Obesity is a growing worldwide health problem, with an alarming increasing prevalence in developed countries, caused by the dysregulation of energy balance. Currently, no wholly successful pharmacological treatments are available for obesity and related adverse consequences. In recent years, hints obtained from several experimental animal models support the notion that purinergic signalling, acting through ATP-gated ion channels (P2X), G protein-coupled receptors (P2Y) and adenosine receptors (P1), is involved in obesity, both at peripheral and central levels. This review has drawn together, for the first time, the evidence for a promising, much needed novel therapeutic purinergic signalling approach for the treatment of obesity with a 'proof of concept' that hopefully could lead to further investigations and clinical trials for the management of obesity.

Abstract

Obesity is a growing worldwide health problem, with an alarming increasing prevalence in developed countries, caused by the dysregulation of energy balance. Currently, no wholly successful pharmacological treatments are available for obesity and related adverse consequences. In recent years, hints obtained from several experimental animal models support the notion that purinergic signalling, acting through ATP-gated ion channels (P2X), G protein-coupled receptors (P2Y) and adenosine receptors (P1), is involved in obesity, both at peripheral and central levels. This review has drawn together, for the first time, the evidence for a promising, much needed novel therapeutic purinergic signalling approach for the treatment of obesity with a 'proof of concept' that hopefully could lead to further investigations and clinical trials for the management of obesity.

Keywords

Obesity - Brown and white adipocytes - Hypothalamus - ATP - Adenosine - Purinergic receptors

Introduction

Obesity, defined as abnormal or excessive fat accumulation, represents a major health issue, with an alarmingly increasing prevalence in developed countries, caused by the dysregulation of energy balance. The World Health Organization in 2016 reported that more than 1.9 billion adults aged 18 years and older were overweight [body mass index (BMI) > 25 kg/m²], and of these, over 650 million adults were obese (BMI > 30 kg/m²) [http://www.who.int/mediacentre/factsheets/fs311/en/]. The imbalance of energy underlying obesity is due to several factors, including genetic predisposition, individual metabolism, excessive caloric and food intake and insufficient physical activity, leading to an increase in adipose tissue. In recent years, the crucial role of adipose tissue in the regulation of energy metabolism has been recognised, which not only dynamically accumulates and releases lipids but also acts as an endocrine organ [1]. Indeed, adipose tissue produces a variety of humoral factors known as adipocytokines (i.e. leptin, adiponectin, resistin and visfatin) that contribute to the regulation of appetite and satiety, fat distribution, insulin secretion and sensitivity, energy expenditure, endothelial function, inflammation and blood pressure [2, 3].

In mammals, adipose tissue can be divided into brown and white adipose tissues [2]. White adipose tissue represents the vast majority of adipose tissue in the organism and is the site of energy storage, whereas brown adipose tissue burns energy for thermogenesis [2]. Adipocytes are the main components of adipose tissue, and adipogenesis has two distinct phases: early differentiation of the adipocytes from a multipotent stem cell and terminal differentiation of preadipocytes into mature adipocytes [4]. Epidemiologic studies have suggested that the number of adipocytes in an adult are approximately constant whether they are lean or obese [5]. Moreover, significant weight gain or loss in adults is not accompanied by respective increases or decreases in the number of adipocytes, rather adipocyte size is correlated with adult adiposity. These observations support the notion that the number of adipocytes a person will have is determined during childhood and adolescence. Indeed, in line with this evidence, environmental exposure in early life can influence adipocyte...
number and has the potential to greatly increase the total body fat mass and may contribute to the development of obesity in adults [5].

Regulation of energy homeostasis is highly controlled by the central nervous system (CNS). Indeed, it receives and integrates signals conveying energy status from the periphery, such as leptin and insulin, leading to modulation of food intake [6]. The autonomic nervous system (ANS) plays an important role in the response to such signals, innervating peripheral metabolic tissues, including brown and white adipose tissues [7]. The ANS consists of two parts: the sympathetic and parasympathetic nervous systems. Since the ANS is involved in the regulation of the cardiovascular system, hormonal secretion and energy balance, it is plausible that altered regulation of either the parasympathetic or sympathetic branches, or both, may contribute to the development of obesity and related metabolic comorbidities [8]. Depression of sympathetic and parasympathetic activity has been associated with increasing body fat, but whether this is causal or consequential was not resolved. Moreover, sympathetic denervation has been reported to lead to an increase in white adipocyte cell number and fat pad mass [9].

Currently, therapeutic strategies against obesity have been largely ineffective, such as 5-hydroxytryptamine modulators, β3 adrenocceptor agonists, lipase inhibitors, melanocortin 4 inhibitors, leptin agonists and ghrelin antagonists [10]. The development of novel anti-obesity drugs based on our current understanding of energy homeostasis is required. The present review explores the possible involvement of purinergic signalling in obesity.

Purinergic signalling [i.e. adenosine 5′-triphosphate (ATP) acting as an extracellular signalling molecule] was proposed in 1972 (see [11]). After early resistance to the concept, when receptors for ATP and adenosine were cloned and characterised in the early 1990s, it was generally accepted and there has been an explosion of interest in the physiology and pathophysiology of purinergic signalling (see [12]). Selective agonists and antagonists to both adenosine (P1) receptor subtypes (A1, A2A, A2B, A3) and P2X ion channel receptor subtypes for ATP (P2X1–7) and P2Y G protein-coupled receptor subtypes to ATP, adenosine 5′-diphosphate (ADP), uridine 5′-triphosphate (UTP) and uridine 5′-diphosphate (UDP) (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11–14) have been developed and clinical trials initiated that have led to the use of purinergic agents for the treatment of several diseases, including clopidogrel, a P2Y12 receptor antagonist for the treatment of stroke and thrombosis, a P2Y2 long-term agonist for the treatment of dry eye and adenosine A1 agonists for the treatment of tachycardia. Clinical trials are currently in progress to explore purinergic agents for the treatment of osteoporosis, chronic cough, visceral pain, bladder incontinence, cancer and neurodegenerative diseases (see [13]).

**Purinergic control of brown adipocytes**

Brown adipocytes, located in specific areas of the body, express constitutively high levels of thermogenic genes making them specialised in energy expenditure and therefore a potential target for anti-obesity therapies [14]. There are also beige cells, which are inducible ‘brown-like’ adipocytes that develop in white fat in response to various activators. The activities of brown and beige fat cells reduced obesity in mice, an effect similar to that seen in lean humans [14], in addition to causing antidiabetic effects [15]. Lipid synthesis by brown adipocytes in rats was increased by sympathetic nerve stimulation, and it was recognised that this was not solely attributable to the action of noradrenaline but included some non-adrenergic mechanisms [16]. The thermogenic function and growth of brown tissue is also controlled by the sympathetic nervous system in rats, but antidromic activity by sensory nerves may also be involved [17]. High-fat diet (HFD) in rats has been associated with a reduction in sympathetic activity to brown adipose tissue [18].

ATP, released as a cotransmitter from sympathetic nerves, was reported to elicit substantial increases in total membrane capacitance of rat brown fat cells, probably via P2Y receptors [19]. ATP mobilises Ca2+ from intracellular stores, supporting the view that P2Y receptors were involved [20]. ATP was also shown by these authors to exert a potent inhibitory effect on the influx of Ca2+ in cultured adult brown adipocytes [20]. Evidence was presented to suggest that modulation of voltage-gated potassium currents in rat brown adipocytes by ATP might be important in controlling adipocyte growth and development [21]. Ca2+-ATPase (SERCA), a family of membrane-bound ATPases that are able to translocate Ca2+ ions across the membrane using the chemical energy derived from ATP hydrolysis, was shown to generate heat in the presence of Ca2+ concentrations similar to those occurring during adrenergic stimulation in rat brown adipocyte mitochondria [22].

