Obstructive sleep apnea: wreaking havoc with homeostasis

THE PHENOTYPIC CHARACTERIZATION of obstructive sleep apnea (OSA) continues to unfold. Recent studies provide evidence that this syndrome has the potential to disturb cardiovascular, neurological, and endocrine homeostatic processes (1, 6, 8, 9). Li et al. (5) present convincing evidence that long-term exposure to hypoxia-reoxygenation, modeling oxygenation patterns of severe sleep apnea, impairs lipid homeostasis in the liver in an animal model of obesity and insulin resistance. This impairment suggests that hypoxia-reoxygenation patterns of sleep apnea could worsen nonalcoholic fatty liver disease.

Nonalcoholic fatty liver disease includes a spectrum of disorders ranging from fatty infiltration to steatosis or steatosis occurs. A second hit by oxidative hepatocytes and also through a high-fat diet (4). As a single hit, presence of insulin resistance-mediated accumulation of fat in these individuals will develop cirrhosis (2). In a recent prospective series of adults presenting to a sleep clinic, a threefold increase in the likelihood of elevated liver enzymes was found in subjects with newly diagnosed severe OSA (11). Liver biopsy, performed only on subjects with abnormal liver enzymes in this same study, identified NASH in the vast majority of subjects with severe OSA, whereas a minority of subjects with mild or no OSA had biopsy-proven NASH (11). The presence of NASH was related to the apnea-hypopnea index, independent of age and body mass index. Subjects with severe OSA, however, had more pronounced insulin resistance. Thus it is not clear whether OSA or the increased insulin resistance in these subjects contributed to the development of NASH.

The pathogenesis of NASH is not well understood, but a widely accepted model of hepatic injury in NASH is the two-hit hypothesis proposed by James and Day (4). The initial hit is fatty infiltration of the liver, which may occur in the presence of insulin resistance-mediated accumulation of fat in hepatocytes and also through a high-fat diet (4). As a single hit, fatty infiltration or steatosis occurs. A second hit by oxidative injury, including a proinflammatory response and lipid peroxidation, is present in histologically documented NASH (4). A high-fat diet and diabetes may increase oxidative stress, but only a subset of diabetics with fatty liver disease progress to NASH (4). The work by Li et al. (5) raises the possibility that, among causes of or contributors to oxidative stress, OSA should be considered.

Li et al. (5) found that leptin-deficient (ob/ob) mice subjected to oxymoglobin desaturations at a frequency of 60 events per hour, modeling severe OSA, for several months developed increased fatty infiltration in the liver. Whether intermittent hypoxia causes a proinflammatory response and lipid peroxidation in the liver, as it does elsewhere (12, 13), and whether longer exposure would convert hepatic histology from fatty infiltration to NASH and, ultimately, cirrhosis should be evaluated. Similarly, it will be important to determine whether this lipid dysregulation is driven by hypoxia or by intermittent hypoxia.

To begin to explore how intermittent hypoxia, modeling OSA oxygenation patterns, might result in increased lipid deposition in the liver, Li et al. (5) used targeted microarray on hepatic tissue. A robust theme from the microarray data was increased expression of lipogenesis genes regulated by sterol regulatory element-binding protein (SREBP) 1, with confirmation of lipogenesis gene responses and SREBP-1 mRNA increase by real-time PCR (11). Although enzyme activities were not measured, the increase in liver triglyceride and phospholipid content strongly supports activation of lipogenesis.

SREBPs are considered master regulators of cholesterol and lipid homeostasis (3). SREBP-1c induces lipogenic genes without affecting cholesterol genes, whereas SREBP-1a increases cholesterol and triglycerides, and SREBP-2 increases cholesterol synthesis (10). Thus the gene response of increased fatty acids without an increase in cholesterol described by Li et al. (5) is more consistent with activation of SREBP-1c. SREBP-1c is induced primarily by insulin and/or feeding, and ob/ob mice at baseline have increased SREBP-1c mRNA in their fatty livers (10). Feeding and insulin levels were not measured in this study, but in a previous study by the same group, ob/ob mice exposed to intermittent hypoxia developed increased insulin levels and insulin resistance (7). Whether the present findings of liver lipogenesis require increased insulin or occur as a direct oxidative insult to hepatocytes requires further study. To better delineate the mechanisms through which intermittent hypoxia induces hepatic lipogenesis, it would be of interest to next examine the effects of intermittent hypoxia on SREBP-1c-null mice and the effects of insulin levels or insulin receptor substrate proteins on the responses to intermittent hypoxia. If SREBP-1c is essential to the process, SREBP-1-null mice should be protected from intermittent hypoxia-induced lipid dysregulation. Similarly, if insulin is essential for the increased SREBP-1c, we should see fatty liver changes vary with insulin levels or insulin receptor substrate protein response in the liver.

Improper diet and insulin resistance have been shown to disturb hepatic lipid homeostasis, and it is now quite likely that OSA, through frequent alterations in tissue oxygen tensions, also impairs hepatic lipid homeostasis. The SREBP-1 molecular window is potentially highly important. If SREBP-1a or SREBP-1c can be confirmed to be essential to the intermittent hypoxia-induced lipid dysregulation, the genetic technology is available to begin to decipher whether this process requires insulin resistance or whether intermittent hypoxia can disrupt liver homeostasis independent of changes in insulin activity or responsiveness. Although further studies are needed in the animal models to identify mechanisms underlying intermittent hypoxia-induced fatty infiltration of the liver and to determine whether this progresses to NASH and/or cirrhosis, it is evident that the oxygenation patterns of OSA have the potential to disturb homeostasis in one more organ.

REFERENCES


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