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Adenosine and preeclampsia

Rocío Salsoso [a, b, *], Marcelo Farías [a], Jaime Gutiérrez [a, c], Fabián Pardo [a, d], Delia I. Chiarello [a], Fernando Toledo [e], Andrea Leiva [a], Alfonso Mate [b, f], Carmen M. Vázquez [b, f], Luis Sobrevia [a, b, g, *]

[a] Cellular and Molecular Physiology Laboratory (CMPL), Division of Obstetrics and Gynaecology, School of Medicine, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago 8330024, Chile
[b] Departamento de Fisiología, Facultad de Farmacia, Universidad de Sevilla, Seville E-41012, Spain
[c] Cellular Signalling and Differentiation Laboratory (CSDL), Medical Technology School, Health Sciences Faculty, Universidad San Sebastian, Santiago 7510157, Chile
[d] Metabolic Diseases Research Laboratory, Center of Research, Development and Innovation in Health - Aconcagua Valley, San Felipe Campus, School of Medicine, Faculty of Medicine, Universidad de Valparaíso, San Felipe 2172972, Chile
[e] Department of Basic Science, Faculty of Science, Universidad de Bio-Bio, Chillán 3780000, Chile
[f] Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocío/Consejo Superior de Investigaciones Científicas/Universidad de Sevilla, Seville 41013, Spain
[g] University of Queensland Centre for Clinical Research (UQCCR), Faculty of Medicine and Biomedical Sciences, University of Queensland, Herston, QLD 4029, Queensland, Australia

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ABSTRACT

Adenosine is an endogenous nucleoside with pleiotropic effects in different physiological processes including circulation, renal blood flow, immune function, or glucose homeostasis. Changes in adenosine membrane transporters, adenosine receptors, and corresponding intracellular signalling network associate with development of pathologies of pregnancy, including preeclampsia. Preeclampsia is a cause of maternal and perinatal morbidity and mortality affecting 3–5% of pregnancies. Since the proposed mechanisms of preeclampsia development include adenosine-dependent biological effects, adenosine membrane transporters and receptors, and the associated signalling mechanisms might play a role in the pathophysiology of preeclampsia. Preeclampsia associates with increased adenosine concentration in the maternal blood and placental tissue, likely due to local hypoxia and ischemia (although not directly demonstrated), microthrombosis, increased catecholamine release, and platelet activation. In addition, abnormal expression and function of equilibrative nucleoside transporters is described in foetoplacental tissues from preeclampsia; however, the role of adenosine receptors in the aetiology of this disease is not well understood. Adenosine receptors activation may be related to abnormal trophoblast invasion, angiogenesis, and ischemia/reperfusion mechanisms in the placenta from preeclampsia. These mechanisms may explain only a low fraction of the associated abnormal transformation of spiral arteries in preeclampsia, triggering cellular stress and inflammatory mediators release from the placenta to the maternal circulation. Although increased adenosine concentration in preeclampsia may be a compensatory or adaptive mechanism favouring placental angiogenesis, a poor angiogenic state is found in preeclampsia. Thus, preeclampsia-associated complications might affect the cell response to adenosine due to altered expression and activity of adenosine receptors, membrane transporters, or cell signalling mechanisms. This review summarizes the evidence available on the potential involvement of the adenosine in the clinical, pathophysiology, and therapeutic features of preeclampsia.

1. Introduction

Adenosine is an endogenous nucleoside that plays a role as intermediary metabolite and is considered an extracellular signalling molecule (Eltzschig, 2009). Adenosine signalling controls

* Corresponding authors. Cellular and Molecular Physiology Laboratory (CMPL), Division of Obstetrics and Gynaecology, School of Medicine, Faculty of Medicine, Pontificia Universidad Católica de Chile, P.O. Box 114-D, Santiago 8330024, Chile.
E-mail addresses: mdsalsoso@uc.cl (R. Salsoso), sobrevia@med.puc.cl (L. Sobrevia).

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several physiological processes in both normal and pathological conditions (Fredholm, 2014; Idzko et al., 2014) via the activation of four different G-protein-coupled adenosine receptors (ARs), i.e., A_1 (A_1AR), A_{2A} (A_{2A}AR), A_{2B} (A_{2B}AR), and A_3 (A_3AR) (Fredholm et al., 2011). This nucleoside is synthetized at the intracellular and extracellular space mostly from adenosine triphosphate (ATP) but also from other substrates (Fredholm, 2007, 2014; Silva et al., 2017). Cell response to adenosine depends on the extracellular concentration of adenosine, which is mainly regulated by the activity of two major families of membrane transporters of nucleosides (Fredholm, 2014; Li et al., 2012; Young, 2016) and its intracellular and extracellular metabolism (Eltzschig, 2009; Idzko et al., 2014; Silva et al., 2017).

Adenosine level is higher in the third trimester of pregnancy in a normal pregnancy (Yoneyama et al., 2000); however, the level of this nucleoside is increased in preeclampsia both in the maternal and foetoplacental circulation (Espinoza et al., 2011; Takeuchi et al., 2001; Yoneyama et al., 1996, 2002a). Preeclampsia is a pregnancy specific syndrome that affects 3–5% of pregnancies worldwide and is one of the main causes of maternal, foetal, and neonatal mortality (Duley, 2009; Mol et al., 2016; Saleem et al., 2014; Word Health Organization (WHO), 2013). Unveiling the pathophysiological mechanisms of preeclampsia is far from complete; however, a two-step model has been proposed (Roberts and Hubel, 2009). Poor placentation may associate with reduced placental blood flow (Chaiworapongsa et al., 2014), which is explained by altered placental angiogenesis and poor remodelling of spiral arteries thus triggering a potential state of placenta hypoxia or ischemia (Chaiworapongsa et al., 2014; Roberts and Hubel, 2009), although the hypothesis of an hypoxic or ischemic environment does not count with direct evidences so remains unproven. Preeclampsia also associates with dysregulation of endothelial function in both the maternal and foetoplacental circulation, and with angiogenesis, which is explained by an imbalanced concentration of proangiogenic and antiangiogenic factors, oxidative stress, and endoplasmic reticulum stress (ERS) (Chaiworapongsa et al., 2014; Charnock-Jones, 2016).

