Effect of deficiency in SREBP cleavage-activating protein on lipid metabolism during intermittent hypoxia

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OBSTRUCTIVE SLEEP APNEA (OSA) is a recurrent collapse of the upper airway during sleep, leading to intermittent hypoxia (IH) (12). OSA affects 4–24% men and 2–9% women in the United States, with the prevalence reaching 50% in obese individuals (45, 61). OSA is associated with increased cardiovascular morbidity and mortality (2, 31, 36, 60). The high risk of adverse cardiovascular outcomes has been attributed to metabolic complications of OSA, including insulin resistance, glucose intolerance, dyslipidemia, atherosclerosis, and fatty liver disease (7, 20, 34, 38, 44, 45, 47, 56). IH has been implicated as a major cause of poor metabolic outcomes of OSA.

We previously developed (26–28, 49) a mouse model of IH and showed that IH directly causes dyslipidemia and atherosclerosis, increasing serum levels of cholesterol, phospholipids, and triglycerides. We have also shown that IH upregulates hepatic sterol regulatory element binding protein (SREBP)-1, a transcription factor controlling biosynthesis of fatty acids, triglycerides, cholesterol esters, and phospholipids (8, 11, 17, 26, 28, 51, 52). Levels of SREBP-2, regulating biosynthesis of cholesterol de novo, were unchanged (21, 23). IH also increased mRNA levels of genes controlled by SREBP-1, including steraryl coenzyme A desaturase 1 (SCD-1) and mitochondrial glycerol-3-phosphate acyltransferase (mGATP), whereas SREBP-2-regulated 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCoAR) was not affected (8, 26, 28, 54, 59).

The goal of the present study was to explore a mechanistic link between IH-induced dyslipidemia and the SREBP-1 pathway. Transgenic mice with SREBP-1 deficiency exhibit compensatory upregulation of SREBP-2 resulting in circulating lipid levels similar to wild-type (WT) controls (29, 53); therefore, we chose mice with conditional deficiency of SREBP cleavage-activating protein (SCAP), which have both SREBP-1 and SREBP-2 disabled (23, 32). ESCAP silences SREBP from the endoplasmic reticulum (ER) to the Golgi complex, where SREBP precursor is processed into an active 68-kDa isoform (4, 16, 18, 32). After SCAP knockout was induced, we exposed SCAP-deficient mice and their WT littermates to IH or intermittent air control for 5 days. IH was induced during the 12-h light phase by decreasing FIO, from 20.9% to 5% for a period of 30 s with rapid reoxygenation to 20.9% through the subsequent 30 s. In WT mice, IH increased fasting levels of serum total and HDL cholesterol, serum triglycerides, serum and liver phospholipids, and mtGATP in the liver. In L-Scap mice, IH did not have any effect on serum and liver lipids, and expression of lipid metabolic genes was not altered. We conclude that hyperlipidemia in response to IH is mediated via the SREBP-1 pathway. Our data suggest that the SREBP-1 pathway could be used as a therapeutic target in patients with both OSA and hyperlipidemia.

METHODS

Animals. Transgenic mice were purchased from the Jackson Laboratory (Bar Harbor, Maine). In B6;129-Scapm1mtg/J (stock no. 004162) or Scapm0/m mice, exon 1 of the SCAP gene is flanked with loxP sites, which are targets for bacteriophage P1 Cre recombinase. B6.Cg-Tg(Mx1-cre)1Cgn/J (stock no. 03556) or MX1-Cre mice have the Cre recombinase gene under control of the interferon-inducible Mx1 promoter. Scapm0/m mice and MX1-Cre mice were crossed. The genotypes were identified by PCR analysis of tail biopsies using the Jackson Laboratory protocols for respective strains. A total of 16 male Scapm0/m; MX1-Cre mice (L-Scap mice) and 16 male Scapm0/m; wild-type (WT) littermates were used in the study. Conditional knockout of the SCAP gene was induced as previously described (23, 32). Briefly, 12-wk-old mice were injected intraperitoneally with double-stranded RNA [polyinosinic acid-polycytidylic acid (pIpC), Sigma-Aldrich, St. Louis, MO] four times q48 h, with the first dose admin-

