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Analysis of the Correlation between GPX7 and Obstructive Sleep Apnea-Hypopnea Syndrome

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Abstract: Obstructive sleep apnea–hypopnea syndrome (OSAHS) is a chronic sleep-related breathing disorder characterized by recurrent collapse of the upper airway during sleep. Its core pathological mechanism involves an imbalance between oxidative stress and inflammatory responses induced by intermittent hypoxia. As an important member of the glutathione peroxidase family, glutathione peroxidase 7 (GPX7) maintains intracellular redox homeostasis through multiple pathways, including the scavenging of reactive oxygen species, regulation of endoplasmic reticulum stress, and modulation of inflammatory responses. This article reviews the relevant literature from China and abroad, systematically summarizes the potential association between GPX7 and the pathogenesis of OSAHS, and analyzes the possible molecular mechanisms underlying their interaction. It aims to provide new perspectives and references for the early diagnosis, disease assessment, targeted treatment, and future research of OSAHS.

Keywords: GPX7; Obstructive Sleep Apnea–hypopnea Syndrome; Intermittent Hypoxia; Oxidative Stress; Target-organ Injury.

1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a chronic sleep-disordered breathing disease with a high prevalence. Epidemiological investigations have shown that nearly one billion people worldwide are affected by OSAHS. Its prevalence exhibits an increasing trend year by year along with rising obesity rates and accelerating population aging [1].The core pathophysiological feature of OSAHS is repetitive upper-airway collapse during nocturnal sleep, which causes cessation or marked reduction of airflow and triggers intermittent hypoxia-reoxygenation cycles. Its main clinical manifestations include nocturnal snoring, apnea, arousals from sleep, as well as daytime sleepiness and inattention [2].

Reactive oxygen species (ROS) are oxygen-derived metabolites generated during organismal metabolism, including H_2O_2, •OH, OH^-, and $•OCl^-$[3] . Electrons are paired in H_2O_2 and OH^-, so these species do not possess radical properties. In contrast, •OH exhibits the highest reactivity and can readily induce severe oxidative damage in the organism[3] . Oxidative stress refers to homeostatic disturbance resulting from an imbalance between intracellular ROS production and scavenging, which leads to lipid peroxidation, oxidative modification of proteins, and DNA damage[4] . Studies have confirmed that excessive ROS production is closely associated with the severity of OSAHS.

Glutathione peroxidases (GPXs) constitute an important antioxidant enzyme system in the organism, which is widely distributed in various human tissues and organs and comprises eight family members[5]. Among them, GPX1-4 and GPX6 are selenocysteine-dependent antioxidant enzymes that can directly utilize glutathione (GSH) to reduce peroxides, whereas GPX5, GPX7 and GPX8 represent non-selenium-dependent isoforms[6] . They exhibit marked specificity in their functions and mechanisms of action.

2. Mechanisms of ROS Generation in OSAHS

2.1. Chronic Intermittent Hypoxia-Induced ROS Production

Chronic intermittent hypoxia (CIH) represents the core pathological feature of OSAHS. Repeated hypoxia-reoxygenation cycles trigger ROS production via three major pathways: mitochondria, NADPH oxidase, and xanthine oxidase[4],which serves as the central driving mechanism for oxidative stress in OSAHS.

mitochondrial pathway

Intermittent hypoxia (IH) targets mitochondria as the central site of oxidative-stress-mediated injury, resulting in decreased mitochondrial membrane potential, opening of the permeability transition pore, structural damage, and DNA damage. Under hypoxic conditions, the activities of mitochondrial electron-transport-chain complexes I and III are inhibited, leading to electron leakage. Upon reoxygenation, leaked electrons react with oxygen molecules to generate reactive oxygen species including superoxide anion, hydrogen peroxide, and hydroxyl radicals, accompanied by insufficient ATP synthesis [7]; Meanwhile, IH up-regulates HIF-1α. In most pathological models, this is accompanied by down-regulated expression of antioxidant enzymes such as SOD2, which impairs the mitochondrial ROS-scavenging capacity[8] . Endoplasmic reticulum redox imbalance also disrupts the proper formation of protein disulfide bonds and mediates intracellular calcium dyshomeostasis[3]. Meanwhile, excessive ROS reciprocally aggravates mitochondrial damage, forming a vicious cycle. Therefore, mitochondrial injury constitutes a key link in IH-induced oxidative stress.

