

P2 Receptors: P2Y G-Protein Family

Key References

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Overview

Once known as P2 purinoceptors, surface receptors for extracellular nucleotides are now called P2 receptors. This subtle change in nomenclature reflects the more varied nature of nucleotidic ligands, other than those containing a purine moiety, that are capable of activating these surface receptors. The current nomenclature system for P2 receptors also is based on their molecular structure and signal transduction mechanisms, so defining a family of metabotropic P2 receptors (P2Y G Protein-Coupled Receptors, GPCRs) and another family of ionotropic P2 receptors (P2X Ligand-Gated Ion Channels, LGICs).

The protein structure of the eight accepted members of the metabotropic P2Y family (P2Y_{1,2,4,6,11,12,13,14}) is characterized by i) extracellular N-terminus and intracellular C-terminus, the former being glycosylated and the latter possessing consensus binding motifs for protein kinases, ii) seven α -helical transmembrane spanning regions (TM1-7) which form the ligand docking pocket, iii) a high level of sequence homology between key transmembrane spanning regions, notably TM3, TM6 and TM7, and iv) structural diversity of intracellular loops and C-terminus among P2Y subtypes, so influencing the degree of coupling with G_{q/11}, G_s and G_i proteins. Each P2Y receptor binds to a heterotrimeric G protein, frequently G_{q/11}, although P2Y₁₁ can couple to both G_{q/11} and G_s whereas P2Y_{12,13,14} couple preferentially to G_i. P2Y receptors also form heterotrimeric assemblies with adenosine (A₁) receptors, and P2Y proteins may be capable of forming homodimeric assemblies. P2Y receptors are directed to discrete regions of cells that express multiple subtypes. Most cell types express more than one P2Y receptor subtype.

At the peptide level, P2Y receptors show a low level of sequence homology, notably over the region delimited by TM1 to TM7 where they are only 19-55% identical. Consequently, members of the P2Y family show significant differences in their pharmacological and operational profiles. Some P2Y receptors are activated principally by nucleoside diphosphates (P2Y_{1,6,12,13}), while others are activated mainly by nucleoside triphosphates (P2Y_{2,4,11}). Some P2Y receptors are activated by both purine and pyrimidine nucleotides (P2Y_{2,4,6,11}), others by purine nucleotides alone (P2Y_{1,12,13}) and, uniquely, P2Y₁₄ is activated by ribose-nucleotides. Upon activation, recombinant P2Y receptors either activate phospholipase C and release intracellular calcium or affect adenylyl cyclase and alter cAMP levels. However, endogenous P2Y receptors show a wider diversity in intracellular signaling and can activate phospholipases A₂, C and D, MEP/MAP kinase, PI-3 kinase, Rho-dependent kinase and tyrosine kinase. Also, endogenous P2Y receptors can couple either positively or negatively to adenylyl cyclase.

The eight P2Y receptors in the human genome belong to the assigned δ -of group the Rhodopsin-like GPCR superfamily which contains over 800 members. Analyses of primary sequence data indicates the presence in the δ -group of another 34 GPCRs that are structurally related to the eight, functionally-proven P2Y receptors. Unfortunately, some of these P2Y-like sequences have been misidentified as nucleotide receptors. For example, P2Y₇ is now known to be a receptor for leukotriene B₄; P2Y₉ is a receptor for lysophosphatidic acid; P2Y₁₅ is a receptor for the citric acid cycle intermediates, α -ketoglutarate and succinate. There is scant evidence to indicate that

human P2Y_{5,10} sequences are nucleotide receptors and, therefore, they should be viewed as orphan receptors. In mice, gene deletion has been achieved for P2Y₁, P2Y₂, P2Y₄, P2Y₁₂ and P2Y₁₃. None are lethal, but knockout of either P2Y₁ or P2Y₁₂ genes results in bleeding disorders. Disruption of P2Y₂ or P2Y₄ genes alters solute transport and secretion in epithelial cells. P2Y₁₃ null mice have not yet been characterized. The P2Y₁₁ gene has not yet been identified in the mouse genome.

