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International Union of Pharmacology. XIX. The IUPHAR Receptor Code: A Proposal for an Alphanumeric Classification System

P. P. A. HUMPHREY[a] AND E. A. BARNARD

Glaxo Institute of Applied Pharmacology, Department of Pharmacology (P.P.A.H.), University of Cambridge, Cambridge, England and Molecular Neurobiology Unit, Division of Basic Medical Sciences (E.A.B.), Royal Free Hospital School of Medicine, London, England

I. Rationale for a Receptor Code

A generally accepted system for defining, characterizing, and classifying transmitter/hormone receptors is desirable for several reasons. First, pharmacologists need a common language so that ambiguity is not created by varied and inconsistent terminologies. It is estimated that a significant fraction of the mammalian genome codes for receptor proteins and subunits; this leads to the prediction of several thousands of individual signal-transducing receptors, even without consideration of the very large group of olfactory and gustatory receptors that exists (see Glusman *et al.*, 1996). Thus, an internationally acceptable classification system for receptors is both desirable and necessary. Second, the development of a systematic scheme of classification is in itself an important generic research approach in biological science. It can bring focus, highlight relationships, and stimulate the recognition and investigation of features common to various classes and groups. It also can indicate deficiencies in our information and add an evolutionary perspective, which may bring its own insights. It remains to be determined why there is, in many cases, such a large variety of receptors for a given chemical messenger transmitter. We need to determine whether all these receptors are functional. It is also interesting to consider how they evolved and how many more endogenous ligands, known and unknown, are to be anticipated. Third, drug discovery benefits greatly from the systematic analysis of the growing body of information on receptors and their subclassification, with the knowledge that each receptor subtype provides a potential new drug target. Thus, it is now well recognized that the identification of well defined receptor subtypes often leads to highly specific drugs with new clinical indications and/or less undesirable side effects. It is reasonable to assume that future computer-based analyses or predictions of drug selectivities will benefit greatly from an established universal framework of a systematic receptor classification.

The term "receptor" is in use in various broad senses, but for pharmacological purposes the term is used specifically (Barnard, 1997; Humphrey, 1997) and refers to proteins which are "signal transducing receptors," as defined and discussed by Kenakin *et al.* (1992). That is, each such protein specifically recognizes and is activated by a native agonist, which is one of numerous different messenger molecules that specifically relay a signal into a cell or between compartments within a cell. Thus, receptors in the pharmacological sense may be in one of three locations: (*a*) in the plasma membrane (the receptors for neurotransmitters, trophins, growth factors, and cytokines, other immunomediators, morphogens, sensory stimulants, and chemoattractants, and circulating hormones); (*b*) in an organelle membrane (e.g., those receptors where the transduction process involves the release of Ca^{2+} from an intracellular store); (*c*) in the cytosol. Case c can involve migration of the ligand-bound receptor to the cell nucleus, as for the receptors that belong to the superfamily of ligand-regulated transcription factors, whose ligands are steroid hormones and certain other fat-soluble hormones (structural class 4 here; see below). For all the natural signal-transducing agonists involved, the general term "transmitter" can be used.

As a consequence of the considerations listed above, much effort has been dedicated recently to the classifi-

[a] Address for Correspondence: P.P.A. Humphrey, Glaxo Institute of Applied Pharmacology, Department of Pharmacology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QJ, England.

TABLE 1
Subdivisions within a complete receptor code

Structural class Indicated by first two numbers; see tables 2–6 for description of associated codes.	1.1–4.4
Receptor family An endogenous agonist (or family of agonists) provides the receptor family code; see table 7 for recommended codes.	Alphanumeric code (up to six upper case characters, but usually three) to be used (e.g., 5HT for 5-hydroxytryptamine or serotonin)
Receptor type See table 8 for examples.	Alphanumeric code (up to five upper case characters) consistent with the approved trivial name or number and its associated recognition and transduction characteristics
Species See table 9.	Three upper case letters will code for species as used by the Human Genome Database project
Splice or other sequence variant Pair of numbers after species code; see table 10.	00–99
Extra category Pair of numbers after splice variant code. This is reserved for further subclassification purposes if considered desirable in the future. Where this and the preceding subdivision are not assigned, the zeros can be omitted for most purposes.	00–99
Final letter code Single upper case letter preceded by a dot.	.P, provisional RC (see text) .S, receptor subunit .M, multimeric receptor of known composition

