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Introduction to the Special Issue on Purinergic Receptors

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Abstract

In this Introduction to the series of papers that follow about purinergic receptors, there is a brief history of the discovery of purinergic signalling, the identity of purinoceptors and the current recognition of P1, P2X and P2Y subtypes. An account of key functions mediated by purinoceptors follows, including examples of both short-term and long-term (trophic) signalling and a table showing the selective agonists and antagonists for the purinoceptor subtypes. References to evolution and roles of purinoceptors in pathological conditions are also presented.

Keywords

Neurotransmission • Secretion • Development • Regeneration • Pathophysiology

Purinergic signalling was proposed in 1972 (Burnstock 1972) and purinergic receptors defined in 1976 (Burnstock 1976). In 1978, it was recognised that there were two families of purinoceptors, named P1 (adenosine) and P2 (nucleotide) receptors (Burnstock 1978). An edited book about purinergic receptors was published in 1981 (Burnstock 1981). Based on pharmacology, P2 receptors were later divided into P2X and P2Y subtypes (Burnstock and Kennedy 1985). P2Z (later named P2X7) receptors (Gordon 1986), P2T (later named $P2Y_{12}$) receptors (Gordon 1986) and P2U (later named $P2Y_2$ and/or $P2Y_4$) receptors (O'Connor et al. 1991) followed. Important advances were made in the early nineties, when transduction mechanisms were identified (Dubyak and El Moatassim 1993) and P1, P2Y and P2X receptors cloned and characterised. Four subtypes of P1 receptors, A_1, A_{2A}, A_{2B} and A_3 receptors (Maenhaut et al. 1990; Fredholm et al. 1994), initially $P2Y_1$ (Webb et al. 1993) and $P2Y_2$ (Lustig et al. 1993) receptors and a year later

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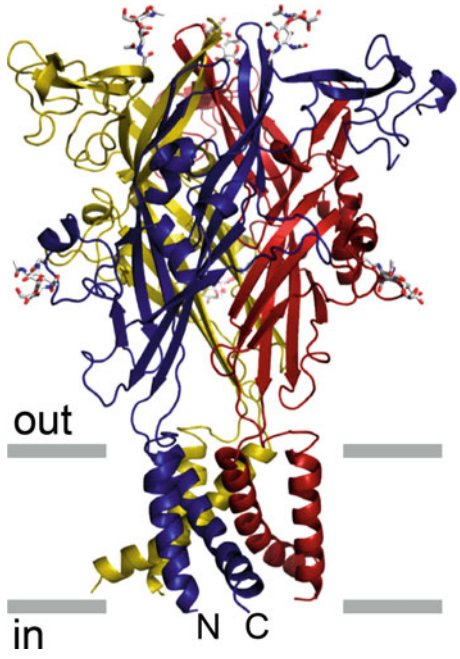

Fig. 1 The architecture of P2X receptors. Stereoview of the homotrimeric ΔzfP2X4 structure viewed parallel to the membrane. Each subunit is depicted in a different colour. N-acetylglucosamine (NAG) and glycosylated asparagine residues are shown in *stick* representation. The *grey bars* suggest the boundaries of the outer (*out*) and inner (*in*) leaflets of the membrane bilayer (Reproduced from Kawate et al. 2009, with permission from Nature Publishing Group)

P2X1 (Valera et al. 1994) and P2X2 (Brake et al. 1994) receptors were identified. These findings were rationalised by Abbracchio and Burnstock (Abbracchio and Burnstock 1994) by defining seven P2X ion channel receptor subtypes and eight P2Y G protein-coupled receptors. A popular comprehensive review about purinoceptors was published by Ralevic and Burnstock (1998) (4094 citations). An important study showed that three P2X receptor subtypes were combined to form trimer ion channels (Nicke et al. 1998) either as homomultimers and heteromultimers (Burnstock 2007a). Reviews about the expression and functions of purinergic receptors for many different cell types (Burnstock and Knight 2004) and the molecular pharmacology of P2X receptors (North 2002) are available and the elegant identification of the crystal structure of the P2X4 receptors (Fig. 1) (Kawate et al. 2009; Hattori and Gouaux 2012). Reviews about P1 (Fredholm et al. 2011; Chen et al. 2014), P2Y (Abbracchio et al. 2006; Erlinge 2011; Jacobson et al. 2015) and P2X (Müller 2015; Habermacher et al. 2016) receptors are available. A valuable book edited by Jacobson and Linden, entitled 'Pharmacology of Purine and Pyrimidine Receptors', was published in 2011 (Jacobson and Linden 2011).

