Exploring the pharmacological mechanisms for alleviating OSA: Adenosine A2A receptor downregulation of the PI3K/Akt/HIF-1 pathway (Review)

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Abstract. Obstructive sleep apnea (OSA) is the most common type of sleep apnea, which leads to episodes of intermittent hypoxia due to obstruction of the upper airway. A key feature of OSA is the upregulation and stabilization of hypoxia-inducible factor 1 (HIF-1), a crucial metabolic regulator that facilitates rapid adaptation to changes in oxygen availability. Adenosine A2A receptor (A2AR), a major adenosine receptor, regulates HIF-1 under hypoxic conditions, exerting anti-inflammatory properties and affecting lipid metabolism. The present study explored the roles of A2AR in OSA regulation, specifically focusing on its effects via the PI3K/Akt/HIF-1 pathway. The findings enhance our understanding the pharmacological potential of A2AR in OSA management and suggest future research directions in exploring its clinical applications.

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Abbreviations: OSA, Obstructive sleep apnea; hsCRP, high-sensitivity C-reactive protein; HIF-1, hypoxia-inducible factor 1; LpL, lipoprotein lipase; FFA, free fatty acid; PPAR-α, peroxisome proliferator-activated receptor alpha; CoA, acetyl coenzyme A; ACLY, ATP citrate lyase; TAGs, triacylglycerols; AGPAT2, acylglycerol-3-phosphate acyltransferase 2; R, receptor

Key words: obstructive sleep apnea, adenosine A2A receptor, hypoxia-inducible factor 1, adenosine, PI3K/Akt

1. Introduction

Over the past two decades, the rapid aging of the population has led to a 30% increase in the prevalence of OSA (1). Epidemiological research estimates that ~936 million adults aged 30-69 globally are affected by OSA, with a prevalence of ~22% in males and 17% in females (2). The COVID-19 pandemic has further exacerbated the incidence of OSA (3), solidifying its status as a common sleep-related breathing disorder in clinical settings (4). OSA is characterized by recurrent obstruction of the upper airway during sleep, leading to periodic hypoxemia, disturbances in sleep continuity and increased respiratory effort. OSA is characterized by intermittent hypoxia during sleep, which activates HIF-1. This activation leads to oxidative stress, damaging cellular components such as DNA, proteins and lipids. The repeated cycles of hypoxia and subsequent oxidative stress create an environment conducive to genetic alterations that may drive the malignant transformation of lung cells (5). OSA triggers a systemic inflammatory response. The intermittent hypoxia and sleep fragmentation associated with OSA activate the sympathetic nervous system, releasing pro-inflammatory cytokines such as IL-6, TNF-α and high-sensitivity C-reactive protein (hsCRP). Chronic inflammation disrupts normal cellular functions and tissue homeostasis, fostering an immunosuppressive microenvironment in the lungs that allows cancer cells to evade immune surveillance and elimination. In addition, inflammatory mediators can directly stimulate cell proliferation and angiogenesis, both crucial for tumor growth and metastasis (6). OSA is linked to significant metabolic changes, disrupting normal lipid metabolism and leading to abnormal lipid profiles, while also affecting glucose metabolism, resulting in insulin resistance and elevated blood glucose levels. These metabolic alterations create a favorable environment for cancer cells to thrive, as hyperglycemia provides an abundant energy source and can stimulate growth factor production (7,8). Notably, OSA has been emerged as a new risk factor for lung cancer (9) and is known to disrupt normal lipid metabolism (10,11).

A hallmark molecular feature of hypoxia in OSA is the upregulation and stabilization of HIF-1 (12-14), a critical genomic mediator of cellular adaptation to low oxygen levels.

HIF-1 plays an essential role in regulating inflammatory pathways by modulating inflammatory responses, particularly preventing excessive reactions. In addition, it is associated with the regulation of genes such as MCAD and LCAD, both of which are involved in lipid metabolism. Recent research has highlighted the potential of A2A receptor (A2AR) blockade to disrupt the hypoxia/HIF-1-adenosine immunosuppressive axis, enhancing the effectiveness of cancer immunotherapy (15). Additionally, A2AR is indispensable for tissue protection under hypoxic conditions and for the regulation of lipid metabolism (16).

OSA is mainly mediated by intermittent hypoxia, which leads to low-grade inflammation (17). Adenosine receptors (ARs) have been shown to mitigate hypoxia-induced inflammation, particularly in the context of acute lung injury. During ischemic and hypoxic events, extracellular concentrations of adenosine, a crucial neurotransmitter involved in the immune response, can increase markedly, reaching levels ≤100 times higher than normal. The upregulation of adenosine and the induction of HIF-1 in response to hypoxia are directly linked, suggesting that HIF-1 activation through A2AR may contribute to anti-inflammatory responses and tissue protection. Although persistently elevated adenosine levels appear to trigger the release of inflammatory cytokines, A2AR is predominantly expressed in mature dendritic cells, leading to a reduction in pro-inflammatory cytokines (18). Previous studies have demonstrated that hypoxia activates adenosine signaling via A2AR (19-21). Additionally, the HIF-1/adenosine axis provides protective effects for the lungs during conditions such as acute respiratory distress syndrome, although it may contribute to inflammation and injury in chronic lung diseases (22).

