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Basal Release of ATP: An Autocrine-Paracrine Mechanism for Cell Regulation

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Abstract

Cells release adenosine triphosphate (ATP), which activates plasma membrane-localized P2X and P2Y receptors and thereby modulates cellular function in an autocrine or paracrine manner. Release of ATP and the subsequent activation of P2 receptors help establish the basal level of activation (sometimes termed “the set point”) for signal transduction pathways and regulate a wide array of responses that include tissue blood flow, ion transport, cell volume regulation, neuronal signaling, and host-pathogen interactions. Basal release and autocrine or paracrine responses to ATP are multifunctional and evolutionarily conserved, and they provide an economical means for the modulation of cell, tissue, and organismal biology.

Introduction

The regulation of cellular function by extracellular hormones, neurotransmitters, nutrients, growth factors, and other factors known as “first messengers” commonly alters the intracellular concentrations of second messengers and, in turn, those of “downstream” signaling components [sometimes termed “third messengers” (1, 2)]. Some cells are also regulated by “inside-out” signaling, whereby cytoplasmic events are transmitted to external ligand-binding domains or receptors (3-5) through bidirectional communication between cells that have ligands and complementary receptors on their plasma membranes (6). The release of intracellular adenosine triphosphate (ATP) and perturbation of function by released ATP is another type of signaling but is less commonly recognized. Such signaling can occur in the same cell that releases ATP (autocrine signaling), on neighboring cells (paracrine signaling), or both.

Evidence for a cellular response to ATP was first noted in the 1920s (7), but even so, the idea that cells could release and respond to released ATP, proposed more than 30 years ago (8), was met with much skepticism (9). Virtually every type of eukaryotic cell releases ATP and has plasma membrane-localized nucleotide-activated (P2) receptors, which implicate ATP and other nucleotides as ubiquitous extracellular modulators of cell function (10, 11). Less well appreciated is the release of ATP under basal conditions and the resulting induction of autocrine and paracrine responses. Basal release of ATP can be increased by minimal perturbation of cells through physical or chemical stimuli. Our focus here is ATP, but cells release other nucleotides [for example, uridine triphosphate (UTP) and related molecules such as uridine diphosphate (UDP) sugars] that have actions akin to those of ATP (12, 13).

Cellular Release of ATP

Multiple mechanisms mediate the release of intracellular ATP in response to mechanical stimulation or extracellular biochemical cues (14). Mechanical stimulation can occur by osmotic swelling or shrinking of cells (15-34), physical perturbation [for example, flow or stretching forces (35-44)], host-pathogen interactions (45-47), or even by changing the extracellular media (48-50). Merely tilting a plate of cells or adding media can induce the release of ATP at sufficient concentrations to trigger cellular signaling pathways (51). Such results imply that numerous—perhaps most—experiments with cultured or isolated cells in which investigators wash cells, replace the extracellular media, or add drugs or other chemicals can promote the release of ATP, which, in turn, alters cellular function by itself or through its metabolic products, such as adenosine (52). Such actions of released ATP are rarely considered in experiments with cultured or isolated cells. Mechanical and chemical stimulation also promotes the release of ATP *in vivo* from skeletal muscle (53), heart (54), and erythrocytes (55) and in the nervous system, including the trigeminal and dorsal root ganglia (56, 57), ventral medulla (58), cochlea (59), and glia (60).

Cellular release of ATP can be detected by many methods, most commonly by luciferase-catalyzed, ATP-dependent generation of light by the substrate luciferin (61). Use of this method is problematic with cells that have substantial amounts of proteases, ATP hydrolytic activity (for example, in granulocytes), or both, and thus alternative assays with different detectors of ATP have been developed (62, 63). Imamura *et al.* described the use of a fluorescence resonance energy transfer (FRET)-based indicator (the ϵ -subunit of the bacterial FoF1-ATP synthase together with cyan and yellow fluorescent proteins) as another approach to detect extracellular ATP (64).

