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Towards a revised nomenclature for P1 and P2 receptors

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The classification of receptors for adenosine, ATP and ADP (collectively called purinoceptors) has seen a number of developments in the past three years. The important division of receptors into two major classes[1] (1) adenosine (P_1) receptors and (2) P_2 purinoceptors, first suggested by Burnstock in 1978 (Ref.2), has been an abiding one that has set the stage for further subdivision of P_2 purinoceptors into P_{2X} and P_{2Y} subtypes on the basis of pharmacological properties[3]. Later, Dubyak[4] summarized the evidence that ATP worked through two different transduction mechanisms: intrinsic ion channels and G protein-coupled receptors. This information, coupled with the cloning of purinoceptors in 1993/94, led Abbracchio and Burnstock[5] to propose that purinoceptors should be classified in two families: G protein-coupled receptors termed P2Y purinoceptors, and intrinsic ion channels termed P2X purinoceptors. Developments in recent years have borne out these expectations and a revised nomenclature, essentially adopting the Abbracchio and Burnstock proposal, can now be proposed.

Adenosine (P1) receptors

The existence of four separate adenosine receptors is well established[6]. In conformity with the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) recommendations, the two A_2 receptors are now named A_{2A} and A_{2B} (rather than A_{2a} and A_{2b}). Although there are reports of binding sites that suggest the existence of additional subtypes[7-11], no evidence for new A_2 receptors has evolved from the extensive cloning efforts of several laboratories. Indeed at least one of these sites (denoted A_4 by the authors) may represent binding to a state of the A_{2A} receptor[12], and a similar explanation may apply to the other putative receptor binding sites. If additional adenosine receptors are cloned and shown to be structurally different from the four known receptors and if, in addition, a distinct pharmacological profile (both binding and functional response) is established they are to be named A_4, A_5, etc. Until such time, naming of putative binding sites is strongly discouraged.

P2 receptors

Although indicating a preference for the use of P2X, P2Y classification, the first NC-IUPHAR subcommittee for Purinoceptors report[1] provisionally divided P2 purinoceptors into six subforms P_{2X}, P_{2Y}, P_{2U}, P_{2t}, P_{2z} and P_{2d}. This classification was, at the time, pointed out to be unsatisfactory and in need of revision for the following two reasons: (1) there may be receptors that preferentially bind pyrimidine rather than purine nucleotides, and (2) the nomenclature did not conform with NC-IUPHAR classification principles (Box 1) – the eventual cloning of P2 receptors would provide a basis for a more logical classification scheme. Both of these contentions have been borne out. In particular, there is now a strong structural basis for a nomenclature scheme.

As described in detail in two recent articles, one in this issue of *TiPS* (Communi and Boeynaems), very compelling evidence now exists for receptors that are structurally similar to receptors for ATP, but strongly prefer, or even are selective for, UTP or UDP (Refs 13, 14). Therefore, we suggest that the family of receptors be named P2 receptors rather than P2 purinoceptors. A P2 receptor is now defined as a receptor for a purine or pyrimidine nucleotide (or dinucleotide). One important corollary to this general nomenclature is that there is little room for potential P3 or P4 receptors. The name P_3 receptor (see Ref. 15) was introduced on the basis of the original definition of P_1 and P_2 receptors and included the block of responses by methylxanthines as a discriminating criterion[16]. In the proposed, new nomenclature, this criterion is dropped. Any unambiguously identified receptor for adenine nucleotides at which methylxanthines also bind and act as antagonists will in future be incorporated into the P2X/P2Y scheme. The name P_4 receptor, proposed for receptors for adenine dinucleotides[17], is no longer useful as, according to the newly advocated nomenclature, such receptors would be likely to fit into the P2Y array of receptors.

Rapid and spectacular advances have occurred in the area of the ionotropic P2X receptors (intrinsic ion channels; see Table 1). Perhaps the most surprising finding is that the ATP-activated large conductance pore, tentatively named P2Z, has been shown to be a member of the family ($P2X_7$)[18]. As is the case for other ionotropic receptors (nicotinic, $GABA_A$

receptors, etc.), functional P2X receptors may be composed of several interacting subunits, which need not be the same. This can lead to the potential generation of a large number of operationally (and perhaps pharmacologically) distinct functional entities. Indeed, it has been found that simultaneous tranfection of the $P2X_2$ and $P2X_3$ subforms leads to the expression of a receptor that shows properties that are typical of neither subform (see Table 1). The use of the presently available pharmacological tools alone for characterization of receptors has presented a number of problems. We are of the opinion that for the time being the nomenclature should apply predominantly structural criteria. As new, selective agonists and antagonists become available however, the situation is expected to improve.

Many G protein-coupled P2 receptors now have been cloned (see Table 2). Nomenclature for these cloned receptors is still very much under discussion but, for the time being we suggest the receptor putatively named p2y3 (Ref. 19) is given in lower case letters because it was cloned from chick. The reason for this caution is because of a precedence for the occurrence of major differences between mammalian and avian G protein-coupled receptors from, for example, β-adrenoceptors. Whereas there is considerable homology in the case of β_2-adrenoceptors (about 90%), the homology in the case of the β_1-adrenoceptor is only about 50%. Moreover, a β-receptor has been cloned from the turkey, for which no mammalian species homologue has been identified despite wide-ranging efforts to do so. In the case of the p2y5 (Ref. 20) and $P2Y_7$ receptors[21], where the sequence homology of the two proteins to previously identified members of the P2Y receptor family is low, we anticipate further findings in this area (Table 2).

