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OLD, NEW AND NOT YET EXPLOITED PURINERCIC VASOMECHANISMS OF THE PULMONARY CIRCULATION

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SUMMARY

• *In the pulmonary circulation, the ultimate role of liberated adenosine-5'-triphosphate (ATP) is to influence vascular tone.*

Extracellular ATP may be derived from sympathetic orpurinergic nerves impinging on blood vessels, in addition to vascular endothelial cells, erythrocytes, thrombocytes and mast cells. Purinergic innervation is more marked on the arterial side than the venous, and produces vasoconstriction through P_{2X} purinoceptors although there is a newly discovered non-P^ purinoceptor mediated vasoconstriction produced by ATP which remains to be characterized. Agonists as well as flow derived shear stress have been shown to release ATP from endothelial cells, which in turn act on either the same cell in an autoregulatory manner, or the ATP may travel short distances in the blood to act on endothelial cells downstream. Activation of endothelial P_{2y} purinoceptors by ATP produces nitric oxide release and vasodilation. There are also P_{2Y} purinoceptors on pulmonary vascular smooth muscle, and it appears that the number ofP_{2Y}purinoceptors located on the smooth muscle is inversely proportional to vessel size.

Unlike other sources of ATP, erythrocytes as well as mast cells are relatively mobile and the magnitude oj their effect can change due to alterations in their number. Thrombocyte derived ATP can be released by episodes ofhypoxia,and the P_{2T} purinoceptor on thrombocytes may have an autoregulatory function. The P_{2Z} purinoceptor is activated by $ATP^{4'}$ and has been shown to inhibit the activity of natural killer cells as well as macrophages inaddition to producing degranulation of mast cells.

It is likely that together with unique features of pulmonary vascular smooth muscle, a combination of purinoceptor mediated mechanisms contributes to the unusual characteristics of the pulmonary circulation. Such a varied and essential role of purinergic regulatory mechanisms in the pulmonary circulation makes purinoceptors sensible targets for therapeutic strategies.

INTRODUCTION

• When lungs evolved in animals, more primitive organisms were already using adenosine-5'-triphosphate (ATP) as a signal transmitter (1-4). Hence it appears that in addition to its intraceflular roles in the pulmonary circulation, ATP has survived years of evolutionary selection as a<transmitter, and it has maintained such a role in the lungs. The pulmonary circulation is highly unusual in sev-

eral respects. Almost the entire systemic blood volume passes through this fjed, yet it has vascular pressure of about 15mmHg, one sixth that of the systemic circulation (5,6). It has the largest capillary bed in the body, where vessels are exposed to 140 percent changes in oxygen tension during each cardiac cycle, and perhaps the most intriguing characteristic of the pulmonary circulation is that its vessels vasoconstrictin response to hypoxia (6,7). These adaptations optimize ventilation with regard to perfusion.

