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Insulin/adenosine axis linked signalling

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ABSTRACT

Regulation of blood flow depends on systemic and local release of vasoactive molecules such as insulin and adenosine. These molecules cause vasodilation by activation of plasma membrane receptors at the vascular endothelium. Adenosine activates at least four subtypes of adenosine receptors (A_1AR, A_{2A}AR, A_{2B}AR, A_3AR), of which A_{2A}AR and A_{2B}AR activation leads to increased cAMP level, generation of nitric oxide, and relaxation of the underlying smooth muscle cell layer. Vasodilation caused by adenosine also depends on plasma membrane hyperpolarization due to either activation of intermediate-conductance Ca^{2+}-activated K^+ channels in vascular smooth muscle or activation of ATP-activated K^+ channels in the endothelium. Adenosine also causes vasoconstriction via a mechanism involving A_1AR activation resulting in lower cAMP level and increased thromboxane release. Insulin has also a dual effect causing NO-dependent vasodilation, but also sympathetic activity- and increased endothelin 1 release-dependent vasoconstriction. Interestingly, insulin effects require or are increased by activation or inactivation of adenosine receptors. This is phenomenon described for D-glucose and L-arginine transport where A_{2A}AR and A_{2B}AR play a major role. Other studies show that A_1AR activation could reduce insulin release from pancreatic β-cells. Whether adenosine modulation of insulin biological effect is a phenomenon that depends on co-localization of adenosine receptors and insulin receptors, and adenosine plasma membrane transporters is something still unclear. This review summarizes findings addressing potential involvement of adenosine receptors to modulate insulin effect via insulin receptors with emphasis in the human vasculature.

1. Introduction

A proper regulation of the vascular tone is essential to maintain vascular and systemic homeostasis compatible with life in humans. Several diseases associate with alterations in the vascular response to vasodilators or vasoconstrictors, including hypertension, diabetes mellitus, and obesity (De Boer et al., 2012; Charkoudian, 1985; Escudero et al., 2014; Higashi and Yoshizumi, 2004; Hink et al., 2003; Jonk et al., 2007; King et al., 1994; Lamireau et al., 2002; Versari et al., 2009; Schalkwijk and Stehouwer, 2005; Sobrevia et al., 2016). These vascular reactivity complications associate with disorders of the heart and blood vessels, referred as cardiovascular disorders (CVDs), including coronary heart, cerebrovascular, and peripheral arterial disease (World Health Organization (WHO), 2016). Vascular endothelial and smooth muscle cells play crucial roles in the efficiency of the vessels to dilate or contract in

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response to circulating or locally released molecules. Among a large variety of these molecules, are the endogenous nucleoside adenosine (Antonioli et al., 2015; Headrick et al., 2013; Westermeier et al., 2011) and the hormone insulin (Baumgard et al., 2016; Manrique et al., 2014; Westermeier et al., 2016; Zaykov et al., 2016), both of which act on plasma membrane receptors of relative high selectivity and specificity triggering differential signalling mechanisms according to the type of receptor(s) activated (Burnstock, 2016; Fredholm et al., 2011; Fredholm, 2014; Westermeier et al., 2016).

The biological effects of adenosine depend on its extracellular concentration and binding to plasma membrane adenosine receptors (ARs) (Fredholm, 2014; Headrick et al., 2013; Riksen and Rongen, 2012). ARs are coupled to stimulatory or inhibitory G proteins, which, among other things, lead to changes in the level of the adenylyl cyclase (AC)-generated cyclic AMP (cAMP), thus modulating cell function and metabolism (Fredholm et al., 2011; Fredholm, 2014). ARs are four subtypes expressed in most cell types, including the human umbilical cord vessels and placenta vasculature, i.e., foetoplacental vasculature (Wyatt et al., 2002; Salsoso et al., 2015). Activation or blockage of ARs could result in greater risk to develop diabetes mellitus, hypertension, or cancer (Fredholm, 2010). Equally, ARs are essential in gestational diabetes mellitus (GDM) (Vásquez et al., 2004; San Martín and Sobrevia, 2006; Guzmán-Gutiérrez et al., 2016) and early or late pre-eclampsia (Escudero et al., 2008; Salsoso et al., 2015)-associated human umbilical vein endothelial dysfunction.