Multiple P2 receptor subtype mRNA was later identified in rat brown fat cells: P2Y2, P2Y6 and P2Y12 metabotropic receptors and P2X1, P2X2, P2X3, P2X4, P2X5 and P2X7 receptors; ATP, ADP, UTP and UDP increased intracellular Ca2+ [23].

Adenosine is present in adipose tissue after breakdown by ectoenzymes of ATP released as a cotransmitter from sympathetic nerves and from adipocytes. Adenosine was shown to regulate hamster brown adipose tissue respiration at an early metabolic step of the stimulus-thermogenesis sequence [24]. Adenosine increased lipolysis and induced thermogenesis in...
brown adipocytes via A2A receptors, and A2A agonists were shown to counteract HFD-induced obesity in mice [25].

**Purinergic control of white adipocytes**

White adipocytes are the major energy reservoir in mammals, and they play a crucial role in the maintenance of energy homeostasis [26].

ATP increased cell membrane capacitance in rat white adipocytes, similar to that produced in brown adipocytes, indicating that the electrophysiology of both kinds of adipocytes is very similar in their response to ATP [27].

Rat white adipocytes express at least two P2Y receptor subtypes, and activation of P2Y11 receptors may mediate inhibition of leptin production and stimulation of lipolysis, suggesting an important role of purinergic transmission in white adipocyte physiology [28]. A combination of ATP and Ca2+ has been reported to augment human white adipocyte vesicular release of adiponectin [29]. This study also investigated the cellular mechanisms involved in the regulation of human white adipocyte exocytosis/secretion by monitoring the membrane capacitance. The authors showed that protein kinase A-independent mechanisms could be correlated with a release of adiponectin vesicles, elucidating previously unknown cellular mechanisms involved in the regulation of white adipocyte exocytosis/secretion [29]. Disturbance of adiponectin secretion in individuals with obesity highlights the control of adipokine release by ATP. Reduction in the plasma level of adiponectin in subjects with obesity precedes the reduction in insulin sensitivity and onset of diabetes [30].

Adenosine monophosphate (AMP) kinase, a cellular energy sensor activated by cellular stresses and also by leptin and adiponectin, has fat-reducing effects in mammalian white adipose tissue and is a potential target for obesity treatment [31]. The authors suggested that chronic AMP kinase activation acts by remodelling adipocyte glucose and lipid metabolism, which then enhances the ability of adipose tissue to remove energy and reduce adiposity [31].

In isolated rat white adipocytes, adenosine, produced following breakdown of ATP, acts as a positive regulator for insulin in the release of leptin via an activation of A1 receptors that involves the phospholipase C-protein kinase C pathway [32].

**Hypothalamic purinergic nervous control of obesity**

In the last decade, many studies have highlighted a fundamental role of the CNS, in particular the arcuate nucleus of the hypothalamus (ARH), in the regulation of food intake and energy balance in mammals [33]. In mammals, the ARH is accessible to circulating signals of energy balance, via the underlying median eminence, as this region of the brain is not protected by the blood-brain barrier [34]. They showed, in particular, that the ARH integrates neurohormonal signalling from the gut and adipose tissue, communicating nutrient availability, including ghrelin, insulin, glucose, leptin and UDP. The ARH contains two primary neuron populations that integrate signals of nutritional status and influence energy homeostasis [35]. One neuronal circuit inhibits food intake, via α-melanocyte-stimulating hormone, and cocaine- and amphetamine-regulated transcripts [36]. The other neuronal circuit stimulates food intake, via the expression of neuropeptide Y and agouti-related peptide (AgRP) [37]. Several studies aimed at finding novel approaches for the management of obesity have focused on the critical role of AgRP neurons in the regulation of appetite, reporting that their direct activation rapidly increases food intake. In contrast, AgRP neuron inhibition [38] or ablation dramatically decreases feeding [39] in mice.

Of the regulators of the central control of feeding behaviour, the family of G protein-coupled receptors has significant therapeutic potential, due to their involvement in the regulation of physiological responses to hormones, neurotransmitters and environmental stimulants [40]. It was shown in mice that the UDP-selective P2Y6 receptor, a P2Y G protein-coupled receptor, is highly expressed in the ARH, particularly in AgRP neurons [41]. The authors provided the first evidence that the activation of P2Y6 receptor signalling, by UDP, increases firing rate and feeding in lean mice [41]. Pharmacological blocking of P2Y6 receptor activation in the CNS, with the selective P2Y6 receptor antagonist MRS 2578, inhibits feeding in mice. These authors showed in a more recent study that the ability of centrally applied UDP to acutely promote feeding is retained in diet-induced obese mice [42]. In contrast, pharmacological blocking of P2Y6 receptor activation in the CNS via intracerebroventricular application of MRS 2578 inhibits food intake in obese mice (see Fig. 1). Moreover, both conventional and AgRP-restricted P2Y6-deficient animals exhibit reduced obesity as well as improved whole-body insulin sensitivity when exposed to long-term HFD feeding. Thus, although further investigations are needed, P2Y6 receptors could represent a potential therapeutic target for the prevention and treatment of obesity and related insulin resistance. Furthermore, since P2Y6 receptors are also expressed on activated microglia in the hippocampus of rats [43] and considering that obesity promotes hypothalamic inflammation, including the activation of microglia [44], this purinergic receptor could hold a potential pathophysiological role in inflammatory processes within the CNS induced by HFD.
Regulatory roles of ATP and P2 receptors in obesity

In a review entitled ‘Leptin and the control of obesity’, it was stated that ‘ATP is a major stimulus for leptin production and secretion’ [10, 45, 46] (see Fig. 2). Bullock and Daly reviewed the evidence for sympathetic nerve innervation of perivascular adipocytes and the function of ATP, released as a sympathetic cotransmitter with noradrenaline, which inhibits lipolysis [47]. In addition, there is strong evidence that the vagus nerve is involved in the development of diet-induced obesity (see [48]) and, since ATP is also a cotransmitter with acetylcholine in vagal nerves, it may be involved in its mechanisms. The likely source of the ATP is sympathetic nerves, and ATP was reported to inhibit insulin-stimulated glucose transport and glycogen synthase in rat fat cells [49].

In a later study also performed on rats, ATP was shown to have a strong effect, while adenosine a mild inhibitory effect, on insulin-stimulated glucose transport [50]. It is possible that ATP, released as a cotransmitter from sympathetic nerves, mediates the long-term effects of leptin on blood pressure involved in obesity hypertension [51]. ATP has antihyperlipidaemic activity by decreasing serum triglyceride levels in rabbits fed a HFD and in hyperlipidaemic patients, suggesting that ATP supplementation could provide an effective approach to control triglyceride levels in obesity [52]. A later paper provided evidence that ATP stimulated lipogenesis in rat adipocytes via a nucleotide UDP, whose synthesis in the CNS depends on the salvage pathway, which is directly controlled by the peripheral supply of the precursor metabolite uridine, typically increased in obesity/diabetes. Pharmacological blocking of P2Y6 receptor activation in the CNS, with the selective P2Y6 receptor antagonist MRS 2578, inhibits feeding in mice (modified from [41] and reproduced with permission from Elsevier).

