

Biological Mechanisms Behind Sleep Apnea and Towards Its Detection

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Abstract

Sleep apnea is a common sleep disorder with profound implications for cardiovascular, metabolic, and neurological health. This paper discusses the biological mechanisms that underlie sleep apnea, including intermittent hypoxia, oxidative stress, and systemic inflammation, driving pathological signaling pathways such as HIF-1 α , NF- κ B, and MAPK. Furthermore, epigenetic modifications, including changes in DNA methylation, microRNA, and long non-coding RNA expression, perpetuate inflammation and vascular dysfunction, enabling automated and accurate detection. This study reviews the pathophysiology of sleep apnea, key biomarkers, and an attempt to classify ML techniques has been made in the attached codes. Refer Figure 1

1 Introduction

Sleep apnea is a common sleep disorder characterized by recurrent episodes of breathing interruption, which results in severe health effects, including systemic inflammation, vascular dysfunction, and metabolic disturbances. This paper examines the biological mechanisms underlying these effects, focusing on key pathways, such as hypoxia-inducible factors, oxidative stress, and inflammatory signaling. The paper also explores the role of epigenetic modifications in perpetuating these pathological states and also demonstrates a small trained model attached to it. [Bal23] [Kat22] [L⁺10] [Muk17] [Zha22] [P⁺21] [Moo23]

2 Common terms used

- **Hypoxia:** A condition in which tissues are deprived of adequate oxygen levels.
- **Oxidative Stress:** An imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them.
- **Apnea:** A temporary cessation of breathing, especially during sleep.
- **Fibrinolysis:** The biological process that breaks down fibrin in blood clots.

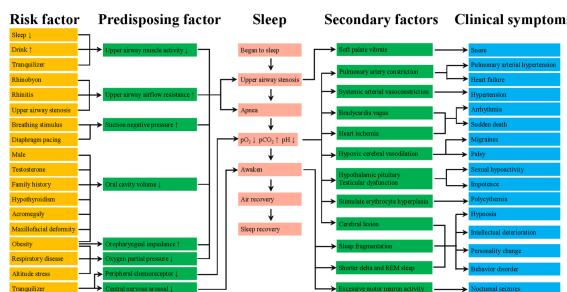


Figure 1: Pathogenesis of OSA

- **Pro-Thrombotic State:** A condition characterized by an increased tendency to form blood clots.
- **Intermittent Hypoxia:** Repeated cycles of low oxygen levels followed by reoxygenation, a hallmark of sleep apnea.
- **Epigenetics:** The study of changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence.
- **Reactive Oxygen Species (ROS):** Chemically reactive molecules containing oxygen, often produced during hypoxia-reoxygenation cycles.
- **Cytokines:** Small proteins involved in cell signaling, particularly in immune responses (e.g., TNF- α , IL-6).
- **Hypoxia-Inducible Factor (HIF-1 α):** A transcription factor activated under low oxygen conditions, regulating genes involved in inflammation and angiogenesis.
- **Endothelial Dysfunction:** Impairment of the inner lining of blood vessels, leading to vascular complications.
- **Machine Learning (ML):** Computational techniques that enable systems to learn patterns from data, applied here to EEG data for sleep apnea detection.
- **NF- κ B (Nuclear Factor Kappa B):** A protein complex that regulates DNA transcription, playing a central role in inflammatory responses.
- **PI3K/Akt Pathway:** A signaling pathway crucial for cell survival and growth, often disrupted in sleep apnea.
- **Circadian Rhythms:** The body's internal clock that regulates sleep-wake cycles and other physiological processes.
- **MicroRNAs (miRNAs):** Small non-coding RNAs that regulate gene expression post-transcriptionally, implicated in inflammation and hypoxia responses.
- **Long Non-Coding RNAs (lncRNAs):** Regulatory RNA molecules involved in controlling gene expression and inflammation.
- **Autonomic Nervous System (ANS):** The system regulating involuntary bodily functions, such as heart rate and breathing, often disrupted in sleep apnea.

