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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$_3$ (5-HT$_3$), 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.

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 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 α8 subunit (Schoepfer et al., 1990) that has not been identified in the mammalian brain, and the glycine receptor α4 subunit (Matzenbach et al., 1994), which is likely to be a pseudogene in man, are not listed. Similarly, the avian GABA$_A$ receptor β4 and γ4 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 (IP$_3$) or ryanodine receptors that

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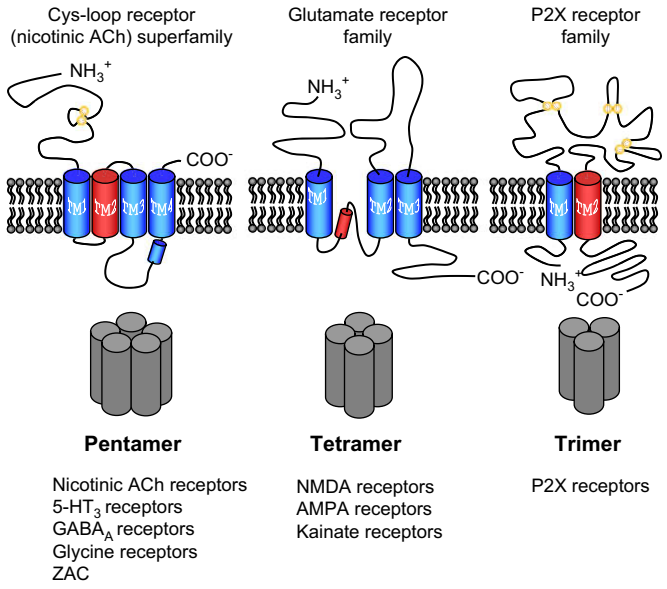

Fig. 1. Schematic representation of the three structural categories of ligand-gated ion channel subunit. The pentameric Cys-loop receptor superfamily comprises the nicotinic acetylcholine (ACh) receptors, 5-hydroxytryptamine$_3$ (5-HT$_3$) and a zinc-activated channel that form cation selective ion channels 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 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$_A$ 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-HT$_3$ and P2X receptor subunits (e.g. 5-HT$_{3A}$; P2X$_3$) 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-HT$_3$. 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. 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 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$_{A1}$, 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.