P2X receptors

Of the P2X receptors, an involvement of both P2X2 and P2X7 receptors has been identified. Obesity promoted a decrease in the expression of P2X2 receptors on enteric neurons of obese male mice [57]. Human adipocytes from metabolic patients express functionally active P2X7 receptors, which modulate the release of inflammatory molecules such as interleukin-6, tumour necrosis factor-α and plasminogen activator inhibitor-1, in part via inflammasome activation [58]. Moreover, these cells also exhibited enhanced P2X7 receptor expression, which might contribute to the subclinical inflammatory status characterising these patients and conferring on them an increased cardiovascular risk [58]. In addition, Rossi and colleagues, in line with this evidence, demonstrated that...
patients affected by metabolic syndrome showed an enhancement of P2X7 receptor expression and inflammasome activation compared to control patients [59]. However, it was claimed in another study on mice that ATP activation of P2X7 receptors was not involved in inflammasome activation in adipose tissue [60]. The P2X7 receptor has been reported to be the primary mediator of oxidative stress-induced exacerbation of inflammatory liver injury in obese mice [61]. Moreover, the fact that P2X7 receptor antagonists significantly decreased carbon tetrachloride exacerbation of liver injury in obesity paved the way for future investigations using the antagonists as potential therapeutic molecules in treating steatohepatitis in obesity in its early phase [61]. Of note, in metabolically unhealthy obese subjects, stromal vascular cells showed upregulation of P2X7 receptors, which are involved in the chronic inflammation of visceral adipose tissue underlying the metabolic changes in obesity [62]. In P2X7 knockout mice, there is abnormal fat distribution, suggesting that P2X7 receptors mediate regulation of adipogenesis and lipid metabolism in age- and sex-dependent manners [63]. ATP-induced inflammation, via P2X7 receptors, drives tissue-resident Th17 cells in metabolically unhealthy obese subjects, and it was suggested that the manipulation of purinergic signalling might represent a new therapeutic target to shift the CD4+ T cell balance under inflammatory conditions [64]. Sulphur-containing AMP and guanosine monophosphate analogues can be hydrolysed to hydrogen sulphide by rat perivascular adipose tissue when P2X7 receptors are activated [65].

**P2Y receptors**

ATP, acting via P2Y receptors, enhanced the migration of preadipocytes and increased adipocyte differentiation in a mouse cell line [66]. P2Y1 receptors mediate regulation of leptin secretion from adipocytes in lean, but not obese mice [67]. ATP, acting via P2Y1 receptors, contributes to the cell surface F1F0-ATP synthase-mediated intracellular triacylglycerol accumulation in mouse adipocytes [68]. Mouse P2Y4 receptors are negative regulators of cardiac adipose-derived stem cell differentiation and cardiac fat formation [69]. Therefore, these receptors could be a potential therapeutic target in the regulation of the cardioprotective function of cardiac fat. Myenteric neurons from P2Y13 receptor knockout mice or treatment with P2Y13 receptor antagonists are resistant to HFD- and palmitic acid-induced neuronal loss; consequently, P2Y13 receptor antagonism might constitute a novel therapeutic strategy in patients affected by intestinal dysmotility involving neuropathy [70]. P2Y6 receptor agonists enhance glucose uptake in mouse adipocytes and skeletal muscle cells [71]. As previously described, the activation of P2Y6 receptor signalling, by UDP, increases firing rate and feeding in lean mice [41].

---

**Fig. 2 Factors influencing leptin synthesis and secretion.** Insulin-mediated glucose uptake determines the rate of glucose metabolism in adipose tissue, and the subsequent generation of ATP is a major stimulus for leptin production and secretion. Some fatty acids may also have an effect (indicated with question mark). Hormones such as glucocorticoids, oestrogen and growth hormone also stimulate leptin secretion. Catecholamines, via the β3 adrenoreceptor, tend to inhibit leptin production. The antidiabetic thiazolidinedione drugs also inhibit leptin production, but the mechanism is not known. ATP acts on P2Y1 receptors to mediate regulation of leptin secretion from adipocytes in lean, but not obese mice, and adenosine acts on A1 receptors to increase leptin secretion (modified from [46] and reproduced with permission from Elsevier).
ATP-sensitive K$^+$ channels

Extracellular ATP modulates several ionic channels, such as K$^+$ channels. Modulation of ATP-sensitive K$^+$ (K$_{ATP}$) channel activity has been the basis of numerous pharmacological studies since these channels are abundant in a variety of tissues and species. K$_{ATP}$ channel activity is coupled with insulin resistance in obesity and type 2 diabetes in mammals [72]. Indeed, insulin activates K$_{ATP}$ channels in hypothalamic neurons of lean but not obese rats, suggesting that hypothalamic K$_{ATP}$ channels have a crucial role in the physiological regulation of food intake and body weight [73]. K$_{ATP}$ function was decreased in obese rats, along with impaired vasodilation in response to exercise [74]. This evidence suggested that the decreased sensitivity of K$_{ATP}$ channels could potentially limit muscle blood flow during exercise, a treatment option known to improve glucose, lipid and weight control [74]. Evidence suggested that K$_{ATP}$ channel-deficient mice exhibit hyperphagia but are resistant to the induction of obesity by a HFD [75].

ATP-binding cassette transporters

ATP-binding cassette (ABC) transporters (ABCA1, ABCG1, ABCG5 and ABCG8) are examples of ATP-dependent pumps involved in mediating macrophage cholesterol efflux in animal models and in vitro experiments [76, 77]. The ABC transporter A1 R230C variant was reported to affect high-density lipoprotein cholesterol levels and to be associated with obesity and obesity-related comorbidities in the Mexican population [78]. The ABC transporter G8 gene was shown to be a determinant of apolipoprotein B-100 kinetics in a study of Australian overweight/obese men [76]. The R219K polymorphism of ABC transporter A1 is related to low high-density lipoprotein level in overweight/obese Thai males [79]. The expression of ABC transporter A1 in monocytes was reduced in Chinese overweight and obese patients, and this was associated with the impairment of cholesterol efflux from monocyte-derived macrophages [80]. Since adipocyte ABC transporter G1 promoted triglyceride storage and fat mass growth, it might represent a potential therapeutic target in the control of fat accumulation [81].

Other purinergic therapeutic possibilities

Cell surface H$^+$-ATP synthase has been claimed to be a potential molecular target for anti-obesity drugs. Of note, treatment with small molecule inhibitors of H$^+$-ATP synthase or antibodies against H$^+$-ATP synthase subunits leads to a decrease in cytosolic lipid droplet accumulation in differentiated adipocytes [82].

Transcriptional regulation of the gene for ATP citrate lyase (one of the lipogenic enzymes) by glucose/insulin and leptin was investigated in hepatocytes and adipocytes of normal and genetically obese rats. In the presence of glucose/insulin, the chloramphenicol acetyltransferase activities were markedly increased in hepatocytes of lean rats but were not significantly increased in those of obese rats [83]. It has been suggested that animal and human obesity is associated with reduction of tissue Na$^+$/K$^+$-ATPase, linked to hyperinsulinemia, influencing thermogenesis and energy balance [84].

Typical signs of Cushing’s syndrome and side effects of prolonged glucocorticoid treatment are features of the metabolic syndrome, such as central obesity with insulin resistance and dyslipidaemia. Changes in AMP-activated protein kinase have been proposed as a novel mechanism to explain the deposition of visceral adipose tissue and the consequent central obesity in individuals with Cushing’s syndrome [85].