3 Signaling Pathways in OSA Pathophysiology

Some of the signalling pathways in the pathophysiology of OSA is given below. The paper will explore some in detail later on.

3.1 Hypoxia-Inducible Factor-1 Alpha (HIF-1 α) and Downstream Effects

HIF- α is a transcription factor central to cellular adaptation to oxygen deprivation. Intermittent hypoxia in OSA stabilizes HIF- α . HIF-1 α induces the expression of genes that promote angiogenesis, such as vascular endothelial growth factor (VEGF), and pro-inflammatory mediators like interleukin-6 (IL- 6). These responses are supposed to be adaptive, but become pathogenic in chronic hypoxia.

3.2 Reactive Oxygen Species (ROS) and Oxidative Stress Pathways

The hallmark of hypoxia-roxygenation cycles in OSA is ROS production in the cells. During re-oxygenation, mitochondria generate excess ROS. This disrupts cellular structures, including DNA, lipids, proteins etc. ROS activates oxidative stress-sensitive pathways such as the NF- κ signaling pathway, which we will discuss in detail later on. This further amplifies inflammation and endothelial dysfunction. The oxidative burden also stimulates MAPK(mitogen activated protein kinase) pathway, driving inflammation, apoptosis and vascular injury.

3.3 NF- κ B and Inflammatory Amplification

The NF- κ B pathway is an important mediator of inflammation in OSA. Activated by the ROS in the cell and hypoxia along with the Toll like receptors(TLRs). This governs expression of pro-inflammatory cytokines (including TNF- α , IL-6, and CRP). Persistent activation of this pathway underlies the chronic inflammatory state in OSA.

3.4 PI3K/Akt Pathway Dysregulation

PI3K stand for phosphoinositide 3-kinase pathway. It is essential for cell survival and angiogenesis. This is inhibited during chronic hypoxia in OSA. This worsens apoptosis, intensifies oxidative stress and impairs vascular repair.

3.5 Endothelin-1 (ET-1) Pathway and Vascular Dysfunction

ET-1 (a potent vasoconstrictor) is upregulated by HIF-1 α in response to intermittent hypoxia. Elevated levels of ET-1 contribute to sustained hypertension; vascular remodeling and increased cardiovascular risk in OSA. Chronic activation of this pathway fosters a pro-thrombotic and pro-inflammatory vascular environment.

3.6 Renin-Angiotensin-Aldosterone System (RAAS)

RAAS is activated by intermittent hypoxia, and it enhances angiotensin-2 production. Angiotensin-2 promotes vasoconstriction, oxidative stress and fibrosis, thus linking OSA to hypertension and cardiovascular remodeling. Elevated aldosterone levels worsens sodium retention, fluid overload.

3.7 AMP-Activated Protein Kinase (AMPK) Impairment

AMPK is a metabolic sensor, which gets dysregulated in OSA due to chronic hypoxia and oxidative stress. The impairment disrupts lipid and glucose metabolism(hence contributing to insulin resistance and metabolic syndrome). AMPK dysfunction also impedes mitochondria biogenesis and energy homeostasis.

3.8 Transforming Growth Factor-Beta (TGF- β) Signaling

In response to hypoxia and inflammation, TGF- β is upregulated which promotes fibrosis and vascular remodeling. It's interdependency with HIF-1 α amplifies fibrotic and inflammatory characteristics of OSA.

3.9 Integration of Pathways

The signaling pathways in OSA are a dynamic bunch. It consists of multiple feedback loops involving hypoxia, inflammation and oxidative stress. We will discuss the self reinforcing cycles in detail.

4 Intermittent hypoxia and inflammation

4.1 Introduction

The interdependency of intermittent hypoxia and inflammation of OSA forms a sort of feedback loop. This contributes to the worsening of the disease due to its positive loop nature.

4.2 Role of intermittent hypoxia

Intermittent hypoxia is a defining feature of OSA. It arises from repeated periods of upper airway obstruction during sleep. These cycles of hypoxia results in cycles of oxygen desaturation and deoxygenation, creating oxidative stress through production of ROS(reactive oxygen species).

