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Review

Purinergic transmission in blood vessels

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ABSTRACT

There are nineteen different receptor proteins for adenosine, adenine and uridine nucleotides, and nucleotide sugars, belonging to three families of G protein-coupled adenosine and P2Y receptors, and ionotropic P2X receptors. The majority are functionally expressed in blood vessels, as purinergic receptors in perivascular nerves, smooth muscle and endothelial cells, and roles in regulation of vascular contractility, immune function and growth have been identified. The endogenous ligands for purine receptors, ATP, ADP, UTP, UDP and adenosine, can be released from different cell types within the vasculature, as well as from circulating blood cells, including erythrocytes and platelets. Many purine receptors can be activated by two or more of the endogenous ligands. Further complexity arises because of interconversion between ligands, notably adenosine formation from the metabolism of ATP, leading to complex integrated responses through activation of different subtypes of purine receptors. The enzymes responsible for this conversion, ectonucleotidases, are present on the surface of smooth muscle and endothelial cells, and may be coreleased with neurotransmitters from nerves. What selectivity there is for the actions of purines/pyrimidines comes from differential expression of their receptors within the vasculature. P2X1 receptors mediate the vasocontractile actions of ATP released as a neurotransmitter with noradrenaline (NA) from sympathetic perivascular nerves, and are located on the vascular smooth muscle adjacent to the nerve varicosities, the sites of neurotransmitter release. The relative contribution of ATP and NA as functional cotransmitters varies with species, type and size of blood vessel, neuronal firing pattern, the tone/pressure of the blood vessel, and in ageing and disease. ATP is also a neurotransmitter in non-adrenergic non-cholinergic perivascular nerves and mediates vasorelaxation via smooth muscle P2Y-like receptors. ATP and adenosine can act as neuromodulators, with the most robust evidence being for prejunctional inhibition of neurotransmission via A_1 adenosine receptors, but also prejunctional excitation and inhibition of neurotransmission via P2X and P2Y receptors, respectively. $P2Y_2$, $P2Y_4$ and $P2Y_6$ receptors expressed on the vascular smooth muscle are coupled to vasocontraction, and may have a role in pathophysiological conditions, when purines are released from damaged cells, or when there is damage to the protective barrier that is the endothelium. Adenosine is released during hypoxia to increase blood flow via vasodilator A_{2A} and A_{2B} receptors expressed on the endothelium and smooth muscle. ATP is released from endothelial cells during hypoxia and shear stress and can act at P2Y and P2X4 receptors expressed on the endothelium to increase local blood flow. Activation of endothelial purine receptors leads to the release of nitric oxide, hyperpolarising factors and prostacyclin, which inhibits platelet aggregation and thus ensures patent blood flow. Vascular purine receptors also regulate endothelial and smooth muscle growth, and inflammation, and thus are involved in the underlying processes of a number of cardiovascular diseases.

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1. Introduction

There are two main classes of purine receptors: adenosine P1 receptors, and P2 receptors recognising purine and pyrimidine nucleotides (ATP, ADP, UTP, UDP) and UDP-sugars (Abbracchio and Burnstock, 1994; Abbracchio et al., 2006; Ralevic and Burnstock, 1998). Nineteen different purine receptor proteins have been cloned and the molecular and pharmacological properties of the homomeric and heteromeric receptors characterised. Nucleotides and nucleosides can be released from many different types of cells relevant to the control of vascular function (see Burnstock, 2006, 2007, 2012). They act on P1 adenosine and P2 purine receptors expressed on the endothelium, vascular smooth muscle and perivascular nerves to mediate vasomotor and trophic effects. Complex integrated responses can be produced through nucleotide interconversion and metabolism, including rapid breakdown of ATP into adenosine which can have its own effects at P1 receptors. This review discusses the diverse roles of purines and pyrimidines as signalling molecules in blood vessels and how this may change under different physiological and pathophysiological conditions. Reviews about the involvement of purinergic signalling in cardiovascular diseases are available (Burnstock, 1989, 2006, 2007; Burnstock and Ralevic, 2014; Burnstock and Verkhratsky, 2012; Erlinge and Burnstock, 2008; Ralevic, 2009; Ralevic and Burnstock, 2003; Schuchardt et al., 2012). The relevance of ectonucleotidases for the treatment of cardiovascular disorders has also been reviewed (Mathieu, 2012). This review considers specifically purinergic autonomic dysfunction in disease and the potential of purine receptors as therapeutic targets.

