P2Y

Overview: P2Y receptors (provisional nomenclature as agreed by NC-IUPHAR Subcommittee on P2Y Receptors, Abbracchio *et al.*, 2003; 2006) are activated by the endogenous ligands ATP, ADP, UTP, UDP and UDP-glucose. The relationship of many of the cloned receptors to endogenously expressed receptors is not yet established, and so it might be appropriate to use wording such as 'UTP-preferring (or ATP-, etc.) P2Y receptor' or '$P2Y_1$-like', etc., until further, as yet undefined, corroborative criteria can be applied.

Nomenclature	$P2Y_1$	$P2Y_2$	$P2Y_4$	$P2Y_6$
Ensembl ID	ENSG00000169860	ENSG00000175591	ENSG00000	ENSG00000171361
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	ADP > ATP	UTP = ATP	UTP > ATP (at rat recombinant receptors, UTP = ATP)	UDP >> UTP > ATP
Selective agonists	2-MeSADP, ADPβS, MRS2365 (Bourdon *et al.*, 2006)	UTPγS (Lazarowski *et al.*, 1996), Ap_4A (Castro *et al.*, 1992), 2-thioUTP (El-Tayeb *et al.*, 2006)	UTPγS (Lazarowski *et al.*, 1996)	UDP, 3-phenacylUDP (PSB0474, El-Tayeb *et al.*, 2006)
Selective antagonists	MRS2500 (8.8, Kim *et al.*, 2003), MRS2279 (8.0, Waldo *et al.*, 2002), MRS2179 (7.0, Boyer *et al.*, 1996), PIT (6.8, Gao *et al.*, 2004)	–	ATP (6.2, Kennedy *et al.*, 2000)	MRS2578 (pIC_{50} 7.4, Mamedova *et al.*, 2004)
Probes	[^{3}H]-MRS2279 (8 nM, Waldo *et al.*, 2002), [^{35}S]-ADPβS, [^{35}S]-ATPαS, [^{35}S]-dATPαS	–	–	–

Nomenclature	$P2Y_{11}$	$P2Y_{12}$	$P2Y_{13}$	$P2Y_{14}$
Other names	–	$P2Y_{ADP}$, P_{2T}	GPR86, GPR94, SP174	KIAAA00001, gpr105
Ensembl ID	ENSG00000176130	ENSG00000169313	ENSG00000181631	ENSG00000174944
Principal transduction	G_s, $G_{q/11}$	$G_{i/o}$	$G_{i/o}$	$G_{q/11}$
Rank order of potency	ATP > UTP	ADP >> ATP	ADP >> ATP	UDP-glucose
Selective agonists	ARC67085 (Communi *et al.*, 1999), NAD^+ (Moreschi *et al.*, 2006), $NAADP^+$ (Moreschi *et al.*, 2008)	ADP, 2-MeSADP	–	MRS2690 (Ko *et al.*, 2007)
Selective antagonists	NF157 (Ullmann *et al.*, 2005)	ATP, ARL66096 (Humphries *et al.*, 1995)	MRS2211 (Kim *et al.*, 2005)	–

ARC69931MX shows selectivity for $P2Y_{12}$ and $P2Y_{13}$ receptors compared with other P2Y receptors (Takasaki *et al.*, 2001; Marteau *et al.*, 2003). NF157 also has antagonist activity at $P2X_1$ receptors (Ullmann *et al.*, 2005). UDP has been reported to be an antagonist at the $P2Y_{14}$ receptor (Fricks *et al.*, 2008).