- **ROS Generation:** Hypoxia disrupts mitochondrial function and activates enzymes such as NADPH oxidase, leading to the accumulation of ROS during reoxygenation.

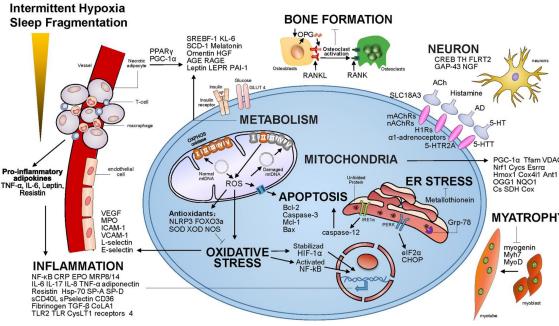


Figure 2: Signalling pathways involved in OSA

- **Hypoxia-Inducible Factor-1 Alpha (HIF-1 α):** Intermittent hypoxia stabilizes HIF-1 α (a transcriptional factor), it promotes the expression of pro-inflammatory and pro-angiogenic genes such as vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6).

The repeated activation of these pathways creates a pro-inflammatory and oxidative environment that damages cellular structures and alters endothelial function.

4.3 Inflammation as a key amplifier

ROS generation stimulates inflammatory singaling pathways, such as NF- κ B(nuclear factor-kappa B) which is a central transcription factor that governs the expression of pro-inflammatory cytokines like TNF α , IL-6 and CRP. Inflammatot worsens hypoxia in several ways:

- **Endothelial Dysfunction:** Pro-inflammatory cytokines impair endothelial cells, reducing their ability to maintain vascular homeostasis. The upregulation of adhesion molecules like soluble E-selectin (sE-Selectin) and the promotion of vascular inflammation marks this dysfunction.
- **Systemic Inflammation:** Elevated cytokines sustains a state of chronic systemic inflammation, creating conditions that further stress vascular and metabolic systems.

4.4 Feedback loop involving hypoxia and inflammation

This cyclical relationship between hypoxia and inflammation can be summarized as follows:

1. **Initiation:** Intermittent hypoxia promotes ROS production and inflammatory signaling.
2. **Amplification:** Inflammatory mediators (like the TNF-Alpha and IL-6) worsens oxidative stress by activating immune cells like macrophages and neutrophils, which further release ROS.
3. **Endothelial Damage:** Oxidative stress and inflammation damage the endothelium, leading to impaired vascular function and reduced oxygen delivery(which worsens hypoxia).
4. **Worsening Hypoxia:** Endothelial dysfunction contributes to poor oxygen exchange and perfusion, intensifying intermittent hypoxia and perpetuating the cycle.

4.5 Example of such a feedback loop

4.5.1 PAI-1: The inhibitor of Fibrinolysis

PAI-1 is a serine protease inhibitor, that inhibits tPA and urokinase-type plasminogen activator (uPA). These enzymes are responsible for converting plasminogen into plasmin, a key protease in the breakdown of fibrin clots. Higher levels of PAI-1 are observed in OSA, which impairs this process, leading to a pro-thrombotic state.

1. **Induction by Hypoxia:** PAI-1 expression is induced by hypoxia, it is regulated by pathways involving hypoxia-inducible factor-1 alpha (HIF-1Alpha). The intermittent hypoxia in OSA upregulates PAI-1 production in endothelial cells and other tissues.