NADPH oxidase (NOX) pathway

The NOX family (predominantly NOX2 and NOX4)

constitutes a key enzymatic source of ROS generation in OSAHS, which is mainly expressed on the cell membrane of vascular endothelial cells, inflammatory cells and other cell types[9]. CIH activates HIF-1α, which can bind to the promoter regions of NOX genes to promote the transcription and membrane translocation of NOX subunits. Meanwhile, CIH-triggered inflammatory responses can also activate the NF-κB pathway to induce phosphorylation-dependent activation of NOX in inflammatory cells, which catalyzes the oxidation of NADPH to generate $O_2^{\bullet-}$. Upon reoxygenation, oxygen molecules further enhance NOX activity, leading to the production of H_2O_2 and peroxynitrite[9]-[11] . In the brain, NOX2 can be up-regulated and activated by angiotensin II, PKC, and intracellular calcium ions, thereby forming a vicious cycle[3]. Studies have confirmed that NOX activity in peripheral blood cells and plasma xanthine/hypoxanthine levels are significantly elevated in patients with OSAHS, and are positively correlated with disease severity. Continuous positive airway pressure (CPAP) treatment can effec [12],[13].

xanthine oxidase (XO) pathway

XO is a key flavoprotein mediating ROS generation, which is predominantly distributed in the liver, intestinal epithelium and vascular endothelial cells. Under physiological conditions, it exists in the form of xanthine dehydrogenase (XDH) [14] . During hypoxia, ATP depletion leads to intracellular accumulation of xanthine/hypoxanthine; meanwhile, XDH is converted into XO and activated[15]. During hypoxia, ATP depletion drives AMP degradation, leading to intracellular accumulation of hypoxanthine/xanthine via the adenosine pathway. Meanwhile, intracellular calcium overload activates calpain, which promotes the conversion of XDH to XO through either irreversible proteolytic cleavage or reversible oxidation of cysteine residues. Upon reoxygenation, XO catalyzes the oxidation of these substrates to uric acid, with concomitant generation of $O_2^{\bullet-}$ and H_2O_2[11],[15]. Clinical studies have shown that plasma XO activity, uric acid, and ROS levels are elevated in patients with OSAHS, and are positively correlated with the apnea-hypopnea index (AHI) and nocturnal hypoxemia index[16],[17]. Animal studies have confirmed that allopurinol, an XO inhibitor, can reduce ROS levels[15]. In addition, ROS generation is also associated with enzyme systems including phospholipase A2, lipoxygenase, cyclooxygenase, and uncoupled nitric oxide synthases[4],[8].

2.2. Sleep Architecture Disturbance and Sympathetic Nerve Activation Promote ROS Production

Sleep architecture disruption in patients with OSAHS can directly impair mitochondrial function and also trigger a systemic stress response, characterized by activation of the hypothalamic-pituitary-adrenal (HPA) axis and increased cortisol secretion. Elevated cortisol indirectly promotes mitochondrial electron leakage and NOX activation through multiple pathways, including enhanced gluconeogenesis-driven mitochondrial metabolic load and up-regulated inflammatory factors[7],[18],[19]. In addition, it can activate the sympathetic nervous system, leading to elevated sympathetic tone and increased catecholamine secretion. Catecholamines ultimately drive excessive ROS production through two mechanisms: direct auto-oxidation and indirect promotion of NOX assembly via PKC signaling activation[19],[20].