Box 1

Some open questions

Debate about the classification of receptors from non-mammalian species still continues but the official recommendations from the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) state that: “Mammalian receptor systems are the basis of IUPHAR classifications. The nomenclature may extend to other vertebrate species provided it does not compromise the mammalian classification. Evolutionary changes may be so great that invertebrate receptors are difficult to classify within mammalian-based nomenclature.”

Research on human receptors may lag behind that on non-human receptors, for reasons of ethical considerations in obtaining human foetal material, and because of the complexity of human systems. The NC-IUPHAR recognizes that the discovery process is often simplified by using non-mammalian organisms. The tremendous importance of genes identified in *Drosophila*, *C. elegans* or in yeast strains is a case in point.

It must be pointed out that the ADP receptor in platelets, which was pharmacologically defined years ago (see Ref. 2), has not yet been cloned. In such a case NC-IUPHAR recommends that the name be given in italics. In order not to preempt the efforts of cloning, we recommend the term $P2Y_{ADP}$ rather than, e.g. $P2Y_8$ or $P2Y_9$. The recently reported $p2y_3$ receptor from the chick[19] shows a preference for ADP, but is clearly different from the

platelet ADP receptor. It is possible, but far from certain, that a mammalian homologue of the chick $p2y_3$ receptor would be the long sought-after receptor.

Since the nomenclature for P2 receptors is based largely on structure numerous questions arise. For example, how should a pharmacologist working in isolated tissues name a new receptor if it responds to UTP in preference to ATP, particularly if it is not clear what molecular type of receptor is involved? In such a situation, the term UTP- (or UDP-) preferring P2(Y) receptor is recommended (the letter Y included only in cases where there is evidence that the receptor is indeed of the Y type, i.e. G protein coupled). The more descriptive term should be used since the observed response could be due to several different cloned receptors, alone or in combination.

For future developments, the reader is refererred to the Web site maintained by G. Burnstock and B. King, who have done the field a great service by providing a ready access to the latest discoveries on P2 receptors[49]. (http://ylem.anat.ucl.ac.uk/research/burnstock/nomenclature.html see also http://mgddk1.niddk.nih.gov:8000/nomenclature.html.)

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Table 1

P2X receptors

P2X receptor subtypes	Species (Accession number)	Pharmacological characteristics[f,l,m]			
		Response to α,β-Me-ATP	**Desensitization**	**Block by PPADS and suramin**	**Refs**
$P2X_1$	Rat (X80477), Human (X83688), Mouse (X84896)	Yes	Yes	Yes	22,23
$P2X_2$	Rat (U14414) Short form (L43511)	No	No	Yes	24,25
$P2X_3$	Rat (X90651, X91167)	Yes	Yes	Yes	26,27
$P2X_2$ and $P2X_3$		Yes	No	Yes	
$P2X_4$	Rat (X91200, X87763, U32497, X93565, U47031)	No	No	No*	28 – 32
$P2X_5$	Rat (X92069)	No	No	Yes	33
$P2X_6$	Rat (X90270)	No	No	No	33
$P2X_7$ (=P2Z)**	Rat (X95882)	Responds to Bz-ATP, No effect of α,β-Me-ATP; Desensitizes less upon repeated agonist application[m]			18

* hP2X4 receptor is blocked by PPADS and suramin [Soto, F., Garcie-Cuyman, M. and Stuhmer, W. (1996) *Neurosci. Abstr*. 137.10]

** It is possible that there may be more than one form of the "P2Z" receptor.

Table 2

P2Y receptors

P2Y subtypes	Species	Accession number	Refs
$P2Y_1$	Human	Z49205, U42029, U42030[a]	34,35
	Cow	X87628	36
	Rat	U22830	37
	Mouse	U22829	37
	Chick	X73268	38
	Turkey	U09842	39
$P2Y_2$	Human	U07225(or S74902)	40,41
	Rat	U09402, L46865, U56839[b]	26,42
	Mouse	L1 4751	43
$p2y_3$ (chick)	Chick	X98283	19
$P2Y_4$	Human	X91852, U40223	44,45
$p2y_5$ (function not established)	Human	P32250(or L06109)	20
$P2Y_6$	Human Rat	X97058 D63665	46 47
$P2Y_7$*	Human	U41070	21
p2y (novel receptor in embryonic nervous system)	Xenopus		48
$P2Z_{ADP}$	Functionally defined ADP receptor (e.g. platelets). Not cloned.		
$P2Y_{Ap4A}$	Functionally defined adenine nucleotide receptor. Not cloned.		

Note that in accordance with the general IUPHAR rules, the names of receptor species for which there is good pharmacological evidence, but which have not been cloned, are given in italics. Conversely, the names of receptors for which there is only data from cloning experiments and for which there is no evidence of a functional role are given in lower case letters.

*The only published data on this receptor suggests that this gene product fulfils the criteria to name this receptor. References:

[a]Leon *et al.* 1995. Direct submission to Genbank,

[b]Seye *et al.* 1996. Direct submission to Genbank.