P2X

Overview: P2X receptors [nomenclature as agreed by NC-IUPHAR Subcommittee on P2X receptors (Khakh *et al*., 2001; Collingridge *et al*., 2009)] are ligand-gated ion channels with a putative trimeric topology (Nicke *et al*., 1998; Jiang *et al*., 2003; Kawate *et al*., 2009), gating primarily Na^+, K^+ and Ca^{2+}, exceptionally Cl^- with two putative TM domains, where the endogenous ligand is ATP. The Nomenclature Subcommittee has recommended that for P2X receptors, structural criteria should be the initial criteria for nomenclature where possible. The P2X receptor nomenclature recommended below reflects the newly accepted format for ligand-gated ion channels (see Collingridge *et al*., 2009). Functional P2X receptors exist as polymeric transmitter-gated channels; the native receptors may occur as either homopolymers (e.g. P2X1 in smooth muscle) or heteropolymers (e.g. P2X2/3 in the nodose ganglion and P2X1/5 in mouse cortical astrocytes, Lalo *et al*., 2008). P2X2, P2X4 and P2X7 receptors have been shown to form functional homopolymers which, in turn, activate pores permeable to low molecular weight solutes (see Surprenant and North, 2009). The hemi-channel pannexin-1 has been implicated in the pore formation induced by P2X7 (Pelegrin and Surprenant, 2009), but not P2X2 (Chaumont and Khakh, 2008), receptor activation.

Nomenclature	P2X1	P2X2	P2X3	P2X4
Ensembl ID	ENSG00000108405	ENSG00000177026	ENSG00000109991	ENSG00000135124
Potent agonists	L-$\beta\gamma$-meATP, $\alpha\beta$-meATP, BzATP	–	$\alpha\beta$-meATP, BzATP	–
Potent antagonists	TNP-ATP (pIC$_{50}$ 8.9, Virginio *et al*., 1998), Ip$_5$I (pIC$_{50}$ 8.5), NF023 (pIC$_{50}$ 6.7); NF449 (pIC$_{50}$ 6.3, Kassack *et al*., 2004)	–	TNP-ATP (pIC$_{50}$ 8.9, Virginio *et al*., 1998), A317491 (7.5, Jarvis *et al*., 2002), RO3 (pIC$_{50}$ 7.5, Ford *et al*., 2006)	–

A317491 and RO3 also block the P2X2/3 heteromultimer (Ford *et al*., 2006; Jarvis *et al*., 2002). NF449 and A317491 and RO3 are more than 10-fold selective for P2X1 and P2X3 receptors respectively.

Nomenclature	P2X5	P2X6	P2X7
Other names	–	–	P_{2Z}
Ensembl ID	ENSG00000083454	ENSG00000099957	ENSG00000089041
Potent antagonists	–	–	Brilliant Blue G (pIC$_{50}$ 8.0, Jiang *et al*., 2000), A804598 (pIC$_{50}$ 8.0), A839977 (pIC$_{50}$ 7.7, Donnelly-Roberts and Jarvis, 2007; Donnelly-Roberts *et al*., 2009; Honore *et al*., 2009), decavanadate (pA$_2$ 7.4, Michel *et al*., 2006a), KN62 (Gargett and Wiley, 1997), A740003 (pIC$_{50}$ 7.4), A438079 (pIC$_{50}$ 6.9, Donnelly-Roberts and Jarvis, 2007)

Agonists listed show selectivity within recombinant P2X receptors of ca one order of magnitude. A804598, A839977, A740003 and A438079 are at least 10-fold selective for P2X7 receptors and show similar affinity across human and rodent receptors (Donnelly-Roberts and Jarvis, 2007; Donnelly-Roberts *et al*., 2009; Honore *et al*., 2009).