Regulatory role of adenosine and P1 receptors in obesity

In early studies on rat adipocytes, adenosine was shown to inhibit lipolysis elicited by noradrenaline [86] due to its inhibition of adenylate cyclase and cyclic AMP production by a guanosine triphosphate-dependent process [87]. Adenosine was shown to be rapidly taken up by isolated fat cells and incorporated into ATP, which, after release, was broken down by ectoenzymes to adenosine [88]. Theophylline, an adenosine antagonist, and dipyridamole, an inhibitor of adenosine uptake, were shown to enhance lipolysis [89]. Sites on adipocyte membranes that bind $[^{3}H]$adenosine were demonstrated and identified as adenosine (P1) receptors [90]. Three subtypes of P1 receptors were described on adipocytes obtained from epididymal and perirenal fat pads [91]. A1 receptors were shown to be present on human adipocytes [92], and in rats, white adipocytes were more responsive than brown adipocytes to inhibition of lipolysis by activation of A1 receptors [93]. Cloning, expression and characterisation of the A1 receptor on mouse and human adipose tissues were reported [94]. A1 receptor activation results in an increase of adipocyte leptin secretion in rats [95]. A1 receptors are highly expressed in adipose tissue, and their contribution to the regulation of lipolysis in pathological conditions like insulin resistance, diabetes and dyslipidemia, where free fatty acids play an important role, has been examined [96]. Agonists to A1 receptors are in clinical trials for obesity. The A2 adenosine receptor subtype, which is positively coupled to adenylate cyclase, was shown to be expressed by preadipocytes, but not activated adipocytes, suggesting that adenosine might play as a bimodal regulatory signal in adipose tissue development in rats [97].

There were contrasting effects of transfected human A1 and A2B receptors into a murine osteoblast precursor cell line, 7F2. A1 receptors mediated adipocyte differentiation, whereas A2B receptors mediated inhibition of adipogenesis and stimulated...
an osteoblastic phenotype [98]. Activated transfected human A1 receptors initiated differentiation of mouse preadipocyte cells [99]. Deletion of adenosine A1 receptors in knockout mice should increase lipolysis and decrease lipogenesis, but an increased fat mass was observed, indicating that there are other actions mediated by A1 receptors [100]. Differentiation of rat mesenchymal stem cells to adipocytes was accompanied by significant increases in the expression of A1 and A2A, and their activation was associated with increased adipogenesis [101]. There is impaired glucose tolerance in A1 receptor knockout mice [102].

Insulin, as well as adenosine, is antilipolytic in rats [103]. Also in rats, adenosine modulation of the stimulation of glucose metabolism in adipocytes by insulin was shown to be mediated by different mechanisms from that mediated by oxytocin [104]. Adenosine, via A1 receptors, increased insulin sensitivity and inhibited lipolysis in adipocytes. After prolonged incubation of rat adipocytes with an A1 adenosine receptor agonist, N6-phenylisopropyl adenosine, there was downregulation of the receptor and insulin resistance [105]. Over-expression of A1 receptors in adipose tissue protects mice from obesity-related insulin resistance, and it was suggested that A1 receptor activation should be considered as a potential therapeutic target for the treatment of obesity-related insulin resistance and type 2 diabetes [106]. Insulin resistance in obese Zucker rats is tissue specific, and BWA1433, an adenosine receptor antagonist, improved glucose tolerance by increasing glucose uptake in skeletal muscle, while decreasing glucose uptake by adipose tissue [107]. There was enhanced sensitivity to both lipolytic stimuli and adenosine suppression of lipolysis in isolated fat cells from streptozotocin-diabetic rats [108].

Adipocytes from hypothroid rats respond to adenosine, but not to adrenaline, with increased glycerol release [109]. Short-term hyperthyroidism modulates adenosine receptors and adenylyl cyclase in rat adipocytes [110]. Studies of membranes from hyperthyroid rats showed no significant alteration on the expression of A1 receptors [111]. Adenosine increases blood flow and glucose uptake in adipose tissue of dogs [112] and in brown adipose tissue of rats [113].

In brown subcutaneous abdominal fat cells from subjects with obesity, the antilipolytic effect of an adenosine analogue was markedly attenuated as compared to that in fat cells from normal-weight subjects [114]. A reduction in the P1 receptor number in adipocyte plasma membranes and reduced adenosine sensitivity in human obesity were reported [115]. Inhibition of isoprenaline-stimulated lipolysis by an adenosine receptor agonist was much attenuated in cells from patients that were massively obese, compared to normal-weight control subjects [116]. Obese rats show reduced adenosinergic modulation of ventilatory responses to acute and sustained hypoxia [117]. It was concluded that this was due to depressed peripheral excitatory mechanisms and to enhanced adenosinergic central depression mechanisms. An adenosine deaminase polymorphism was shown to be associated with obesity, and adenosine receptor agonists were recommended as therapeutic targets for obesity and dyslipidemia [118]. Data was presented to suggest that inhibition of lipolysis by adenosine appears to be greater in African-American women with obesity and that this might possibly be one explanation for the observation that African-American women with obesity have more difficulty in losing weight than Caucasian women with obesity [118].

A HFD induced changes in glucose homeostasis, inflammation and obesity. A2B receptors were upregulated in lean mice by a HFD, while A2B receptor knockout mice under this diet developed greater obesity and signs of type 2 diabetes [119]. The authors showed further that in human subjects with obesity, A2B receptor expression correlated strongly with expression of the insulin receptor substrate 2, and suggested that A2B receptor agonists have potential for the treatment of type 2 diabetes and obesity. A recent study by Antonioli and co-workers reported that A2B receptors participate to obesity-related enteric dysmotility, modulating the activity of excitatory tachykinergic nerves in HFD mice [120]. A review about adenosine and adipogenesis is available [121]. High plasma levels of adenosine were found in children with obesity [122] and in overweight pregnant women [123]. Non-alcoholic fatty liver disease is an obesity-related condition. A study provided insight into the lipolytic actions of caffeine (a P1 receptor antagonist) through autophagy in mammalian liver and its potential beneficial effects in non-alcoholic fatty liver disease [124]. Obesity causes macrophage activation, which, in turn, causes insulin resistance in target organs. Adenosine, acting via A2B receptors, prevented adipose tissue inflammation and insulin resistance; therefore, it suggests a possible therapeutic strategy for inhibiting adipose tissue inflammation [125]. Evidence was presented that there may be a role for the ectonucleotidase CD73 and A2A receptors in inflammation observed in patients with type 2 diabetes and obesity mediated via apoptosis [126]. Adenosine protects rats from a HFD by reducing glucose and insulin levels, suppressing elevation of corticosterone and attenuating intestinal inflammation [127].

**Concluding comments**

Several important conclusions can be drawn from this review:

1. P2Y<sub>6</sub> receptors influence hypothalamic control of feeding, and the P2Y<sub>6</sub> receptor antagonist MRS 2578 inhibits food intake in obese mice. Therefore, P2Y<sub>6</sub> receptors are a potential therapeutic target for the prevention and treatment of obesity.
2. A2A receptor agonists, acting on adipocytes, counteract HFD-induced obesity in mice, indicating A2A receptors as a potential drug target for anti-obesity therapies.
3. P2Y_{11} receptors have stimulatory effects on lipolysis in adipocytes. Therefore, these receptors deserve further explorations.

4. Both P2X_{7} receptors, which mediate inflammation, and K_{ATP} are beginning to be explored for the treatment of obesity.

