, EAA5
GluK4	GLU <sub>K1</sub> , KA1, KA-1, EAA1
GluK5	GLU <sub>K2</sub> , KA2, KA-2, EAA2
GluN1	GLU <sub>N1</sub> , NMDA-R1, NR1, GluR $\zeta$ 1
GluN2A	GLU <sub>N2A</sub> , NMDA-R2A, NR2A, GluRe1
GluN2B	GLU <sub>N2B</sub> , NMDA-R2B, NR2B, hNR3, GluRe2
GluN2C	GLU <sub>N2C</sub> , NMDA-R2C, NR2C, GluRe3
GluN2D	GLU <sub>N2D</sub> , NMDA-R2D, NR2D, GluRe4
GluN3A	GLU <sub>N3A</sub> , NMDA-R3A, NMDAR-L, chi-1
GluN3B	GLU <sub>N3B</sub> , NMDA-R3B
GluD1	GluR $\delta$ 1
GluD2	GluR $\delta$ 2

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