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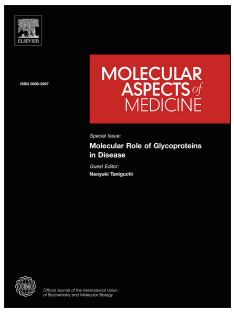

Molecular implications of adenosine in obesity

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Molecular implications of adenosine in obesity

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VITAE

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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.

Key words: adenosine; obesity; adenosine receptor; adipogenesis; insulin resistance; thermogenesis.

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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.

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 (Fernandez 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 & 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; Csoka 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 (Fernández-Sánchez 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 (Siersbaek 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 et al, 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 balance, it is able to store energy as triglycerides, while in a negative energy balance (caused by exercise or fasting), it is responsible for degrading fat into FFA to be used as energy in the peripheral organs (Frühbeck et al, 2014; Rodriguez et al, 2015). However, as part of their endocrine function, adipocytes secrete adipokines capable of increasing insulin sensitivity (i.e., adiponectin) or insulin resistance (i.e., TNFα or resistin) (Blüher et al, 2014).

Obesity presents an increase in fat mass related to hypertrophy and hyperplasia due to a high rate of adipogenesis (Hausman et al, 2001). Thus, this effect will produce an excess storage of fat and, in accordance with the function of adipose tissue as an endocrine organ, alterations in adipokines secretion, resulting in adipose tissue dysfunction (Rosen et al, 2000). These alterations included the secretion of monocyte chemoattractant protein-1 (MCP-1) and TNFα, promoting a whole-body inflammatory state that is maintained over time, which is referred to as a chronic inflammation (Guilherme et al, 2008).

It has been shown that adenosine is able to promote adipogenesis via activation of A1 receptor, but also to inhibit adipogenesis mediated by the activation of the A_{2B} receptor in the preadipocyte (Gharibi et al, 2012). It has been reported that the A_{2B} receptor is highly expressed in human primary preadipocytes in culture, and its activation reduces the transformation from preadipocytes to adipocytes (Eisenstein et al, 2014). This phenomenon seems to be mediated by KLF4, since the knock down of expression in stromal vascular cells from mouse adipose tissue inhibits this effect, indicating the existence of a novel A_{2B}

receptor-KLF4 inhibition axis. However, it has been shown that an elevated adenosine concentration is necessary to activate this receptor (Fredholm et al, 2001; Patel et al, 2003); thus, it is likely that this receptor is not active until the concentration of adenosine is a high as it is during obesity, when the increased adipogenesis has already occurred. Supporting this hypothesis, adipose tissue from obese patients exhibits an increased expression of the *ADORA2B* gene, which encodes the A_{2B} receptor (Johnston-Cox et al, 2012), that is highly correlated with KLF4 expression (Eisenstein et al, 2014). However, further investigation is necessary to evaluate if this could be a mechanism to ameliorate the increase in adipocytes during obesity or whether it is possible to revert this process.

2.2 Role of adenosine in obesity-associated insulin resistance

Substantial evidence shows that obesity is closely related with a state of insulin resistance (McArdle et al., 2013), which is considered to be a key step in the development of diabetes and metabolic syndrome (Ginsberg, 2000). Insulin resistance is characterized by low sensitivity and/or responsiveness to insulin by target organs and tissues (Hardy et al., 2012; Savage et al., 2005), resulting in alterations in glucose uptake or metabolism. It has been reported that the insulin-dependent glucose uptake in a postprandial state is mainly dependent on GLUT4-mediated transport in skeletal muscle, which accounts for approximately 60-70% of the insulin-dependent glucose uptake in the body, and adipose tissue, which accounts for approximately 10% (Wilcox, 2005). However, though glucose uptake is not insulin-dependent in liver, this organ is responsible for approximately 30% of the insulin-mediated glucose disposal in the body, which occurs through insulin-regulated metabolic processes in the liver, such as glycogenesis, the inhibition of gluconeogenesis,

and releasing of glucose (Wilcox, 2005). Thus, it is typically thought that in an insulin-resistant state, insulin actions on these tissues are altered.

Several studies have demonstrated the existence of a relationship between adenosine and insulin. The activation of the A_1 receptor has been shown to be related to insulin-dependent glucose uptake in muscle, since reduced endogenous adenosine concentrations or the blockage of the A_1 receptor decrease insulin-mediated glucose uptake (Thong et al, 2007). Meanwhile, in endothelial cells treated with an A_{2A} receptor antagonist, the increased L-arginine transport induced by insulin is blocked (Guzmán-Gutierrez et al, 2016). Nevertheless, the effect of adenosine on insulin responsiveness is not quite clear, and its actions in the vascular bed have been recently well discussed (see review by Silva et al, 2016). Human studies on the use of non-selective antagonists of adenosine receptors (e.g., aminophylline or pentoxifylline) have shown that adenosine is involved in glucose homeostasis and insulin metabolism (Arias et al., 2001; Corssmit et al., 1994, 1996). Studies in animals support this finding and link adenosine with obesity-associated insulin resistance (Table 1).

In rats with insulin resistance induced by obesity, the inhibition of adenosine receptors by the systemic administration of general antagonist (i.e., 8-phenyltheophylline and BWA1433) increased insulin sensitivity in muscle and liver (Challis et al., 1984; Crist et al., 2001, 1998), but reduced the insulin response in adipose tissue (Crist et al., 1998). Conversely, in lean mice the general activation of the adenosine receptors generates glucose intolerance (Figler et al., 2011). Thus, adenosine could be involved in alterations of insulin resistance and glucose homeostasis in obesity, generating differential effects on adipose tissue, skeletal muscle and liver likely due to the involvement of different adenosine receptors isoforms (Figure 1).

2.2.1. Adipose tissue

As discussed above, WAT is involved in the pathophysiology of insulin resistance, participating in systemic metabolic control. WAT is divided in different depositions zones, the main ones being the abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT is located in the lower parts of the body and is primarily involved in storage capacity, being considered important to the accumulation of triglycerides in periods of excess energy intake and to their release in periods of fasting, starvation or exercise (Bjørndal et al., 2011). On the other hand, VAT surrounds inner organs and is divided according to its localization in omental, mesenteric, retroperitoneal, gonadal and pericardial (Bjørndal et al., 2011). Since VAT has less insulin sensitivity than SAT, it does not respond to the anti-lipolytic insulin effect, increasing lipolysis and FFA plasma levels (Berg and Scherer 2005; Rodríguez et al. 2007). Moreover, VAT shows a higher secretion of pro-inflammatory and proatherogenic factors, such as TNFα, IL-6, C reactive protein, angiotensinogen, plasminogen activator inhibitor-1 and vascular endothelial growth factor (VEGF), among others (Berg and Scherer 2005). Thus, VAT has been shown to be tightly related to the development of insulin resistance and metabolic syndrome (Bjørndal et al., 2011; Hardy et al., 2012).

