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Molecular implications of adenosine in obesity

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ABSTRACT

Adenosine has broad activities in organisms due to the existence of multiple receptors, the differential adenosine concentrations necessary to activate these receptors and the presence of proteins able to synthetize, degrade or transport this nucleoside. All adenosine receptors have been reported to be involved in glucose homeostasis, inflammation, adipogenesis, insulin resistance, and thermogenesis, indicating that adenosine could participate in the process of obesity. Since adenosine seems to be associated with several effects, it is plausible that adenosine participates in the initiation and development of obesity or may function to prevent it. Thus, the purpose of this review was to explore the involvement of adenosine in adipogenesis, insulin resistance and thermogenesis, with the aim of understanding how adenosine could be used to avoid, treat or improve the metabolic state of obesity. Treatment with specific agonists and/or antagonists of adenosine receptors could reverse the obesity state, since adenosine receptors normalizes several mechanisms involved in obesity, such as lipolysis, insulin sensitivity and thermogenesis. Furthermore, obesity is a preventable state, and the specific activation of adenosine receptors could aid in the prevention of obesity. Nevertheless, for the treatment of obesity and its consequences, more studies and therapeutic strategies in addition to adenosine are necessary.

Abbreviations: ADORA2B, adenosine A_{2B} receptor gene; ATP, adenosine triphosphate; BAT, brown adipose tissue; BWA1433, 1,3-dipropyl-8-(p-acrylic) phenyl xanthine; C/EBPα, CCAAT/enhancer-binding protein alpha; C/EBPβ, CCAAT/enhancer-binding protein beta; C/EBPδ, CCAAT/enhancer-binding protein delta; cAMP, cyclic adenosine 3′,5′-monophosphate; CX3CL1, chemokine (C-X3-C motif) ligand 1; FAS, fatty acid synthase; FFA, free fatty acids; FGF21, fibroblast growth factor 21; GLUT4, glucose transporter type 4; HFD, high-fat diet; HMEC-1, human vascular endothelial cell line 1; IL-10, interleukin-10; IL-1β, interleukin-1 beta; IL-4, interleukin-4; IL-6, interleukin-6; IR, insulin receptor; IRS2, insulin receptor substrate 2; KLF4, Kruppel-like factor 4; KLFs, Kruppel like factors; LPL, lipoprotein lipase; MCP-1, monocyte chemoattractant protein-1; mRNA, messenger ribonucleic acid; Myf5−, myogenic factor 5 negative; Myf5, myogenic factor 5; Myf5+, myogenic factor 5 positive; Myh11, myosin heavy chain 11; NST, non-shivering thermogenesis; Pax7+, paired box 7 positive; PET−CT, positron emission tomography combined with computed tomography; PGC1α, peroxisome proliferator-activated receptor γ co-activator 1 α; PKA, protein kinase A; PPARγ, peroxisome proliferator-activated receptor gamma; PTP1, protein tyrosine phosphatase 1; SAT, subcutaneous adipose tissue; Sca-1+, stem cell antigen-1 positive; SNS, sympathetic nervous system; ST, shivering thermogenesis; TNFα, tumor necrosis factor-α; UCP1, uncoupling protein 1; VAT, visceral adipose tissue; *Vegfa*, vascular endothelial growth factor A gene; WAT, white adipose tissue.

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1. Introduction

The nucleoside adenosine is an endogenous purine formed by and adenine and D-ribose bound by a β-N9-glycosidic bond that is produced by the degradation of ATP, ADP and AMP. Produced in almost all mammalian cells, the extracellular adenosine concentration is highly regulated, and depend of ATP, ADP and AMP levels, CD73 and adenosine deaminase (ADA) enzymatic activity and the nucleoside uptake transport capacity of the cell (Fernández et al., 2013; Zabielska et al., 2015). The broad actions of adenosine are largely due to the existence of multiple receptors. However, the receptor expression, the adenosine concentration required for receptor activation, and the presence of proteins able to synthetize, degrade or transport this nucleoside are also important factors that regulate the actions of adenosine. Hence, it is possible to observe a dichotomous effect of adenosine in several tissues, where it can participate in a physiological and pathophysiological manner (Fredholm, 2014, 2010). The effects of adenosine are mediated by the A_1, A_{2A}, A_{2B} and A_3 receptors, which are G protein-coupled receptors that exhibit different expression patterns depending on the tissue and disease state (Koupenova and Ravid, 2013). Regardless of their expression pattern, these adenosine receptors have been demonstrated to be involved in glucose homeostasis, inflammation, adipogenesis and insulin resistance (Crist et al., 2001; Csóka et al., 2014; Eisenstein et al., 2014). Thus, it is expected that adenosine could participate in obesity.

Obesity is defined as the over-storage of lipids in adipose tissue that occurs when there is an imbalance between the energy intake and energy used (Shoelson et al., 2007). This phenomenon is associated with metabolic syndrome, which is characterized by multiple systemic complications including hypertension, dyslipidemia, diabetes mellitus and insulin resistance (Fernandez-Sanchez et al., 2011; Ouchi et al., 2011). Since adenosine seems to be associated with many different effects, it is possible that it not only participates in the obesity stage, but is also involved in the initiation of obesity, and it may have anti-obesity activities as well. However, the role of this nucleoside in obesity is not well studied. During obesity, many metabolic alterations occur that can damage several organs, such as vascular, adipose, skeletal muscle or liver tissue, resulting in the dysfunction of these tissues (Pardo et al., 2015). Thus, we aim to explore the involvement of adenosine in this phenomenon before obesity occurs (i.e., adipogenesis) to avoid it and during obesity (i.e., insulin resistance) to treat it as well as to understand its potential as therapeutic target to improve the metabolic state (i.e., thermogenesis).