ARs are also critical in the biological effects of insulin in the human vasculature (Guzmán-Gutiérrez et al., 2012, 2016; Salsoso et al., 2015), and other cell types, including skeletal muscle (Figler et al., 2011; Han et al., 1998; Law et al., 1988; Sacramento et al., 2015; Thong et al., 2007) and adipocytes (Ciaraldi, 1988; Green, 1987; Lönnroth et al., 1988; Martin and Bockman, 1986; Wong et al., 1984). Interestingly, different levels of expression of insulin receptors (IRs), as well as triggering of their corresponding associated signalling mechanisms, is reported in human umbilical vein endothelial cells (HUVECs) from GDM pregnancies compared with cells from normal pregnancies (Guzmán-Gutiérrez et al., 2016; Westermeier et al., 2011, 2015). This condition results in endothelial cell activation increasing the expression and activity of nitric oxide synthases (NOS) in HUVECs (Westermeier et al., 2011) and human placental microvascular endothelial cells (hPMECs) (Salomón et al., 2012). Thus, a close relationship between adenosine and ARs, and insulin and IRs is a mechanism that modulates cell function, including vascular endothelial and smooth muscle cells, in health and disease.

This review addresses potential cellular and molecular mechanisms behind the biological actions of adenosine via ARs as modulator of insulin effect via IRs with emphasis in the human vasculature.

2. Adenosine

Adenosine is an endogenous purine nucleoside that results from the β-N^9-glycosidic bond between adenine and D-ribose, and is synthesized, released, and taken up by most, if not all the cells (Pelleg and Porter, 1990), including human foetoplacental vascular endothelial (Ho et al., 2016; Vásquez et al., 2004; Westermeier et al., 2011, 2016) and smooth muscle cells (Aguayo et al., 2001; Aguayo and Sobrevia, 2000; Ho et al., 2016). This nucleoside is widely recognized for being a local regulator of cellular function, mediating autocrine and paracrine mechanisms in response to acute alterations meeting the associated energy demands of cells (Chen et al., 2013; Headrick et al., 2011). These physiological processes include the local regulation of vascular tone in adults (Ballard, 2014; Kaufmann et al., 2007) and newborns (Westermeier et al.,

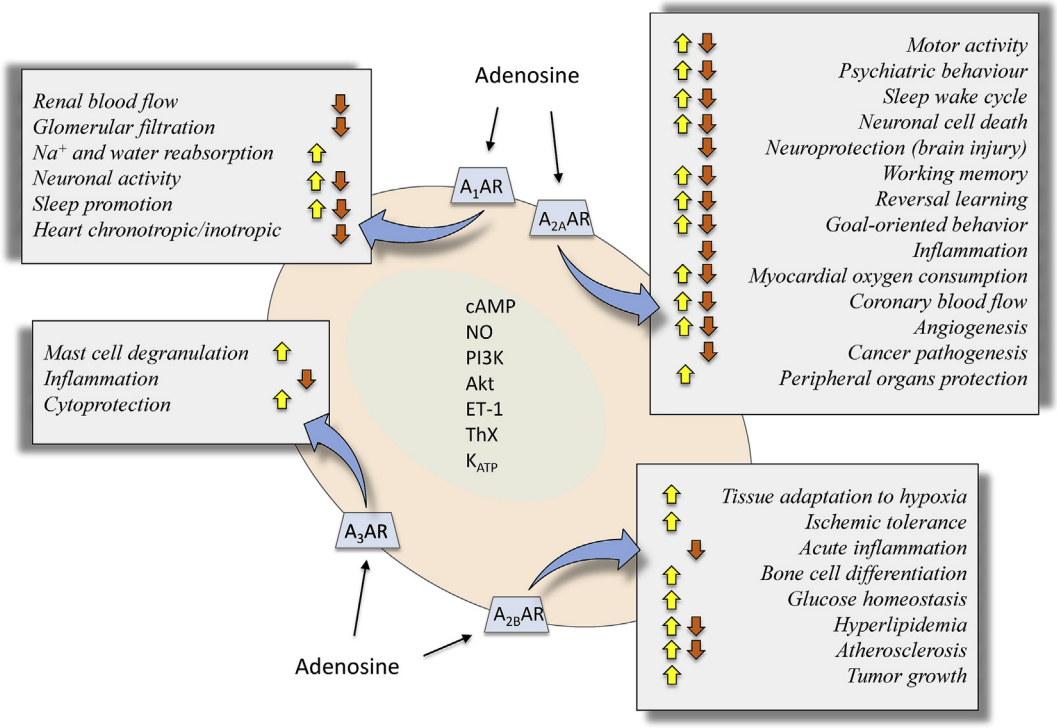

Fig. 1. Biological effects of adenosine via adenosine receptors activation. Adenosine activates adenosine receptor subtype 1 (A_1AR), 2_A (A_{2A}AR), 2_B (A_{2B}AR), or A_3 (A_3AR). The biological effect is an increase (⇧) or decrease (⇩) of the indicated phenomena. Activation of these receptors mediates cell signalling mechanisms involving cyclic AMP (cAMP), nitric oxide (NO), phosphatidylinositol 3 kinase (PI3K), protein kinase B (Akt), endothelin 1 (ET-1), tromboxanes (ThX), ATP-activated K^+ channels (K_{ATP}). Composed from references addressed in the text and Table 1.