Altered metabolic responses to intermittent hypoxia in mice with partial deficiency of hypoxia-inducible factor-1α

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Li, Jianguo, Marta Bosch-Marce, Ashika Nanayakkara, Vladimir Savransky, Susan K. Fried, Gregg L. Semenza, and Vsevolod Y. Polotsky. Altered metabolic responses to intermittent hypoxia in mice with partial deficiency of hypoxia-inducible factor-1α. Physiol Genomics 25: 450–457, 2006. First published February 28, 2006; doi:10.1152/physiolgenomics.00293.2005.—We have previously shown that exposure of C57BL/6J mice to intermittent hypoxia (IH) leads to 1) hypertriglyceridemia due to upregulation of pathways of lipid biosynthesis, including sterol regulatory element binding protein (SREBP)-1 and stearoyl CoA desaturase (SCD)-1; and 2) hypercholesterolemia due to impaired cholesterol uptake. The goal of the present study was to examine whether hypoxia-inducible factor (HIF)-1 is implicated in changes in lipid metabolism induced by IH. Lean HIF-1α (Hif1α)-/− mice, which are heterozygous for a null allele at the locus encoding the HIF-1α subunit, and their wild-type (WT) Hif1α+/+ littermates were exposed to IH or control conditions for 5 days. IH increased fasting blood glucose, serum total cholesterol, and high-density lipoprotein-cholesterol, phospholipids, triglycerides (TG), and leptin in mice of both genotypes, whereas serum insulin and interleukin-6 were elevated only in WT mice. The impact of IH on serum TG levels in WT mice was significantly greater than that in Hif1α+/+ mice (95 ± 9 vs. 66 ± 6 mg/dl, P < 0.05), whereas cholesterol and glucose levels were affected independently of genotype. Under hypoxic conditions, mRNA and protein levels of SREBP cleavage-activating protein (SCAP) and SCD-1 and protein levels of nuclear isoform of SREBP-1 in the liver were induced to significantly higher levels in WT mice than in Hif1α+/+ mice. We conclude that 1) the effect of IH on serum TG levels is mediated through HIF-1α, 2) HIF-1α may impact on posttranscriptional regulation of SREBP-1, and 3) the effect of IH on serum cholesterol levels was not altered by partial HIF-1α deficiency.

lipid biosynthesis; sterol regulatory element binding protein; stearoyl coenzyme A desaturase; triglycerides; liver

OBSTRUCTIVE SLEEP APNEA (OSA) is characterized by recurrent collapse of the upper airway during sleep leading to periods of intermittent hypoxia (IH) and sleep fragmentation (14). OSA is present in 2% of women and 4% of men in the general United States population, but the prevalence rises to 40–60% in obese individuals (44, 63). OSA is associated with multiple metabolic disturbances, including insulin resistance, glucose intolerance, dyslipidemia, and fatty liver disease, independent of underlying obesity (20, 21, 36, 42–45, 59, 60). Current evidence indicates that metabolic complications are linked to the hypoxic stress associated with OSA.

A murine model of IH has been utilized to explore causal links between OSA and metabolic syndrome (29, 30, 41). We (30) have recently shown that exposure to IH for 5 days leads to hypercholesterolemia and hypertriglyceridemia and an increase in liver triglyceride (TG) content in lean C57BL/6J mice, whereas liver cholesterol content remained unchanged. We have also demonstrated that hypercholesterolemia was not related to any changes in cholesterol biosynthesis. IH increased TG biosynthesis in the liver by upregulating sterol regulatory element binding protein (SREBP)-1, a key transcription factor of lipid biosynthesis (16–18, 30, 54), and downstream pathways, including an important enzyme of TG biosynthesis, stearoyl-CoA desaturase (SCD)-1 (30, 38, 39, 57). The mechanisms by which IH upregulates SREBP-1 are unknown.

IH induces the transcriptional activity of hypoxia-inducible factor (HIF)-1 (7, 65), suggesting that HIF-1 may regulate SREBP-1 pathways augmenting lipid biosynthesis. HIF-1 is a master regulator of oxygen homeostasis and controls a variety of physiological responses to hypoxia, including erythropoiesis, angiogenesis, and glucose metabolism (10, 23, 49–51). The effects of HIF-1 on lipid metabolism have not been studied.