cation of the pharmacologically better-known neurotransmitter receptors. However, molecular biology has created a dramatic increase in information on the existence and structure of receptors, often preceding any data on their function, thereby reversing the traditional order of pharmacological data acquisition. The IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), with its various Subcommittees,[b] has been constituted to review current approaches to receptor characterization and to define a generic scheme of nomenclature (Vanhoutte *et al.*, 1994, 1996; Humphrey *et al.*, 1994). Although progress has been made in standardizing trivial names in several receptor areas (and this initiative will continue), it is suggested that an all-embracing, rational system of coding receptors should be introduced [an alphanumeric receptor code (RC)[c]], analogous to the EC (Enzyme Commission) enzyme codes introduced by the International Union of Biochemistry and Molecular Biology (IUBMB). It will differ from the EC system (which was set up before the era of molecular biology) in that the proposed codes are intended to convey structural information (relevant to the mode of receptor transduction) together with additional elements relating to operational characteristics, set out in a hierarchical order. This should provide a unique, unambiguous, and authoritative descriptor for each receptor protein. Each RC, assigned by NC-IUPHAR, is intended to be used in publications for definitive identification, in conjunction with a suitable (ideally, approved) trivial name. It also will be used in *The* IUPHAR *Compendium of Receptor Characterization and Classification* (July 1998), together with the planned IUPHAR *Receptor Database* which will link uniquely nucleotide and protein databases to comprehensive data on receptor function and drug-related operational characteristics (recognition and transduction).

The details presented here constitute a proposal, sanctioned by NC-IUPHAR (see acknowledgment), which provides a basis for a broad and full debate within the

[b] Composition of the IUPHAR Committee on Receptor Nomenclature and Drug Classification: E.A. Barnard, T.I. Bonner, W.C. Bowman, P.B. Bradley, B.N. Dhawan, C.T. Dollery, B.B. Fredholm, C.R. Ganellin, T.P. Godfraind, M. Hamon, T.K. Harden, P.P.A. Humphrey, S.Z. Langer, T. Masaki, R. Paoletti, R.R. Ruffolo, M. Spedding, U.G. Trendelenburg, P.M. Vanhoutte, S.P. Watson. Technical subcommittee (and corresponding members): E.A. Barnard, T.I. Bonner, D. Hoyer, P.P.A. Humphrey, P. Leff, J. Lomasney, N.P. Shankley, D.H. Jenkinson, S.P. Watson (and R.B. Barlow, J.W. Black, D.E. Clarke, D. Colquhoun, R.F. Furchgott, J.P. Green, T.P. Kenakin, R.J. Lefkowitz, D.R. Waud).

[c] Abbreviations: ATP, adenosine triphosphate; CFTR, cystic fibrosis transmembrane regulator; EAA, excitatory amino acid; EC, Enzyme Commission; FMRF, Phe-Met-Arg-Phe amide; JAK, Janus kinase; Kir, inward rectifier potassium channel; NC-IUPHAR, IUPHAR Committee on Receptor Nomenclature and Drug Classification; RC, receptor code; Trk, a tyrosine kinase subunit of neurotrophin receptors. The other abbreviations used are defined in table 7.

TABLE 2
Main structural class codes

Code	Structural class[a]
1.0	Ion-channel receptors
2.0	Seven transmembrane domain (G protein-coupled) receptors
3.0	Enzyme-associated receptors (with subunits having one membrane-inserted domain)
4.0	Transcriptional regulator receptors

[a] Each main receptor structure class is subdivided as outlined in Tables 3-6. If the subclass is not known definitively, the main class only will be identified as 1.0, 2.0, etc. These classes are provisional, and additional classes and subclasses may need to be added as knowledge increases. Literature references on receptors in many of the subclasses listed can be found in The IUPHAR Compendium of Receptor Characterization and Classification.

