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Adenosine receptors: Modulators of lipid availability that are controlled by lipid levels

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ABSTRACT

Adenosine as well as agonists and antagonists for the four adenosine receptor subtypes (A1R, A2AR, A2BR and A3R) play a role in several key physiological and pathophysiological processes, including the regulation of vascular tone, thrombosis, immune response, inflammation, and angiogenesis. This review focuses on the adenosine-mediated regulation of lipid availability in the cell and in the systemic circulation as well in humans and animal models. Therefore, adenosine, mainly by acting on A1R, inhibits lipolysis activity, leading to reduction of the circulating fatty acid levels. This nucleoside can also participate in the early development of atherosclerosis by inhibiting the formation of foam cells via stimulation of cholesterol efflux through A2AR expressed on macrophages and reduction of the inflammatory process by activating A2AR and A2BR. Adenosine also appears to modulate intracellular cholesterol availability in Niemann-Pick type C1 disease and Alzheimer disease via A2AR and A3, respectively. Remarkably, the role of adenosine receptors in the regulation of plasma total cholesterol and triglyceride levels has been studied in animal models. Thus, an anti-atherogenic role for A2BR as well as a pro-atherogenic role of A2AR and A1 have been proposed; A3R has not been shown to participate in the control of lipid levels or the development of atherosclerosis. Surprisingly, and despite the role of A2A in the inhibition of foam cell formation among isolated cells, this receptor appears to be pro-atherogenic in mice. Remarkably, the role of adenosine receptors in human dyslipidaemia and atherosclerosis must to be elucidated. Additionally, it has been reported that increased lipid levels impair the effects of adenosine/adenosine receptors in controlling vascular tone, and we speculate on the possibility that this impairment could be due to alterations in the composition of the membrane microdomains where the adenosine receptors are located. Finally, a possible role for adenosine/adenosine receptors in the phenomena of dyslipidaemia in pregnancy has been proposed.

1. Introduction

Adenosine is a nucleoside that has been implicated in a wide variety of biological functions, including the regulation of lipid (e.g., cholesterol, triglycerides and fatty acids) availability in the cell (Reiss and Cronstein, 2012) and in the systemic circulation

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(Koupenova et al., 2012a). The effects of adenosine are mediated by the action of this nucleoside on four different adenosine receptors (ARs). Interestingly, the adenosine levels in the extracellular space are also modulated by the synthesis and transport of the nucleoside into the cell (Karmouty-Quintana et al., 2013). Based in the role of adenosine in the regulation of lipid availability, this molecule, as well as specific agonists and antagonists that can increase or inhibit AR function, respectively, have been proposed as therapeutic agents for classical diseases related to disturbed lipid levels, such as diabetes and atherosclerosis, and diseases that involve the nervous system, such as Niemann-Pick type C1 and Alzheimer disease. This article reviews the evidence showing the mechanism of adenosine/AR modulation of lipid levels. We also propose a possible regulatory mechanism of ARs on the increased levels of circulating lipids. Finally, we propose a possible role for adenosine/ARs in the development of maternal dyslipidaemia during pregnancy.

2. Adenosine synthesis and signalling

Adenosine is a purine nucleoside with a wide variety of basic functions in the vascular, nervous, respiratory, endocrine and reproductive systems that are mediated by the activation of ARs localized to the extracellular surface of the cell membrane (Ralevic and Dunn, 2015). Adenosine participates in the regulation of the immune response (Di Virgilio and Vuerich, 2015), angiogenesis (Auchampach, 2007), thrombosis (Fuentes et al., 2014), lipolysis (Peng et al., 2009; Schwabe et al., 1974), plasma lipid levels (Koupenova et al., 2012b), vasodilatation; additionally, it has been shown to affect the cardiovascular system (Eisenstein et al., 2015), the placenta (Sobrevia et al., 2015) and cholesterol efflux and inflammation, the latter two of which are involved in the development of atherosclerosis (Reiss and Cronstein, 2012).

2.1. Adenosine synthesis

Extracellular and intracellular adenosine synthesis as well as the function of nucleoside membrane transporters are key biological processes that modulate the extracellular availability of adenosine as well as the function and signalling of ARs.

