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Adenosine signaling in diabetes mellitus and associated cardiovascular and renal complications

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ABSTRACT

Diabetes mellitus is characterized by abnormal glucose and lipid metabolism, and subsequent hyperglycemia and dyslipidemia, which results from defects in pancreatic islet beta-cells insulin secretion and/or decreased insulin sensitivity in metabolically active organs (*i.e.* liver, skeletal muscle and adipose tissue). Accumulating evidence highlights a critical role for the adenosine system in the regulation of insulin and glucose homeostasis and the pathophysiology of type 2 diabetes (T2D). Adenosine is a key diverse extracellular signaling molecule that regulates several aspects of tissue function by activating four G-protein-coupled receptors (*i.e.* A_1, A_{2A}, A_{2B} and A_3 receptors). Moreover, adenosine receptor signaling plays a critical role in inflammation, immune system, and oxidative stress, factors that are also important in metabolic disorders. This review discusses the role of the adenosine receptor system in the development or progression of diabetes mellitus, with specific focus on T2D, and associated complications linked to the cardiovascular and renal systems.

1. Introduction

Type 2 diabetes (T2D) is characterized by dysregulation of glucose metabolism due to progressive reduction in insulin secretion from pancreatic β cells and increased insulin resistance in peripheral metabolically active organs (Stumvoll et al., 2005; Tuomi et al., 2014). This pathological situation is often associated with obesity and low-grade inflammation that leads to elevation of pro-inflammatory cytokines, free fatty acids (FFA) and glucose in the circulation, which is in turn associated with defective functioning of other organs (Osborn and Olefsky, 2012). The prevalence of T2D continues to increase and has clearly become a global health problem (Gobal et al., 2011). In 2014, more than 420 million people worldwide were diagnosed with diabetes (i.e., a prevalence of 8.5% among adults above 18 years of age), which can be compared with approximately 100 million in 1980 (i.e., prevalence of 4.7%). This rise is largely reflected by an increase in associated risk factors such as physical inactivity and obesity, but also urbanization and an aging population (Chen et al., 2012). Therefore, finding new promising and safer pharmacological approaches are imperative. The occurrence of T2D is associated with several adverse complications, e.g. increased risk of developing cardiovascular and renal disorders.

Although diabetes-associated severe complications affect many people, there are currently very limited global estimates of diabetes-related end-stage renal disease and cardiovascular events, partially explained by variations in population characteristics and methodological dissimilarities between studies (Fazeli Farsani et al., 2013). Further studies are urgently needed to better understand the underlying mechanisms and treatment options to reduce morbidity and mortality associated with the triad of metabolic, cardiovascular and renal disorders. Given the significant societal burden of T2D, apart from health style choices, strong interest has been generated to develop new pharmacological or nutritional

Abbreviations: Akt, Protein Kinase B; ARE, antioxidant response element; ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; AMPK, 5′ AMP-activated protein kinase; ADA, adenosine deaminase; cAMP, cyclic adenosine monophosphate; CRP, C-reactive protein; ELAM-1, endothelial leukocyte adhesion molecule-1; FFA, free fatty acids; Gi, G protein inhibitory; Gs, G protein stimulatory; eGFR, estimated glomerular filtration rate; IL-1β, interleukin 1-beta; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor kappa B; NO, nitric oxide; NOX, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; PKA, protein kinase A; ROS, reactive oxygen species; SREBP-1, sterol regulatory element binding protein-1; T2D, type 2 diabetes; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1; VAT, visceral adipose tissue.

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approaches to prevent its development or ameliorate complications associated with the disease.

There is a growing amount of evidence indicating that adenosine signaling pathways have critical roles in modulating the progression of T2D mainly via interfering with the function of metabolism-regulating organs (Antonioli et al., 2015). Although, there are several experimental and clinical studies showing changes in adenosine receptor expression and signaling during the development of metabolic and cardiovascular complications, the design and efficacy of targeting adenosine receptors with proper pharmacological agents is not trivial. The main reasons for this are *i)* the large discrepancies observed between pharmacological and genetic approaches in cells and animals and *ii)* the ubiquitous expression of adenosine receptors throughout the body requiring tissue specific pharmacological targeting to limit side-effects (Chen et al., 2013). In this Review, we provide background on the adenosine signaling system, outlining the role of this nucleoside in the pathophysiological mechanisms underlying T2D and associated complications focusing specifically on the cardiovascular and renal systems.

2. The adenosine system in metabolic regulation

Adenosine is ubiquitously present, an important purine molecule and an intermediate metabolite, a building block for adenine and nucleic acid biosynthesis or to ATP formation (Chen et al., 2013). Adenosine has many intracellular and extracellular signaling functions with the latter being better characterized and studied so far (Antonioli et al., 2015). Adenosine can be generated intracellularly by hydrolysis of AMP or S-adenosylhomocysteine, but is also formed in the extracellular space through degradation of adenine nucleotides (i.e. ATP, ADP and AMP). Extracellularly, adenosine signals through the activation of four distinct G-protein coupled receptor subtypes denoted A_1, A_{2A}, A_{2B} and A_3 (Fredholm et al., 2001, 2011a). According to the current scientific data, the A_1 and A_3 receptors are coupled to G_i (or G_o and G_q) proteins, which can inactivate adenylyl cyclase (AC) and lower intracellular levels of cAMP. In contrast, the A_{2A} and A_{2B} receptors are positively coupled to G_s (or G_{olf} and G_q) proteins and exert opposite effects leading to increased cAMP levels (Fredholm et al., 2001, 2011a; Trincavelli et al., 2010).