TABLE 3
Subclasses within structural class 1
(ion-channel receptors)

Code	Subclass	Examples	
1.1	*Superfamily of Cys-loop receptors*		
	(Cockcroft *et al.*, 1990; Karlin and Akabas, 1995) Includes ion channels gated by GABA, glycine, 5-HT, acetylcholine (nicotinic), and glutamate (anion channel) (Nistri and Arenson, 1983; Cully *et al.*, 1994, 1996)	1.1	GABA
		1.1	GLY
		1.1	GLU
		1.1	ACH
		1.1	5HT
1.2	*Glutamate-gated cation channels*		
	Includes NMDA and non-NMDA receptors	1.2	GLU
1.3	*Related to voltage-gated cation channels*		
	Includes receptors for cyclic nucleotides and for IP_3 as well as the "ryanodine receptor"[a]	1.3	IP3
1.4	*Related to epithelial Na^+ channels; non-peptide–gated*		
	Includes P2X receptors for ATP (North and Barnard, 1997) and proton-gated cation channels (Waldmann *et al.*, 1997)	1.4	NUCT
1.5	*Related to epithelial Na^+ channels; peptide-gated*		
	e.g., FMRF-gated Na^+ channel (Lingueglia *et al.*, 1995)	1.5	FMRF
1.6[b]	*Related to inward rectifier K^+ channels*		
	e.g., ATP-activated K^+ channel (Lesage *et al.*, 1995; Takumi *et al.*, 1995) and the ATP-antagonized K^+ channel (K_{ATP}) (Clement *et al.*, 1997; Gribble *et al.*, 1997; Tucker *et al.*, 1997)[c]	1.6	NUCT
1.7[b]	*Related to ATPase-linked transporters*		
	e.g., CFTR (ATP-activated anion channel) (Baukrowvitz *et al.*, 1994)[d]	1.7	NUCT
1.8[b]	*Related to neurotransmitter transporters*		
	e.g., glutamate-activated chloride channel/EAA transporter (Fairman *et al.*, 1995; Picaud *et al.*, 1995)[d]	1.8	GLU

[a] It should be noted that subclass 1.3 will contain at least two protein superfamilies, which do not share any sequence homology. One comprises the cyclic nucleotide receptors and the second comprises the IP_3 and the ryanodine receptors.
[b] It is recognized that the definition of subclasses 1.6, 1.7, and 1.8 may require modification as knowledge of them increases, but they serve to illustrate the full potential of the proposed coding system.
[c] Several K_{ATP} channel subtypes are known in different tissues, differing greatly in their response to inhibitory sulfonyl ureas (SUR) and to channel-opening drugs such as diazoxide. Their structures, as known so far by DNA cloning, contain two unrelated subunits, an inward rectifier K^+ channel protein (from the Kir.6 series) and a sulfonylurea- and nucleotide-binding protein (SUR); a family of SURs produce variations in the K_{ATP} pharmacology (Inagaki *et al.*, 1996). Therefore, K_{ATP} channel subunits will be numbered in two series; for the KIR (6.1), etc., subunits as 1.6.KIR.61.S [or 62.S, etc.] and for the SUR1, etc., subunits 1.6.SUR.01.S [or 02.S etc.], and the entire K_{ATP} channel as 1.6.NUCT.01.M [or 02.M, etc.] when definitive evidence for the subunit composition is known.
[d] Although genes for types 1.7 and 1.8 have each been cloned, expressed, and shown to correspond to channels seen in native tissues (Baukrowvitz *et al.*, 1994; Fairman *et al.*, 1995), the precise relationship of the ion channel to the transporter in these types is at present unclear. Transporters are not necessarily ligand-gated channels: however, in addition to the case of glutamate transporters, transporters of serotonin (5-HT) and of dopamine incorporate, respectively, a 5-HT-gated channel (Galli *et al.*, 1997) or a dopamine-gated channel (Sonders *et al.*, 1997), and this principle may hold also for norepinephrine and γ-aminobutyric acid transporters (Sonders and Amara, 1996).

pharmacological community at large and with scientists from other disciplines and their representative bodies.

