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Sleep apnea: An overlooked cause of lipotoxicity?

Chenjuan Gu[a,b], Haris Younas[a], Jonathan C. Jun[a,*]

[a] Division of Pulmonary and Critical Care, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA
[b] Department of Pulmonary and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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ABSTRACT

Obstructive sleep apnea (OSA) is a common sleep disorder associated with diabetes and cardiovascular disease. However, the mechanisms by which OSA causes cardiometabolic dysfunction are not fully elucidated. OSA increases plasma free fatty acids (FFA) during sleep, reflecting excessive adipose tissue lipolysis. In animal studies, intermittent hypoxia simulating OSA also increases FFA, and the increase is attenuated by beta-adrenergic blockade. In other contexts, excessive plasma FFA can lead to ectopic fat accumulation, insulin resistance, vascular dysfunction, and dyslipidemia. Herein, we propose that OSA is a cause of excessive adipose tissue lipolysis contributing towards systemic "lipotoxicity". Since visceral and upper-body obesity contributes to OSA pathogenesis, OSA-induced lipolysis may further aggravate the consequences of this metabolically harmful state. If this hypothesis is correct, then OSA may represent a reversible risk factor for cardio-metabolic dysfunction, and this risk might be mitigated by preventing OSA-induced lipolysis during sleep.

Introduction

Obstructive sleep apnea (OSA) is a common breathing disorder associated with risks of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD). At least some of this association is attributable to the fact that OSA is common amongst those with visceral obesity [1]. These individuals often have increased neck and tongue fat and smaller lung volumes, which serve to reduce upper airway caliber [2,3]. This predisposition of viscerally obese individuals to develop OSA has fueled the claim that OSA is no more than an "epiphenomenon" of obesity [4]. However, some studies support the concept that OSA can induce cardiometabolic dysfunction [5,6]. Proposed causal mechanisms include over-activation of sympathetic nervous system (SNS) [7,8], tissue hypoxia [9–11], oxidative stress [12,13] and inflammation [14,15]. Comparatively less attention has been directed towards changes in lipid metabolism during sleep. Specifically, high levels of free fatty acids (FFA) are recognized to impair metabolic and vascular function [16,17]. We suggest that OSA causes dysregulation of FFA metabolism during sleep, which in turn mediates several of its adverse cardiometabolic consequences.

The hypothesis

We hypothesize that OSA causes lipotoxicity by inappropriately stimulating lipolysis during sleep. Under normal circumstances, sleep decreases metabolic demand, oxygen consumption [18], fatty acid oxidation (FAO) [19] and adipose tissue lipolysis [20]. OSA and its components of sleep fragmentation/arousal, hypoxemia and hypercapnia independently and synergistically activate the sympathetic nervous system (SNS) as measured by catecholamines [21–23], heart rate elevation or variability [24,25], and muscle sympathetic nerve activity [26,27]. Autonomic impacts of OSA have also been simulated in animal models [28,29]. Subsequently, circulating catecholamines and sympathetic nerve endings in white adipose tissue can stimulate tissue lipolysis [30]. The mobilized FFA may not be appropriately utilized for energy during sleep, leading to ectopic lipid deposition in liver, skeletal muscle and vascular endothelium. Intermediates of incompletely oxidized fatty acids in these tissues subsequently cause lipotoxicity [31–34]. Hence, OSA may induce a mismatch between lipolysis and FAO during sleep, creating the "perfect storm" for lipotoxicity (Fig. 1).

Evaluation of the hypothesis

OSA and intermittent hypoxia stimulate lipolysis

Evidence is accumulating that OSA increases circulating FFA. In a Spanish study comparing OSA patients to BMI-matched controls, OSA patients had higher fasting serum FFA levels. FFA levels were related to AHI in a multiple regression model after adjustment for age, sex, BMI

* Corresponding author at: Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Rm 5A50.B, Baltimore, MD 21224, USA.
E-mail address: jjun2@jhmi.edu (J.C. Jun).

