Protein A001684
- Protein Overview
- XML Export

Author-entered Data
V1.0, Peer Reviewed
Published 27 Sep 2006
- Abstract
- Full Text
- Network Map
- States
- Transitions
- Functions
- Protein Classes

Automated Data
Not Reviewed
As At Publication
- Sequence
- Interactions
- Pathways
- Domains & Motifs
- Protein Structure
- Orthologs

Automated Data
Not Reviewed
Latest from 1 Dec 2008
- Sequence
- Interactions
- Pathways
- Domains & Motifs
- Protein Structure
- Orthologs
- Blast Data

UCSD-Nature Molecule Pages
Published online: 27 Sep 2006 | doi:10.1038/mp.a001684.01

Nucleotide receptor P2x4

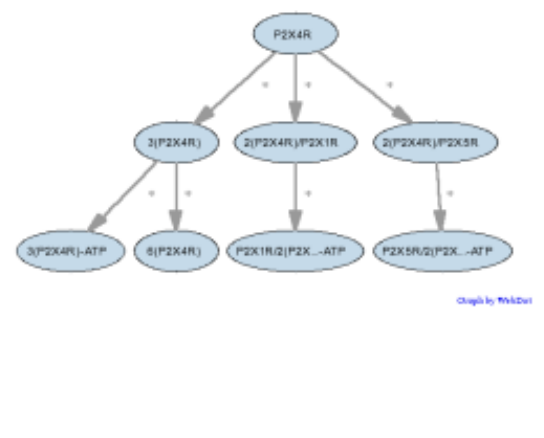
Xuenong Bo, Geoff Burnstock, Bruce T Liang

Dept Cardiol and Vasc Biol, University of Connecticut Health Center, CT 06030-1601, US.
Correspondence should be addressed to Bruce T Liang: bliang@uchc.edu

full summary text
open help browser

The $P2X_4$ receptor is a cation-selective channel capable of permeating Na^+, K^+ and Ca^{2+}. Most of the data available refer to the rat $P2X_4$ receptor, which shares a high identity with the mouse $P2X_4$ receptor. The calcium permeability is relatively high; calcium contributes 8% of the total current through the human $P2X_4$ receptor in the presence of 1.8 mM extracellular calcium. When the ligand ATP is present continuously (for example 50–100 s at 100 •M ATP) in the presence of a low extracellular calcium concentration, the $P2X_4$ receptor becomes more permeable to larger cations such as *N*-methyl-D-glucamine. $P2X_4$ receptors show a unitary conductance of about 9 pS. Both the current amplitude and the mean open times are reduced by Mg^{2+} ions.

Alternative names for this molecule: ATP-gated ion channel subunit P2X4; Nucleotide receptor P2x4; P2rx4; P2X purinoceptor 4; P2x purinoceptor subunit 4; P2X(4) receptor; P2X4; P2X4 receptor; Purinergic receptor P2X, ligand-gated ion channel 4



This molecule exists in 8 states, has 7 transitions between these states, has 3 receptor functions and has 3 channel functions.

View high resolution network map

UCSD-Nature Molecule Pages
Published online: 27 Sep 2006 | doi:10.1038/mp.a001684.01

open help browser

Nucleotide receptor P2x4

Xuenong Bo, Geoff Burnstock, Bruce T Liang

Dept Cardiol and Vasc Biol, University of Connecticut Health Center, CT 06030-1601, US.
Correspondence should be addressed to Bruce T Liang: bliang@uchc.edu

Protein Function

Channel transport function, kinetics

The $P2X_4$ receptor is a cation-selective channel capable of permeating Na^+, K^+ and Ca^{2+}. Most of the data available refer to the rat $P2X_4$ receptor, which shares a high identity with the mouse $P2X_4$ receptor. The calcium permeability is relatively high; calcium contributes 8% of the total current through the human $P2X_4$ receptor in the presence of 1.8 mM extracellular calcium. When the ligand ATP is present continuously (for example 50–100 s at 100 •M ATP) in the presence of a low extracellular calcium concentration, the $P2X_4$ receptor becomes more permeable to larger cations such as *N*-methyl-D-glucamine. $P2X_4$ receptors show a unitary conductance of about 9 pS. Both the current amplitude and the mean open times are reduced by Mg^{2+} ions.

PM ID	Authors	Title	Journal	Pub Date
9016352	Garcia-Guzman M, Soto F, Gomez-Hernandez JM, Lund PE, Stühmer W	Characterization of recombinant human P2X4 receptor reveals pharmacological differences to the rat homologue.	Mol Pharmacol, 51, 1	Jan 1997
10204538	Khakh BS, Bao XR, Labarca C, Lester HA	Neuronal P2X transmitter-gated cation channels change their ion selectivity in seconds.	Nat Neurosci, 2, 4	Apr 1999
10688055	Negulyaev YA, Markwardt F	Block by extracellular Mg2+ of single human purinergic P2X4 receptor channels expressed in human embryonic kidney cells.	Neurosci Lett, 279, 3	4 Feb 2000
10204537	Virginio C, MacKenzie A, Rassendren FA, North RA, Surprenant A	Pore dilation of neuronal P2X receptor channels.	Nat Neurosci, 2, 4	Apr 1999