Based on these findings, along with research showing that targeting the hypoxic-A2AR pathway can release anti-tumor T cells with immunosuppressive properties (23), A2AR has emerged as a critical receptor for mediating hypoxia-related tissue protection and regulating HIF-1 due to its anti-inflammatory effects (16). The molecular process by which A2AR regulates HIF-1 involves cytokine interactions and the activation of intracellular pathways such as Protein Kinase C (PKC), ATP-sensitive Potassium Channel (KATP), p38 MAPK and PI3K/Akt (24,25). These intricate networks present a promising therapeutic target for A2AR, particularly through the PI3K/Akt/HIF-1 pathway in the treatment of OSA (Fig. 1). The present study aimed to clarify the current prevalence of OSA and its associated hazards, including intermittent hypoxia, sleep disorders and its role as a risk factor for diseases such as lung cancer. It provided an in-depth exploration of the pharmacological mechanisms of A2AR in OSA, focusing on its effects on inflammation and lipid metabolism related to OSA through the PI3K/Akt/HIF-1 pathway.

2. Literature review

Interplay between OSA, inflammation and lipid metabolism. The oxidative stress caused by OSA has complex and multifaceted effects on lipid metabolism and cardiovascular health (26). In terms of lipid metabolism, the reactive oxygen species (ROS) produced by oxidative stress will attack the polyunsaturated fatty acids in the lipids, causing lipid peroxidation, such as the oxidation of low-density lipoprotein (LDL), which is more likely to be absorbed by the macrophages in the artery wall to form foam cells and start the formation of atherosclerotic plaque (27-29). Meanwhile, oxidative stress can alter the activity of enzymes involved in lipid metabolism, such as lipoprotein lipase (LpL), disrupting the balance between lipid synthesis and breakdown (30). It can also interfere with cholesterol transport and metabolism, affecting LDL receptors and related functions such as hydroxymethylglutaryl-CoA reductase, leading to lipid metabolism disorders (31). In terms of cardiovascular health, due to oxidative stress generated by OSA, LDL oxidation is the key to the development of atherosclerosis. Its accumulation in the arterial wall triggers inflammatory reaction, forms fat stripes and develops into plaques; and plaque rupture can cause thrombosis and cardiovascular events (32,33). In addition, oxidative stress damages endothelial cells, reducing their release of NO, leading to vasoconstriction, increased platelet aggregation and causing problems such as hypertension (34,35). In addition, oxidative stress activates inflammatory pathways and immune system, promotes the release of pro-inflammatory cytokines, intensifies the process of atherosclerosis and affects the function of immune cells (36-38). It also directly damages mitochondria in myocardial cells, affects energy production, leads to the decline of myocardial contractility and interferes with calcium ion regulation to damage myocardial function (39-41). It can be seen that oxidative stress caused by OSA has a significant effect on lipid metabolism and cardiovascular health.

The sleep disorder and intermittent hypoxia characteristic of OSA can trigger sympathetic excitation and inflammation, leading to vascular endothelial damage, altered coagulation function, abnormal lipid metabolism and disruptions in glucose homeostasis (42,43). The physiological consequences of OSA activate the sympathetic nervous system, induce oxidative stress and trigger systemic inflammatory responses (44). The systemic inflammatory cascade is thought to play a crucial role in both the onset and progression of OSA (45). Studies have shown that systemic inflammation associated with OSA is caused by the overflow of inflammatory cytokines from the upper airway mucosa to the bloodstream (46). Clinical studies have measured plasma concentrations of inflammatory markers in patients with OSA compared with control groups, revealing elevated levels of hsCRP, IL-6, TNF-α and pentraxin-3 among individuals with OSA (47). In addition, in a mouse experiment, the changes of atherosclerosis induced by intermittent hypoxia occurs with the increased expression of proinflammatory cytokines, chemokines and adhesion molecules, the increased migration of inflammatory cells and the expansion of the population of macrophages in the arterial wall (48,49). Other studies have also confirmed that the hypoxic state of OSA preferentially activated the pro-inflammatory factor NF-κB-mediated pathway, possibly caused by an inflammatory response to hypoxic exposure via adipocytes (50-52). This inflammatory shift is further associated with increased polarization of pro-inflammatory M1 macrophages, elevated expression of inducible nitric oxide synthase and worsening insulin resistance (53). This inflammatory response mechanism plays a crucial role in the pathogenesis of OSA-related cardiometabolic processes, ultimately leading to the development of cardiovascular disease and establishing a vicious cycle (54).