II. Criteria for Receptor Characterization

It generally is acknowledged that studies toward the pharmacological characterization and classification of neurotransmitter/hormone/autacoid receptors should involve work on both function and structure (e.g., see Humphrey *et al.*, 1993, 1994; Vanhoutte *et al.*, 1994; Hoyer *et al.*, 1994; Humphrey, 1997). Receptor structure, in terms of its amino acid sequence, is unambiguous and will allow the allocation of a database code to the unequivocally identified protein. Function is equally important and not necessarily sufficiently predictable from structure, although it may be. Thus, one amino acid difference may make important differences in the drug recognition characteristics of a receptor (cf., the rat and human neurokinin NK_1 receptors) or by contrast significant differences in receptor sequence homology may make little such difference (e.g., in human 5-HT_{1B} and 5-HT_{1D} receptors or somatostatin receptors sst_1 and sst_4) (see Sachais *et al.*, 1993; Hoyer *et al.*, 1994, 1995). It is therefore essential to establish which drugs are specific and selective for a particular receptor, either as agonists or antagonists, and to provide appropriate quantitative measurements of key parameters (see Kenakin *et al.*, 1992; Jenkinson *et al.*, 1995). The affinities (as dissociation equilibrium constants) of ligands often are measured from radioligand binding studies, and such data (at least for antagonists) should be equivalent to the corresponding data from functional studies. It has been argued that parameters from both types of studies clearly cannot be considered on semantic grounds under the umbrella term "functional" and hence the term "operational" has been introduced (Humphrey *et al.*, 1994; Humphrey, 1997). Doubts about the use of "operational" in this context have been expressed because of its prior (and currently accepted) use in reference to agonism and agonist-specific parameters, which involve an efficacy component with more than just a binding (and recognition) parameter being involved (Kenakin *et al.*, 1992; Black and Leff, 1983). However, this strengthens the argument for using the term "operation" which, importantly, implies an added involvement of receptor "activation" and hence transduction. The alternative term "recognition" more specifically refers to the binding characteristics or binding affinities of drugs (both agonist and antagonist) for a given receptor but does not necessarily encompass all aspects of receptor function, as the term "operational" undoubtedly does.

Transduction in the context of receptor characterization is intended to refer to the steps that allow the binding of an agonist at the receptor to be linked to the transmission of a signal into a cell or between compart-

TABLE 4
Subclasses within structural class 2
(G protein-coupled receptors)

Code	Subclass	Examples	
2.1	*"Rhodopsin" subclass*		
	The vast majority of seven transmembrane domain, G protein-coupled receptors are included in this subclass[a]	2.1	ADR
2.2	*Secretin receptor subclass*		
	This is the second largest subclass and comprises receptors for calcitonin, CGRP, corticotropin-releasing factor, gastric inhibitory peptide, glucagon, glucagon-like peptide, growth hormone releasing factor, PACAP, parathyroid hormone, secretin and vasoactive intestinal peptide	2.2 2.2	SEC CGRP
2.3	*Metabotropic glutamate/$GABA_B$ receptor subclass*	2.3	GLU

The subclasses shown have been classified according to their protein sequences so that within a subclass all receptor types share significant similarity (i.e., ≥20% sequence identity) throughout the predicted hydrophobic transmembrane domains (Kolakowski, 1994; see also the G protein-Coupled Receptor Database at www.gcrdb.ulthscsa.edu).

