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Purinergic Signaling in the Airways

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Abstract——**Evidence for a significant role and impact of purinergic signaling in normal and diseased airways is now beyond dispute. The present review intends to provide the current state of knowledge of the involvement of purinergic pathways in the upper and lower airways and lungs, thereby differentiating the involvement of different tissues, such as the epithelial lining, immune cells, airway smooth muscle, vasculature, peripheral and central innervation, and neuroendocrine system. In addition to the vast number of well illustrated functions for purinergic signaling in the healthy respiratory tract,**

increasing data pointing to enhanced levels of ATP and/or adenosine in airway secretions of patients with airway damage and respiratory diseases corroborates the emerging view that purines act as clinically important mediators resulting in either proinflammatory or protective responses. Purinergic signaling has been implicated in lung injury and in the pathogenesis of a wide range of respiratory disorders and diseases, including asthma, chronic obstructive pulmonary disease, inflammation, cystic fibrosis, lung cancer, and pulmonary hypertension. These ostensibly enigmatic actions are based on widely different mechanisms, which are influenced by the cellular microenvironment, but especially the subtypes of purine receptors involved and the activity of distinct members of the ectonucleotidase family, the latter being potential protein targets for therapeutic implementation.

I. Introduction

A seminal article describing the potent actions of adenine compounds on the heart and blood vessels was published by Drury and Szent-Györgyi in 1929. Many years later, ATP was proposed as the transmitter responsible for nonadrenergic, noncholinergic neurotransmission in the gut and bladder and the term 'purinergic' was introduced by Burnstock in 1972. Early resistance to this concept seemed to stem from the fact that ATP was recognized first for its important intracellular roles in many biochemical processes, and the intuitive feeling was that such a ubiquitous and simple compound was unlikely to be used as an extracellular messenger.

Implicit in the concept of purinergic signaling was the existence of purinergic receptors, mediating potent actions of extracellular ATP on many different cell types (Burnstock and Knight, 2004). Purinergic receptors were first defined in 1976; 2 years later, a basis for distinguishing two types of purinoceptor, identified as P1 and P2 (for adenosine and ATP/ADP, respectively), was proposed (Burnstock, 1978). At approximately the same time, two subtypes of the P1 (adenosine) receptor were recognized, but it was not until 1985 that a pharmacological basis for distinguishing two types of P2 receptor (P2X and P2Y) was found (Burnstock and Kennedy, 1985). In 1993, the first G protein-coupled P2 receptors were cloned, and a year later, two ion-gated receptors were cloned. In 1994, Abbracchio and Burnstock, on the basis of molecular structure and transduction mechanisms, proposed that purinoceptors should belong to two major families: a P2X family of ligand-gated ion channel receptors and a P2Y family of G protein-coupled purinoceptors. This nomenclature has been widely adopted, and seven P2X subtypes and eight P2Y receptor subtypes are currently recognized, including receptors that are sensitive to pyrimidines as well as purines (Ralevic and Burnstock, 1998; Burnstock, 2007b).

It was assumed for some time that the only source of extracellular ATP acting on purinoceptors was damaged or dying cells, but it is now recognized that ATP release from healthy cells is a physiological mechanism (see Burnstock, 1999). ATP is released as a cotransmitter from both peripheral and central neurons but also from many non-neuronal cell types during mechanical deformation in response to shear stress, stretch, or osmotic swelling, as well as hypoxia and stimulation by various agents. The precise transport mechanism(s) involved in ATP release remain under debate. There is compelling evidence for Ca^{2+}-dependent exocytotic vesicular release of ATP from nerves, but for ATP release from non-neuronal cells, various transport mechanisms have been proposed, including ATP-binding cassette transporters, connexin or pannexin hemichannels, or possibly plasmalemmal voltage-dependent anion channels, as well as vesicular release (see Bodin and Burnstock, 2001; Lazarowski, 2012). ATP released from cells is regulated by a number of proteins for which the catalytic site is located on the outer side of the plasma membrane (Yegutkin et al., 2008). The CD39 family consists of ectonucleoside triphosphate diphosphohydrolases that hydrolyze nucleoside 5′-tri- and diphosphates. Another family of enzymes with three subtypes includes ecto-nucleotide pyrophosphatase/phosphodiesterases with a broad substrate specificity. Alkaline phosphatases are also used, and ecto-5′-nucleotidase (CD73), which breaks down AMP to adenosine. ATP-induced Ca^{2+} wave propagation occurs widely in glial cells, osteoclasts, chondrocytes, epithelial cells, fibroblasts, and cancer cells and usually involves P2Y receptors (see, for example, Gallagher and Salter, 2003). Selective agonists and antagonists to many of the P1, P2X, and P2Y receptor subtypes are now available (see Burnstock, 2012).

A number of reviews on different aspects of purinergic signaling in the airways are available: extracellular purinergic regulation of airways secretion and ciliary activity (Braiman et al., 2000; Rooney, 2001; Shimura, 2001; Leipziger, 2003; Schwiebert and Zsembery, 2003; Davis and Lazarowski, 2008; Barth and Kasper, 2009; Lazarowski and Boucher, 2009; Dietl et al., 2010); nervous control of the airways (Burnstock, 1988; Wegner, 2001; Brouns et al., 2006; Taylor-Clark and Undem, 2006; Funk et al., 2008); purinergic signaling in airway diseases (Ahmad et al., 2006; Spicuzza et al., 2006; Ackland et al., 2007); and pulmonary vasculature (Liu and Barnes, 1994). Here, we intend to provide a more comprehensive overview of airway-related purinergic signaling.

II. Lung and Intrapulmonary Airways

A. Epithelial Lining

1. Alveolar and Transport Epithelium. Evidence for regulation of surfactant secretion from alveolar type II

(ATII[1]) cells by ATP and ADP acting on P2 receptors was presented in 1986 (Rice and Singleton, 1986). Later it was suggested that P2Y receptors mediated the mobilization of $[Ca^{2+}]_i$ involved in surfactant secretion (Rice and Singleton, 1987, 1989) but that A_2 receptors were also implicated after breakdown of ATP to adenosine (Griese et al., 1991). Plasma membrane ADP activity was identified in rat lung (Dawson et al., 1986). ATP, ADP, AMP, and adenosine were shown to stimulate phosphatidylcholine secretion in primary cultures of ATII pneumocytes (Gilfillan and Rooney, 1987). Both P1 and P2 receptor signal transduction was identified in ATII cells (Warburton et al., 1989a), and ATP-induced surfactant secretion seemed to be mediated via activation of protein kinase C (Chander et al., 1995). ATP was shown to be present in bronchoalveolar lavage in concentrations sufficient to mediate surfactant phospholipid secretion in vivo (Rice et al., 1989). Pulmonary surfactant is a complex lipoprotein mixture, and ATP was shown to stimulate the synthesis of surfactant protein A in rat lung (Wali et al., 1993). Luminal ATP activates an apical P2 receptor that stimulates K^+ secretion across cultured human airways epithelium (Clarke et al., 1997). Multiple modes of regulation of Cl^- secretion from airway epithelial cells by extracellular ATP, UTP, and adenosine were identified (Stutts et al., 1994; Barker and Gatzy, 1998; Poulsen et al., 2006). Ca^{2+}-dependent release of arachidonic acid from airway epithelium in response to P2U (i.e., $P2Y_2$ and/or $P2Y_4$) receptor activation by UTP and ATP was reported (Lazarowski et al., 1994). A P2U receptor was cloned from rat ATII cells and shown to be functional by expression in an unrelated cell line (Rice et al., 1995). Besides the potential involvement in secretion by directly increasing $[Ca^{2+}]_i$ via P2Y receptors, extracellular ATP was also shown to lead to membrane depolarization and activation of L-type Ca^{2+} channels in the alveolar epithelial cell line L2 (Dietl et al., 1995). It was suggested that the resulting "near membrane $[Ca^{2+}]_i$ hotspots" might play an important role in surfactant exocytosis. Depending on the substrate conditions, $P2Y_2$ receptors were identified in distal lung epithelial cells isolated from fetal rats (Clunes et al., 1998).

Release of ATP from lung epithelial cells was detected with bioluminescence (Taylor et al., 1998). ATP release to mechanical and osmotic stimuli were quantitated using a capillary cell culture system with Calu-3, a human lung cell line (Guyot and Hanrahan, 2002). Both elevating apical flow rate and reducing osmolarity strongly increased ATP release. Nucleotide release provides a mechanism for airway surface liquid homeostasis (Lazarowski et al., 2004). Mechanical stress results in the local release of ATP, which produces a wave of increasing $[Ca^{2+}]_i$ that spreads to other cells, mediated via P2Y receptors (Hansen et al., 1993; Homolya et al., 2000). Alveolar type I (ATI) epithelial cells release 4-fold more ATP in response to stretch than ATII cells, and it was concluded that ATI cells are mechanosensors in the lung and that paracrine stimulation of ATI cells by ATP released from these cells plays a role in regulating surfactant secretion (Patel et al., 2005). Cell deformation by surface tension forces in the proximity of the air-liquid interface causes Ca^{2+}-dependent exocytotic ATP release (Ramsingh et al., 2011), which may provide a simple sensing mechanisms to detect low content of surface liquid or surfactant, leading via ATP to compensatory secretion of fluid, mucus, and surfactant. Released ATP exerts an autocrine regulation of epithelial NaCl absorption, mainly by inhibiting the amiloride-sensitive epithelial Na^+ channel (ENaC) and ion conductance via a P2Y receptor-dependent increase in Ca^{2+} (Poulsen et al., 2005; Bao et al., 2007). Evidence that the released ATP reached sufficient concentrations at the airway surface to activate $P2Y_2$ receptors has been provided, supporting the view that this is a physiological mechanism for epithelial cell volume regulation (Okada et al., 2006). UTP, as well as ATP, is released from ATII-like A549 epithelial cells, probably by exocytosis, because the secretion is Ca^{2+}-dependent (Tatur et al., 2008). Thrombin promotes release of ATP from lung A549 epithelial cells through the coordinated activation of Rho- and Ca^{2+}-dependent signaling pathways; the ATP release was inhibited by connexin hemichannel blockers (Seminario-Vidal et al., 2009). The contribution of pannexin 1 to ATP release from airway epithelium has also been suggested (Ransford et al., 2009). Van Scott et al. (1995) claimed that P2U receptors (i.e., $P2Y_2$ and/or $P2Y_4$) mediate regulation of ion transport across nonciliated bronchiolar epithelial (Clara) cells.

Mouse airway epithelium was reported to express $P2Y_2$ protein, where the immunostaining was most prominent in Clara cells (De Proost et al., 2009; Brouns et al., 2012; Fig. 1). mRNA for $P2Y_2$, $P2Y_4$, and $P2Y_6$ receptors were coexpressed in epithelial cell lines (IHAEo, 16HBE14o, and A549) derived from human lungs (Communi et al., 1999). $P2Y_2$ receptor-mediated inhibition of ion transport in distal lung epithelial cells has been reported (Ramminger et al., 1999). Extracellular

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[1]Abbreviations: α,β-meATP, α,β-methylene ATP; 5-HT, 5-hydroxytryptamine; Ap_4A, diadenosine pentaphosphate; ARDS, acute respiratory stress syndrome; ATII, alveolar type II; ATPγS, adenosine-5'-(γ-thio)-triphosphate; BALF, bronchoalveolar lavage fluid; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CGS 21680, 2-[p-(2-carboxyethyl)phenethylamino]-5'-N-ethylcarboxamidoadenosine; COPD, chronic obstructive pulmonary disease; DRG, dorsal root ganglion; ENaC, epithelial Na^+ channel; IL, interleukin; INS37217, P^1-(uridine 5')-P^4-(2'-deoxycytidine 5')tetraphosphate; LPS, lipopolysaccharide; MRS2365, (N)-methanocarba-2-methylthio-ADP; NA, noradrenaline; NANC, nonadrenergic/noncholinergic; NBD, nucleotide-binding domain; NEB, neuroepithelial body; NTS, nucleus tractus solitarius; PBC, pre-Bötzinger complex; PECAM, platelet endothelial cell adhesion molecule; PMN, polymorphonuclear leukocyte; RT-PCR, reverse transcription polymerase chain reaction; SMAR, smooth muscle-associated airway receptor.
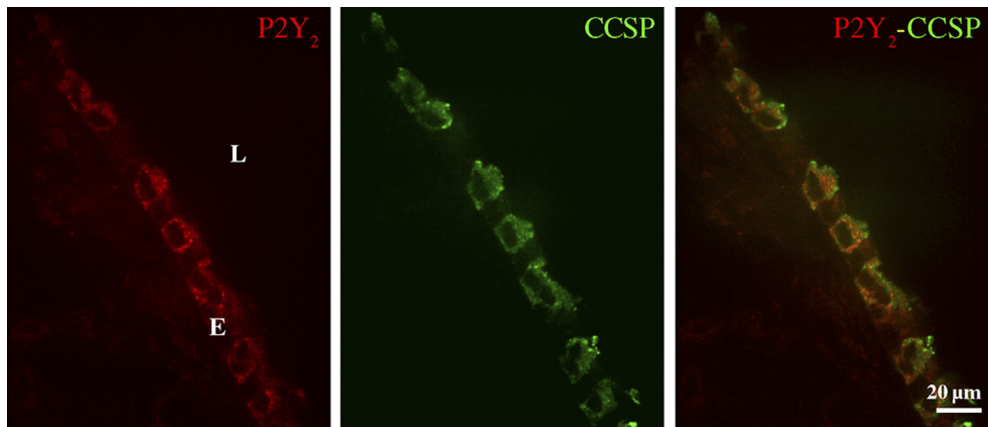
Fig. 1. Double immunostaining for $P2Y_2$ receptors (red fluorescence) and Clara cell-specific protein (CCSP; green fluorescence) in a mouse intrapulmonary airway. Left, $P2Y_2$ expression is seen in most cells of the airway epithelial layer (E) but with varying intensities. Center, CCSP staining of Clara cells. Right, combination of the red and green channels reveals the most prominent $P2Y_2$ expression in Clara cells. L, airway lumen.

nucleotides induce cyclooxygenase-2 up-regulation and prostaglandin E_2 production in A549 cells (Marcat et al., 2007a). Luminal $P2Y_2$ receptors on epithelial cells in distal bronchi of pigs regulate Cl^- secretion and Na^+ absorption (Inglis et al., 1999). ATP, acting through P2Y receptors, regulates the secretion of ions, mucin, and surfactant phospholipids by rat respiratory epithelium (Kishore et al., 2000). Nucleotides induce interleukin (IL)-6 release from human airway epithelia via $P2Y_2$ receptors and p38 mitogen-activated protein kinase-dependent pathways (Douillet et al., 2006). Diadenosine pentaphosphate (Ap_4A) increased $[Ca^{2+}]_i$ in HBE1 cells derived from human bronchial epithelial cells, probably acting via $P2Y_2$ receptors (Laubinger et al., 2001). Multiple P2Y receptor subtypes seem to be present on both apical and basolateral membranes of human airway-derived Calu-3 cells (Chambers et al., 2002), including $P2Y_1$ receptors (Son et al., 2004). UTP stimulates alveolar fluid clearance in the distal airspaces of rat lungs (Sakuma et al., 2004). $P2Y_{14}$ receptor mRNA was shown to be expressed in human lung epithelial cells and in the lung epithelial cell lines A549 and BEA5-2B (Müller et al., 2005). Ap_4A, ATP, and UDP induce arachidonic acid release and nitric-oxide synthase expression in A549 lung epithelial cells via P2Y receptors (Laubinger et al., 2006). Expression and functional $P2Y_6$ receptors were demonstrated in primary cultures of normal human bronchial epithelial cells; they were shown to be located only on the apical membranes, and stimulation with UDP-induced Cl^- secretion (Dulong et al., 2007). 16HBE14o cells were shown to express $P2Y_1$, $P2Y_2$, $P2Y_4$, and $P2Y_6$ receptors under different culture conditions and $P2Y_6$ receptors were present on both apical and basolateral membranes that regulate Cl^- secretion (Wong et al., 2009). However, the $P2Y_6$ receptors seem to be differentially coupled to different downstream signaling pathways at the two sites.

A_1, A_{2A}, A_{2B}, and A_3 receptors are expressed in both ATI and ATII cells in rats and mice, and further findings suggested that physiological concentrations of adenosine allow the alveolar epithelium to counterbalance active Na^+ absorption with Cl^- efflux, via A_1 receptors (Factor et al., 2007). Adenosine increased phosphatidylcholine secretion in rat-cultured ATII pneumocytes via A_2 receptors (Gilfillon and Rooney, 1987) and resulted in A_1 receptor-mediated inhibition of surfactant secretion (Gobran and Rooney, 1990). A_{2B} receptors are highly expressed on murine ATII epithelial cells (Cagnina et al., 2009). Apical adenosine regulates basolateral Ca^{2+}-activated K^+ channels in Calu-3 cells (Wang et al., 2008). It was claimed that volume-sensitive anion channels (K^+ and Na^+) are regulated by an autocrine mechanism involving swelling-induced ATP release and then hydrolysis to adenosine to act on P1 receptors (Musante et al., 1999; Szkotak et al., 2001). Control of cystic fibrosis transmembrane conductance regulator (CFTR)-mediated airway surface ligand secretion by adenosine and ENaC has been claimed (Tarran, 2007). Adenosine promotion of cellular migration in bronchial epithelial cells is mediated by A_{2A} receptors via activation of protein kinase A (Allen-Gipson et al., 2007). Adenosine induces fibronectin expression in A549 lung epithelial cells, and it was suggested that this might be involved in tissue remodeling (Roman et al., 2006). Elevated lung adenosine can lead to abnormal alveolar development by interfering with cell proliferation and apoptosis (Banerjee et al., 2004). Histamine-induced bronchospasm is potentiated by adenosine (Nieri et al., 1997), possibly via A_1 receptors (Breschi et al., 1998).

