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Adenosine contribution to normal renal physiology and chronic kidney disease

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ABSTRACT

Adenosine is a nucleoside that is particularly interesting to many scientific and clinical communities as it has important physiological and pathophysiological roles in the kidney. The distribution of adenosine receptors has only recently been elucidated; therefore it is likely that more biological roles of this nucleoside will be unveiled in the near future. Since the discovery of the involvement of adenosine in renal vasoconstriction and regulation of local renin production, further evidence has shown that adenosine signaling is also involved in the tubuloglomerular feedback mechanism, sodium reabsorption and the adaptive response to acute insults, such as ischemia. However, the most interesting finding was the increased adenosine levels in chronic kidney diseases such as diabetic nephropathy and also in non-diabetic animal models of renal fibrosis. When adenosine is chronically increased its signaling via the adenosine receptors may change, switching to a state that induces renal damage and produces phenotypic changes in resident cells. This review discusses the physiological and pathophysiological roles of adenosine and pays special attention to the mechanisms associated with switching homeostatic nucleoside levels to increased adenosine production in kidneys affected by CKD.

1. Introduction

The adenosine nucleoside was identified as a bioactive molecule when Drury and Szent-György (1929) discovered its influence in several physiological tasks such as cardiovascular function. The role of adenosine in renal physiology was first studied in the 60s when it was discovered that infusion of adenosine to the renal artery increased renal vascular resistance (Hashimoto and Kumakura, 1965; Haddy and Scott, 1968). This evidence promptly lead to the notion that adenosine decreases glomerular filtration, and then its role on sodium excretion rates and influence on renin activity were characterized (Tagawa and Vander, 1970; Osswald, 1975).

Since the competitive nature of methylxanthines, including caffeine and theophylline, on the effects of adenosine in the heart (De Gubareff and Sleator, 1965) and brain (Sattin and Rall, 1970) were recognized, it was convincingly supported the idea that specific receptors for this nucleoside may exists (Cobbin et al., 1974). In the 90's adenosine receptors from human and mammals were cloned. There are four different adenosine receptors, named A_1, A_{2A}, A_{2B}, and A_3, belonging to the receptor family with seven transmembrane domains, coupled to diverse types of G proteins, which exhibit different affinities to their adenosine ligand (Fredholm et al., 2001, 2011). Since their identification, multiple studies have searched for the presence of adenosine receptors in renal cells, using diverse experimental approaches, to correlate their localization with a physiological function (see Table 1). Knockout animal models of these receptors have recently been generated, some of which have been a valuable tool for evaluating the effects of adenosine in the kidney (Sun et al., 2001; Tak et al., 2014; Yang et al., 2016). Therefore, discovering the biochemical mechanisms

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Table 1
Adenosine receptor distribution in the kidney.

Adenosine receptor subtype and localization	Specie/Cell culture	Method	References
Adenosine A_1 receptor			
Podocytes and distal convoluted tubules	Rat	Immunohistochemistry	Pawelczyk et al., 2005
Isolated kidney glomeruli and podocytes	Rat/cultured podocytes	RT-PCR	Valladares et al., 2008
Thin limbs of Henle, collecting duct system and to a lesser extent in the medullary thick ascending limb.	Mouse/rat	RT-PRC	Vitzthum et al., 2004
Microdissected afferent arteriole	Mouse	RT-PCR	Lu et al., 2015
Microdissected efferent arteriole	Mouse	RT-PCR	Al-Mashhadi et al., 2009
Juxtaglomerular cells	Primary cultures Mouse	Immunolabeling/confocal microscopy/RT-PCR	Ortiz-Capisano et al., 2013
Mesangial cells	SV40 transformed mouse mesangial cell line	RT-PCR	Zhao et al., 2002
Proximal tubule cells	Human papillomavirus 16 (HPV-16) transformed HK-2 cells	Real time RT-PCR	Tang and Zhou, 2003
Adenosine A_{2A} receptor			
Glomeruli	Mouse/Rat	RT-PCR	Vitzthum et al., 2004
Conditionally immortalized podocyte cell line	Mouse	RT-PCR/Immunocytochemistry	Awad et al., 2008
Juxtaglomerular cells	Primary cultures of isolated mouse juxtaglomerular cells.	RT-PCR	Ortiz-Capisano et al., 2013
Juxtamedullary afferent arterioles	Rat	In vitro blood-perfused juxtamedullary nephron technique combined with videomicroscopy.(Functional assay)	Feng and Navar, 2010
Microdissected efferent arterioles	Mouse	RT-PCR	Al-Mashhadi et al., 2009
Proximal tubule cells	Human papillomavirus 16 (HPV-16) transformed HK-2 cells	Real time RT-PCR	Tang and Zhou, 2003
Adenosine A_{2B} receptor			
Cortical thick ascending limb of Henle and in the distal convoluted tubule	Mouse/rat	RT-PCR	Vitzthum et al., 2004
Glomeruli and tubules	Human	Immunohistochemistry	Zhang et al., 2013
Juxtaglomerular cells	Mouse	Primary cultures of isolated mouse juxtaglomerular cells/RT-PCR	Ortiz-Capisano et al., 2013
Juxtamedullary afferent arterioles.	Rat	In vitro blood-perfused juxtamedullary nephron technique combined with videomicroscopy.	Feng and Navar, 2010
Renal inner medullary collecting duct	Immortalized cell line mIMCD-K2/murine model.	Western	Rajagopal and Pao, 2010
Isolated glomeruli and podocytes	Rat/cultured podocytes	RT-PCR/Immunohistochemistry	Valladares et al., 2008
Microdissected efferent arterioles.	Mice	RT-PCR	Al-Mashhadi et al., 2009
Mesangial cells	SV40 transformed mouse mesangial cell line from adult male Wistar-Kyoto rats	RT-PCR/Inhibition assay with MRS1754	Zhao et al., 2002 Jackson et al., 2010; Jackson et al., 2011
Fibroblast	Rat cell line NRK-49F	RT-PCR	Wilkinson et al., 2016
Initial segment of the inner medullary collecting duct	Murine cell line mIMCD-K2	Western blotting	Rajagopal and Pao, 2010
Adenosine A_3 receptor			
Microdissected isolated afferent arteriole	Mouse	RT-PCR	Lu et al., 2015
Microdissected efferent arterioles	Mouse	RT-PCR	Al-Mashhadi et al., 2009
Mesangial cells	SV40 transformed mouse mesangial cell line	RT-PCR	Zhao et al., 2002
Glomeruli and tubules	Human	Immunohistochemistry	Kretschmar et al., 2016
Proximal tubules	Human papillomavirus 16 (HPV-16) transformed HK-2 cells and rat purified proximal tubules	Western blot	Kretschmar et al., 2016

that control adenosine extracellular availability and influence its biological activity has been a daunting task. A series of ectoenzymes that metabolize precursor nucleotides to generate adenosine were also identified. Additionally, nucleoside transporter systems which control adenosine flux through the plasmatic membrane, involved in presenting the ligand to activate signaling via adenosine receptors, were also characterized (Quezada et al., 2013; Shirley et al., 2009).

In this review we will discuss the contribution of adenosine and its receptors to fundamental renal physiological functions. We will also present evidence that supports the role on adenosine in renal fibrosis progression, which is considered a common event during chronic kidney disease (CKD), independent of its origin, and which strongly correlates with progressive loss of renal function.