DOI: 10.53469/jcmp.2024.06(11).48

Research Progress on Insulin Resistance Mechanism of Intermittent Hypoxia in Skeletal Muscle

Jiwu Li[1], Xuefeng Shi[2,*]

[1]Graduate School of Qinghai University, Xining, Qinghai, 810000, China
[2]Department of Respiratory and Critical Care Medicine, Qinghai Provincial People's Hospital, Xining, Qinghai 810000, China
Correspondence Author

Abstract: ***Sleep apnea syndrome (SAS) is a common clinical disease, which is characterized by repeated episodes of apnea or hypoxia, leading to intermittent hypoxia (IH) and sleep awakening. Many clinical studies show that diabetes is the main complication of SAS. Previous studies have shown that nocturnal IH is the main complication of SAS. Previous studies have shown that nocturnal IH is the main cause of hyperglycemia in SAS patients. Therefore, IH is closely related to the pathogenesis of type 2 diabetes, but the pathophysiology and molecular structure of IH are not well understood. Therefore, IH is closely related to the pathogenesis of type 2 diabetes, but the pathophysiology and molecular mechanism of abnormal glucose metabolism induced by IH have not been fully revealed. In healthy people, skeletal muscle accounts for 70%-80% of IH. In healthy people, skeletal muscle accounts for 70%-80% of glucose intake stimulated by insulin, which plays a key role in regulating glucose homeostasis. IR in skeletal muscle has long been considered as a characteristic of type 2 diabetes. IR in skeletal muscle has long been considered as a characteristic of type 2 diabetes mellitus and plays a major role in the pathogenesis of the disease. This review provides a new idea for the role of IH in the disease. This review provides a new idea for the role of IH in the pathological process of diabetes by expounding the regulation of IH on skeletal muscle, and brings a new dawn for the treatment of SAS complicated with diabetes.***

Keywords: Sleep apnea syndrome, Intermittent hypoxia, Insulin resistance, Type 2 diabetes, Skeletal muscle**.**

1. Introduction

Sleep apnea syndrome (SAS) is a sleep apnea disorder in which recurrent partial or complete obstruction of the upper airway occurs during sleep [1]. SAS is characterized by recurrent nocturnal obstruction of the upper airway, which may lead to a range of physiological effects, including fluctuating intrathoracic pressure, decreased sleep quality, hypercapnia, and intermittent hypoxia (IH) [2]. These pathophysiologic changes may lead to chronic disease in multiple organs, including cardiovascular disease, cerebrovascular disease, decreased immune function, and metabolic abnormalities (e.g., insulin resistance, pancreatic β-cell dysfunction, and elevated free fatty acid levels).

Many clinical studies have shown thatdiabetes mellitus is a major complication of SAS.SAS is more prevalent in patients with cardiovascular risk factors, such as type 2 diabetes mellitus (T2DM), hypertension, or other diagnosed cardiovascular diseases, with prevalence rates ranging from 30% to 60% in these patients [3]. Some foreign studies have shown that developed rodent cell culture models, IH patterns mimicking the saturation profile of blood O2 during SAS provide important insights into the molecular mechanisms of SAS-related complications [4]. IH is the symbol of SAS, which not only plays an important role in the pathogenesis of SAS, but also reduces blood sugar control and insulin resistance in patients with T2DM and diabetes-related complications. [5]. IH is known to enhance through insulin resistance (IR) Sympathetic tone, pro-inflammatory state and elevated cytokine levels may also lead to a severe IR state in SAS patients, which raises blood glucose levels [6]. However, as of now, the pathophysiology and molecular mechanisms of IH-induced abnormalities in glucose metabolism are not fully understood. Therefore, clarifying the pathogenesis of IH in patients with diabetes mellitus combined with SAS is very important for finding new therapeutic ideas and approaches for T2DM. In this paper, the current understanding of pathophysiology and molecular mechanism induced by IH is reviewed.