There is strong evidence that adenosine, which has many physiological roles, is also critically involved in pathological processes (Antonioli et al., 2015; Chen et al., 2013; Fredholm, 2014; Layland et al., 2014). The adenosine receptors are widely expressed in metabolism-regulating organs (pancreas, liver, muscle and adipose tissue) (Antonioli et al., 2015), in the cardiovascular system (Headrick et al., 2011; Layland et al., 2014) and in the kidney (Carlstrom et al., 2015; Vallon and Osswald, 2009). This triad of localization implies important roles in regulating metabolic, cardiovascular and renal functions and interdependencies during pathology. In addition adenosine receptors are abundant on immune cells and several studies have demonstrated important modulation of pro- and anti-inflammatory responses via purinergic signaling (Cekic and Linden, 2016; Hasko et al., 2008).

Adenosine A_1 and A_{2A} receptors are generally viewed as high affinity, whereas the A_{2B} and A_3 receptors are considered as low affinity (Fredholm, 2014). Endogenous adenosine will be more potent where the adenosine receptor subtypes are highly expressed than where they are less abundant. At high extracellular levels of adenosine, reuptake occurs via nucleoside transporters and followed by rapid phosphorylation to AMP by adenosine kinase (K_m = 100 nmol/L) or degradation to inosine by adenosine deaminase (K_m = 20–100 μmol/L) (Fredholm et al., 2001). Adenosine is known to accumulate in the extracellular space in response to metabolic stress, cell damage, hypoxia and inflammation (Antonioli et al., 2013; Cekic and Linden, 2016; Fredholm, 2014). The concentration of the nucleoside will therefore be different among tissues during physiological conditions (30–200 nmol/L), and may reach very high levels during various pathophysiological conditions (1–30 μmol/L) (Fredholm, 2014). The latter is often accompanied by enhanced expression of the A_{2A} and A_{2B} receptors (Ahmad et al., 2009; Eltzschig et al., 2003; Gilbo and Coles, 1975; Hart et al., 2011).

Increasing evidence highlights a critical role of the adenosine system in the regulation of glucose homeostasis and the pathophysiology of T2D (Andersson, 2014; Antonioli et al., 2015; Koupenova and Ravid, 2013). Although adenosine signaling is known to affect insulin secretion (Johansson et al., 2007a; Ohtani et al., 2013; Yang et al., 2012) and insulin sensitivity (Csoka et al., 2014; Figler et al., 2011; Johnston-Cox et al., 2012; Yang et al., 2015) other studies show adenosine-mediated modulation of proliferation and regeneration of beta-cells (Andersson et al., 2012). In addition, alterations of the immune cell response (Antonioli et al., 2013; Csoka et al., 2014) and oxidative stress (Peleli et al., 2015; Yang et al., 2015, 2016) have also been proposed, which may further modulate glucose homeostasis.

2.1. Regulation of insulin release

T1D is an autoimmune disease leading to pancreatic beta-cell death and impaired insulin release. Although the underlying disease mechanisms are different, T2D is also characterized by impaired insulin secretion and beta-cell failure (Cnop et al., 2005). All four adenosine receptor subtypes are expressed in rodent pancreatic tissue and beta-cell-derived cell lines (Ohtani et al., 2013), and numerous studies have indicated an important role of adenosine-mediated signaling in regulating beta-cell function (Antonioli et al., 2015).

The role of adenosine receptors in the pancreas has been studied both under normal physiological conditions and under conditions of metabolic dysfunction. Early studies suggested that adenosine, in a concentration-dependent manner (0.1–10 μM), decreased glucose-stimulated insulin secretion from rat pancreatic islets (Bertrand et al., 1989; Ismail et al., 1977), which has also been demonstrated in recent studies of mouse pancreatic islets (Ohtani et al., 2013). Pharmacological inhibition of the A_1 receptor in rats or genetic ablation of the same receptor in mice leads to enhanced glucose-stimulated insulin release via mechanisms that at least in part can be explained by increased metabolic activity of cells and increased cAMP content (Johansson et al., 2007a; Salehi et al., 2009; Zywert et al., 2011). Moreover, the A_1 receptor appears also to be involved in the regulation of alpha-cell-mediated glucagon release. *In situ* perfusion studies of the pancreas demonstrated that the amplitude of second-phase insulin pulses were greater in the absence of A_1 receptor and this was associated with 50% prolongation of the pulse cycles of glucagon (Salehi et al., 2009). Finally, a recent study using a model of aging-associated metabolic dysfunction, suggested better insulin secretion of islets from $A_1^{-/-}$ mice compared with wild-type controls (Yang et al., 2015). Although further mechanistic studies are warranted, the authors suggested that preserved beta-cell function and insulin release in the A_1 knockouts were associated with lower oxidative stress and attenuated angiotensin II-mediated contraction of islet arterioles.

Apart from the A_1 receptor, the A_{2A} receptor has also been studied under physiological conditions in the pancreas. It has been suggested that A_{2A} receptor activation is associated with enhanced insulin release (Ohtani et al., 2013). Moreover, early studies with perfused rat pancreas indicated that adenosine elevates glucagon secretion at low glucose levels through the activation of A_2 receptors (Chapal et al., 1985). In a more recent study, extracellular