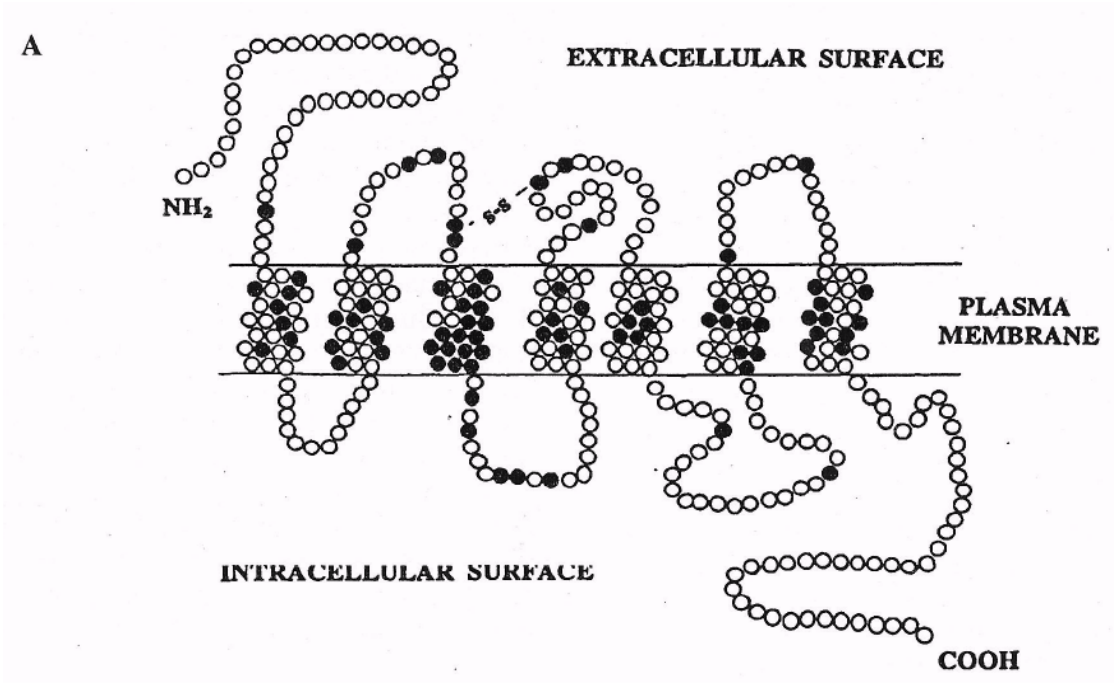
PURINOCEPTORS

• Based on differential rank orders of agonist potency, pharmacologic antagonism, transduction mechanism and now cloning, adenosine receptors are classified as P_{15} of which the A_t, A_2 and A_3 are subtypes, whereas ATP receptors are classified as P_2 (8-10). P_2purinoceptors are subclassified into P^, P_{2Y}, P_{2U} (P^), P_{2T}, P^ and P_m (Table 1) (10-12). The P^ purinoceptor is a ligand gated cation changnel (13,14). The P_{2Y} purinoceptors are coupled to G-proteins (11), they activate phospholipase C, leading to augmented hydrolysis of phosphoinosrtides which then produce liberation of intracellular calcium and activation of protein kinase C (10-12). Recombinant P_{2Y}purinoceptors when expressed in Xenopus oocytes and stimulated with agonist, activate a Ca^{2+}-dependent Cl~ channel producing slow oscillatory inward currents, that are characteristic of G-protein coupled receptors (15,16). P_{2Y} purinoceptors have subtle differences and have been further classified into P_{2Y1}, P_{2Y2} and P_{2Y3} receptors based on pharmacological differences between cloned P_{2Y} purinoceptors (10,11) (Fig. 1A). *P_{2Z}* purinoceptors are believed to be activated by $ATP^{4"}$. They mediate permeabilization of the plasmalemma of mast cells and other cells which are found in blood (10,17). P_{2T} purinoceptors, for which the principal agonist is ADP while ATP is a competitive antagonist, are found predominantly

Table 1. *P purinoceptor characteristics.*

RECEPTOR	P_{2X}	P_{2Y}	$P_{2U}(P_{2N})$	P_{2T}	P_{2Z}	P_{2D}
TYPE	Intrinsic ion channel (Na^+,K^+,Ca^+)	G-Protein coupled (IP^3/Ca^{2+}/DAG)	G-Protein coupled (IP^3/Ca^{2+}/DAG)	G-Protein coupled (IP^3/Ca^{2+}/DAG/cAMP)	non-selective pore	G-Protein coupled (IP^3/Ca^{2+}/DAG)
AGONIST PROFILE	i)ATP>ATPγS> 2meSATP ii)α,βmeATP> β,γ meATP> ATP>2meSATP	2meSATP>>ATP >>α,βmeATP	UTP ≥ATP>> α,βmeATP	2-ADP	ATP^{4-}	AP_xA
ANTAGONIST	Desensitization by α,βmeATP. Blocked by suramin, $ANAPP_3$ and PPADS.	Blocked by suramin, reactive blue-2		ATP	Oxidized ATP	

Abbreviations used: IP_3 - inositol -1,4,5-triphosphate, DAG - diacylglycerol, UTP - uridine-S'-triphosphate; ATPyS - non-hydrolyzable analogue of ATP; a,pmeATP - a,p methylene ATP.



