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The Role of Cyclooxygenase Enzymes and Microparticles in Obstructive Sleep Apnea Related Cerebrovascular Incidents

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ABSTRACT

Obstructive Sleep Apnea (OSA) is a sleep disorder caused by breathing problems that occur during sleep due to airway obstruction. Obstructive Sleep Apnea is quite common, but is often overlooked and misdiagnosed and untreated. Many studies have proven the relationship between OSA and pathological diseases such as cardiovascular disease and stroke. Intermittent Hypoxia (IH) that occurs in OSA patients can cause endothelial dysfunction and play a role in the atherogenesis of peripheral and central blood vessels of the brain. Hypoxic conditions cause the release of microparticles, inflammatory mediators and increase the expression of the enzyme Cyclooxygenase (COX) in the vascular endothelium. This causes an increase in inflammation-related prostanoid production which in turn causes endothelial damage and increases the risk of atherosclerotic plaque formation. This review article will discuss the role of inflammatory mediators, especially COX enzymes in OSA-related cerebrovascular incidents.

Keywords: cerebrovascular incidents, cyclooxygenase, intermittent hypoxia, obstructive sleep apnea

INTRODUCTION

Obstructive Sleep Apnea is a sleep disorder which is quite common and has an impact on people's quality of life. Obstructive Sleep Apnea is associated with an increased risk of traffic accidents, as well as cardiovascular morbidity and mortality.[1] Obstructive Sleep Apnea is a condition caused by repeated episodes of decreased muscle tone or collapse of the soft tissues of the upper airway required for airway patency. Obstructive Sleep Apnea symptoms include snoring, daytime sleepiness, headaches, sexual dysfunction, mood and behavior disturbances. Based on various studies, OSA is an independent predictor of cardiovascular and cerebrovascular disorders. Cardiovascular and cerebrovascular diseases associated with OSA include hypertension, heart failure, stroke, cardiac arrhythmias, myocardial ischemia, and pulmonary arterial hypertension. In addition, OSA is also associated with metabolic disorders which in turn are also risk factors for cardiovascular disease.[1]

Obstructive Sleep Apnea is a chronic disease that affects approximately 3-7% of the population and associated with an increased risk of cardiovascular and cerebrovascular disease. Obstructive Sleep Apnea is characterized by cessation of breathing during sleep due to repeated closure of the pharyngeal area, resulting in chronic intermittent hypoxia (IH). In healthy populations, exposure to IH might impair peripheral and cerebral vascular regulation, manifesting as increased resting blood pressure and slightly reduce cerebrovascular

resistance during hypoxia.[2] The mechanisms involved in the occurrence of vascular dysfunction associated with OSA are multifactorial. IH-induced inflammation is a fundamental factor leading to increased cardiovascular and cerebrovascular morbidity. Prostanoids are formed through the catabolism of Arachidonic Acid (AA) by COX enzymes.[3] Cyclooxygenase has 2 isoenzymes, namely COX-1 and COX-2, both of which are important mediators in the inflammatory response and vital regulators in peripheral blood vessels.[4,5] The increased risk of cerebral and peripheral vascular disease which is associated with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and selective COX-2 inhibitors emphasizes the importance of prostanoids in vascular regulation. Although nonselective and selective inhibition of COX-2 increase the risk of cardiovascular and cerebrovascular disease, there is still considerable controversy regarding the important role of COX-1 and COX-2 in forming prostanoids for vascular regulation. Under IH conditions, the concentration of prostanoids shifts towards vasoconstriction and atherogenesis. However, whether the shift of this concentration has an effect on increased blood pressure and changes in regulation of Cerebral Blood Flow (CBF) is still unknown.[6]

OSA AS A RISK FACTOR FOR STROKE

Obstructive Sleep Apnea is a risk factor for cardiovascular disease (CVD) and stroke. Apnea Hypopnea Index (AHI) ≥ 30 is a risk factor for stroke, compared to mild OSA with AHI ≥ 10. High blood pressure, increased cholesterol, lifestyle, type 2 Diabetes Mellitus (DM), and an unhealthy diet together with OSA are major risk factors for stroke. Mohsenin conducted a study in patients with OSA who also had stroke. This study primarily examined polysomnographic descriptions that showed more sleep disturbances in stroke patients with OSA compared to controls. The severity of OSA has a relationship with the severity of the initial symptoms of stroke and clinical outcomes after stroke. Other studies have also emphasized that OSA is more common in stroke patients regardless of neurological damage to the brain area and lesions. The severity of OSA plays an important role in the incidence of stroke and serves as an independent risk factor of stroke that affects mortality and morbidity. One longitudinal prospective study examining older people (aged 70-100 years) showed that patients with severe OSA (AHI≥30) had a higher incidence of stroke than patients without OSA. Stroke patients with OSA have poorer prognosis, longer hospital stay and spend more time in rehabilitation.[7]