[a] From the strict structural viewpoint, Class 2.1 is not homogeneous. All its members comprise a seven-transmembrane amino acid chain, but in a very few, the active receptor is formed from this by a proteolytic cleavage. The first described was the thrombin receptor (2.1.THR), in which the agonist thrombin specifically cleaves the receptor chain to liberate a new N-terminal segment and activate the receptor (Vu *et al.*, 1991). Others are the thyrotropin receptor (2.1.TSH), where a peptidase produces two extracellular chains (Misrahi *et al.*, 1994), and other protease-activated receptors where the natural agonist is an unidentified trypsin-like protease (Nystedt *et al.*, 1995; Ishihara *et al.*, 1997).

TABLE 5
Subclasses within structural class 3
(enzyme-associated single transmembrane domain receptors)

Code	Subclass	Examples	
3.1	*Receptors with intrinsic tyrosine kinase (TK) activity*		
	e.g., single-subunit TK receptors with extracellular Ig domains; single-subunit TK receptors without extracellular Ig domains; multiple-subunit TK receptors formed by posttranslational cleavage	3.1 3.1 3.1	PDGF EGF INS
	Trk receptors for neurotrophins	3.1	NT1
3.2	*Non-enzyme–containing receptors associating with extrinsic tyrosine kinase*		
	This includes a wide range of receptor types including: (*a*) receptors that use JAK-type kinases; (*b*) receptors that associate with other tyrosine kinases, and (*c*) tyrosine-kinase-associated receptors with the ligand-binding subunit membrane anchored by a glycolipid, such as that for ciliary neurotrophic factor. These receptors are multisubunit, with a ligand-specific α subunit and a subunit type for signal transduction (for examples see Jing *et al.*, 1996; Klein *et al.*, 1997)	3.2 3.2 3.2 3.2 3.2	IL1 GH INF CNTF GDNF NTN
3.3	*Receptors with serine/threonine kinase activity*		
	e.g., receptors for transforming growth factor β	3.3	TGF
3.4	*Intrinsic cyclase receptors*		
	e.g., receptors with guanylate cyclase activity	3.4	ANP

ments of a cell. This necessarily will involve specific changes in the receptor protein (if it is in the ion-channel class) or, in other cases, relayed to associated proteins which execute the primary signaling step. Transductional data should not involve the categorization of more downstream second-message cascades themselves, although such information might be used judiciously to infer events upstream. Even if more tightly defined, the use of transductional data to characterize receptors is controversial but it has been invaluable nevertheless in the classification of 5-HT receptors (Humphrey *et al.*, 1993; Hoyer *et al.*, 1994). Thus 5-HT_{1C} (now called 5-HT_{2C}) and 5-HT_2 (now called 5-HT_{2A}) receptors were predicted to belong to the same receptor group on the basis of shared transduction mechanisms. This was confirmed later when both receptor genes were cloned and the respective proteins were shown to share a high degree of homology (Hoyer *et al.*, 1994). In contrast, although both 5-HT_3 and 5-HT_4 receptor types can be blocked by tropisetron (albeit at different concentrations), it was obvious on the basis of transduction that the two receptors were quite distinct even before both genes had been cloned (Humphrey *et al.*, 1993; Hoyer *et al.*, 1994). Thus, at the very least, consideration of the transduction mechanism involved will distinguish between a ligand-gated ion channel receptor and a G protein-coupled receptor (i.e., the 5-HT_3 and 5-HT_4 receptor, respectively). It should be noted that the structural classes proposed here reflect known fundamentally different transduction mechanisms for each. It follows that a knowledge of receptor transduction mechanisms from functional studies is important but how much value should be attached to such operational data specifically for receptor characterization purposes in isolation remains to be determined. However, there is a growing view that the unique intracellular face of each membrane-bound receptor protein will dictate preferred stoichiometric interactions with adjacent proteins, which will be characteristic of the receptor type involved. On the basis of these arguments, essential operational data for receptor characterization would include all drug recognition and drug interaction data, from both functional as well as radioligand binding studies, together with data on receptor transduction mechanisms directly related to receptor activation.