P2 Receptors: P2Y G-Protein Family

CURRENT NAME ^a	P2Y ₁	P2Y ₂	P2Y ₄	P2Y ₆	P2Y ₁₁ ^b
ALTERNATE NAME	P2Y	P2U	Pyrimidinoceptor	Pyrimidinoceptor	PY
STRUCTURAL INFORMATION	372 aa (human)	376 aa (human)	365 aa (human)	328 aa (human)	371 aa (human)
SELECTIVE AGONISTS ⁹	ADPβS (A8016), 2-MeSADP (M152), 2-MeSATP (A023), MRS 2365, PAPET-ATP	UTP (U1006), UTP _γ S, ATP _γ S (A1388), INS 37217, INS 365	UTP (U1006), INS 37217, INS 365	UDP (U4125), UDPβS, Up ₃ U, 5-BrUDP, IDP (I4375)	AR-C67085MX, dATP (D6500), ADPβS (A8016), BzATP (B6396), α,β-MeATP (M6517)
SELECTIVE ANTAGONISTS	A3P5PS (A1651), BzATP (B6396), PPADS (P178), MRS 2179 (M3808), MRS 2279, MRS 2500, RB-2 (R115), Suramin (S2671)	Suramin (S2671)	PPADS (P178) (weak), ATP (A2383) (human), RB-2 (R115) (rat), BzATP (B6396) (rat)	MRS 2578 (M0319), RB-2 (R115), PPADS (P178), Suramin (S2671)	Suramin (S2671), RB-2 (R115), AMPA _α S (A1640)
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG) possibly G _i	G _{q/11} (increase IP ₃ /DAG) possibly G _i	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG) G _s (increase in cAMP)
RADIOLIGANDS OF CHOICE	[³ H]-MRS 2279	Not known	Not known	Not known	Not known
TISSUE EXPRESSION	Platelets, endothelia, smooth muscle, CNS neurons, astrocytes, DRG neurons, osteoblasts, β-islet cells	Epithelia, endothelia, smooth muscle, pituitary, astrocytes, hepatocytes	Epithelia, smooth muscle, CNS neurons, astrocytes, retina, cochlea, placenta	Epithelia, smooth muscle, heart, gall-bladder, retina, cochlea, placenta, spleen, monocytes	Epithelia, endothelia, smooth muscle, granulocytes, dendritic cells, spleen, kidney
PHYSIOLOGICAL FUNCTION	Ca ²⁺ -release, platelet shape change, smooth muscle relaxation, transmitter release	Ca ²⁺ -release, Cl ⁻ secretion, smooth muscle hyperplasia, ciliary beating, hormone release	Ca ²⁺ -release, Cl ⁻ secretion, GIRK inhibition, endolymph K ⁺ -gradient	Ca ²⁺ -release, Cl ⁻ secretion, GIRK inhibition, IL-8 secretion	Ca ²⁺ -release, Cl ⁻ secretion, cAMP elevation, renin secretion, IL-12 secretion
DISEASE RELEVANCE	Bleeding disorders, hypotension, stroke, epilepsy, osteoporosis, Type II diabetes	Cystic fibrosis, chronic bronchitis, dry eye, smooth muscle proliferation, reactive gliosis	Diarrhea, GI malabsorption, brain water homeostasis, smooth muscle antiproliferation, hearing defects	Inflammatory bowel disease, inflammation, atherosclerosis, cholestasis/gallstones, hearing defects	Smooth muscle proliferation, neutropenia, leukemia, inflammation, diabetic nephropathy

FOOTNOTES

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CURRENT NAME ^a	P2Y ₁₂ ^c	P2Y ₁₃	P2Y ₁₄	P2Y _{Ap4A} ^d
ALTERNATE NAME	P2Y _T or P2T ^e SP1999	GPR 86	GPR 105 KIAA0001 VTR 15-20 ^f	P2D
STRUCTURAL INFORMATION	342 aa (human)	333 aa (human)	338 aa (human)	Not known
SELECTIVE AGONISTS ^g	2-MeSADP (M152), ADP (A5285), ADPβS (A8016), Ap ₃ A (D1387), IDP (I4375)	2-MeSADP (M152), ADP (A5285), ADPβS (A8016), Ap ₃ A (D1387), IDP (I4375)	UDP-glucose (U4625), UDP-galactose (U4500), UDP-N-acetylglucosamine (U4375)	Ap4A (D1262)
SELECTIVE ANTAGONISTS	AR-C67085MX, AR-C69931MX, C1330-7, 2-MeSAMP (M1434), BzATP (B6396), RB-2 (R115), Suramin (S2671), Clopidogrel (C0614) ^h	AR-C67085MX, AR-C69931MX, Ap ₄ A (D1262), 2-MeSAMP (M1434), PPADS (P178), RB-2 (R115), Suramin (S2671), MRS2211	Not known	lpsI (D6938)
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	β-[³² P]-2-MeSADP	β-[³² P]-2-MeSADP	Not known	[³ H]-Ap4A
TISSUE EXPRESSION	Blood platelets, chromaffin cells, glia, microglia	Glia, spleen, lymph nodes, bone marrow, dendritic cells	Placenta, adipose tissue, stomach & intestine, glia, astrocytes, neutrophils, lymphocytes, hemopoietic stem cells, dendritic cells	Not known
PHYSIOLOGICAL FUNCTION	cAMP modulation, Ca ²⁺ -channel inhibition, hemostasis	cAMP modulation, hematopoiesis, immune responses	cAMP modulation, neuroimmune responses, chemoattraction, immune responses	Not known
DISEASE RELEVANCE	Thromboembolism, diabetic thromboembolism, cardiovascular disease	Not known	Reactive astrogliosis, inflammation, tumor recognition	Not known