B

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                                                                    TMl
P2Y1    :MTEALISAALNGTQPELLAGGWAAGNATTKCSLTKTGFQFYYLPTVYILVFITGFLGNSVAIWM
P2U     :.............MAADLEPWNSTINGTWEGDELGYKCRFNEDFKYVLLPVSYGVVCVLGLCLNVVALY
                          TM2                                       TM3
P2Y1    :FVFHMRPWSGISVYMFNLALADFLYVLTLPALIFYYFNKTD.....WIFGDVMCKLQRFIFHVN
P2U     :FLCRLKTWNASTTYMFHLAVSDSLYAASLYAASLPLLVYYYARGDHW.PFSTVLCKLVFYTNLY
                                    TM4
P2Y1    :LYGSILFLTCISVHRYTGVVH.PLKSLGRLKKKNAVYVSSLVWALVVAVIAPILFYSGTGVRRNK
P2U     :CSILFLTCISVHRCLGVRPLHSLRWGRARYARRVAAVVMVLVLACQAPVLYFVTTSVRGTRFL
                                    TM5
P2Y1    :TITCYDTTADEYLRSYFVYSMCTTVFM.....FCIPFIVILGCYGLIVKALI.....YKDLDNS....PLRRK
P2U     :RITCHDTSARELFSHFVAYSSVMLGLLFAV.PFSVILVCYVLMA...RRLLKPAYGT..TGGLPRAKRK
              TM6                                                   TM7
P2Y1          :SIYLVnVLTVFAVSYLPFHVMKTLNLRARLDFQTPQMCAFNDKVYATYQVTR...GLASLNSCV
P2U     :SVRTIALVLAVFALCFLPFHVTRTLY.....YSFRSLDLSCHTLNAINMAYKITRPL....ASANSCL

P2Y1    :DPILYFLAGDTFRRRLSRATRKSSRRSEPNVQSKSEEMTLNILTEYKQNGDTSL
P2U     :DPVLYFLAGQRLVRFARDAKPPTEPTPSPQARRKLGLHRPNTTVRKDLSVSSDDSRRTESTPAGS

P2U     :ETKDIRL
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Figure 1. Representation of the amino acid sequence for P_m, P_{2Y}, P^ P_{2U}purinoceptors. A) Schematic diagram comparing the amino acid sequence of P_m, P_{2y}, and P_{2Y3} receptors, and showing putative membrane spanning domains. The shaded circles depict amino acid residues that are conserved between the three receptors. The open circles represent non-conserved residues, and the filled circles show residues that are known to be important in the function of other Gprotein coupled receptors. Subclassification of the P_{2Y}- G-protein linkedpurinocep tor family into P_m, P_{2Y2} and P_{2Y3} is based on the following clones: P_{2Yl} (Clone 803; see Ref. 16) and P_{2Y2} (Clone P2R; see Ref. 15). Another recombinant brain derived receptor (see Ref. 11) when expressed, responds to agonists with yet another activity series and has a strong preference for ADP. Northern hybridization revealed the presence ofmRNAfor this receptor in the brain and in several peripheral tissues. It has been designated P_{2Y3}. B) The amino acid sequence for P_{2Yl} and P_{2U}purinoceptors derivedfrom cDNA and aligned for maximum homology. The chicken P_m purinoceptors has362aminoacid^(seeRef.7),andthemouseP_{2U}purinoceptorhas373aminoacids(seeRef.25).Thelikelystartpositions of the transmembrane helices, as deduced from hydropathy plots, are shown by the symbols TMl to TM7.

on platelets and their megakaryocyte progenitors (18,19). P_{2U} purinoceptors are also coupled to phospholipase C via G-proteins (20,21), but unlike P_{2Y} purinoceptors they are activated by UTP as well as ATP (22,23). There is a high degree of sequence homology between P_{2Y1} and P_{2U} purinoceptors (Fig. IB). Other subclassess of P_2 purinoceptors have been proposed, such as P_3, P,^, and P^ (24-27), for which clearly delineated differences have not yet been shown. The $P_{i;2N}$ subtype may be synonymous with P_{2U} purinoceptors (10,12), and it may be best to consider them as a subclass of P_{2Y} purinoceptors due to their coupling with G-proteins.