5. Growing lines of evidence suggest that a subtle balance of adipogenic and osteogenic differentiation of mesenchymal stem cells is crucial in tissue homeostasis and a loss of adipo-osteogenic balance leads to pathophysiological conditions, such as obesity.

6. P2Y_{1} receptors are responsible for the extracellular ATP-mediated intracellular triglyceride accumulation in adipocytes. The P2Y_{1} receptor antagonist MRS 2500 significantly inhibited triacylglycerol accumulation, suggesting the P2Y_{1} receptor as a novel therapeutic target for the treatment of lipid disorders.

7. P2Y_{4} receptors are negative regulators of cardiac adipose-derived stem cell differentiation and cardiac fat formation. Therefore, these receptors could be potential therapeutic targets in the regulation of the cardioprotective function of cardiac fat.

8. Activation of P2Y_{13} receptors mediates HFD- and palmitic acid-induced myenteric neuronal loss in mice. Myenteric neurons from mice lacking the P2Y_{13} receptors or treated with a selective P2Y_{13} receptor antagonist are resistant to HFD- and palmitic acid-induced loss. Antagonism of P2Y_{13} receptors might constitute a novel therapeutic strategy in patients with obesity affected by intestinal dysmotility.

9. Adipocyte ABC transporter G1 promoted triglyceride storage and fat mass growth. Thus, it might represent a potential therapeutic target in the control of fat accumulation.

10. A_{1} receptor agonists are in clinical trials for obesity. Over-expression of A_{1} receptors in adipose tissue protects mice from obesity-related insulin resistance.

11. A_{2B} receptors prevent HFD-induced hallmarks of type 2 diabetes, adipose tissue inflammation and insulin resistance. Therefore, the A_{2B} receptor might represent a possible therapeutic strategy.

Purinergic signalling offers proof-of-concept potential for the development of novel therapeutic approaches to treat obesity, mostly from studies in animal models. Currently, pharmacological obesity treatment options are palliative and limited. An excess of body fat is associated with cardiovascular disorders and metabolic syndromes, including insulin-independent diabetes and dyslipidemia; therefore, a combination of lifestyle changes and new drugs may be the most efficacious approach to achieving sustained weight loss for the majority of patients with obesity. In particular, strategies to combat obesity may include drugs that regulate bodyweight acting through CNS pathways or via peripheral adiposity signals and the gastrointestinal tract.

There are a number of promising studies on several animal models and systems that could be translated to human applications. Current data obtained with experimental models support the notion that the purinergic system consists of adenosine receptors, metabotropic P2Y receptors and ionotropic P2X_{7} receptors, which are all thought to contribute to the pathology of obesity. The enormous flexibility and diversity of the purinergic system can be exploited in drug design for therapeutic intervention and the development of anti-obesity drugs, although further understanding is needed. Indeed, the development of selective agonists and antagonists for the different purinergic receptor subtypes could be combined with the investigation of the interactions of purinergic signalling with other established signalling systems in relation to obesity. Hopefully, the potential use of purinergic compounds that are orally bioavailable and stable in vivo for the treatment of obesity will soon be prepared by medicinal chemists that can be used in clinical trials.

Acknowledgments The authors thank Dr. Gillian E. Knight for her assistance with the preparation of this manuscript.

Compliance with ethical standards

Conflicts of interest Geoffrey Burnstock declares that he has no conflict of interest.

Daniela Gentile declares that she has no conflict of interest.

Ethical approval This review article does not contain any studies with human participants or animals performed by either of the authors.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Coelho M, Oliveira T, Fernandes R (2013) Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci 9:191–200

2. Saely CH, Geiger K, Drexel H (2012) Brown versus white adipose tissue: a mini-review. Gerontology 58:15–23

3. Burnstock G (2014) Purinergic signalling in endocrine organs. Purinergic Signalling 10:189–231

4. Henry SL, Bensley JG, Wood-Bradley RJ, Cullen-McEwen LA, Bertram JF, Armitage JA (2012) White adipocytes: more than just fat depots. Int J Biochem Cell Biol 44:435–440