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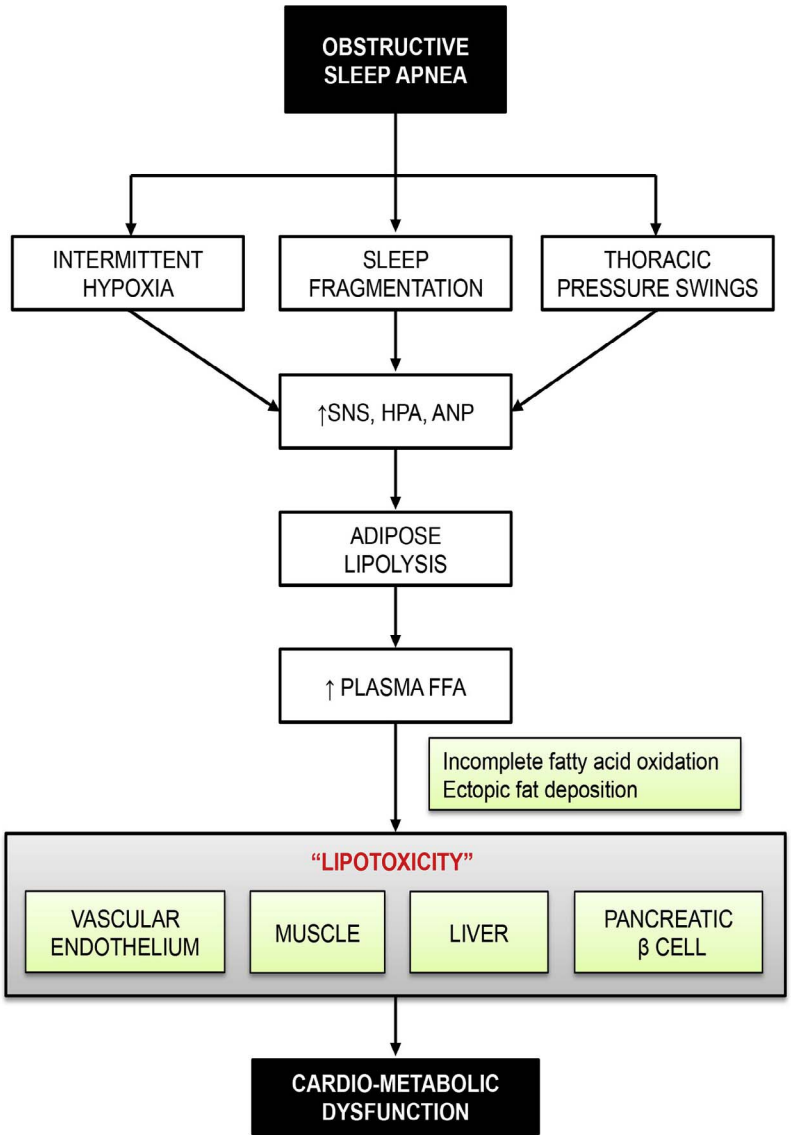

Fig. 1. Hypothesis of lipotoxicity underlying cardiometabolic dysfunction in OSA patients. SNS, sympathetic nervous system; HPA, hypothalamic pituitary axis; ANP, atrial natriuretic peptide; FFA, free fatty acid.

and the presence of metabolic syndrome [35]. Our laboratory demonstrated that OSA increased plasma FFA in CPAP-naïve heart failure patients, and this increase was abolished with oxygen [36]. More recently, we confirmed that OSA elicited by CPAP withdrawal dynamically increased nocturnal plasma FFA in non-heart failure patients, and FFA levels fluctuated with heart rate and respiratory events during sleep [24]. In animal models of OSA, chronic intermittent hypoxia (IH) increased FFA, accelerated dyslipidemia and atherosclerosis in apolipoprotein E-deficient mice fed a high cholesterol diet [37]. IH also increased plasma FFA in mice, which was abolished by β blockade with propranolol [38] or a lipolysis inhibitor, acipimox [39]. Likewise, SNS-mediated lipolysis occurs during high altitude hypoxia in healthy humans [40]. Hence, OSA and other hypoxic stimuli cause adipose tissue lipolysis resulting in episodic or chronic FFA elevation. OSA may stimulate lipolysis by several pathways, including the SNS, hypothalamic-pituitary-adrenal (HPA) axis, and natriuretic peptides, which will be described below.

Mechanisms of OSA-mediated lipolysis

Sympathetic nervous system activation

OSA is a recognized cause of SNS activation. During sleep, patients with OSA endure repetitive episodes of upper airway obstruction, IH, intra-thoracic pressure changes, and arousals [41]. These events are accompanied by increases in heart rate, blood pressure [24,42], catecholamines [21,22], and muscle sympathetic nerve activity [26,27]. Moreover, OSA increases risks of diurnal hypertension [43,44], signifying "spillover" of sympathetic activation from the sleep to wake period. In numerous studies, augmented SNS activity during sleep is reversed by continuous positive airway pressure (CPAP). Simulation of OSA with IH increased cardiac SNS activity in awake healthy volunteers [45]. Nocturnal exposure of IH in healthy humans increased BP beyond the exposure period, as well as augmented muscle SNS activity [46,47]. Animal models of OSA have also recapitulated these findings. For example, rats exposed to IH demonstrated catecholamine elevations [28] while pigs subjected to mechanical airway obstruction increased heart rate and coronary blood flow, which was eliminated by β-adrenergic receptor blockade with propranolol [48]. Thus, multiple lines of evidence show that OSA increases systemic SNS activity during sleep, with carryover effects into wakefulness. The SNS is the classical activator of lipolysis and exerts this control via circulating catecholamines and direct innervation of adipose tissues [30].

Hypothalamic-pituitary-adrenal (HPA) activation

Cortisol acts synergistically with catecholamines to stimulate adipocyte lipolysis [49]. Kritikou et al. showed that OSA patients have