WAT plays a central role in the control of systemic insulin resistance by regulating insulin sensitivity in other insulin target tissues, including skeletal muscle and liver, the two major organs involved in the control of glucose homeostasis (Hardy et al., 2012; Wilcox, 2005). Mechanisms linking WAT and obesity-associated insulin resistance include the secretion of adipokines (i.e., adiponectin and leptin) and proinflammatory cytokines (i.e., TNFα, IL-6 or IL-1). Adiponectin is an insulin sensitizer whose secretion by VAT is

reduces in obesity, while leptin is also a sensitizer of insulin whose levels are increased in obesity but with reduced effects (Yadav et al., 2013). Meanwhile, TNFα, IL-6 or IL-1 have deleterious effects on insulin actions and are increased in obesity (Hardy et al., 2012; McArdle et al., 2013). On the other hand, insulin resistance itself and the expansion of VAT increases the release of FFA into the blood stream, and this increase generates the accumulation of triglycerides in other tissues such as skeletal muscle and liver, a phenomenon known as lipotoxicity, promoting insulin resistance and cardiovascular risk (Guilherme et al., 2008; Kahn and Flier, 2000; McArdle et al., 2013). Thus, the understanding of mechanisms regulating VAT in obesity seems to be relevant in elucidating the control of systemic insulin resistance.

It has been shown that adipocytes from WAT express the A_1, A_3, A_{2A} and A_{2B} receptors (in order of abundance) (Gnad et al., 2014). Most studies in animal models of obesity have shown that the specific activation of the A_1 receptor reduces obesity-associated systemic insulin resistance (Dhalla et al., 2007; Schoelch et al., 2004), an effect that, according to specific KO or overexpression in obese mice, is ascribed mainly to WAT (Dong et al., 2001; Johansson et al., 2007).

On the other hand, the treatment of obese rats with BWA1433, an antagonist that mainly inhibits the A_1 and A_{2B} receptors (LaNoue et al., 2000), showed that even though the systemic glucose homeostasis was improved (Xu et al., 1998), the insulin-induced glucose uptake in adipose tissue was impaired (Crist et al., 1998), an effect likely mediated by the inhibition of the A_1 receptor, which is the adenosine receptor most highly expressed in WAT, as described above. It has been reported that in lean rats, adipocytes release adenosine spontaneously and, by both autocrine and paracrine processes, increase insulin signaling through A_1 receptor activation (Takasuga et al., 1999). Along with this effect, a

higher adenosine concentration was found in adipose tissue from obese subjects (Kaartinen et al., 1991), which could be related to the increased activation of A_1 receptor signaling observed in adipose tissue from patients with obesity and in obese rats (Berkich et al., 1995; Kaartinen et al., 1991). Additionally, A_1 receptor expression is reduced in SAT from obese patients (Kaartinen et al., 1991), an effect that could be due to desensitization in response to the higher extracellular adenosine concentrations. However, although the increase in this signaling pathway in obesity is likely due to increased local adenosine concentrations, as mentioned above, an altered insulin response in adipose tissue is still present (Crist et al., 1998; Dong et al, 2001), and this local increase of adenosine could be used to avoid the worsening of insulin resistance. Thus, the primary evidence shows that the increase of adenosine in obesity seems to help to reduce the deleterious effects of insulin resistance in obesity on adipose tissue through the activation of A_1 receptor.

Adenosine also participates in the regulation of adipocyte lipolysis exerting a potent anti-lipolytic effect through its interaction with the A_1 receptor (Frühbeck et al. 2014). This activation reduced the synthesis of FFA in the adipocyte (Johansson et al, 2007). FFA is used as an important energy source during fasting, and its formation is inhibited by insulin (Dhalla et al, 2007). A_1 receptor activation blocks lipolysis via the activation of an inhibitory G protein (Gi) and the subsequent inhibition of adenylate cyclase (Clifford et al., 1998; Liang et al., 2002; Schoelch et al., 2004). Indeed, A_1 receptor antagonism or the inhibition of Gi protein-coupled adenosine receptors (such us leptin or TNFα) can lead to an increased in lipolysis (Botion et al. 2001; G Frühbeck, Gómez-Ambrosi, and Salvador 2001; Yang et al. 2009). Therefore, it is though that the increase of A_1 receptor activity in obesity, probably induced by an increased adenosine concentration, alters the hormonal control of lipolysis, promoting the reduction in lipolysis and the higher gain weight in

obese rats (Berkich et al., 1995; Schoelch et al., 2004; Vannucci et al., 1989) and thus, contributing to the lipolysis inhibition induced by insulin. Furthermore, this phenomenon could explain why transgenic mice overexpressing the A_1 receptor in adipose tissue and fed a high-fat diet (HFD) do not develop obesity-associated insulin resistance despite the presence of high body weight (Dong et al., 2001). Indeed, it has been determined that A_1 receptor expression in the adipose tissue of patients with obesity is inversely related to the ability to lose weight (Barakat et al., 2006; Johnson et al., 2001). Additionally, along with reduced lipolysis, the increased activity of the A_1 receptor also increases glucose uptake by adipocytes, leading to increased triglyceride content in adipose tissue and increasing the likelihood of obesity (Leto and Saltiel, 2012). Thus, through A_1 receptor activation, adenosine seems to play an important role in the excess weight gain seen in obesity, but its activation could improve systemic glucose homeostasis in obese patients (Figure 2). Furthermore, some researchers have proposed lipolysis inhibitors, such as A_1 receptor antagonists, as a therapeutic target (Dalla et al, 2009).

A_{2A} receptor activity has also been shown to be involved in lipolysis. According to Gnad et al (2014), the specific activation of the A_{2A} receptor increases lipolysis in adipocytes; moreover, the systemic activation of this receptor by a specific agonist in obese mice reduces WAT deposits, resulting in weight loss. Nevertheless, the predominance of lipolysis inhibition in obesity despite the increase in adenosine concentration might be due to the high expression of the A_1 receptor and the inability to reach adenosine concentration necessary to activate the A_{2A} receptor. This idea is supported by findings showing that increasing the adenosine concentration to over 1000 µmol/l in primary cultures of human white adipocytes or the overexpression of the A_{2A} receptor in white adipocytes results in an increase in lipolysis (Gnad et al., 2014).