HIF-1 is a heterodimer consisting of an O2-regulated HIF-1 α-subunit and a constitutively expressed HIF-1 β-subunit (61, 62). Homozygosity for a null allele at the Hif1α locus results in embryonic lethality (23). Hif1α+/− mice, which are heterozygous for the null allele, develop normally but manifest impaired physiological responses that have implicated HIF-1 in the control of erythropoietic, ventilatory, and pulmonary vascular responses to chronic hypoxia (27, 55, 64). The metabolic effects of HIF-1α deficiency have not been explored.

The purpose of the present study was to examine the effects of partial loss of HIF-1 function on lipid metabolism during IH. We hypothesized that IH would increase serum lipid levels in Hif1α+/− wild-type (WT) mice, whereas Hif1α+/− heterozygous-null (HET) mice with partial HIF-1α deficiency would manifest an attenuated response. We subjected HET mice and their WT littermates to our previously described mouse model of IH (30, 41) and examined 1) IH-induced changes in fasting serum lipid levels, 2) IH-induced changes in liver lipid content, and 3) IH-induced changes in hepatic lipid biosynthesis pathways.

METHODS

Animals. HET and WT mice were maintained on an outbred C57BL/6J × 129 genetic background by interbreeding as previously...
described (23). The offspring of HET × WT matings were genotyped by PCR analysis of tail biopsies. A total of 20 HET and 16 WT male littermate mice were analyzed in the study. The study was approved by the Johns Hopkins University Animal Care and Use Committee and complied with American Physiological Society guidelines for animal studies. For all blood samples, injections, and surgical procedures, anesthesia was induced and maintained with 1–2% isoflurane administered through a facemask.

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 (41). 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 oxygen fraction (FiO2) over a defined and repeatable profile that simulated the timing and magnitude of arterial oxygen desaturation changes seen in OSA patients (58). During each period of IH, the 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.

Ten HET mice and eight WT littermates were placed in the IH chamber for 5 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 09:00) on a standard chow diet with free access to water. In a separate series of animals, 10 HET mice and 8 WT mice were exposed to intermittent room air (IA; control groups) for 5 days in identical chambers and were weight matched to the IH group daily during the experiment by varying the food intake (Table 1). Weight matching procedures, anesthesia was induced and maintained with 1–2% isoflurane (forward), and 5 GCCTCTAGTCTAGGTCCAAA-GACTGTG-3 (reverse), and 5-CCCCCTATCCC-3 (probe). The primer sequences for VEGF were 5-TACAGCGGGAAGAAGCTTCT-3 (forward), 5-GCGGTCAA-3 (forward), and 5-TCCCTGCAAAAACAC-3 (reverse). The use of multiple inputs into the cage produced a uniform nadir FiO2 level throughout the cage.

Sample collection. Mice were fasted for 5 h before being bled and euthanized. Arterial blood (1 ml) was obtained by direct cardiac puncture exposure under 1–2% isoflurane anesthesia. Serum was separated and frozen at -80°C. After the blood withdrawal, animals were euthanized with pentobarbital (60 mg ip). Livers and epididymal fat pads were excised, weighed, and immediately frozen for future analysis.

Sample processing. Serum total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL)-cholesterol, phospholipids (PL), free fatty acids (FFA), and TG were measured using test kits from Wako Diagnostics (Richmond, VA). Glucose was measured in blood using an Accu-Chek Comfort Curve Kit from Roche Diagnostics (Indianapolis, IN). Serum leptin and insulin levels were measured using ELISA kits from Linco Research (St. Charles, MO), and the hepatic antibodies and bovine anti-goat-HRP conjugate from Santa Cruz Biotechnology (Santa Cruz, CA), and goat anti-rabbit CCL3 and SCD-1 goat anti-mouse polyclonal antibodies from Sigma-Aldrich (St. Louis, MO). Goat anti-rabbit SCAP and SCD-1 goat anti-mouse polyclonal antibodies were used to detect SCAP and SCD-1 expression. The VEGF primers and probes were synthesized as previously described (29, 30).

Liver lipid isolation and measurements for future analysis were performed as previously described (29, 30).