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istered 14 days before the beginning of the exposure to stimulate interferon production. The deletion of exon 1 was confirmed by PCR with genomic DNA from the liver using 5′-TCAGTGTTAGGATCGTCTTGCAAGCC-3′ and 3′-primer 5′-AAC-CCAGGTCTTACGTAGTGCGATCC-3′. The deleted allele yielded a 530-bp fragment. The sequence of the primers was kindly provided by Dr. Guosheng Liang (Eli Lilly, Indianapolis, IN). The study was approved by the Johns Hopkins University Animal Care and Use Committee and complied with the American Physiological Society’s “Guiding Principles in the Care and Use of Animals.” For all blood samples, injections, and surgical procedures, anesthesia was induced and maintained with 1–2% isoflurane administered through a face mask.

Experimental design. A gas control delivery system was designed to regulate the flow of room air, nitrogen, and oxygen into customized cages housing the mice as previously described (42). A maximum of three mice were housed continuously in a single customized cage (dimensions 27 × 17 × 17 cm) with constant access to food and water. A series of programmable solenoids and flow regulators altered the inspired O2 fraction (FiO2) over a defined and repeatable profile that simulated the timing and magnitude of arterial oxygen desaturation changes seen in OSA patients (55). During each period of IH, FiO2 was reduced from 20.9% to 4.9 ± 0.1% over a 30-s period and then rapidly reoxygenated to room air levels in the subsequent 30-s period. The use of multiple inputs into the cage produced a uniform nadir FiO2 level throughout the cage.

Eight L-Scap− mice and eight WT littermates were placed in the IH chamber for five consecutive days. Food intake and body weight were monitored daily for each animal. All animals were kept in a controlled environment (22–24°C with a 12:12-h light-dark cycle; lights on at 0900) on a standard chow diet with free access to water.

In a separate series of animals, eight L-Scap− mice and eight WT mice were exposed to intermittent room air (IA, control groups) for 5 days in identical chambers and weight matched to the IH group daily during the experiment by varying food intake (Table 1). Weight matching was conducted in pairs. The IH and IA states were induced during the light phase, alternating with 12 h of constant room air during the dark phase.

Sample collection. Animals were approximately 15 wk of age at the time of death. Mice fasted for 5 h before bleeding and death. Arterial blood (1 ml) was obtained by direct cardiac puncture under 1–2% isoflurane anesthesia. Serum was separated and frozen at −80°C. After blood withdrawal, the animals were euthanized with pentobarbital (60 mg ip). Livers were surgically removed, weighed, and immediately frozen for future analysis.

Sample processing. Serum total cholesterol, LDL cholesterol, HDL cholesterol, phospholipids, free fatty acids, and triglycerides were measured with test kits from Wako Diagnostics (Richmond, VA). Glucose was measured in blood with the Accu-Chek Comfort Curve kit from Roche Diagnostics (Indianapolis, IN). Serum insulin levels were measured with ELISA kits from Linco Research (St. Charles, MO). To evaluate the degree of insulin resistance, the homeostasis model assessment (HOMA) index was calculated with the following formula: HOMA = fasting serum insulin (µIU/ml) × fasting blood glucose (mmol/l)/22.5 (33, 42). Liver lipid isolation and measurements were performed as previously described (26, 28).

Immunoblot in liver tissue. Total liver lysate was prepared as previously described (27, 28). Total protein was measured with a DC kit from Bio-Rad (Hercules, CA). Aliquots (70 µg) of total liver lysate were fractionated with 4–15% SDS-PAGE followed by immunoblot assays of SREBP-1, SCAP, and SCD-1, using polyclonal antibodies from Santa Cruz Biotechnology (Santa Cruz, CA); mitoPAT, using antibodies kindly donated by Dr. Sandra Schreyer (AstraZeneca, Göteborg, Sweden); and α-actin, using polyclonal antibodies from Sigma-Aldrich. Goat anti-rabbit-immunoglobulin-horseradish peroxidase (HRP) conjugate was from Bio-Rad, and bovine anti-goat-HRP conjugate was from Santa Cruz Biotechnology. Densitometry was performed with a Kodak DC290 ZOOM digital camera (2 megapixel) and UN-SCAN-IT Gel Automated Digitizing System version 5.1 software (Silk Scientific, Orem, UT). The results were expressed as ratios of optical density of the bands representing proteins of interest [SCD-1, low density lipoprotein receptor (LDLR), (scavenger receptor class B, member 1 (SR-B1))] to optical density of the band representing α-actin.

