

International Union of Pharmacology. XXXI. Recommendations for the Nomenclature of Multimeric G Protein-Coupled Receptors

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Abstract—A receptor is defined by the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) as a protein, or a complex of proteins, which recognizes physiologically relevant ligands that can regulate the protein to mediate cellular events (Ruffolo et al., 2000). This definition does not include associated proteins, which are not required for agonist recognition and/or receptor assembly. Thus, G proteins are not included in the nomenclature of G protein-coupled receptors (GPCRs). Similarly, proteins which modify

receptor disposition, such as proteins with a PDZ domain (Sheng and Sala, 2001), and which associate with the cytosolic portion of the receptor are not included. The question arises, however, as to the way to name multimeric receptors where subunits influence receptor assembly and agonist recognition. The essential issue is whether to name the individual proteins or the association of proteins? NC-IUPHAR recommends that, where possible, the functional receptor complex be given a different name from that of the subunits.

I. Introduction

In this issue of *Pharmacological Reviews*, two families of GPCRs are considered where a modulatory protein influences agonist binding. The two cases are distinct. The GABA_B family consists of two seven-transmembrane proteins that are believed to function in vivo only as a heterodimer. There is no evidence for more than one receptor within this family. The calcitonin receptor family also consists of two seven-transmembrane proteins, but here the receptor pharmacology is influenced by the existence of single-transmembrane domain proteins, termed receptor activity modifying proteins (RAMPs).

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¹ Abbreviations: GPCRs, G protein-coupled receptors; GABA, γ -aminobutyric acid; RAMPs, receptor activity modifying proteins; NC-IUPHAR, International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification; CT, calcitonin; CL, calcitonin-like; AMY, amylin; AM, adrenomedullin.

The NC-IUPHAR subcommittee on calcitonin receptors presently recognizes seven receptors within this family.

II. γ -Aminobutyric Acid_B Receptor Family

In the case of the GABA_B receptor, the GABA_{B1} subunit acts as the acceptor protein for the agonist, and the structurally similar GABA_{B2} subunit is necessary for transport of the receptor to the cell surface and G protein activation. The NC-IUPHAR subcommittee on GABA_B receptors finds no clear evidence for multiple types of the GABA_B receptor. Therefore, the multimeric receptor is referred to as a GABA_B receptor, made up of GABA_{B1} and GABA_{B2} subunits (Bowery et al., 2002).

III. Calcitonin Receptor Family

In the second case (Poyner et al., 2002), the pharmacology of the two related seven-transmembrane proteins is influenced by the expression of three RAMPs. The two seven-transmembrane components are known as the calcitonin (CT) receptor and the calcitonin-like (CL) re-

ceptor. CT is functional when expressed on its own and serves as a receptor for calcitonin. However, in the presence of RAMP1, 2, or 3, CT also becomes a receptor for amylin as well as calcitonin—with each complex having a unique pharmacology. Each receptor complex is given a separate name although they probably co-exist as a mixed population. They are named AMY₁, AMY₂, and AMY₃ corresponding to RAMP1, 2, and 3, respectively, to reflect the fact that all respond to amylin. In addition, they also respond in varying degrees to calcitonin but this nomenclature enables distinction with the CT receptor, which only responds to calcitonin. CL is only functional when complexed with RAMP1, 2, or 3. The complex of CL and RAMP1 is known as the CGRP (calcitonin gene-related peptide) receptor, whereas a complex of CL and RAMP2 or RAMP3 are known as AM₁ and AM₂ receptors, respectively, to reflect the fact that they respond to adrenomedullin.

Nevertheless, in systems where an accessory protein may change the pharmacology of an agonist, caution should be exercised, because different degrees of protein expression may markedly modify responses and apparent receptor distribution.

IV. Conclusions

The definition of a receptor, at the level of either a single protein or an association of proteins, allows a pragmatic approach to classification, which is the only approach possible in the face of combinatorial association of multiple subunits. NC-IUPHAR will use this same approach in naming other receptor classes, including ion channels and nuclear receptors. The decision to base the classification at the level of the single protein, or the association of proteins, is dependent on many different parameters, the importance of which depends on the receptor class in question.

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