Electrophysiological data and mRNA analysis of primary cultures of human and mouse pulmonary epithelia revealed the presence of P2X receptors on both the apical and basolateral membranes of well differentiated cells, occupation of which stimulated Cl^- transport (Taylor et al., 1999). Expression of P2X4 and P2X6 receptor isoforms in bronchial epithelium has been shown by in situ hybridization (Buell et al., 1996; Collo et al., 1996). Biochemical evidence was presented to show that P2X4 receptors on human 16HBE14o airway epithelial

cells mediated ATP-gated calcium entry channels that induced a sustained increase in $[Ca^{2+}]_i$ (Zsembery et al., 2003). Molecular and biochemical data show coexpression of P2X4 and P2X6 subtypes in 16HBE14o and CF (IB3-1) human bronchial epithelial cells (Liang et al., 2005). They additionally showed that novel transient lipid transfection-mediated delivery of small-interference RNA fragments specific to P2X4 and P2X6 receptors into IB3-1 cells inhibited extracellular ATP-induced Ca^{2+} entry. P2X4 receptors have been shown to be expressed on exocytotic vesicles known as lamellar bodies in ATII cells, and when lamellar bodies fuse with the plasma membrane, activated P2X4 receptor-mediated local Ca^{2+} signals facilitate fusion pore expansion and subsequent surfactant secretion (Miklavc et al., 2011). P2X7 receptors were found to be expressed on the ATI-like E10 cell line (Barth et al., 2007). There seems to be an interaction between P2X7 receptor protein and Caveolin-1 in lipid rafts in E10 cells (Barth et al., 2007, 2008). Reverse transcription polymerase chain reaction (RT-PCR) studies revealed that NT-1 and A549 cells expressed P2X4, P2X5, and P2X6 receptor mRNA, whereas P2X7 receptors were detected only on NT-1 cells (Théâtre et al., 2009). Activation of P2X7 receptors increases surfactant secretion by releasing ATP from ATII cells and subsequently stimulating $P2Y_2$ receptors on the ATII cells (Mishra et al., 2011). In mouse lungs, P2X7 protein seems to be expressed on ATI cells (unpublished observations) (Fig. 2).

Hydrogen peroxide is found in exhaled breath and is produced by airway epithelia. Apical production of hydrogen peroxide by human epithelial cells was stimulated by ATP but not ADP (Forteza et al., 2005).

A novel type of ATP-diphosphohydrolase was identified in bovine lung (Picher et al., 1993; Sévigny et al., 1997). Adenylate kinase and nucleoside diphosphokinase contribute to nucleotide metabolism on human airway surfaces (Donaldson et al., 2002).

2. Ciliated Cells. Mucociliary clearance serves as a primary host defense mechanism for removing dust and microorganisms from the lungs. ATP released mechanically from airway epithelial cells has a ciliostimulatory action in animal and human respiratory mucosa (Saano et al., 1991). In human and ovine ciliated airway epithelial cells, purinergic stimulation increases both $[Ca^{2+}]_i$ and ciliary beat frequency, and the regulator of G protein signaling protein 2 modulates these actions (Nlend et al., 2002). Extracellular ATP was shown to directly gate a cation-selective channel in rabbit ciliated epithelial cells (Korngreen et al., 1998), indicating the presence of P2X receptors. $P2Y_2$ receptor agonists increased lung mucociliary clearance in sheep (Sabater et al., 1999). The number of immunohistochemically positive cells for ATPase strongly correlated with ciliary motility in vitro, and cultures without ciliary activity did not exhibit ATPase staining (Schütz et al., 2002). Purinergic stimulation of ovine airway epithelial cells for 1 min transiently increased $[Ca^{2+}]_i$ and ciliary beat frequency, but stimulation of human epithelial cells led to an increase in ciliary beat frequency that outlasted the calcium transient by at least 20 min, perhaps indicating that ATP is triggering a signaling cascade (Lieb et al.,
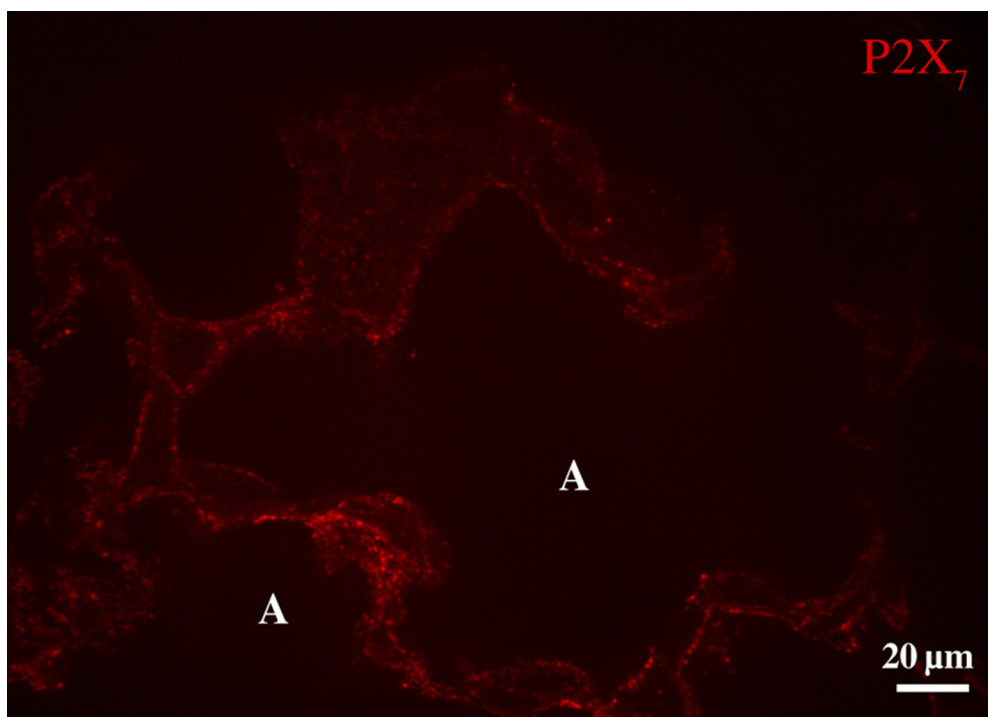

FIG. 2. Immunostaining for P2X7 receptors (red fluorescence) in an alveolar region of the mouse lung, revealing a clear P2X7 expression on the surface membrane of alveolar type I cells. A, alveolar spaces.

2002). cAMP and cGMP augment ATP-driven ciliary beat frequency increases at the level of isolated axonemes (Wyatt et al., 2005).

Airway ciliated epithelial cells have been shown to express the calcium-sensitive transmembrane adenyl cyclase isoforms AC1 and AC8 on the apical membrane, suggesting that they are involved in the purinergic regulation of ciliary beating (Nlend et al., 2007). Extracellular sodium regulates airway ciliary motility by inhibiting P2X receptor activation (Ma et al., 1999). In addition to ectonucleotidases that degrade ATP mechanically released from epithelial cells, ecto adenylate kinase mediates adenosine reformation into nucleotides, thereby prolonging the effects of ATP and ADP on airway epithelial surfaces (Picher and Boucher, 2003).

3. Goblet Cells. Mucin release from airway goblet cells is stimulated by ATP acting via P2 receptors (Kim and Lee, 1991). P2U (i.e., $P2Y_2$ and/or $P2Y_4$) receptors were later implicated in ATP and UTP regulation of mucin secretion in SPOCl cells, an airway goblet cell line (Abdullah et al., 1996, 2003), and in differentiated human bronchial cells (Kemp et al., 2004). Inhaled ATP causes mucin release from goblet cells in rats (Shin et al., 2000) and humans (Kemp et al., 2004). UTP can enhance both mucin secretion and mucin gene expression through different signaling pathways in cultures of human tracheobronchial tissues (Chen et al., 2001). $P2Y_2$ receptors provide a major pathway for the regulation of mucin secretion by ATP and UTP acting on the apical membranes of goblet cells (Huang et al., 2001) via phospholipase C pathways (Conway et al., 2003). The increase in $[Ca^{2+}]_i$ is due to mobilization of intracellular stores by activation of P2Y receptors (Rossi et al., 2007). ATP is secreted from goblet airway cells during Ca^{2+}-regulated mucin exocytosis, suggesting that ATP is released from mucin granules to signal neighboring ciliated cells to promote ion/water transport, perhaps via adenosine A_{2B} receptors, for hydration of secreted mucins into the airway lumen (Kreda et al., 2008). This group later reported that mucin granules contained ADP and AMP levels that exceeded ATP levels by nearly 10-fold (Kreda et al., 2010). Okada et al. (2011) published in vitro data suggesting that increased goblet cell nucleotide release and resultant adenosine accumulation might provide compensatory mechanisms to hydrate mucins by paracrine stimulation of ciliated cell ion and water secretion and to modulate inflammatory responses.

4. Neuroepithelial Bodies. Pulmonary neuroepithelial bodies (NEBs) are densely innervated groups of neuroendocrine cells that are invariably surrounded by a population of presumed airway epithelial stem cells, referred to as Clara-like cells. NEBs have been suggested to have several functions in the regulation of physiological processes in the lungs during prenatal, perinatal, and postnatal life (Adriaensen et al., 2003; Linnoila, 2006), but the strongest evidence to date im-

plicates them in airway oxygen sensing (Cutz et al., 2003) involved in the autonomic regulation of breathing.

Vagal sensory nerve terminals, arising from the nodose ganglion, in rat pulmonary NEBs were first shown to express P2X3 receptors by Brouns et al. (2000). These vagal nerve fibers are myelinated but lose their myelin sheaths just before branching and protruding intraepithelially between NEB cells (Brouns et al., 2003b). They also showed that these fibers were not activated by capsaicin and were immunoreactive to calbindin. A second sensory nerve population, arising from dorsal root ganglia (DRG), innervated NEBs and expressed calcitonin gene-related peptide and substance P but not P2X3 receptors. In a developmental study, vagal nodose sensory nerve endings expressing P2X3 receptors were the first to selectively innervate NEBs, from fetal stage GD16 onward. This suggested a role for purinergic regulation of NEBs during intrauterine life, when the density of NEBs was high, suggesting that NEBs may act as chemoreceptors for hypoxia before the carotid body chemoreceptors, which are known to be relatively immature at birth (Brouns et al., 2003a). This group later showed that approximately 40% of NEBs were innervated by vagal sensory fibers, approximately 50% by calcitonin gene-related peptide-immunoreactive DRG sensory fibers, and approximately 10% by intrinsic pulmonary nitrergic nerves (Van Genechten et al., 2004). Another research group demonstrated that both P2X2 and P2X3 receptor immunoreactivity on hamster NEBs was identified with 5-hydroxytryptamine (5-HT), a marker for NEBs (Fu et al., 2004). They further showed 1) that ATP induced a nondesensitizing inward current typical of P2X2 receptor-mediated responses, whereas α,β-methylene ATP (α,β-meATP), an agonist for P2X3 receptors, produced a slowly desensitizing inward current, perhaps indicating involvement of a P2X2/3 heteromultimer, and 2) that hypoxia and ATP induced 5-HT release from NEB cells.

In rodent studies of the neurochemical characterization of sensory receptor terminals in NEBs, it was shown that subpopulations of myelinated vagal sensory fibers expressing P2X2/3 receptors supplied NEBs (Fig. 3), and schematics were presented (Brouns et al., 2009, 2012; Fig. 4).

Quinacrine histochemistry indicated high amounts of vesicular ATP in NEB cells (Brouns et al., 2000; De Proost et al., 2009), and live cell imaging, using "reporter patching" with human embryonic kidney 293 cells overexpressing P2X2 receptors, indicated quantal ATP release after depolarization and paracrine interactions between NEB and Clara-like cells. It was concluded that in addition to ATP acting on P2X3 receptors on vagal sensory nerve endings in NEBs, local paracrine purinergic signaling in the NEB microenvironment, in which ATP released from activated NEB cells induces a secondary activation of the surrounding stem cell-like Clara-like cells via $P2Y_2$ receptors, may be important for airway
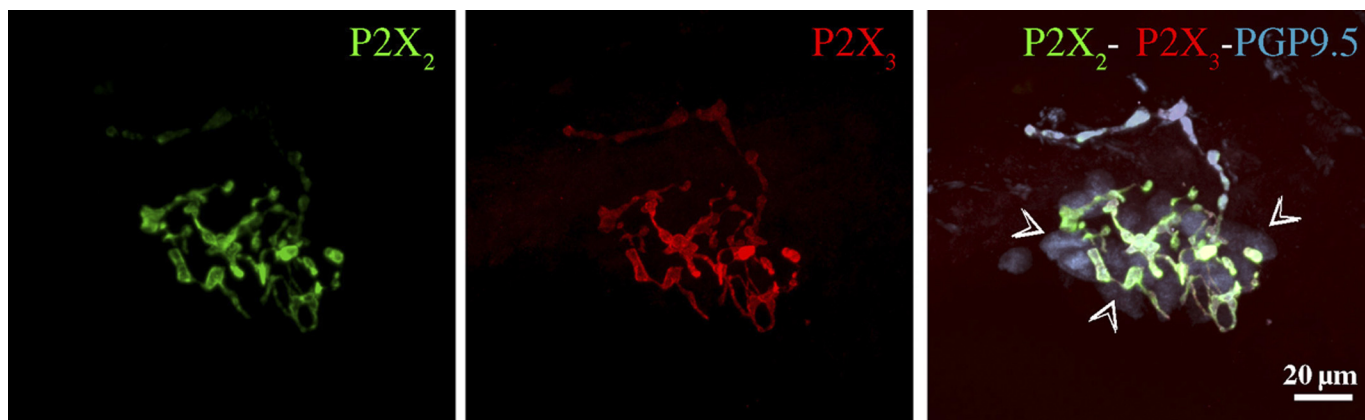
FIG. 3. Triple immunostaining for P2X2 receptors (green fluorescence), P2X3 receptors (red fluorescence), and PGP9.5 (blue fluorescence; marker for nerve fibers and NEB cells) in a mouse intrapulmonary airway. P2X2 and P2X3 receptors are invariably coexpressed in vagal sensory nerve terminals in the NEB (arrowheads).

epithelial regeneration after injury and/or the pathogenesis of small-cell lung carcinomas.

B. Immune Cells

Extracellular ATP serves as a danger signal to alert the immune system of tissue damage. P2 receptors are widely expressed in cells of the immune system, as illustrated mainly during the last decade for many species, and are now believed to underlie various functions in health and disease. In addition, adenosine is a signaling nucleoside that has been implicated in the regulation of immune function and may serve both pro- and anti-inflammatory functions in pulmonary disease.

1. Alveolar Macrophages. Extracellular adenine nucleotides have been known for many years to stimulate a Ca^{2+}-dependent respiratory burst (superoxide production) in alveolar macrophages that is mediated via purinergic receptors (Murphy et al., 1993). P2Y receptors mediate up-regulation of inducible nitric-oxide synthase mRNA and protein in alveolar macrophages (Greenberg et al., 1997).

Bovine alveolar macrophages, as well as B and T lymphocytes, express P2X7 receptors (Smith et al., 2001). Rat alveolar macrophages (NR8383) express functional P2X4 and phospholipase C-coupled P2Y$_1$ and P2Y$_2$ receptors (Bowler et al., 2003), and treatment with ATP results in an increased reactive oxygen species-mediated stress response and secretion of proinflammatory cytokines (Cruz et al., 2007). ATP can release cytokines and/or chemokines from rat alveolar macrophages (NR8383), which lack the P2X7 receptor, via P2Y$_2$ receptors (Stokes and Surprenant, 2007). In rat alveolar macrophages, freshly isolated from bronchoalveolar lavage fluid (BALF), the ATP-induced Ca^{2+}-release from intracellular stores seems to be reduced by nicotine via nicotinic acetylcholine receptors (Mikulski et al., 2010).

Although RT-PCR revealed transcripts for P2X1, P2X3, P2X4, P2X5, and P2X7 receptors in mouse alveolar macrophages, functional and pharmacological data point to a major participation of P2X4 and P2X7 receptors in pulmonary immune function (Kessler et al., 2011). Protein expression was confirmed for P2X1 and P2X4 receptors in control mouse lungs (unpublished observation) (Fig. 5).

Primary human alveolar macrophages obtained from BALF were shown to express mRNA for a large panel of purinoreceptors, namely P2X1, P2X4, P2X5, and P2X7, and P2Y$_1$, P2Y$_2$, P2Y$_4$, P2Y$_6$, P2Y$_{11}$, P2Y$_{13}$, and P2Y$_{14}$. Moreover, extracellular ATP induces Ca^{2+} transients and increased IL-1β and IL-6 secretion via P2X receptors, supporting the hypothesis that purinoreceptors may be involved in the pathogenesis of inflammatory lung diseases (see section VI) (Myrtek et al., 2008).

