Vessel tone and remodeling

Geoffrey Burnstock

Changes in blood flow and hypoxia lead to endothelial-mediated control of vascular tone. An additional nucleotide receptor on endothelial cells has been identified that mediates release of nitric oxide and vasodilation (pages 133–137).

Vascular shear stress (caused by biomechanical forces associated with changes in blood flow) and hypoxia stimulate endothelial cells to release ATP. Purinergic P2 nucleotide receptors on endothelial cells bind ATP, which triggers secretion of nitric oxide, resulting in vasodilation. Although P2Y G-protein-coupled receptors are known to mediate this response, in this issue Yamamoto *et al.* report that ion-channel $P2X_4$ receptors also control vascular tone and vessel remodeling, at least in some blood vessels[1].

Purinergic signaling, in which purine nucleotides and nucleosides act as extracellular signaling molecules, controls vascular tone[2] (**Fig. 1**). Purinergic signaling also controls the long-term changes in cell proliferation, differentiation, migration and death that occur in restenosis, hypertension, atherosclerosis and ischemia[3].

There are several types of purinergic receptors. P1 receptors bind adenosine, and P2 receptors bind ATP and ADP. P2 receptors can be classified as either ion-channel (P2X) or G-protein-coupled (P2Y) receptors[4,5].

ATP, released as a cotransmitter with noradrenaline, binds $P2X_1$ receptors on medial vascular smooth muscle to produce vasoconstriction[6] (**Fig. 1**). During shear stress, endothelial cells secrete ATP[7], activating the $P2Y_1$ receptor and inducing vasoconstriction. $P2Y_1$ receptor signaling is subject to selective agonist action by ADP and $P2Y_2$ receptors are selectively activated by the pyrimidines UTP and UDP. Endothelial cells also express other types of purinergic receptors ($P2Y_4$ and $P2Y_6$)[8]; and yet another type of receptor ($P2Y_{11}$) is present on endothelial cells of human mammary artery and umbilical vein[9].

Purine and pyrimidine nucleotides released from endothelial cells, and adenosine from the enzymatic breakdown of ATP, also act on endothelial cells and smooth muscle to induce cell proliferation, differentiation, motility and death in vessel remodeling[3].

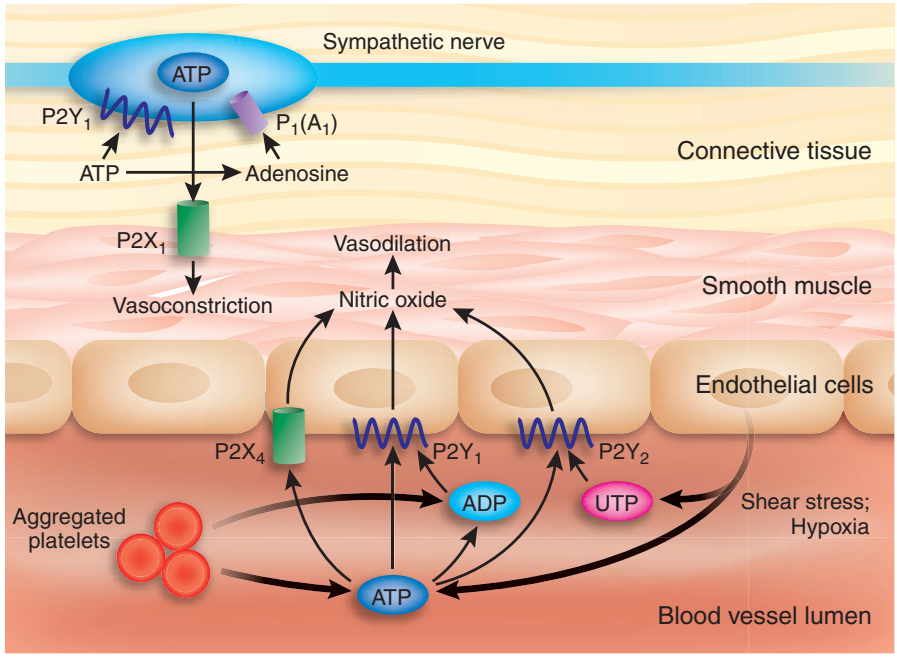

Figure 1 Purines and pyrimidines control vascular tone through P2 receptors. ATP, along with noradrenaline and neuropeptide Y, released from perivascular sympathetic nerves bind the $P2X_1$ receptors—as well as $P2X_2$ and $P2X_4$ receptors in some vessels—on smooth muscle, resulting in vasoconstriction. $P1(A_1)$ receptors on sympathetic nerves bind adenosine—which arises from enzymatic breakdown of ATP—and inhibit release of transmitters. During conditions of shear stress and hypoxia, endothelial cells release ATP and UTP, which bind $P2Y_1$ and $P2Y_2$ receptors and trigger production of nitric oxide and subsequent vasodilation. ATP and ADP secreted by aggregating platelets also stimulate these receptors. Yamamoto *et al.* show that $P2X_4$ receptors mediate the release of nitric oxide in some vessels in response to ATP.

A previous study reported that endothelial cells of arteries and veins express different levels of $P2X_4$ receptors—high levels on saphenous veins and low levels on mammary arteries[10]. But the function of this receptor was unknown. Yamamoto *et al.* now find that, in some blood vessels, $P2X_4$ receptors induced vascular dilation in a nitric oxide–dependent manner. This finding contrasts with another study that examined $P2X_1$ receptors on the endothelium of rat mesenteric arteries. $P2X_1$ receptors mediated endothelial-dependent vasodilation, but a nitric oxide synthase inhibitor had no effect on dilation[11].