Regulation of Activity

Modulation by ions such as protons, copper, zinc, Mg^{2+}, or molecules such as cibacron blue and ivermectin

Decreasing the extracellular pH decreases the potency and, in some reports, the maximal ATP-activated current amplitude as well. The current–voltage relationship of the ATP-activated current is not affected by the pH. Mutagenesis of histidine 286 to alanine completely abrogates the sensitivity to pH, whereas mutagenesis of the other three histidine residues has no effect on the pH sensitivity. Zinc can enhance the ATP-activated current through the rat $P2X_4$ receptor with a leftward shift of the dose–response curve. This zinc-induced increase in ATP potency occurs in a voltage-independent manner. Copper ions, in contrast, inhibit the ATP-evoked current, decreasing the maximal current without altering the EC_{50}. Mutagenesis of histidine 140 to alanine abrogates the copper-induced inhibition of the $P2X_4$ current. Mutation of histidine 241 to alanine in both rat and human $P2X_4$ receptors enhances sensitivity to the antagonists suramin and pyridoxal-phosphate-6-azophenyl-2′,4′-disulphonic acid (PPADS). Extracellular magnesium decreases the mean open time of the single human $P2X_4$ channel without affecting the mean closed time, possibly by means of an open-channel block near or at the exterior surface of the channel pore. Other ions such as cobalt, barium, and manganese do not alter the ATP-activated current through the $P2X_4$ receptor, although one recent report showed that cobalt can cause a long-lasting and irreversible activating effect on the $P2X_4$ receptor-mediated current. Ivermectin is a positive allosteric modulator of current mediated by $P2X_4$ receptor but not of that mediated by $P2X_2$, $P2X_3$, $P2X_2/P2X_3$, or $P2X_7$ receptors. The unique ability of ivermectin to potentiate only the $P2X_4$ receptor-mediated current distinguishes the $P2X_4$ receptor from other channels and can identify the presence or absence of this

receptor in the native tissue. Another example of a positive modulator, possibly also through an allosteric mechanism, is cibacron blue, which increases the potency with which ATP evokes the current mediated through the $P2X_4$ receptor. Ethanol can inhibit the $P2X_4$ current, providing a possible explanation for the action of ethanol in the brain, where the $P2X_4$ receptor is the most abundant P2X receptor.

PM ID	Authors	Title	Journal	Pub Date
10737610	Acuña-Castillo C, Morales B, Huidobro-Toro JP	Zinc and copper modulate differentially the P2X4 receptor.	J Neurochem, 74, 4	Apr 2000
10718748	Clarke CE, Benham CD, Bridges A, George AR, Meadows HJ	Mutation of histidine 286 of the human P2X4 purinoceptor removes extracellular pH sensitivity.	J Physiol, 523 Pt 3	15 Mar 2000
15629187	Coddou C, Lorca RA, Acuña-Castillo C, Grauso M, Rassendren F, Huidobro-Toro JP	Heavy metals modulate the activity of the purinergic P2X4 receptor.	Toxicol Appl Pharmacol, 202, 2	15 Jan 2005
12819199	Coddou C, Morales B, González J, Grauso M, Gordillo F, Bull P, Rassendren F, Huidobro-Toro JP	Histidine 140 plays a key role in the inhibitory modulation of the P2X4 nucleotide receptor by copper but not zinc.	J Biol Chem, 278, 38	19 Sep 2003
10688055	Negulyaev YA, Markwardt F	Block by extracellular Mg2 + of single human purinergic P2X4 receptor channels expressed in human embryonic kidney cells.	Neurosci Lett, 279, 3	4 Feb 2000
10188989	Wildman SS, King BF, Burnstock G	Modulation of ATP-responses at recombinant rP2X4 receptors by extracellular pH and zinc.	Br J Pharmacol, 126, 3	Feb 1999
10903981	Xiong K, Li C, Weight FF	Inhibition by ethanol of rat P2X(4) receptors expressed in Xenopus oocytes.	Br J Pharmacol, 130, 6	Jul 2000
10322050	Xiong K, Peoples RW, Montgomery JP, Chiang Y, Stewart RR, Weight FF, Li C	Differential modulation by copper and zinc of P2X2 and P2X4 receptor function.	J Neurophysiol, 81, 5	May 1999
15331152	Xiong K, Stewart RR, Weight FF, Li C	Role of extracellular histidines in antagonist sensitivity of the rat P2X4 receptor.	Neurosci Lett, 367, 2	2 Sep 2004