5. La Merrill M, Birnbaum LS (2011) Childhood obesity and environmental chemicals. Mt Sinai J Med 78:22–48

6. Luquet S, Magnan C (2009) The central nervous system at the core of the regulation of energy homeostasis. Front Biosci (Schol Ed) 1:448–465
7. Peterson HR, Rothchild M, Weinberg CR, Fell RD, McLeish KR, Pfeifer MA (1988) Body fat and the activity of the autonomic nervous system. N Engl J Med 318:1077–1083
8. Moreira MC, Pinto IS, Mourao AA, Fajemiroje JO, Colombani E, Reis AA, Freiria-Oliveira AH, Ferreira-Neto ML, Pedrino GR (2015) Does the sympathetic nervous system contribute to the pathophysiology of metabolic syndrome? Front Physiol 6:234
9. Youngstrom TG, Bartness TJ (1998) White adipose tissue sympathetic nervous system denervation increases fat pad mass and fat cell number. Am J Phys 275:R1488–R1493
10. Misra M (2013) Obesity pharmacotherapy: current perspectives and future directions. Curr Cardiol Rev 9:33–54
11. Burnstock G (1972) Purinergic nerves. Pharmacol Rev 24:509–581
12. Burnstock G (2007) Physiology and pathophysiology of purinergic neurotransmission. Physiol Rev 87:659–797
13. Burnstock G (2006) Pathophysiology and therapeutic potential of purinergic signaling. Pharmacol Rev 58:58–86
14. Harms M, Seale P (2013) Brown and beige fat: development, function and therapeutic potential. Nat Med 19:1252–1263
15. Rines AK, Verdeguer F, Puigserver P (2015) Adenosine activates thermogenic adipocytes. Cell Res 25:155–156
16. Minokoshi Y, Saito M, Shimazu T (1988) Sympathetic activation of rat brown adipocytes. J Biol Chem 263:28556–28563
17. Himms-Hagen J, Cui J, Lynn Sigurdson S (1990) Sympathetic and sensory nerves in control of growth of brown adipose tissue: effects of denervation and of capsaicin. Neurochem Int 17:271–279
18. Sakaguchi T, Arase K, Fisler JS, Bray GA (1989) Effect of a high-fat diet on firing rate of sympathetic nerves innervating brown adipose tissue in anesthetized rats. Physiol Behav 45:1177–1182
19. Lee SC, Pappone PA (1997) Effects of P2 purinergic receptor stimulation in brown adipocytes. Am J Phys 273:C679–C680
20. Omatsu-Kanbe M, Matsuura H (1999) Inhibition of store-operated Ca2+ entry by extracellular ATP in rat brown adipocytes. J Physiol 521(Pt 3):601–615
21. Wilson SM, Pappone PA (1999) P2 receptor modulation of voltage-gated potassium currents in brown adipocytes. J Gen Physiol 113:125–138
22. de Meis L, Arruda AP, da Costa RM, Benchimol M (2006) Differential regulation of Ca2+ signaling and membrane trafficking by multiple P2 receptors in brown adipocytes. J Membr Biol 207:131–142
23. Schimmel RJ, McCarthy L (1984) Role of adenosine as an endogenous regulator of respiration in hamster brown adipocytes. Am J Phys 246:C301–C307
24. Gao Y, Ottaway N, Schriever SC, Legutko B, Garcia-Caceres C, de la Fuente E, Mergen C, Bour S, Thaler JP, Seeley RJ, Filosa J, Stern JE, Perez-Tilve D, Schwartz MW, Yi CX (2014) Hormones and diet, but not body weight, control hypothalamic UCP2 and UCP3 expression. Cell Metab 19:323–335
25. Gnad T, Scheibler S, von Kügelgen I, Scheele C, Kilic A, Glode Idzko M, Kloppenburg P, Bruning Jens C (2015) Hypothalamic UDP increases in obesity and promotes feeding via P2Y6-dependent activation of AgRP neurons. Cell 162:1404–1417
26. de Lartigue G (2016) Role of the vagus nerve in the development of obesity and future directions. Curr Cardiol Rev 9:33–54
27. Broberger C, Johansen J, Johansson C, Schalling M, Hokfelt T (1998) The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. Proc Natl Acad Sci U S A 95:15043–15048
28. Vasquez VA, LaRusso F, Dominici S, Di Bari U, Gaidhu MP, Ceccid EB, de la Fuente E, Mergen C, Bour S, Thaler JP, Seeley RJ, Filosa J, Stern JE, Perez-Tilve D, Schwartz MW, Yi CX (2014) Hormones and diet, but not body weight, control hypothalamic UCP2 and UCP3 expression. Cell Metab 19:323–335
29. Komai AM, Brünmark C, Musovic S, Olofsson CS (2014) PKA-independent cAMP stimulation of white adipocyte exocytosis and adipokine secretion: modulations by Ca2+ and ATP. J Physiol 592:5169–5186
30. Yamauchi T, Kadowaki T (2013) Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. Cell Metab 17:185–196
31. Conklin JD, Bell PC, Kozak BA (2012) The role of adenosine monophosphate kinase in remodeling white adipose tissue metabolism. Exerc Sport Sci Rev 40:96–104
32. Cheng JT, Liu IM, Chi TC, Shinozuka K, Lu FH, Wu TJ, Chang CJ (2000) Role of adenosine in insulin-stimulated release of leptin from isolated white adipocytes of Wistar rats. Diabetes 49:20–24
33. Schwartz GJ, Azzara AV, Heanner MK (2013) Roles for central leptin receptors in the control of meal size. Appetite 71:466–469
34. Wynne K, Stanley S, McGowan B, Bloom S (2005) Appetite control. Endocrinol 114:291–318
35. Cone RD, Cowley MA, Butler AA, Fan W, Marks DL, Low MJ (2001) The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. Int J Obes Relat Metab Disord Suppl 55:S68–S67
36. Elias CF, Lee CE, Kelly JF, Ahima RS, Kuhar M, Saper CB, Elmquist JK (2001) Characterization of CART neurons in the rat and human hypothalamus. J Comp Neurol 432:1–19
37. Broberger C, Johansen J, Johansson C, Schalling M, Hokfelt T (1998) The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. Proc Natl Acad Sci U S A 95:15043–15048
38. Krashes MJ, Koda S, Ye C, Rogan SC, Adams AC, Cusher DS, Maratos-Flier E, Roth BL, Lowell BB (2011) Rapid, reversible activation of AgRP neurons drives feeding behavior in mice. J Clin Invest 121:1424–1428
39. Luquet S, Perez FA, Hnasko TS, Palmert RD (2005) NPY/AgRP neurons are essential for feeding in adult mice but can be ablated in neonates. Science 310:683–685
40. Allen JA, Roth BL (2011) Strategies to discover unexpected targets for drugs active at G protein-coupled receptors. Annu Rev Pharmacol Toxicol 51:117–144
41. Steculorum SM, Paege S, Bremser S, Evers N, Hinzy Y, Iidzko M, Kloppenburg P, Bruning Jens C (2015) Hypothalamic UDP increases in obesity and promotes feeding via P2Y6-dependent activation of AgRP neurons. Cell 162:1404–1417
42. Steculorum SM, Timper K, Engstrom Raud L, Evers N, Paeger S, Bremer S, Kloppenburg P, Bruning JC (2017) Inhibition of P2Y6 signaling in AgRP neurons reduces food intake and improves systemic insulin sensitivity in obese. Cell Rep 18:1587–1597
43. Coizumi S, Shigemoto-Mogami Y, Nasu-Tada K, Shinozaki Y, Ohsawa K, Tsuda M, Joshi BV, Jacobson KA, Kohsaka S, Inoue K (2007) UDP acting at P2Y6 receptors is a mediator of microglial phagocytosis. Nature 446:1091–1095
44. Gao Y, Ottaway N, Schriever SC, Legutko B, Garcia-Caceres C, de la Fuente E, Mergen C, Bour S, Thaler JP, Seeley RJ, Filosa J, Stern JE, Perez-Tilve D, Schwartz MW, Yi CX (2014) Hormones and diet, but not body weight, control hypothalamic microglial activity. Glia 62:17–25
45. Szakadeczki T (2007) Intracellular mediators in regulation of leptin secretion from adipocytes. Physiol Rev 86:546–581
46. Wilding JP (2001) Leptin and the control of obesity. Curr Opin Pharmacol 1:656–661
47. Bulloch JM, Daly CJ (2014) Autonomic nerves and perivascular fat: interactive mechanisms. Pharmacol Ther 143:61–73
48. de Lartigue G (2016) Role of the vagus nerve in the development and treatment of diet-induced obesity. J Physiol 594:5791–5815
49. Tamura S, Dubler RE, Lamer J (1983) Stimulation of maximal intracellular insulin action on glycogen synthase by preincubation
of adipocytes with adenosine 5′-triphosphate. J Biol Chem 258: 719–724

50. Hashimoto N, Robinson FW, Shibata Y, Flanagan JE, Kono T (1987) Diversity in the effects of extracellular ATP and adenosine on the cellular processing and physiologic actions of insulin in rat adipocytes. J Biol Chem 262:15026–15032

51. Hall JE, Hildebrandt DA, Kuo J (2001) Obesity hypertension: role of leptin and sympathetic nervous system. Am J Hypertens 14: 1035–115S

52. Zhang L, Liang L, Tong T, Qin Y, Xu Y, Tong X (2016) Antihyperlipidemic activity of adenosine triphosphate in rabbits fed a high-fat diet and hyperlipidemic patients. Pharm Biol 54: 2358–2363

53. Schödel J, Weise I, Kléinger R, Schmidt M (2004) Stimulation of lipogenesis in rat adipocytes by ATP, a ligand for P2-receptors. Biochem Biophys Res Commun 321:767–773

54. Chowdhury HH, Grílce S, Zorc RG (2005) Correlated ATP-induced changes in membrane area and membrane conductance in single rat adipocytes. Ann N Y Acad Sci 1048:281–286

55. Yu Z, Jin T (2010) Extracellular high dosages of adenosine triphosphate induce inflammatory response and insulin resistance in rat adipocytes. Biochem Biophys Res Commun 402:455–460

56. Nair S, Chacko P, Arnold C, Diehl AM (2003) Hepatic ATP reserve and efficiency of replenishing: comparison between obese and nonobese normal individuals. Am J Gastroenterol 98: 460–470

57. Mizuno MS, Crisma AR, Borelli P, Schäfer BT, Silveira MP, Castelucci P (2014) Distribution of the P2X2 receptor and chemical coding in ileal enteric neurons of obese male mice (ob/ob). World J Gastroenterol 20:13991–13997

58. Madec S, Rossi C, Chiarugi M, Santini E, Salvati A, Ferrannini E, Solini A (2011) Adipocyte P2X7 receptors expression: a role in modulating inflammatory response in subjects with metabolic syndrome? Atherosclerosis 219:552–558