In addition, adenosine could be involved in the secretion of adiponectin and leptin, which are key molecules in systemic insulin sensitization. It has been reported that the activation of the A_1 receptor by a specific agonist, or even by endogenous adenosine, increases plasma leptin levels in rats (Rice et al., 2000). These results were complemented by *in vitro* studies showing that rat epididymal fat tissue increases leptin secretion in response to A_1 receptor activation (Rice et al., 2000). Additionally, the activity of the A_1 receptor was shown to increase the release of adiponectin from isolated rat adipocytes in response to insulin (Szkudelski et al., 2011). Thus, alterations in A_1 receptor expression in WAT due to obesity might be involved in alterations in endocrinal function, such as leptin and adiponectin release.

Obesity causes the increased activation and enhanced recruitment of macrophages in the adipose tissue, generated by a pro-inflammatory environment that also promotes systemic insulin resistance (Chawla et al., 2011; Patsouris et al., 2008). About anti-inflammatory effect of adenosine, A_{2B} receptor activation in monocytes and macrophages is involved in the alternative activation of macrophages, which results in the secretion of anti-inflammatory cytokines (i.e., IL-10, IL-4) (Csoka et al., 2012; Koscsó et al., 2013). Furthermore, Csoka et al (2014) and collaborators found that A_{2B} receptor -/- mice exhibited an increase in activated macrophages and inflammatory markers in adipose tissue. Moreover, A_{2B} receptor-specific activation blocks the fatty acid-stimulated activation of macrophages *in vitro* (Csóka et al., 2014). Macrophage activation switches the synthesis of anti-inflammatory cytokines for pro-inflammatory cytokines such as TNFα or IL-6, which are known to promote systemic insulin resistance. Supporting this idea, Johnston-Cox et al (2012) found that the expression of A_{2B} receptor mRNA correlates positively with the mRNA expression of insulin receptor substrate 2 (IRS2), a key signaling protein in the

insulin response, in adipose tissue from obese patients, showing the probable involvement of the A_{2B} receptor in insulin sensitization. However, the obesity-induced alterations in glucose metabolism were not further impaired in A_{2B} receptor -/- mice (Csóka et al., 2014), indicating that A_{2B} receptor signaling might be involved in that mechanism, and proposing it as a potential target to improve insulin sensitivity in obesity. Even more, the restitution of the expression of A_{2B} receptor in macrophages is enough to protect from inflammation and insulin resistance in a HFD–induced obesity model in A_{2B} receptor -/- mice (Johnston-Cox et al, 2014).

2.2.2. Skeletal muscle

As mentioned above, adenosine receptor activation impairs insulin action in skeletal muscle. In contrast to adipose tissue, the probable mechanisms involved in the effects of adenosine in skeletal muscle are less clear. According to Crist et al. (2001), in the skeletal muscle of rats with HFD-induced obesity there is a reduction in insulin receptor (IR) phosphorylation in response to insulin, probably due to an increase in the phosphatase activity of protein tyrosine phosphatase 1 (PTP1). Interestingly, the general antagonism of adenosine receptors reduced PTP1 activity and increased insulin-stimulated IR phosphorylation, indicating a potential role of the adenosine receptors in the impairment of the skeletal muscle response to insulin (Crist et al., 2001). Currently, it is unclear which adenosine receptors are the primary mediators of this action. A_1 receptor -/- mice did not exhibit changes in the HFD-induced reduction of glucose uptake in skeletal muscle (Johansson et al., 2007), showing that this receptor does not seem to participate in the alterations of skeletal muscle glucose homeostasis induced by obesity. Conversely, studies have shown that the A_{2A} and A_{2B} receptors are highly expressed in the skeletal muscle of

humans, mice and rats (Crist et al., 1998; Johansson et al., 2007; Lynge and Hellsten, 2000), thus it would expect that the general antagonism of adenosine receptor effect on insulin receptor activation could be mediated by one of these receptors.

It has been reported that A_{2A} receptor -/- mice did not exhibit changes in the skeletal muscle response to insulin at basal conditions, showing that this isoform is not involved (Figler et al., 2011). In addition, the absence of the A_{2B} receptor resulted in the avoidance of the skeletal muscle insulin resistance induced by the injection of a general adenosine receptor agonist (Figler et al., 2011). Moreover, in an insulin-resistant diabetic mouse model, the specific inhibition of the A_{2B} receptor increased the glucose uptake in skeletal muscle induced by insulin (Figler et al., 2011). Thus, upon the general activation of adenosine receptors, the A_{2B} receptor could be responsible for the induction of insulin resistance in skeletal muscle in obese animals. However, whether endogenous adenosine is involved in the activation of this receptor in the skeletal muscle of obese patients is unknown.

2.2.3. Liver

Though the liver is a central organ in the control of glucose homeostasis and is therefore important in the systemic insulin resistance phenomenon (Wilcox, 2005), there are few studies regarding the potential role of adenosine receptors in obesity-induced insulin resistance in the liver. Similar to skeletal muscle, the general inhibition of adenosine receptors improves the HFD-induced impairment response to insulin in the rat' liver (Crist et al., 1998). Studies suggest that the A_{2B} receptor is potentially involved in this effect; however, the data are controversial. One study showed that obese mice exhibit an increase in A_{2B} receptor expression in the liver. Additionally, the specific activation of the A_{2B}

receptor in mice increased liver IRS2 expression and restored the obesity-associated altered glucose homeostasis (Johnston-Cox et al., 2012).

In accordance with these findings, A_{2B} receptor -/- mice showed impaired glucose homeostasis, reduced IRS2 expression and increased TNFα expression in the liver (Johnston-Cox et al., 2012). However, it has been reported that a specific antagonist of the A_{2B} receptor reduced hepatic glucose production in mice and its activation reduced glucose tolerance in the whole animal (Figler et al., 2011; Tilg et al., 2011). Additionally, the same study showed that single nucleotide polymorphisms in the *ADORA2B* gene are highly correlated with plasma levels of IL-6 and C-reactive protein in diabetic patients (Figler et al, 2011), which have been associated with the development of insulin resistance (Blüher et al., 2005; Tangvarasittichai et al., 2016). Thus, studies in animal models show that the A_{2B} receptor could be involved in the hepatic regulation of glucose homeostasis; however, its role in patients with obesity is still unknown.