Interactions with Ligands and Other Proteins

Subunit organization

The P2X subunits seem to be arranged as a trimer that forms the basis for a functional channel. The channel may thus be a trimer or a hexamer. Each subunit has intracellular amino and carboxy termini and two transmembrane (TM) domains. Charged residues close to TM1 and TM2 have a function in ATP binding. The subunits are arranged in a head-to-tail orientation in the trimeric structure. Crosslinking of purified $P2X_1$ or $P2X_3$ receptors yields dimers and trimers, which is consistent with trimers as an essential structural element of these P2X receptors. When blue native PAGE was used, these P2X receptors migrated entirely as non-covalently linked homotrimers. With the use of an entirely different approach of injecting concatenated complementary DNAs encoding trimeric, tetrameric, or hexameric $P2X_2$ receptors in oocytes, a similar conclusion was drawn that not four but maximally three subunits form the P2X channel. This was based on the observation that only cDNA encoding the concatenated trimer resulted in inhibition by [2-(trimethylammonium)ethyl] methanethiosulfonate (MTSET), which was linearly correlated with the number of mutant $P2X_2$ subunits independently of the position of the mutant subunit in the trimer. The putative amino-acid residue Phe 230 is important in binding the adenine ring of ATP, and Lys 190, His 286, and Arg 278 residues coordinate the interaction of the negatively charged α-, β-, and γ-phosphate groups, respectively.

Ligands: agonists, antagonists, allosteric modulator

Homomeric $P2X_4$ receptors are activated by ATP and 2-methylthioATP but not by α,β-methylene-ATP (α, β-meATP). α,β-meATP and adenosine-5′-tetraphosphate (APA4) are partial agonists at the human and

mouse $P2X_4$ receptor but not at the rat receptor. $P2X_4$ receptor is relatively insensitive to blockade by suramin and PPADS, which makes it unique among the P2X receptor subtypes. The human and mouse $P2X_4$ receptors, however, are both more sensitive than the rat $P2X_4$ receptor to blockade by PPADS. The human $P2X_4$ receptor is also more sensitive than the rat or mouse $P2X_4$ receptor to suramin, which is accounted for by the presence of lysine (human) rather than glutamine (rat and mouse) at position 78.

Interacting proteins

Both $P2X_1$ and $P2X_5$ receptors have been shown to form heteromers with the $P2X_4$ receptor, whereas $P2X_1$ and $P2X_5$ receptors can interact and form a functional heteromer. The $P2X_4$ and $P2X_6$ receptors have also been shown to coimmunoprecipitate when they both expressed in either oocytes or HEK-293 cells. There is a small difference between the extent of α,β-meATP-induced stimulation of the current at the homomeric $P2X_4$ and that at the $P2X_4/P2X_6$ receptors. However, the heteromeric rat $P2X_4/P2X_6$ receptor is more sensitive than the homomeric rat $P2X_4$ receptor to blockade by suramin, PPADS and Reactive Blue-2. A limitation of the coexpression study is that both sets of homomers, in addition to the coimmunoprecipitated heteromer, are also likely to be present.

PM ID	Authors	Title	Journal	Pub Date
10884596	Afework M, Burnstock G	Age-related changes in the localization of P2X (nucleotide) receptors in the rat adrenal gland.	Int J Dev Neurosci, 18, 6	Oct 2000
9016352	Garcia-Guzman M, Soto F, Gomez-Hernandez JM, Lund PE, Stühmer W	Characterization of recombinant human P2X4 receptor reveals pharmacological differences to the rat homologue.	Mol Pharmacol, 51, 1	Jan 1997
11341329	Gartland A, Hipskind RA, Gallagher JA, Bowler WB	Expression of a P2X7 receptor by a subpopulation of human osteoblasts.	J Bone Miner Res, 16, 5	May 2001
14523092	Jiang LH, Kim M, Spelta V, Bo X, Surprenant A, North RA	Subunit arrangement in P2X receptors.	J Neurosci, 23, 26	1 Oct 2003
10694247	Jones CA, Chessell IP, Simon J, Barnard EA, Miller KJ, Michel AD, Humphrey PP	Functional characterization of the P2X(4) receptor orthologues.	Br J Pharmacol, 129, 2	Jan 2000
10460235	Khakh BS, Proctor WR, Dunwiddie TV, Labarca C, Lester HA	Allosteric control of gating and kinetics at P2X(4) receptor channels.	J Neurosci, 19, 17	1 Sep 1999
10864944	King BF, Townsend-Nicholson A, Wildman SS, Thomas T, Spyer KM, Burnstock G	Coexpression of rat P2X2 and P2X6 subunits in Xenopus oocytes.	J Neurosci, 20, 13	1 Jul 2000
9736638	Lê KT, Babinski K, Séguéla P	Central P2X4 and P2X6 channel subunits coassemble into a novel heteromeric ATP receptor.	J Neurosci, 18, 18	15 Sep 1998
10336430	Lê KT, Boué-Grabot E, Archambault V, Séguéla P	Functional and biochemical evidence for heteromeric ATP-gated channels composed of P2X1 and P2X5 subunits.	J Biol Chem, 274, 22	28 May 1999
9886680	Miller KJ, Michel AD, Chessell IP, Humphrey PP	Cibacron blue allosterically modulates the rat P2X4 receptor.	Neuropharmacology, 37, 12	Dec 1998
9606184	Nicke A, Bäumert HG, Rettinger J, Eichele A, Lambrecht G, Mutschler E, Schmalzing G	P2X1 and P2X3 receptors form stable trimers: a novel structural motif of ligand-gated ion channels.	EMBO J, 17, 11	1 Jun 1998
15686495	Nicke A, Kerschensteiner D, Soto F	Biochemical and functional evidence for heteromeric assembly of P2X1 and P2X4 subunits.	J Neurochem, 92, 4	Feb 2005
12447447	Omatsu-Kanbe M, Isono T, Matsuura H	Multiple P2 receptors contribute to a transient increase in intracellular Ca2+ concentration in ATP-stimulated rat brown adipocytes.	Exp Physiol, 87, 6	Nov 2002