2. Obesity

Adipose tissue is considered a 'master regulator' of systemic energy homeostasis that is involved in the regulation of key metabolic organs, such as the liver, pancreas, kidney or skeletal muscle (Kusminski et al., 2016), and its dysfunction is associated with the disrupted metabolic homeostasis and insulin resistance seen in obesity. Because of this, approaches to treat the dysfunctional adipose tissue are arising as novel therapeutic strategies.

There are three kinds of adipose tissue recognized in organisms: white adipose tissue (WAT), brown adipose tissue (BAT), and the recently described beige or "brown-in-white" adipose tissue (Lidell et al., 2013; Wu et al., 2012). WAT is the major site of adipose depot and its main role is the storage of energy by adipocytes in the form of lipid droplets (Moseti et al., 2016). In a healthy state, this fat is released into the blood stream as free fatty acids (FFA), which are used as an energy source by several organs (Siersbæk et al., 2010). During fasting and exercise, lipolysis occurs, leading to the release of FFA and glycerol into the blood stream. Meanwhile, in the postprandial state, adipocytes begin starts to store high levels of lipids and glucose in the form of triglycerides as an energy resource. Additionally, elevated amounts of insulin in the postprandial state increase glucose uptake and the inhibition of lipolysis, contributing to the storage of glucose as triacylglycerol (Summers et al., 1999).

Despite its participation in glucose uptake, WAT is involved in the regulation of systemic insulin-induced glucose uptake sensitization through its function as an endocrine organ, secreting adiponectin, leptin or pro-inflammatory cytokines, such as tumour necrosis factor-α (TNFα), interleukin-6 (IL-6), or IL-1β, which are inducer of insulin resistance (McArdle et al., 2013). The hyperplasia (increased adipocyte number) and hypertrophy (increased adipocyte size) of this organ have been tightly related to obesity-associated metabolic alterations (McArdle et al., 2013). In this regard, adipogenesis plays an important role, and its dysregulation is considered to be one of the key events occurring in the first steps of obesity, promoting large adipocyte formation and excess fat storage, which induce the release of pro-inflammatory cytokines and the dysregulation of adipokine secretion (Ouchi et al., 2011). Thus, a novel pharmacological intervention could allow for the prevention of the increase adipose tissue by inhibiting adipogenesis, avoiding the hypertrophy of adipose tissue in obesity. In this matter, it has been shown that adenosine, through the activation of adenosine receptors, could play an important role in the modulation of these processes in obesity, regulating lipolysis, insulin sensitivity in key metabolic organs such as adipose, liver or skeletal muscle, and even adipogenesis.

2.1. Adipogenesis

The process responsible for the increase in WAT formation is adipogenesis. This process includes several molecular events that induce changes in cell morphology and secretion molecules, generating a mature adipocyte containing lipid droplets (Moseti et al., 2016). Several studies have shown that the main nuclear factor regulators of adipogenesis are peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer binding protein α (C/EBPα) (Gross et al., 2016; Lefterova et al., 2014; Rosen and Spiegelman, 2000). Moreover, Rosen et al. (2002) have shown that PPARγ is capable of promoting adipogenesis in cultured mammalian cells lacking C/EBPα, but C/EBPα was unable to promote adipogenesis in an immortalized line of fibroblasts lacking PPARγ. Nevertheless, C/EBPα-deficient cells produce dysfunctional adipocytes with a low capacity to store lipid droplets (Wu et al., 1999), indicating that both nuclear factors are necessary for proper adipocyte function. During differentiation, the gene expression pattern in the cell continues to change, making it possible to classify *early*, *intermediate* and *late* markers, along with increased triglyceride accumulation (Gregoire et al., 1998). In response to high levels of glucose and fatty acids, the preadipocyte increases C/EBPβ and C/EBPδ expression in the *early state* (Siersbæk et al., 2014). This results in an increase in PPARγ and C/EBPα expression, leading to the *intermediate state* (Wu et al., 1999). Finally, when the preadipocyte is transformed into an adipocyte at the *late state*, it expresses specific markers, such as glucose transporter 4 (GLUT4), lipoprotein lipase (LPL) and fatty acid synthase (FAS) (Moseti et al., 2016). In the *early state*, one of the markers is the family of Kruppel-like factors (KLFs), of which isoform 4 (KLF4) has been characterized as an early marker of adipogenesis initiation (Birsoy et al., 2008) and whose expression seems to be crucial in this process (Birsoy et al., 2008). Interestingly, a recent study showed that KLF4 is essential in the adipogenesis inhibition mediated by the A_{2B} receptor activation (Eisenstein et al., 2014).

2.1.1. Role of adenosine in obesity-related adipogenesis

Adipose tissue as an energy depository, in a positive energy