Release of ATP by cells occurs through multiple mechanisms. Early studies suggested that the cystic fibrosis transmembrane regulator (CFTR) was responsible for this release; however, later work indicated that it was more likely that CFTR regulates, rather than mediates, the release of ATP (49, 65, 66). Multiple types of membrane channels mediate ATP release, including connexin and pannexin hemichannels (67, 68), maxi-anion channels (69, 70), volume-regulated anion channels (71, 72), and the P2X₇ receptor (73). Mechanisms for the release of ATP have been recently reviewed (9, 74-76). In addition to release through channels, nonexcitatory cells can release ATP by exocytotic mechanisms in response to biochemical and mechanical stimuli, much as neurons do on depolarization (77-79).

Receptor Targets of Extracellular ATP

Extracellular ATP exerts a wide range of cellular effects by activating plasma membrane-localized receptors that belong to one of two classes: heterotrimeric guanine nucleotide-binding protein (G protein)-coupled P2Y receptors and ion channel P2X receptors. Mammalian cells have eight P2Y receptor subtypes, two of which are preferentially activated by ATP (P2Y₂ and P2Y₁₁), although ATP or ATP-derived products, such as adenosine diphosphate (ADP), interact with other P2Y receptors (10) (Table 1). P2Y receptors regulate signal transduction through the heterotrimeric G proteins of the G_i, G_{q/11}, and G_s families (10).

By contrast with the selectivity of P2Y receptors for different nucleotides, ATP activates all of the seven mammalian P2X receptors (11). P2X receptors have three subunits that are assembled in homomeric or heteromeric complexes (80, 81). One P2X receptor, P2X₄ from zebrafish, has been crystallized and has three intersubunit binding sites for ATP; occupancy by ATP appears to promote subunit rearrangement and opens the ion channel (82). P2Y receptors have not been crystallized, but the use of other techniques has led to predictions regarding their three-dimensional structures (83).

In addition to its ability to activate P2X and P2Y receptors, extracellular ATP is hydrolyzed by membrane ecto-nucleotidases, including adenosine triphosphatases (ATPases) (84, 85). Ectonucleoside triphosphate diphosphohydrolases (E-NTPDases) hydrolyze nucleotide diphosphates and triphosphates to generate nucleotide monophosphates, and they are the largest family of ectonucleotidases, consisting of E-NTPDase1 to 8, including E-NTPDase1 (CD39), E-NTPDase2 (CD39L1), E-NTPDase3 (CD39L3), E-NTPDase5 (CD39L4), and E-NTPDase6 (CD39L2) (86). There are five members of the family of ectonucleotide pyrophosphatase and phosphodiesterases (E-NPPs), the second largest ectonucleotidase family, which hydrolyze nucleotide triphosphates to generate nucleotide monophosphates and extracellular inorganic pyrophosphate (87) and can convert cyclic adenosine monophosphate (cAMP) to adenosine (88). Alkaline phosphatases, another family of ecto-ATPases, consist of four isoforms (84). Ecto-5'-nucleotidase (CD73) catalyzes the conversion of AMP to the nucleoside adenosine (89). Adenosine, the final product of ecto-ATPase action, activates P1 (also known as A1 to A3) receptors, which are G protein-coupled receptors that couple to G_s or G_i proteins (90). The function of cells that release ATP can be altered by the activation of P2 receptors [or P1 receptors if adenosine is generated (Fig. 1)]; P1 or P2Y receptors and ecto-ATPases heterooligomerize and may form membrane networks (91). Stimulation of the receptors by agonists changes membrane potential, the cellular content of ions and second messengers, or both and, in turn, alters the abundance and activity of effector molecules and components regulated by such signaling events.

Autocrine and Paracrine Actions of Extracellular ATP

The release of ATP alters cell physiology in multiple ways. Among these is basal release of ATP, which acts through autocrine or paracrine stimulation of P2 receptors (and following its hydrolysis to adenosine, of P1 receptors) to contribute to the set point of second-messenger systems (52). Such set points, which reflect the activation of signaling pathways, help define the dynamic range of responses: ATP affects the abundance of intracellular Ca^{2+} and cAMP and the activation of protein kinases, including cAMP-dependent protein kinase (PKA), protein kinase C (PKC), and Ca^{2+} - and calmodulin-dependent protein kinases. The contribution of released ATP and its metabolites to signaling events and cell function are rarely considered in studies of signal transduction or downstream cellular responses of other ligands. Treatment of cells with adenosine 5'-triphosphatase (an apyrase), which rapidly hydrolyzes ATP, is a means of defining such a contribution. Apyrase is commonly used in studies of platelet activation and aggregation in order to block the secondary wave of aggregation that is mediated by ADP released from platelet storage granules. Use of apyrase has shown that endogenously released ATP contributes to ambient levels of activation of signal transduction pathways. There are many other examples of cell types in which apyrase or other approaches have been used to identify a role for ATP release in cell regulation (Table 2).