10531403	Stoop R, Thomas S, Rassendren F, Kawashima E, Buell G, Surprenant A, North RA	Contribution of individual subunits to the multimeric P2X(2) receptor: estimates based on methanethiosulfonate block at T336C.	Mol Pharmacol, 56, 5	Nov 1999
10037762	Torres GE, Egan TM, Voigt MM	Hetero-oligomeric assembly of P2X receptor subunits. Specificities exist with regard to possible partners.	J Biol Chem, 274, 10	5 Mar 1999
15632318	Yan Z, Liang Z, Tomic M, Obsil T, Stojilkovic SS	Molecular determinants of the agonist binding domain of a P2X receptor channel.	Mol Pharmacol, 67, 4	Apr 2005

Regulation of Concentration

Expression of the $P2X_4$ receptor has been shown to be increased after spinal cord injury. After nerve injury, the receptor expression increases strikingly in microglia but not in neurons or astrocytes. Blockade by $P2X_4$ receptor antagonist and $P2X_4$ receptor antisense oligonucleotide suppressed tactile allodynia, which is pain hypersensitivity after nerve damage. Intraspinal administration of microglia with increased $P2X_4$ receptor expression reproduced tactile allodynia in naive animals. Thus, blockade of $P2X_4$ receptors in microglia may represent a new approach to the treatment of pain caused by nerve injury.

PM ID	Authors	Title	Journal	Pub Date
12917686	Tsuda M, Shigemoto-Mogami Y, Koizumi S, Mizokoshi A, Kohsaka S, Salter MW, Inoue K	P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury.	Nature, 424, 6950	14 Aug 2003

Subcellular Localization

$P2X_4$ receptor is located on the cell surface in the plasma membrane. Patch-clamp recording of intact murine cardiac ventricular myocytes showed that 2-methylthioATP can evoke a current with a current–voltage relationship and a reverse potential similar to those of a current in $P2X_4$ receptor-overexpressing mouse ventricular myocytes. That both ivermectin and zinc were able to potentiate the 2-methylthioATP-induced current in the wild-type murine myocyte provides further evidence for the concept that $P2X_4$ receptor is probably an important subunit of the native P2X receptor on the surface of the heart cell.

In rabbit osteoclasts, the $P2X_4$ receptor also seems to mediate an ATP-induced non-selective cation current. This is consistent with the functional expression of the $P2X_4$ receptor on the surface of osteoclasts.

PM ID	Authors	Title	Journal	Pub Date
10564660	Naemsch LN, Weidema AF, Sims SM, Underhill TM, Dixon SJ	P2X(4) purinoceptors mediate an ATP-activated, non-selective cation current in rabbit osteoclasts.	J Cell Sci, 112 (Pt 23)	Dec 1999
16449800	Shen JB, Pappano AJ, Liang BT	Extracellular ATP-stimulated current in wild-type and P2X4 receptor transgenic mouse ventricular myocytes: implications for a cardiac physiologic role of P2X4 receptors.	FASEB J, 20, 2	Feb 2006

Major Sites of Expression

Heart

ATP is released as co-transmitter from the sympathetic nerve endings and also from platelets, erythrocytes, endothelium, and possibly hypoxic myocardium within the circulatory system. The P2X receptors mediate ATP-stimulated contractility of the cardiac myocyte and intact heart. $P2X_4$ receptor is expressed in adult rat and mouse cardiac myocytes by immunoblotting of purified myocyte preparations and by immunohistochemistry. Intercalated discs are strongly positive for $P2X_4$ receptors. messenger RNA for $P2X_4$ receptor is also found in intact human heart. The $P2X_4$ receptor is probably an important subunit of the P2X receptor channel that mediates the contractility effect of ATP. This is based on the observation that the contractile effect is mimicked by 2-methylthioATP but not α,β-meATP and is relatively insensitive to blockade by suramin, features similar to those of the heterologously expressed $P2X_4$ receptor. In the chick embryo cardiac myocyte, the native $P2X_4$ receptor exists in glycosylated and nonglycosylated forms. Only the glycosylated $P2X_4$ receptor is expressed on the cell surface, and this is much more easily extracted by various detergents or aqueous media. Treatment of these cardiac myocytes with antisense oligonucleotides specific to the 5′region of the chick $P2X_4$ receptor abrogates the P2X agonist-stimulated increase in calcium influx and in myocyte contractile amplitude.