PURINERGIC MECHANISMS OF THE PULMONARY CIRCULATION

• Pulmonary vascular smooth muscles possess K^+ channels which are directly inhibited by hypoxia, producing depolarization and consequently vasodonstriction (28-30). Other factors can contribute to the increase ,i«/y,asGular pressure produced by .hypoxia through additional vasoconstriction or withdrawal of vasadilation. Perivascular nerves, endothelial cells and blood born cells are the three major sources from which ATP may be released in the mammalian lung. ATP has a vasodilator effect via P_{2Y} purinoceptjors (31-33) of a type similar to P_{2Y2} (15), or via P^ purinoceptors, a vasoconstrictor effect (31, 33-35). In other va'scular beds, sensory neurons are known to release ATP and in this way produce vasomotor effects (4),.,although to date there has not been any such report with regard to the pulmonary circulation. A combination of mechanisms, including purinergic, provide the basis for the jinufual physiology of the pulmonary circulation, the focus of this review will be on mechanisms whetf ATP is the transmitter... acting on P_2 purinDGeptors.

PURINERGIC VASOCONSTRICTION

Periy;ascular nerves which release ATP

In the pulmonary circulation, there,is a large variation in the distribution and density of innervation dependanton.species (5,36) as well as development tal stage (6,37). The adrenergic system is understood with considerable depth (5,38,39), whereas appreciation of the purinergic system is more recent (40). Although ATP can potentially be released from sympathetic nerves as a cotransmitter along with noradrenaline and neuropeptide Y, to date visualization of non-sympathetic-purinergic innervation to pulmonary vessels has not been reported. There are quinacrine sensitive paratracheal neurones (Belai and Burnstock, personal communication) which need to be studied more closely to establish their identity and potential function. Quinacrine is a fluorescent acridine dye, which binds nucleotides with some selectivity for ATP, and can be used to label cells where ATP is concentrated (41-43). Quinacrine, sometimes in combination with strategic neurotoxins, has been successfully used in non-pulmonary tissues where purinergic innervation is known to exist (44,45).

Vasoconstriction by P_{2X} purinoceptors

With [^{3}H] a,p-meATP as a high affinity ligand for autoradiographic localization of P^ purinoceptors, togetherwithnon-radiolabelledpurinoceptorligands, in cat as well as in human tissue, was found that all vessels in the pulmonary circulation could be labelled (46). However, both medium and small-sized arteries had a higher density of specific binding sites than the large elastic arteries or veins. It was concluded that both P^and P_{2Y} purinoceptors are present in small intrapulmonary arteries and that the purinergic innervation is more marked on the arterial side than the venous. In the rat, investigation with intracellular recording from small intrapulmonary arteries of 100-200 lim external diameter revealed an excitatory junctional potential which was resistant to sympathectomy (40) produced by either guanethidine, 6-hydroxydopa-mine or reserpine (47). Using a,p-meATP, the potent and slowly degradable P^ purinoceptor agonist (48) to desensitize P^ purinoceptors, Inoue and Kannan (40) showed that the magnitude of excitatory junctional potentials produced by electrical stimulation cbuld be significantly attenuated without changing the membrane potential by the desensitization procedure. Furthermore, the membrane depolarization induced by ATP was significantly reduced, but not

completely inhibited by a,p-meATP produced desensitization, while the depolarization induced by noradrenaline or serotonin was not affected (40). Such studies are supported by others using isolated vessels and the vascular bed, which showed that pulmonary vessels of various species contain P^ purinoceptors which produce vasoconstriction when stimulated (33,34,49).

In some tissues, the P^ purinoceptor is coupled to prostaglandin synthesis (10,51,52). Furthermore, it is known that ATP is sequentially brocken down to adenosine by ectoenzymes (53-55). In this regard it was shown that ATP produces vasoconstriction in the pulmonary vascular circulation in part by a direct effect and in part indirectly following metabolism of ATPto adenosine (34). An A^'llke" receptor coupled to a phospholipase is activated by adenosine,, to produce the release of thromboxane A_2. The direct effect of ATP through the ?,,, purinoceptor is not coupled to a phospholipase (34). Observations such as these prompted examination of the role of P^ purinoceptors in the vasoconstriction evoked by acute hypoxia (50). Desensitization of the P_M purinoceptor with repeated application of a,P~ meATP blocked vasoconstriction in response to p,"y -meATP, a P^ purinoceptor selective agonist, but did not affect the vasoconstriction in response to hypoxia (50).