Released ATP modulates cellular responses to neurotransmitters and hormones. ATP receptors induce actions that may be additive or antagonistic to those of other agonists; in addition, released ATP causes heterologous desensitization of receptors and thereby alters responses to other types of agonists (92, 93). Released ATP also influences cellular function by modulating the abundance of intracellular Ca^{2+} , including by the generation and propagation through gap junctions of Ca^{2+} waves between cells (21, 36, 37, 43, 44). Heterogeneity in the abundance of P2Y₂ receptors and their activation by extracellular nucleotides help determine variations in Ca^{2+} signaling among cells in a population (94). Relatively few studies of mechanisms that regulate Ca^{2+} abundance and Ca^{2+} -dependent processes have also assessed the contribution of ATP release to these processes when stimuli are used that elicit such release. Below, we highlight examples of cellular regulation that

occur by release of and response to endogenous ATP, which include such processes as tissue blood flow, control of cell volume, growth and metastatic potential of malignant cells, neuronal activity, neural development, and response to pathogens.

Regulation of Tissue Blood Flow

Constitutive release of ATP from the luminal membrane of vascular endothelial cells modulates vascular tone through P2X and P2Y receptors on those cells (18, 87, 95). ATP is also released as a cotransmitter with norepinephrine from perivascular sympathetic nerves onto vascular smooth muscle cells, where it promotes vasoconstriction by activating P2X₁ receptors (96). In addition to basal release of ATP, increased release from endothelial cells occurs in response to shear stress, hypoxia, or ischemia and promotes P2 receptor-mediated vasodilation (97-100). P2 receptor-regulated signaling cascades release vasodilators that include nitric oxide (101, 102), prostaglandins (103, 104), and endothelium-derived hyperpolarizing factor (105-107).

Cells exposed to the luminal membrane of the vascular endothelium contribute to the regulation of vascular tone and blood flow by releasing ATP that acts in a paracrine manner (Fig. 2). An important role for erythrocytes as oxygen sensors that release ATP under hypoxic conditions to modulate vascular tone was outlined in a series of studies by Bergfield *et al.*, Ellsworth *et al.*, and Dietrich *et al.* (108-110). During oxygen deprivation, cerebral and other arterioles release ATP, which promotes vasodilation and increases blood flow (110). This vasodilation is regulated by P2Y₁₃ receptors, which are activated by ADP and inhibit the release of ATP from erythrocytes, thus creating a feedback loop for the control of blood flow (111). Low basal concentrations of ATP and ADP are found outside of platelets and are regulated by NTPDase-1 (112, 113). On activation, platelets release ADP from storage granules, thereby altering blood flow and platelet aggregation. Clopidogrel and related compounds are drugs used in the treatment of thromboembolic disease that target platelet P2Y₁₂ receptors for which ADP is the physiological agonist (114). ATP released by leukocytes influences the function of other blood cells and of vascular endothelial cells (47, 115-121); ATP released in the kidney regulates blood flow and renal function (122).

Ion Transport and Control of Cell Volume

Extracellular ATP has an important impact on ion transport in numerous cell types (Table 2), in particular, in response to changes in their osmotic environment ("osmotic stress") (123). To maintain their volume under such conditions, cells increase ionic secretion by a process termed regulatory volume decrease (RVD) (124). Osmotic stress promotes the release of ATP, which, through its activation of P2 receptors, contributes to RVD by triggering a Ca²⁺-dependent increase in the secretion of ions (27-30, 32, 33, 125). Inhibition of ATP signaling (by ATP scavengers, such as apyrase, or P2 receptor blockers, such as suramin) slows volume recovery and blocks Cl⁻ currents (27, 30). Increasing ATP conductance, by increasing the abundance of multidrug resistance (Mdr) proteins in hepatic cells, results in a more rapid recovery after hypotonic exposure (28). This release of ATP is dependent on the volume of the cell; increasing hypoosmotic pressure increases the release of ATP (30). Inhibition of Ca²⁺ signaling inhibits membrane currents, but swelling-induced increases in the concentration of Ca²⁺ are unaffected by apyrase or suramin, which suggests the existence of P2 receptor-independent Ca²⁺ signaling and Ca²⁺-independent purinergic signaling pathways (126).