Obstructive Sleep Apnea is associated with neurological deficits in stroke patients. OSA severity level ≥ 25 can worsen the stroke severity. Obstructive sleep apnea is present in many stroke patients before stroke occurs, regardless of the existing neurological deficit. Obstructive sleep apnea is common in older men with stroke and also associated with type 2 diabetes, contributing to the greater risk of death after stroke. Other studies also emphasize that further risk factors for stroke are OSA, age, male gender, ethnicity, hypertension, and atrial fibrillation (AF). Cardiac arrhythmias are more common in OSA patients compared to those without OSA and related to higher stroke events compared to the control group. Atrial Fibrillation is one of the main risk factors for thromboembolic stroke. The underlying pathology of AF may worsen in the presence of OSA and associated with other comorbidities such as high blood pressure and cardiomyopathy. In OSA patients, cardioembolic stroke is more common in the presence of AF. When AF is treated with anticoagulant drugs, the incidence of stroke decreases significantly.[7]

SLEEP DISORDERS AND INFLAMMATION

Sleep is one of the most widely observed phenomena in mammals and plays an

important role in the regulation of physiological and psychological systems. The important role of sleep in the physiology of animal and human models is evidenced by the effects induced by sleep disturbances, especially sleep deprivation. Serious physiological consequences include decreased neurogenesis, cognitive dysfunction, altered metabolism, cardiovascular disease, impaired immunity, and disruption of the blood-brain barrier. Acute and chronic sleep disturbances are associated with impaired balance of energy, cellular and humoral immunity changes. Experimental studies have shown that acute and chronic sleep disturbances result in problems of the immune response, characterized by deficits in cellular components and increased levels of proinflammatory mediators, such as Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), IL-6, IL 17A, and C-Reactive Protein (CRP).[8] Sleep disorders also increase the levels of other inflammatory mediators such as COX-2, Nitric Oxide Synthase (NOS), Endothelin-1 (ET-1), Vascular Endothelial Growth Factor (VEGF), and Insulin-like Growth Factor-1 (IGF 1).[9,10]

OSA AND STROKE PATHOPHYSIOLOGY

Apnea episodes or hypoxemia in OSA initiate the inflammation and there is a cascade of inflammatory markers such as IL, 1, IL 6, TNF-α, and Interferon γ. These inflammatory markers damage the vascular endothelial lining and increase platelet aggregation leading to further oxidative stress and vascular endothelial damage. Repetitive oxidative stress and vascular damage in OSA patients can cause CVD and stroke.[11] Apnea or hypoxemia condition also stimulates sympathetic system related to catecholamine release and increased blood pressure causing platelet aggregation leading to CVD and stroke.[12] Episodes of apnea and hypoxia not only stimulate the sympathetic system, but also suppress the parasympathetic pathways. This inhibition helps in the release of inflammatory mediators, leading to more severe oxygen desaturation, platelet aggregation and endothelial damage.[13]

The release of inflammatory mediators and sympathetic system activation in OSA patients increase the risk of CVD and stroke. Recurrent episodes of apnea and hypoxemia lead to overproduction of Reactive Oxygen Species (ROS), oxygen desaturation and hypoxia further causes ischemia in the brain and causes TIA and stroke. A study shows that OSA can play a role in causing Silent Brain Infarction (SBI). Patients with moderate to severe OSA with SBI also show increased of inflammatory markers. OSA patients with Continuous Positive Airway Pressure (CPAP) therapy, obtained significant improvement in inflammatory markers. White matter is more frequently affected in OSA patients. This condition is a predisposing factor for stroke and the severity is equal with the severity of OSA. Some theories that explain this relationship, when oxyhemoglobin saturation is less than 90% and AHI ≥ 15 in stroke patients, oxygen desaturation causes hyperintensity in the white matter of TIA and stroke patients.[7]

THE ROLE OF MICROPARTICLES IN OSA PATIENTS

Obstructive sleep apnea is a very common disease characterized by recurrent episodes of partial or complete upper respiratory tract obstruction during sleep, leading to repeated decrease in oxygen saturation, increase in intrathoracic negative pressure and frequent awakenings from sleep. There is clear evidence of an independent association between OSA and cardiovascular events. Incidence rates of coronary heart disease and stroke are higher in men with severe OSA. Recent data show that OSA also contributes to cardiac systolic and diastolic dysfunction, as well as an increased incidence of cardiac arrhythmias. Data from clinical and experimental studies indicate that intermittent hypoxia is the main component that links OSA to

atherosclerosis. Intermittent hypoxia induces endothelial dysfunction, systemic vascular inflammation, oxidative stress and activation of vascular smooth muscle cells, and causes various vascular risk factors such as dyslipidemia, insulin resistance and hypertension. [13,14]