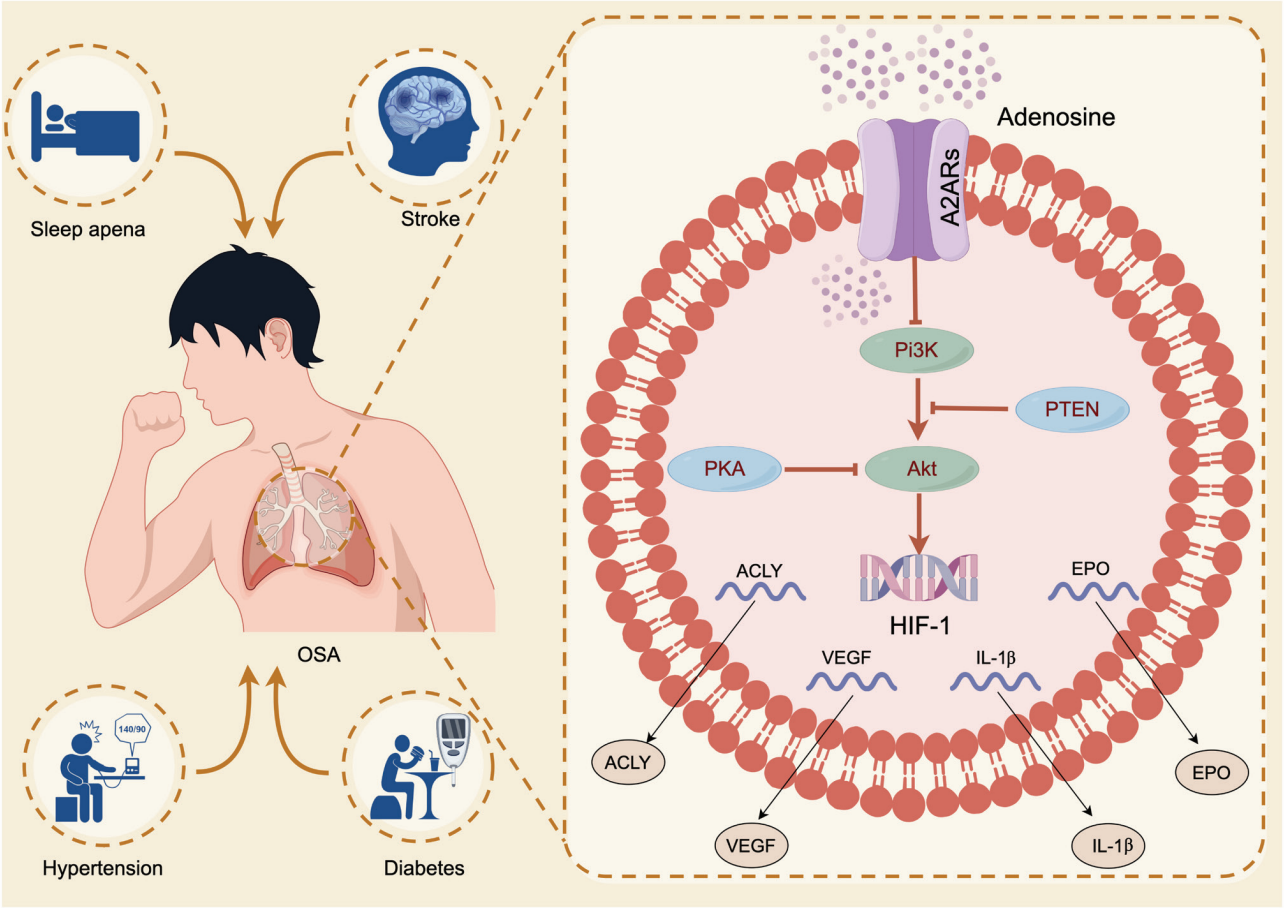

Figure 1. A2AR inhibits the PI3K/Akt/HIF-1 pathway in OSA to play an anti-inflammatory and regulatory role in lipid metabolism. patients with OSA tend to suffer from sleep apnea and have a higher risk of stroke, hypertension, diabetes and other diseases. A2AR plays a crucial role in this situation by inhibiting the PI3K/Akt/HIF-1 pathway, thereby exerting anti-inflammatory effects and regulating lipid metabolism. After activation, A2AR initiates a series of inhibitory effects on key signaling molecules. Specifically, A2AR activation leads to inhibition of PI3K, followed by inhibition of Akt. This inhibition of Akt subsequently leads to downregulation of HIF-1. Through this signaling cascade, some downstream targets are indirectly affected, including ACLY, a key enzyme in lipid metabolism, which is inhibited. In addition, VEGF is an important factor in angiogenesis and is also inhibited. In addition, the expression of pro-inflammatory cytokines such as IL-1 β and EPO is downregulated. This process emphasizes the crucial role of A2AR in regulating OSA inflammation and lipid metabolism by inhibiting the PI3K/Akt/HIF-1 pathway. A2AR HIF-1, hypoxia inducible factor-1; OSA, obstructive sleep apnea; ACLY, ATP citrate lyase; EPO, erythropoietin; PTEN, phosphatase and tensin homolog; PKA, protein kinase A.

Lipid metabolism plays a pivotal role in the development of OSA (55,56). In patients with OSA, the concentrations of triglycerides, total cholesterol and low-density lipoprotein cholesterol increase, while the levels of high-density lipoproteins cholesterol decrease accordingly (57). A genome-wide association study confirms the genetic link between OSA and triglycerides levels (58). Notably, dyslipidemia and OSA share common genetic loci, such as peroxisome proliferator-activated receptor (PPAR)-γ (59) or apolipoprotein E (APOE) polymorphism (60). PPAR-γ is a major regulator of several genes related to lipid metabolism, including LpL, which is downregulated by hypoxia in a HIF-1-dependent manner (61). The e4 variant of APOE (APOE-e4) is independently associated with abnormal lipid metabolism and can exacerbate OSA progression and cognitive dysfunction through age-related lipid bioenergetics dysfunction (62-64). Additionally, abnormal blood lipids can lead to insulin resistance. The increase in free fatty acid (FFA) levels caused by enhanced fat breakdown reduces insulin-mediated glucose uptake in skeletal muscle by disrupting insulin signaling (65). Furthermore, FFAs activate the NF-κB pathway, leading to the production of pro-inflammatory cytokines such as TNF-α, IL1β and IL-6 in peripheral tissues. Animal studies have indicated that intermittent hypoxia leads to pancreatic and insulin resistance in insulin-sensitive organs and adipose tissue (66,67). In addition, the hypoxic stress associated with OSA activates the hypothalamic-pituitary-adrenal axis, resulting in elevated cortisol levels, which ultimately contribute to insulin resistance (68). This hypoxic stress mechanism also contributes to the development of other diseases that induce insulin resistance through oxidative stress and pancreatic islet cell apoptosis via the TRB3 and phosphorylated JNK pathways, thereby contributing to the onset of type 2 diabetes and hyperlipidemia in OSA populations (69).