Extracellular ATP contributes to RVD in other cell types, although the precise mechanisms by which cell volume is regulated vary. In erythrocytes, P2 receptors potentiate RVD by stimulating K⁺ efflux in a Ca²⁺-dependent manner (127, 128). In African green monkey kidney (Vero) cells, ATP activates K⁺ currents by increasing the concentration of

cytosolic Ca^{2+} and activating Ca^{2+} -dependent K^+ channels (129, 130). In human intestinal 407 cells, ATP-induced mobilization of Ca^{2+} stimulates K^+ currents and mediates the hypotonicity-promoted activation of extracellular signal-regulated kinase 1 (ERK1) and ERK2 (131, 132). In rat biliary cells, release of ATP from the apical and basolateral membranes facilitates RVD in response to hypotonic stress (31). Antibody-tethered luciferase molecules, which facilitate the analysis of local concentrations of ATP, have been used in experiments with human bronchial epithelial cells to show that upon hypotonic challenge, the concentration of ATP just outside the cell membrane increases 100- to 1000-fold compared with that under basal (isotonic) conditions and approaches a concentration of $1\text{ }\mu\text{M}$ (133). Loss of CFTR and CFTR-mediated autocrine ATP signaling are potentially responsible for defective regulation of cell volume and the altered function of airway epithelia in cystic fibrosis, in particular, as related to the airway surface fluid layer (33).

Extracellular ATP signaling regulates excitatory amino acid (EAA) release from astrocytes, in particular, from osmotically swollen astrocytes, by modulating volume-regulated anion channels (134, 135). Astrocytes contain P2Y_1 receptors, activation of which increases the concentration of intracellular Ca^{2+} and causes the release of glutamate, likely through the actions of $\text{PKC-}\alpha$ and $\text{PKC-}\beta\text{I}$ (136, 137). Ambient concentrations of extracellular ATP modulate Na^+ transport in renal epithelial cells, including in collecting duct cells through the activation of P2Y_2 (138). Activation of basolateral P2Y_2 receptors inhibits arginine vasopressin-induced water transport in the medullary collecting duct (139). Mice deficient in P2Y_2 receptors have salt-resistant hypertension, alterations in renal epithelial cell regulation of ions, and perturbation of renal concentrating mechanisms (140-142).

Propagation and Metastatic Potential of Cancer Cells

Autocrine and paracrine ATP signaling contribute to tumorigenesis, in part because extracellular ATP serves as a growth factor (143). The basal rate of ATP release is increased and the extent of hydrolysis of extracellular nucleotides is decreased in neoplastic tissues and cells; such changes, through P2 receptor signaling, potentially increase cell proliferation (144, 145). Extracellular ATP may contribute to tumorigenesis in multiple ways. Concentrations of extracellular ATP that are $10\text{ }\mu\text{M}$ and higher enhance the death of cervical (146), gastrointestinal (23, 147), and prostate cancer cells (148) by a mechanism that may involve the activation of P2X_7 ; resistance to cell death may contribute to the enhanced proliferation of such cells. Certain cancer cells, including B lymphocytic leukemia (149) and carcinomas of the prostate and thyroid (150, 151), have an increased abundance of P2X_7 receptors, which are potential therapeutic targets for cell killing (151). Release of ATP by cancer cells exerts paracrine effects and influences tumor biology: ATP released from fibrosarcoma cells increases the intracellular concentration of Ca^{2+} in endothelial cells and may contribute to invasion and metastasis (152). The effects described above with regard to the impact of released ATP on tissue blood flow also may contribute to the growth and microenvironment of tumors.

Neuronal Signaling and Neural Development

ATP is an excitatory cotransmitter in neuronal cells (67). Release of ATP from neuron-like PC12 cells modulates cell function (153). The release of ATP and its actions and those of its hydrolytic products have roles in other neuronal and neuroendocrine cells, for example, as neurotransmitters and gliotransmitters in the retina, olfactory epithelium, taste buds, and cochlea; nucleotide receptor signaling thus contributes to sensory transduction and to the function of other types of neurons (154, 155).