In summary, we propose that the pharmacological criteria for receptor characterization will depend on the integration of data from studies on both receptor structure and receptor operation. When such an integrated

TABLE 6
Subclasses within structural class 4
(transcriptional regulator receptors)

Code	Subclass	Examples	
4.1	*Nonsteroid receptors*		
	This subclass comprises the heterodimeric receptors for nonsteroid ligands including retinoic acid, thyroid hormone, and vitamin D	4.1	TH VITD3
4.2	*Steroid receptors*		
	This subclass comprises the homodimeric receptors for steroids including cortisone, aldosterone, progesterone, and testosterone	4.2	PROG

Nuclear receptors constitute a distinctive class which has great therapeutic relevance but recently has been overlooked somewhat by pharmacologists. With the discovery of multiple orphan nuclear receptors and hence of other potential structural subclasses (see Kastner et al., 1995; Mangelsdorf et al., 1995; Laudet et al., 1998), we suggest that effort should be applied to further subclassification of this class on the basis of the integrated pharmacological approach proposed here.

TABLE 7
Family codes[a]

Acetylcholine	ACH	Melatonin	MLT
Adenosine	ADO	Nerve growth factor	NGF
Adenosine and uridine triphosphates	NUCT	Neurokinins	NK
Angiotensin	ANG	Neuropeptide Y	NPY
Atrial natriuretic peptide	ANP	Neurotrophins	NT1 (etc)
Hydroxy leukotrienes	BLT	Neurotensin	NTSN
Bradykinin	BK	Neurturin	NTN
Calcitonin	CALC	Norepinephrine/epinephrine	ADR
Cannabinoids	CBD	Olfactory	OLF
Cholecystokinin	CCK	Opioids	OP
Calcitonin gene related peptide	CGRP	Oxytocin	OXY
Cysteinyl leukotrienes	CLT	Pituitary adenylate cyclase activating peptide	PACAP
Ciliary neurotrophic factor	CNTF	Platelet derived growth factor	PDGF
Dopamine	DA	Progesterone	PROG
Epithelial-derived growth factor	EGF	Prostaglandins	PG
Endothelins	ET	Secretin	SEC
γ-Aminobutyric acid	GABA	Serotonin (5-hydroxytryptamine)	5HT
Glial-derived nerve factor	GDNF	Somatostatin	SRIF
Glutamate	GLU	Transforming growth factor β	TGF
Glycine	GLY	Thrombin	THR
Growth hormone	GH	Thyroid hormone	TH
Gustatory	GUS	Thyrotropin	TSH
Histamine	HIST	Vasopressin	VASO
Interleukins	IL, IL1 (etc)	Vasoactive intestinal polypeptide	VIP
Insulin	INS	Vitamin D3	VITD3
Inositol 1,4,5-trisphosphate	IP3		

[a] This list is not exhaustive but represents receptor families for which classifications are well developed and a few illustrations of newer receptor families that are not well classified.

pharmacological profile is detailed sufficiently it will be possible to register an IUPHAR RC with confidence.

III. Proposal for a Systematic Receptor Code

A systematic numbering system for all known pharmacological receptors allows definitive labeling of a particular receptor by an international pharmacological authority (NC-IUPHAR), while providing valuable classified information about its characteristics. Each RC would provide a unique identifier for each receptor within *The* NC-IUPHAR *Receptor Database*, which contains extensive pharmacological information on receptor characterization and classification. This would be analogous to the EC numbering system used for enzymes. If necessary such codes could be changed when new information and understanding dictated that change was essential. A full alphanumeric code could provide a universally accessible record of numbering and subclassification of receptors which would reflect the state of current knowledge for the structure and characteristics of each receptor. The coding system would not replace trivial names, which usually would be used, but it would circumvent some of the problems associated with attempts to standardize such trivial names.