- **A novel vasoconstrictor mechanism**

In the presence of 100 |iM N^G-nitro-L-arginine-methyl-ester (L-NAME) and under basal tone, the vasoconstriction evoked by ATP injected into the Krebs perfusate of the rat pulmonary circulation does not change following desensitization of P,^ purinoceptors with a,p-meATP (Fig. 2) (35). Since desensitization of P^ purinoceptors on isolated pulmonary vascular smooth muscle by a,p-meATP

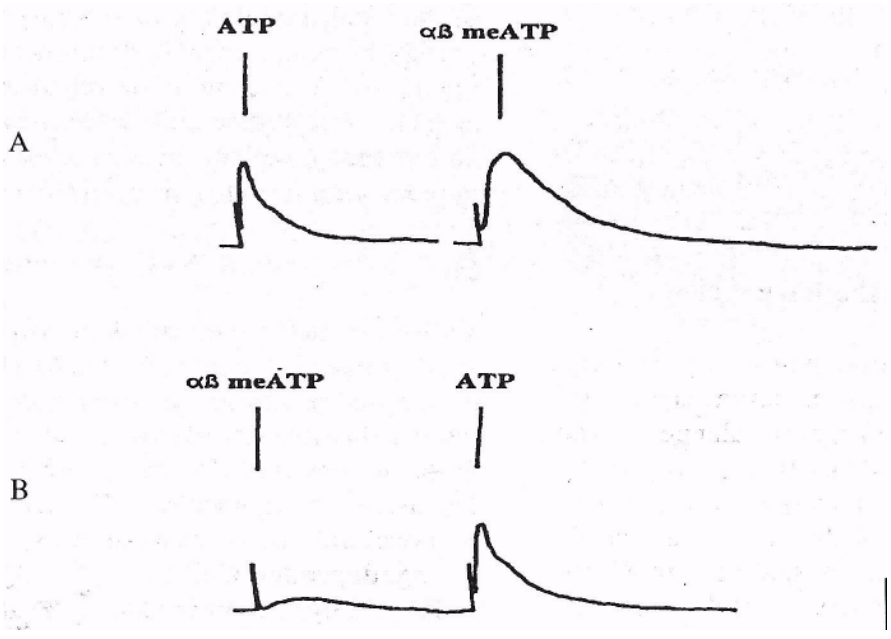

Figure 2. *Polygraph traces showing responses of the pulmonary vascular pressure topurinergic agonists. A) The response to 1.0 /jmoleATP and 0.001 jjtnole cc,fi-meATP before desensitization ofP^purinoceptors. The P^purinoceptor was desensitized using multiple injections of a, fl-meATP without shifting the basal vascular pressure.* ***B)*** *Following P^purinoceptor desensitization ATP is still capable of evoking vasoconstriction, demonstrating the presence of vasoconstrictor P_2purinoceptors in addition to those of the P^ subtype.*

significantly reduces ATP evoked depolarization (40), the above described observation may indicate that ATP, injected into the vascular lumen, produces the release of a vasoconstrictor from endothelium. Another possibility is that exogenous ATP is stimulating P_rpurinoceptors on vascular smooth muscle. Hence, there exist at least two exciting possibilities which need to be verified before the source of this newly discovered vasoconstriction can be established.

This ATP evoked vasoconstriction through the non-P^ purinoceptor mechanism is not sensitive to indomcthacin, although in this preparation the vasoconstriction evoked by adenosine or a,p-meATP is[1] attenuated after inhibition of prostaglandin synthesis (35). Furthermore, glibenclamide will attenuate PJX purinoceptor mediated vasoconsiriction in [lie rat pulmonary circulation but not that mediated by the non-P^, purinoceptor mechanism. The location, cellular mechanism, and role of these non-P,v purinoceptors which are activated by ATP remains to be established. Hence, there exists in the rat pulmonary circulation two ATP mediated vasoconstrictor mechanisms that can be distinguished from each other in at least three ways. These exciting new observations put purine nucleotides back into contention as a mediator of hypoxic pulmonary vasoconstriction.