Real-time PCR in liver tissue. Total RNA was extracted from liver with TRIzol (Life Technologies, Rockville, MD), and cDNA was synthesized with the Advantage RT for PCR kit from Clontech (Palo Alto, CA). Real-time reverse transcriptase-PCR (RT-PCR) was performed with primers from Invitrogen (Carlsbad, CA) and Taqman MGB probes from Applied Biosystems (Foster City, CA). The sequences of primers and probes for SREBP-1, SREBP-2, SCAP, GPAT, SCD-1, and HMGC-CoAR were described previously (25, 26, 28). The primer sequences for 18S were 5′-CTCTTTCGAGCCCT-GTAATTG-3′ (forward), 5′-AACGTGACACCTTCAATAGCC-TATT (reverse), and 5′-AGTCCACTTTAATCCTT (probe). The threshold cycle (Ct) was determined for each sample. mRNA expres-

Table 1. Baseline characteristics of L-Scap− and WT mice exposed to intermittent hypoxia for 5 days

<table>
<thead>
<tr>
<th></th>
<th>WT Mice</th>
<th>L-Scap− Mice</th>
<th>Effect of IH (P)</th>
<th>Effect of SCAP</th>
<th>Interaction</th>
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<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Age at beginning of exposure, wk</td>
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<td>14</td>
<td>14</td>
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<tr>
<td>Body wt, g</td>
<td>Day 0</td>
<td>21.6±1.2</td>
<td>20.7±1.1</td>
<td>20.4±1.3</td>
<td>&gt;0.05</td>
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<tr>
<td></td>
<td>Day 5</td>
<td>21.3±1.0</td>
<td>20.3±0.9</td>
<td>20.3±0.9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Liver wt g</td>
<td>0.98±0.05</td>
<td>0.85±0.04</td>
<td>0.80±0.04</td>
<td>0.79±0.03</td>
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<tr>
<td>% Body wt</td>
<td>4.6±0.2</td>
<td>4.3±0.2</td>
<td>4.4±0.1</td>
<td>4.5±0.2</td>
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<tr>
<td>Epididymal fat g</td>
<td>0.19±0.02</td>
<td>0.23±0.01</td>
<td>0.14±0.04</td>
<td>0.06±0.02*</td>
<td>&gt;0.05</td>
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<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>194±13</td>
<td>183±13</td>
<td>145±21</td>
<td>105±14</td>
<td>&gt;0.05</td>
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<tr>
<td>Fasting serum insulin (ng/ml)</td>
<td>0.20±0.02</td>
<td>0.20±0.03</td>
<td>0.15±0.04</td>
<td>0.14±0.02</td>
<td>&gt;0.05</td>
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<tr>
<td>HOMA (mmol × µU/l)</td>
<td>2.8±0.4</td>
<td>2.8±0.6</td>
<td>1.49±0.36</td>
<td>1.02±0.21</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE for n mice. SCAP, sterol regulatory element binding protein cleavage-activating protein; L-Scap−, Scapfl/fl; MX1-Cre; WT, Scapfl/fl wild type; IH, intermittent hypoxia; IA, intermittent air; HOMA, homeostatic model assessment. The HOMA index is calculated as a product of fasting insulin (Io, µU/l) and fasting glucose (Go, mmol/l) values divided by the constant 22.5: HOMA = (Io × Go)/22.5. *P < 0.01, difference between WT and L-Scap− mice during IH.
sion levels were normalized to 18S rRNA concentrations with the following formula: gene of interest/18S = 2^{(Ct(18S) - Ct(gene of interest)).

Statistical analyses. All values are reported as means ± SE. Comparisons between the IH and IA groups of L-Scap− and WT mice were performed with general linear model ANOVA followed by Tukey and Bonferroni post hoc tests. A P value of < 0.05 was considered significant.