A 7TM orphan receptor suggested to be a '$P2Y_{15}$' receptor (Inbe *et al.*, 2004) appears not to be a genuine nucleotide receptor (see Abbracchio *et al.*, 2006), but rather responds to dicarboxylic acids (He *et al.*, 2004). Further P2Y-like receptors have been cloned from non-mammalian sources; a clone from chick brain, termed a $p2y_3$ receptor (ENSGALG00000017327), couples to the $G_{q/11}$ family of G proteins and shows the rank order of potency ADP > UTP > ATP = UDP (Webb *et al.*, 1996a). In addition, human sources have yielded a clone with a preliminary identification of p2y5 (ENSG00000139679) and contradictory evidence of responses to ATP (King and Townsend-Nicholson, 2000; Webb *et al.*, 1996b). This protein has recently been suggested to be receptor for lysophosphatidic acid (Pasternack *et al.*, 2008; Yanagida *et al.*, 2009), as has the clone clone termed p2y9 (LPA_4, ENSG00000147149, Noguchi *et al.*, 2003). The clone p2y7 (ENSG00000196943), originally suggested to be a P2Y receptor (Akbar *et al.*, 1996), has been shown to encode a leukotriene receptor (Yokomizo *et al.*, 1997). A P2Y receptor that was initially termed a p2y8 receptor (P79928) has been cloned from *Xenopus laevis*; it shows the rank order of potency ADPβS > ATP = UTP = GTP = CTP = TTP = ITP > ATPγS and elicits a Ca^{2+}-dependent Cl^- current in *Xenopus* oocytes (Bogdanov *et al.*, 1997). The p2y10 clone (ENSG00000078589) lacks functional data. Diadenosine polyphosphates also have effects on as yet uncloned P2Y-like receptors with the rank order of potency of Ap_4A > Ap_5A > Ap_3A, coupling via $G_{q/11}$ (Castro *et al.*, 1992). P2Y-like receptors have recently been described on mitochondria (Belous *et al.*, 2004). $CysLT_1$ and $CysLT_2$ leukotriene receptors respond to nanomolar concentrations of UDP, although they are activated principally by leukotrienes C_4 and D_4 (Mellor *et al.*, 2001; 2003); Human (ENSG00000144230) and rat GPR17, which are structurally related to CysLT and P2Y receptors, are also activated by leukotrienes as well as UDP and UDP-glucose (Ciana *et al.*, 2006). Activity at the rat GPR17 is inhibited by submicromolar concentrations of MRS2179 and ARL69931 (Ciana *et al.*, 2006).

Abbreviations: **2-MeSADP**, 2-methylthio-adenosine-5′-diphosphate; **2-MeSATP**, 2-methylthio-adenosine-5′-triphosphate; **ARC67085**, 2-propylthio-βγ-dichloromethylene-ATP; **ARC69931MX**, N^6-(2-methylthioethyl)-2-(3,3,3-trifluoropropylthio)-βγ-dichloromethylene-ATP, also known as cangrelor; **ARL66096**, 2-propylthio-βγ-difluoromethylene ATP (previously FPL66096); **ATPγS**, adenosine 5′-(3-thio)triphosphate; **MRS2179**, N^6-methyl-2′-deoxyadenosine-3′,5′-bisphosphate; **MRS2211**, pyridoxal-5′-phosphate-6-azo (2-chloro-5-nitrophenyl)-2,4-disulfonate;

MRS2279, 2-chloro-N^6-methyl-(*N*)-methanocarba-2′-deoxyadenosine-3′,5′-bisphosphate; **MRS2365**, (*N*)-methanocarba-2-MeSADP; **MRS2500**, N^6-methyl-(*N*)-methanocarba-2′-deoxyadenosine-3′,5-bisphosphate; **MRS2578**, *N*,*N*″-1,4-butanediyl *bis*(*N*′-[3-isothiocynatophenyl)] thiourea; **MRS2690**, 2-thiouridine-5′-diphosphoglucose; **NF157**, 8,8′-[carbonylbis[imino-3,1-phenylenecarbonylimino(4-fluoro-3,1-phenylene) carbonylimino]]bis-1,3,5-naphthalene trisulfonic acid hexasodium salt; **PIT**, 2,2′-pyridylisatogen tosylate

Further Reading

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