The A_3 receptor also has a potential role in the liver involvement in glucose homeostasis. It has been reported that inosine, an endogenous nucleotide derived from the deamination of adenosine (Barankiewicz & Cohen, 1985), through A_3 receptor activation, can stimulate gluconeogenesis, glycogenolysis and the release of glucose in isolated rat hepatocytes (Guinzberg et al., 2006). Furthermore, the same group showed that the activation of this receptor by both, adenosine and inosine, is the responsible for the hepatic-induced hyperglycemia in response to ischemia-reperfusion stress in rats (Cortes et al., 2009). Thus, due to the increase in adenosine concentrations in obesity, A_3 receptor activation could be involved in obesity-associated alterations in glucose homeostasis; however, whether this adenosine receptor is involved in obesity is still unknown.

2.3 Association of adenosine with thermogenesis during obesity

The imbalance between energy intake and energy expenditure observed in obesity gave rise the hypothesis that excess calories could be converted into heat through adaptive thermogenesis, a therapeutic approach to obesity. Thermogenesis involves the loss of energy as heat (energy expenditure) by coordinated mechanisms, such as shivering and non-shivering in response to low environmental temperature or diet, in order to maintain the core temperature (Daanen and Van Marken Lichtenbelt, 2016; Celi et al., 2015). Shivering thermogenesis (ST) refers to the increased heat production caused by rhythmic skeletal muscle contractions while non-shivering thermogenesis (NST) involves heat production by chemical reactions in the mitochondria of brown adipocytes, through the activation of uncoupling protein-1 (UCP1) activation, stimulated by the sympathetic nervous system (SNS) or by non-adrenergic pathways, such as natriuretic peptides, FGF21, bile acids or irisin, among others, which induce heat production through uncoupling respiration from ATP synthesis (Blondin et al., 2015; Villarroya and Vidal-Puig, 2013).

2.3.1 Thermogenesis in adipose tissue

In newborns, BAT is located in the cervical, interscapular, axillary, perirenal and paraaortic areas (Park et al, 2016). In adults, the detection of the glucose uptake, detected by positron emission tomography combined with computed tomography (PET–CT), has demonstrated the presence of active BAT depots located in the supraclavicular, neck, paravertebral and perirenal regions (Peng et al, 2015; Izzi-Engbeaya et al, 2014). These BAT depots in adults are composed of two types of cells, classical (brown) and brown adipocyte-like (beige) cells. Beige adipocytes are brown-like white adipocytes with a characteristic genetic expression pattern that during exercise, cold exposure or stimulation

with several molecules (i.e., irisin, FGF21, follistatin) induced an increase in UCP1 protein levels, and show thermogenic properties, in a process termed “fat browning” (Thuzar and Ho, 2016; Rodriguez et al, 2015). Beige depots are located mainly in the inguinal and epididymal WAT (Dempersmier and Sul, 2015; Park et al., 2014).

It is noteworthy that the different varieties of adipose tissue come from different precursors. Classical brown adipocytes originate from the myogenic lineage of Myf5-positive, stem cell antigen-1-positive and paired box 7-positives cells (Myf5+/Sca-1+/Pax7+) of the dermomyotome, a common progenitor of skeletal muscle and dermis, while all white adipocytes originate from a Myf5-negative (Myf5-) precursor (Dempersmier et al, 2015). Meanwhile, beige adipocytes come from a heterogeneous population of cells (Mulya and Kirwan, 2016). Depending on different metabolic factors, beige adipocytes can be derived from Myf5- lineage precursor cells and from Myf5+ cells or smooth muscle-like precursors positive for myosin heavy chain 11 (Myh11) (Long et al., 2014; Sanchez-Gurmaches and Guertin, 2014). However, it has been reported that adrenergic stimulation increases the amount of beige adipocyte cells in WAT from adult humans and rats (Frontini et al, 2013; Himms-Hagen et al, 2000). Since these cells do not present pre-existing proliferation precursors (Frontini et al, 2013) and have reduced proliferative indexes (Himms-Hagen et al, 2000), these findings support the idea that the increase of beige adipocytes is mainly due to white into brown transdifferentiation, phenomenon known as ‘browning’ (Cinti S, 2016).

BAT is characterized as a highly vascularized tissue, innervated by the SNS and is highly oxidative due to the presence of multilocular fat cells with abundant mitochondria aimed to produce heat (adaptative thermogenesis) through the utilization of glucose and lipids (Lizcano and Vargas, 2016). The activation of both brown and beige fat involves

input from the SNS through β-adrenergic receptors, which trigger PPARγ coactivator 1α (PGC1α) and a cascade of intracellular changes via cyclic AMP (cAMP). This results in the increased lipolysis of intracellular triglycerides, raising FFA levels that are used by uncoupling protein 1 (UCP1) located in the inner mitochondrial membrane, acting as a H^+/fatty acid symporter (Peng et al., 2015; Park et al., 2014). Through this, mechanism the uncoupling of mitochondrial respiration is initiated, separating oxidative phosphorylation from ATP synthesis and resulting in a futile cycle that generates heat instead of ATP (non-shivering thermogenesis). To compensate for the lack of ATP adrenergic stimulation enhances BAT glucose uptake and glycolysis (Albert et al., 2016; Labbé et al., 2016). Thus, the ability of beige adipocytes to increase energy expenditure in order to produce heat by the stimulation of the SNS or the administration of β-adrenergic receptor agonists, such as chronic cold exposure, exercise or diet, is a promising target to evaluate in obesity.

2.3.2 Role of adenosine in thermogenesis during obesity

It has been reported that thermogenic tissue is inversely related to body mass index and body fat percentage (Granneman, 2015; Peng et al., 2015; Vosselman et al., 2015). Nevertheless, there are multiple environmental and metabolic factors involved in BAT activation and the browning of WAT. Browning implies morphologic and molecular changes, such as the size reduction, mitochondriogenesis and multilocularization of lipid droplets (Giordano et al., 2016; van der Lans et al., 2013). Thus, triggering this thermogenic profile in WAT could be an excellent approach to reducing the obesity-associated deleterious effects. It is thought that adenosine, through the A_{2A} receptor, increases lipolysis and NST in brown and white human adipocytes; moreover, it has been reported that the concentration of adenosine required to achieve the half-maximal activation

of lipolysis in primary human brown and white adipocytes is 3 nmol/l and 1170 nmol/l, respectively (Gnad et al, 2014). Nevertheless, it has been also observed that adenosine inhibits lipolysis in WAT through A_1 receptor activation (Johansson et al, 2008). On the one hand, this opposite effect could be explained by the differential expression of the adenosine receptors in the adipocytes, since the A_1 receptor is highly expressed in white adipocytes while the expression of the A_{2A} receptor is significantly higher in BAT than in WAT (Gnad et al, 2014). On the other hand, this phenomenon could be explained by different local concentrations of adenosine in each tissue.