2. Evidence for IH-induced IR

Previous studies have shown that IH and sleep architecture disruption are the main causes of elevated blood glucose in patients with Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS). Among them, IH can induce the occurrence of hyperglycemia and IR [7]. Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia due to multiple etiologies and caused by defects in insulin secretion and/or utilization. Among the most prominent pathological features of T2DM are IR and defective β-cell function.IR refers to the reduced sensitivity to insulin action in the target organs of insulin action (mainly liver, muscle and adipose tissue). Skeletal muscle is one of the main target organs of insulin action, which plays an important role in maintaining the dynamic balance of glucose in the body, and it is also one of the earliest and most important parts of the body where occurs in the susceptible population of insulin [8]. Studies have shown that IH can regulate IRin skeletal muscle [9]. Dysfunction of pancreatic islet β-cells caused by oxidative stress and inflammatory factors is also thought to be involved in the pathology of IH-induced glucose intolerance. Other organs, such as the skeletal muscle, the central nervous system, and gastrointestinal tract are also thought to be involved in IH-induced glucose intolerance and IR [7].

3. The Way IH Induces IR in Skeletal Muscle

3.1 Abnormal Myokine Expression/Secretion

Myokines are a large group of muscle-secreted proteins, peptides and metabolites that have been reported to have endocrine activity, most of which are physical activity and

secreted in response to other endocrine signals [10]. Myokines are a collective term for cytokines secreted by skeletal muscle and released from skeletal muscle during muscle contraction [11] IH has been shown to up-regulate a number of myokines, such as IL-8, Osteonectin (also known as secretory protein is acidic and rich in cysteine) and myosin (also known as C1q/TNF-related protein 15 or erythropoietin), which are all involved in inflammation and glucose metabolism through transcriptional activation of the myokine genes in both human and mouse muscle cells [12] The up-regulation of actin induced by IH may be an important research goal to understand the causes and ways of inducing glucose intolerance. These myokines are autocrine/paracrine and endocrine and may have beneficial effects on other major organs involved in the regulation of energy homeostasis by mediating exercise [13-14]. Adipose tissue appears to be an important target for myokines, which play a role in regulating energy flow and fuel supply during muscle contraction. During muscle movement, myokines help to regulate energy flow within muscle cells, ensuring that the muscle receives an adequate supply of fuel to sustain the movement.IL-6 was the first myokine to be identified, and levels of IL-6 secreted by skeletal muscle are significantly elevated during exercise and muscle contraction. Several clinical studies have shown that during exercise, a substance such as IL-6 helps to reduce the accumulation of visceral adipose tissue [15], thus potentially improving IR. In addition, there are a variety of other myokines that are secreted by skeletal muscle and affect the pancreas, liver, and adipose tissue, and may affect glucose tolerance through a variety of mechanisms. Many myokines act not only on other organs but also on themselves (autocrine), leading to skeletal muscle hypertrophy and increased insulin sensitivity (increased glucose uptake). On the other hand, myokines such as muscle growth inhibitors act on themselves (autocrine), leading to reduced skeletal muscle mass, decreased insulin sensitivity and promotion of hepatic fat deposition [11]. Myokines are involved in the anti-inflammatory effects of physical activity and counteract the metabolic abnormalities of IR and diabetes mellitus [16-17]. Therefore, abnormalities in myokine secretion and function may have a direct effect on enhancing IR. However, the mechanisms by which myokines affect IR have not been fully elucidated [13, 16–18].

In addition, there are few studies on the direct effects of IH on myokine secretion. Takasawa et al. [19] studied the changes in myokine levels and their regulatory mechanisms by IH, and the results showed thatIH elevatedthe levels of IL-8 and ON (osteopontin) and MN (myosin) mRNA in mammalian muscle cells, that octamer-binding transcription factor-1 (octamer transcription factor -1) was a key factor in the IH-induced up-regulation of IL-8 and MN mRNA expression levels, and that nuclear factor erythroid related factor-2 (nuclear factor erythroid related factor -2) was a key factor in the IH-induced up-regulation of IL-8 and MN mRNA expression levels. erythroid related factor -2) is a key factor in IH-induced upregulation of ON mRNA expression. There are no other studies about the direct relationship between myokines and IH. Therefore, further studies are needed.

3.2 Activation of the Sympathetic Nervous System

IH activates the sympathetic nervous system, leading to elevated serum catecholamine concentrations [2], which accelerates lipolysis and leads to the release of more free fatty acids (non-esterified fatty acid). Evaluation of plasma free fatty acids may lead to lipid accumulation in skeletal muscle and liver. Meanwhile, FFA reduces tyrosine phosphorylation of insulin receptor substrate -1 and insulin receptor substrate -2, which in turn reduces insulin-stimulated glucose transport in skeletal muscle and liver, ultimately leading to IR. In addition, excessive amounts of catecholamines may inhibit insulin secretion, prevent muscle uptake of glucose, and increase gluconeogenesis and hepatic glucagon secretion. These contribute to IR.