- **Integrator role of the innervation**

Well over half of the total pulmonary vascular resistance lies in vessels under neural control (5, 56). thus ATPreleased from perivascular nerves can participate in the control of a sizeable portion of the pulmonary circulation. In this respect, it was shown that hypoxic stimulation of the carotid and aortic chemoreceptors reflexly decreased the compliance of ihe large pulmonary arteries over the entire vascular bed (57,58).

However, alveolar hypoxia increases predominantly the resistance of intrapulmonary arteries (7,57), and vasoconstriction in response to hypoxia is resistant to sympathectomy (59-61). There is still much to be learned regarding the physiological implications of pulmonary blood vessel innervation (5) and thus the role of ATP released from perivascular nerves. Whether or not nerve mediated regulation enhances alveolar-capillary gas exchange by redirecting pulmonary blood flow is entirely speculative (7,57,62), a more likely function of the neuronal input is to maintain a proper balance between the resistance and compliance characteristics of the pulmonary circulation to ensure comportment between the output of the right and left ventricles (5,63).

PURIHERG1C VASODILATOR MECHANISMS

Releasable ATP of endothelium

Endothelial cells play an important role as the inactivator of circulating vasoactive substances, and ectoenzymes on their plasma membrane are responsible for the degradation of purincs (8,53-55). Adenosine is taken up by an active mechanism and subsequently synthesized into ATP (64,65). Vasoactive agents are differentially released in response to various stimuli and in this way play a major role in the local modulation of the circulation (56,66). Furthermore, endothelialcells arehcterogenous with regard to their content of relcasable vasoactive agents as well as their cell surface receptors (66-69), and this may explain the characteristic reaction to various stimuli of different vascular beds.

2 Liberation of ATP from endothelial cells

Various stimuli have been demonstrated to release ATP from endothelial cells (66.70,71). The release of vasoactive substances from endothelial cells is likely to involve K* efflux and Ca^{2+} influx in addition to the liberation of $Ca.^{2+}$ from intracellular stores by inositol-l,4,5-triphosphate (72-74). As with other non-excitable cells, endothelial cells do not have voltage dependent $Ca^{24"}$ channels (74,76). The efflux of K~ will hyperpolarize the cell and thus increase the driving force for Ca^{2}* entry. In addition to agonist evoked ATP release from endothelial cells (75, Bodin and Burnstock. personal communication), we found that increased flow derived shear stress will also evoke release of ATP in the pulmonary circulation (76). Pulmonary vascular flow increases as much as 100 fold during the cardiac cycle (37), therefore, ATP is constantly being released by in-

creases in flow which occur during each systole (74). We have found ihatsuramin, the P_2purinoceptor antagonist (77-79), will raise pulmonary vascular pressure under condition of increasing flow and flow derived shear stress (78). The ATP release in response to increased flow could be blocked by glibenclamidc (76), a blacker of intracellular ATP sensitive K^+ channels (80) although the ability of glibenclamidc to block $Ca^{:+}$ regulated K~ channels has also been demonstrated (81.82). We concluded that flow evoked ATP release would also be functional under hypoxic condition (76). where shear stress would increase due to vasoconstriction (7,83,84). The ATP that released from pulmonary cndothelial cells could either act on the same endothelial cell in an autoregulatory mechanism, or travel short distances in the blood to act on endothelial $P_{,y}$ purinoceptors downstream in an autocrine manner (56, 66, 85).

pH related effects on ATP release

During hypoxic conditions, lactic may be released to the extracellular space (86), and ATP liberation (87, 88), as well as the nitric oxide released by ATP. is dependent on a rise in [Ca^{2+}]. which in part is due to Ca^{2+} influx (75,89). Although there is evidence that Ca^{2+} binding to cell membranes is pH dependent (90,91). and alkalinixation of extracellular- buffer enhances agonist-induced Ca^{2}" influx in bovine aortic endothelial cells (92-94). how, if at all. variations in pH affect endothelium in relation to purinergic mechanism is an important question which has not yet been addressed.