Purinoceptors modulate both short-term signalling in neurotransmission, neuromodulation and secretion and long-term (trophic) signalling in cell proliferation, differentiation and death in development and regeneration (see Burnstock 2016). Selective agonists and antagonists to purinoceptor subtypes currently available are summarised in Table 1. The evolution of purinoceptors (Burnstock 1996; Fountain and Burnstock 2009; Burnstock and Verkhratsky 2012) and the plasticity of expression and roles of purinoceptors in pathological conditions (Burnstock 2006, 2007b, 2013) have been reviewed. The intracellular expression of purinoceptors is being explored (Burnstock 2015) and the expression of purinoceptors during development and ageing has also been reviewed (Burnstock and Dale 2015). Detailed analysis of various aspects of purinoceptors will be presented in the following articles.

Table 1 Characteristics of purine-regulated receptors

Receptor		Main distribution	Agonists	Antagonists	Transduction mechanisms
P1 (Ado)	**A_1**	Brain, spinal cord, testis, heart, autonomic nerve terminals	CCPA>R-PIA=S-ENBA; CVT-510; GR79236, 2′-MeCCPA, SDZ WAG 994, INO-8875, MRS 5474	DPCPX, N-0840, MRS1754, WRC-0571, PSB36, SLV320, CGS 16943, PQ-69	G_i/G_o ↓cAMP
	A_{2A}	Brain, heart, lungs, spleen	HENECA>CGS 21680=CVT-3146; ATL-146e; Regadenoson, apadenoson, UK-432.097	KF17837, SCH58261, ZM241385, KW 6002	G_S ↑cAMP
	A_{2B}	Large intestine, bladder	Bay60-6583, NECA	PSB603, MRE-2029-F20, MRS1754, PSB0788 MRS1706, PSB1115, Alloxazine, GS-6201	G_S ↑cAMP
	A_3	Lung, liver, brain, testis, heart	IB-MECA> MRS5698>MRS5168> 2-Cl-IB-MECA; DBXRM; VT160; HEMADO, MRS5980	MRS1220, L-268605, MRS1191, MRS1523(rat), VUF8504, VUF5574, MRS1334(human), PSB10	G_i/G_o, G_q/G_{11}, ↓cAMP, PLC-β activation
P2X	**P2X1**	Smooth muscle, platelets, cerebellum, dorsal horn spinal neurons	BzATP > ATP = 2-MeSATP≥α,β-meATP=L-β,γ-meATP (rapid desensitization); PAPET-ATP	NF864>NF449>IP_5I≥TNP-ATP> RO 0437626> NF279, NF023, RO1, MRS2159	Intrinsic cation channel (Ca^{2+} and Na^+)
	P2X2	Smooth muscle, CNS, retina, chromaffin cells, autonomic and sensory ganglia, pancreas	ATP≥ATPγS≥2-MeSATP>>α,β-meATP (pH + zinc sensitive); β,γ-CF_2ATP	PSB-1011>RB2, isoPPADS>PPADS>Suramin, NF770, NF778, Aminoglycoside	Intrinsic ion channel (particularly Ca^{2+})
	P2X3	Sensory neurons, NTS, some sympathetic neurons	2-MeSATP≥ATP≥ Ap_4A ≥ α,β-meATP (rapid desensitization); PAPET-ATP; BzATP	TNP-ATP, AF353, A317491, RO3, isoPPADS > NF110 > PPADS, Ip_5I, phenol red, RN-1838, Spinorphin	Intrinsic cation channel
	P2X4	CNS, testis, colon, endothelial cells, microglia	ATP>>α,β-meATP>> CTP, 2-MeSATP Ivermectin potentiation	5-BDBD>>TNP-ATP, PPADS>BBG, Paroxetine, phenolphthalein, CO donor (CORM 2), 5MPTP	Intrinsic ion channel (especially Ca^{2+})
	P2X5	Proliferating cells in skin, gut, bladder, thymus, spinal cord, heart, adrenal medulla	ATP=2-MeSATP=ATPγS>>α,β-meATP>AP_4A	BBG>PPADS, Suramin	Intrinsic ion channel
	P2X6	CNS, motor neurons in spinal cord	– (only functions as a heteromultimer)	–	Intrinsic ion channel
	P2X7	Immune cells including dendritic cells (mast cells, macrophages), pancreas, skin, microglia	BzATP>ATP ≥2-MeSATP >>α,β-meATP (clemastine potentiates)	KN62, BBG, KN04, MRS2427, O-ATP, RN-6189, Perazine, AZ10606120, A740003, A-438079, A-804598, GSK-1370319, Comp 31 (GSK), AZD-9056, CE-224,535, JNJ-47965567, JNJ-42253432 (penetrates BBB),	Intrinsic cation channel and a large pore with prolonged activation