The hypertrophy, hyperplasia, and inflammation of WAT in obesity are factors involved in the reduction of thermogenic adipose tissue (Shimizu et al, 2014; Polyak et al, 2016). In this context, there is a report showing that HFD-induced BAT inflammation in mice is accompanied by the increased expression of lipogenic enzymes, which results in the 'whitening' of BAT (i.e., BAT to WAT). This process is characterized by an increased expression of lipogenic enzymes and morphologicals alterations such as the coalescence of lipid droplets and elevated mitochondrial ROS production (Polyák et al, 2016; Shimizu et al, 2014). As mentioned before, obesity is associated with a chronic inflammatory state. It has been reported that one of the pro-inflammatory cytokines increased during obesity is the chemokine fractalkine (CX3CL1), which is a chemoattractant synthesized by adipocytes and mediates macrophage adhesion to WAT and BAT during the development of obesity through the activation of its specific receptor, CX3CR1, which is highly expressed on monocytes and T cells in humans (Polyák et al., 2016, 2014; Jung et al., 2000). This whitening of BAT during obesity could increase the lipogenic profile. Interestingly, it has been observed that in neuronal and microglial cells, fractalkine is capable of releasing adenosine as a neuroprotective response (Lauro, 2015) only in the

presence of a functional A_1 receptor (Lauro et al., 2010, 2008). Thus, it is possible that, as occurs in neuronal and microglial cells, the increased fractalkine-CX3CR1 binding during obesity could be associated with the increased extracellular adenosine concentrations and A_1 receptor activation also seen in obesity.

Due to the high vascularization of BAT, the endothelial dysfunction observed in obesity could enhance this whitening of BAT (Elias et al, 2012). In fact, it has been reported that the deletion of the *Vegfa* gene in the adipose tissue of non-obese mice resulted in BAT whitening (Shimizu et al, 2014); therefore, the improvement of vascular function in BAT could help restore thermogenic function during obesity. Adenosine is known to play an important role in vascular function; for example, it has been reported that the treatment of a melanoma mouse model with an A_{2B} receptor agonist enhanced *Vegfa* expression and vessel density in tumors (Sorrentino et al, 2015). Moreover, another study showed that the A_{2B} receptor increased the production of VEGF-A via cAMP-PKA-CREB in human vascular endothelial cell line 1 (HMEC-1) (Du et al., 2015). Thus, adenosine may be playing a role in the modulation of BAT during obesity. However, more studies are necessary.

In contrast to BAT, which constitutively expresses high levels of thermogenic genes such as UCP1, beige adipocytes require constant stimulation for the induction of thermogenic genes (Wu et al., 2013; Petrovic et al., 2010). In fact, a recent study demonstrated the reversible thermogenic profile of beige adipocytes (Park, et al 2014). Thus, the plasticity of adipose tissue to change its metabolic profile and increase energy expenditure in a stimulus-dependent manner is currently one of the main approaches to reverse the obesity and is the focus of numerous studies (Contreras et al., 2016; Ramseyer and Granneman, 2016; Liu et al., 2015.; Lo and Sun, 2013).

Finally, recent studies in animals have indicated the involvement of the A_{2A} receptor in the browning of WAT. It has been reported that cold- or β-adrenergic agonist-induced activation of sympathetic signaling, which is associated with browning, is attenuated by the ablation of the A_{2A} receptor (Dempersmier and Sul, 2015). Moreover, the direct injection of lentiviral vectors expressing the A_{2A} receptor into WAT depots induced the formation of beige adipocytes in an HFD-induced obese mouse model (Gnad et al, 2014), and its specific activation in BAT and WAT increased the expression of thermogenic markers, including a 7-fold increase of UCP1 in WAT, reflecting the browning of WAT (Gnad et al, 2014). Additionally, there is a report showing that A_{2B} receptor activation increases the levels of C/EBPβ, IRF4, and PPARγ in adipose tissue (Csóka et al 2014), which are nuclear factors associated with the formation of BAT in transgenic mice overexpressing PPARγ in adipose tissue (Zhou et al, 2014). Thus, it seems that adenosine could be involved in the activation of adaptative thermogenesis in BAT and in the induction of beige adipocyte formation, indicating that the adenosine or adenosine receptor-mediated browning of WAT is a potential probable novel target in the treatment of obesity.

3. Adenosine as a therapeutic target

Because of all the effects attributed to adenosine, the therapeutic response could vary according to obesity state, tissue and adenosine receptor involvement. As described above, the effect of adenosine depends on the type and number of receptors expressed, modulating the potency of the effect and on the expression of enzymes that synthesize, degrade or transport adenosine, which results in specific microdomain adenosine concentrations that activate the receptors in both autocrine and paracrine manners (Fredholm et al, 2014).

Few studies on obesity have determined the concentration of adenosine in plasma or adipose tissue (Table 2). Neither a proposal for the metabolic consequences of an elevated adenosine concentration in obese patients is at present proposed. When the concentration of adenosine during obesity has been determined by different methodologies and in various organs, an approximate 1.5-fold increase compare to the normal state has been observed, which seems to show that the adenosine concentration rises systemically during obesity. Though the adenosine concentration observed in normal plasma could activate the A_1, A_{2A} and A_3 receptors, this concentration is not able to activate A_{2B} (Table 3) (Fredholm, 2014; Funaya et al, 1997). Nevertheless, Patel et al (2003) described the activation of the A_{2B} receptor with a 2 μmol/l concentration of adenosine mediated by pH variations. Even though the adenosine concentration may increase by 5-fold in pathological conditions (Fredholm, 2014), specific alterations in the synthesis, degradation or transport of adenosine in the tissue could increase or reduce the local adenosine concentration and activate the adenosine receptors specifically expressed in that tissue.