P2X4 receptor expression of human and rat alveolar macrophages is regulated by physiological stimuli, whereby P2X4 receptors become functional in response to initial phagocytic activity, but return to nonfunctional during sustained classic macrophage activation (Stokes and Surprenant, 2009). Endogenous extracellular ATP induces an up-regulation of purinergic receptors on neutrophils and alveolar macrophages. ATP also stimulates the recruitment of neutrophils to the lungs via P2Y$_2$ receptors and, as such, contributes to smoke-induced lung inflammation and development of emphysema (Cicko et al., 2010; Lommatzsch et al., 2010; see further on). P2X7 receptors were reported on macrophages in human BALF from patients with chronic obstructive pulmonary disease (COPD) (see section VI) (Lommatzsch et al., 2010).

Extracellular ATP, via the up-regulation of P2X7 receptors—as observed on alveolar macrophages in BALF and airway and blood neutrophils and eosinophils—has been implicated in the pathogenesis of airway inflammation (Müller et al., 2011), smoke-induced lung inflammation and emphysema (Lucatelli et al., 2011) in both rodents and humans. In mouse lungs, A$_1$ adenosine receptors were reported to be predominantly expressed on alveolar macrophages and to play an anti-inflammatory and/or protective role in adenosine-dependent pulmonary injury (Sun et al., 2005). Although mRNA for all
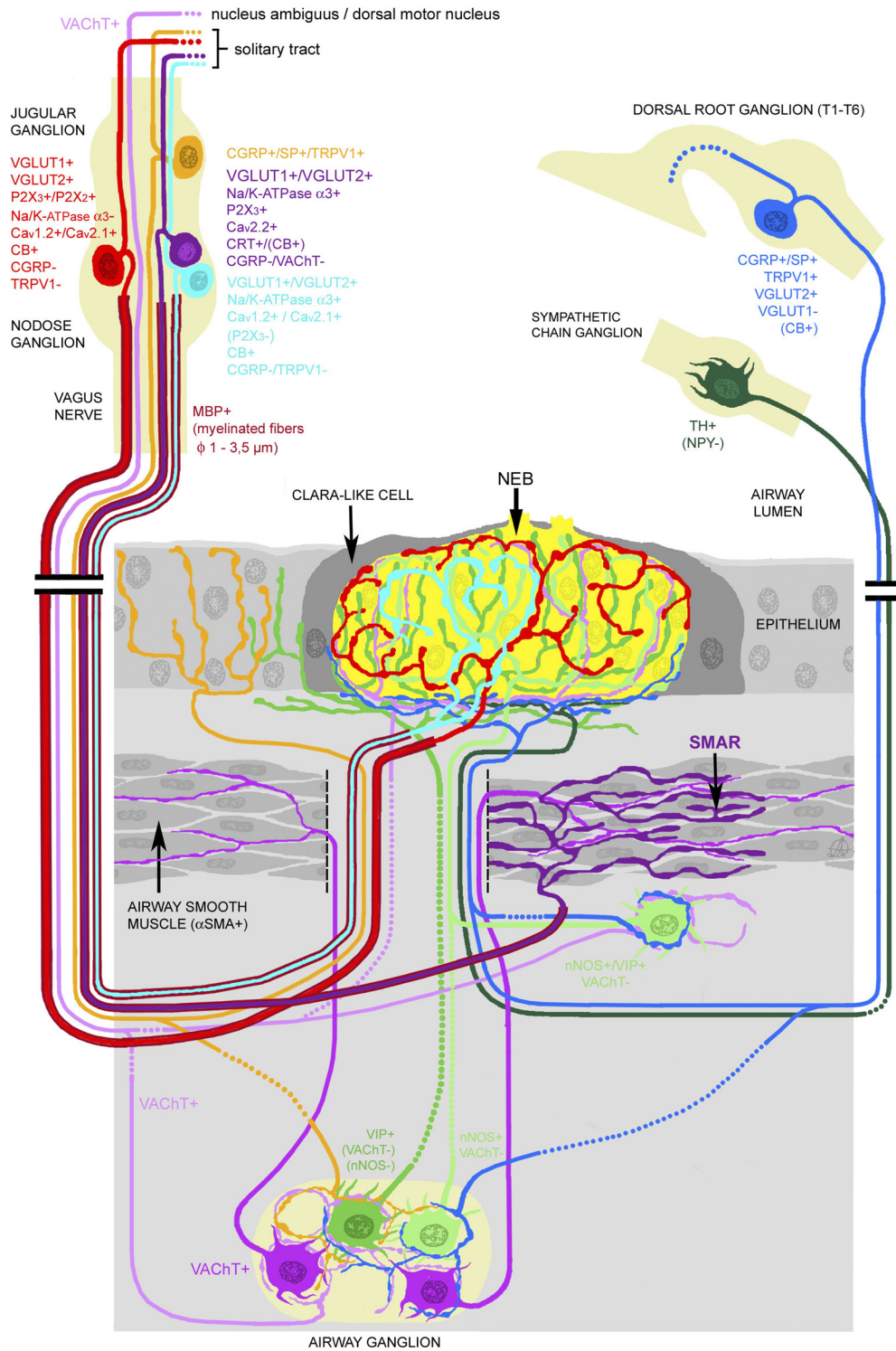
FIG. 4. Schematic representation of the main innervation of airway smooth muscle and of the sensory innervation of complex NEB receptors in rat lungs. Known characteristics of the represented neuronal populations are included in the scheme in the same color as the respective structures. The pulmonary NEB cells (yellow) express ATP, calcitonin gene-related peptide (CGRP), calbindin (CB), 5-HT, calcitonin, vesicular acetylcholine transporter (VAChT), P2X2 purinergic receptors, and $Ca_v2.1$ voltage-gated calcium channels. Clara-like cells (dark gray) can be distinguished by their location and immunoreactivity for Clara cell-specific protein, $P2Y_2$, and $Ca_v2.3$. The lower part of the scheme shows airway smooth muscle that receives nerve terminals from postganglionic parasympathetic neurons located in an airway ganglion, and laminar nerve terminals of vagal SMARs (dark purple) that intercalate between the smooth muscle cells. The center of the scheme represents a pulmonary NEB and its extensive interactions with sensory nerve terminals. The upper left part shows the vagal nodose afferent, and the upper right part the dorsal root afferents. CRT, calretinin; MB, myelin basic protein; nNOS, neuronal nitric-oxide synthase; SMA, smooth muscle actin; TRPV, transient receptor potential vanilloid; VGLUT, vesicular glutamate transporter; VIP, vasoactive intestinal peptide. [Reproduced from Brouns I, Pintelon I, Timmermans JP, and Adriaensen D (2012) Novel insights in the neurochemistry and function of pulmonary sensory receptors. *Adv Anat Embryol Cell Biol* 211:1–115, vii. Copyright © 2012 Springer. Used with permission.]
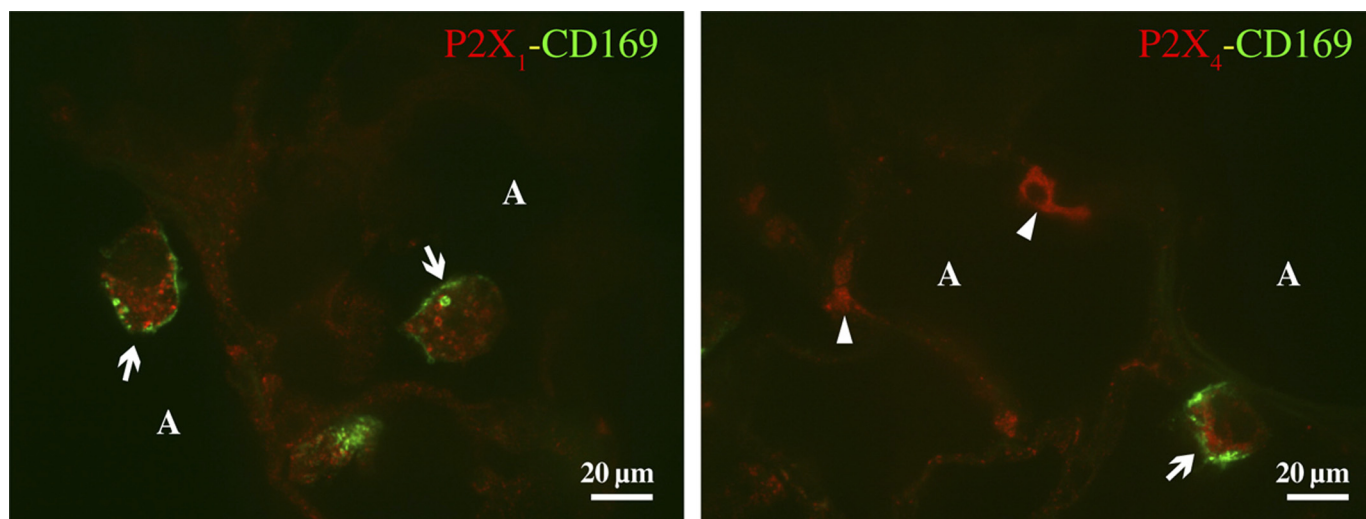
FIG. 5. Double immunostaining for P2 receptors (red fluorescence) and CD169 (green fluorescence), as a marker for alveolar macrophages (arrows) in control mouse lungs—macrophages were not activated. Left, P2X1 expression in CD169 positive alveolar macrophages. Right, P2X4 staining of a macrophage; note that other alveolar cells, presumably alveolar type II cells (arrowheads), appear to express P2X4. A, alveolar spaces.

adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) could be detected in human alveolar macrophages, only A_{2A} receptor expression was strongly up-regulated after lipopolysaccharide (LPS) treatment. In addition, adenosine-mediated inhibition of tumor necrosis factor-α and some chemokines seemed to be mediated mainly via A_{2A} adenosine receptors (Buenestado et al., 2010).

2. Lung Dendritic Cells. P2 receptors are expressed by human and mouse airway dendritic cells, and purinergic signaling is now believed to have a key role in allergen-driven airway inflammation (e.g., asthma) (see section VI) as a result of the recruitment and activation of lung myeloid dendritic cells that induce Th2 responses (Idzko et al., 2007). ATP was shown to trigger 1) migration to the airways of monocyte-derived dendritic cells and eosinophils and 2) production of reactive oxygen species involved in asthmatic airway inflammation via $P2Y_2$ receptors (Müller et al., 2010).

3. Mast Cells. Adenosine was reported to both inhibit and potentiate IgE-dependent histamine and 5-HT release from lung mast cells; A_2 receptors are involved (Hughes et al., 1984; Ott et al., 1992). Immunological identification of A_{2B} receptors was reported in human lung mast cells (Feoktistov et al., 2003). Adenosine closes the K^+ channel in human lung mast cells and inhibits their migration via A_{2A} receptors (Duffy et al., 2007). A_3 receptors were shown to play an important role in adenosine-mediated lung mast cell degranulation (Reeves et al., 1997; Zhong et al., 2003). ATP mediates anti-IgE-induced release of histamine from human lung mast cells, probably via $P2Y_1$ and/or $P2Y_2$ receptors (Schulman et al., 1999), but they have also been reported to express functional P2X1, P2X4, and P2X7 receptors (Wareham et al., 2009).

C. Airway Smooth Muscle

ATP produced strong contractions of human lung bronchiolar segments, whereas adenosine elicited only very weak contractions (Finney et al., 1985). ATP stimulated Ca^{2+} oscillations and contraction of airway smooth muscle of mouse lung slices, probably via $P2Y_2$ or $P2Y_4$ receptors (Bergner and Sanderson, 2002). In a later article, a more detailed analysis of the actions of ATP on human and rat bronchial smooth muscle led to the conclusion that ATP induces a transient contractile response mainly mediated by P2X4 receptors, but P2Y receptors were also present (Mounkaïla et al., 2005). RT-PCR and Western blot analyses carried out on primary cultures of human airway smooth muscle showed expression of $P2Y_1$, $P2Y_2$, $P2Y_4$, and $P2Y_6$ receptors and ATP, UTP, ADP, and UDP all produced a significant increase in $[Ca^{2+}]_i$ and contraction (Govindaraju et al., 2005).

Adenosine receptor antagonists induced bronchoconstriction in rats (Salonen et al., 1982), whereas enprofylline, another xanthine, produced bronchodilation, apparently without adenosine receptor antagonism (Lunell et al., 1983). Adenosine caused bronchoconstriction in a rat model, but analysis suggested that adenosine acts by stimulating postjunctional vagal nerve endings and mast cells (Pauwels and Van der Straeten, 1987). Inflammatory mediators inhibited by indomethacin may be involved in adenosine bronchoconstriction (Crimi et al., 1989). In perfused lungs sensitized with ovalbumin, adenosine produced bronchoconstriction, but at high concentrations, it had bronchodilator actions (Thorne and Broadley, 1992). The ADP receptor antagonist 8-phenyltheophylline blocked relaxant but not contractile responses. It has been claimed that 5-HT may mediate adenosine-induced airway contraction (Matera et

al., 1995). Adenosine-mediated bronchoconstriction was characterized to be mediated by A_1, A_{2B}, and A_3 but not A_{2A} receptor subtypes (Pauwels and Joos, 1995). A_1 receptors mediated mobilization of Ca^{2+} in human bronchial smooth muscle cells (Ethier and Madison, 2006). Other studies suggested that xanthine-resistant A_3 receptors dominated (Thorne et al., 1996). Experiments on rabbit airway smooth muscle suggested that adenosine causes relaxation via an A_2 receptor that releases nitric oxide from the epithelium (Ali et al., 1997). Adenosine enhanced endothelium-induced bronchoconstriction in guinea pigs (Kanazawa et al., 1997). A_{2B} receptors mediate increase in cytokine release from bronchial smooth muscle cells (Zhong et al., 2004) and mediate the relaxing effects of adenosine on guinea pig airways (Breschi et al., 2007).

D. Innervation

In addition to sympathetic, parasympathetic, and sensory nerves, many neurons in intrinsic ganglia are derived from a separate population of neural crest cells (Freem et al., 2010), which suggests that, as in the gut and heart, intrinsic neurons may allow local reflex activity independent of the central nervous system (see Burnstock, 2009a).

1. Nonadrenergic/Noncholinergic Neurotransmission. NANC neurotransmission was recognized early to participate in autonomic control of pulmonary smooth muscle (Koelle, 1975; Diamond and O'Donnell, 1980). It is now well established that ATP is a cotransmitter both with noradrenaline (NA) in sympathetic nerves and with acetylcholine in parasympathetic nerves (see Burnstock, 2007a). ATP has been considered a NANC transmitter in inhibitory vagal nerves supplying the airways (Irvin et al., 1980, 1983; Souhrada et al., 1980; Satchell, 1982; Pauwels et al., 1990). Adenosine inhibits NANC excitatory transmission in guinea pig trachea (Kamikawa and Shimo, 1989), in retrospect probably by acting on P1 (A_1) receptors on nerve terminal varicosities to inhibit transmitter release (Schmidt et al., 1995).

2. Sensory Nerves, Reflex Activity, and Pain. In canine lungs, ATP activates pulmonary vagal C fiber sensory nerve terminals, mediated by P2X receptors (Pelleg and Hurt, 1996), and causes reflex bronchoconstriction (Katchanov et al., 1998). In another study, activation of P2X receptors on vagal afferent terminals evoked Bezold-Jarisch depressor cardiorespiratory reflexes in anesthetized rats (McQueen et al., 1998). Because α,β-meATP initiated the reflex in this study, it is likely that P2X1 and/or P2X3 receptors were involved. ATP stimulated both capsaicin-sensitive and -insensitive vagal bronchopulmonary C fibers in the mouse via P2X receptors (Kollarik et al., 2003). Vagal C fibers innervating the pulmonary system are derived from cell bodies situated in both jugular (neural crest-derived) and nodose (placodal) vagal sensory ganglia. Only the nodose C-fiber population responds to P2X receptor activation (Undem

et al., 2004; Nassenstein et al., 2010). In addition, intrapulmonary myelinated nodose airway mechanosensors (A-fiber stretch receptors) have been reported to be activated by ATP via P2X receptors (Lee et al., 2004). ATP evoked an inward current in 34 of 39 pulmonary sensory neurons in nodose ganglia via P2X receptors (Ni and Lee, 2008). Evidence has been presented for both A_1 and A_{2A} receptors on vagal sensory C fibers in guinea pig lungs (Chuaychoo et al., 2006). The sensory transduction of pulmonary reactive oxygen species by capsaicin-sensitive vagal lung afferent fibers was found to be mediated by both transient receptor potential vanilloid 1 and P2X receptors (Ruan et al., 2005).

In rodents, subpopulations of myelinated vagal sensory fibers expressing P2X2/3 receptors were shown to terminate both in NEBs (see section II.4) (Brouns et al., 2000, 2009, 2012) (Figs. 3 and 4) and in airway smooth muscle as so-called smooth muscle-associated airway receptors (SMARs) (Brouns et al., 2006, 2012) (Figs. 4 and 6). Neuronal tracing from the airways, combined with immunocytochemistry, calcium imaging, and electrophysiological recording on dissociated vagal nodose airway-related neurons revealed that a considerable part of the traced neurons coexpress P2X3 and the cold-sensitive channel transient receptor potential melastatin 8 (Xing et al., 2008).