59. Rossi C, Santini E, Chiarugi M, Salvati A, Comassi M, Vitolo E, Madec S, Solini A (2014) The complex P2X7 receptor/ inflammasome in perivascular fat tissue of heavy smokers. Eur J Clin Investig 44:295–302

60. Sun S, Xia S, Ji Y, Kersten S, Qi L (2012) The ATP-P2X7 signalling axis is dispensable for obesity-associated inflammasome activation in adipose tissue. Diabetes 61:1471–1478

61. Chatterjee S, Rana R, Corbett J, Kadiiska MB, Goldstein J, Mason LA, Fainboim L, Arruvito L (2016) ATP-induced inflammation drives tissue-resident Th17 cells in metabolically unhealthy obese (MHO) adipose tissue. Endocrinology 151:2060–2070

62. Balasubramanian R, Robaye B, Boeynaems JM, Jacobson KA (2014) Enhancement of glucose uptake in mouse skeletal muscle cells and adipocytes by P2Y6 receptor agonists. PLoS One 9: e116203

63. Wasada T (2002) Adenosine triphosphate-sensitive potassium (KATP) channel activity is coupled with insulin resistance in obesity and type 2 diabetes mellitus. Intern Med 41:84–90

64. Lemaire A, Vanorlé M, Horckmans M, di Pietrantonio L, Clouet Lemaire A, Vanorlé M, Horckmans M, di Pietrantonio L, Clouet

65. Beltowski J, Guranowski A, Jamroz-Wisniewska A, Wolski A, Voss U, Turesson MF, Robaye B, Boeynaems JM, Olde B, Erlinge D, Ekblad E (2014) The enteric nervous system of P2Y13 receptor null mice is resistant against high-fat-diet- and palmitic-acid-induced neuronal loss. Purinergic Signal 10:455–464

66. Chatterjee S, Rana R, Corbett J, Kadiiska MB, Goldstein J, Mason LA, Fainboim L, Arruvito L (2015) Purinergic signaling modulates human visceral adipose inflammatory responses: implications in metabolically unhealthy obesity. J Leukoc Biol 97:941–949

67. Beaucage KL, Xiao A, Pollmann SI, Grol MW, Beach RJ, Holdsworth DW, Sims SM, Darling MR, Dixon SJ (2014) Loss of P2X7 nucleotide receptor function leads to abnormal fat distribution in mice. J Immunol 196:3287–3298

68. Frisdal E, Le Lay S, Hooton H, Poupel L, Olivier M, Alili R, Riaño D, Villalobos-Comparan M, Coral-Vazquez R, Menjivar M, Yescas-Gomez P, Königsoerg-Fainstein M, Romero-Hidalgo S, Tusie-Luna MT, Canizales-Quinteros S (2007) The ATP-binding cassette transporter A1 R230C variant affects HDL cholesterol levels and BMI in the Mexican population: association with obesity and obesity-related comorbidities. Diabetes 56: 1881–1887

69. Arakaki N, Kita T, Shibata H, Higuti T (2007) Cell-surface H+–ATP-binding cassette transporter A1 cells and adipocytes by P2Y6 receptors. J Biol Chem 258: 13919–1400

70. Xu M, Zhou H, Wang J, Li C, Yu Y (2009) The expression of ATP-binding cassette transporter A1 in reverse cholesteryl transport and atherosclerosis. Curr Opin Lipidol 16:307–315

71. Villarreal-Molina MT, Aguilar-Salinas CA, Rodriguez-Cruz M, Plengpanich W, Villard EF, Gilibert S, Lhomme M, Superville S, Tusie-Luna MT, Canizales-Quinteros S (2007) The ATP-binding cassette transporter A1 R230C variant affects HDL cholesteryl levels and BMI in the Mexican population: association with obesity and obesity-related comorbidities. Diabetes 56: 1881–1887

72. Kitjaroentham A, Hananantachai H, Tungtrongchitr A, Pououdong S, Tungtrongchitr R (2007) R219K polymorphism of ATP binding cassette transporter A1 related with low HDL in overweight/obese Thai males. Arch Med Res 38:834–838

73. Xu M, Zhou H, Wang J, Li C, Yu Y (2009) The expression of ATP-binding cassette transporter A1 in Chinese overweight and obese patients. Int J Obes 33:851–856

74. Frisdal E, Le Lay S, Hooton H, Poupel L, Olivier M, Alii R, Plengpanich W, Villard EF, Gilibert S, Lhomme M, Superville A, Miftah-Alkhair L, Chapman MJ, lingga-Thie GM, Venteclif N, Poitou C, Tordjman J, Lesnik P, Kontush A, Huby T, Dugail I, Clement K, Guerin M, Le Goff W (2015) Adipocyte ATP-binding cassette G1 promotes triglyceride storage, fat mass growth, and human obesity. Diabetes 64:840–855

75. Arakaki N, Kita T, Shibata H, Higuti T (2007) Cell-surface H+– ATP synthase as a potential molecular target for anti-obesity drugs. FEBS Lett 581:3405–3409

80. Xu M, Zhou H, Wang J, Li C, Yu Y (2009) The expression of ATP-binding cassette transporter A1 in Chinese overweight and obese patients. Int J Obes 33:851–856

81. Frisdal E, Le Lay S, Hooton H, Poupel L, Olivier M, Alii R, Plengpanich W, Villard EF, Gilibert S, Lhomme M, Superville A, Miftah-Alkhair L, Chapman MJ, lingga-Thie GM, Venteclif N, Poitou C, Tordjman J, Lesnik P, Kontush A, Huby T, Dugail I, Clement K, Guerin M, Le Goff W (2015) Adipocyte ATP-binding cassette G1 promotes triglyceride storage, fat mass growth, and human obesity. Diabetes 64:840–855

82. Arakaki N, Kita T, Shibata H, Higuti T (2007) Cell-surface H+– ATP synthase as a potential molecular target for anti-obesity drugs. FEBS Lett 581:3405–3409
83. Fukuda H, Iritani N (1999) Regulation of ATP citrate-lyase gene expression in hepatocytes and adipocytes in normal and genetically obese rats. J Biochem 126:437–444

84. Iannello S, Milazzo P, Belfiore F (2007) Animal and human tissue Na,K-ATPase in obesity and diabetes: a new proposed enzyme regulation. Am J Med Sci 333:1–9

85. Kola B, Christ-Cram M, Lolli F, Arndali G, Giacchetti G, Boscaro M, Grossman AB, Korbutis M (2008) Changes in adenosine 5'-monophosphate-activated protein kinase as a mechanism of visceral obesity in Cushing’s syndrome. J Clin Endocrinol Metab 93:4969–4973

86. Dole VP (1962) Insulin-like actions of ribonucleic acid, adenylic acid, and adenosine. J Biol Chem 237:2758–2762

87. Londos C, Cooper DM, Schlegel W, Rodbell M (1978) Adenosine analogs inhibit adipocyte adenylate cyclase by a GTP-dependent process: basis for actions of adenosine and methylxanthines on cyclic AMP production and lipolysis. Proc Natl Acad Sci U S A 75:5362–5366

88. Fredholm BB, Hjemdahl P (1979) Uptake and release of adenosine in isolated rat fat cells. Acta Physiol Scand 105:257–267

89. González-Nicolás J, Jiménez J, Page-Paüelas A, Zabala MT, Moreno FJ (1989) Regulation of lipid metabolism by dipiridamole and adenosine antagonists in rat adipocytes. Int J BioChem Physiol 21:883–888

90. Trost T, Schwabe U (1981) Adenosine receptors in fat cells. Identification by (3H)-N-(3-phenylisopropyl)adenosine binding. Mol Pharmacol 19:228–235