3.3 Decreased GLUT4 Expression and Reactive Oxygen Species Production

Studies have shown that the changes of GLUT4 mRNA expression and GLUT4 protein expression in skeletal muscle may be the hypothesized mechanism of the influence of IH on glucose imbalance and insulin sensitivity [20]. The results of the study showed that IH animals displayed lower GLUT4 expression at both mRNA and protein levels in skeletal muscle. The reduction in GLUT4 mRNA levels, total GLUT4 expression may be an important mechanism for the inability of animals to transport glucose into the intracellular space under IH conditions, leading to elevated blood insulin levels and reduced insulin sensitivity. This finding may be related to reduced insulin effectiveness during IH. Under IH conditions, as the oxygen supply to skeletal muscle decreases, oxidative metabolism and glycolysis slow down, and therefore insulin's ability to process glucose is reduced. Reduced GLUT4 expression may also be associated with reactive oxygen species (ROS). During IH, repeated hypoxia and reoxygenation promote ROS production [21]. ROS are not only toxic byproducts of substance metabolism, but also modulators of metabolites, which can activate a variety of inflammatory factors via NF-κB, e.g., IL-6 (Interleukin-6) and TNF-α (Tumor Necrosis Factor-α) [22-23]. IL-6 and TNF-α decrease the expression of GLUT4 and IRS-1, and reduce glucose transport [24].

3.4 Specific Activation of the AMPK Pathway in Skeletal Muscle

Thomas et al. reported in 2017 that IH impairs insulin sensitivity by promoting specific activation of the skeletal muscle pathway. The study used 8-week-old C57BL/6J male mice, and 8- to 10-week-old C57BL/6J AMPKα2-/- and muscle-specific AMPKα1α2 -/-(mdKO) mice. Experiments revealed that cIH causes systemic IRby IRindex (HOMA-IR) and insulin sensitivity test (ITT). Mechanistically, dysregulation of IRS-1 signaling levels is regulated through a complex mechanism involving the phosphorylation of multiple tyrosine and serine/threonine residues [25], which is thought to be involved in cIH-induced IR [26-27]. It has been found that under cIH conditions, in a tissue-specific manner, insulin-induced phosphorylation of tyrosine and serine/threonine residues is reduced, which leads to an increase in AMPK activity. Liver, eWAT, and skeletal muscle samples were collected at the peak of the glucose tolerance test (GTT) curve (i.e., 15 min min after glucose administration) and analyzed for insulin and AMPK pathways. The phosphorylation status of protein kinase B, protein kinase B in

any tissue was not affected by cIH during GTT. However, in skeletal muscle of cIH mice, phosphorylation of AMPKα on Thr172 in significantly increased. These results suggest that IH may impair insulin sensitivity promoting specific activation of the skeletal muscle AMPK pathway.

3.5 Tumor Necrosis Factor-α Production

The direct role of IH is the oxidative imbalance generated by ROS and the activation of the inflammatory cascade by increasing pro- and anti-inflammatory cytokines; e.g., TNF-α, IL-1, etc. [28]. Rodriguez et al. [29] TNF-α was subsequently identified among various biomarkers and was significantly associated with oxygen desaturation indices in patients with SAS. Overseas scholars have studied the effects of TNF-α on insulin signaling and glucose uptake in healthy individuals. It was found that TNF-α infusion resulted in skeletal muscle IR, achieved by inhibiting the phosphorylation of Akt substrate 160, a protein containing the structural domain of Rab GAP (GTPase-activating protein), which plays a role in insulin signaling by facilitating the exocytosis of GLUT4 to the cell membrane to promote glucose uptake and metabolism. We have also mentioned previously the relationship between changes in GLUT4 mRNA expression and protein expression in skeletal muscle and IH and IR.

4. Therapeutic Interventions for SAS-related T2DM

Continuous positive airway pressure ventilation (CPAP) therapy is the mainstay of treatment for OSAS and improves patients' quality of life. Some studies have shown that CPAP therapy improves metabolic control and insulin sensitivity, but there are also findings that show insignificant effects on HbA1c levels and body mass index. The results of the studies are controversial and may be influenced by factors such as the method of assessment of insulin sensitivity, characteristics of the study population and duration of treatment. Therefore, we can consider several alternatives to CPAP therapy, including upper airway surgery, maxillary mandibular advancement surgery, and gastric bypass surgery. However, in general, CPAP therapy has a significant effect on improving glucose tolerance and control, especially in patients with SAS and diabetes.