In summary (Figure 3), first, the activation of the A_{2B} receptor could be necessary to avoid obesity, since its activation results in the inhibition of adipogenesis and improves insulin resistance. Second, treatment with the adenosine receptor antagonist BWA1433 improved glucose tolerance, increasing glucose uptake in muscle and liver and reducing it in adipose tissue, but also inhibited on adiponectin secretion, promoting insulin resistance (Crist et al, 1998; Xu et al, 1998). These results highlight the differential adenosine receptor pattern among tissues, however, whether this effect is produced by the inactivation of the A_1 or A_{2B} receptors is still unclear. In WAT, the expression of the A_{2A} receptor is lower than that of the A_1 receptor, and it is therefore expected that the main adenosine effects would be the improvement of insulin response in WAT and the inhibition of lipolysis,

promoting weight gain. Third, the activation of the A_{2A} receptor is involved in the browning process, resulting in increased lipolysis and leading to a reduction in adipocyte size but also to the release of FFA into the blood, which could cause other side effects. Nevertheless, the treatment with a specific tissue-directed A_{2A} receptor agonist could be a pharmacological approach to reverse the obesity-associated adipose tissue increases and comorbidities, along with increased exercise and diet regulations to reduce the levels of FFA in blood.

4. Concluding remarks

The pharmacological modulation of the adenosine receptors could be beneficial in the obesity treatment. Since adenosine is involved in the adipogenesis, insulin sensitivity and thermogenesis activation, an adequate strategy could allow to reduce obesity prevalence. Adenosine treatment as a unique therapy will be difficult to implement due to the diverse systemic effects of this nucleoside. Thus, it is necessary to dissect the tissue-specific effects to prevent any secondary consequences. In conclusion, in order to revert obesity and its comorbidities, the modulation of adenosine receptors seems to be an attractive approach.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

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Table 1. Tissue specific adenosine receptor effects involves on obesity

Receptors	Activation	Inactivation	Effect	Tissue	Reference
A_1	NA		Lipolysis inhibition	Adipocytes primary culture from male mouse	Johansson et al, 2007
A_1	Partial agonist ARA		Reduces insulin resistance	Whole-body of male obese ZF rats	Schoelch et al., 2004
A_1	Agonist CPA		Increases leptin secretion	Adipocytes from epididymal fat tissue of male Sprague Dawley rats	Rice et al., 2000
A_1		Non-selective Antagonist BWA1433	Reduces glucose uptake	Adipose tissue of ZF rats	Crist et al., 1998
A_1		Antagonist DPCPX	Inhibition of adiponectin secretion	Epididymal fat tissue from male Wistar rats	Szkudelski et al., 2011
A_{2A}	Agonist PSB-0777		Increase lipolysis	Inguinal WAT and gonadal fat depots from mouse	Gnad et al., 2014
A_{2B}	Agonist BAY 60-6583		Restores IRS-2 levels	Liver of WT mice after 16 weeks HFD	Johnston-Cox et al., 2012
A_{2B}	Agonist BAY 60-6583		Inhibits Adipogenesis	Stromal Vascular Cell from mouse inguinal adipose tissue	Eisenstein et al, 2014
A_{2B}		Non-selective Antagonist BWA1433	Increase glucose uptake	Gastrocnemius and soleus muscles from ZF rats	Crist et al., 1998
A_{2B}		A_{2B} KO mice	Enhance adipose tissue inflammation	Epididymal adipose tissue	Csóka et al., 2014
A_{2B}		Antagonist ATL-801	Increases glucose uptake	Skeletal muscle and brown adipose tissue from diabetic mice	Figler et al., 2011
A_{2B}		A_{2B} KO mice	Elevate TNF-α, IL-6 and CD11b levels	Liver from KO mice with HFD	Johnston-Cox et al., 2012
A_3	Agonist IB-MECA		Stimulate glucose release	Isolated hepatocytes from Male Wistar rats	Guinzberg et al., 2006

Legend for Table 1 in the next page.

Legend for Table 1

NA:l-noradrenaline hydrochloride; ARA: [1S,2R,3R,5R]-3-methoxymethyl-5-[6-(1-[5-trifluoromethyl-pyridin-2-yl]pyrrolidin-3-[S]-ylamino)-purin-9-yl]cyclopentane-1,2-diol; CPA: N6-cyclopentyladenosine; BWA1433: 1,3-dipropyl-8-(p-acrylic) phenyl xanthine; DPCPX: 8-cyclopentyl-1,3-dipropylxanthine; PSB-0777: 4-[2-[(6-Amino-9-b-D-ribofuranosyl-9H-purin-2-yl)thio]ethyl]benzenesulfonic acid ammonium salt; BAY 60-6583: 2-[[6-Amino-3,5-dicyano-4-[4-(cyclopropylmethoxy)phenyl]-2-pyridinyl]thio]-acetamide; IB-MECA:1-Deoxy-1-[6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-N-methyl-β-D-ribofuranuronamide; KO: knockout; ATL-801:N-[5-(l-cyclopropyl-2,6-dioxo-3-propyl-7H-purin-8-l)pyridin-2-yl]-N-ethylpyridine-3-carboxamide; IRS-2:insulin receptor substrate 2; TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6; CD11b: cluster of differentiation molecule 11B; ZF: Zucker fatty; WAT: white adipose tissue; WT: wild type; HFD: high-fat diet.

Table 2. Adenosine concentration in obese human patients.

Sample	Adenosine concentration		Significance	Fold changes (obese/control)	Methods of measurement	References
	Control	Obese				
Adipose tissue (pmol/g wet weight)	0.42 ± 0.06	0.67 ± 0.14	P = 0.06	~1.59	Radioimmunoassay	Kaartinen et al, 1991
Plasma (μmol/l/mg protein)	1.2 ± 0.1	1.8 ± 0.2	P < 0.05	~1.5	High performance liquid chromatograph system	Escudero et al, 2012
Plasma (μmol/l)	0.062 ± 0.003				Radioimmunoassay	Funaya et al, 1997