2.3. Mutual Promotion between Inflammatory Response and ROS Production

ROS can activate the NF-κB signaling pathway, initiating the transcriptional expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8) and inflammation-related enzymes (iNOS and COX-2) [8], [10].Meanwhile, IH can activate the NLRP3 inflammasome, promoting the maturation and secretion of IL-1β and IL-18, thereby amplifying inflammatory injury. Conversely, activated inflammatory cells and pro-inflammatory cytokines can promote ROS synthesis and upregulate the activity of oxidation-related enzymes. Moreover, oxidative stress induces abnormal apoptosis of inflammatory cells, which perpetuates the inflammatory response[10],[21]. Numerous studies have confirmed that in patients with OSAHS, ROS levels are positively correlated with inflammatory cytokines such as TNF-α and IL-6, and both are closely associated with the AHI[22]. NLRP3 silencing can effectively downregulate inflammatory levels[21]. These mechanisms can disrupt cytokine homeostasis, induce upper airway mucosal remodeling, and aggravate airway obstruction. They can also damage target tissues including blood vessels, myocardium, and neurons, ultimately leading to multiple complications such as hypertension [20], coronary heart disease, cognitive dysfunction [12], and diabetes mellitus[10]. Therefore, sustained ROS generation and persistent inflammatory activation constitute the core mechanism underlying OSAHS pathogenesis and the progression of its multi-system complications.

3. Roles of ROS in the Pathophysiological Processes of Diseases

3.1. Signal-Transducing Effect

ROS can activate multiple signaling pathways. In addition to the NF-κB pathway, these include:1. HIF-1α signaling pathway: IH can activate HIF-1α, enabling it to bind to hypoxia response elements (HRE) and initiate the transcriptional expression of target genes (VEGF, EPO, and GLUT1), thereby promoting angiogenesis, erythropoiesis, and glucose metabolic reprogramming. Meanwhile, HIF-1α exacerbates oxidative stress and inflammatory responses[8],[23],[24]; 2. Nrf2/ARE pathway: ROS induces the dissociation of Nrf2 from Keap1; following nuclear translocation, Nrf2 binds to antioxidant response elements (ARE) and upregulates the expression of antioxidant molecules such as SOD, GPX, and GSH[23],[25]. In chronic severe OSAHS, decompensation of the Nrf2 pathway may occur, resulting in diminished antioxidant defense capacity. 3. MAPK pathway: ROS can activate the MAPK family (ERK1/2, JNK, and p38), thereby promoting cell proliferation, apoptosis, and inflammatory cytokine release[23]. These mechanisms collectively mediate IH-induced oxidative stress and tissue injury.

3.2. Aggravation of Airway Obstruction and Sleep Disturbance

ROS can damage the lipid, protein, and nucleic acid structures of upper airway mucosal epithelial cells and activate matrix metalloproteinases (MMPs), thereby inducing mucosal congestion and edema, increased apoptosis, extensive collagen degradation, and diminished tissue

elasticity, ultimately leading to upper airway structural laxity and luminal stenosis[10],[26]. CIH can also upregulate NOX4 expression in airway smooth muscle cells, inducing smooth muscle hypertrophy and thereby aggravating airway obstruction[27]. Studies have confirmed that in the upper airway mucosa of patients with OSAHS, levels of ROS and MDA, a lipid peroxidation product, are significantly elevated, whereas the activities of antioxidant molecules such as SOD and GSH are decreased[12],[27]. In addition, ROS levels are positively correlated with the severity of sleep disturbance: the higher the ROS levels, the lower the sleep efficiency, accompanied by reduced slow-wave sleep and increased arousal frequency[28]. This association may be mediated by multiple pathways, including ROS-induced neuronal structural and functional damage, central neuroinflammation, and dysregulated melatonin secretion. The specific molecular regulatory mechanisms remain unclear, and antioxidants can improve sleep architecture.