Table 1. Baseline characteristics of WT and HET mice exposed to IH for 5 days

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age, wk</th>
<th>Body Weight, g</th>
<th>Daily Food Intake, g</th>
<th>Liver Weight</th>
<th>Epididymal Fat</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Day 0</td>
<td>Day 5</td>
<td>Day 0</td>
<td>% Body weight</td>
</tr>
<tr>
<td>WT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>8</td>
<td>15 ± 1</td>
<td>24.4 ± 1.0</td>
<td>24.0 ± 1.0</td>
<td>2.8 ± 0.2</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td>IH</td>
<td>8</td>
<td>15 ± 1</td>
<td>24.0 ± 0.8</td>
<td>23.9 ± 0.9</td>
<td>2.9 ± 0.2</td>
<td>3.0 ± 0.1</td>
</tr>
<tr>
<td>HET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>10</td>
<td>15 ± 1</td>
<td>25.5 ± 0.3</td>
<td>24.5 ± 0.8*</td>
<td>2.6 ± 0.2</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>IH</td>
<td>10</td>
<td>15 ± 1</td>
<td>25.2 ± 0.8</td>
<td>24.1 ± 0.8*</td>
<td>2.9 ± 0.1</td>
<td>2.8 ± 0.1</td>
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</table>

Values are means ± SE; n, no. of mice. WT, wild-type (hypoxia-inducible factor-1α (HIF1α)−/−) mice; HET, HIF1α−/− homozygous-null mice; IA, intermittent room air; IH, intermittent hypoxia. *P < 0.05 for the difference between day 0 and day 5.
WT mice and not affected by IH. Serum lipid levels were not significantly different between genotypes under normoxic conditions. IH led to significant increases in fasting serum total cholesterol, HDL-cholesterol, PL, TG, and FFA in both HET and WT mice (Fig. 1). Changes in LDL-cholesterol did not reach statistical significance. Elevations in serum levels of all lipid fractions except TG were similar in HET and WT mice. Partial HIF-1α deficiency significantly blunted the increase in fasting serum TG levels in response to IH (66.6 ± 5.8 mg/dl in HET mice vs. 95.0 ± 9.4 mg/dl in WT mice, *P < 0.05; Fig. 1).

IH caused increases in fasting blood glucose and serum leptin levels in both HET and WT mice. Fasting serum insulin and IL-6 levels were elevated in WT mice but not in HET mice (Fig. 2). In addition, partial HIF-1α deficiency attenuated the increase in serum leptin levels in hypoxic mice, but the difference between genotypes was not statistically significant (1.5 ± 0.2 ng/ml in HET mice vs. 2.0 ± 0.3 ng/ml in WT mice, *P = 0.06; Fig. 2).

Hepatic lipid content and adipose LPL activity in HET and WT mice exposed to IH. Liver PL and cholesterol content were not statistically different in HET and WT mice regardless of the exposure (Table 2). There was a trend for liver cholesterol content to decrease after IH (*P = 0.07), whereas liver PL content was not affected. Liver TG content was nearly identical in both genotypes at baseline, whereas after IH, it was significantly higher in WT mice than in HET mice (Table 2). LPL activity in epididymal adipose tissue was increased after hypoxic exposure, but the difference did not reach statistical significance (*P = 0.1). There was no significant difference between the genotypes in the LPL activity (Table 2).

Fig. 1. Effect of 5 days of intermittent hypoxia (IH) or intermittent room air (IA) on fasting serum total cholesterol (CL; A), low-density lipoprotein-cholesterol (LDL-C; B) and high-density lipoprotein-cholesterol (HDL-C; C), phospholipid (PL; D), triglyceride (TG; E), and free fatty acid (FFA; F) levels in hypoxia-inducible factor (HIF)-1α heterozygous-null (Hif1a+/−) mice (HET mice) and wild-type (WT) Hif1a+/+ mice. *P < 0.05 and †P < 0.001 for the difference between IH and IA.