Table 3. Half-concentration activation of human adenosine receptor

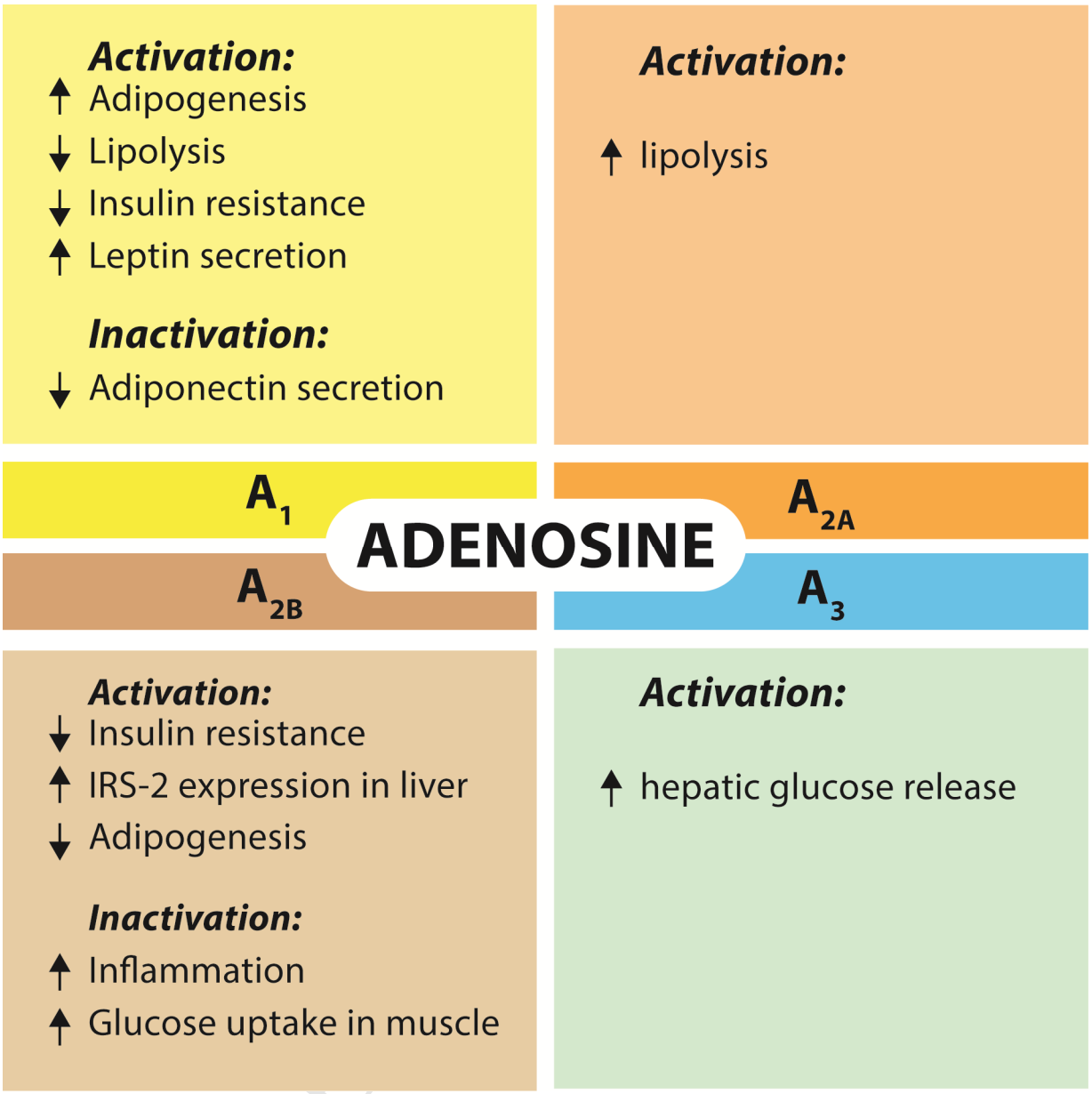
Receptor	EC50 or Ki (μmol/l)	Model	Method	Reference
A_1	0.31	CHO cells transfected with recombinant human A_1 receptor	cAMP determination	Fredholm et al., 2001
A_{2A}	0.73	CHO cells transfected with recombinant human A_{2A} receptor	cAMP determination	Fredholm et al., 2001
A_{2B}	2	HEK-293 transfected with recombinant human A_{2B} receptor	Microphysiometry (pH variations)	Patel et al., 2003
	23.5	CHO cells transfected with recombinant human A_{2B} receptor	cAMP determination	Fredholm et al., 2001
	15	VA13 cells	cAMP determination	Bruns 1980
A_3	0.29	CHO cells transfected with recombinant A_3 receptor	cAMP determination	Fredholm et al., 2001

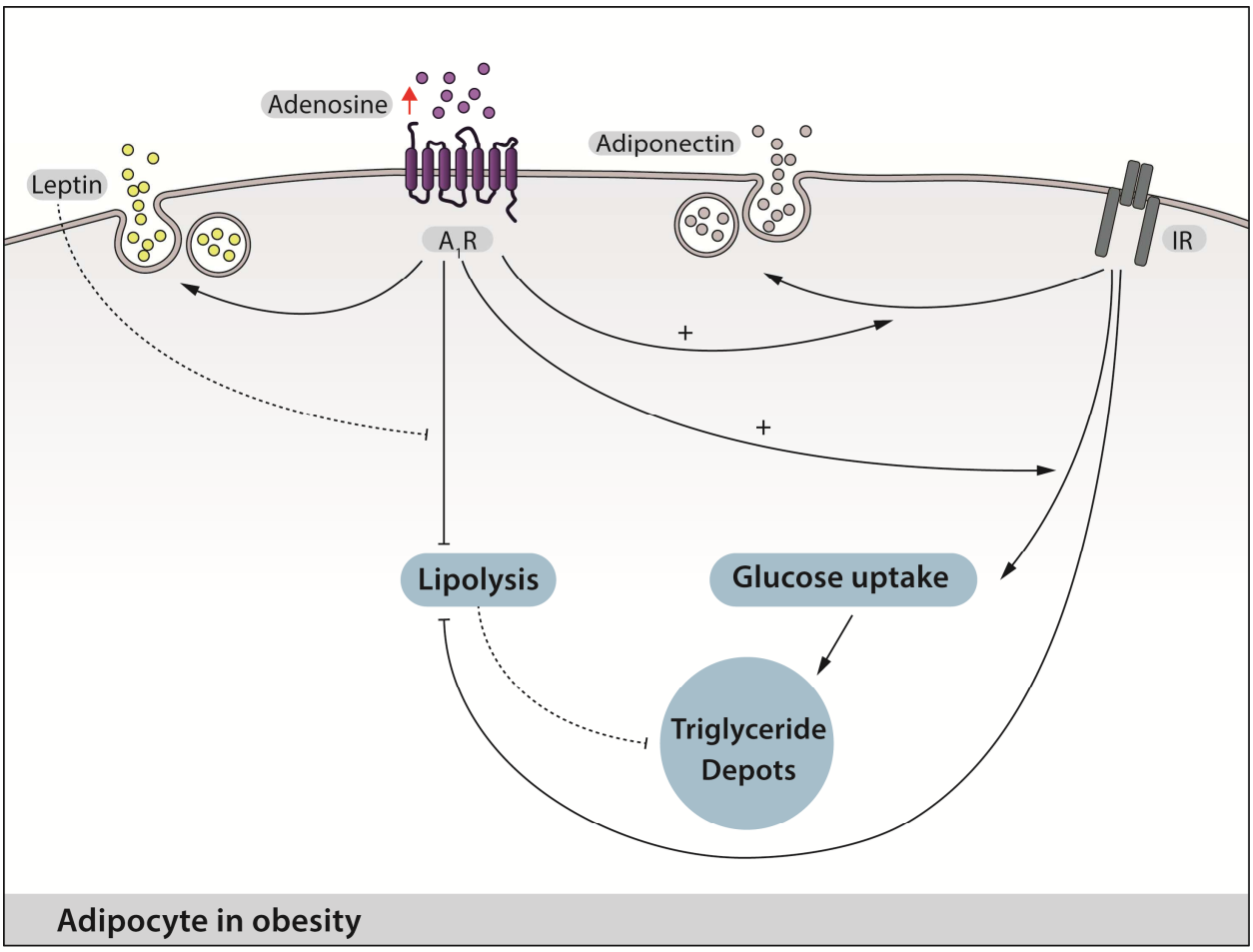
Fig 1. Adenosine effects mediated by its receptor on obesity. Adenosine could act mediated A_1, A_{2A}, A_{2B} and A_3 receptors at different levels, with a variety of effects. The activation of A_1 receptor will increase adipogenesis, reduce lipolysis and insulin resistance and increase leptin secretion, but the inactivation will reduce adiponectin secretion. The activation of A_{2A} receptor will increase lipolysis. A_{2B} receptor activation will reduce insulin resistance, increase IRS-1 expression in liver, ad will reduce adipogenesis on preadipocytes, meanwhile, the inactivation of this receptor will increase inflammation and glucose uptake in muscle. Finally, A_3 receptor activation increases hepatic glucose release.