FOOTNOTES

a The P2Y_{1-n} series comprises 15 putative G protein-coupled receptors, but only 8 are accepted as nucleotide receptors: P2Y₃ may be an ortholog of P2Y₆; P2Y_{5,10} are not yet proven to be functional P2 receptors; P2Y₇ is a LTB₄ leukotriene receptor; P2Y₉ is a receptor for lysophosphatidic acid; P2Y₁₅ is a receptor for the citric acid cycle intermediates, α-ketoglutarate and succinate; another receptor (turkey p2y) may be related to P2Y₄; P2Y₈ (532 aa) was cloned from *Xenopus laevis*, where it occurs mainly in early development during neurogenesis and is activated by ATP, UTP and CTP, and weakly antagonized by suramin.

b In human, P2Y₁₁ exists as several isoforms of a chimeric receptor generated by intergenic splicing between the SSF1 and P2Y₁₁ genes on chromosome 19p31.

c P2Y₁₂ is the previously named P2Y_{AC} receptor that couples negatively to adenylyl cyclase.

d P2Y_{Ap4A} is a temporary name until the P2D receptor is cloned.

e The P2Y_T receptor is best fitted by a three-receptor model comprising P2Y₁₂ coupled negatively to adenylyl cyclase, P2Y₁ activating phospholipase C and P2X₁ coupled to an ion-channel permeable to Na⁺ and Ca²⁺ ions.

f VTR15-20 is a truncated form of rat P2Y₁₄, comprising 80% of the ORF for P2Y₁₄.

g ATP is a full agonist only at P2Y_{2,8,11}, and a partial agonist or antagonist at human P2Y₁. P2Y_{1,6,12,13} are activated preferentially by the nucleoside diphosphate, ADP.

h Clopidogrel is a prodrug and converted into its active form by cytochrome P450.

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Abbreviations

A3P5PS: Adenosine 3'-phosphate 5'-phosphosulphate
ADP β S: Adenosine 5'-O-(2-thiodiphosphate)
AMP α S: Adenosine 5'-O-(thiomonophosphate)
Ap3A: Diadenosine triphosphate
AR-C67085MX: 2-Propylthio-D- β , γ -dichloromethylene-ATP
AR-C69931MX: N⁶-[2-(Methylthio-ethyl)-2-(3,3,3-trifluoropropyl)thio-5'-adenylic acid
dATP: Deoxy-adenosine 5'-triphosphate
C1330-7: N¹-(6-Ethoxy-1,3-benzothiazol-2-yl)-2-(7-ethoxy-4-hydroxy-2,2-dioxo-2H-2-6benzo[4,5][1,3]thiazolo[2,3-c][1,2,4]thiadiazin-3-yl)-2-oxo-1-ethanesulfonamide
IDP: Inosine 5'-diphosphate
INS37217: P(1)-(Uridine 5')-P(4)- (2'-deoxycytidine 5')tetraphosphate tetrasodium salt
INS365: Diuridine tetraphosphate
2-MeSADP: 2-Methylthioadenosine-5'-diphosphate
2-MeSAMP: 2-Methylthioadenosine-5'-monophosphate
MRS 2179: 2'-Deoxy-N⁶-methyladenosine-3',5'-bisphosphate
MRS 2279: (N)-Methanocarba-N⁶-methyl-2-chloro-2'-deoxyadenosine-3',5'-bisphosphate
MRS2365: (N)-Methanocarba-2-Methylthioadenosine-5'-diphosphate
MRS2578: 1,4-di-(Phenylthioureido) butane
MRS2500: (N)-Methanocarba-N⁶-methyl-2-iodo-2'-deoxyadenosine-3',5'-bisphosphate
PPADS: Pyridoxal-5-phosphate-6-azophenyl-2',4'-disulphonic acid
RB-2: Reactive blue 2
UDP: Uridine 5'-diphosphate
UDP β S: Uridine 5'-O-(2-thiodiphosphate)
Up3U: Diuridine triphosphate
UTP: Uridine 5'-triphosphate
UTP γ S: Uridine 5'-O-(3-thiotriphosphate)

FOOTNOTES