The role of Adenosine A2A receptor (A2AR) in inflammation and lipid metabolism. A growing body of evidence indicating that A2AR mediates potent anti-inflammatory responses in various cell types across multiple inflammation models (70,71) has spurred the development of A2AR agonists aimed at attenuating inflammation in disorders such as chronic obstructive pulmonary disease (COPD) and asthma (72). Research has

shown that A2AR agonists can modulate immune responses by reducing the infiltration of pro-inflammatory T cells into the central nervous system, an essential mechanism for controlling flare-ups in multiple sclerosis (73). In a mouse model of carrageenan-induced pleurisy, the administration of the A2AR agonist CGS 21680 markedly reduced neutrophil infiltration, nitric oxide levels, cytokine production, NF-κB expression and PARP activation (74). By contrast, A2AR knockout mice exhibited increased inflammation characterized primarily by enhanced activity of macrophages and neutrophils, along with elevated mucin production in the bronchial airways and increased levels of the chemoattractant proteins chemokine (C-X-C motif) ligand and MCP-1 (75,76). These findings suggest that A2AR plays a protective role in pulmonary inflammation. Furthermore, the positive allosteric modulator AEA061 enhances inosine-mediated A2AR activation, leading to inhibition of pro-inflammatory cytokines and chemokine production by splenic monocytes (77). Studies have also demonstrated that activating A2AR can restore cAMP levels in myocardial tissue while inhibiting the NF-κB signaling pathway, markedly improving cardiac dysfunction associated with cirrhosis and exerting both anti-inflammatory and anti-apoptotic effects (78). In the context of psoriasis, A2AR activation inhibits M1 macrophage activation through the NF-κB-KRT16 pathway, which is crucial for initiating both innate and adaptive immunity (75). Additionally, inhalation of A2AR agonists has shown therapeutic potential for patients suffering from COVID-19-related inflammatory lung disease (79). These findings collectively highlight the therapeutic promise of A2AR modulation in various inflammatory conditions.

A2A receptors play a crucial role in regulating various physiological and pathological processes in adipocytes (80). Activation of A2AR can induce anti-inflammatory effects that are essential for the survival of beta cells, enhance insulin secretion, reduce food intake and promote thermogenesis and fat breakdown (81). For instance, studies have demonstrated that A2AR agonists, such as CGS21680 and PSB-0777, activate lipolysis in both humans and mice (82-84), improve glucose tolerance and protect C57Bl/6 mice from diet-induced obesity, highlighting the promising thermogenic effects of adenosine. Further investigations showed that the A2AR agonist CGS21680, when injected into Swiss strain mice fed a high-fat diet, produced similar effects on glucose homeostasis without significant changes in weight or obesity rates, while also decreasing certain inflammatory markers (85). Additionally, A2AR signaling has been linked to the regulation of CD8+ T cell responses through the coordination of glutathione metabolism (86). Notably, stimulation of A2AR expression on macrophages has been shown to release cholesterol, which inhibits the formation of foam cells (84). The structural dynamics of A2AR are influenced by its phospholipid environment and cholesterol, resulting in a propensity to bind lipid isoform modulators (87). In therapeutic applications, liposome treatments combined with adenosine or specific A2AR agonists have markedly improved joint scores in post-traumatic osteoarthritis rats and mice with high-fat diet-induced osteoarthritis (88). In addition, research indicates that the loss of A2AR in macrophages and liver cells leads to increased inflammation, elevated expression and transcriptional activity of SREBP1c and enhanced adipogenic events, exacerbating the severity of non-alcoholic fatty liver disease (89). Studies have also shown that deficiencies in C3a and C5a receptors can promote adipocyte browning and reduce diet-induced obesity by activating the inosine/A2AR pathway (90,91). Lastly, ongoing research and development efforts are focusing on dual-active adenosine A2A/A3 receptor ligands, such as LJ-4378, which have demonstrated anti-obesity effects and offer new treatment strategies for obesity and related metabolic diseases (92).

3. Mechanistic pathways

A2AR's Anti-inflammatory mechanism via PI3K/Akt/HIF-1 pathway. A2AR plays a significant role in exerting anti-inflammatory and tissue-protective effects, particularly in hypoxic environments, by modulating the PI3K/Akt/HIF-1 signaling pathway. OSA is associated with chronic inflammation and tissue remodeling, leading to progressive declines in pulmonary function (26). In OSA mouse models, a notable accumulation of proinflammatory M1-like macrophages, characterized by heightened CD36 expression, has been observed in the aorta, alongside elevated levels of inflammation-related transcription factors (93). During intermittent hypoxia, OSA triggers the release of proinflammatory factors, including TNF, CRP, IL-6 and IL-8, while increased NF-κB and TNF-α levels have been linked to OSA-related daytime sleepiness (94-96).

In this context, A2AR mitigates inflammation through the PI3K/Akt pathway. Notably, while serotonin receptor inhibition can limit the efficacy of intermittent hypercapnic-hypoxia therapies, blocking the A2AR pathway has demonstrated enhanced respiratory recovery (97). Additionally, A2AR influences the regulation of apnea, particularly in conditions such as apnea of prematurity, where its effects are mediated by caffeine inhibitors (98). The flavonoid compound Baicalin has also been shown to alleviate chronic hypoxia-induced pulmonary hypertension by activating the A2AR-induced Stromal Cell-Derived Factor 1(SDF-1)/C-X-C Chemokine Receptor Type 4 (CXCR4)/PI3K/Akt signaling pathway (95). In cases of liver ischemia/reperfusion injury, inhalation of high hydrogen concentrations has demonstrated ameliorative effects via the A2AR-mediated PI3K/Akt pathway (94).