- **Vasodilation evoked by endotlielial ATP**

There is evidence for a vasodilator function of ATP which is released from endothelial cells in response to increased flow (Fig. 3). Furthermore, endothelial ATP may function to counter vasoconstriction during hypoxia. In some species, the vasodilau'on evoked by P .purinoceptors is endothelium dependent (31). and blocked by inhibition of nitric oxide synthesis with L-NAME (33), demonstrating that activation of pulmonary endothelial P_{2Y} purinoceptors by ATP evoked release of nitric oxide.

Endothelial P . purinoceptors are coupled to a phospholipase C by a GPT-binding protein such that activation of the P_{2Y} purinoceptor induces a rapid and transient rise of inositol-1.4,5-triphosphate in endothelial cells (84.95,96). In the pulmonary circulation, the vasodilator effect of P_{2Y} purinoceptor stimulation is not dependent on the release of vasodilator prostaglandins (32,97). Similarly, the vasodilation effect of ATP in the pulmonary vascular bed is not mediated by adenosine (32,98).

Endothelium independent vasodilation

After confirming that endothelium was removed by showing the absence of a vasodilator response to acetylcholine, Liu and colleagues (31) found a persistanl vasodulaiion by human small pulmonary arteries in response to ATP. Such a vasodilation was also produced by non-hydrolyzablc analogues of ATP, therefore degradation of ATP to adenosine and A, purinoceptor mediated vasodilation could be excluded. The same group has found $P_{,Y}$ purinoceptors to be on endothelium of only large (2-4mm) human pulmonary arteries (49,99). and they have concluded that P_{2Y} purinoceptor localization differs between big and small pulmonary arteries such that the number of P_{2Y} purinoceptors located on the smooth muscle are inversely proportional to the size of the vessel. From these studies it is logical to postulate that the big arterioles which have a large number of P_{2Y} purinoceptors on their endothelial surfaces would show a more marked effect on endothelial cell damage than the small arterioles.

B Regulation of vascular tone by endothelium

More and more it is becoming clear that vascular smooth muscle is situated between two opposing regulators. A vasoconstrictor innervation adjusts vascular tone relative 10 ihe perfusion requirement of the whole animal, and a vasodilator endolhelium adjusts vascular tone relative lo Ihe local milieu (100,101). Following endothelium cell damage. P^ purinoceplor derived vasoconstriction could produce vasospasms, and if the endothelial cell damage is more extensive hypertension may ensue (6). In view of this, the smooth muscle $P_{,Y}$ purinoceptors have particular importance in the therapeutic use of