5. Summary

This paper reviews the regulatory effects of IH on skeletal muscle, which include cytokines, protein expression, sympathetic nervous system, signaling pathways, etc., to illustrate the effects of IH on IR in skeletal muscle in many ways. Whether IH causes IR is an extremely complex question. At the cellular level, hypoxia increases glucose uptake, and this goes hand in hand with inhibition of insulin signaling. The potential mechanisms by which IH induces glucose metabolic dysfunction are thus found to be numerous and complex, and some of them interact with each other.

In recent years, the interaction between IH and metabolic dysfunction is a hot research topic. Studies have shown that SAS may lead to impaired glucose metabolism through the combined effects of sleep fragmentation, sympathetic nerve excitation and oxygen stress induced by IH. IH not only plays a key role in the pathogenesis of SAS, but also plays a key role in the pathophysiology of metabolic disorder induced by SAS. IH plays a key role in the development of glucose metabolism dysfunction in SAS, and leads to complications of SAS through various channels, including cardiovascular and cerebrovascular diseases. In order to clarify the mechanism behind these processes, it is urgent to conduct molecular, clinical and transformation studies in vitro and in vivo to better understand the mechanism and causes of glucose transport, which is very important for clinical application.

Fund Project

2022 Kunlun Elite of Qinghai Province High-End Innovation and Entrepreneurship leading Talents (NO.2023-1);
Qinghai Science and Technology Department (No. 2024-ZJ-934).

References

[1] LU Manlu, ZHU Jiwei, DING Honghong, et al. Research progress on the relationship between obstructive sleep apnea hypopnea syndrome and intestinal flora [J]. International Journal of Medicine and Health, 2024, 30(10): 1585-1589.

[2] MESARWI O A, LOOMBA R, MALHOTRA A. Involvement of Expression of GLUT4 in Skeletal Muscle. med Sci Monit. [J]. American Journal of Respiratory and Critical Care Medicine, 2019, 199(7): 830-841. (This document was not found, please verify substitution)

[3] PASCHOU S A, BLETSA E, SALTIKI K, et al. Sleep apnea and cardiovascular risk in patients with prediabetes and type 2 diabetes [J]. Nutrients, 2022, 14(23): 4989.

[4] PRABHAKAR N R, PENG Y J, NANDURI J. Hypoxia-inducible factors and obstructive sleep apnea [J]. J Clin Invest, 2020, 130(10): 5042-5051.

[5] TANG S S, LIANG C H, LIU Y L, et al. Intermittent hypoxia is involved in gut microbial dysbiosis in type 2 diabetes mellitus and obstructive sleep apnea- hypopnea syndrome [J]. World J Gastroenterol, 2022, 28(21): 2320-2333.

[6] LEE J Y, KIM C W, LEE K C, et al. Effect of intermittent hypoxia on metabolic syndrome and insulin resistance in the general male population [J]. Medicina, 2021, 57(7): 668.

[7] UCHIYAMA T, OTA H, OHBAYASHI C, et al. Effects of intermittent hypoxia on cytokine expression involved in insulin resistance [J]. Int J Mol Sci, 2021, 22(23): 12898.

[8] JIANG Chunbo, LU Zhili, LIANG Guoqiang. Improvement of insulin resistance in skeletal muscle of aged diabetic rats by Zi Kidney Pill based on APN/AdipoR1/AMPK signaling pathway [J]. Chinese Journal of Traditional Chinese Medicine, 2023, 41(12):36-44.

[9] TAKASAWA S, SHOBATAKE R, ITAYA-HIRONAKA A, et al. Upregulation of IL-8, osteonectin, and myonectin mRNAs by intermittent hypoxia via OCT1- and NRF2- mediated mechanisms in skeletal muscle cells [J]. J Cell Mol Med, 2022, 26(24): 6019-6031.