Research has confirmed that A2AR inhibits the PI3K/Akt signaling pathway, which is essential for limiting inflammation and promoting anti-inflammatory responses in TLR-induced macrophages (99,100). This pathway negatively regulates TLR and NF-κB signaling in macrophages (101,102). The Bu-Shen-Fang-Chuan formula, commonly prescribed for COPD in China, has been shown to reduce TNF-α and IL-6 levels in bronchoalveolar fluid and serum, curbing cigarette smoke-induced inflammation, partially mediated through the PI3K/Akt pathway (103). A2AR also modulates HIF-1 expression; studies indicate that both Akt and HIF-1 protein levels increase in human mesenchymal stem cells in response to hypoxia, with Akt expression peaking earlier than HIF-1 (104,105). The use of PI3K inhibitors such as LY294002 and dual PI3K/mTOR inhibitors such asNVP-BEZ235 suppresses Akt activation, as well as HIF-1 and VEGF expression induced by hypoxia. Wortmannin, an Akt inhibitor, also

inhibits HIF-1 expression at the protein level without affecting mRNA levels (104).

Activation of specific HIF-1 target genes can induce proinflammatory genes, notably IL-1β (106-108). However, in hypoxic macrophages, the activation of the PI3K/Akt pathway upregulates TLR4 expression through HIF-1 activation (109). The HIF-1 dimer then binds to the hypoxia response element in the promoter region, initiating the expression of over 100 genes involved in hypoxic adaptation, including those that promote VEGF and EPO, which promote angiogenesis and erythropoiesis (110,111). HIF-1 also regulates NF-κB, leading to increased levels of cytokines such as IL-8 (112,113), while IL-17 levels correlate with OSA severity (114). Therefore, A2AR inhibits the phosphorylation of PI3K and Akt, indirectly downregulating HIF-1 (115). This mechanism drives the reduction of immune and inflammatory responses, thereby protecting tissues in hypoxic conditions (116).

A2AR's lipid metabolism mechanism via PI3K/Akt/HIF-1 pathway. A2AR plays a significant role in regulating lipid metabolism through the PI3K/Akt/HIF-1 pathway (115). Activation of A2AR inhibits the phosphorylation of PI3K and Akt, crucial steps in lipid metabolism regulation. Notably, HIF-1, activated downstream of this pathway, promotes lipid droplet accumulation and fatty acid reprogramming under hypoxic conditions.

Endogenous cannabinoids are naturally occurring lipids that bind to cannabinoid receptors and play a crucial role in regulating metabolism, particularly in energy balance, fat storage and glucose homeostasis (117). In the context of OSA, these cannabinoids can contribute to metabolic disorders and exacerbate conditions such as obesity, insulin resistance and type 2 diabetes. Elevated levels of endogenous cannabinoids, particularly anandamide and ethanolamine, have been observed in patients with OSA, along with increased levels of saturated fatty acids and n-3 fatty acids, which can enhance appetite and promote fat accumulation, both of which are linked to sleep quality (118,119). Additionally, patients with OSA often exhibit elevated levels of adenosine, adrenaline, norepinephrine and aldosterone, further complicating their metabolic profiles (120). In another animal study, intermittent hypoxia was demonstrated to mediate the expression of hypoxia-inducible factor 1αin pancreatic β-cells. This leads to increased reactive oxygen species and ultimately resulted in insulin resistance (12).

A2AR activation not only stimulates lipolysis and thermogenesis but also enhances the browning of adipose tissue. Specifically, A2AR activation enhances reverse cholesterol transport from peripheral tissues back to the liver, aided by macrophages, which helps prevent their transformation into foam cells (121). Furthermore, supplementation with adenosine has been shown to increase A2AR protein levels and enhance the expression of key lipolytic genes, such as ATGL and HSL, in adipose tissue, thereby providing a protective effect against diet-induced obesity. Additionally, elevated levels of inflammatory factors in the upper and lower airways of hypoxic mice, combined with the detrimental cycle between OSA and airway inflammation, contribute markedly to insulin resistance (122).

Metabolic changes in patients with OSA include increased lactic acid and specific fatty acids, such as arabinose and glyceraldehyde (123). Additionally, genes involved in cholesterol metabolism, such as malic enzyme and acetyl-CoA carboxylase, are impaired due to hypoxia associated with OSA (124,125). The role of HIF-1 in lipid uptake is crucial, as it induces the expression of fatty acid binding proteins (FABP3 and FABP7) and adipocyte differentiation-related protein (ADRP), necessary for lipid droplet formation. HIF-1 also promotes fatty acid synthase expression, enhancing fatty acid synthesis while inhibiting the oxygen-dependent stearoyl-CoA desaturase enzyme, which can affect cellular membrane integrity (126).

Furthermore, HIF-1 targets ATP citrate lyase (ACLY), which is upregulated in hypoxic tumor cells, influencing fatty acid biosynthesis and acetyl-CoA production. For example, in goose liver cells, insulin regulates lipid deposition through the PI3K/Akt/mTOR pathway, while HIF-2α upregulation under hypoxia activates lipid synthesis, promoting the progression of non-alcoholic fatty liver disease and hepatocellular carcinoma (127).

The synthesis of fatty acids leads to increased production of neutral triacylglycerols (TAGs), stored as lipid droplets for energy. HIF-1 induces key enzymes such asAGPAT2 and lipin-1, which facilitate LD accumulation and viability, also contributing to chemoresistance in hypoxic environments. The products of AGPAT2 can further be utilized for new membrane formation. Under hypoxia, unsaturated fatty acid oleate is preferentially released from TAGs into the phospholipid pool to balance saturated lipid accumulation (128). In addition, lipid signaling molecules such as sphingosine kinase 1 can stimulate HIF-1 activity. In summary, A2AR regulates dyslipidemia in OSA through the PI3K/Akt/HIF-1 pathway, highlighting its potential as a therapeutic target in managing lipid metabolism disorders.