2. Purine receptors

Subtypes of adenosine/P1 and P2 receptors are listed in Fig. 1, together with their endogenous agonists and, where relevant, their G protein coupling. There are four adenosine P1 receptors, A_1, A_{2A}, A_{2B} and A_3, all of which couple to G proteins. A_1 and A_3 adenosine receptors couple primarily to $G_{i/o}$ proteins and mediate inhibition of adenylyl cyclase, and A_{2A} and A_{2B} adenosine receptors couple to G_s proteins and can activate adenylyl cyclase, leading to a reduced and increased accumulation of cyclic AMP respectively (Ralevic and Burnstock, 1998). All four adenosine receptors are expressed on vascular smooth muscle and endothelial cells, with distinct roles identified in control of vascular tone and cell proliferation (discussed in subsequent sections).

P2 receptors are divided into ionotropic P2X receptors and G protein-coupled P2Y receptors (Abbracchio et al., 2006). There are seven different P2X receptor proteins (P2X1–P2X7), each having two transmembrane domains and an extracellular loop, which can combine to form trimeric homomultimeric or heteromultimeric receptors (Barrera et al., 2005; Jiang et al., 2003; Kawate et al., 2009; Nicke et al., 1998). P2X1–7 receptors are receptors for ATP and act as cation channels to cause membrane depolarisation (Li et al., 2010; North, 2002). P2X receptors have different sensitivities to ATP and its stable analogue α, β-methylene ATP (α, β-meATP), different rates of current decay, and can be differentially regulated by extracellular calcium, zinc and protons (Khakh and North, 2006; Khakh et al., 2001; North, 2002; Roberts et al., 2006; Saul et al., 2013). P2X1 and P2X4 are the main P2X receptor proteins expressed in vascular smooth muscle cells; P2X7 receptors may

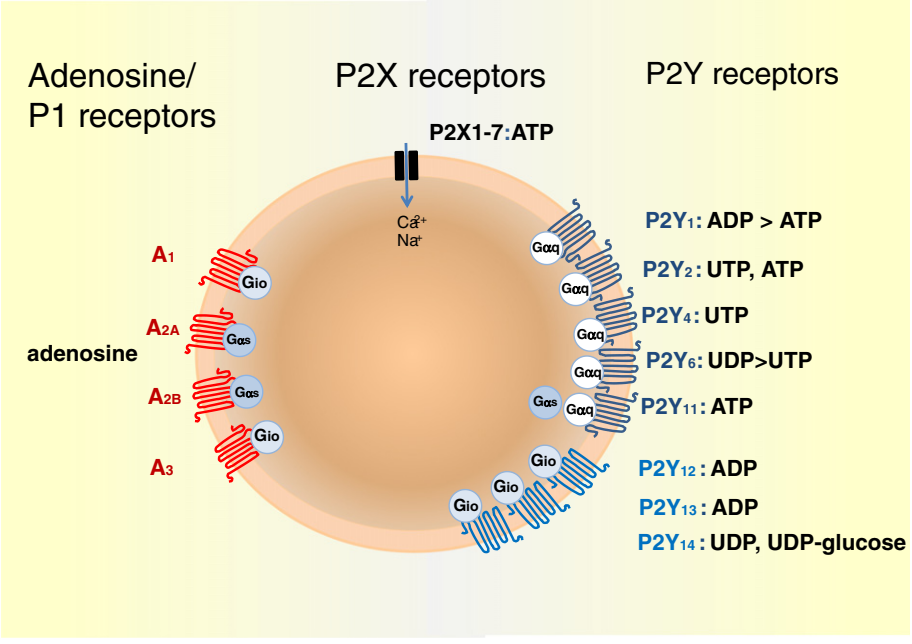

Fig. 1. Endogenous agonist selectivities for cell surface receptors for adenosine (adenosine/P1 receptors) and for purine nucleotides and UDP-sugars (P2X and P2Y receptors). P2X1-7 receptors are ionotropic receptors which can form heteromultimers (e.g. P2X1/4). The G protein coupling of adenosine/P1 receptors and P2Y receptors is shown.