Extracellular adenosine synthesis begins with the phosphoester hydrolysis of its precursor molecule ADP or ATP, which is released by tissues (e.g., brain) (Bekar et al., 2008), electrically stimulated sensor cells (Yamashiro et al., 2017), extracellular vesicles, platelet vesicles (Weissmüller et al., 2008) and platelets in the blood (Kohli et al., 2016). ATP is rapidly converted to ADP and AMP via the enzyme ecto-nucleoside triphosphate diphosphohydrolase 1 (CD39) (Grenz et al., 2007; Köhler et al., 2007) and is further metabolized to form adenosine via ecto-5-nucleotidase (CD73) (Fredholm et al., 2007). CD39 and CD73 are extracellular membrane enzymes (Caldwell et al., 1997) that regulate the availability of adenosine (Fig. 1) (Robson et al., 2005). After adenosine uptake by adenosine transporters (see below), adenosine is either rapidly metabolized to inosine by the enzyme adenosine deaminase (ADA) (Colgan et al., 2006; Lloyd and Fredholm, 1995) or converted to AMP by the enzyme adenosine kinase (Fig. 1) (Eltzschig, 2009; Fredholm et al., 2007). The extracellular levels of adenosine are also influenced by extracellular ecto-adenosine deaminase (ecto-ADA, that metabolize adenosine to inosine), which is physiologically relevant because its activity regulates AR function (Karmouty-Quintana et al., 2013; Pacheco et al., 2005). Indeed, increased ecto-ADA activity is considered a marker of inflammation (Vinapamula et al., 2015) and atherosclerosis (Kutryb-Zajac et al., 2016).

The intracellular production of adenosine corresponds to the metabolism of intracellular ATP, ADP, and AMP via the action of cytoplasmic 5′-nucleotidases. Additionally, adenosine can be synthetized by hydrolysing S-adenosyl-homocysteine via the enzyme S-adenosylhomocysteine hydrolase (Samsel and Dzierzbicka, 2011). Adenosine is then released into the extracellular environment by nucleoside membrane transporters (Fig. 1).

2.2. Adenosine transport

The activation of ARs depends on the extracellular adenosine levels; thus, adenosine transport plays an essential role in the function of the receptors (Pardo et al., 2013). Pharmacological studies using adenosine transporter inhibitors have revealed the relevance of the adenosine transport in health and disease.

Extracellular adenosine is uptaken via nucleoside transporters, which have been stratified into two families: equilibrative nucleoside transporters (ENTs, SLC29), which are characterized by facilitated diffusion and sodium-independent transport of nucleosides and nucleobases; and concentrative nucleoside transporters (CNTs, SCL28), a sodium-dependent transport system (Fig. 1) (Yang and Leung, 2015).

The ENT family is formed by four members termed ENT 1 to 4. All of them transport adenosine but differ in their capacity to transport other nucleosides or nucleobases (Yang et al., 2008). ENT1 and ENT2 are ubiquitously localized broad-selectivity ENTs that have been classified based on their sensitivity to inhibition by nitrobenzylthioinosine (NBTI) as either “es” (i.e., equilibrative-sensitive, $Ki < 1$ μM, ENT1) or “ei” (i.e., equilibrative-insensitive, $Ki > 1$ μM, ENT2) (Löffler et al., 2007; Young et al., 2008). ENT3 and ENT4 have also been classified as “es”, but ENT3 is expressed in the placenta, liver, and tumour tissues (Baldwin et al., 2004; Hyde et al., 2001), and ENT4 is ubiquitously expressed and has pH-dependent activity (Baldwin et al., 2004; Barnes et al., 2006).

The CNT family is characterized by active sodium-dependent transport and contains three members termed CNT 1 to 3, all of which have been cloned. These transporters differ in their substrate selectivity: CNT1 transports pyrimidine nucleosides and adenosine (*cif*, concentrative system, insensitive to NBTI, formicin B inhibitor), CNT2 transports purine nucleosides and uridine (*cit*, concentrative system, insensitive to NBTI, a thymidine inhibitor), and CNT3 transports both pyrimidine and purine nucleosides (*cib*, concentrative system, insensitive to NBTI, a tubercidine inhibitor) (Löffler et al., 2007; Pastor-Anglada et al., 2008; Podgorska et al., 2005). CNTs are expressed in several cell types, including renal proximal tubule cells (Elwi et al., 2009), hepatocytes (Govindarajan et al., 2008), colonic cells (e.g., HT-29 cells) (Fernández-Calotti et al., 2016), human syncytiotrophoblasts (Errasti-Murugarren et al., 2011), endothelial cells (Parkinson et al., 2011) and endothelial progenitor cells (Guzmán-Gutiérrez et al., 2010).

2.3. Adenosine receptors

Extracellular adenosine serves as a signalling molecule by activating one of four Ars denoted as the A1 receptor (A1R), A2A receptor (A2AR), A2B receptor (A2BR) and A3 receptor (A3R) (Fig. 1). Ars compose the P1 purinergic receptor family and are G-protein coupled receptors (Burnstock et al., 2011; Fredholm et al., 2011). Regarding the structure of the receptors; they have a short (7–13 residues) N-terminal domain, a C-terminal domain (32–120 residues) and several transmembrane domains that have between 39 and 61% sequence identity among the different Ars (Burnstock, 2006). All four Ars co-exist in most tissues; however, different tissues usually have a dominant receptor subtype with the other subtypes playing a modulatory or a compensatory role. Thus, the different biological functions of adenosine depend of the expression pattern of Ars on individual cell types or in a specific tissue (Feoktistov et al., 2002; Liu and Hofmann, 2002; Wyatt et al., 2002).