Cardiac transgenic expression of the human $P2X_4$ receptor results in enhanced basal contractility with no associated heart pathology. This suggests a physiological function for the $P2X_4$ receptor, that of stimulating cardiac contractility. Crossing the $P2X_4$ receptor transgenic mouse with the calsequestrin (CSQ) model of hypertrophy and heart failure more than doubled the lifespan. The prolonged survival of the binary CSQ/$P2X_4$ receptor mouse is associated with an improved ratio of left ventricular weight to body weight and a restored β-adrenergic responsiveness. The beneficial phenotype of the binary mouse correlates with improved left ventricular developed pressure and $\pm\Delta Pressure/\Delta time$. The enhanced cardiac performance is manifested in young binary animals and persists in older animals. These data suggest that increased contractility probably underlies the survival benefit from overexpression of the $P2X_4$ receptor. Increased expression or activation of this receptor may represent a new approach in the therapy of heart failure.

Vasculature

The $P2X_4$ receptor is expressed in human endothelial cells cultured from umbilical vein, aorta, pulmonary artery, and skin microvessels. The use of competitive polymerase chain reaction (PCR) demonstrated that the expression of $P2X_4$ receptor mRNA is much greater than the expression of the $P2X_1$, $P2X_3$, $P2X_5$, and $P2X_7$ subunits. Antisense oligonucleotides specifically targeted against the human $P2X_4$ receptor decreased the $P2X_4$ receptor mRNA and protein, and attenuated the ATP-evoked calcium influx in human umbilical vein endothelial cells (HUVECs). The $P2X_4$ receptor co-localizes with VE-cadherin at the endothelial cell–cell junction exclusively and can be coimmunoprecipitated with VE-cadherin. The $P2X_6$ receptor is also co-localized there; together these molecules may regulate endothelial cell–cell interaction and adhesiveness. An SP1 transcription-factor-binding site on the 5' promoter region of the human $P2X_4$ receptor can mediate an increase in the transcription for $P2X_4$ receptor mRNA. Shear stress can decrease the amount of SP1 and thus results in a decreased production of $P2X_4$ receptor mRNA.

Both pharmacological evidence and evidence based on reverse transcriptase mediated PCR (RT–PCR) suggest the expression of $P2X_4$ receptor in vascular smooth muscle cells, although $P2X_4$ receptor is generally less abundant in vascular smooth muscle than in endothelial cells. In rat vascular smooth muscle cells from coronary arteries, RT–PCR-based mRNA expression for the $P2X_4$ receptor (along with that for $P2X_1$ and $P2X_2$ receptors) is found exclusively in the muscle layer adjacent to the internal elastic lamina). In rat hepatic mesentery arteries, the $P2X_4$ receptor participates in nerve-mediated vasoconstriction, whereas another P2X receptor, the $P2X_1$ receptor, is the principal subtype that mediates calcium signaling in portal vein vascular myocytes.

Neurons and glial cells

$P2X_4$ receptors are widely distributed in both peripheral and central nervous systems. In the peripheral nervous system, $P2X_4$ receptors are present in the neurons in many different ganglia, including dorsal root, superior cervical, pelvic, trigeminal, mesenteric, enteric, olfactory and retinal. In the central nervous system, $P2X_4$ receptors are highly expressed in Purkinje cells in the cerebellum. They are also present in hippocampus, olfactory bulb, and brainstem. Although P2X receptor-mediated responses have been observed in many different types of neuron, no specific function has been attributed to it. One reason is that no specific agonist or antagonist is available for the identification of $P2X_4$-receptor-mediated responses; another is the recent reports supporting the hypothesis that native P2X receptors are trimeric, and probably heteromeric. Hence, $P2X_4$ receptor may be a subunit in the native P2X receptor. $P2X_4$ receptors are also expressed on astrocytes and Muller cells. The $P2X_4$ receptor on hyperactive microglia in the spinal cord was reported to be responsible for tactile allodynia after peripheral nerve injury.

Immune cells

$P2X_4$ receptors are found in macrophages from rat and humans. In rat alveolar macrophages, $P2X_4$ receptors mediate the ATP-induced inward current. Similarly, $P2X_4$ receptors probably mediate the ATP-induced inward current and transient depolarization in human monocyte-derived macrophages. A membrane potential oscillation then results from calcium-activated potassium channels in these cells. Together with a P2Y receptor-mediated increase in interleukin-6 (IL-6) transcription, ATP released from inflamed or metabolically compromised cells may be a ‘danger signal’ in activating the immune system. Of the other P2X receptor subtypes, the $P2X_7$ receptor is found in human eosinophils, promyelocytes, and neutrophils, and has been proposed as the main functional P2X receptor in these cells.