RESULTS

Baseline characteristics and serum and liver lipid levels. Exposure to IH for 5 days did not induce significant weight loss in either genotype, but L-Scap− mice were ~5% lighter than their WT littermates (Table 1). IH had no effect on liver weight or the amount of epididymal fat in both WT and L-Scap− mice. SCAP deficiency resulted in a small reduction in absolute liver weight, whereas liver weight normalized to body weight was identical to that in WT mice. A mutation in the SCAP gene led to a significant loss of epididymal fat. Moreover, IH caused loss of epididymal fat in L-Scap− mice but not in WT mice (Table 1). IH had no significant effect on fasting blood glucose, serum insulin, and the HOMA index of insulin resistance in either genotype. Compared with WT mice, L-Scap− mice showed a decrease in fasting blood glucose level and insulin resistance and a trend to decrease in fasting serum insulin levels (Table 1), which was consistent with the published data (23, 32).

Similar to our previous observations (25, 28), WT mice exposed to IH for 5 days exhibited significant increases in fasting levels of total cholesterol, HDL cholesterol, phospholipids, and triglycerides (Fig. 1). Levels of LDL cholesterol and free fatty acids were unchanged. Compared with WT mice, L-Scap− mice showed significantly lower levels of serum total cholesterol, LDL cholesterol, and phospholipids, whereas levels of HDL cholesterol, triglycerides, and free fatty acids did not differ. In SCAP-deficient mice, IH did not induce an increase in any of the serum lipid fractions (Fig. 1).

SCAP deficiency resulted in low liver triglyceride content, whereas liver cholesterol, phospholipid, and free fatty acid content were similar to those in WT mice (Fig. 2). IH had no effect on liver cholesterol, triglyceride, and free fatty acid content in both genotypes. In response to IH, WT mice exhibited a ~25% increase in liver phospholipid content, which was not evident in SCAP-deficient animals (Fig. 2).

SCAP, IH, and lipid biosynthetic pathways. Compared with WT mice at normoxic conditions, L-Scap− mice exhibited a 71% decrease in SCAP, a 98.7% decrease in SCD-1, a 95% decrease in SREBP-1, a 60% decrease in HMG-CoAR, a 55% decrease in SREBP-2, and a 30% decrease in mtGPAT mRNA levels in the liver (Fig. 3). In WT mice, IH upregulated SREBP-1 and mtGPAT, inducing ~65% increases in mRNA levels of both genes, whereas SREBP-2 and HMG-CoAR were

Fig. 1. Effect of intermittent hypoxia (IH) or intermittent air (IA) on fasting serum levels of total cholesterol (TC; A), LDL cholesterol (LDL-C; B), HDL cholesterol (HDL-C; C), phospholipids (PL; D), triglycerides (TG; E), and free fatty acids (FFA; F) in Scapfl/fl; MX1-Cre (L-Scap−) and Scapfl/fl; wild-type (WT) mice. Lines over bars denote the differences between genotypes (WT vs. L-Scap−). *P < 0.05, difference between IH and IA.
not affected (Fig. 3). IH did not have an impact on SCD-1 and decreased SCAP gene mRNA levels. In SCAP-deficient animals, IH had no effect on SREBP-1 and mtGPAT mRNA levels. In WT mice, exposure to IH for 5 days significantly increased protein levels of SCAP, mtGPAT, and the active isoform of SREBP-1 (by 72%, 75%, and 83%, respectively; Fig. 4), whereas SCD-1 protein level was unchanged. In contrast, IH had no effect on these key factors of lipid metabolism in L-Scap−/− mice.

**DISCUSSION**

We showed previously that IH leads to dyslipidemia in C57BL/6J mice in association with upregulation of the
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SREBP-1 pathway of lipid biosynthesis in the liver. The purpose of the present study was to explore changes in lipid metabolism in response to IH in mice with interrupted SREBP pathways (conditional SCAP knockout, L-Scap— mice). Several novel findings resulted from the study. First, SCAP-deficient mice did not exhibit any IH-induced increases in serum total cholesterol, HDL cholesterol, phospholipid, and triglyceride levels and liver phospholipid content, which were present in WT mice, suggesting that IH induces dyslipidemia via the SCAP/SREBP mechanism. Second, SCAP-deficient mice did not show any IH-induced increases in mRNA and protein levels of SREBP-1 and mtGPAT and protein levels of SREBP-1 in the liver, which were present in WT mice, suggesting that IH directly affects SREBP-1 and downstream genes of lipid biosynthesis. In the discussion below, we explore the relationships linking IH and the SREBP pathway.