Plasminogen Activator Inhibitor (PAI-1)

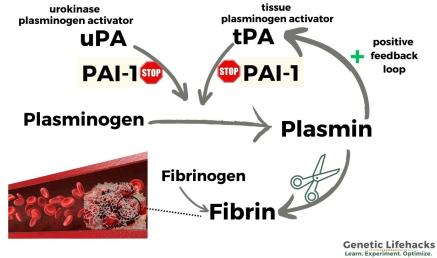


Figure 3: PAI-1 loop

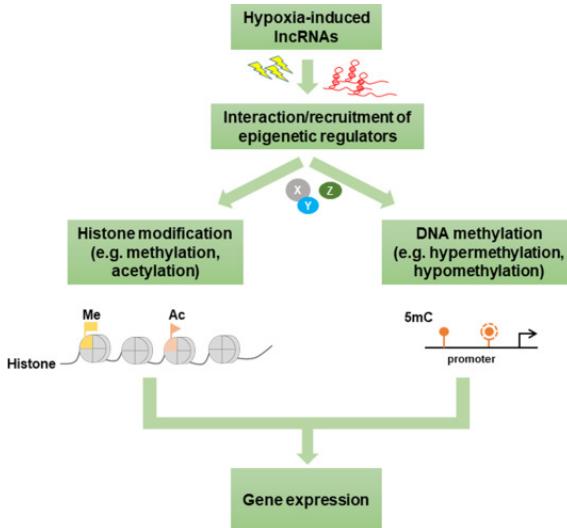


Figure 4: Hypoxia induced effects

2. **Inflammatory Amplification:** PAI-1 levels are further increased in response to inflammatory cytokines such as TNF-Alpha and IL-6 (which are overproduced in OSA).
3. **Pro-Thrombotic State:** Increased PAI-1 inhibits tPA, which leads to fibrinolytic resistance and persistent clot formation, which worsens hypoxia and vascular damage(which further worsens OSA).

4.5.2 Coagulation-Fibrinolysis imbalance

The interplay between PAI-1 and tPA in OSA outlines a feedback loop that worsens vascular health:

1. **Triggering Hypoxia:** Repeated oxygen desaturation episodes due to intermittent hypoxia increase PAI-1Alpha and tPA expression levels.
2. **Endothelial Damage:** The higher than normal levels of ROS and inflammatory cytokines stimulates the release of both proteins even more.
3. **Pro-Thrombotic State:** Increased PAI-1Alpha inhibits tPA, leading to decreased fibrinolysis and clot persistence. This creates vascular microthrombi, which worsens local hypoxia by impairing blood flow(which is true for all vascular problems described in the paper).
4. **Hypoxia-Amplified Expression:** The hypoxia from microthrombi induces further PAI-1Alpha and tPA production, promoting the cycle.

This loop not only perpetuates the vascular injury seen in OSA but also creates a systemic pro-thrombotic state, linking OSA to comorbid conditions such as deep vein thrombosis, pulmonary embolism, and ischemic stroke.

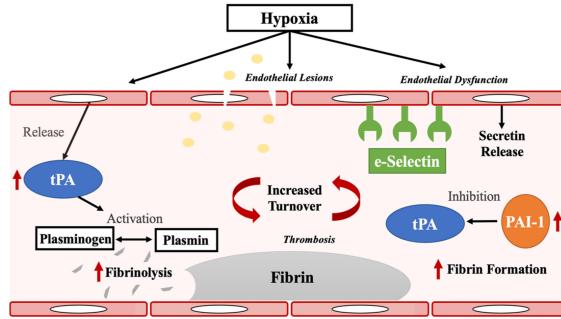


Figure 5: Proposed mechanisms in the relationship between obstructive sleep apnea, PAI-1, tPA, and sE-Selectin. Hypoxia in sleep apnea causes endothelial damage or injury. This is associated with (1) increased release of sE-selectin; and (2) stimulation of local fibrin aggregation. Increased tPA and PAI-1 activity reflects enhanced fibrin formation/fibrinolysis turnover, perhaps contributing to the known increased risk of stroke in sleep apnea.