4. Discussion

Adenosine, deriving from ATP degradation, mediates its physiological effects through four distinct subtypes of G-protein-coupled receptors named A1R, A2AR, A2BR and A3R. Previous research has shown that hypoxia and inflammation can lead to the accumulation of extracellular ATP/ADP due to the cell membrane damage (129). Consequently, it is important to investigate the pharmacological effects of adenosine receptors in the context of OSA (129-135) (Table I). During sleep apnea, adenosine is released as a response to hypoxia, which can promote sleep and reduce apnea episodes through the activation of A1R/A3R (131) and the inhibition of A2AR (136). High doses of caffeine, a well-known adenosine receptor antagonist, may provide an improved means of apnea management (137). In addition, adenosine plays a role in sensitizing the carotid body during intermittent hypoxia (134). Caffeine has been shown to decrease both baseline and hypoxia-induced (5% O_2) chemosensory activity in the carotid sinus nerve of rats with intermittent hypoxia (134). Therefore, blocking adenosine receptors and modulating adenosine metabolism in the carotid body could aid in the management of sleep apnea (135). Other research indicates that increased expression of A2AR during hypoxia may help protect cells from the damaging effects of low oxygen levels (138). Conversely, A2AR deficiency has been linked to airway inflammation and

Table I. Adenosine receptors play different roles during hypoxia conditions.

Adenosine receptors	Functions	Molecular changes	Signaling pathways	(Refs.)
A1R	Anti-inflammatory	iNOS↓ GLUT1↓ HK2↓	MAPK	(129,131)
A2AR	Tissue healing neuroprotection lipid metabolism regulation vasodilatation anti-inflammatory	GLUT1↑ iNOS↑ HIF-1↑ VEGF↑ IL-1β↑ EPO↑	PI3K/Akt cAMP/PKA/ CREB PKC	(7,15,16)
A2BR	Tissue protection	iNOS↑ p38↑ TNF-a↓ VEGF↑ HIF-1↑ IL-8↑	p38MAPK	(132,133)
A3R	Anti-inflammatory	iNOS↓ VEGF↓ GLUT1↓ HK2↓	MAPK	(134,135)

↑, enhancement; ↓, decreased. iNOS, Inducible nitric oxide synthase; GLUT1, glucose transporter 1; HK2, hexokinase 2; EPO, erythropoietin; HIF-1, hypoxia inducible factor-1; VEGF, vascular endothelial growth factor; IL-1β, interleukin 1 beta; p38, p38 mitogen-activated protein kinase; TNF-α, tumor necrosis factor alpha; IL-8, interleukin 8; MAPK, mitogen-activated protein kinase; cAMP, cyclic adenosine monophosphate; PKC, protein kinase C; CREB, cAMP response element-binding protein.

hyperresponsiveness (139). Mirtazapine, a prescription drug that acts as an A2AR antagonist, appears to be ineffective in markedly improving sleep apnea and may even contribute to weight gain, potentially worsening OSA (140). There is speculation that appropriate use of A2AR agonists could inhibit the PI3K/Akt pathway, indirectly reducing the expression of HIF-1 and pro-inflammatory cytokines while enhancing lipid metabolism. Notably, the inhibitory effect of A2AR activation on respiratory drive appears to vary with age. Thus, further research is needed to clarify the pharmacological effects of A2AR in the treatment of OSA and clinical trials should be conducted to explore its potential therapeutic applications.

Intermittent hypoxia in OSA can contribute to inflammation-related cardiac metabolic diseases, with vascular inflammation and remodeling linked to increased leukocyte-endothelial cell interactions and T cell activation. While HIF-1 is expressed in unstimulated cells, NECA (an A2AR agonist) does not enhance HIF-1 mRNA expression in the absence of LPS stimulation. This indicates that LPS-induced A2AR expression crucial for the LPS/NECA-mediated upregulation of HIF-1. The NF-κB pathway is influenced by HIF-1, acting as a potent inflammatory activator that drives the release of TNF, IL-6, IL-8 and C-C motif chemokine ligand 2/monocyte chemoattractant protein-1 (MCP-1). Although OSA is hypothesized to elevate ROS levels, more evidence is necessary to fully support this (141). HIF-1 regulates the expression of various factors, including EPO, VEGF, inducible nitric oxide synthase and heme oxygenase, along with molecules involved in glucose metabolism, mitochondrial function and cellular adaptation to intermittent hypoxia during oxidative stress. Inhibition of HIF-1 reduces the expression of VEGF and Bcl2 interacting protein 3, thereby protecting against delayed cell death. Notably, the protective effects mediated by the PI3K/Akt and HIF-1 pathways may be reversed in the hypoxic microenvironment of cancer, highlighting the regulatory role of A2AR on HIF-1 as a potential therapeutic target for OSA. Intermittent hypoxia can downregulate endothelial nitric oxide synthase and enhance endothelin-1 production through the Erk1/2 pathway, while also increasing phosphorylation via the PI3K/Akt pathway, leading to endothelial dysfunction (142). Beyond the influences of inflammation and lipid metabolism, further investigation into the pharmacological effects of the PI3K/Akt/HIF-1 pathway on glucose metabolism, mitochondrial function and cell apoptosis in relation to OSA is warranted.

In addition, repeated exposure to hypoxic conditions can lead to significant alterations in gene transcription and post-translational protein modifications, resulting in changes in plasma concentrations of lipids, proteins and other biological compounds (143). The advent of large metabolomic datasets has enabled the use of metabolites as biomarkers for disease progression (46). Research indicates that the pathogenesis of cardiovascular disease and metabolic complications associated with OSA may be markedly linked to specific metabolic changes. Mendelian randomization studies have identified associations between OSA and >10 metabolites, including the plasma metabolite 3-Dehydrocarnitine. The biosynthetic pathway of valine, leucine and isoleucine is implicated in OSA pathogenesis (144). However, there is a lack of exploration into how inflammation alters metabolic pathways in the development of OSA and its complications. Therefore, understanding the involvement of metabolites in inflammation is critical for unraveling OSA pathogenesis and identifying potential therapeutic targets (145).