The visceral pleura has historically been considered insensitive to painful stimuli. However, more recent studies have revealed sensory fibers with complex laminar terminals that express P2X3 receptors embedded in the elastic fiber network of the rodent visceral pleura (Pintelon et al., 2007; Brouns et al., 2012; Fig. 7). These fibers probably originate from nerve cell bodies in DRGs and have been reported to mediate nociception in other visceral organs (see Burnstock, 2009b).

E. Vasculature

Evidence for release of NA and ATP as cotransmitters from sympathetic nerves supplying rabbit pulmonary arteries was reported 30 years ago (Katsuragi and Su, 1982). An important advance was made when it was shown that excitatory junctional potentials recorded in the smooth muscle of rat intrapulmonary arteries in response to sympathetic nerve stimulation were mediated by ATP (Inoue and Kannan, 1988). Adenosine, acting prejunctionally, mediates release of transmitter from sympathetic nerves supplying the rabbit pulmonary artery (Husted and Nedergaard, 1985). Perivascular nerve stimulation of rabbit pulmonary artery elicits release of NA and ATP (Mohri et al., 1993). It has been claimed that inhibitory purinergic neurotransmission is endothelium-dependent in pulmonary vessels (Liu and Barnes, 1994).

Porcine pulmonary vessels express P2 receptors that mediate the synthesis and release of prostacyclin (Hellewell and Pearson, 1984). In the isolated, blood-
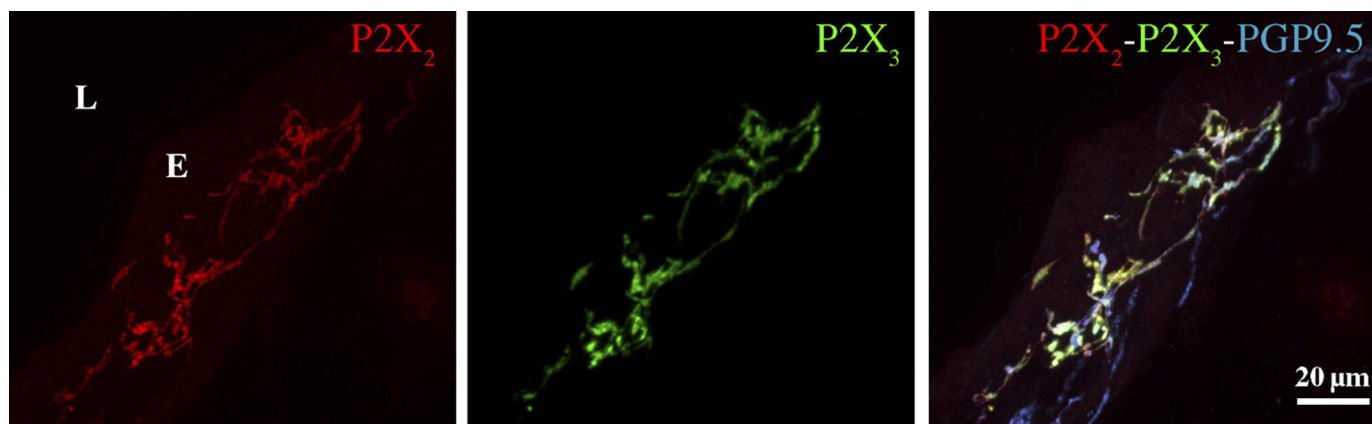
FIG. 6. Triple immunostaining for P2X2 receptors (red fluorescence), P2X3 receptors (green fluorescence), and PGP9.5 (blue fluorescence) in a mouse intrapulmonary airway. P2X2/3 stained laminar terminals of a SMAR are intermingled with PGP9.5 labeled nerve fibers that are present in the airway smooth muscle bundle right beneath the epithelium (E). L, airway lumen.

perfused, and ventilated rat lung, P2X receptors activated by α,β-meATP caused vasoconstriction, whereas P2Y receptors, probably located largely on the endothelium, mediated a small vasodilator response (Liu et al., 1989; McCormack et al., 1989a). Vasoconstriction of the rat pulmonary vascular bed by UTP and ATP is resistant to suramin antagonism (Rubino and Burnstock, 1996) and is probably mediated by $P2Y_4$ receptors. ATP- and ADP-induced increase in $[Ca^{2+}]_i$ in rat pulmonary artery myocytes was found to be mediated by P2X and P2U ($P2Y_2$ and/or $P2Y_4$) receptors (Guibert et al., 1996; Hartley and Kozlowski, 1997). In endothelium-denuded rat pulmonary arteries, $P2Y_2$ and a UDP-sensitive receptor (presumably $P2Y_6$) were identified on myocytes (Hartley et al., 1998). Although ATP was a potent vasoconstrictor in perfused rat lung (Rubino and Burnstock, 1996), it was only a weak agonist in isolated rat pulmonary artery (Rubino et al., 1999). UTP and UDP are equipotent in inducing vasoconstriction of rat intrapulmonary arteries (Rubino et al., 1999). There is regional variation in P2 receptor expression mediating constriction in the rat pulmonary arterial circulation; P2Y re-

ceptor agonist potencies were similar in large and small vessels, but P2X receptor agonists were more potent in small arteries (Chootip et al., 2002). ATP was reported to produce vasoconstriction via P2X1 receptors in the feline pulmonary vascular bed (Neely et al., 1991). In mouse airways, arterial smooth muscle seems to express P2X1 (unpublished observations) (Fig. 8) and $P2Y_{11}$ protein (unpublished observations) (Fig. 9) with regional selectivity, whereas airway smooth muscle is negative.

An early article described hydrolysis of ATP to adenosine by cultures of porcine pulmonary endothelial cells and uptake of adenosine to be rapidly phosphorylated by adenosine kinase (Dieterle et al., 1978). Inhibition of ecto-ATPase by adenosine-5'-(γ-thio)-triphosphate (ATPγS), α,β-meATP, and adenylyl-imidodiphosphate in bovine pulmonary artery endothelial cells has been reported (Chen and Lin, 1997). Adenosine was shown to mediate vasodilation via P1 receptors but apparently does not mediate the pulmonary vasodilator response to ATP in the feline pulmonary vascular bed (Neely et al., 1989). As mentioned above, ATP produces vasoconstriction via P2X1 recep-
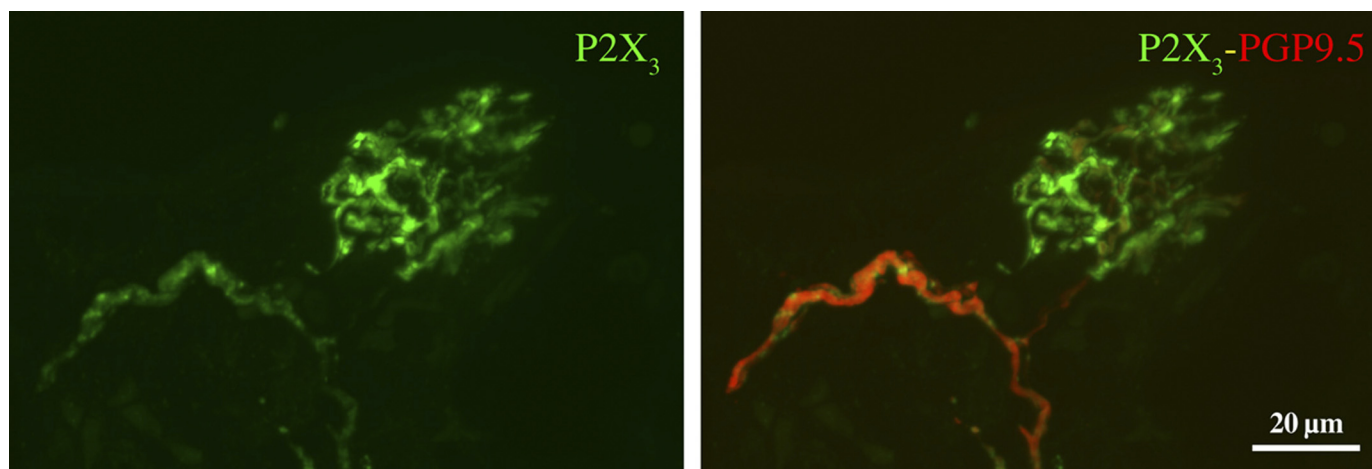

FIG. 7. P2X3 receptor expression (green fluorescence) in a typically structured sensory visceral pleura receptor (VPR) of a mouse lung. PGP9.5 immunostaining (red fluorescence) labels all nerve fibers and terminals.
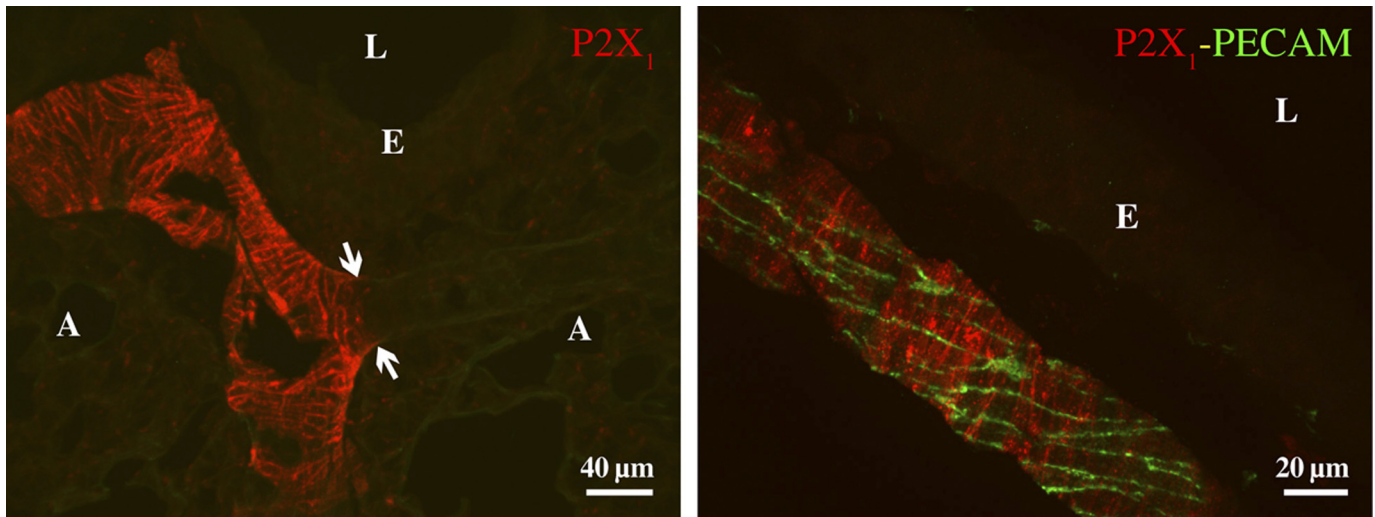
FIG. 8. Double immunostaining for P2X1 receptors (red fluorescence) and PECAM (green fluorescence; marker for endothelial cells) in small and terminal airways of mouse lungs. Left, P2X1 expression in smooth muscle cells of a small (resistance) artery. Note the abrupt end of the expression in a small vessel that branches off (arrows). Right, additional PECAM staining clearly reveals P2X1 expression in arterial smooth muscle cells, but not in the endothelial cells in this volume projection of confocal images of another small artery. In addition, the airway smooth muscle, which is invisible in these images but known to be invariably located just beneath the epithelial layer (E), appears P2X1-negative. A, alveolar spaces; L, airway lumen.

tors but also in part by the action of adenosine on A_1-like receptors after its breakdown in pulmonary arteries of cats (Neely et al., 1991), guinea pigs (Wiklund et al., 1987), and sheep (Biaggioni et al., 1989). However, P1 receptors mediate relaxation of bovine bronchial arteries (Alexander and Eyre, 1985). In human pulmonary arter-

ies, the adenosine vasodilator effects are mediated by A_2 receptors (McCormack et al., 1989b). In juvenile rabbit pulmonary arteries and veins, the relaxations to adenosine were found to be endothelium-dependent (Steinhorn et al., 1994). Adenosine, acting via A_2 receptors, mediates vasodilation in the perfused adult rabbit lung
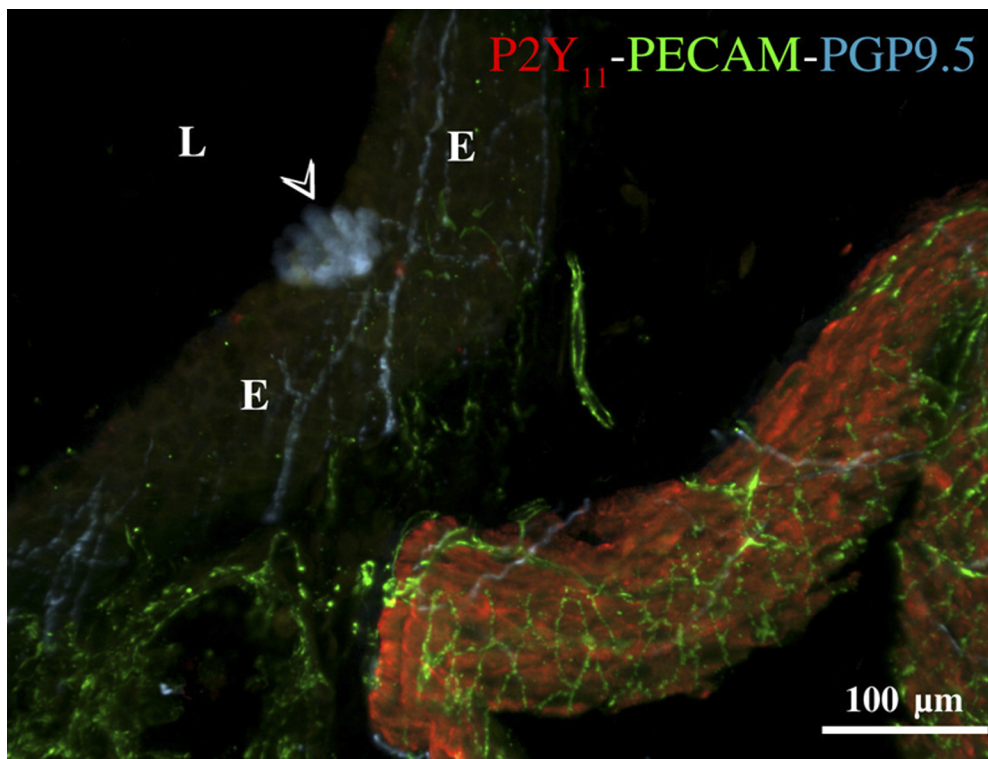
FIG. 9. Multiple immunostaining for P2 receptors (red fluorescence), PECAM (green fluorescence; marker for endothelial cells), and PGP9.5 (blue fluorescence; marker for nerve fibers and NEBs) in a mouse intrapulmonary airway. $P2Y_{11}$ expression is strong in smooth muscle cells of a large artery in the airway wall but absent from the airway smooth muscle that is invisible in this image but known to be invariably located just beneath the epithelial layer (E). Note that also the NEB (open arrowhead), nerve fibers, and endothelial cells are $P2Y_{11}$ negative. L, airway lumen.

(Pearl, 1994), and it was asserted that this dilation was due to direct action on the vascular smooth muscle (El-Kashef et al., 1999). Adenosine mediates both contractile and relaxant effects on the main pulmonary artery of guinea pigs via A_1 and A_{2B} receptors, respectively (Szentmiklósi et al., 1995). In addition, in the feline pulmonary vascular bed, adenosine causes vasoconstriction via A_1 receptors and vasodilation via A_2 receptors but apparently not by releasing NO (Cheng et al., 1996). LPS binds to and activates A_1 receptors on human pulmonary artery endothelial cells to induce the release of IL-6 and thromboxane A_2 (Wilson and Batra, 2002) and may contribute to the pathophysiology of acute lung injury.

Endothelium-dependent relaxation of human pulmonary arteries by ATP has been demonstrated (Greenberg et al., 1987; Dinh Xuan et al., 1990), probably via $P2Y_2$ receptors (Hasséssian and Burnstock, 1995). ATP and UTP, acting via endothelial $P2Y_1$, $P2Y_2$, and/or $P2Y_4$ receptors, elicits vasodilation of bovine and rabbit pulmonary arteries, partly via mobilization of intracellular Ca^{2+} and subsequent prostacyclin release (Lustig et al., 1992; Chen et al., 1996; Qasabian et al., 1997). Shear stress evokes release of ATP from endothelial cells, which causes NO release and pulmonary vasodilation (Hasséssian et al., 1993; Kiefmann et al., 2009). ATP release from endothelial cells induced by NA was greater in the distal (smaller) arteries compared with proximal pulmonary arteries of the rabbit (Takeuchi et al., 1995). In addition to ATP released from endothelial cells, ATP release from erythrocytes contributes to release of NO and subsequent vasodilation (Sprague et al., 1996, 2003; Kotsis and Spence, 2003). Protein kinase C mediates inhibition of endothelial $P2Y_1$ and $P2Y_2$ receptor-mediated phosphoinositide turnover in bovine pulmonary artery (Chen and Lin, 1999). Intercellular communication via Ca^{2+} waves upon mechanical stimulation of calf pulmonary artery endothelial cells is mediated by nucleotides (Moerenhout et al., 2001). Shear stress stimulates human pulmonary artery endothelial cells to release ATP, which then activates Ca^{2+} influx in endothelial cells via P2X4 receptors (Yamamoto et al., 2003). $P2Y_4$ receptor knockout mice do not exhibit normal endothelial cell responses; increased $[Ca^{2+}]_i$, subsequent production of NO, and adaptive vascular remodeling are lost (Ando and Yamamoto, 2009). ATP causes NO-mediated pulmonary vasodilation predominantly via endothelial $P2Y_2$ receptors in newborn rabbits (Konduri et al., 2004).