**IH, SCAP, and SREBP.** The results of this study confirmed our previous finding (28) that, in the presence of intact pathways of lipid biosynthesis, short-term IH increases serum and liver lipid levels and upregulates SREBP-1. We now show that interruption of the SREBP-1 pathway in L-Scap— mice eliminates all changes in lipid metabolism induced by IH. What are the mechanisms by which IH affects SREBP? One possibility is that IH induces the transcription factor hypoxia-inducible factor 1 (HIF-1) (25, 41, 50). We showed previously (25) that IH upregulates SCAP expression in the liver and that this effect is not present in mice with partial deficiency in HIF-1α, an O2-regulated subunit of HIF-1. In turn, an increase in SCAP would accelerate traffic of immature SREBP from the ER to the Golgi complex, prompting release of active SREBP and an increase in lipid biosynthesis with resulting dyslipidemia (4, 16, 18, 32, 52). Our present study demonstrated that in WT mice, but not in SCAP-deficient mice, IH increased SCAP protein levels. In contrast, SCAP mRNA was decreased at hypoxic conditions in both genotypes, which may be related to either differences in the genetic background or administration of plpC with a subsequent burst in interferon. It is conceivable that IH initially upregulates SCAP mRNA via the HIF-1 mechanism, leading to SCAP protein increase, but hypoxia and interferon interact to impair RNA stability (3, 21, 48), resulting in a decline in SCAP mRNA levels in hypoxic animals. It is also possible that IH may have a differential effect on SCAP transcription and translation. Thus our data suggest that IH may lead to dyslipidemia by increasing SCAP protein level; further experiments are necessary to clarify how IH affects SCAP with antisense RNA or a conditional knockout with a Cre promoter not requiring interferon for induction.

It is also possible that IH affects SREBP-1 via mechanisms other than SCAP. Indeed, SCAP regulates both SREBP-1 and SREBP-2 (4, 16, 18, 32, 52), whereas IH significantly increased only SREBP-1. Mutant mice might have lacked metabolic responses to the hypoxic stimulus merely because SCAP must be expressed at sufficient levels to facilitate posttranscriptional modifications of SREBP-1.

**What mechanisms, other than HIF-1 and SCAP, could impact on SREBP-1 during IH?** SREBP-1 is upregulated by insulin, glucose, and free fatty acids (9, 10, 14, 46), all of which can be increased by IH (25). In the present study, IH did not impact on any of these metabolic parameters, suggesting that effects of IH on SREBP-1 expression are not mediated via the glucose-insulin axis. The lack of IH-induced changes in insulin, glucose, and free fatty acids could be attributed to low body weight and fat mass of experimental animals, genetic background, or plpC treatment. Finally, IH may upregulate SREBP-1 transcription directly. Hughes et al. (19) and Todd et al. (57) demonstrated in fission yeast that low O2 directly activates an SREBP-1 analog, Sre1p. Low O2 tension inhibits multiple enzymes of lipid biosynthesis, resulting in a decrease in sterol synthesis and transient depletion of intracellular sterols, which, in turn, increases Sre1p expression and stimulates transcription of oxygen-dependent enzymes of lipid metabolism to maintain sterol homeostasis (57). A similar mechanism may be present in mammalian cells with the intact SCAP/SREBP axis, but not in cells deficient in SCAP. Thus there are several putative mechanisms by which IH may affect the SREBP pathway of lipid biosynthesis in the liver.

**IH, mtGPAT and dyslipidemia.** We have provided novel evidence that IH affects key enzymes of lipid biosynthesis via SREBP-1. Our previous data (27, 28, 49) indicated that one mechanism by which IH leads to hyperlipidemia is upregulation of SCD-1. SCD-1 inserts a double bond in the Δ9 of...
saturated fatty acids, converting saturated fatty acids into monounsaturated fatty acids (MUFA) (39, 40). MUFA serve as a substrate for biosynthesis of cholesterol esters, triglyceride, and phospholipids. An increase in SCD-1 upregulates lipoprotein secretion, which may lead to hypercholesterolemia (28, 39, 40). Surprisingly, the present study showed that SCD-1 was unchanged in both genotypes. Similar to previously discussed insulin and glucose data, the lack of a SCD-1 response to IH could be attributed to low body weight and low body fat of experimental animals, differences in genetic background, or plpC injections.

