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Sleep apnea: An overlooked cause of lipotoxicity?

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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.

Keywords

Sleep apnea; Sympathetic nervous system; Lipolysis; Free fatty acid; Lipotoxicity

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 viscera

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Conflict of interest

The authors declare that they have no conflict of interest.

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 stimulated 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 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 higher 24-hr cortisol levels compared to controls, and the cortisol profile was reduced by CPAP [50]. Similarly, CPAP withdrawal increased nocturnal cortisol and was shown to increase dynamically with awakenings from sleep [24].

Natriuretic peptides—Natriuretic peptides control sodium handling by the kidneys, regulating blood volume and pressure. Atrial natriuretic peptide (ANP) is secreted by heart muscle in response to atrial stretch and sympathetic activity. ANP receptors are present in adipose tissue, and ANP applied to fat cells *in vitro* potently stimulates lipolysis [51]. In a study of heart failure patients, CPAP significantly lowered ANP in conjunction with improvements in ejection fraction and mitral regurgitant fraction [52]. Similarly, CPAP reduced ANP levels in small studies of non-heart failure patients [53, 54]. However, a cross-sectional study did not find a relation between morning ANP and OSA severity [55].

Consequences of OSA-induced lipolysis

Circulating FFA levels fluctuate widely, reflecting the balance between adipose tissue lipolysis and endothelium/tissue lipid take. Increased plasma FFA in OSA patients therefore reflects, at least transiently, excess FFA availability. In subjects with “flexible” metabolism [56], these shifts in substrate availability may be inconsequential or even beneficial. In fact, treatment of OSA with CPAP causes weight gain [57], suggesting that untreated OSA may increase the oxidation of at least a portion of mobilized FFA. However, mobilized FFA that do not undergo complete oxidation may be re-esterified (fatty acid-triacylglycerol recycling)

or deposit in non-adipose tissues as intermediates such as diacylglycerol or ceramide [58, 59]. These molecules impair insulin receptor signaling in skeletal muscle [33, 60]. In experimental settings, acute elevation of plasma FFA increased intramyocellular triglyceride content and whole body IR within 4 hours [33]. Increased FFA in other tissues such as liver, pancreas, or vascular endothelium leads to hepatic steatosis and dyslipidemia [31, 61–63], β -cell apoptosis [64], and inflammatory endothelial dysfunction [34, 65], respectively. Compared to wakefulness, sleep reduces oxygen consumption and fatty acid oxidation [18, 20, 66]. Stimulation of lipolysis during sleep could therefore increase fatty acid-triacylglycerol cycling and ectopic lipid deposition. Thus, the spectrum of metabolic abnormalities associated with OSA may be mediated by inappropriate stimulation of lipolysis during sleep.

EMPIRICAL DATA

There is some evidence, mostly indirect in nature, to suggest that OSA causes ectopic lipid deposition. Increased fatty acid-triacylglycerol cycling may alter fat distribution - shifting fat from subcutaneous to visceral depots, to the liver, or into circulating lipoproteins. Some [67–70] but not other studies [71, 72] have shown regression of visceral adiposity in OSA patients after chronic CPAP therapy. In terms of hepatic fat, OSA is associated with non-alcoholic fatty liver disease [73–77]. CPAP use may improve liver enzymes and liver fat content [78, 79] but was without effect in other studies [80, 81]. With regard to plasma lipids, a meta-analysis reported that CPAP modestly reduced cholesterol and triglycerides in association with reduced autonomic activity [82]. Skeletal muscle accounts for at least 75% of insulin-mediated glucose disposal [83], and is the most studied site of fatty acid-induced IR. Several studies indicate that OSA inhibits insulin-mediated glucose uptake in skeletal muscle. We found that CPAP withdrawal increased plasma FFA and glucose. The elevation in glucose was ascribed to reduced glucose clearance, not an increase in nocturnal hepatic glucose output [24]. In rodent studies, chronic IH caused IR as measured by hyperinsulinemic euglycemic clamps, and decreased glucose oxidation in oxidative muscle fibers [7]. Weiszenstein *et al.* showed that chronic IH-induced IR could be prevented by administering the lipolysis inhibitor, acipimox [39]. Diabetes-prone Tallyho/JngJ (TH) mice exposed to IH exhibited pancreatic β -cell apoptosis and dysfunction, in association with increased FFA levels in plasma and pancreatic tissue [11]. Healthy volunteers exposed to 8 hours of IH showed increase in the expression of toll receptor 2 (TLR-2) in peripheral blood mononuclear cells. TLR-2 is a proinflammatory mediator shown to foster atherosclerosis [84, 85], which can be activated by long chain saturated fatty acids [86]. Acute IH [87] or sustained hypoxia in humans [40] stimulates lipolysis, conditions under which fat oxidation may be simultaneously reduced [88]. Overall, even though data is robust that OSA increases FFA, more studies are needed to prove that OSA is a cause of systemic lipotoxicity.

CONSEQUENCES AND DISCUSSION

To reiterate our hypothesis, we predict that an exuberant lipolytic response to OSA can lead to cardiometabolic dysfunction. We acknowledge that this hypothesis is but one of many other possible theories in the field. For example, a prevailing theory contends that tissue hypoxia and/or re-oxygenation mediate inflammation and oxidative stress in OSA [89].

Oxygen desaturation is associated with impaired glucose metabolism and IR in some OSA cohorts [90, 91]. Human [45] and animal studies [92, 93] have shown that IH induces glucose intolerance and IR. Interestingly, hypoxia improves insulin sensitivity in healthy obese men [94] and increases glucose transport in skeletal muscle [95] calling into question a direct injurious role of hypoxia. Rather, it appears that SNS activation by hypoxemia affects glucose metabolism: pharmacologic SNS blockade [38] or surgical removal of the arterial oxygen sensor, the carotid body prevent IH-induced changes [8].

OSA is a complex disorder with variable causes and clinical manifestations, and afflicts patients with different degrees of metabolic fitness. As such, metabolic responses to OSA will certainly differ. Indeed, we observed marked variability in lipolytic and glycemic responses to OSA in our recent CPAP withdrawal study [24], and only some of this variability could be explained by diabetes status or OSA severity. To test our hypothesis, further studies are needed to determine whether: (1) SNS stimulation is the main cause of adipose tissue lipolysis in OSA; (2) OSA stimulates lipolysis in excess of fatty acid oxidation; (3) OSA causes ectopic lipid deposition in tissues such as liver and skeletal muscle; (4) inhibition of lipolysis can prevent cardio-metabolic consequences of OSA. If our hypothesis is confirmed, we will reveal a root cause of metabolic dysfunction in OSA, and establish a new pharmacologic target to protect against OSA cardiometabolic consequences.

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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.