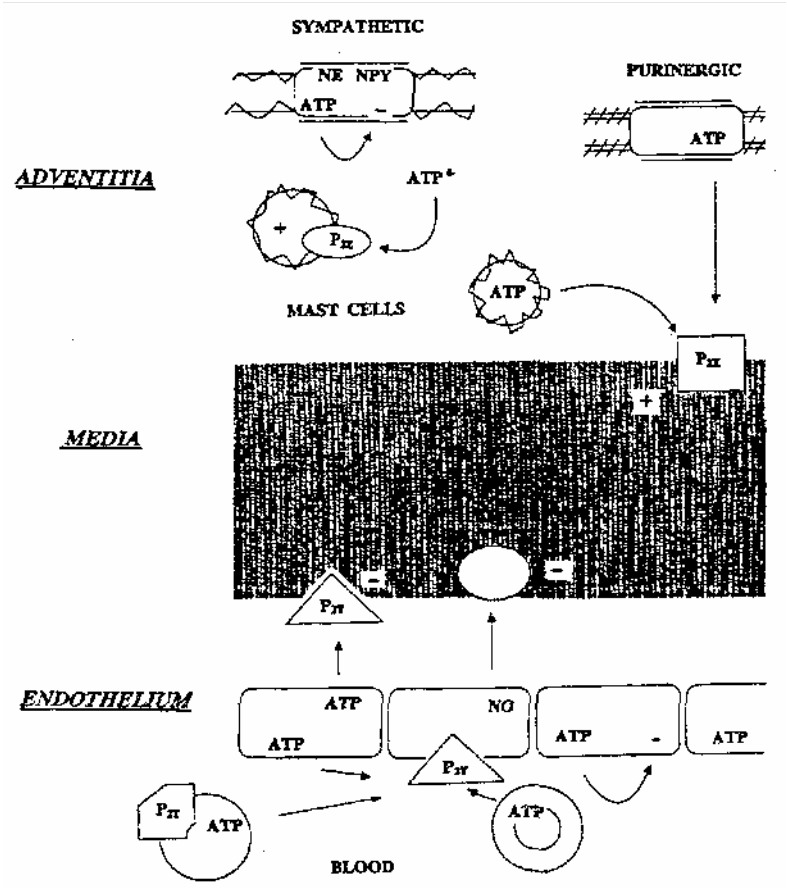

***Figure** 3. A schematic diagram representing the purinergic components of the vasoactive mechanisms in t/ie pu!monar\ circulation discussed in the texi. Stimuli acting on purinergic nerves, endolhelial cells, mast cells or erythrocytes will produce the release of ATP. Depicted are the P^.P.^pu rinoceptors of vascular smooth muscle, and the P .ypurinoceptors ofendotlielial cel/s. Also shown are the mobile thrombocytes and mast cells with respectively P^purinocepforsandP purinoceptors. Tlievasoconstrictor P.purinoceptorsrhat are active even after a, fi-meATP produced desensiiization are not placed since Their location remains to be established.*

purines for pulmonary vasodilation.

PURIMERGIC MECHANISMS OF BLOOD BORN CELLS

• Constituents of blood which release ATP

In addilion lo neurons and endolhelial cells of the pulmonary circulation, erylhrocytes and mast cells release ATP in response to various stimuli (5.102-107). Unlike other sources of ATP. these cells are relatively mobile and the magnitude of their effect can change due to alterations in their number (Fig. 3}. Thus an increase in heamatocrit following chronic alveolai[1] hypoxia (6,108) would alter purine mediated effects in the lungs.

• Vasoactive ATP released from erythrocytes and thrombocytes

Kivity and Soutirada (107) reported that vasoconstiiction in response to hypoxia was stronger in 100% plasma than in artificial perfusales composed of dextran or albumin, and they found that the presence of thrombocytes (platelets) in the perfusate led to a potentiation of the hypoxic response. Furthermore, repealing the hypoxic challenge with plasma as perfusate led to a noticeable increase in the size of the vasoconstriction in response to hypoxia wiih each repetition. Kiviiy and Soutirada (107) suggest thai Ihe mechanism for the apparent

increase with repeated challenges may be due to Ihe lack of the protective adenosine which is initially released to vasodilatc. Tn light of Ihe fact that ATP has been shown to be released from erythrocytes by episodes of hypoxia (105). and that lumenderived ATP vasodilated the pulmonary vascular bed by evoking nitric oxide release (33), ihe role of the crythrocyle derived ATP as a protector agent during hypoxia can not be excluded. The function of tlirombocyte derived ATP is even less clear.

- **Mast cell derived asoactive ATP**

Mast cells are plentiful in the walls and lumen of the airways, and pcriaitcrial mast cells (5,6,108) constitute another source of ATP with a potential vascular role (Fig. 3). The P^ purinoceptor is activated by ATP- (10.12.18) and mediates degranulation of inast cells (17,109-112") as well as the inhibition of ihe activity of natural killer ceils and macrophages (113.114). It has been shown that in response to acute hypoxia lung mast cells degranulate (6,11 rill 7) releasing substances which can increase plasma extravasation as during inllammaiion, and it is reported that mast cell number increases in response to conditions of chronic hypoxia(6.1 18). Some studies have found a lack of correlation between mast cell concentration in the lungs of various species and the vigor of the pulmonary prcssor response to hypoxia (5,6). The question of whether changes in mast cell number in animals exposed to chronic condition of hypoxia is (he cause or the result of hypertension is still an open question, and the role of ATP in relation to mast cells is understood even less.

CONCLUSION

• Recognition of purinergic vasomechanisms have opened significant new avenues to our understanding of how pulmonary vascular tone is maintained and regulated. The finding of a novel P, purinoceptor evoked vasoconsiriction puts ATP back into contention as a mediator of hypoxic pulmonary vasoconstriction. and although appreciation of this non-adrenergic and non-cholinergic system is relatively recent, the studies show promise that drugs targeted to purinergic vasomechanisms will have therapeutic use in pulmonary vascular medicine (119,120).

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