

Endothelium-Derived Vasoconstriction by Purines and Pyrimidines

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The article by Tölle et al¹ claims to show for the first time that adenosine 5'-tetraphosphate (AP4) is released on mechanical stimulation from human microvascular endothelial cells in the perfused rat kidney and, further, that AP4 is the most potent mediator of vascular smooth muscle constriction via P2X₁ receptors or, indeed, via noradrenergic.

It is well established that ATP and UTP released from endothelial cells in response to shear stress produced by changes in blood flow act largely on P2Y receptor subtypes (but also some P2X receptor subtypes) on endothelial cells to release nitric oxide (NO), leading to vasodilatation (Figure).^{2–5} Endothelium-derived contracting factors have been identified, notably endothelin-1, prostaglandin H₂, thromboxane A₂, and superoxide anions.^{6,7} Tölle et al¹ present compelling evidence for the release of AP4 from endothelial cells in response to mechanical stimulation, which then acts as a vasoconstrictor of the smooth muscle of microvessels in the kidney via P2X₁ receptors. The presence of P2X₁ receptors on vascular smooth muscle is well established, and they have been shown to respond to ATP released as a cotransmitter with noradrenaline from perivascular sympathetic vasoconstrictor nerves.⁸ However, P2X₁ receptors have also been described on endothelial cells of human internal mammary and radial arteries and saphenous vein.⁹ Occupation of endothelial P2X₁ receptors in rat mesenteric arteries resulted in a small vasoconstriction, followed by a profound and sustained endothelium-dependent vasodilatation, although not via NO.¹⁰ In P2X₁ knockout mice, the vasoconstrictor response to ATP released by nerve stimulation is abolished.¹¹ However, whether the constrictive responses to AP4 are also abolished in P2X₁ knockout mice has not been examined, nor are there any studies of changes in P2X₁ receptor-mediated endothelium-dependent vasodilatation. Presumably there are no P2X₁ receptors on endothelial cells of the kidney microvessels; otherwise, there would be competing vasodilator effects of AP4. A study of the role of P2X₁ receptors in renal microvascular autoregulatory behavior in response to increases in renal perfusion pressure suggested that ATP released from macula densa cells¹² was mediated by P2X₁

receptors and the reduction of the autoregulatory responses in P2X₁ knockout mice supported this hypothesis.¹³

AP4 activates P2Y, as well as P2X receptors.¹⁴ The decreasing effect of AP4 on blood pressure is mediated by P2Y receptors on endothelial cells, but under certain conditions, such as hemorrhage, AP4 produces vasoconstriction via smooth muscle P2X receptors, where it was noted to be more potent than ATP.¹⁵

In addition to AP4, uridine adenosine tetraphosphate (Up4A) was also identified as a highly potent purinergic endothelium-derived vasoconstrictor by this group.¹⁶ However, in their present article, the researchers show that AP4 is more potent than Up4A, being an active vasoconstrictor in nanomolar concentrations. It is puzzling why the actions of ATP released from endothelial cells in response to shear stress are directed largely to endothelial cell P2 receptors, leading to vasodilatation (rather than smooth muscle P2X₁ receptors), whereas AP4 released from endothelial cells is

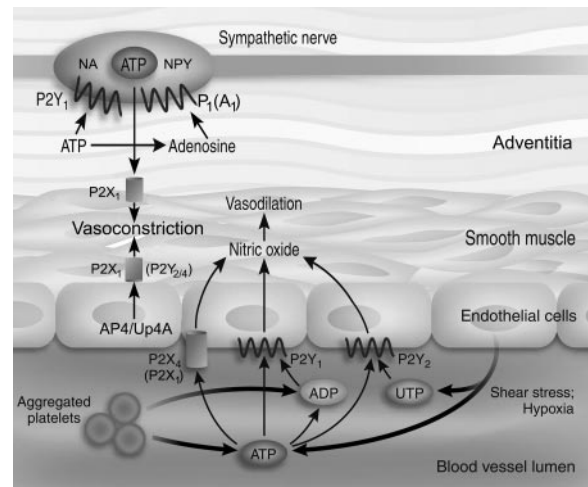


Figure. Purines and pyrimidines control vascular tone through P2 receptors. ATP, along with noradrenaline and neuropeptide Y, released from perivascular sympathetic nerves bind the P2X₁ receptors (as well as P2X₂, P2X₄, and P2Y₂ receptors in some vessels) on smooth muscle, resulting in vasoconstriction. P1(A₁) receptors on sympathetic nerves bind adenosine, which arises from enzymatic breakdown of ATP, to inhibit transmitter release, as do P2Y₁ prejunctional receptors. During conditions of shear stress and hypoxia, endothelial cells release ATP and UTP, which bind P2Y₁ (via ADP) and P2Y₂ and, in some vessels, P2X₁ and P2X₄ receptors to trigger production of nitric oxide and subsequent vasodilation. ATP and ADP secreted by aggregating platelets also stimulate these receptors. It is claimed that AP4 and Up4A are released from endothelial cells under mechanical stress to produce vasoconstriction via muscle P2X₁ receptors and in the case of Up4A probably also via P2Y₂ and P2Y₄ receptors. Modified and with permission of the Nature Publishing Group from Burnstock G. Vessel tone and remodeling. *Nat Med.* 2006;12:16–17.

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claimed in this article to act on P2X₁ receptors on smooth muscle, leading to vasoconstriction. This raises the question as to whether ATP is released into the lumen while AP4 and Up4A are released from the basolateral surface of the endothelial cells.

It is possible that AP4 is released from perivascular nerves together with ATP; it has been shown to be a potent agonist on rat midbrain synaptic terminal P2 receptors.¹⁷ AP4 has also been shown to be stored in chromaffin granules and in platelets, where it can be released into the circulation, inhibiting the platelet aggregation induced by adenosine diphosphate¹⁸ and regulating blood pressure.¹⁹

It is clear that purinergic signaling is a major mechanism involved in the regulation of vascular tone, but there is still much to be learned about the sites and mechanisms of release of purines from endothelial cells that mediate vasodilatation and vasoconstriction and the variations in purinergic pathways that exist between different vessels.

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Disclosures

None.

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