4.5.3 Epigenetical

The changes in miRNA expression, lncRNA regulation, and DNA methylation collectively sustain a feedback mechanism that worsens the pathophysiological effects of OSA. This feedback loop can be summarized as follows:

1. Hypoxia triggers the upregulation of particular miRNAs (like the miR-155, miR-146a), lncRNAs, and changes in DNA methylation patterns.
2. These changes amplify inflammation, thereby leading to the increased expression of pro-inflammatory cytokines like TNF- α , IL-6, and CRP(again).
3. Systemic inflammation increases oxidative stress and further promotes hypoxia by damaging endothelial cells, increasing vascular permeability, and impairing blood flow(which decreases O₂ supply).
4. Chronic inflammation and endothelial dysfunction worsens hypoxia, and the cycle repeats, with epigenetic modifications locking the cells into a pro-inflammatory state.

This continuous activation of inflammatory pathways and the dysregulation of metabolic and immune responses ensure that OSA continues to have wide-reaching effects on the cardiovascular, metabolic, and neurological systems, and this fuels a positive feedback loop. Check out Figure 5.

5 Epigenetics

5.1 Long Non-Coding RNAs

LncRNAs are another class of non-coding RNAs that have recently emerged as key regulators of gene expression in OSA. LncRNAs are involved in a wide range of cellular processes, including chromatin remodeling, gene silencing, and the modulation of transcription factors.

- **Regulation of Inflammatory Pathways:** In OSA, lncRNAs are found to play a role in the regulation of the inflammatory response via interaction with several transcription factors, such as NF-KappaB. For example, some lncRNAs affect gene expression that plays a role in immune cell activation, apoptosis, and cell cycle control. Disruption of these circuits can result in an increase in systemic inflammation, one of the features of OSA.
 - Example: A number of lncRNAs have been shown to control the expression of cytokines and enzymes modulating oxidative stress. These regulative functions increase the inflammatory cycle in OSA, by stimulating the influx of immune cells to the vasculature and by participating to endothelial injury and vascular impairment.

The capacity for lncRNAs to influence chromatin and gene expression has made them crucial in the establishment of OSA-associated inflammation. Through the promotion of the chronic activation of immune reactions, lncRNAs guarantee that the systemic consequences of OSA persist to improve.

5.2 MicroRNAs

MiRNAs are small noncoding RNAs that control gene expression by targeting complementary sites on the target mRNAs and inducing mRNA degradation or translation repression, respectively. MiRNAs have been suggested to play a role in regulating the host response to hypoxia and inflammation, both hallmarks of OSA.

- Hypoxia and miRNA Expression: Intermittent hypoxia, as a feature of OSA, induces alterations in miRNA expression. For instance, miR-155 and miR-146a are two miRNAs that are upregulated in response to hypoxia. These miRNAs have a target role in major inflammatory genes, including genes within the NF- κ B signaling pathway. Silencing these targets induces a pro-inflammatory milieu in OSA that perpetuates the inflammatory cycle.
 - **miR-155:** This miRNA contributes to the activation of the NF- κ B pathway, a key immune response regulator. Circulation of miR-155 in OSA has been demonstrated to be associated with the enhancement of pro-inflammatory cytokine release, which in turn is responsible for the systemic inflammation present in the disease.
 - **miR-146a:** Known for its anti-inflammatory properties, miR-146a modulates the Toll-like receptor (TLR) pathway, which plays a significant role in immune cell activation. In OSA, the downregulation of miR-146a leads to increased NF- κ B signaling, further worsening inflammation.

Thus, these miRNAs can lock the body into an inflammatory state as discussed before, creating a feedback loop that amplifies OSA's pathological effects. By regulating gene expression post-transcriptionally, miRNAs ensure that the inflammatory response is sustained, making them critical players in the progression of OSA.

5.3 DNA methylation

DNA methylation, one of the most investigated epigenetic modification, is the insertion of methyl group to cytosine base of DNA. This change typically inhibits gene expression through either inability to bind transcription factors or as a result of recruiting proteins with transcription inhibitory function. Hypoxia-Induced DNA Methylation Changes: As a result of intermittent hypoxia DNA methylation patterns are changed, specifically at genes that are related to inflammation and cellular metabolism. Such epigenetic alterations may "imprint" cells with an inflammatory phenotype and perpetuate the pathophysiological consequences of OSA.

