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THEORETICAL REVIEW

Obstructive sleep apnea and cognitive impairment: Addressing the blood–brain barrier

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SUMMARY

Increasing data support a connection between obstructive sleep apnea (OSA) and cognitive impairment but a causal link has yet to be established. Although neuronal loss has been linked to cognitive impairment, emerging theories propose that changes in synaptic plasticity can cause cognitive impairment. Studies demonstrate that disruption to the blood–brain barrier (BBB), which is uniquely structured to tightly maintain homeostasis inside the brain, leads to changes in the brain's microenvironment and affects synaptic plasticity. Cyclical intermittent hypoxia is a stressor that could disrupt the BBB via molecular responses already known to occur in either OSA patients or animal models of intermittent hypoxia. However, we do not yet know if or how intermittent hypoxia can cause cognitive impairment by mechanisms operating at the BBB. Therefore, we propose that initially, adaptive homeostatic responses at the BBB occur in response to increased oxygen and nutrient demand, specifically through regulation of influx and efflux BBB transporters that alter microvessel permeability. We further hypothesize that although these responses are initially adaptive, these changes in BBB transporters can have long-term consequences that disrupt the brain's microenvironment and alter synaptic plasticity leading to cognitive impairment.

Introduction

The study of obstructive sleep apnea (OSA) is important because its incidence and prevalence is likely to be increasing and because OSA is associated with many chronic diseases. Obesity is the major risk factor for OSA in middle-aged adults[1–4] and with obesity rates increasing, it is likely that the prevalence and incidence rates of OSA in the general population are also increasing.[5,6] OSA is associated with cardiovascular and metabolic diseases but its association with cognitive impairment is less well studied. In the last decade, studies have shown an association of OSA to various cardiovascular diseases,[7] metabolic disorders[8,9] and an increased risk of cancer mortality.[10] Studies are showing an association of OSA to cognitive impairment. Surprisingly, 70–80% of patients with Alzheimer's dementia meet the criteria for OSA (OSA defined as apnea hypopnea index (AHI) > 5) with 38–48% of this population having an AHI >20[11–14] compared to 5.4% OSA in age-matched controls without Alzheimer's.[13] In elderly women, the prevalence of OSA (AHI > 15) was found to be associated with increased risk of future development of dementia or mild cognitive impairment.[15] This association between OSA and seemingly different classes of diseases- cardiovascular, metabolic, cancer and neurodegenerative diseases- raises the possibility of a common underlying pathogenetic mechanism that links OSA primarily or secondarily to these chronic diseases. Common underlying mechanisms include chronic intermittent hypoxia[15,16] and sleep fragmentation.[17–21]

Cognitive impairment can be the consequence of intermittent hypoxia causing neuronal loss in the hippocampus[22] and wake-active neurons.[23] But frank neuronal loss may not be essential for cognitive impairment to occur. Changes in the brain's 10^{14} synaptic connections is what allows us to learn, form memories and respond to environmental stimuli.[24] Dendritic spines are the

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List of abbreviations

ABC transporter	ATP binding cassette transporter
AHI	apnea-hypopnea index
AP-1	activator protein-1
ARNT	aryl hydrocarbon receptor nuclear translocator
ATP	adenosine triphosphate
BBB	blood-brain barrier
BCRP1	breast cancer resistance protein
b-FGF	basic fibroblast growth factor
BMI	body mass index
BOLD fMRI	blood-oxygen level dependent functional magnetic resonance imaging
C/EBP	CCAAT/enhancer binding proteins
CIH	chronic intermittent hypoxia
CNS	central nervous system
CPAP	continuous positive airway pressure
DLL4	delta like ligand 4
EAAT	excitatory amino-acid transporter
EBF	early B-cell factor
ELISA	enzyme-linked immunosorbent assay
EPAS-1	endothelial PAS domain-containing protein 1
GABA	gamma-aminobutyric acid
GAT2	gamma-aminobutyric acid transporter 2
GLUT1	glucose transporter 1
Hif	hypoxia inducible factors
HRE	hypoxia responsive elements
IL-6	interleukin-6
MCT	monocarboxylate transporter
MIP-2	macrophage inflammatory protein-2
MRP1	multidrug resistance protein 1
NET	norepinephrine transporter
NFκB	nuclear factor kappa B
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PG	prostaglandins
PPAR	peroxisome-proliferator activated receptors
PPRE	peroxisome proliferator response element
PUFA	polyunsaturated fatty acids
RNS	reactive nitrogen species
ROS	reactive oxygen species
RT-PCR	real-time polymerase chain reaction
RXR	retinoid X receptor
SERT	serotonin transporter
SOD	superoxide dismutase
SUR1	sulfonylurea receptor 1
TNF-α	tumor necrosis factor-alpha
uPAR	urokinase receptor
VEGF	vascular endothelial growth factor
VVO	vesicle-vacuolar organelles

Glossary of terms:

Mild cognitive impairment:	definition from the National Institute of Ageing – a condition in which people have memory or other thinking problems greater than normal for their age and education, enough to be noticed and measured, but not compromising a person's independence.
Homeostasis:	the ability for a biological system to maintain its internal environment while continuously interacting with and adjusting to stimuli originating from within or outside the system.
Oxidative stress:	a net overproduction of reactive species as well as non-radical species (e.g., hydrogen peroxide, lipid peroxide) that leads to damage of specific molecules and consequential injury to cells and/or tissue.
Cellular oxygen sensor:	molecules that respond to the mismatch of oxygen demand and supply and attempts to maintain an optimal oxygen partial pressure.
Chronic inflammation:	inflammation that is characterized by its persistence and lack of resolution
Angiogenesis:	formation of new blood vessels from pre-existing vessels to supply oxygen and nutrients
Leak:	increased passage of molecules (e.g., ions, water, glucose) in a pericellular manner (through tight junctions)
Microvessel permeability:	the ability of blood vessels to allow small molecules (e.g., ions, water, glucose) and cells (e.g., leukocytes) to pass in a transcellular manner (through transporters, pores and channels)

structural basis of these synaptic connections and their structure is regulated in response to synaptic plasticity (the strength of a synapse, or connection, between two neurons that changes in response to its history of use or disuse).[25] It has also been argued that toxins (like Aβ accumulation)[26] impair structural and functional plasticity of these synapses. Therefore, we propose that intermittent hypoxia causes changes at the BBB, and although this has not yet been described, we know that sustained hypoxia causes changes at the BBB.[27] In this review, we identify mechanisms whereby intermittent hypoxia may alter blood–brain barrier permeability, causing changes in synaptic plasticity and consequently, cognitive impairment.

To address these concepts, this review will be divided into three main sections. The first section will outline the structure and function of the blood–brain barrier (BBB) while the second section will review how cyclical intermittent hypoxia can generate reactive oxygen species (ROS), stabilize and activate oxygen sensors and perpetuate the state of chronic inflammation (see Fig. 1). In the third section we discuss how cyclical intermittent hypoxia might alter microvessel permeability by: 1) changing the expression of influx and efflux transporters at the BBB due to increased nutrient and oxygen demand but also possibly through 2) an acute leak through the tight junctions of the BBB or 3) a leak through vascular pores during angiogenesis.

The blood–brain barrier

The structure of the BBB gives rise to a uniquely resistant and highly regulated barrier. This unique barrier is able to maintain homeostasis within the brain, different from other organs, all the while dynamically responding to regional increases in metabolic demand within the brain. This first part of this review will be further divided into two sections: 1) structure of the BBB; and 2) the normal function of the BBB.