Signalling mechanisms involved in human placental dysfunction seen in different types of preeclampsia are still unclear; however, compelling evidence involves adenosine signalling in this process. In this review we discuss the potential pathophysiological role of adenosine in the development of preeclampsia.

2. Adenosine

2.1. Generation of adenosine

Adenosine is an endogenous purine nucleoside composed of an adenine-group attached to a ribose sugar (Eltzschig, 2009). It is mainly generated by the breakdown of adenine nucleotides. Intracellularly, adenosine is generated from the hydrolysis of AMP by 5′-nucleotidase (5′NT); however, intracellular disruption of *S*-adenosylhomocysteine (SAH) mediated by *S*-adenosylhomocysteine hydrolase (SAHase) also contributes to adenosine formation (Fredholm, 2007, 2014; Silva et al., 2017). In addition, adenosine is also generated at the extracellular space where degradation of adenine nucleotides, specifically ATP and ADP by the ectonucleotide triphosphate diphosphohydrolase 1 (also referred as CD39), followed by AMP hydrolysis to adenosine by ecto-5′-nucleotidase (also referred as CD73) (Chen et al., 2013). Therefore, adenosine level mostly depends on the production of ATP and, consequently, of AMP. When ATP consumption is increased in relation to the ATP synthesis, thus decreasing the ATP/ADP ratio, AMP increases and hence adenosine production. On the other hand, two important enzymes are involved in the reduction of adenosine bioavailability, i.e., adenosine kinase (AK) and adenosine deaminase (ADA), which use adenosine to form AMP and inosine, respectively (Eguchi et al., 2015; Silva et al., 2017).

Basal physiological concentration of adenosine at the extracellular space is reported as 30–200 nmol/L (Chen et al., 2013; Fredholm, 2014; Idzko et al., 2014). However, under pathological conditions such as hypoxia, ischemia, or inflammation, adenosine level could reach up to ~1 μmol/L as a result of increased release and generation from adenine nucleotides (Ballarin et al., 1991; Eltzschig, 2009; Chen et al., 2013; Fredholm, 2014; Idzko et al., 2014). Since these pathological conditions also result in increased extracellular ATP reaching 4–8 mmol/L, CD39 and CD73 activity could contribute to further increase extracellular adenosine generation (Chen et al., 2013). Adenosine release takes place in multiple cell types including endothelial cells, astrocytes, cardiomyocytes, neutrophils, and trophoblast cells (Fredholm, 2014). However, the main source of adenosine in plasma is ADP and ATP released from activated platelets (Eltzschig, 2013; Idzko et al., 2014). Thus, besides that determination of adenosine concentration is an important point, it is necessary to take into account that determination of this nucleoside's concentration in blood may by altered by nucleotide release from platelets during blood sampling, a phenomenon that *per se* could result in activation of platelets. Intracellular and extracellular adenosine concentration is also regulated by the activity of plasma membrane nucleoside transporters (Young, 2016). Interestingly, other mechanisms, although not fully confirmed, include the release of nucleotides through pannexin or connexin hemichannels (Faigle et al., 2008; Lazarowski, 2012). Thus, an equilibrated synthesis and degradation of adenosine, and release and uptake of this nucleoside by plasma membrane transporters seems essential to maintain its physiological concentrations in health and disease.

2.2. Adenosine transporters

Two major families of plasma membrane nucleoside transporters have been characterized in mammalian cells, i.e., the equilibrative nucleoside transporters (ENTs), which are Na^+-independent and drive nucleosides in favour of a concentration gradient, and the concentrative nucleoside transporters (CNTs), which are Na^+-dependent and drive nucleoside uptake following an extracellular-*to*-intracellular Na^+ gradient (Li et al., 2012; Young, 2016). Four members of the ENTs family of solute carriers (*SLC29A* genes) have been reported in human tissues (hENT1, hENT2, hENT3, hENT4) (San Martin and Sobrevia, 2006; Young, 2016). ENT1 is a protein of 456 amino acids with apparent K_m of 50–200 μmol/L for transport of purine and pyrimidine nucleosides. ENT2 protein (456 amino acids) transport nucleobases, such as hypoxanthine, besides purine and pyrimidine nucleosides, and exhibits apparent K_m in the same range of ENT1 (40–150 μmol/L for adenosine). ENT3 protein (475 amino acids) is functional in intracellular organelles such as lysosomes, and transport purine and pyrimidine nucleosides in a pH-dependent manner, although kinetic parameters for adenosine transport have not yet been reported (Silva et al., 2017; Sobrevia et al., 2016; Young, 2016). ENT4 protein (530 amino acids) is a member of this family of membrane transporters that behaves as a polyspecific organic cation transporter that mediates uptake of substrates such as serotonin and dopamine more efficiently than adenosine. Since ENT4-mediated adenosine uptake is favoured by an acidic extracellular pH, this membrane transporter might play a role in pathological conditions such as ischemia (Wang et al., 2012).

ENT1 and ENT2 are functionally the most relevant adenosine transporters in most cell types. Since differences between intracellular and extracellular adenosine are small under physiological