Uridine adenosine tetraphosphate has been identified as an endothelium-derived vasoconstrictor (Jankowski et al., 2005) that stimulates endothelium-independent contraction of the isolated rat pulmonary artery (Gui et al., 2008). Luminal ATP-induced contraction of rabbit pulmonary arteries has been reported (Baek et al., 2008).

Pulmonary artery rings from fetal sheep show diminished endothelium-mediated relaxation to ADP compared with postnatal sheep (Abman et al., 1991). ATP and adenosine increase pulmonary blood flow in perinatal lamb via P1 and P2 receptors that are independent of prostacyclin synthesis (Konduri et al., 1992), later identified as A_{2A} and $P2Y_1$ receptors (Konduri et al., 2000), and shown to act via NO (Konduri and Mital, 2000). An increase in ATP release during oxygen exposure may contribute to birth-related pulmonary vasodilation in lambs (Konduri and Mattei, 2002).

Distension of the main pulmonary artery in anesthetized dogs stimulates vagal afferent activity (Moore et al., 2004), possibly via purinergic mechanosensory transduction, where ATP released in response to stretch acts on P2X3 receptors expressed on sensory nerve terminals in the vessel wall (see Burnstock, 2007a).

It has long been known that, unlike in most other vascular beds, hypoxia induces pulmonary vasoconstriction (von Euler and Liljestrand, 1946), leading to pulmonary hypertension. However, hypoxia can also result in pulmonary vasodilation, which, in contrast to the systemic circulation, was shown not to be mediated by adenosine (Gottlieb et al., 1984). The pulmonary hypertensive response to endotoxin was first reported by Hinshaw et al. (1957), and damage to the endothelium may play a role in the development of pulmonary hypertension in humans (Greenberg et al., 1987). ATP-$MgCl_2$ (the naturally occurring form of ATP in the body is bound to magnesium) has been shown to reduce the vasoconstriction associated with hypoxic pulmonary hypertension (Paidas et al., 1988). On the basis of studies in lambs, it was subsequently proposed that ATP and adenosine may have a beneficial role in the management of pulmonary hypertension in children (Konduri, 1994). Adenosine can decrease pulmonary artery pressure and vascular resistance in patients with primary pulmonary hypertension who respond to calcium-channel blockers (Inbar et al., 1993).

Extracellular nucleotides enhance leukocyte adherence to pulmonary artery endothelial cells via P2Y receptors. Because adherence of leukocytes is an important early step in acute vascular injuries, it was speculated that nucleotide-induced leukocyte adherence could be essential in mediating vascular injuries in such conditions as respiratory distress syndrome and septic shock (Dawicki et al., 1995).

Extracellular ATP is a proangiogenic factor for pulmonary artery vasa vasorum endothelial cells, potentiating the effect of both vascular endothelial growth factor and β-fibroblast growth factor (Gerasimovskaya et al., 2008). Hypoxia, through hypoxia-inducible transcription factor-1α and -2α, induces angiogenesis by up-regulating cytokines. The adenosine A_{2A} receptor is an angiogenic target of hypoxia-inducible transcription factor-2α in human pulmonary endothelial cells and mediates increases in cell proliferation, cell migration, and tube

formation (Ahmad et al., 2009). The authors further show that there is increased expression of A_{2A} receptors in human lung cancer.

Permeability edema is a life-threatening complication accompanying acute lung injury. Extracellular ATP, produced during inflammation, induces a rapid and dose-dependent increase in transendothelial electrical resistance, and restoration of endothelial barrier integrity is achieved via ATP and adenosine acting on endothelial P2Y and A_2 receptors (Lucas et al., 2009).

Dormant pulmonary vein conduction can be provoked by ATP after extensive encircling pulmonary vein isolation, and it has been claimed that radio frequency application for provoked ATP-reconnection may reduce atrial fibrillation recurrence (Hachiya et al., 2007). Adenosine restores atriovenous conduction after ostial isolation of pulmonary veins (Tritto et al., 2004).

III. Trachea

A. Epithelial Cells

Intravenous ATP prevented the decrease in tracheal ciliary beat frequency that occurs in the incised trachea in control anesthetized rats after 70 min (Saano et al., 1990). Luminal administration of ATP increased tracheal ciliary beat frequency, whereas adenosine reduced the ATP effects (Wong and Yeates, 1992). ATP, acting via an epithelial P2 receptor, stimulated eicosanoid metabolism in rabbit trachea, leading to the production of prostaglandin E_2 (Aksoy et al., 1995). ATP evoked Cl^- secretion across tracheal epithelium (Satoh et al., 1995) via multiple P2Y receptors on both apical and basolateral regions (Hwang et al., 1996). ATP caused a rapid increase in both $[Ca^{2+}]_i$ and ciliary beat frequency in cultured rabbit tracheal epithelial cells (Korngreen and Priel, 1996; Uzlaner and Priel, 1999). ATP and UTP induced mucin release from primary hamster tracheal surface epithelial cells via P2U receptors (Kim et al., 1996). ATP directly gates a cation-selective channel via P2X receptors in rabbit tracheal ciliated epithelial cells (Korngreen et al., 1998). From $P2Y_2$ receptor knockout studies, it was concluded that the $P2Y_2$ receptor was the dominant P2Y receptor subtype that regulates epithelial Cl^- transport in the mouse trachea (Cressman et al., 1998, 1999).

RT-PCR and pharmacological studies identified $P2Y_1$, $P2Y_2$, P2X4, and P2X7 receptors that regulate the increase in $[Ca^{2+}]_i$ in freshly isolated rat tracheal epithelial cells (Marino et al., 1999). The P2X receptors on rabbit tracheal ciliated cells were also identified as P2X4 and P2X7 subtypes (Ma et al., 2006). Mechanically induced release of ATP resulted in Ca^{2+} waves in rabbit tracheal epithelial cells (Evans and Sanderson, 1999; Woodruff et al., 1999) and enhanced ciliary beat frequency (Winters et al., 2007). Oscillations in ciliary beat frequency and $[Ca^{2+}]_i$ in rabbit tracheal epithelial cells were induced by ATP (Zhang and Sanderson, 2003).

Hypo-osmotic stress stimulated ATP release from tracheal ciliary cells, leading to increase in ciliary beat frequency (Kawakami et al., 2004). Activation of P2 receptors inhibited ENaC in mouse tracheal epithelial cells via hydrolysis of phosphatidylinositol-bisphosphate (Kunzelmann et al., 2005). $P2Y_6$ receptors increase Ca^{2+} and CFTR-dependent Cl^- secretion in mouse trachea (Schreiber and Kunzelmann, 2005). ATP and ADP stimulated goblet cells in the superfused epithelium to secrete mucin; P2 receptors were present on both apical and basolateral membranes (Davis et al., 1992).

ATP evoked an increase in $[Ca^{2+}]_i$ and mucus glycoprotein secretion from tracheal submucosal glands in cats (Shimura et al., 1994), chloride secretion in humans (Yamaya et al., 1996), and $[Ca^{2+}]_i$ in pigs (Zhang and Roomans, 1999) via P2U receptors. Both $P2Y_2$ and $P2Y_4$ receptors were characterized in human tracheal gland cells (Merten et al., 1998). It was claimed that a receptor for Ap_4A different from P2 receptors was present on the human tracheal gland cells (Saleh et al., 1999b).

Adenosine evoked mucus secretion in canine trachea that was blocked by P1 receptor antagonists (Johnson and McNee, 1985). Mucosal adenosine also stimulated Cl^- secretion in canine tracheal epithelium (Pratt et al., 1986). Adenosine induced cAMP-dependent inhibition of ciliary activity in rabbit tracheal epithelium (Tamaoki et al., 1989). Adenosine inhibits endothelin-1 production and secretion in guinea pig tracheal epithelial cells via A_{2B} receptors and cAMP formation (Pelletier et al., 2000). A_3 receptor-mediated potentiation of mucociliary transport, probably through Ca^{2+}-mediated stimulation of airway epithelial ciliary motility, has been reported (Taira et al., 2002).

B. Smooth Muscle and Its Innervation

NANC inhibitory neurons supplying the guinea pig, dog, and human trachea were recognized early (Coburn and Tomita, 1973; Coleman and Levy, 1974; Richardson and Bouchard, 1975; Richardson and Béland, 1976; Kalenberg and Satchell, 1979; Russell, 1980), and the inhibitory response to field stimulation was claimed to show features of purinergic neurotransmission (Coburn and Tomita, 1973; Coleman and Levy, 1974).

A_1 and A_3 receptor agonists were shown to inhibit NANC relaxation in isolated guinea pig trachea (Dellabianca et al., 2009). Adenosine deaminase reduced the inhibitory response to adenosine and NANC inhibitory nerve stimulation in guinea pig trachea (Satchell, 1984b). ATP and adenosine caused relaxations of the guinea pig trachea, although adenosine was more potent than ATP (Farmer and Farrar, 1976; Mizrahi et al., 1982; Small, 1982), and Satchell (1984a) suggested that ATP acts on adenosine receptors after breakdown. However, in contradiction, Welford and Anderson (1988) later claimed that ATP itself can cause relaxation without being metabolized to adenosine. Evidence for more than one type of purine receptor was presented for iso-

lated guinea pig trachea, mediating relaxation with a potency order of adenosine > 5′-AMP > ATP > ADP (Jones et al., 1980). Excitatory junctional potentials and contraction, which were reported to be blocked by atropine, were recorded in guinea pig tracheal smooth muscle in response to nerve stimulation, followed by prolonged relaxations that were blocked by indomethacin, suggesting mediation by prostaglandins (Kamikawa and Shimo, 1976). Later, EP$_2$ prostaglandin receptors were shown to mediate tracheal relaxation to ATP (Fortner et al., 2001). Others reported that neither vasoactive intestinal peptide nor ATP mediated NANC inhibitory neurotransmission in the guinea pig trachea (Karlsson and Persson, 1984). α,β-MeATP contracted guinea pig tracheal smooth muscle, suggesting that a P2X receptor was involved (Candenas et al., 1992), in retrospect probably a P2X1 or P2X3 receptor. ATP and UTP contracted the isolated, perfused trachea; removal of the epithelium decreased it, suggesting that factors released from the respiratory epithelium might be contributing (Fedan et al., 1993a). In a sister article, the authors showed that concentrations of ATP higher than those causing contraction of the perfused trachea relaxed the smooth muscle via a P2, but not P1, receptor (Fedan et al., 1993b). Propofol attenuated ATP-induced contraction of rat trachea through inhibition of P2 receptor binding (Yamaguchi et al., 2007). It was claimed in a more recent article that ATP caused contractions and increased [Ca^{2+}]$_i$ in single smooth muscle cells from porcine trachea via P2X4 receptors (Nagaoka et al., 2009). An ecto-ATP-diphosphohydrolase similar to that described in lung was shown to be localized in the membranes of nonvascular smooth muscle cells of the bovine trachea (Picher et al., 1994).

Adenosine caused contraction of spiral strips and relaxation of transverse strips of guinea pig trachea (Satchell and Smith, 1984). A$_2$ receptors were identified in tracheal smooth muscle by pharmacological analysis (Brackett et al., 1990; Losinski and Alexander, 1995). Ghai et al. (1987) presented evidence for both A$_1$ and A$_2$ receptors on guinea pig tracheal smooth muscle. Adenosine relaxed guinea pig trachea via an A$_{2B}$ receptor (Brown and Collis, 1982; Karlsson and Persson, 1984). Relaxation of the trachea is also produced by xanthines, but this is independent of adenosine antagonism (Darmani and Broadley, 1986; Small et al., 1988). Advenier et al. (1988) suggested that epithelium had an influence on the mechanical response of guinea pig trachea to adenosine, but a later article (Thorne and Broadley, 2001) did not support this possibility. However, treatment with caffeine for 10 weeks led to changes in adenosine-induced relaxation that did seem to involve the epithelium (Brugós et al., 2007). Adenosine induced a cholinergic tracheal reflex contraction in guinea pig in vivo via an A$_1$ receptor-dependent mechanism (Reynolds et al., 2008). A$_2$ receptor deficiency led to impaired tra-

cheal relaxation via the NADPH oxidase pathway in allergic mice (Nadeem et al., 2009).

IV. Nasal Mucosa

Both basolateral and apical application of ATP induces Cl$^-$ secretion in human nasal epithelium (Clarke and Boucher, 1992). Extracellular ATP increases fluid transport by human nasal epithelial cells in culture (Benali et al., 1994). Evidence was presented to suggest that ATP acts as a cotransmitter with NA in sympathetic nervous control of blood vessels of the nasal mucosa of cats and dogs (Lacroix et al., 1994). UDP activates a receptor, distinct from the P2Y$_2$ receptor, on human nasal epithelial cells (Lazarowski et al., 1997), which in retrospect was a P2Y$_6$ receptor. Extracellular sodium regulates ciliary motility in epithelial cells isolated from surgically excised nasal polyps by inhibiting P2X receptor-mediated responses (Ma et al., 1999). ATP, UTP, UDP, and adenosine-stimulated ciliary activity of human nasal epithelial cells via P2Y$_2$, P2Y$_6$, and A$_{2B}$ receptors, whereas P2Y$_1$, P2Y$_4$, and P2Y$_{11}$ receptors were not involved (Morse et al., 2001). ATPase expression in nasal epithelial cells showed correlation with ciliary activity (Schütz et al., 2002). UTP and ATPγS were shown to induce mucin secretion via Ca^{2+}-dependent pathways in human nasal epithelial cells (Choi et al., 2003). Purinergic stimulation via P2 receptors induces Ca^{2+}-dependent activation of Na$^+$-K$^+$-2Cl$^-$ cotransporter in human nasal epithelium (Shin et al., 2004). RT-PCR studies of human nasal epithelial cells showed expression of mRNA for P2X3, P2X4, P2X7, P2Y$_1$, P2Y$_2$, P2Y$_4$, P2Y$_6$, P2Y$_{11}$, and P2Y$_{12}$, and functional studies showed that luminal membranes express P2Y$_2$, P2Y$_6$, and probably P2Y$_{11}$ receptors, whereas basolateral membranes express P2Y$_2$ receptors; P2X3, P2X4, P2X7, P2Y$_4$, and P2Y$_{12}$ did not seem to be functional in normal epithelial cells (Kim et al., 2004). Immunohistochemical studies of P2 receptor proteins showed P2X3 receptors on neurons of the rat nasal mucosa, P2X5 and P2X7 receptors on respiratory epithelial cells, P2Y$_1$ receptors on respiratory epithelial cells and submucosal glands, and P2Y$_2$ receptors on mucous secretory cells (Gayle and Burnstock, 2005). Zinc increased ciliary beat frequency in a calcium-dependent way in mouse nasal septal epithelial cultures through activation of P2X receptors and may thus be a useful agent for stimulating mucociliary clearance (Woodworth et al., 2010).

V. Central Control of Respiration

The ventrolateral medulla contains a network of respiratory neurons that are responsible for the generation and shaping of respiratory rhythm; it also functions as a chemoreceptive area mediating the ventilatory response to hypercapnia. Evidence has been presented that ATP acting on P2X2 receptors expressed in ventrolateral medulla neurons influences these functions

(Gourine et al., 2003). A potentially important role for P2 receptor synaptic signaling in respiratory motor control is suggested by the multiple physiological effects of ATP in hypoglossal activity associated with the presence of P2X2, P2X4, and P2X6 receptor mRNA in the nucleus ambiguus and the hypoglossal nucleus (Collo et al., 1996; Funk et al., 1997), and microinjection of ATP into the caudal nucleus tractus solitarius (NTS) in the working heart-brainstem preparation of rats produces respiratory responses (Antunes et al., 2005). P2X receptors have been shown to be involved in the histamine-induced enhancement of the cough reflex severity in guinea pigs by mediating direct activation of rapidly adapting receptors, whereas P2Y receptors mediate increase in histamine release, indirectly increasing the cough reflex sensitivity (Kamei and Takahashi, 2006).