Fig. 2. Effect of 5 days of IH or IA on fasting blood glucose (A), fasting serum insulin (B), leptin (C), and interleukin (IL)-6 (D) levels in HET and WT mice. *P < 0.05 for the difference between IH and IA within a genotype.
increases in SCAP and SCD-1 gene expression and protein affected TG biosynthetic pathways in the liver, attenuating IL-6 levels caused by IH. Finally, partial HIF-1 deficiency abolished increases in fasting serum insulin and higher in HET mice than in WT littermates (Fig. 4). SREBP-2 was not affected. SREBP-1 mRNA levels were significantly increased expression of key genes of fatty acid increase after IH. In both HET and WT mice, IH led to low expression of VEGF at baseline with a barely detectable level of VEGF in the livers of WT mice (Fig. 3). HET mice had a 76.9 ± 11.7% increase in the active nuclear isoform of SREBP-1 (nSREBP-1) in WT mice exposed to IH, whereas HET mice demonstrated a reduction in nSREBP-1 levels (Fig. 5, A and B). In addition, partial HIF-1α deficiency significantly attenuated the hypoxia-induced increase in SCAP mRNA and protein levels (Figs. 4C and 6, A and B), suggesting that HIF-1α may regulate SREBP-1 at the posttranscriptional level (5, 33). In contrast to nSREBP-1, there was a mild reduction in the active nuclear isoform of SREBP-2 under hypoxic conditions in both WT and HET mice (Fig. 5, C and D). Furthermore, SCD-1, a gene product regulated by SREBP-1, exhibited a significantly greater induction by IH in WT mice compared with HET mice at both the mRNA and protein levels (Figs. 4D and 6, C and D). There was no difference in the levels of α-actin between genotypes (Figs. 5, E and F, and 6, E and F).

DISCUSSION

We have previously shown in lean C57BL6/J mice that short-term IH causes hypertriglyceridemia and hypercholesterolemia and that the increase in serum TG, but not in serum cholesterol, levels was induced by activation of the SREBP-1 pathway of lipid biosynthesis in the liver. The purpose of this study was to examine the effects of HIF-1 on lipid metabolism during IH. The study yielded several novel findings. First, partial HIF-1α deficiency blunted increases in serum and liver TG caused by IH, whereas the hypoxia-induced increase in serum cholesterol was not altered. Second, partial HIF-1α deficiency abolished increases in fasting serum insulin and IL-6 levels caused by IH. Finally, partial HIF-1α deficiency affected TG biosynthetic pathways in the liver, attenuating increases in SCAP and SCD-1 gene expression and protein levels and nSREBP-1 protein levels. In the DISCUSSION below, we explore the relationships and putative pathways linking HIF-1 and lipid metabolism.

IH, TG metabolism, and HIF-1α. The simultaneous increases in serum and liver TG content in WT mice suggest that IH upregulated lipid biosynthesis in the liver, which is consistent with our previous report (30). There was no decrease in LPL activity in adipose tissue, indicating that the effects of IH on lipid metabolism were not caused by impaired TG clearance. The main finding of the present study was that partial HIF-1α deficiency attenuated the hypoxia-induced increases in fasting serum TG and liver TG content, suggesting that the IH-induced hyperlipidemic response is mediated by HIF-1α.

The present data in WT mice confirmed our previous reports (29, 30) showing that IH upregulates SREBP-1 and downstream pathways of lipid biosynthesis, especially SCD-1, which controls the synthesis of monounsaturated fatty acids, providing the substrate for subsequent TG biosynthesis (38, 39). IH had a more pronounced effect on SREBP-1 mRNA levels in HET mice than in WT mice (Fig. 3A), implying that HIF-1α does not regulate SREBP-1 expression at the transcriptional level. However, partial HIF-1α deficiency abolished the hypoxia-induced increase in nSREBP-1 (Fig. 4, A and B), which suggests that HIF-1α affects SREBP-1 at the posttranscriptional level. In addition, HET mice manifested an impaired induction of SCD-1 after IH compared with WT mice, which might be a downstream effect of the impaired nuclear localization of SREBP-1. The impaired induction of SCD-1 in HET mice in response to IH might account for the attenuated increases in serum and liver TG (Fig. 7).