Obstructive Sleep Apnea causes pathological conditions that can increase risk factors for atherosclerosis such as hypertension, diabetes and dyslipidemia, and is thought to have a direct proatherogenic effect on the vessel wall. An increasing number of recent studies are focusing on the role of microparticles (MP) in atherogenic processes. Microparticles are vesicles with a small plasma membrane secreted by various vascular cells or blood cells and contain both membrane and cytosolic elements. A case-control study has shown that MP is increased in OSA. These MPs include Platelet-Derived Microparticles (PMP), Endothelium-Derived Microparticles (EMP) and Leukocyte-Derived Microparticles (LMP). Endothelial and leukocyte-derived MP levels are increased in OSA.[14,15]

There are evidences, in both animal and human models of intermittent hypoxia, that OSA is related to endothelial dysfunction, whereby endothelial dysfunction is an important factor in the development of atherosclerosis. Experimental data have also shown that MP can cause endothelial dysfunction. Microparticles released in vitro by Apoptotic T-lymphocytes impair endothelial function by stimulating the formation of oxygen free radicals and decreased Ser1179 of endothelial Nitric Oxide Synthase (eNOS). The study conducted by Priou et al., by collecting blood samples from OSA patients showed that MP from OSA patients was characterized by nocturnal desaturation which caused *ex vivo* in the aorta and small mesenteric arteries when injected into rats. Incubation of endothelial cells *in vitro* with MP from OSA patients for 24 hours resulted in decreased NO production, regardless of oxidative stress conditions. Furthermore, decreased cellular NO production was correlated with circulating levels of CD62L+ LMP, suggesting a specific role for CD62L+ LMP in the development of OSA-associated endothelial dysfunction. In a subsequent study, MP from OSA patients injected into rats induced *ex vivo* in the aorta. Molecular investigations showed that MP from OSA patients reduced eNOS activity and subsequently NO production, increased aortic COX-1 and COX-2 expression, and increased production of thromboxane A2 and prostacyclin. Overall, these findings support the potential implications of circulating MP-associated endothelial dysfunction in OSA patients.[15,16]

There are evidences that OSA is associated with inflammation of the blood vessels, which is considered to be a major cause of the atherogenic process. OSA patients have increased serum levels of TNF-a, IL-6, IL-8, CRP and adhesion molecules (CD62L, soluble CD62E, CD62P, Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Adhesion Molecule-1 (VCAM-1). Microparticles are key factors in the inflammatory process, and contribute to the production of various pro-inflammatory cytokines and chemokines from the endothelium. Microparticles isolated from human atherosclerotic plaques were found to stimulate IL-1β and IL-6 release and induce expression of ICAM-1, VCAM- 1 and CD62E. When incubated for 24 hours with endothelial cells, MP isolated from OSA patients induced the overexpression of pro-inflammatory molecules, including CD62E, COX-2 and ICAM-1. When injected into mice, MP from OSA patients induced the overproduction of pro-inflammatory enzymes such as COX-1 and COX-2 in the aorta, and also overproduction of pro-inflammatory cytokines in the supernatant of the animal aorta (thromboxane A2, 8-isoprostane, prostacyclin and prostaglandin E2). Overall, these findings support a role for MP in vascular inflammation associated with OSA.[15]

It is clearly demonstrated that the process of atherogenesis is related to oxidative stress and lipid peroxidation. In animal models of OSA, intermittent hypoxia increases the formation of ROS in blood vessel walls, induces lipid peroxidation and induces the formation Low-Density Lipoprotein (LDL) which is a substrate for atherosclerotic plaques. The study of Jelic et al., showed an increase in oxidative stress in endothelial cells taken from the blood vessels of OSA patients. Increased lipid peroxidation and increased levels of oxidized LDL were observed in OSA patients. Microparticles can modulate oxidative stress.-sensitive mechanism xanthine oxidase.[14,17]

ROLE OF COX IN OSA-RELATED CEREBROVASCULAR INCIDENTS

As previously explained, sleep disorder such as OSA can cause intermittent hypoxic conditions which increases the release of inflammatory mediators. Interleukin-1 will cause the release of IL-6 and Prostaglandin E2 (PGE2) in endothelial cells. In vivo studies in rats have shown that IL-1 induces disease conditions induced by binding of IL-1 to the IL-1 Receptor-1 (IL-1R1). The mechanism that might occur is the induction of COX-2 in endothelial cells in the brain after IL-1R1 activation is characterized by an increase in PGE2 synthesis. Interleukin-6 has a pyrogenic effect when released endogenously during systemic inflammation. *Interleukin-6* will bind to its receptor IL-6 Receptor-α (IL-6Rα) on brain endothelial cells which then gives its effect. Furthermore, IL-6 will induce COX-2 to increase PGE2 production.[18]