Several P2X receptors (particularly P2X1 and P2X3) may be inhibited by desensitization using stable agonists (e.g. $\alpha\beta$-meATP); suramin and PPADS are non-selective antagonists at r & hP2X1–3,5 and hP2X4, but not rP2X4,6,7 (Buell *et al*., 1996), and can also inhibit ATPase activity (Crack *et al*., 1994). Ip$_5$I is inactive at rP2X2, an antagonist at rP2X3 (pIC$_{50}$ 5.6) and enhances agonist responses at rP2X4 (King *et al*., 1999). Antagonist potency of NF023 at recombinant P2X2, P2X3 and P2X5 is two orders of magnitude lower than that at P2X1 receptors (Soto *et al*., 1999). The P2X7 receptor may be inhibited in a non-competitive manner by the protein kinase inhibitors KN62 and chelerythrine (Shemon *et al*., 2004), while the p38 MAP kinase inhibitor SB202190 and the cyclic imide AZ11645373 show a species-dependent non-competitive action (Donnelly-Roberts *et al*., 2004; Michel *et al*., 2006b; Stokes *et al*., 2006; Michel *et al*., 2009). The pH-sensitive dye used in culture media, phenol red, is also reported to inhibit P2X1 and P2X3 containing channels (King *et al*., 2005). Some recombinant P2X receptors expressed to high-density bind [^{35}S]-ATPγS and [^{3}H]-$\alpha\beta$-meATP, although the latter can also bind to 5′-nucleotidase (Michel *et al*., 1995). [^{3}H]-A317491 and [^{3}H]-A804598 have been used as high-affinity antagonist radioligands for P2X3 (and P2X2/3) and P2X7 receptors respectively (Donnelly-Roberts *et al*., 2009).

Abbreviations: **$\alpha\beta$-meATP**, $\alpha\beta$-methylene-adenosine 5′-triphosphate; **$\beta\gamma$-meATP**, $\beta\gamma$-methylene-adenosine 5′-triphosphate; **A317491**, 5-({[3-phenoxybenzyl][(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]amino}carbonyl)-1,2,4-benzenetricarboxylic acid; **A438079**, 3-(5-(2,3-dichlorophenyl)-1*H*-tetrazol-1-yl) methyl pyridine; **A740003**, (*N*-(1-{[(cyanoimino)(5-quinolinylamino) methyl]amino}-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide; **A839977**, 1-(2,3-dichlorophenyl)-*N*-[2-(pyridin-2-yloxy)benzyl]-1H-tetrazol-5-amine; **A804598**, (*S*)-1-(1-(4-bromophenyl)ethyl)-2-cyano-3-(quinoline-5-yl)guanidine; **ATPγS**, adenosine 5′-(3-thio)triphosphate; **AZ11645373**, 3-[1-[4-(3-nitrophenyl)phenoxy]-4-pyridin-4-ylbutan-2-yl]-1,3-thiazolidine-2,4-dione; **Ip$_5$I**, diinosine-5′,5″-pentaphosphate; **KN62**, 1-(*N,O-bis*[5-isoquinolinesulphonyl]-*N*-methyl-L-tyrosyl)-4-phenylpiperazine; **NF023**, 8,8′-(carbonyl*bis*[imino-3,1-phenylene carbonylimino])bis-1,3,5-naphthalenetrisulfonic acid; **NF449**, 4,4′,4″,4‴-(carbonylbis[imino-5,1,3-benzenetriyl-bis{carbonylimino}])tetrakisbenzene-1,3-disulfonic acid octasodium salt; **PPADS**, pyridoxalphosphate-6-azophenyl-2′,4′-disulphonate; **RO3**, 5-(methyl[2-methylethyl-4,5-dimethoxyphenyl]-2,4pyridinediamine; **SB202190**, 4-[4-(4-fluorophenyl)-5-pyridin-4-yl-1*H*-imidazol-2-yl]phenol; **TNP-ATP**, 2′,3′-*O*-(2,4,6-trinitrophenyl)-ATP

Further Reading

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