Extracellular ATP signaling regulates neuronal cell proliferation and differentiation. PC12 cells and dorsal root ganglion neurons release ATP, which, through the activation of P2Y_2

receptors, is a coactivator of neurotrophin-TrkA-dependent neuronal differentiation (156, 157). Such results identify ATP as a morphogen and P2Y₂ as a morphogen receptor during neural development, perhaps through mechanisms that include P2Y₂-TrkA crosstalk and activation of Src family kinases (156, 157). ATP promotes cell proliferation in certain neurons [for example, in the chick neural retina at early embryonic stages (158)]. P2Y receptor antagonists inhibit proliferation and promote the differentiation of neural progenitor cells through P2Y₁ receptors (159, 160). Multiple P2 receptors are likely involved in neuronal differentiation and proliferation, as there is evidence that nerve growth factor-promoted differentiation of PC12 cells increases the abundance of P2X receptors (161).

Host-Pathogen Interactions

Autocrine and paracrine ATP signaling can contribute to cellular response to pathogens, such as the production and release of inflammatory mediators, including cytokines. In some cases, agents that contribute to pathogenicity increase the extent of basal release of ATP. For example, treatment of microglia with the bacterially derived endotoxin lipopolysaccharide (LPS) releases ATP and promotes the production of interleukin 1 β (IL-1 β) and IL-10 (162-164). LPS-stimulated release of ATP also promotes the release of IL-1 α from endothelial cells and that of IL-6 from fibroblasts (165, 166). Microbial components and uric acid (a “danger signal” released from dying cells) promote the secretion of IL-1 β and IL-18 from monocytes by stimulating the release of ATP (47), although uric acid can activate the IL-1-processing inflammasome in the absence of P2X₇ receptor activity (167). Released ATP is thus a proinflammatory signal during the acute inflammation that occurs in damaged or infected tissues.

ATP signaling in response to pathogens stimulates apoptosis through activation of P2X₇ receptors, perhaps as an attempt to fight infection (162, 166). Bacterially derived peptides such as the *N*-formyl peptide *f*Met-Leu-Phe [(*f*MLP) in humans and certain other animals] and W-peptide (Trp-Lys-Tyr-Met-Val-d-Met-NH₂ in mice) stimulate the release of ATP from neutrophils and stimulate neutrophil migration and phagocytosis (116). In an analogous manner, salivary histatin 5 (Hst 5), a human antimicrobial peptide, stimulates the release of ATP from the fungus *Candida albicans* and promotes cell death through the activation of a P2X₇-like receptor (168, 169).

The survival of some pathogens is enhanced by their modulation of nucleotide release and signaling by host cells. Intracellular survival of *Mycobacterium avium* subspecies paratuberculosis depends on the release of ATP; treatment of infected monocytes with the ATP scavenger apyrase decreases the number of intracellular bacilli (170). Respiratory syncytial virus blocks the clearance of fluid by the bronchoalveolar epithelium through a mechanism that involves nucleotide release and activation of host P2Y receptors (171). *Leishmania amazonensis* releases nucleoside diphosphate kinase, which decreases the concentration of extracellular ATP and prevents ATP-induced cytolysis of macrophages and thus preserves the integrity of host cells to the benefit of the parasite (172). OppA, the ecto-ATPase of *Mycoplasma hominis*, induces ATP release and death of infected HeLa cells, which may promote dissemination of the microorganism (173). Of note, the saliva of biting insects such as *Aedes aegypti* (the mosquito host for yellow fever), *Culicoides variipennis*, and *Phlebotomus papatasi* contain apyrases that hydrolyze ATP (174-176). Thus, release of extracellular ATP influences interactions between pathogens and their target cells, as well as affecting the innate immune response. Other data implicate a role for the release of ATP and ATP-mediated responses in lymphocyte functions that contribute to adaptive, as well as to innate, immunity (47, 118, 177). Autocrine and paracrine ATP signaling have other functional roles, including regulation of the secretion and function of endocrines (168, 178-183), the functions of muscles and tendons (48, 184, 185), the formation and resorption

of bone (186, 187), and the proliferation of stem cells (41, 42) (Table 2). The diverse array of cellular responses to extracellular ATP illustrates its importance as a signaling molecule that regulates many biologic activities.