Tumor Necrosis Factor-α activates the Nuclear Factor Kappa β (NF$\kappa\beta$) signaling pathway, which in turn increases PGE2 level through COX-2. Cyclooxygenase-2 plays an important role in the inflammatory response in the blood-brain barrier, especially the COX-2 derivative, namely PGE2, which causes an increase in the permeability of the blood-brain barrier.[19] Other cytokines, such as IL-1, use other signaling pathways that eventually coalesce in the induction of COX-2, in particular IL-1R1 signaling through p38 Mitogen-Activated Protein Kinase (MAPK) and c-Jun to induce COX-2 synthesis, whereas IL-6 receptor activation leads to COX-2 expression through activation of Signal Transducer and Activator Transcription-3 (STAT-3). Activation of NFκB by TNF-α and IL-1β also correlated with COX-2 expression in microvascular endothelial cells. Both NF Kappa B Inhibitor α (IκBα) and COX-2 are expressed on the same endothelial cells, indicating a potential interaction between transcription factors and COX-2 expression in endothelial cells in brains with systemic inflammation. [10,20]

Previous study conducted by Nacher et al., in experimental rats that experienced OSA for 3 hours (60 apnea/hour, apnea 15 seconds) or 3 hours IH (15 seconds hypoxia and 15 seconds normoxia) decreased Prostaglandin I2 (PGI2) and increased TXA2 metabolites compared to the control group. The study by Gautier Veyret et al., reported a 70% increase in COX-1 mRNA and a 25% increase in COX-2 mRNA in mice exposed to chronic IH (8 weeks, 60 second IH cycle, 8 hours/day).[21] Lesion size IH-induced atherosclerosis correlated with COX-1 and thromboxane synthase mRNA, and selective COX-1 inhibition reduced the size of atherosclerotic lesions following IH exposure. This study supports the important role of COX-1 in the etiology of cardiovascular disease due to chronic IH exposure.[6]

Upregulation of the Renin-Angiotensin System (RAS) through increased activation of the sympathetic system is involved in increases the blood pressure. Renin-Angiotensin System suppression through salt administration and kidney denervation in rats can prevent increase in blood pressure induced by IH. In swine models with OSA, renal denervation reduced blood pressure post-apneic and inhibited the increase components of the RAS in circulating associated with 4 hours of obstructive apnea.[6]

Inhibition of Type 1 Angiotensin-II Receptors (AT1Rs) prevents the increase in blood pressure by inhibiting oxidative stress and decrease NO bioavailability. Increased superoxide formation, angiotensin-II also increases COX-2 expression in vascular smooth muscle by binding to AT1Rs, and increased COX-2 activity strengthens the effect of angiotensin-II on vascular smooth muscle cells. In addition, prostanoids mediate the release of renin from the kidney in response to sympathetic activation and this appears to be highly COX-2-dependent because renin release is reduced by COX-2 inhibition. Based on this study, it was concluded that the RAS-induced increase in blood pressure with IH may be COX-2-dependent. [6,22,23]

CONCLUSION

Obstructive Sleep Apnea is a serious disease caused by cardiovascular disease or increases the severity and development of cardiovascular disease. Strong evidence suggests that OSA is an independent risk factor for stroke, exacerbates stroke-induced brain tissue damage, increases the risk of recurrent stroke, and contributes to brain atrophy and dementia in the elderly. The main molecular and cellular mechanisms involved in cerebrovascular dysfunction in OSA patients are endothelial dysfunction and oxidative stress. Obstructive Sleep Apnea causes intermittent hypoxic condition both acute and chronic which causes the release of microparticles and inflammatory mediators. Several studies demonstrated the important role of MP in the occurrence of endothelial dysfunction in OSA patients. Cyclooxygenase-2 is an enzyme induced by inflammatory conditions which will produce prostanoids. Prostanoids are one of the main factors causing endothelial dysfunction and involved in the process of atherogenesis in both peripheral and central circulation of brain.

Obstructive Sleep Apnea can last in the long term because most individuals with OSA are not diagnosed, so that disturbances in cerebral circulation occur for a long time which can make a person susceptible to stroke, transient ischemic attack (TIA) and dementia. The incidence of cerebrovascular disease associated with OSA is predicted to increase because the world's population is currently older and associated with obesity which is a risk factor for OSA. In the future, it is necessary to consider the management of MP and COX in OSA patients to prevent stroke or improve prognosis of stroke.

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