Evidence showing P2X receptor subtypes (P2X1, P2X2, P2X5, and P2X6) within areas of the ventrolateral medulla in the brainstem has been presented, and it was shown that activation of these receptors was implicated in respiratory networks including the Bötzinger and pre-Bötzinger complex (PBC) (Thomas et al., 2001). Recent data indicated that ionotropic glutamate and P2X receptors in the rostral ventrolateral medulla of the Bötzinger complex play roles in opposite directions in the control of respiratory responses to chemoreflex activation in awake rats (Moreaes et al., 2011). It has been shown in rodents that the ATP-adenosine balance is a determining factor in the purinergic modulation of the PBC inspiratory rhythm and that the underlying pathways seem to differ between mice and rats (Zwicker et al., 2011). Another article showed that the chemosensitive regions of the ventrolateral medulla were immunoreactive for the P2X2 receptor, which mediates ATP potentiation of respiratory discharge frequency (Lorier et al., 2004). P2X receptors mediate central inspiratory facilitation by low-frequency vagal afferent inputs in the rabbit (Takano et al., 2004). Microinjection of ATP into different regions of the NTS produces different respiratory responses. ATP injection into the intermediate NTS produced apnea (Bianchi et al., 1995); injected into the caudal NTS, it caused excitation of neurons involved in ventilatory pathways activated by the chemoreflex (Antunes et al., 2005). Increase of pCO_2 in the arterial blood triggers the release of ATP from three chemosensitive regions on the ventral surface of the medulla oblongata, and blockade of ATP receptors at these sites diminishes the chemosensory control of breathing (Gourine et al., 2005). Occupation of $P2Y_1$ receptors in the PBC, a key site of inspiratory rhythm generation, led to increase in frequency (Lorier et al., 2007). In a developmental study, ATP applied locally into PBC slices potently increased activity as early as embryonic day 19, the youngest rats tested (Huxtable et al., 2007). Local application of the $P2Y_1$ agonists 2-methylthio-ADP and (N)-methano-carba-2-methylthio-ADP (MRS2365) to neurons in the XII nucleus evoked a tonic discharge, although UTP also

had an effect (de Souza Alvares et al., 2007), perhaps indicating involvement also of $P2Y_2$ receptors. Further experiments led to the conclusion that ATP is a potent excitatory modulator of the inspiratory network with a dynamic interaction between the actions of ATP at P2 receptors and ectonucleotidases that degrade it to metabolites that act on P2Y and P1 receptors (Huxtable et al., 2009). Connexin hemichannel-mediated CO_2-dependent release of ATP in the medulla oblongata contributes to central respiratory chemosensitivity (Huckstepp et al., 2010). Astrocytes in the brainstem chemoreceptor area are highly chemosensitive; they respond to decreases in pH with increases in $[Ca^{2+}]_i$ and release of ATP, which led to activation of chemosensitive neurons and induced adaptive increases in breathing (Gourine et al., 2010). It was demonstrated that PBC glia also respond to ATP, with increased $[Ca^{2+}]_i$ and glutamate release, and may therefore contribute to the ATP sensitivity of PBC networks and possibly to the hypoxic ventilatory response (Huxtable et al., 2010).

Adenosine mechanisms were originally implicated in the central nervous regulation of breathing in several species (Hedner et al., 1982; Mueller et al., 1984; Wessberg et al., 1984; Eldridge and Millhorn, 1987; Norsted et al., 1987; Bissonette et al., 1991; Barros and Branco, 2000). Adenosine injected into the caudal nucleus of the NTS decreased respiratory frequency by an action on A_{2A} receptors expressed on glutamatergic nerve terminals (Phillis et al., 1997). A medial thalamic sector was shown to be involved in adenosine-induced apnea (Koos et al., 2000). Intracerebroventricular administration of P2 receptor antagonists reduced the minimum alveolar concentration of inhaled volatile anesthetics (Masaki et al., 2000).

In a study of perinatal development in rats, it was concluded that respiration is already modulated by adenosine acting on A_1 receptors in the medulla oblongata in the period around birth (Herlenius et al., 2002). A_{2A} receptors interact with GABAergic pathways in the medulla oblongata to modulate respiration in neonatal piglets (Wilson et al., 2004), whereas A_1 receptors were reported to modulate the activities of both inspiratory and expiratory neurons in the medial region of the nucleus retrofacialis of neonatal rats (Wang et al., 2005). Activation of central A_{2A} receptors enhances superior laryngeal nerve stimulation-induced apnea in piglets via a GABAergic pathway (Abu-Shaweesh, 2007). Adenosine release from NTS does not seem to mediate hypoxia-induced respiratory depression in rats (Gourine et al., 2002). The reduced hypoxic ventilatory response observed in obese Zucker rats was attributed to depressed adenosinergic peripheral excitatory mechanisms and to enhanced central depression mechanisms (Lee et al., 2005).

Reviews concerned with purinergic signaling in the brain stem associated with airways functions are available (Spyer and Thomas, 2000; Gourine and Spyer,

2003; Gourine et al., 2004; Gourine, 2005; Spyer and Gourine, 2009; Spyer, 2009).

VI. Diseases of the Airways

Inflammation is a feature of most diseases of the airways, including asthma, COPD, CF, dyspnea, allergy, infection and injury. Mucous hyperproduction in the airways is also characteristic of all pulmonary obstructive diseases, including chronic bronchitis, asthma, COPD, CF and primary ciliary dyskinesia.

The release of purine nucleotides from airway epithelial cells is often dramatically increased during inflammatory processes and is believed to play an important role in the pathophysiology of chronic lung disease (see Adriaensen and Timmermans, 2004). Measurement of adenosine, ATP, and AMP in sputum or exhaled breath condensate has been used as a noninvasive method to track airway inflammation (Huszár et al., 2002; Esther et al., 2008). Extracellular ATP was reported to sensitize airway smooth muscle cells to contractile agonists (e.g., metacholine) via P2X receptor activation, without enhancing the induced $[Ca^{2+}]_i$ rise, and the resulting hyper-responsiveness was referred to as "Ca^{2+} sensitization" (Oguma et al., 2007). Erythromycin therapy has been used to decrease airway secretion in chronic inflammatory airway diseases (Kondo et al., 1998), perhaps by selectively inhibiting Ca^{2+} influx through P2X receptor channels (Zhao et al., 2000). Uridine and 4-thiouridine have anti-inflammatory effects, reducing edema formation, leukocyte infiltration, and tumor necrosis factor in a lung inflammation model (Evaldsson et al., 2009). Alveolar macrophages (also see section II.B.1) play a pivotal role in the development of chronic lung inflammatory reactions such as idiopathic pulmonary fibrosis, silicosis, asbestosis, hypersensitivity pneumonitis, sarcoidosis, and mycobacterium tuberculosis. P2X7 receptors are expressed in alveolar macrophages, which upon stimulation activate the proinflammatory IL-1 to IL-5 cytokine cascade and the formation of multinucleated giant cells, a hallmark of granulomatous reactions (Lemaire and Leduc, 2004). P2X7 receptors may be a relevant target for therapeutic intervention in lung hypersensitivity reactions associated with chronic inflammatory responses. ATP also promotes tumor necrosis factor-α-elicited IL-8 expression via P2X ion channel-triggered Ca^{2+} entry (Théâtre et al., 2009). Adenosine promotes IL-6 release from airway epithelium during inflammation (Sun et al., 2008). There is a role for the vagal parasympathetic reflex bronchoconstriction in dyspnea, which seems to be exaggerated in inflammatory airway disease (Undem and Nassenstein, 2009). Paruchuri et al. (2009) reported that leukotrienes E_4-induced pulmonary inflammation is mediated by the P2Y$_{12}$ receptor.

Anti-inflammatory effects of adenosine have been described previously (Schrier et al., 1990; Vass and Horváth, 2008). Adenosine, probably via A_1 receptors, sig-

nificantly elevated the sensitivity of C-fiber afferents in rat lung (Gu et al., 2003). Interaction between adenosine and IL-13 evoked a stimulation that may contribute to the nature and severity of airway inflammation and fibrosis (Blackburn et al., 2003). Mast cell involvement in adenosine-mediated airway hyper-reactivity was reported in a murine model of ovalbumin-induced lung inflammation (Wyss et al., 2005). A_3 receptor signaling is needed for migration of eosinophils into the airways, and influences airway inflammation, mucus production, and fibrosis (Young et al., 2004; Morschl et al., 2008). A_{2B} receptors are reportedly involved in airway inflammation via induction of IL-19 release from human bronchial epithelial cells, resulting in tumor necrosis factor-α release from monocytes, which in turn up-regulates A_{2B} receptor expression (Zhong et al., 2006). An A_{2B} receptor antagonist has been proposed as a clinical candidate for chronic inflammatory airway disease (Elzein et al., 2008). A protective role for A_{2B} receptor signaling during the acute stages of lung inflammation has been proposed (Zhou et al., 2009b). CD39 and CD73 ectonucleotidases are critical mediators of pulmonary neutrophil transmigration in LPS-induced lung inflammation (Reutershan et al., 2009).

A. Asthma

Asthma is a chronic inflammatory disease of the airways, characterized by recurring bronchospasm, expressed by wheezing, coughing, chest tightness, and shortage of breath.

The involvement of adenosine in asthma has been the subject of considerable attention over the years, after it was shown that it produced powerful bronchoconstriction in asthma, although it had little effect in healthy lungs; xanthines, antagonists of adenosine receptors, were widely used for treatment of asthma (for reviews, see Persson, 1982; Kawasaki et al., 1983; Holgate et al., 1987, 1990; Feoktistov and Biaggioni, 1996; Fozard and Hannon, 2000; Meade et al., 2001; Fozard and McCarthy, 2002; Holgate, 2002, 2005; Polosa et al., 2002; Fozard, 2003; Lee et al., 2003; Livingston et al., 2004; Caruso et al., 2006, 2009; Russo et al., 2006; Brown et al., 2008b; Wilson, 2008). It was suggested that the hyper-responsive effects of adenosine in isolated bronchi was due to indirect actions by liberation of histamine and leukotrienes (Björck et al., 1992).

Although theophylline and caffeine are well established antagonists to adenosine receptors, their bronchodilator action in patients with asthma does not seem to be due to this mechanism of action; for example, enprofylline is 4 to 5 times more potent than theophylline although it was reported to be devoid of adenosine receptor antagonism (Persson et al., 1981). Adenosine, acting through A_2 receptors, was reported to both stimulate and inhibit histamine release from mast cells in the lung (Hughes et al., 1984; Ott et al., 1992). Inhaled adenosine, but not guanosine, is a potent bronchocon-

strictor in asthma (Cushley et al., 1983). Antagonism of adenosine-induced bronchoconstriction in asthma by oral theophylline was described previously (Mann and Holgate, 1985). Data were presented to suggest that adenosine-induced bronchoconstriction was not mediated by parasympathetic or sympathetic reflexes (Mann et al., 1985). Inhalation of dipyridamole, which inhibits adenosine uptake, increased adenosine-induced bronchospasm in patients with asthma (Crimi et al., 1988). Patients with asthma have neutrophils that exhibit diminished responsiveness to adenosine and it was suggested that this may be responsible for the severity and persistence of inflammation in the airways of patients with asthma (Sustiel et al., 1989). Superoxide generation and its modulation by adenosine in neutrophils from patients with asthma was noted (Meltzer et al., 1989).

There is elevated expression of A_1 receptors in bronchial biopsy specimens from patients with asthma (Brown et al., 2008a). Administration of an aerosolized phosphorothioate antisense oligodeoxynucleotide targeting the A_1 receptor desensitized the animals for subsequent challenge with either adenosine or dust-mite allergen, suggesting that adenosine is an important mediator of both airway inflammation and obstruction (Nyce and Metzger, 1997). Lowering adenosine levels with adenosine deaminase therapy had striking effects on gene expression analyzed with cDNA arrays in inflammatory airway disease associated with elevated adenosine (Banerjee et al., 2002). It has been claimed that airway bronchoconstrictor responses to aerosolized adenosine in mice occur largely through A_3 receptor activation and that mast cells contribute significantly to these responses (Tilley et al., 2003). The anti-inflammatory properties of theophylline in asthma include an inhibition of circulating progenitor cells (Wang et al., 2003). Adenosine cooperates with inflammatory cytokines to stimulate mucin production in the asthmatic airway (McNamara et al., 2004). Intravenous adenosine in healthy subjects does not induce bronchospasm, but causes dyspnea, most likely by an effect on vagal C fibers in the lungs (Burki et al., 2005). A more recent article claimed that all four P1 receptor subtypes play various roles in the airway responses to inhaled 5′-AMP in sensitized guinea pigs (Smith and Broadley, 2008). Genetic polymorphisms of A_1 and A_{2A} receptors were associated with aspirin-intolerant asthma (Kim et al., 2009).

In summary, several widely different mechanisms have been proposed to account for the potent bronchoconstriction produced by adenosine in patients with asthma (but not healthy patients):

1. Inhibition of release of histamine from lung mast cells via A_{2B} receptors (Forsythe and Ennis, 1999) and/or A_3 receptors (Hua et al., 2008). An increase in mast cell degranulation was reported in adenosine deaminase-deficient mice (Zhong et al., 2001).

Adenosine also potentiates the immediate response to allergen in patients with asthma.
2. Enhancement of the potent bronchoconstrictor effects of endothelin 1 released from epithelial cells (Kanazawa et al., 1997).
3. Proinflammatory effects of adenosine in patients with asthma (see Rorke et al., 2002; Caruso et al., 2009).
4. A_1 receptors are up-regulated in bronchial smooth muscle and epithelial cells (Brown et al., 2008a).
5. Adenosine production is increased by hypoxia, inflammatory cell activation, and allergen challenge and is elevated in patients with asthma. It is also increased in exercise-induced bronchoconstriction in asthma (Vizi et al., 2002).
6. Increased incidence of adenosine-induced dyspnea in asthma may be due to adenosine sensitization of vagal C fibers (Burki et al., 2006) via A_1 receptors (Hua et al., 2007).

However, which of the above or other mechanisms are involved still needs to be resolved.

Although the early emphasis was on the roles of adenosine in asthma, there have been an increasing number of studies concerned with the roles of nucleotides in this disease. For example, data were presented to suggest that ATP plays an important modulatory role in histamine release from human lung mast cells, and it was suggested that it may be involved in allergic/asthma reactions (Schulman et al., 1999). ATP was shown to be a more potent bronchoconstrictor and to have greater effects on dyspnea and other symptoms than AMP in patients with asthma (Basoglu et al., 2005). P2X7 receptor function is altered in asthma; P2X7 pore activity is associated with change in nasal lavage neutrophil counts during the development of asthma symptoms (Denlinger et al., 2009).

In allergic patients with asthma, inflammation is triggered by specific inhalation of allergens, such as house dust-mite allergen and pollen spores or nonspecific triggers such as air pollution and viral infection. Activation of dendritic cells is essential for the immune response to allergens. In allergic patients with asthma, inhaled adenosine-induced bronchoconstriction was claimed to be mediated by A_1 receptors (Marmo et al., 1985). This was also demonstrated in allergic rabbits; a role for A_3 receptors was not found (el-Hashim et al., 1996; Abebe and Mustafa, 1998). Challenge of sensitized Brown Norway rats with ovalbumin induced a marked airway hyperresponsiveness to adenosine, which, in contrast to several other findings (mentioned previously), was believed to be largely due to an increased release of histamine and 5-HT from mast cells (Hannon et al., 2001). Theophylline attenuated adenosine-enhanced airway inflammation but could not reverse allergen-induced airway inflammation (Fan and Mustafa, 2002). A selective A_{2A} receptor agonist, 2-[p-(2-carboxyethyl)phenethylamino]-

$5'$-N-ethylcarboxamidoadenosine (CGS 21680), inhibited allergic airway inflammation in the rat (Fozard et al., 2002). In contrast, A_{2B} and A_3 receptors were reported to play an important role in adenosine-induced bronchoconstriction in an allergic mouse model (Fan et al., 2003). In other mouse allergy models, A_{2B} receptors were identified as the main receptor subtype involved in increases in ion transport (Kornerup et al., 2005; Mustafa et al., 2007). Mast cells were shown to be involved in adenosine-mediated bronchoconstriction and inflammation in an allergic mouse model (Oldenburg and Mustafa, 2005). Mast cells were claimed to be activated after adenosine challenge in allergic, but not nonallergic, patients with asthma (Bochenek et al., 2008). AMP and an A_1 receptor-selective agonist induced airway obstruction in sensitized guinea pigs by a mechanism unrelated to release of histamine from mast cells but probably through stimulation of sensory nerves and reflex activity (Keir et al., 2006). A_3 receptor signaling contributed to airway mucin secretion after allergen challenge in mice (Young et al., 2006). Allergen inhalation decreased adenosine receptor expression in sputum and blood of patients with asthma (Versluis et al., 2008). A_{2A} receptor deficiency led to impaired tracheal relaxation in allergic mice (Nadeem et al., 2009). Allergen-induced airway hyper-responsiveness was absent in ecto-$5'$-nucleotidase (CD73)-deficient mice (Schreiber et al., 2008).