Conclusions

In addition to the essential role of ATP as the primary unit of energy in cells, its release and autocrine and paracrine effects influence a large number of cell types and responses. This raises an important question: Why would a cell release life-sustaining energy stores in order to generate a signaling molecule? In most cells, the intracellular concentration of ATP is ~1 mM (188); concentrations of extracellular ATP in the near-membrane environment are in the low micromolar range, but such concentrations are sufficient to trigger functional changes (116, 133, 189, 190). The ability of low concentrations of ATP (relative to those found intracellularly) to induce responses and the favorable concentration gradient, potency, and efficacy of ATP as a signaling molecule make it a highly efficient means for autocrine and paracrine regulation of cells. Adenosine, which is generated by ATPase-catalyzed hydrolysis, enhances the scope of action of extracellular ATP. Some cells produce extracellular enzymes that regenerate ATP and help potentiate responses activated by the released nucleotide (191). The diverse array of receptors for ATP and adenosine and the range of ecto-ATPases and kinases that regulate extracellular concentrations create a highly economical, versatile, and tightly regulated system to facilitate cellular regulation by extracellular ATP derived from internal pools of nucleotides.

ATP signaling may have evolved as a danger signal in response to the release of ATP by damaged cells. Extracellular ATP is a chemorepellent in two unicellular eukaryotes, *Tetrahymena thermophila* and *Paramecium tetraurelia*, which migrate away from sources of the nucleotide (192, 193). ATP depolarizes these cells, modulates changes in the concentration of intracellular Ca^{2+} , and directs the cells to reverse their direction of movement. In *P. tetraurelia*, the ATP receptor pharmacologically resembles mammalian P2X_1 receptors (193). P2X -like receptors have been characterized in *Schistosoma mansoni* (194) and in *Dictyostelium discoideum*, in which they function as osmoregulators (195).

The evolutionary origin of ATP signaling may have a parallel with that of the cAMP signaling system, which directs *D. discoideum* migration in conditions of starvation; when released from cells, cAMP acts as a chemoattractant and influences the migration of neighboring cells (196). Analogously, release of ATP by murine and human neutrophils directs cell migration in an autocrine manner (116), and its release by apoptotic cells has been implicated as a paracrine “find-me” signal to promote phagocytic clearance (197). Perhaps cAMP and ATP are used by different organisms as alternative nucleotides for autocrine and paracrine signaling, a notion consistent with the evolutionary expression of P2Y receptors (198) and with the proposal that cAMP is part of a metabolic code in prokaryotes and eukaryotes (2). Of note, cells use ATP and UTP (12, 13), a purine and pyrimidine, not only for the synthesis of DNA and RNA but also as extracellular signaling molecules.

Released ATP thus plays a large number of autocrine and paracrine roles in the regulation of cell physiology. Many cell types release functionally relevant concentrations of ATP in response to stimuli that minimally perturb the cells. Extracellular ATP signaling helps establish the set point of signaling pathways and affects the responses of cells to other stimuli. To what extent do the cellular release of ATP and the signaling pathways regulated by ATP and its metabolic products contribute to responses previously (and perhaps, in part, mistakenly) attributed to other molecules? Given the conserved nature of ATP release and

signaling pathways, we believe that the role of released ATP in signal transduction, physiology, and pathophysiology has yet to be fully discovered.

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Fig. 1. Autocrine and paracrine actions of extracellular ATP

Cells release ATP into the extracellular space where it can activate P2X and P2Y receptors, or, after hydrolysis of ATP by ecto-ATPases to generate adenosine, P1 receptors on the cells that released ATP (autocrine signaling) or on neighboring cells (paracrine signaling).

Fig. 2. Control of blood flow by autocrine and paracrine ATP signaling

Extracellular ATP modulates vascular smooth muscle cell tone by activating P2Y₁₃ receptors on the luminal membrane of endothelial cells, which in turn leads to the production of nitric oxide (NO), prostaglandins (PGs), and endothelium-derived hyperpolarizing factor (EDHF). During oxygen deprivation, endothelial cells and erythrocytes release increased amounts of ATP, which leads to the increased activation of P2Y₁₃ and vasodilation.

Table 1
Isoforms of P2Y and P2X receptors and their primary endogenous agonists

G proteins that are associated with P2Y receptors are also shown. ATP is shown in parentheses if it acts as a secondary agonist.