91. García-Sáinz JA, Toner ML (1985) Rat fat-cells have three types of adenosine receptors (R1, R2, and R3). Differential effects of pertussis toxin. Biochem J 232:439–443

92. Green A, Swenson S, Johnson JL, Partin M (1989) Characterization of human adipocyte adenosine receptors. Biochem Biophys Res Commun 163:137–142

93. Saggerson ED, Jamal Z (1990) Differences in the properties of A1-type adenosine receptors in rat white and brown adipocytes. Biochem J 269:157–161

94. Tatis-Kotsidis I, Erlanger BF (1999) A1 adenosine receptor of human and mouse adipose tissues: cloning, expression, and characterization. Biochem Pharmacol 58:1269–1277

95. Rice AM, Fain JN, Rivkees SA (2000) A1 adenosine receptor activation increases adipocyte leptin secretion. Endocrinology 141:1442–1445

96. Dhalla AK, Chisholm JW, Reaven GM, Belardinelli L (2009) A1 adenosine receptor: role in diabetes and obesity. Handb Exp Pharmacol 271:271–295

97. Vassaux G, Gaillard D, Mari B, Ailhaud G, Negrel R (1993) Differential expression of adenosine A1 and A2 receptors in preadipocytes and adipocytes. Biochem Biophys Res Commun 193:1123–1130

98. Gharibi B, Abraham AA, Ham J, Evans BA (2012) Contrasting effects of A1 and A2b adenosine receptors on adipogenesis. Int J Obes 36:397–406

99. Tatis-Kotsidis I, Erlanger BF (1999) Initiation of a process of differentiation by stable transfection of ob17 preadipocytes with the cDNA of human A1 adenosine receptor. Biochem Pharmacol 58:167–170

100. Johansson SM, Lindgren E, Yang JN, Herling AW, Fredholm BB (2008) Adenosine A1 receptors regulate lipolysis and lipogenesis in mouse adipose tissue-interactions with insulin. Eur J Pharmacol 597:92–101

101. Gharibi B, Abraham AA, Ham J, Evans BA (2011) Adenosine receptor subtype expression and activation influence the differentiation of mesenchymal stem cells to osteoblasts and adipocytes. J Bone Miner Res 26:2112–2124

102. Faulhaber-Walter R, Jou W, Mizel D, Li L, Zhang J, Kim SM, Huang Y, Chen M, Briggs JP, Gavrilova O, Schernmann JB (2011) Impaired glucose tolerance in the absence of adenosine A1 receptor signaling. Diabetes 60:2578–2587

103. Solomon SS, Turpin BP, Duckworth WC (1980) Comparative studies of the antilipolytic effect of insulin and adenosine in the perfused isolated fat cell. Horm Metab Res 12:601–604

104. Goren HJ, Hanif K, Dudley R, Hollenberg MD, Lederis K (1986) Adenosine modulation of fat cell responsiveness to insulin and oxytocin. Regul Pept 16:125–134

105. Green A (1987) Adenosine receptor down-regulation and insulin resistance following prolonged incubation of adipocytes with an A1 adenosine receptor agonist. J Biol Chem 262:15702–15707

106. Dong Q, Ginsberg HN, Erlanger BF (2001) Overexpression of the A1 adenosine receptor in adipose tissue protects mice from obesity-related insulin resistance. Diabetes Obes Metab 3:360–366

107. Crist GH, Xu B, Lanoue KF, Lang CH (1998) Tissue-specific effects of in vivo adenosine receptor blockade on glucose uptake in Zucker rats. FASEB J 12:1301–1308

108. Solomon SS, Schwartz Y, Rawlinson T (1987) Lipolysis in diabetic adipocytes: differences in response to growth hormone and adenosine. Endocrinology 121:1056–1060

109. Fredholm BB, Vernet L (1984) Accumulation and inactivation of adenosine by fat cells from hypothyroid rats. Acta Physiol Scand 121:155–163

110. Rapiejko PJ, Malbon CC (1987) Short-term hyperthyroidism modulates adenosine receptors and catalytic activity of adenylate cyclase in adipocytes. Biochem J 241:765–771

111. Bumgarner JR, Ramkumar V, Stiles GL (1989) Altered thyroid status regulates the adipocyte A1 adenosine receptor-adenylate cyclase system. Life Sci 44:1705–1712

112. Martin SE, Bockman EL (1986) Adenosine regulates blood flow and glucose uptake in adipose tissue of dogs. Am J Phys 250:F4973–F4977

113. Ohisalo JJ, Ranta S, Huhtaniemi IT (1986) Attenuated adenosine receptor-modulates glucose homeostasis and obesity. PLoS One 9:e40644

114. Wermeling C, Hasko G, Scarpignato C, Blandizzi C, Colucci R, Bernardini N, Segnani C, Ippolito C, Csoka B, Nemeth ZH, Benvenuti L, Giron MC, Caputi V, Marsilio I, Orso G, Farb MG, LeBrasseur N, Ravid K (2012) The A2b adenosine receptor modulates glucose homeostasis and obesity: an involvement of A2B adenosine receptors. Purinergic Signal 13:497–510
121. Eisenstein A, Ravid K (2014) G protein-coupled receptors and adipogenesis: a focus on adenosine receptors. J Cell Physiol 229:414–421

122. Escudero A, Carreño B, Retamal N, Celis C, Castro L, Aguayo C, Acurio J, Escudero C (2012) Elevated concentrations of plasma adenosine in obese children. Biofactors 38:422–428

123. Badillo P, Salgado P, Bravo P, Acuño J, Gonzalez MA, Oyarzum C, San Martin R, Escudero C (2016) High plasma adenosine levels in overweight pregnant women. Reprod Sci 23:210A

124. Sinha RA, Farah BL, Singh BK, Siddique MM, Li Y, Wu Y, Ilkayeva OR, Gooding J, Ching J, Zhou J, Martinez L, Xie S, Bay BH, Summers SA, Newgard CB, Yen PM (2014) Caffeine stimulates hepatic lipid metabolism by the autophagy-lysosomal pathway in mice. Hepatology 59:1366–1380

125. Csóka B, Koscsó B, Törö G, Kókai E, Virág L, Németh ZH, Pacher P, Bai P, Haskó G (2014) A2B adenosine receptors prevent insulin resistance by inhibiting adipose tissue inflammation via maintaining alternative macrophage activation. Diabetes 63:850–866

126. Guzman-Flores JM, Cortez-Espinoza N, Cortés-Garcia JD, Vargas-Morales JM, Cataño-Cañizalez YG, Rodriguez-Rivera JG, Portales-Perez DP (2015) Expression of CD73 and A2A receptors in cells from subjects with obesity and type 2 diabetes mellitus. Immunobiology 220:976–984

127. Lee CY (2015) Adenosine protects Sprague Dawley rats from high-fat diet and repeated acute restraint stress-induced intestinal inflammation and altered expression of nutrient transporters. J Anim Physiol Anim Nutr (Berl) 99:317–325
Author/s:
Burnstock, G; Gentile, D

Title:
The involvement of purinergic signalling in obesity

Date:
2018-06-01

Citation:
Burnstock, G. & Gentile, D. (2018). The involvement of purinergic signalling in obesity. PURINERGIC SIGNALLING, 14 (2), pp.97-108. https://doi.org/10.1007/s11302-018-9605-8.

Persistent Link:
http://hdl.handle.net/11343/253593

File Description:
Published version

License:
CC BY