Allergen challenge caused short-term accumulation of ATP in the airways of subjects with asthma and mice with experimentally induced asthma; when ATP levels were neutralized using apyrase or, in mice, treated with P2 receptor antagonists, the features of asthma were reduced, including eosinophilic inflammation, Th2 cytokine production and bronchial hyper-reactivity (Idzko et al., 2007). The authors concluded that the adjuvant effects of ATP were due to the recruitment and activation of lung myeloid dendritic cells that induced Th2 responses. ATP contributes to the induction of inflammation in allergic asthma by activation and recruitment of various inflammatory cells (Willart and Lambrecht, 2009). Evidence has been presented that $P2Y_1$ receptors are involved in allergic airway inflammation, which could be at least partly explained by its role in the regulation of dendritic cell maturation (Maitre et al., 2008). Extracellular adenine nucleotides inhibit the release of major monocyte recruiters by human monocyte-derived dendritic cells and pharmacological data support the involvement of $P2Y_{11}$ and $P2Y_1$ purinergic receptors (Horckmans et al., 2006). In a recent article, it is proposed that purinergic signaling via $P2Y_2$ receptors in the respiratory epithelium is a critical sensor for airway exposure to airborne allergens, which may provide novel opportunities to dampen hypersensitivity in the Th2-type immune responses in asthma (Kouzaki et al., 2011). In a study from a different group, it was also claimed that ATP acts as a "danger signal" by inducing inflammation via $P2Y_2$ receptors, via recruitment of

neutrophils to the lungs; $P2Y_2$ receptor-deficient mice showed reduced pulmonary inflammation and development of emphysema after short-term smoke exposure (Cicko et al., 2010). It has also been demonstrated that P2X7 receptors are implicated in the pathophysiology of allergy-induced lung inflammation (Faffe et al., 2009). For example, low-intensity aerobic exercise attenuates the epithelial response in allergic asthma in a mouse model, reducing P2X7 receptor expression, synthesis of Th2 cytokines, chemokines, adhesion molecules, and proteases that regulate inflammation, remodeling, and hyper-responsiveness (Vieira et al., 2011). It has also been proposed that targeting P2X7 receptors on hematopoietic cells, such as dendritic cells or eosinophils, might be a novel therapeutic option for the treatment of allergic asthma (Müller et al., 2011).

B. Chronic Obstructive Pulmonary Disease

COPD refers to chronic bronchitis and emphysema, diseases in which the airways become narrowed, causing shortness of breath. In contrast to asthma, the limited airflow is poorly reversible and usually gets progressively worse over time. COPD is caused by noxious particles or gas, most usually from tobacco smoking, which triggers an inflammatory response in the lungs. The inflammatory response in the larger airways is known as chronic bronchitis, whereas inflammation in the alveoli is known as emphysema.

As for asthma, the main purinergic emphasis has been on the role of adenosine receptors in COPD (Polosa et al., 2002; Polosa, 2002; see reviews by Peleg and Schulman, 2002; Blackburn, 2003; van den Berge et al., 2004, 2007; Caruso et al., 2006; Mohsenin and Blackburn, 2006; Trevethick et al., 2008; Polosa and Blackburn, 2009; Zhou et al., 2009b, 2010). Enprofylline, a xanthine lacking adenosine receptor antagonism, was shown to be a potent bronchodilator in patients with COPD (Lunell et al., 1982). A_{2B} receptors on human mast cells are a strategic target for COPD (Spicuzza et al., 2003). The affinity of A_1, A_{2A}, and A_3 receptors expressed in different cells in peripheral lung parenchyma was significantly decreased in patients with COPD, whereas their density was increased; the affinity of A_{2B} receptors was not altered, but their density was significantly decreased (Varani et al., 2006). There were no significant differences in mast cell numbers between patients with COPD or asthma and age-matched healthy control subjects (Liesker et al., 2007). Activation of A_{2A} receptors inhibited inflammatory cell activation in COPD (Bonneau et al., 2006). Inhaled A_{2A} receptor agonists have been used for the treatment of COPD (Mantell et al., 2008; Trevethick et al., 2008; Thomas et al., 2008). It has been shown that after a 1-year smoking cessation airway inflammation in COPD persisted or was aggravated and that this may be due to an increase in neutrophils expressing A_3 receptors and macrophages expressing A_1 receptors (Versluis et al., 2009). Dyspnea, a side effect of

adenosine infusion, is not correlated with impaired respiratory resistance in patients with COPD (Fricke et al., 2008). It has been reported that oxidative/nitrosative stress selectively altered A_{2B} receptors in COPD (Varani et al., 2010). Mice lacking the A_{2B} receptor revealed enhanced airway inflammation and remodeling (Zhou et al., 2009a).

ATP seems to be implicated in COPD and asthma as well as adenosine (Adriaensen and Timmermans, 2004; Mortaz et al., 2010). However, ATP in exhaled breath condensate was reported to be the same for healthy people and patients with COPD (Lázár et al., 2008). ATP-induced pulmonary vasodilation has been described in patients with COPD (Gaba et al., 1986; Gaba and Préfaut, 1990). Activation of purinergic signaling by cigarette smoke seems to be involved in the pathogenesis of emphysema (see Fig. 10); cigarette smoke induces ATP release from neutrophils, which plays a crucial role in release of the chemokine CXC18 that is largely responsible for neutrophil recruitment into the sites of inflammation, and of elastase that leads to the destruction of lung tissue (Mortaz et al., 2009). Mortaz et al. (2010) later suggest that P2X7 receptors might be involved. In murine model experiments focused on emphysema, changes in lung innate immune cell recruitment were associated with both $P2Y_2$ and P2X7 receptors (Cicko et al., 2010; Lucattelli et al., 2011).

In summary, adenosine-induced bronchoconstriction in both COPD and asthma involves mast cell degranu-lation and neural pathways, whereas the direct effects on smooth muscle are less clear. Production of inflammatory cytokines via A_{2B} receptors is also involved. A_{2A} agonists and A_1, A_{2B}, and A_3 antagonists have been used for the treatment of COPD.

C. Airway Infections

Erythromycin is an antibiotic used widely for the treatment of upper and lower respiratory tract infections. One of the most conspicuous effects of erythromycin is the suppression of fluid secretion from bronchial epithelial cells in the treatment of bronchitis. Erythromycin has been shown to block the P2X receptor-mediated Ca^{2+} influx and may represent one mechanism by which it exerts its antisecretory effects in the treatment of chronic respiratory tract infections (Zhao et al., 2000). During bacterial infections of the lung, the airway epithelial cells play a central role in activating the innate immune response (i.e., release of proinflammatory cytokines and subsequent recruitment of neutrophils) to fight the infection. *Pseudomonas aeruginosa* produces a common bacterial pathogen that causes chronic infections in immunocompromised hosts, such as patients with CF. In mouse airways, luminal exposure to the protein flagellin, a structural component of this pathogen, led to inhibition of Na^+ absorption by the ENaC, probably because of the release of ATP and occupation of P2Y receptors, which activate the mitogen-activated protein kinase pathway leading to inhibition of ENaC
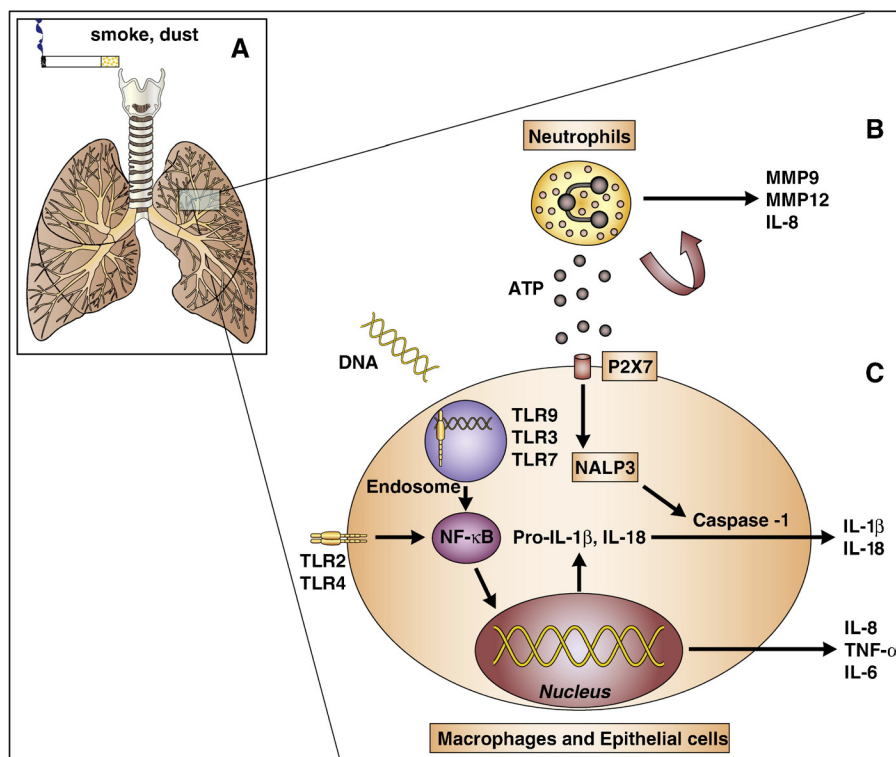
FIG. 10. Diagrammatic representation of the possible mechanism of action of ATP in pathogenesis of lung emphysema. MMP, matrix metalloproteinase; NALP3, Nacht, leucine-rich repeat and PYD domains-containing protein 3; NF-κB, nuclear factor-κB; TLR, Toll-like receptor; TNF, tumor necrosis factor. [Reproduced from Mortaz E, Folkerts G, Nijkamp FP, and Henricks PA (2010) ATP and the pathogenesis of COPD. *Eur J Pharmacol* 638:1–4. Copyright © 2010 Elsevier. Used with permission.]

(Kunzelmann et al., 2006). In another article, bacterial flagellin was shown to interact with Toll-like receptors, and the cell surface glycolipid, asialoGM1, was shown to activate an innate immune response. The release of ATP induced by flagellin was dependent on a Toll signaling cascade, revealing a role for autocrine extracellular ATP in Toll-like receptor signaling (McNamara et al., 2006). ATP-induced increases in $[Ca^{2+}]_i$ in airway epithelial cells synergized with *P. aeruginosa* flagellin in activating the immune response (Fu et al., 2007). Extracellular nucleotides regulate expression and release of the antimicrobial chemokine CCL20 in primary human airway epithelial cells; $P2Y_2$ and $P2Y_6$ agonists increased CCL20 release (Marcet et al., 2007b). It was concluded that nucleotides modulate chemokine release and leukocyte recruitment in inflamed airways by acting on P2Y receptors on both epithelial and immune cells.

Mucociliary clearance constitutes the first line of defense against airways infection. Inhaled pathogens are trapped by a mucus layer positioned above ciliated epithelia. In the airways, adenine nucleotides support a complex network mediating host defenses. ATP released by the epithelium into the airway surface liquid layer regulates mucus clearance via P2 receptors and, after breakdown to adenosine, via P1 receptors (Zuo et al., 2008). ATP-induced activation of the NADPH oxidase homolog dual oxidase 1 mediated airway epithelial responses to bacterial stimuli (Boots et al., 2009). They showed further that epithelial IL-8 production in response to bacterial stimuli involved ATP release and dual oxidase 1 activation. Patients with pulmonary tuberculosis had significantly higher adenosine deaminase activity in bronchoalveolar lavage fluid (Orphanidou et al., 1998) and in the sputum (Dimakou et al., 2009). ATP is a modulator of lung inflammation in pneumonia in cattle; it is released by activated macrophages and damaged cells (McClenahan et al., 2009). It was shown in this study that ATP caused striking morphological and permeability changes in bovine pulmonary epithelial cells and that both epithelial cells and pulmonary microvascular endothelial cells expressed mRNA for P2X7 receptors, with a P2X7 receptor antagonist reversing the changes in permeability induced by ATP.

The pneumovirus respiratory syncytial virus is the most common cause of lower respiratory tract disease in infants and children. It has a detrimental inhibitory effect on alveolar clearance, an effect that appears to be mediated by UTP, perhaps released by the bronchoalveolar epithelium in response to infection (Davis et al., 2004). This suggests that $P2Y_2$ receptor antagonists may be useful for the treatment of severe respiratory syncytial virus bronchiolitis. Respiratory syncytial virus infection causes fluid accumulation and decreased Na^+ transfer across respiratory epithelial cells, probably via UTP released from epithelial cells (Chen et al., 2009). In addition, influenza A virus inhibits alveolar fluid clearance in BALB/C mice (Wolk et al., 2008).

D. Lung Injury

Acute lung injury and acute respiratory stress syndrome (ARDS) are major causes of respiratory failure, characterized by edema, neutrophil infiltration with hemorrhage, and increased production of inflammatory cytokines. In rats treated with α-naphthylthiourea to induce acute lung injury, particularly to the endothelium, as demonstrated by pulmonary edema, the ectoenzymes catalyzing ADP and AMP hydrolysis were little effected (Grantham and Bakhle, 1988). Sublethal oxidant injury inhibited ATP-induced surfactant secretion (Warburton et al., 1989b). ARDS can be the result of trauma (as well as smoke inhalation, aspiration, and sepsis). The need to support the failing lung with mechanical ventilation is potentially lifesaving; unfortunately, however, alveolar overdistension and pulmonary shear stress may itself cause lung injury (ventilator-induced lung injury), increasing bronchoalveolar leakage leading to lung edema. It has been suggested that ventilator-induced lung injury may involve stretch-associated release of ATP from epithelial cells or pulmonary neuroendocrine cells in NEBs (Brouns et al., 2000, 2003a,b; Rich et al., 2003), which may therefore be a therapeutic target for this condition. ATP-dependent calcium signaling during ventilator-induced lung injury is amplified by hypercapnia (Briva et al., 2011). The protective effect of ATP-$MgCl_2$ in ischemia-reperfusion lung injury seems to require the presence of leukocytes (Chen et al., 2003).

Pulmonary fibrosis can be caused by injury, although it may also be secondary to other lung disorders or may even be idiopathic. Lung injury induced by bleomycin, an intercalating agent that causes DNA strand breaks, causes lung fibrosis, and it was reported that suramin, a P2 receptor antagonist, did not affect transforming growth factor β activity, which is presumed to play a role in pulmonary fibrosis (Lossos et al., 2000). However, it has been proposed that ATP, released from airways after administration of bleomycin, constitutes a major endogenous danger signal that engages the P2X7 receptor pannexin-1 axis, leading to IL-1β maturation and lung fibrosis (Riteau et al., 2010). In patients with idiopathic pulmonary fibrosis, alterations in adenosine metabolism were described and this study also presented evidence that A_{2B} receptor signaling could promote the production of inflammatory and fibrotic mediators in patients with these disorders (Zhou et al., 2010). Chronic adenosine elevations are associated with pulmonary fibrosis in adenosine deaminase-deficient mice, suggesting that adenosine functions as a profibrotic signal in the lung (Chunn et al., 2005).

Lung epithelial cells release ATP during ozone exposure, which protects against ozone toxicity by inhibiting apoptotic and necrotic cell death; P2 receptor antagonists diminished this protective action (Ahmad et al., 2005). Lung injury produced by the gaseous contami-

nant nitrogen dioxide resulted in a loss of ATP and a reduction in cell viability (Bakand et al., 2006). The cytotoxic effects of gaseous airborne contaminants NO_2, SO_2, and NH_3 were compared, and ATP levels were shown to be reduced with all three gases (Bakand et al., 2007). ATP-mediated activation of dual oxidase 1, an NADPH oxidase homolog within the tracheobronchial epithelium, results in epithelial cell migration and wound repair after injury by environmental pollutants (Wesley et al., 2007). Inhalation of industrial environmental arsenic has long been known to lead to respiratory compromise, including lung cancer. In a recent study, it was shown that short-term exposure to low concentrations of sodium arsenide reduced the ability of lung epithelial cells to respond to wound-induced purinergic signaling via both P2X and P2Y receptors (Sherwood et al., 2011). The P2 receptor agonist ATPγS had a protective effect against acute lung injury induced in a murine model by the bacterial endotoxin LPS (Kolosova et al., 2008). ATP released during mechanical ventilation caused lung injury via P2Y receptors (Matsuyama et al., 2008). LPS and mechanical ventilation modify purinoceptor expression in the lung. LPS caused expression of A_1, A_{2A}, and A_{2B} and P2Y receptors to be increased, and A_3 receptors to be decreased, whereas high-volume ventilation reduced $P2Y_4$ mRNA levels (Riesenman et al., 2008). On the basis of a study of LPS administration in isolated and ventilated rabbit lungs, it was suggested that adenosine A_2 receptor-mediated stimulation might be beneficial during acute lung injury (Heller et al., 2007). Both A_{2A} receptors (Reutershan et al., 2007) and A_{2B} receptors (Eckle et al., 2008) have been claimed to be involved in the attenuation of acute lung injury.

Adenosine prevented phorbol myristate acetate-induced canine lung injury via an A_2 receptor mechanism (Adkins et al., 1993). A_{2A} receptors mediated adenosine-stimulated wound healing of bronchial epithelial cells (Allen-Gipson et al., 2006). A_{2A} receptor activation reduced lung injury in trauma/hemorrhagic shock (Haskó et al., 2006). Purinergic sensory transduction pathways contribute to activation of the nasal sensory irritation response to inspired irritant vapors are present in the mouse; the involved nerve terminals may serve as sensors of airway cell damage (Vaughan et al., 2006). Patients with ARDS and high altitude pulmonary edema build up excess lung fluid that leads to alveolar hypoxia. The decrease in fluid clearance in these conditions is due in part to down-regulation of plasma membrane adenosine triphosphatase (Zhou et al., 2008). The migration of polymorphonuclear leukocytes (PMN) into the lung plays a critical role in the development of LPS-induced acute lung injury; A_3 receptors have been claimed to inhibit this effect (Wagner et al., 2010). The protective effects of A_3 receptor activation in attenuating reperfusion lung injury are mediated in part through up-regulation of phosphorylated extracellular signal-regulated

kinase (Matot et al., 2006). Chemoattractants induce the release of ATP from migrating PMN, which is rapidly hydrolyzed to adenosine; PMN express A_{2A} and A_3 receptors that mediate suppression and stimulation of chemotaxis, respectively, and removal of adenosine or inhibition of A_3 receptors blocks PMN migration (Junger et al., 2006).