Receptor	Primary endogenous agonists	Associated G proteins
P2Y ₁	ADP (ATP)	G _q
P2Y ₂	ATP, UTP	G _q and G _{i/o}
P2Y ₄	UTP (ATP)	G _q and G _{i/o}
P2Y ₆	UDP	G _q
P2Y ₁₁	ATP	G _s and G _q
P2Y ₁₂	ADP (ATP)	G _{i/o}
P2Y ₁₃	ADP	G _s and G _{i/o}
P2Y ₁₄	UDP glucose	G _{i/o}
P2X ₁ to P2X ₇	ATP	N.A.

Autocrine and paracrine activities of released ATP

Table 2

If known, specific receptors are listed. P2X or P2Y is noted where the receptor class, but not the specific subtype, is known. P2 is listed if information on the specific receptor type is not known. Key: ↑, increase; ↓, decrease; PLC, phospholipase C; Aβ, amyloid β-protein; Aβ₄₂, 42-residue amyloid β-protein; EDTA, ethylenedi-aminetetraacetic acid; GnRH, gonadotropin-releasing hormone; NO, nitric oxide; JNK, c-Jun N-terminal kinase; SAPK, stress-activated protein kinase; PMA, phorbol 12-myristate 13-acetate; NFAT, nuclear factor of activated T cells; COX2, cyclooxygenase-2; MMP-3, matrix metalloproteinase 3; phos., phosphorylation; HEK 293, human embryonic kidney cells; E_{Na}C, epithelial sodium channel; EBIO, 1-ethyl-2-benzimidazolinone; API, activator protein-1.

Cell type	Stimulation	P2 target	Physiological effect
<i>CNS and neuroendocrine</i>			
Astrocytes	Mechanical	P2Y ₁ /P2Y ₂	↑PLC activity (35), ↑[Ca ²⁺] _i (35, 36)
	Hypotonic stress	P2Y ₁ /P2Y ₁	Activation or modulation of volume-regulated channels (15, 16)
Chromaffin cells	Ba ²⁺	P2	Inhibition of non-L type Ca ²⁺ channels (199)
Microglia	LPS	P2X ₇	↑IL-1β release, ↑apoptosis (162, 200)
		P2Y _{1,11}	↑IL-10 release (163, 164)
Neuroendocrine cells	Aβ	P2X ₇	↑IL-1β release, ↑ATP release, ↑[Ca ²⁺] _i (201)
	Aβ ₄₂	P2X ₇	↑ROS generation (202)
Neural progenitor	Basal	P2Y ₁₂	↓Adenylyl cyclase activity (178)
Anterior pituitary	Basal	P2Y(1)	↑[Ca ²⁺] _i (159, 160)
	A23187	P2Y ₂	Release of luteinizing hormone (179)
	EDTA and/or GnRH	P2X _{2/5}	↑[Ca ²⁺] _i (180)
	Thyrotropin-releasing hormone	P2	↑Prolactin release (181)
<i>Heart and circulatory</i>			
Endothelial cells	LPS	P2X ₇	↑IL-1α release (165)
	Hypotonic stress	P2, P2X _{4/5}	↑[Ca ²⁺] _i (17-20), ↑NO production (17)
Endothelial and/or epithelial cells	Hypoxia	P2	↑Growth factor-induced DNA synthesis (203)
	Lung expansion	P2Y ₂	↑[Ca ²⁺] _i , ↑NO production (204)
Glomerular vasculature	β-blockers	P2Y	↑NO release (205)
Vascular smooth muscle	Stretch and/or mechanical stress	P2	↑JNK/SAPK activity (184)
<i>Blood cells</i>			