3.3. Involvement in the Development of Related Metabolic Disorders

ROS can impair pancreatic β-cell function, inhibit insulin synthesis and secretion, and reduce insulin receptor sensitivity, thereby inducing insulin resistance and diabetes mellitus[29]. Meanwhile, by mediating lipid peroxidation, ROS promotes oxidative modification of low-density lipoprotein (LDL), accelerates atherosclerosis progression, disrupts lipid metabolism, and induces dyslipidemia. In addition, obesity can activate systemic oxidative stress, whereas ROS promotes adipocyte proliferation and differentiation, thereby exacerbating obesity progression[30]-[32]. Animal studies have shown that intermittent hypoxia exposure can increase the number of macrophages in adipose tissue and promote their polarization toward a pro-inflammatory phenotype, accompanied by increased ROS production[31]. However, there remains a lack of definitive evidence regarding whether obesity exacerbates OSAHS-related oxidative stress injury.

3.4. Mediation of Associated Vascular Injury

Excessive ROS can damage vascular endothelial cells and induce their apoptosis, while inhibition of eNOS activity leads to decreased NO synthesis and upregulated ET-1 expression, ultimately resulting in vasoconstriction, elevated blood pressure, and endothelial dysfunction[33]. Meanwhile, it mediates signaling pathways including PI3K/Akt and MAPK to promote the proliferation and migration of vascular smooth muscle cells[23],[34]. ROS can also activate the platelet glycoprotein IIb/IIIa receptor. By inducing tyrosine phosphorylation of the β3 subunit, ROS enhances its fibrinogen-binding capacity, rendering platelets hyperresponsive to agonists such as TXA_2, and thereby promoting thrombosis[35].

3.5. Neural Dysregulation

ROS can inhibit voltage-gated potassium channels in type I glomus cells of the carotid body, triggering cellular depolarization and calcium influx and subsequent release of excitatory neurotransmitters such as acetylcholine and ATP. This enhances afferent impulses in the carotid sinus nerve, activating neurons and glial cells in the nucleus tractus solitarius (NTS) and inducing secretion of pro-inflammatory cytokines including IL-1β and TNF-α, ultimately mediating central nervous and respiratory regulatory dysfunction [3], [8], [10].

4. Biological Characteristics of Glutathione Peroxidase 7 (GPX7)

4.1. Structure of GPX7

GPX7, also known as NPGPx, is localized to the endoplasmic reticulum (ER). Its gene comprises three exons and encodes a protein of 187 amino acids with a molecular mass of approximately 22 kDa. GPX7 possesses two unique features characteristic of ER secretory proteins: an N-terminal ER signal peptide and a C-terminal atypical KDEL motif[6],[36]. The promoter region of the GPX7 gene contains ARE. Nrf2 can bind to these AREs in accordance with the cellular oxidative stress status to regulate GPX7 transcriptional expression. Under specific conditions, a small fraction of GPX7 protein can translocate to the Golgi apparatus[6].

4.2. Functions and Mechanisms of GPX7

GPX7 utilizes Cys57 and Cys86 as key catalytic residues and lacks a GSH-binding domain. It regulates target protein activity through a disulfide bond shuffling mechanism, thereby functioning as both an oxidative stress sensor and a signal transducer[37].