Recent reviews about adenosine receptors as promising targets for acute lung injury and ARDS are available (Schepp and Reutershan, 2008; Eckle et al., 2009).

E. Cystic Fibrosis

CF (also known as mucoviscidosis) is a hereditary disease caused by a mutation in the gene for the CFTR protein. It affects cells in the lung as well as in the intestine and in exocrine glands. CFTR is essential for maintaining water balance by enabling the transport of Cl^- ions across cell membranes, and its absence in CF results in the production of thick mucus. Mucociliary clearance in CF lung is limited by airway dehydration, leading to persistent bacterial infection and inflammation in the airways.

There are some outstanding reviews concerned with purinergic signaling in CF (Schultz et al., 1995; Ramsey, 1996; Weisman et al., 1998; Yerxa, 2001; Boucher, 2002, 2004, 2007; Kellerman et al., 2002; Bucheimer and Linden, 2004; Marcet and Boeynaems, 2006; Tarran et al., 2006; Clunes and Boucher, 2008).

Cloning and characterization of the *CFTR* gene was reported in 1989 (Riordan et al., 1989). Evidence for the regulation of ion transport by ATP and UTP in normal and CF human airway epithelium was described previously (Mason et al., 1991), in retrospect probably via $P2Y_2$ and/or $P2Y_4$ receptors. In particular, ATP and UTP activated Cl^- secretion in the nasal epithelia of patients with CF (Knowles et al., 1991). P2 receptor purinergic compounds are being explored for the treatment of CF, to bypass the defective function of CFTR, and to restore Cl^- secretion and/or inhibit Na^+ absorption (Brown et al., 1991; Stutts and Boucher, 1999; Mall et al., 2000; Yerxa et al., 2002). The long-lasting $P2Y_2$ receptor agonist P^1-(uridine 5')-P^4-(2'-deoxycytidine 5')tetraphosphate (INS37217) increases the duration of mucociliary clearance stimulation and therefore has significant advantages over other $P2Y_2$ agonists for the treatment of CF (Kellerman et al., 2002; Yerxa et al., 2002; Goralski et al., 2010). ATP regulates Cl^- channels in both normal and CF cultured human airway epithelia (Stutts et al., 1992) and in cultured human tracheal gland cells (Merten et al., 1993). Control of CFTR Cl^- conductance by ATP is through nonhydrolytic binding (Quinton and Reddy, 1992). Nucleotide activation of CFTR is by a cAMP-independent mechanism (Cantiello et al., 1994). Evidence has been provided that the anti-inflammatory mediator lipoxin A_4 is decreased in CF. In vitro experiments showed that lipoxin A_4 enhances the airway surface liquid layer height in CF and non-CF

epithelia, and this effect is inhibited by, among others, the P2Y$_{11}$ receptor antagonist NF340 (Urbach et al., 2012). The same authors also showed that lipoxin A$_4$ stimulates a carbenoxolone-sensitive apical ATP release.

A$_1$ receptor agonists mobilize [Ca^{2+}]$_i$ and activate K$^+$ and Cl$^-$ currents in normal and CF airway epithelial cells (Rugolo et al., 1993). A$_{2A}$ receptors participate in regulation of Cl$^-$ secretion via a Ca^{2+}-dependent signaling pathway and appears to be at least partially conserved in CF airway epithelial cells (Chao et al., 1994). Evidence has also been presented for the presence and function of A$_1$ receptors in modulating Cl$^-$ secretion in normal and CF airway epithelial cells (McCoy et al., 1995). A$_{2B}$ receptors mediate activation of CFTR as well as of the clinically important CFTR mutation R117H (Clancy et al., 1999). Single-nucleotide polymorphisms of the A$_{2B}$ receptor gene are much more frequent in African Americans than in whites, but none of the polymorphisms identified are likely to be modifiers in CF (Tang et al., 2005). Bronchoalveolar lavage from patients with CF exhibited high adenosine concentrations, which was correlated with an increase in 5′-nucleotidase and a decrease in adenosine deaminase activity (Picher et al., 2006). Regulation of purinergic signaling by NTPDase1 (CD39) and NTPDase3 is remodelled in CF (Fausther et al., 2010). A$_{2B}$ receptors preserve epithelial barrier integrity in the lung (Eckle et al., 2008), suggesting that the colocalization of NTPDase1 and ecto 5′-nucleotidase on basolateral surfaces may contribute to the defense mechanism by locally enhancing adenosine availability. Adenosine regulates CFTR via A$_{2B}$ receptors and prostanoids (Li et al., 2006).

An important advance was the cloning and expression of a human P2U nucleotide receptor, a target for CF pharmacotherapy (Parr et al., 1994). A murine P2U receptor cDNA was cloned from neuroblastoma-glioma hybrid (NG108-15) cells (Lustig et al., 1993). Gating of CFTR Cl$^-$ channels is regulated by phosphorylation and ATP hydrolysis (Hwang et al., 1994). It was argued that incremental phosphorylation differentially regulates the interactions between nucleotides and the two nucleotide-binding domains (NBD1 and NBD2) of CFTR, and that ATP hydrolysis at one NBD controls channel opening, whereas ATP hydrolysis at the other regulates channel closing (Gunderson and Kopito, 1994; Zhou et al., 2006). NBD1 and NBD2 function as adenylate kinases, but not ATPases (Gross et al., 2006). Uridine-5′-(γ-thio)-triphosphate, a potent hydrolysis-resistant agonist at P2U receptors, was developed as a promising compound for treating CF (Lazarowski et al., 1996). Purified CFTR does not function as an ATP channel (Li et al., 1996). CF is caused by a single deletion mutation (ΔPhe508) within the first nucleotide binding fold (NBF1) of the CFTR protein (Ko et al., 1997). ATP depletion induces loss of respiratory epithelial functional integrity and down-regulates CFTR expression (Brézillon et al., 1997). An ATP-activated Na$^+$/H$^+$ exchanger was shown to be located at the basolateral surface of nasal epithelial cells from patients with CF (Paradiso, 1997).

A characteristic feature of CF is chronic bacterial infection by *P. aeruginosa*, which accumulates diffusible *N*-acylhomoserine lactone signal molecules that activate virulence factor genes. *N*-Acylhomoserine lactone down-regulates expression of P2Y$_2$ and P2Y$_4$ receptors, altering the responses to ATP and UTP (Saleh et al., 1999a). Flagellin of *P. aeruginosa* inhibits ENaC expression in airway epithelium, reducing Na$^+$ absorption to enhance local mucociliary clearance, a mechanism that is attenuated in CF (Kunzelmann et al., 2006). The action of LPS on ENaC was mediated in part by the protein kinase C and phospholipase C pathways and by purinergic signaling (Boncoeur et al., 2010). In intact distal bronchi of porcine lungs, UTP stimulated Cl$^-$ secretion by a Ca^{2+}-independent mechanism and inhibited Na$^+$ absorption by a Ca^{2+}-dependent mechanism; both effects are likely to favor increased hydration of the airway surface and may therefore be beneficial in CF (Inglis et al., 1999). Inhibition of amiloride-sensitive epithelial Na$^+$ absorption by nucleotides in human normal and CF airways was reported (Mall et al., 2000). In CF airway epithelium, unlike normal epithelium, the mucosal ATP/UTP-dependent anion secretory response was mediated exclusively by [Ca^{2+}]$_i$ (Paradiso et al., 2001). Low doses of glucocorticoids, such as dexamethasone, are used for basal immunosuppressive and anti-inflammatory treatment of asthma and CF. Inhibition of ATP-mediated Cl$^-$ secretion by dexamethasone in human bronchial epithelium has been reported (Urbach et al., 2002).

Extracellular zinc as well as ATP restores Cl$^-$ secretion across CF airway epithelia by triggering calcium entry via P2X receptors (Zsembery et al., 2004; Hargitai et al., 2010). Synergistic stimulation with zinc and ATP suggested a significant role for the P2X4 receptor. However, possible roles for P2X5 and P2X6 receptors were not excluded, and in a later article from this group, it was suggested that P2X4/6 heteromultimers might be involved (Liang et al., 2005). The activity of CFTR is required for deformation-induced ATP release from erythrocytes; in CF, where CFTR is normally reduced or absent, ATP was not released from erythrocytes by mechanical deformation (Sprague et al., 1998). Cyclic compressive stress, mimicking normal tidal breathing, results in ATP release and thereby regulates airway surface liquid in normal lungs and improves clearance in the lungs of patients with CF (Button et al., 2007; Button and Boucher, 2008). Dysregulation of extracellular pH regulation is characteristic of CF and involves purinergic signaling (Kaunitz and Akiba, 2009). Maneuvers directed at increasing motion-induced nucleotide release may be therapeutic for patients with CF (Tarran et al., 2005).

Women with CF exhibit reduced survival compared with men. It was suggested that estrogen may reduce the breathing-induced ATP release and ATP receptor-mediated increase in $[Ca^{2+}]_i$ that results in Cl^- secretion (Coakley et al., 2008). Antiestrogens may therefore be beneficial in the treatment of CF because they increase Cl^- secretion. Bestrophines are up-regulated during inflammation and augment Ca^{2+} transients elicited via $P2Y_2$ receptors, influencing CF (Barro-Soria et al., 2010).

F. Lung Cancer

A549 human lung epithelial-like adenocarcinoma cells express P2U (i.e., $P2Y_2$ and/or $P2Y_4$) receptors, which, when occupied, lead to increases in $[Ca^{2+}]_i$ (Clunes and Kemp, 1996) but do not inhibit forskolin-evoked cAMP accumulation in these cells (Remsbury et al., 1996). Calcium-dependent release of ATP and UTP (with subsequent increase in adenosine levels) from A549 cells has been reported (Tatur et al., 2008).

A phase II study of intravenous ATP in patients with previously untreated non–small-cell lung cancer led to the conclusion that ATP, at least at the dose and administration schedule employed, was an inactive agent in patients with advanced non–small-cell lung cancer (Haskell et al., 1998).

Erythromycin is widely used in the treatment of respiratory tract infections. It has also been shown to selectively inhibit the Ca^{2+} influx induced through P2X4 receptor activation in A549 lung tumor cells (Zhao et al., 2000). In this study, it was also shown with RT-PCR that A549 cells express $P2Y_2$, $P2Y_4$, and $P2Y_6$ as well as P2X4 receptors.

Cachexia is a common feature of patients with lung cancer and is associated with metabolic alterations, including elevated lipolysis, proteolysis, and gluconeogenesis. An increase in glucose turnover during high-dose ATP infusion in patients with advanced non–small-cell lung cancer was reported, perhaps contributing to the reported beneficial effects of ATP on body weight in patients with advanced lung cancer (Agteresch et al., 2000a). Later randomized clinical trials led to the conclusion that ATP has beneficial effects on weight, muscle strength, and quality of life in patients with advanced non–small-cell lung cancer, as well as on enhancing median survival from 3.5 to 9.3 months (Agteresch et al., 2000b; Dagnelie and Agteresch, 2004; Beijer et al., 2009). ATP infusion restores hepatic energy levels in patients with advanced lung cancer, especially in patients who are losing weight (Leij-Halfwerk et al., 2002). ATP has been claimed to reduce radiation-induced damage (Swennen et al., 2008a), and clinical trials are under way to assess the effect of concurrent ATP and radiotherapy treatment on outcome in patients with non–small-cell lung cancer (Arts et al., 2008).

ATP induced a significant dose-dependent growth inhibition of five different cell lines: human large-cell lung carcinoma (H460), human papillary lung adenocarcinoma (H441), human squamous cell lung carcinoma (H520), human small cell lung carcinoma (GLC4), and human mesothelioma (MER082) (Agteresch et al., 2003). ATP also had cytotoxic effects on the PC14 lung adenocarcinoma cell line and enhanced the antitumor effect of etoposide (VP16) in both PC14 and A549 cell lines (Hatta et al., 2004). Calu-3 cells are derived from pleural effusion associated with human lung adenocarcinoma, and both mucin and ATP were released from these cells, probably in response to $P2Y_2$ receptor activation (Kreda et al., 2007). It has been claimed that extracellular ATP, UTP, and UDP stimulate proliferation of A549 lung tumor cells via $P2Y_2$ and $P2Y_6$ receptors, as well as an ADP-sensitive receptor that was not the $P2Y_1$ subtype (Schafer et al., 2003).

ATP-based chemotherapy response assay has been used to guide the outcome of platinum-based drug chemotherapy for nonresectable non–small-cell lung cancer (Moon et al., 2007, 2009). It has been suggested that tumor-infiltrating immune cells can benefit the tumor by producing factors that promote angiogenesis and suppress immunity; adenosine levels are high in tumors. A_{2B} receptors on host immune cells may participate in these effects, and A_{2B} receptor knockout mice exhibited significantly attenuated growth in a Lewis lung carcinoma isograft model (Ryzhov et al., 2008). Cisplatin is a widely used anticancer agent for the treatment of lung cancer. ATP increased the cytotoxicity of cisplatin in a human large-cell lung carcinoma cell line (H460) (Swennen et al., 2008b, 2010).

Exposure of human lung cancer cell lines A549 and H1299 to 8-chloro-adenosine induced cell arrest at the G_2/M phase and mitotic catastrophe, followed by apoptosis (Zhang et al., 2004; Gu et al., 2006; Li et al., 2009). $3'$-Deoxyadenosine (cordycepin) exerted an inhibitory effect on the growth of the mouse Lewis lung carcinoma cell line by stimulating A_3 receptors (Nakamura et al., 2006). The A_3 receptor agonist thio-2-chloro-N^6-(3-iodobenzyl)-$5'$-N-methylcarboxamidoadenosine inhibited cell proliferation through cell-cycle arrest and apoptosis of A549 human lung carcinoma cells (Kim et al., 2008).

G. Rhinosinusitis

Rhinosinusitis refers to inflammation of the nasal sinuses due to injury, allergy, or autoimmunity. Inhaled AMP caused airway narrowing in a significantly higher proportion of subjects with allergic rhinitis (Prieto et al., 2001). A randomized, double-blind trial concluded that novel agonists and antagonists to A_{2A} and A_3 receptors had limited clinical benefit in both early- and late-phase responses to intranasal allergen challenge (Rimmer et al., 2007). Reversal of chronic rhinosinusitis-associated sinonasal ciliary dysfunction, as the result of stimulation by ATP, was reported (Chen et al., 2007).

H. Pulmonary Hypertension

See also section I.E. Adenosine is an effective vasodilator in patients with pulmonary hypertension (Schrader et al., 1992). In a recent article, it has been shown that in rats with hypobaric hypoxia-induced pulmonary hypertension, there is a significant increase in P2X4 receptor mRNA and protein expression and in P2X1 receptor protein in the right ventricle (Ohata et al., 2011).

VII. Concluding Comments

In airway epithelia, extracellular ATP contributes to mucous ciliary clearance, a critical process required to maintain the airways clear of inhaled particles or pathogens. It mediates Cl^-, K^+, and fluid secretion; inhibits Na^+ absorption; increases ciliary beat frequency; potentiates regulatory volume decreases after hypotonic cell swelling; and triggers mucin release. These responses involve $P2Y_2$ and P2X4 and P2X7 receptors. ATP seems to be involved in signal transduction in a multitude of sensory lung receptors (NEBs, SMARs, visceral pleura receptors) via P2X3 receptors on vagal and spinal sensory nerves. Considering the stem cell characteristics of Clara-like cells in the NEB microenvironment, local purinergic signaling may be of great importance for normal airway function, for airway regeneration after injury, and/or for the pathogenesis of small-cell lung carcinomas.

As should be clear from the preceding extensive lists of examples, purinergic signaling, via different subtypes of P1 and P2 purinoceptors, seems to be involved in the physiological regulation of normal functions in virtually all cell and tissue types in the airways. In addition, the reported expression profiles of the different purinoceptor types may be up-regulated and/or changed as a consequence of pathological modifications.

Regarding the potential sources of extracellular purines involved in these signaling pathways, the situation also turned out to be complex. Besides a considerable number of cell types that release ATP as a transmitter via stimulated and strictly regulated exocytosis, many cells and tissues have been shown to release ATP via different mechanisms, such as connexin or pannexin hemichannels, voltage-dependent anion and P2X7 receptor channels, and vesicular release, and as a response to physiological stimuli (e.g., mechanical, hypoxia, osmotic).

In normal physiological situations, functionally released ATP is rapidly degraded by strategically located ectonucleotidases. In pathophysiological situations, however, the extracellular environment often seems to contain aberrant concentrations of ATP, not only because of enhanced stimulation and release by "normal sources" and/or insufficient breakdown but also because most cells harbor considerable cytoplasmic amounts of ATP that may be massively released in a noncontrollable way when cells or tissues are damaged (e.g., inflammation, physical damage).

All together, the ubiquitous expression of the many subtypes of purinoceptors in all cells and tissues that function in the multitude of normal physiological roles of extracellular ATP, in combination with the often enhanced and uncontrolled availability of extracellular ATP, unfortunately represents a huge potential for pathological purinergic "cross-signaling" between different cell and tissue types. On the other hand, thorough knowledge of the receptor subtypes and the pathways involved may also create interesting possibilities for targeted therapeutic interventions.

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Wrote or contributed to the writing of the manuscript: Burnstock, Brouns, Adriaensen, and Timmermans.

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