- **TNF- α and Inflammation:** For example, the promoter region of the TNF-Alpha gene can undergo hypermethylation during hypoxic episodes, which leads to a reduction in expression of TNF- α . However, in OSA, chronic hypoxia can lead to alterations in DNA methylation, increasing TNF- α production and further worsening inflammation. This feedback loop of hypoxia-induced gene expression changes sustains the systemic inflammation seen in OSA.
 - **Insulin Resistance:** In addition, DNA methylation controls genes responsible for metabolic regulation, including genes in the insulin signaling pathway. Changes in gene methylation of these genes may lead to insulin resistance, and the OSA is linked to metabolic disorders such as type 2 diabetes.

Essentially, DNA methylation is a pathological molecular "memory" of hypoxic events, enabling the perpetuation of cells that promote inflammation and metabolic derangement. This, in turn, may have long-term implications on the patient, such as cardio-metabolic comorbidities due to OSA.

6 Circadian Rhythmicity and Sleep Apnea

6.1 Impact on Circadian Clocks

Intermittent hypoxia (IH), the pathophysiological signature of obstructive sleep apnea (OSA), has a deep tuning effect on circadian rhythms in all tissues. Research shows that IH alters expression of circadian clock genes, especially in lung and heart (sites of predominant hypoxic insult). These perturbations change the amplitude and average expression of rhythmic genes, which in turn have systemic consequences.

Throughout the lung about 74% of rhythmic genes are altered by IH, with broad effects on the circadian properties of genes (i.e., amplitude, midline estimating statistics of rhythm [MESOR]). Comparable but less dramatic changes are reported in the heart, where IH can modulate expression genes involved in circadian regulation as well as tissue adaptation to hypoxia.

6.2 Link to Systemic Comorbidities

Disruption of circadian rhythms in these tissues is associated with systemic OSA complications such as cardiovascular disease and metabolic disease. Abnormal circadian rhythms are implicated in the pathophysiological process of endothelial dysfunction, oxidative stress and inflammatory phenomena, further attenuating the pathophysiological outcomes of OSA. These results emphasize that circadian regulation is critical for homeostasis and that circadian regulation could be therapeutic target.

7 Additional Mechanisms and Impacts

7.1 Mitochondrial Dysfunction

Mitochondria, the powerhouses of the cell, are highly sensitive to oxygen fluctuations. Repeated hypoxia-reoxygenation cycles in OSA create oxidative stress and mitochondrial damage:

- **Increased ROS Production:** Hypoxia disrupts the electron transport chain (ETC) in mitochondria, leading to electron leakage and ROS overproduction during reoxygenation. These ROS damage mitochondrial DNA, lipids, and proteins, impairing mitochondrial function and energy metabolism.
- **Mitochondrial DNA Damage:** ROS-induced mutations in mitochondrial DNA impair the expression of key proteins required for ATP synthesis. Damaged mitochondria initiate mitophagy to eliminate dysfunctional organelles, but excessive damage overwhelms this system, leading to cellular energy deficits.
- **Reduced ATP Production:** Impaired oxidative phosphorylation decreases ATP levels, affecting energy-demanding tissues such as the brain, heart, and skeletal muscles. Energy deficits contribute to systemic fatigue, reduced exercise tolerance, and metabolic dysregulation in OSA patients.

8 Conclusion

Sleep apnea is a multifactorial disorder, with wide-ranging cardiovascular, neurological, and metabolic consequences. The present paper has pointed out the complex biological processes that underlie the condition, such as intermittent hypoxia, oxidative stress, systemic inflammation and related signaling pathways. Epigenetic changes, e.g., DNA methylation, miRNA and long non-coding RNA alterations, meanwhile drive these pathologic states, and associate sleep apnea with and links to hypertension, diabetes and neurodegenerative diseases.

9 Footnote

The author has attached the link to ML model to detect sleep apnea based on EEG data. <https://github.com/NJP6969/Sleep-apnea-ML> Relating the report to what was taught in class was done, to the best of the author's capabilities.

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