The proposed RC would consist of a set of divisions, separated from each other by full points; each division conveys a different category of information about the receptor, as summarized in table 1. Thus, according to the system proposed, the rat 5-HT_{1A} receptor (as a G protein-coupled recombinant receptor for 5-HT, classified pharmacologically as the 1A subtype) would have a RC of 2.1.5HT.1A.RNO.00.00 and the human 5-HT_3 (as the first ligand-gated cation channel receptor subunit for 5-HT) would have an RC of 1.1.5HT.01.HSA.00.00.S. Other examples to illustrate the coding system are the rat muscarinic acetylcholine receptor (2.1.ACH.M1.RNO.00.00) and the human $P2X_1$ receptor subunit (1.4.NUCT.01.HSA.00.00.S). These RCs are based on the assignment of the coded information explained in this document. (See tables 2–8.)

An RC will be reserved for the polypeptide product(s) of a single orthologous gene. Species variants will share a common RC but will be differentiated by a three-letter species code (see tables 9 and 10). A provisional RC can be assigned without cloning of the relevant gene providing it has been characterized robustly in whole tissues (e.g., histamine H_3 receptor). This may prove difficult in the brain, or in other tissues if multiple subtypes co-occur. Where this is so, the minimum requirement for a recombinant receptor to be accepted as a functional entity will be that robust operational (which must include transductional) data are provided for the heterologously expressed receptor and that its messenger ribonucleic acid, or the protein itself, is shown to occur in vivo. Recombinant receptors which have not been shown to be functional in whole tissues (e.g., 5-ht_{5b}) would be assigned only a provisional RC code number designated by a terminal upper case "P" (e.g., 2.1.5HT.05B.RNO.00.00.P).

TABLE 8
Receptor type codes
The use of an alphanumeric abbreviation for the receptor type category would allow either for recognizable reference to trivial names or direct reference for more recently identified receptors to the simple numbering system used by molecular biologists. Parenthetically, it is suggested that in some cases, for example the muscarinic acetylcholine and dopamine receptor families, consideration should be given as to whether the latter current schemes are still appropriate (see Humphrey, 1997). Regardless, the two options for designating an RC are outlined below and each subcommittee could choose one for their receptor family.

1. For well established classifications, the receptor type category will be represented by an upper case alphanumeric code that is recognizable as analogous to the trivial nomenclature, e.g., for the G protein-coupled serotonin receptors (see Hoyer *et al.*, 1994; Eglen *et al.,* 1997):
   2.1.5HT.01A. for the 5-HT_{1A} receptor
   2.1.5HT.01B. for the 5-HT_{1B} receptor
   2.1.5HT.01D. for the 5-HT_{1D} receptor
   2.1.5HT.02A. for the 5-HT_{2A} receptor
   2.1.5HT.07. for the 5-HT_7 receptor, etc.
   2.1.ADR.A1A. for the α_{1A} adrenoceptor
   2.1.ADR.B1. for the β_1 adrenoceptor, etc.

2. Where subclassification has not been attempted, a simple chronological numeric code may be assigned, although this approach seems scientifically parsimonious and circumvents an opportunity to provide additional classifying information (e.g., as for dopamine receptors; see Humphrey, 1998).[a]
   2.1.DA.01.
   2.1.DA.02., etc.

[a] It is recognized that there is a view strongly held by some that an arbitrary numeric code should be used for all receptor types, which would circumvent past problems associated with incorrectly assigning trivial names. However, after much discussion at NC-IUPHAR meetings, it was agreed that many pharmacologists would not readily accept a system which, for example, groups together the adrenoceptor family without distinguishing between alpha and beta types, with their very different pharmacological characteristics. Nevertheless, if consistent yet arbitrary numeric codes were considered desirable in the future, it would be simple to number each receptor type according to its established position in the database.