Yamamoto *et al.* showed that endothelial cells from mouse pulmonary microvessels express the $P2X_4$ receptor. $P2X_4$ receptor knockout mice had higher blood pressure and excreted smaller amounts of nitric oxide products in their urine than wild-type mice. In $P2X_4$-deficient mice, flow-induced release of nitric oxide and vasodilation were impaired in cremaster muscle arterioles, and mesenteric and carotid arteries. The authors also showed that adaptive vascular remodeling, or vessel size decrease, which normally

The author is at the Autonomic Neuroscience Centre, Royal Free & University College Medical School, London NW3 2PF, UK.
E-mail: g.burnstock@ucl.ac.uk

occurs in response to chronically low blood flow, was blocked in the $P2X_4$ receptor–deficient mice.

As these findings provide insight into the molecular mechanisms underlying vascular tone and remodeling, the authors speculate that this report may help develop new therapies for blood pressure disorders. Unfortunately, selective agonists and antagonists for the $P2X_4$ receptors are not yet available. ATPγS is a potent but not selective $P2X_4$ agonist, whereas the nonspecific P2 receptor antagonists suramin, pyridoxal phosphate-6-azophenyl-2', 4'-disulphonic acid and Reactive blue 2 do not inhibit $P2X_4$ receptor–mediated responses; indeed they potentiate the ATP response by inhibiting ectonucleotidases[4]. The wide variation in vascular control by purines and pyrimidines must also be recognized; further investigation is needed to establish which vessels in which species use $P2X_4$ receptors as the principal endothelial P2 receptor subtype mediating release of nitric oxide.

The importance of purinergic signaling in cardiovascular diseases[12] is highlighted by the recent use of $P2Y_{12}$ receptor antagonists, like clopidogrel, for the treatment of thrombosis and stroke—by the use of P1 receptor agonists, such as adenosine, for treatment of supraventricular tachycardia (rapid heart rate originating in the lower heart chambers).

Although considerable effort has been expended to produce selective agonists and antagonists for P1 and P2 receptor subtypes[13], drugs that target the different subtypes, including the $P2X_4$ receptor, and that are not degraded *in vivo*, are still awaited.

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A channel to neurodegeneration

Ariel Y Deutch & Danny G Winder

In people with Parkinson disease, neurons in certain brain regions are more likely to die than others. A potassium channel may be the key to understanding this differential neuronal death.

Neurodegenerative disorders are bigots. None attack all brain cells, and many discretely target neurons in only a few areas. Why there is a loss of midbrain dopamine neurons that are next to ones spared in Parkinson disease is intensely studied. In a surprising twist on the usual suspects, a study in the December issue of *Nature Neuroscience* may explain the differential vulnerability of dopamine cells in Parkinson disease[1].

In Parkinson disease, dysfunction of the mitochondrial electron transport chain, increases in reactive oxygen species, and decreases in ATP production contribute to dopamine cell death in the substantia nigra[2], a region in the midbrain. The dopamine neurons of the substantia nigra, and the striatal dopamine innervation derived from these neurons, undergo a selective (or regionally specific) pattern of degeneration in Parkinson disease. Symptoms arise when dopamine axons in the striatum are lost. In contrast, the dopamine neurons in an adjacent midbrain region, the ventral tegmental area, are much less affected.

What governs the differential loss of midbrain dopamine neurons in Parkinson disease remains a source of speculation. Potential explanations include differing degrees of expression of the dopamine transporter (through which xenobiotics access dopamine neurons), the presence or absence of the calcium binding protein calbindin, and variations in molecules that counter oxidative stress[4,5]. But none of these explanations has proven completely satisfactory.

Liss *et al.* now provide evidence that ATP-sensitive potassium (K_{ATP}) channels may help determine the selective loss of substantia nigra, but not ventral tegmental area, dopamine cells in Parkinson disease[1]. K_{ATP} channels are metabolic sensors that couple cellular energy metabolism to membrane potential by regulating potassium flux. In the midbrain dopamine neurons, the K_{ATP} channels are composed of a pore-forming inward-rectifying potassium channel subunit known as Kir6.2 and a regulatory sulfonylurea receptor subunit known as Sur1. Sulfonylureas are drugs used in the treatment of type 2 diabetes that close K_{ATP} channels and densely bind neurons of the substantia nigra.

Liss *et al.* reported that the mRNA encoding K_{ATP} channels comprising Kir6.2 and Sur1 are abundantly expressed in substantia nigra dopamine neurons. They found that metabolic challenges with parkinsonism-inducing toxins, such as MPTP, cause rapid hyperpolarization and electrical 'silencing' of dopamine cells in the substantia nigra, but not in the ventral tegmental area. In contrast, nigral dopamine neurons from Kir6.2 knockout mice were not hyperpolarized with these toxins.

MPTP treatment of mice causes extensive loss of substantia nigra dopamine neurons and the dopamine innervation of the striatum[6]; in contrast, Liss *et al.* found that Kir6.2 knockout mice are relatively resistant to MPTP. When *weaver* mice— which suffer a developmentally specific loss of substantia nigra neurons[7]—were crossed with Kir6.2 null mice, the absence of K_{ATP} channels attenuated the loss of substantia nigra dopamine neurons in these mice. These studies suggest that the K_{ATP} channel may help determine whether a dopamine neuron

Ariel Y. Deutch is in the Departments of Psychiatry and Pharmacology, and the National Parkinson Foundation Center of Excellence at Vanderbilt University; Danny G. Winder is in the Department of Molecular Physiology and Biophysics and the National Parkinson Foundation Center of Excellence at Vanderbilt University, Vanderbilt University Medical Center, Nashville, Tennessee 37212, USA.
E-mail: ariel.deutch@vanderbilt.edu