Epithelial cells

Epithelial cells from animal and human airway express several P2 purinergic receptors, including both the P2X and P2Y receptors. Rat trachea epithelial cells expressed mRNAs for $P2X_4$ receptors and $P2X_7$ receptors. In cystic fibrosis (CF) and non-cystic fibrosis (non-CF) human epithelia, both $P2X_4$ and $P2X_5$ receptors were the predominant genes expressed. P2X receptor agonists such as 2′- and 3′-*O*-(4-benzoyl-benzoyl)-ATP (BzBz-ATP) or α,β-meATP were able to stimulate transepithelial Cl^- transport in both wild-type and cystic fibrosis transmembrane conductance regulator (CFTR)-null mice. In both CF and non-CF human airway epithelial cells, the $P2X_4$ receptor channel is the major entry channel for calcium and is stimulated by extracellular ATP. The sustained increase in cellular calcium mediated through the $P2X_4$ receptors may result in Cl^- secretion in both CF and non-CF epithelia, suggesting a potential novel therapeutic target.

Endocrine and bone cells

Multiple P2 purinergic receptors a\re expressed in bone cells, where they modulate osteoblast proliferation, bone formation, osteoclast formation, and osteoclast-mediated resorption pit formation. $P2X_7$ receptor is expressed on the osteoclast, although the $P2X_2$ receptor seemed to be important in bone resorption by osteoclasts. The $P2X_7$ receptor is functionally expressed in a subpopulation of human osteoblasts and can mediate ATP-induced apoptosis. In cells of endocrine tissues, $P2X_4$ receptors are expressed in aged rat adrenal, thyroid follicular, and brown adipose cells. In anterior pituitary cells, the $P2X_4$ receptor is the major calcium entry pathway for prolactin secretion.

PM ID	Authors	Title	Journal	Pub Date
10863025	Barden JA, Bennett MR	Distribution of P2X purinoceptor clusters on individual rat dorsal root ganglion cells.	Neurosci Lett, 287, 3	30 Jun 2000
10570953	Berchtold S, Ogilvie AL, Bogdan C, Mühl-Zürbes P, Ogilvie A, Schuler G, Steinkasserer A	Human monocyte derived dendritic cells express functional P2X and P2Y receptors as well as ecto-nucleotidases.	FEBS Lett, 458, 3	24 Sep 1999
9489506	Bogdanov Y, Rubino A, Burnstock G	Characterisation of subtypes of the P2X and P2Y families of ATP receptors in the foetal human heart.	Life Sci, 62, 8	1998
12970084	Bowler JW, Bailey RJ, North RA, Surprenant A	P2X4, P2Y1 and P2Y2 receptors on rat alveolar macrophages.	Br J Pharmacol, 140, 3	Oct 2003
12845522	Bo X, Kim M, Nori SL, Schoepfer R, Burnstock G, North RA	Tissue distribution of P2X4 receptors studied with an ectodomain antibody.	Cell Tissue Res, 313, 2	Aug 2003
11119707	Ferrari D, Idzko M, Dichmann S, Purlis D, Virchow C, Norgauer J, Chiozzi P, Di Virgilio F, Luttmann W	P2 purinergic receptors of human eosinophils: characterization and coupling to oxygen radical production.	FEBS Lett, 486, 3	15 Dec 2000
12898701	Fumagalli M, Brambilla R, D'Ambrosi N, Volonté C, Matteoli M, Verderio C, Abbracchio MP	Nucleotide-mediated calcium signaling in rat cortical astrocytes: Role of P2X and P2Y receptors.	Glia, 43, 3	Sep 2003
11430696	Glass R, Burnstock G	Immunohistochemical identification of cells expressing ATP-gated cation channels (P2X receptors) in the adult rat thyroid.	J Anat, 198, Pt 5	May 2001
12088286	Glass R, Loesch A, Bodin P, Burnstock G	P2X4 and P2X6 receptors associate with VE-cadherin in human endothelial cells.	Cell Mol Life Sci, 59, 5	May 2002
11742801	Gorodeski GI	Expression, regulation, and function of P2X(4) purinergic receptor in human cervical epithelial cells.	Am J Physiol Cell Physiol, 282, 1	Jan 2002
15194822	Hanley PJ, Musset B, Renigunta V, Limberg SH, Dalpke AH, Sus R, Heeg KM, Preisig-Müller R, Daut J	Extracellular ATP induces oscillations of intracellular Ca2+ and membrane potential and promotes transcription of IL-6 in macrophages.	Proc Natl Acad Sci U S A, 101, 25	22 Jun 2004
12970352	He ML, Gonzalez-Iglesias AE, Stojilkovic SS	Role of nucleotide P2 receptors in calcium signaling and prolactin release in pituitary lactotrophs.	J Biol Chem, 278, 47	21 Nov 2003
11033445	Hoebertz A, Townsend-Nicholson A, Glass R, Burnstock G, Arnett TR	Expression of P2 receptors in bone and cultured bone cells.	Bone, 27, 4	Oct 2000
11606481	Hu B, Mei QB, Yao XJ, Smith E, Barry WH, Liang BT	A novel contractile phenotype with cardiac transgenic expression of the human P2X4 receptor.	FASEB J, 15, 14	Dec 2001