Cell type	Stimulation	P2 target	Physiological effect
Erythrocytes	<i>P. falciparum</i> infection	P2Y ₁	↑Osmolyte permeability (45)
Lymphoid cells	Basal	P2X ₇	↑Proliferation (206)
Macrophages	<i>M. tuberculosis</i> infection	P2X ₇	Apoptosis (46)
Megakaryocytes	Spontaneous	P2Y ₁	↑Repetitive inward Ca ²⁺ currents (207)
Monocytes	Microbial components and/or uric acid	P2X ₇	↑IL-1β, IL-18 secretion (47)
Neutrophils	fMLP	P2Y ₂	Cell polarization (116)
Platelets	Thrombin and/or thromboxane	P2X ₁	↑[Ca ²⁺] _i (94)
Connective tissue			
Osteoblasts	Mechanical and/or hypotonic stress	P2Y ₁ /P2Y ₂	↑[Ca ²⁺] _i (21, 37-39), Egr1 synthesis (39)
Fibroblasts	Mechanical stimulation	P2Y ₂	↑[Ca ²⁺] _i (40)
	LPS, PMA	P2X ₇	↑Fibronectin, IL-6 release, apoptosis (166)
Multipotent stromal cells	Oscillatory fluid flow	P2/P2Y ₁	↑[Ca ²⁺] _i , Calcineurin activation, NFAT translocation, proliferation (41, 42)
Tendon	Medium change and/or UTP	P2Y ₆	↓IL-1β, COX2, MMP-3 (48)
<i>Eye</i>			
Retinal glial cells	Hypotonic stress	P2Y ₁	↑K ⁺ , Cl ⁻ channel conductance (22)
GI tract			
Colon cancer cells	Gram-negative flagella	P2Y	↑[Ca ²⁺] _i , ↑Erk1/2 phosphorylation, ↑mucin transcription, PLC activation (208)
	Hypotonic stress	P2X ₇	↑Caspase 3/8 and annexin V activation, cytochrome c release, cell death (23)
Distal colon	Mechanical and/or hypotonic stress	P2Y	↓Short circuit current (24)
<i>Kidney</i>			
HEK 293	Basal	P2X ₇	↑Proliferation in absence of serum (209)
Nephron	Mechanical and/or hypotonic stress	P2	↑[Ca ²⁺] _i (25)
Renal epithelial	Stretch	P2	↑E _{Na} C activation (210)
	Aldosterone	P2	↑E _{Na} C activity, contraction (211)
	Hypotonic stress	P2	↑[Ca ²⁺] _i (26)
	Basal	P2Y	↓Arach. acid release, cAMP production (52)

Cell type	Stimulation	P2 target	Physiological effect
<i>Muscle</i>			
Dystrophic myotubules	Basal and/or stretch	P2	$\uparrow$ Na ⁺ /H ⁺ exchanger activity (185)
<i>Pancreas, liver, and bile duct</i>			
Pancreatic β -cells	Glucose	P2Y	$\uparrow$ [Ca ²⁺] _i (212)
Hepatocytes	Hypotonic stress	P2	Cl ⁻ permeability and/or RVD (27-30)
	Mechanical	P2	$\uparrow$ [Ca ²⁺] _i (43)
Biliary epithelial	Hypotonic stress	P2	$\uparrow$ Cl ⁻ permeability (31)
Cholangiocytes	Forskolin	P2	$\uparrow$ [Ca ²⁺] _i , HCO ₃ ⁻ secretion (213)
Reproductive			
Cervical epithelial cells	Media serum removal	P2X ₇	$\uparrow$ Caspase 3/9, apoptosis (146)
Prostate cancer	Mechanical	P2	$\uparrow$ [Ca ²⁺] _i (44)
	dc electrical field pulse	P2	$\uparrow$ [Ca ²⁺] _i , tumor growth, c-Fos induction (214)
<i>Respiratory</i>			
Airway epithelial	PKA/ATP	P2Y ₂	Cl ⁻ channel stimulation (215)
	Medium displacement	P2Y ₂	$\uparrow$ Inositol Phosphate synthesis (49)
	Hypotonic stress	P2	RVD (32, 33)
	EBIO and/or chlorzoxazone	P2Y ₁	Cytosolic Ca ²⁺ mobilization (216)
	Hypotonic stress	P2Y ₆	$\uparrow$ [Ca ²⁺] _i (34)
<i>Skin</i>			
Keratinocytes	Media change	P2Y	$\uparrow$ IL-6, $\uparrow$ [Ca ²⁺] _i (50)
Thyroid			
Thyrococytes	Basal	P2Y ₂	$\uparrow$ IL-6 secretion, $\uparrow$ [Ca ²⁺] _i (182)
		P2Y _{1/2}	$\uparrow$ Erk1/2 phos., $\uparrow$ AP1 activation (183)