In contrast to SCD-1, IH led to significant increases in mtGPAT mRNA and protein levels in WT mice. There are two isoforms of GPAT, mitochondrial and microsomal (5, 6, 11). GPAT catalyzes the first step of the synthesis of triglycerides and glycerophospholipids, the acylation of glycerol-3-phosphate into lysophosphatidic acid (6). Recently cloned microsomal GPAT mediates biosynthesis of triglycerides (5). We have studied exclusively mtGPAT, which is a key enzyme of the biosynthesis of triglycerides, phospholipids, and cholesterol esters (11, 30). mtGPAT is transcriptionally regulated by SREBP-1 (8). Transgenic mice with mtGPAT deficiency exhibit not only low serum and liver triglyceride levels but also low serum cholesterol levels as a result of a decrease in lipoprotein secretion (15). We have demonstrated that upregulation of mtGPAT in IH occurs in conjunction with increases in liver phospholipid content, serum cholesterol, phospholipid, and triglyceride levels. We have also shown that the effects of IH on mtGPAT and lipid metabolism were absent in mice with SCAP deficiency. Thus our data suggest that IH leads to dyslipidemia via SREBP-1-mediated activation of mtGPAT in the liver.

**IH, SCAP, and adipose tissue.** SCAP deficiency in the liver could also affect lipid metabolism in adipose tissue. Our data indicate that L-Scap−/− mice exhibited significant loss of epididymal fat during IH, which did not occur in WT mice. One explanation of this phenomenon would be compensatory up-regulation of the SREBP pathway in adipose tissue in mice deficient in hepatic SCAP (23) with superimposed increases in SREBP due to the hypoxic stimulus (19, 28). An increase in SREBP-1 would activate not only lipid biosynthesis but also lipolysis via hormone-sensitive lipase (13). Lipolysis may be enhanced further by IH-induced circulating catecholamines and sympathetic activity (1, 22, 24, 37). Alternatively, it is also conceivable that IH exerts opposite effects on lipogenesis in liver and fat, inhibiting lipid biosynthesis in adipose tissue. Thus, although a mechanism of excessive loss of adipose tissue in L-Scap−/− mice during IH is unknown, it is likely to be mediated via the SREBP pathway.

**Caveats.** Our study had several limitations. First of all, our study did not determine whether metabolic effects of IH were caused by the hypoxic stimulus per se or by IH-induced sleep fragmentation (43). Second, our findings in severe IH of a relatively short duration may not be relevant for mild IH, sustained hypoxia, or chronic IH. In addition, SCAP knockout could elicit a different phenotypic response during chronic exposure, because adipose tissue can compensate for lack of hepatic lipogenesis (23). Third, IH was administered only during the light phase, and our findings may not be applicable to the dark phase, since circadian periodicity impacts metabolism (58). Fourth, plpC administration with an ensuing surge in interferon could have metabolic consequences, obscuring effects of IH. Finally, SCAP deficiency caused a significant decrease in baseline serum levels of total and LDL cholesterol, phospholipids, liver triglycerides, and hepatic mRNA levels of SREBP-1, SREBP-2, SCAD-1, and HMG-CoAR, raising the possibility that lack of IH-induced hyperlipidemia in L-Scap−/− mice was a “treatment effect” rather than a specific disruption of the metabolic pathways. This argument can be countered by mtGPAT data: mtGPAT mRNA levels in L-Scap−/− and WT mice were identical at baseline but different after hypoxic exposure. In addition, serum HDL cholesterol and triglycerides and liver phospholipids, similar in L-Scap−/− and WT mice at baseline, were increased under hypoxic conditions in WT, but not L-Scap−/− mice, which could be related to differences in mtGPAT induction by IH in the two genotypes (11, 30). Thus our data suggest that the effect of SCAP deficiency on IH-induced changes in lipid metabolism is specifically related to hepatic mtGPAT.

**Conclusions and implications.** In conclusion, the present study is a continuation of our previous work exploring causal relationships between OSA and the metabolic syndrome (25–28, 42, 49). Here we have provided mechanistic evidence that IH-induced dyslipidemia occurs because of upregulation of the SREBP-1 pathway of lipid biosynthesis in the liver and that interruption of SREBP-1 processing abolishes all IH-induced changes in lipid metabolism. We speculate that SCAP, SREBP-1, and mtGPAT could be used as potential therapeutic targets to treat metabolic complications in patients with OSA.

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