GPX7 maintains ER homeostasis primarily through regulation of the Ero1α-PDI axis and the GRP78-mediated unfolded protein response (UPR) pathway[37],[38]. H_2O_2 generated by Ero1α can activate GPX7. Activated GPX7 oxidatively activates PDI through disulfide bond modification, enhancing its isomerase activity and promoting proper folding of nascent proteins, while simultaneously scavenging excess ROS and inhibiting oxidative stress accumulation[36],[38],[39]. GPX7 can also specifically bind to the Cys41 and Cys420 residues of GRP78 via disulfide bonds[37], enhancing its chaperone function, improving the repair efficiency of misfolded proteins, and reducing the accumulation of unfolded proteins. This indirectly prevents the dissociation of GRP78 from the three canonical UPR sensors—Ire1, PERK, and ATF6—thereby inhibiting excessive UPR activation and effectively alleviating oxidative stress-induced ER damage[36]. In addition, GPX7 participates in inflammatory responses and fibrotic processes through two regulatory mechanisms: a ROS-dependent modulation of the NF-κB pathway, and a non-ROS-dependent pathway involving direct targeting of the TNFR1/TRAF2 axis[40]. GPX7 overexpression can reduce intracellular ROS levels and suppress the expression of pro-inflammatory and pro-fibrotic genes, whereas GPX7 deficiency activates inflammatory cascades and induces extracellular collagen deposition and tissue fibrosis[40]. Meanwhile, GPX7 regulates CPEB2 protein activity, enhancing its translational repression of HIF-1α mRNA. Under oxidative stress, disruption of disulfide bonds leads to upregulated HIF-1α translation[41].

4.3. Association of GPX7 with Diseases

GPX7 exhibits expression and functional heterogeneity across different diseases. In digestive system malignancies, esophageal cancer frequently shows downregulated GPX7 expression due to promoter hypermethylation, which promotes tumor proliferation, invasion, and metastasis through ROS accumulation-mediated NF-κB pathway activation. Its low expression is closely associated with

advanced tumor stage and poor prognosis[42],[43].In contrast, hepatocellular carcinoma (HCC) generally exhibits aberrant GPX7 overexpression, which enhances tumor cell proliferation and survival through the PI3K-AKT pathway[44];In neurological diseases, GPX7 exerts a bidirectional regulatory role. In glioma, GPX7 is significantly upregulated and accelerates malignant progression by inhibiting ferroptosis and modulating the tumor immune microenvironment[45];whereas in amyotrophic lateral sclerosis (ALS), GPX7 is downregulated, exacerbating neuronal oxidative stress and dysregulation of O-GlcNAcase-mediated protein modification, thereby promoting neurodegeneration[46]. In skeletal diseases, GPX7 primarily exerts a protective role. Its downregulation induces endoplasmic reticulum stress and mTOR pathway inhibition, resulting in impaired osteogenic differentiation and enhanced adipogenic differentiation of bone marrow mesenchymal stem cells (BMSCs)[47],[48]. In osteoarthritis (OA), decreased GPX7 expression is accompanied by increased ferroptosis in chondrocytes, exacerbating extracellular matrix (ECM) degradation[47],[48]. The specific molecular regulatory mechanisms remain unclear. In metabolic diseases, obesity is accompanied by downregulated GPX7 expression. By elevating intracellular ROS levels, GPX7 deficiency renders preadipocytes hypersensitive to insulin-mediated differentiation signals, promoting excessive lipid accumulation and thereby leading to systemic insulin resistance and dysregulation of glucose and lipid metabolism [49]. Meanwhile, GPX7-related dysregulation of oxidative homeostasis also contributes to the pathogenesis of diabetes mellitus and its complications[49]. The aforementioned differential expression suggests the clinical application value of GPX7 as an auxiliary diagnostic and prognostic biomarker, as well as a potential targeted therapeutic target for multi-system diseases.

5. Conclusion

Collectively, GPX7 governs ER protein folding, redox homeostasis, inflammation, differentiation, lipid metabolism, and oncogenic signaling, thereby impacting tumor, metabolic, skeletal, and neurodegenerative disorders. Given the striking overlap between OSAHS pathophysiology and GPX7 function, GPX7 likely modulates OSAHS onset and progression, representing a novel mechanistic and therapeutic entry point. Future work should: (1) define GPX7 expression trajectories across OSAHS stages in large cohorts and validate its biomarker utility; (2) map the GPX7 regulatory network in CIH, focusing on HIF-1α/Nrf2/ER-stress crosstalk to complete the oxidative-stress mechanism chain; and (3) develop GPX7-targeted interventions combined with standard therapy to break the oxidative-inflammatory vicious cycle.

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