TABLE 9
Species codes[a]

BBO	*Bos bovinus* (cow)
CAE	*Cercopithecus aethiops* (African green monkey)
CFA	*Canis familiaris* (dog)
CGR	*Cricetulus griseus* (hamster)
CJA	*Callithrix jacchus* (marmoset)
CPO	*Cavia porcellus* (guinea-pig)
FCA	*Felis catus* (cat)
HSA	*Homo sapiens* (man)
MML	*Macaca mulatta* (Rhesus monkey)
MMU	*Mus musculus* (mouse)
MPU	*Mustela putorius furo* (ferret)
MRU	*Macropus rufus* (red kangaroo)
OCU	*Oryctolagus cuniculus* (rabbit)
OOV	*Ovies ovies* (sheep)
PPA	*Papio papio* (baboon)
PPY	*Pongo pygmaeus* (orangutan)
PTR	*Pan troglodytes* (chimpanzee)
RNO	*Rattus norvegicus* (rat)
SSC	*Sus scrofa* (pig)

[a] These abbreviations are proposed to establish and maintain consistency with existing internationally authoritative nomenclature databases (e.g., GDB, MEDLINE). Alternative abbreviations to denote the species when using trivial receptor names have been published by NC-IUPHAR, and these are still appropriate for use in textual discussion referring to trivial names (see Vanhoutte *et al.*, 1996).

TABLE 10
Splice variant codes[a]

It is proposed that the splice variants will be numbered chronologically according to identification within a species, e.g., EP_3 receptors for prostaglandins (Coleman *et al.*, 1994; Narumiya, 1996) can be coded as:
   2.1.PG.EP3.HSA.01
   2.1.PG.EP3.HSA.02
   2.1.PG.EP3.HSA.03
   2.1.PG.EP3.HSA.04
   2.1.PG.EP3.OCU.01, etc.

Splice variants for a given receptor may have been identified in one species but not in others, e.g., two mouse splice variants have been demonstrated unequivocally for the somatostatin sst_2 receptor but not for the human orthologue (Vanetti *et al.*, 1993; Schindler *et al.*, 1996). They can be coded as:
   2.1.SRIF.1A.HSA.00
   2.1.SRIF.1A.MMU.01
   2.1.SRIF.1A.MMU.02

[a] No code for trinucleotide repeats is recommended; these can be described in the text associated with the relevant RC.

For structural classes in which hetero-oligomeric receptors occur, RCs for individual subunits often will be represented instead of the entire multimeric receptor, because the composition of the latter is usually indeterminate at present. Subunit RCs will be indicated by a terminal upper case "S" [e.g., 1.4.NUCT.01.00.00.S in the case of the $P2X_1$ receptor subunit for adenosine triphosphate (ATP)]. Where the subunit composition of an endogenous heteromeric receptor becomes known, that receptor is represented by a unique RC of its own (indicated by a terminal upper case "M" to represent a "multimeric" receptor); its subunit composition would be indicated in the database by listing the component RCs (S), and their stoichiometry when definitely known. For many transmitter-gated ion-channel receptors in Class 1, where a subunit combinatorial system occurs, the exact stoichiometry is not known currently. However, the situation is less complex for hetero-oligomers occurring in Class 3 where there is usually a fixed composition of subunits for each receptor type.

IV. Conclusions

We have provided justification for a systematic method of coding receptors of all structural types. The RC system proposed is designed not just to be informative but also to provide a distinct alphanumeric descriptor for each receptor protein. It is intended that each individual RC will not only define each receptor type unambiguously by way of a simple reference for publication purposes, but that it will also associate automatically with a large body of information in an authoritative pharmacological database. This database would supply an urgent need of pharmacologists and other scientists interested in the correlation and integration of data on receptor operation with that on receptor structure. *The* IUPHAR *Receptor Database* will link not only with existing databases already established for gene nucleotide sequences and amino acid sequences of receptor proteins, but will also uniquely provide detailed pharmacological data on the characteristics of receptor

recognition and transduction. The latter data will be approved by international panels of experts in each of the many existing and future NC-IUPHAR subcommittees established for the different receptor families (see Vanhoutte *et al.*, 1994).

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