HIF-1α may act on SREBP-1 via SCAP. SCAP facilitates the transport of SREBPs from the endoplasmic reticulum to the Golgi apparatus, where the active nuclear isoform of SREBPs is cleaved by specific proteases (5, 16, 18, 33, 53) (Fig. 5). Notably, the SCAP gene promoter contains a putative HIF-1α binding site, 5′-ACGTG-3′ (35, 61). HET mice exhibited an impaired induction of SCAP in response to IH (Figs. 4C and 6, A and B). Thus HIF-1α may upregulate lipid biosynthesis in the liver during IH by stimulating SREBP-1 activity via SCAP.

IH, insulin, SREBP-1, and HIF-1α. Another possible mechanism of SREBP-1 activation by HIF-1α is via the effects of insulin. Serum insulin levels were increased by IH in WT, but not in HET, mice (Fig. 2B). However, insulin affects SREBP-1

Table 2. Lipid content in the liver and LPL activity in the epididymal fat of WT and HET mice exposed to IH for 5 days

<table>
<thead>
<tr>
<th>Liver Lipid Content, mg/g tissue</th>
<th>Adipose Tissue LPL Activity, µmol FFA·h⁻¹·g⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT IA 6.0±0.6</td>
<td>9.2±0.5</td>
</tr>
<tr>
<td>IH 8.3±0.5*</td>
<td>8.1±0.4</td>
</tr>
<tr>
<td>HET IA 7.0±1.1</td>
<td>7.0±1.1</td>
</tr>
<tr>
<td>IH 5.2±0.5*</td>
<td>8.9±0.3</td>
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Values are means ± SE. TG, triglycerides; PL, phospholipid; LPL, lipoprotein lipase; FFA, free fatty acid. *P = 0.05 for the difference between WT and HET mice at the same condition.

Lipid biosynthesis pathways in livers of HET and WT mice exposed to IH. IH caused a threefold increase in the expression of VEGF in the livers of WT mice (Fig. 3). HET mice had a low expression of VEGF at baseline with a barely detectable increase after IH. In both HET and WT mice, IH led to significantly increased expression of key genes of fatty acid and TG biosynthesis, SREBP-1, SCAP, and SCD-1 (Fig. 4), whereas the master regulator of cholesterol biosynthesis (52, 54) SREBP-2 was not affected. SREBP-1 mRNA levels were significantly greater induction by IH in WT mice compared with HET mice at both the mRNA and protein levels (Figs. 4D and 6, C and D). There was no difference in the levels of α-actin between genotypes (Figs. 5, E and F, and 6, E and F).

**Fig. 3.** Expression of VEGF by real-time RT-PCR assays of RNA isolated from livers of HET and WT mice after exposure to IH or IA for 5 days. *P < 0.05 for the difference between IH and IA.
at the transcriptional level (9), whereas an increase in $SREBP1$ gene expression by IH was greater in HET mice than in WT mice (Fig. 3A). On the other hand, partial HIF-1α deficiency alleviated the IH-induced hypertriglyceridemia and TG accumulation in the liver (Fig. 1), which causes insulin resistance and high serum insulin levels (3, 8, 25, 26, 34, 40, 46). Therefore, it is conceivable that IH activates HIF-1, which, in turn, upregulates SREBP-1 at the posttranscriptional level, leading to hypertriglyceridemia and TG accumulation in the liver and secondary hyperinsulinemia (Fig. 7).

IH also led to an increase in circulating leptin in WT mice (Fig. 2C), which is consistent with our previous observations in C57BL/6J mice (30, 41). This increase in leptin was reduced in HET mice, although the difference was not statistically significant. Leptin gene expression is regulated by HIF-1 (1). Leptin, a hormone controlling body weight and metabolic rate (4, 13, 66), is also an inflammatory cytokine, and an increase in leptin may reflect the effect of HIF-1 on systemic inflammation (15, 19, 32, 48). Another indicator of systemic inflammation is IL-6 (2, 6), which was also increased by IH in WT mice (Fig. 2D). An increase in IL-6 was not observed in HET mice. HIF-1 is not known to regulate IL-6 directly. Alternatively, as discussed above, HIF-1 activation may enhance TG biosynthesis, leading to hypertriglyceridemia and hyperinsulinemia. In turn, hyperinsulinemia may raise serum levels of both IL-6 and leptin (28, 47, 56). Thus HIF-1 can potentially enhance the systemic inflammatory response in IH via hyperlipidemia and augmented TG biosynthesis in the liver (Fig. 7).