In the clinical management of OSA, a variety of treatment approaches are currently available, each with its own distinct characteristics and implications. These treatment modalities primarily encompass continuous positive airway pressure (CPAP), oral appliance therapy, surgical interventions, lifestyle changes, drug treatment and hypoglossal nerve stimulation. CPAP is effective for moderate to severe OSA, improving symptoms and quality of life, but requires maintenance and can be uncomfortable (146,147). Oral appliances are portable and work well for mild OSA, though less effective for

Table II. Comparison of Different Treatments for Obstructive Sleep Apnea.

Treatment Method	Principle	Advantages	Disadvantages	Treatment duration	Applicable criteria	Contraindications
CPAP	Positive ventilation to pressure keep airway open	Improves symptoms, reduces risks, widely applicable	Discomfort, difficult to adhere, needs maintenance	Long-term use every night, months to lifetime	Moderate to severe and with complications	Severe lung diseases, facial trauma, unable to cooperate
Oral appliance	Adjusts mandible or tongue to expand airway	Portable, some tolerance, effective for mild	Limited for moderate to severe, tooth discomfort, needs adjustment	Long-term wear every night, months to years, regular review	Mild or moderate to severe patients intolerant to CPAP, mandibular retraction	Severe dental diseases, temporomandibular disorders, allergy
Surgery	Remove excess tissue in pharynx to expand airway	Some long-term efficacy, suitable for anatomical abnormalities	High risk, long recovery, not for all	Preoperative preparation, surgery, recovery, months to years, possible lifelong follow-up	Anatomical abnormalities and poor response to conservative treatment	Severe cardiopulmonary diseases, coagulation disorders, uncontrolled underlying diseases, mental disorders
Lifestyle changes (such as weight loss, smoking and alcohol cessation)	Weight loss to improve airway compression and breathing	No side effects, beneficial for health, adjunctive treatment	Slow effect, insufficient for moderate to severe alone	Long-term adherence, 6 months - 2 years for weight loss	All patients, overweight and with bad habits	Adjustment under doctor's guidance in special cases
Drug treatment (such as modafinil, acetazolamide	Adjust neurotransmitters to improve breathing	Some effectiveness, adjunctive treatment	Limited effect, side effects	Weeks to months, regular review	Mild or with abnormal nerve regulation	Allergy, liver and kidney insufficiency, glaucoma
Hypoglossal nerve stimulation	Stimulates hypoglossal nerve to prevent tongue prolapse	Minimally invasive, some tolerance, an option	Need to adjust parameters, long-term effect to be observed, high price	Long-term stimulation every night, years, regular review	Moderate to severe with tongue prolapse and poor response to conservative treatment	Nerve disorders, mental disorders, allergy

CPAP, continuous positive airway pressure.

severe cases and may cause discomfort (148). Surgical options, such as uvulopalatopharyngoplasty, offer long-term benefits for patients with clear anatomical issues but carry risks and long recovery times (149,150). Lifestyle changes complement treatments with no major side effects, though their impact is gradual (151). Drug treatments may help mild OSA but are generally limited (152-154). Hypoglossal nerve stimulation is a less invasive alternative to CPAP or surgery, with good tolerance but concerns over cost and long-term efficacy (155). Consequently, given the diverse nature of these treatment options for OSA, it becomes of utmost importance to conduct a comprehensive comparison of different treatments for OSA (Table II) Such a comparison can provide valuable insights for healthcare providers and patients alike, enabling them to

make more informed decisions regarding the most appropriate treatment approach based on individual circumstances (149).

The relationship between OSA and lipid profiles remains a complex area of study. While some clinical evidence indicates that CPAP devices can improve certain aspects of dyslipidemia by alleviating apnea-hypopnea, much of this data are derived from observational studies. CPAP may lead to reductions in inflammatory cytokines and inhibit lipid peroxidation, as evidenced by decreased levels of malondialdehyde and endothelial lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) (156). However, its effect on oxidized low-density lipoprotein (oxLDL) levels in patients with OSA with comorbidities appears negligible after one year of treatment (157). By contrast, randomized controlled trials assessing the effects of CPAP on lipid metabolism have produced inconclusive results, with two meta-analyses yielding conflicting evidence (57). Large population-based studies generally highlight a relationship between OSA and dyslipidemia; however, they often fail to adequately control for confounding factors such as diet, exercise and the use of lipid-lowering medications, introducing potential biases. Thus, there is a pressing need for new clinical studies with larger sample sizes that account for these variables. Such research should also facilitate the screening of comorbid conditions for more timely interventions, ultimately enhancing patient outcomes.

The use of A2AR agonists presents several limitations and challenges that must be carefully addressed. These agonists may exhibit non-specific effects on other adenosine receptors, potentially leading to side effects, so enhancing their specificity and selectivity is crucial. Additionally, the pharmacological efficacy and pharmacokinetics of A2AR agonists can impact their clinical application, making it essential to optimize drug structure to improve bioavailability, stability and half-life (158). This optimization could enhance efficacy and reduce dosing frequency, contributing to more convenient and effective treatment. Safety and tolerability are paramount, as long-term use of A2AR agonists may result in adverse reactions, particularly in the cardiovascular, digestive and nervous systems. Comprehensive evaluations of safety and tolerability are necessary to establish appropriate dosing and treatment plans (159). Furthermore, given the complex and multifactorial nature of inflammatory diseases, relying solely on A2AR agonists may yield limited effectiveness (160). Exploring combination therapies with other drugs represents a promising avenue for future research, aiming to enhance overall treatment efficacy while minimizing side effects. In addition, individual patient responses to A2AR agonists can vary markedly, making it vital to understand each patient's genetic background, disease subtype and immune status for developing personalized treatment plans, which could substantially improve treatment effectiveness and reduce adverse reactions (161).