(continued)

Table 1 (continued)

Receptor		Main distribution	Agonists	Antagonists	Transduction mechanisms
				decavanadate, AZ11657312, A-839977, GSK1482160	
P2Y	**$P2Y_1$**	Epithelial and endothelial cells, platelets, immune cells, osteoclasts, brain	MRS2365>2-MeSADP=Ap_5(γB)>> ADPβS>ATP >2-MeSATP=ADP, 2-Cl-ADP	MRS2500 > MRS2279 > MRS2179, PIT, A3P5P, BPTU	G_q/G_{11}; PLC-β activation
	$P2Y_2$	Immune cells, epithelial and endothelial cells, kidney tubules, osteoblasts	2-thio-UTP>UTP, MRS2698≥ATP, INS 365> INS 37217, UTPγS>Ap_4A>MRS 2768, Up_4-phenyl ester	AR-C126313>Suramin> RB2, PSB-716, MRS2576, PSB-0402, AR-C118925, AR-C118925	G_q/G_{11} and possibly G_i/G_o; PLC-β activation
	$P2Y_4$	Endothelial cells, placenta, spleen, thymus	2′-azido-dUTP> UTPγS, UTP≥ATP≥ Ap_4A Up_4U MRS4062	ATP (human)>Reactive Blue 2>Suramin, MRS2577, PPADS	G_q/G_{11} and possibly G_i; PLC-β activation
	$P2Y_6$	Airway and intestinal epithelial cells, placenta, T cells, thymus, microglia (activated)	MRS2693> UDPβS , PSB0474> INS48823, Up_3U, 3-phenacyl-UDP>>UDP>UTP>>ATP, α,β-meUDP, MRS2957, MRS4129, 5-OMe-UDP αB	MRS2578>Reactive Blue 2, PPADS, MRS2567, MRS2575 (human)	G_q/G_{11}; PLC-β activation
	$P2Y_{11}$	Spleen, intestine, granulocytes	ATPγS>AR-C67085MX>BzATP≥ATP, NF546, NAD^+, $NAADP^+$, S*p*-2-propylthio-ATP-α-B	NF157>Suramin>RB2, 5′-AMPS, NF340, AMP-α-5,	G_q/G_{11} and G_S; PLC-β activation
	$P2Y_{12}$	Platelets, glial cells	2-MeSADP≥ADP>ATP, ADP-β-S	AR-C69931MX> AZD6140 (Ticagrelor), INS50589>RB2>2-MeSAMP AR-C66096, CT50547,PSB-0413, Carba-nucleosides, MRS2395, AR-C67085, [^{3}H] PSB-0413; clopidogrel, AZD1283; ACT-246475	$G\alpha_i$; inhibition of adenylate cyclase
	$P2Y_{13}$	Spleen, brain, lymph nodes, bone marrow, erythrocytes	ADP=2-MeSADP>2-MeSATP, ATP	AR-C69931MX>AR-C67085>MRS2211, 2-MeSAMP	G_i/G_o
	$P2Y_{14}$	Placenta, adipose tissue, stomach, intestine, discrete brain regions, mast cells	MRS2690>UDP>UDP glucose≥UDP-galactose, UDP-glucosamine, MRS2905, MRS4183	PPTN, MRS4174	G_q/G_{11}
	GPR17	Oligodendrocytes	Uracil nucleotides/cysteinyl-leukotrienes, MDL29,951	PZB01415033	G_i, adenylate cyclase inhibition

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Abbreviations: Ap_5(γB), Adenosine pentaphosphate γ-boranophosphate; BBG, Brilliant blue green; 5-BDBD, 5-(3-Bromophenyl)-1,3-dihydro-2H-benzofuro[3,2-e]-1,4-diazepin-2-one BzATP, 2'-&3'-*O*-(4-benzoyl-benzoyl)-ATP; cAMP, cyclic AMP; CCPA, chlorocyclopentyl adenosine; CTP, cytosine triphosphate; IP_3, inosine triphosphate; Ip_5I, di-inosine pentaphosphate; 2-MeSADP, 2-methylthio ADP; 2-MeSATP, 2-methylthio ATP; NECA, 5'-*N*-ethylcarboxamido adenosine; PLC, phospholipase C; RB2, reactive blue 2; P2X receptor subtype agonist potencies based on rat preparations, while P1 and P2Y receptor subtype agonist potencies are based on human preparations

Compliance with Ethical Standards

Conflicts of Interest The author declares that he has no conflicts of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by the author.

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