IH, cholesterol metabolism, and HIF-1. Partial HIF-1α deficiency did not affect serum cholesterol levels during IH. Both HET and WT mice exhibited significant increases in serum total cholesterol and HDL-cholesterol levels (Fig. 1). In both

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Fig. 4. Expression of genes involved in lipid metabolism by real-time RT-PCR assays of RNA isolated from livers of HET and WT mice after exposure to IH or IA for 4 days. A: sterol regulatory element binding protein (SREBP)-1; B: SREBP-2; C: SREBP cleavage-activating protein (SCAP); D: stearoyl CoA desaturase (SCD)-1. *P < 0.05 and †P < 0.001 for the difference between IH and IA.

Fig. 5. Analysis of SREBPs in liver nuclear extracts. Expressions of the active nuclear isoforms of SREBP-1 and SREBP-2 [nSREBP-1 (A and B) and nSREBP-2 (C and D), respectively; 68 kDa] and α-actin (E and F; 43 kDa) were determined by immunoblot assays of nuclear extracts prepared from livers of WT and HET mice exposed to IH or IA for 5 days. A, C, and E: representative samples from 2 control mice (lanes 1 and 2) compared with 2 representative samples from mice exposed to IH (lanes 3 and 4). B, D, and F: optical densities of the nSREBP-1, nSREBP-2, and α-actin bands per the same amount of total protein (70 μg). *P < 0.05 for the difference between mice exposed to IH or control conditions within a genotype.
genotypes, IH did not alter SREBP-2 mRNA and protein levels in the liver (Figs. 4 and 5). In agreement with our previous report (30), these data suggest that IH-induced hypercholesterolemia is caused by the mechanisms other than de novo cholesterol biosynthesis.

Caveats and conclusions. The presence of only partial HIF-1α deficiency in HET mice limits our ability to interpret negative results and does not exclude the possibility that HIF-1 contributes to IH-induced changes in fasting blood glucose, serum cholesterol, PL, and FFA levels. Another limitation of the study was that reliable measurement of HIF-1α in the liver was not feasible due to instant ubiquitination of this protein under normoxic conditions by a prolyl hydrolase (22, 24). However, one of key HIF-1-regulated genes, VEGF (10), was overexpressed in livers of WT mice exposed to IH but not in mice with partial HIF-1α deficiency (Fig. 3), implying that IH induced HIF-1 in the liver.

Our previous reports, in combination with clinical data, have indicated that IH due to OSA may lead to insulin resistance and hyperlipidemia, which are defining components of the metabolic syndrome. Our present data suggest that IH due to OSA may exacerbate the metabolic syndrome via a direct effect of HIF-1 on SREBP-1-controlled pathways of lipid biosynthesis in the liver.
The data presented in this study suggest that HIF-1-regulated pathways link IH and the metabolic syndrome (Fig. 7). We hypothesize that IH-induced HIF-1 upregulates SCAP expression, leading to increased nuclear translocation of nSREBP-1c, which, in turn, upregulates SCD-1 expression. SCD-1 accelerates the biosynthesis of monounsaturated fatty acids, leading to increased TG biosynthesis and elevated levels of liver and serum TG, which, in turn, lead to increased serum insulin levels and systemic inflammation, as evidenced by increased serum levels of IL-6. Taken together with the previously established role of HIF-1 as a master regulator of glucose transport and glycolysis (23, 51), these studies demonstrate that HIF-1 orchestrates multiple metabolic responses to hypoxia.

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REFERENCES

35. Nakajima T, Hamakubo T, Kodama T, Inazawa J, and Emi M. Genomic structure and chromosomal mapping of the human steroid regu-
41. Polotsky VY, Li J, Punjabi NM, Rubin AE, Smith PL, Schwartz AR, and O’Donnell CP. Intermittent hypoxia increases insulin resistance in genet-
44. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, and Smith PL. Sleep-disordered breathing and insulin resistance in middle-
55. Shimoda LA, Manalo DJ, Sham JS, Semenza GL, and Sylvester JT. Partial HIF-1α deficiency impairs pulmonary arterial myocyte electro-