The present study made significant contributions to our understanding of OSA and its associated aspects, proving valuable to the scientific community. It explored various elements related to OSA, examining traditional mechanisms such as intermittent hypoxia and sleep disruptions while focusing on adenosine receptors, particularly A2AR. By integrating the effects of A2AR on inflammation, lipid and glucose metabolism, mitochondrial function and cell apoptosis through the PI3K/Akt/HIF-1 pathway, the current review presented a comprehensive view of the complex interactions within OSA. This holistic understanding aids researchers in developing more targeted hypotheses and experimental designs, revealing previously overlooked connections among physiological processes. In contrast to earlier reviews that primarily addressed basic OSA pathophysiology and the effects of intermittent hypoxia on vascular endothelial damage and systemic inflammation (162), the present review offered a deeper analysis of the molecular mechanisms of A2AR and broader implications. It built on this foundation by exploring the regulatory role of A2AR in the PI3K/Akt/HIF-1 pathway and its consequences for inflammation and lipid metabolism, providing a more nuanced perspective on OSA. In addition, the present review emphasized the intricate interplay between inflammation and metabolic changes in OSA. It highlighted how specific metabolites contribute to OSA pathogenesis and how inflammation affects metabolic pathways, addressing an area less explored in prior research. This focused approach encourages further investigation into these interactions, potentially leading to the identification of novel biomarkers for early diagnosis and new therapeutic targets for more effective treatments. By contrast, another previous review centered on the relationship of OSA with cardiovascular diseases, examining how OSA-induced changes in blood pressure, lipid profiles and endothelial function contribute to cardiovascular morbidity (57). While this is an important area, it did not comprehensively address the role of metabolites or the interaction between inflammation and metabolism as our review does. By specifically focusing on these aspects, the present study underscored the significance of understanding metabolite involvement in inflammation, which could reveal new insights into the pathogenesis of OSA and therapeutic opportunities. Additionally, the present review discussed the potential clinical applications of A2AR agonists in treating inflammatory diseases beyond COPD and asthma, highlighting their limitations and challenges. By broadening the scope of the clinical utility of A2AR, it provided critical insights for researchers and clinicians, guiding future research and optimizing the use of A2AR agonists in various disease contexts. By contrast, a previous review primarily focused on traditional OSA treatment options, such as CPAP, oral appliances and surgery, without exploring the emerging potential of A2AR agonists (163). In conclusion, the present review stands out for its comprehensive integration of multiple mechanisms, its focus on the interplay between inflammation and metabolism and its exploration of clinical applications and limitations. Compared to earlier reviews, it offers a more detailed and multi-faceted perspective, advancing knowledge in the field of OSA and providing valuable resources for future research and clinical applications.

5. Future directions

Although the significance of inflammation and metabolic changes in OSA is recognized, there are still several areas that require further research. First, the mechanism of A2AR in OSA needs deeper exploration. This includes understanding its effect on different cell types and signaling pathways. Additionally, the effects of A2AR on different age groups and its influence on respiratory drive demand further investigation.

Exploring the potential value of A2AR agonists in treating OSA and determining the optimal dosage and treatment duration is crucial. Large-scale randomized controlled trials should be conducted to evaluate the effectiveness of CPAP and other treatment methods on various aspects of patients with OSA. Currently, the effect of CPAP on lipid metabolism is controversial and most existing studies are observational, lacking large-scale randomized controlled trials to determine its exact efficacy. Finally, by employing modern technologies such as metabolomics and genomics, further research can be carried out on the detailed interaction mechanisms between inflammation and metabolism in OSA. Studying OSA-related metabolites and biomarkers can improve the accuracy of early diagnosis, enable timely intervention, reduce the occurrence of complications and help discover new therapeutic targets. However, the role of specific metabolites in the pathogenesis of OSA still needs further clarification. In summary, further research is needed in multiple aspects of OSA, including the mechanism of A2AR, the effectiveness of treatment methods such asCPAP and the role of metabolites in pathogenesis. These efforts will enhance our understanding of OSA and lead to improved diagnosis and treatment strategies.

6. Conclusion

OSA is intricately linked to inflammation and dyslipidemia, conditions often exacerbated by OSA-related comorbidities. The present study delved into the molecular mechanisms underlying OSA, emphasizing the role of A2AR in modulating these processes. It found that A2AR exerts an inhibitory effect on the PI3K/Akt/HIF-1 pathway, markedly influencing inflammation and lipid metabolism associated with OSA. This supports the hypothesis that adenosine receptors are the main molecular process drivers of OSA onset. Furthermore, A2AR activation appears to stimulate key factors such as Akt and HIF-1, which are known to play roles in the regulation of intermittent hypoxia. However, the complexity of interactions among these factors suggests that further investigation is warranted. The potential of A2AR as an anti-inflammatory agent and a regulator of lipid metabolism, particularly through its influence on the PI3K-Akt-HIF-1 pathway under hypoxic conditions, is promising. Additionally, non-selective adenosine receptor antagonists, such as caffeine, have been shown to improve sleep apnea symptoms, indicating that A2AR may serve as a viable target for pharmacological interventions aimed at alleviating inflammation and dyslipidemia associated with OSA. Future research should explore the implications of OSA-related comorbidities, particularly the pathways involved in OSA-associated dyslipidemia. These insights could illuminate the cellular processes driving OSA and aid in identifying potential therapeutic targets for prevention and treatment.

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Availability of data and materials

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Authors' contributions

NM wrote the first draft of the manuscript. PL prepared the review tables and figures. NL, YH, NM and LK were responsible for critical revisions of the article. YH contributed to the acquisition of funds. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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