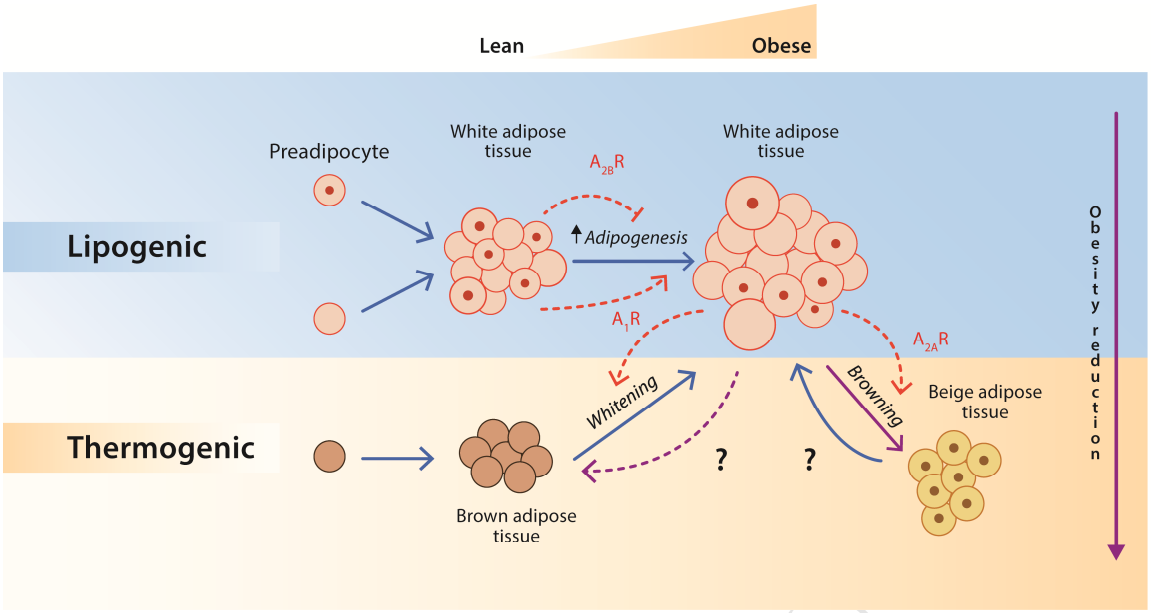
Fig 2. Involvement of A_1 receptor in the adipocyte during obesity. A_1 receptor (A_1R) act as insulin sensitizer, increasing the effect of glucose uptake and adiponectin release mediated by insulin receptor (IR). On the other hand, A_1R is able to increase leptin release and inhibit lipolysis. Insulin also decrease lipolysis in the adipocyte. Leptin has lipolytic effect mediated adenylate cyclase/Gi protein, inhibiting antilipolysis adenosine effect. Lipolysis inhibition and increased glucose uptake will increase triglyceride depots.

Fig 3. Adenosine receptor association in obesity during adipogenesis and thermogenesis. Different preadipocytes origins will produce lipogenic and thermogenic tissue, as withe and brow adipose tissue, respectively, present at normal state (lean). During obesity, preadipocite will increase adipogenesis, producing a hypertrophy and hyperplasia of the white adipose tissue. Also, obesity is able to produce inflammation of the brown adipose tissue, producing the

'whitening'. It is described, that some adipocytes are able to transdifferentiate to beige adipose tissue (browning). Mediated the increase of thermogenic adipose tissue (purple arrow) is possible to reduce obesity. Adenosine receptor (red arrows) can participate activating (A1 receptor) or inhibiting (A_{2B} receptor) adipogenesis, increasing whitening (A_1 receptor) or rising browning (A_{2A} receptor). Nevertheless, the production of original brow adipose tissue from white adipose tissue and the transformation of the beige adipose tissue to white adipose tissue are unknown.


Activation:
Adipogenesis
Lipolysis
Insulin resistance
Leptin secretion
Inactivation:
Adiponectin secretion
A1
Activation:
lipolysis
A2A
ADENOSINE
A2B
A3
Activation:
Insulin resistance
IRS-2 expression in liver
Adipogenesis
Inactivation:
Inflammation
Glucose uptake in muscle
Activation:
hepatic glucose release


Adenosine
Leptin
Adiponectin
A1R
IR
+
+
Lipolysis
Glucose uptake
Triglyceride
Depots
Adipocyte in obesity



Obesity reduction