11864978	Hu B, Senkler C, Yang A, Soto F, Liang BT	P2X4 receptor is a glycosylated cardiac receptor mediating a positive inotropic response to ATP.	J Biol Chem, 277, 18	3 May 2002
11299224	Korenaga R, Yamamoto K, Ohura N, Sokabe T, Kamiya A, Ando J	Sp1-mediated downregulation of P2X4 receptor gene transcription in endothelial cells exposed to shear stress.	Am J Physiol Heart Circ Physiol, 280, 5	May 2001
11571780	Kukley M, Barden JA, Steinhäuser C, Jabs R	Distribution of P2X receptors on astrocytes in juvenile rat hippocampus.	Glia, 36, 1	Oct 2001
10446426	Marino A, Rodrig Y, Métioui M, Lagneaux L, Alzola E, Fernández M, Fogarty DJ, Matute C, Moran A, Dehaye JP	Regulation by P2 agonists of the intracellular calcium concentration in epithelial cells freshly isolated from rat trachea.	Biochim Biophys Acta, 1439, 3	18 Aug 1999
11406501	Mei Q, Liang BT	P2 purinergic receptor activation enhances cardiac contractility in isolated rat and mouse hearts.	Am J Physiol Heart Circ Physiol, 281, 1	Jul 2001
11600670	Mironneau J, Coussin F, Morel JL, Barbot C, Jeyakumar LH, Fleischer S, Mironneau C	Calcium signalling through nucleotide receptor P2X1 in rat portal vein myocytes.	J Physiol, 536, Pt 2	15 Oct 2001
9647332	Nori S, Fumagalli L, Bo X, Bogdanov Y, Burnstock G	Coexpression of mRNAs for P2X1, P2X2 and P2X4 receptors in rat vascular smooth muscle: an in situ hybridization and RT-PCR study.	J Vasc Res, 35, 3	1998 May-Jun
9723951	Phillips JK, McLean AJ, Hill CE	Receptors involved in nerve-mediated vasoconstriction in small arteries of the rat hepatic mesentery.	Br J Pharmacol, 124, 7	Aug 1998
12003818	Ramirez AN, Kunze DL	P2X purinergic receptor channel expression and function in bovine aortic endothelium.	Am J Physiol Heart Circ Physiol, 282, 6	Jun 2002
11160443	Rubio ME, Soto F	Distinct Localization of P2X receptors at excitatory postsynaptic specializations.	J Neurosci, 21, 2	15 Jan 2001
11788340	Schwiebert LM, Rice WC, Kudlow BA, Taylor AL, Schwiebert EM	Extracellular ATP signaling and P2X nucleotide receptors in monolayers of primary human vascular endothelial cells.	Am J Physiol Cell Physiol, 282, 2	Feb 2002
11359833	Suh BC, Kim JS, Namgung U, Ha H, Kim KT	P2X7 nucleotide receptor mediation of membrane pore formation and superoxide generation in human promyelocytes and neutrophils.	J Immunol, 166, 11	1 Jun 2001
9037385	Tanaka J, Murate M, Wang CZ, Seino S, Iwanaga T	Cellular distribution of the P2X4 ATP receptor mRNA in the brain and non-neuronal organs of rats.	Arch Histol Cytol, 59, 5	Dec 1996
10510328	Taylor AL, Schwiebert LM, Smith JJ, King C, Jones JR, Sorscher EJ, Schwiebert EM	Epithelial P2X purinergic receptor channel expression and function.	J Clin Invest, 104, 7	Oct 1999
12917686	Tsuda M, Shigemoto-Mogami Y, Koizumi S, Mizokoshi A, Kohsaka S, Salter MW, Inoue K	P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury.	Nature, 424, 6950	14 Aug 2003
12495655	Valdecantos P, Briones R, Moya P, Germain A, Huidobro-Toro JP	Pharmacological identification of P2X1, P2X4 and P2X7 nucleotide receptors in the smooth muscles of human umbilical cord and chorionic blood vessels.	Placenta, 24, 1	Jan 2003

12451317	Wang L, Karlsson L, Moses S, Hultgårdh-Nilsson A, Andersson M, Borna C, Gudbjartsson T, Jern S, Erlinge D	P2 receptor expression profiles in human vascular smooth muscle and endothelial cells.	J Cardiovasc Pharmacol, 40, 6	Dec 2002
9853714	Xiang Z, Bo X, Burnstock G	Localization of ATP-gated P2X receptor immunoreactivity in rat sensory and sympathetic ganglia.	Neurosci Lett, 256, 2	6 Nov 1998
10899068	Yamamoto K, Korenaga R, Kamiya A, Qi Z, Sokabe M, Ando J	P2X(4) receptors mediate ATP-induced calcium influx in human vascular endothelial cells.	Am J Physiol Heart Circ Physiol, 279, 1	Jul 2000
15130891	Yang A, Sonin D, Jones L, Barry WH, Liang BT	A beneficial role of cardiac P2X4 receptors in heart failure: rescue of the calsequestrin overexpression model of cardiomyopathy.	Am J Physiol Heart Circ Physiol, 287, 3	Sep 2004
9831914	Zhong Y, Dunn PM, Xiang Z, Bo X, Burnstock G	Pharmacological and molecular characterization of P2X receptors in rat pelvic ganglion neurons.	Br J Pharmacol, 125, 4	Oct 1998
12566439	Zsembery A, Boyce AT, Liang L, Peti-Peterdi J, Bell PD, Schwiebert EM	Sustained calcium entry through P2X nucleotide receptor channels in human airway epithelial cells.	J Biol Chem, 278, 15	11 Apr 2003

Phenotypes

Phenotypes are specific to the functions of $P2X_4$ receptors in different tissues, as described in the sections on the major sites of expression.