[10] GONZALEZ-GIL A M, ELIZONDO-MONTEMAYOR L. The role of exercise in the interplay between myokines, hepatokines, osteokines, adipokines, and modulation of inflammation for energy substrate redistribution and fat mass loss: a review [J]. Nutrients, 2020, 12(6): 1899.
[11] de OLIVEIRA DOS SANTOS A R, de OLIVEIRA ZANUSO B, MIOLA V F B, et al. Adipokines, myokines, and hepatokines: Crosstalk and metabolic repercussions [J]. Int J Mol Sci, 2021, 22(5): 2639.
[12] TAKASAWA S. Up-regulation of diabetes-associated myokines by intermittent hypoxia in mammalian skeletal muscle cells [C/OL]. 2019 [2024-03-31].
[13] LAURENS C, BERGOUIGNAN A, MORO C. Exercise-released myokines in the control of energy metabolism [J]. Frontiers in physiology, 2020, 11.
[14] DI FELICE V, COLETTI D, SEELAENDER M. Editorial: myokines, adipokines, cytokines in muscle pathophysiology, volume II [J]. Front Physiol, 2022(13): 907956.
[15] WEDELL-NEERGAARD A S, LANG LEHRSKOV L, CHRISTENSEN R H, et al. Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signaling. A randomized controlled trial [J]. Cell Metab, 2019, 29(4): 844-855.e3.
[16] ECKEL J. Myokines in metabolic homeostasis and diabetes [J]. Diabetologia, 2019, 62(9): 1523-1528.
[17] GARNEAU L, AGUER C. Role of myokines in the development of skeletal muscle insulin resistance and related metabolic defects in type 2 diabetes [J]. Diabetes Metab, 2019, 45(6): 505-516.
[18] ATAKAN M M, KOŞAR Ş N, GÜZEL Y, et al. The role of exercise, diet, and cytokines in preventing obesity and improving adipose tissue [J]. Nutrients, 2021, 13(5): 1459.
[19] TAKASAWA S, SHOBATAKE R, ITAYA - HIRONAKA A, et al. Upregulation of IL-8, osteonectin, and myonectin mRNAs by intermittent hypoxia via OCT1- and NRF2- mediated mechanisms in skeletal muscle cells [J]. J Cell Mol Med, 2022, 26(24): 6019-6031.
[20] WANG X, YU Q, YUE H, et al. Effect of intermittent hypoxia and rimonabant on glucose metabolism in rats: Involvement of expression of GLUT4 in skeletal muscle [J]. Med Sci Monit, 2015(21): 3252-3260.
[21] WANG N, SHI X F, KHAN S A, et al. Hypoxia-inducible factor-1 mediates pancreatic β-cell dysfunction by intermittent hypoxia [J]. Am J Physiol Cell Physiol, 2020, 319(5): C922-C932.
[22] HE Y, LI Z, XU T, et al. Polystyrene nanoplastics deteriorate LPS-modulated duodenal permeability and inflammation in mice via ROS drived-NF-κB/NLRP3 pathway [J]. Chemosphere, 2022, 307(Pt 1): 135662.
[23] GUO H, GUO H, XIE Y, et al. Mo3 Se4 nanoparticle with ROS scavenging and multi-enzyme activity for the treatment of DSS-induced colitis in mice [J]. Redox Biol, 2022(56): 102441.
[24] THOMAS A, BELAIDI E, MOULIN S, et al. Chronic intermittent hypoxia impairs insulin sensitivity but improves whole-body glucose tolerance by activating skeletal muscle AMPK [J]. Diabetes, 2017, 66(12): 2942-2951.
[25] TAKATANI T, SHIRAKAWA J, SHIBUE K, et al. Insulin receptor substrate 1, but not IRS2, plays a dominant role in regulating pancreatic alpha cell function in mice [J]. J Biol Chem, 2021(296): 100646.
[26] ZENG S, WANG Y, AI L, et al. Chronic intermittent hypoxia-induced oxidative stress activates TRB3 and phosphorylated JNK to mediate insulin resistance and cell apoptosis in the pancreas [J]. Clin Exp Pharmacol Physiol, 2024, 51(3): e13843.
[27] MURPHY A M, THOMAS A, CRINION S J, et al. Intermittent hypoxia in obstructive sleep apnoea mediates insulin resistance through adipose tissue inflammation [J]. Eur Respir J, 2017, 49(4): 1601731.
[28] UCHIYAMA T, OTA H, OHBAYASHI C, et al. Effects of intermittent hypoxia on cytokine expression involved in insulin resistance [J]. Int J Mol Sci, 2021, 22(23): 12898.
[29] CAMPOS-RODRIGUEZ F, ASENSIO-CRUZ M I, CORDERO-GUEVARA J, et al. Effect of continuous positive airway pressure on inflammatory, antioxidant, and depression biomarkers in women with obstructive sleep apnea: a randomized controlled trial [J]. Sleep, 2019, 42(10): zsz145.