Splice Variants

$P2X_4$ receptor orthologs have been cloned from rat, mouse, human, chick, *Xenopus laevis*, and zebrafish. Partial $P2X_4$ receptor cDNA sequences have also been identified in rabbit, guinea-pig, dog, and cow. Mouse $P2X_4$ receptor shares 94% identity with rat $P2X_4$ and 87% with human $P2X_4$, and all three orthologs have 388 amino acids. Chick $P2X_4$ receptor has 385 (384 in another clone) amino-acid residues and shares about 75% identity with the mammalian $P2X_4$ receptor. *Xenopus* $P2X_4$ receptor has 391 residues and shares 67% identity with the rat $P2X_4$ receptor. Zebrafish has two $P2X_4$ receptor paralogs (as a result of duplicated genes for the receptor). These two paralogs share only 61% identity between them. Zebrafish $P2X_{4.1}$ has 389 residues and shares 51% identity with rat $P2X_4$. All the $P2X_4$ receptor orthologs in mammalian, bird, amphibian, and fish have the conserved ten extracellular cysteine residues and many N-glycosylation sites.

Several human $P2X_4$ receptor splice variants have been reported. In one of the alternatively spliced cDNAs, the 5′-untranslated region and the first 90 residues in the coding region of full-length human $P2X_4$ receptor are replaced by a 35-residue coding sequence that is highly homologous with a region of chaparonin proteins in the hsp-90 family. Alternatively spliced RNAs were identified in smooth muscle and brain by RT–PCR. Injection of cRNA of the alternatively spliced variant into *Xenopus* oocytes resulted in no ATP-gated currents. Two other $P2X_4$ receptor spliced cDNAs have been reported: $P2X_{4b}$ is formed by the insertion of an additional 16 residues near the end of the first transmembrane domain, and $P2X_{4c}$ is formed by deleting a cassette of 130 residues starting from the same position as $P2X_{4b}$. Transfection of $P2X_{4c}$ did not form functional channels in HEK cells. In $P2X_{4b}$-transfected HEK cells, small, inconsistent ATP-evoked responses are detected. The mouse spliced variant has already been described.

PM ID	Authors	Title	Journal	Pub Date
10515189	Carpenter D, Meadows HJ, Brough S, Chapman G, Clarke C, Coldwell M, Davis R, Harrison D, Meakin J, McHale M, Rice SQ, Tomlinson WJ, Wood M, Sanger GJ	Site-specific splice variation of the human P2X4 receptor.	Neurosci Lett, 273, 3	8 Oct 1999
9511769	Dhulipala PD, Wang YX, Kotlikoff MI	The human P2X4 receptor gene is alternatively spliced.	Gene, 207, 2	30 Jan 1998

12127972	Diaz-Hernandez M, Cox JA, Migita K, Haines W, Egan TM, Voigt MM	Cloning and characterization of two novel zebrafish P2X receptor subunits.	Biochem Biophys Res Commun, 295, 4	26 Jul 2002
11334629	Juranka PF, Haghighi AP, Gaertner T, Cooper E, Morris CE	Molecular cloning and functional expression of Xenopus laevis oocyte ATP-activated P2X4 channels.	Biochim Biophys Acta, 1512, 1	2 May 2001
14580944	Kucenas S, Li Z, Cox JA, Egan TM, Voigt MM	Molecular characterization of the zebrafish P2X receptor subunit gene family.	Neuroscience, 121, 4	2003
10550989	Ruppelt A, Liang BT, Soto F	Cloning, functional characterization and developmental expression of a P2X receptor from chick embryo.	Prog Brain Res, 120	1999
9931497	Townsend-Nicholson A, King BF, Wildman SS, Burnstock G	Molecular cloning, functional characterization and possible cooperativity between the murine P2X4 and P2X4a receptors.	Brain Res Mol Brain Res, 64, 2	5 Feb 1999

Antibodies

Most of the antibodies available for the $P2X_4$ receptor are raised against the C terminus. A monoclonal antibody has also been raised against the ectodomain of the $P2X_4$ receptor (Bo *et al*. 2003).

PM ID	Authors	Title	Journal	Pub Date
12845522	Bo X, Kim M, Nori SL, Schoepfer R, Burnstock G, North RA	Tissue distribution of P2X4 receptors studied with an ectodomain antibody.	Cell Tissue Res, 313, 2	Aug 2003

nature publishing group

Permitted Use of Material

Privacy Policy