Interleukin-6 contributes to early fasting-induced free fatty acid mobilization in mice

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Wueest S, Item F, Boyle CN, Jirkof P, Cesarovic N, Ellingsgaard H, Böni-Schnetzler M, Timper K, Arras M, Donath MY, Lutz TA, Schoenle EJ, Konrad D. Interleukin-6 contributes to early fasting-induced free fatty acid mobilization in mice. Am J Physiol Regul Integr Comp Physiol 306: R861–R867, 2014. First published April 2, 2014; doi:10.1152/ajpregu.00533.2013.—Contracting muscle releases interleukin-6 (IL-6) enabling the metabolic switch from carbohydrate to fat utilization. Similarly, metabolism is switched during transition from fed to fasting state. Herein, we examined a putative role for IL-6 in the metabolic adaptation to normal fasting. In lean C57BL/6J mice, 6 h of food withdrawal increased gene transcription levels of IL-6 in skeletal muscle but not in white adipose tissue. Concomitantly, circulating IL-6 and free fatty acid (FFA) levels were significantly increased, whereas respiratory quotient (RQ) was reduced in 6-h fasted mice. In white adipose tissue, phosphorylation of hormone-sensitive lipase (HSL) was increased on fasting, indicating increased lipolysis. Intriguingly, fasting-induced increase in circulating IL-6 levels and parallel rise in FFA concentration were absent in obese and glucose-intolerant mice. A causative role for IL-6 in the physiological adaptation to fasting was further supported by the fact that fasting-induced increase in circulating IL-6 levels was significantly blunted in lean IL-6 knockout (KO) and lean C57BL/6J mice treated with neutralizing IL-6 antibody. Consistently, phosphorylation of HSL was significantly reduced in adipose tissue of IL-6-depleted mice. Hence, our findings suggest a novel role for IL-6 in energy supply during early fasting.

metabolic adaptation; lipolysis; energy supply

WHILE MOST TISSUES rely on glucose as energy substrate in the postprandial state, energy production from free fatty acid (FFA) becomes increasingly important upon fasting (7, 26). Increased fat oxidation reduces the need for glucose (from glycogen stores or gluconeogenesis) as an energy source. Moreover, fasting leads to increased production of ketone bodies in the liver (mainly in the form of β-hydroxybutyrate), which can serve as alternative energy source (7, 9, 20). During fasting, FFAs are increasingly released from white adipose tissue, mainly as a consequence of reduced circulating insulin levels, to comply with the increased demand of liver and other organs (23). Mechanistically, reduced insulin levels increase protein kinase A-dependent phosphorylation of hormone-sensitive lipase (HSL) in white adipose tissue, leading to increased lipolysis (12).

Similar to the adaptation to fasting, increased FFA mobilization is crucial during prolonged exercise (3). During physical activity, catecholamine and muscle-derived interleukin 6 (IL-6) stimulate adipocyte lipolysis, which in turn ensures adequate FFA supply (14). Indeed, IL-6 alone can induce lipolysis in vivo and in vitro (17). Moreover, indirect calorimetry in IL-6 KO mice revealed an elevated respiratory quotient (RQ) suggesting increased reliance on glucose oxidation for energy production compared with wild-type (WT) mice (8). Hence, IL-6 might be required for the “metabolic switch” of fuel utilization, from predominantly carbohydrate to more lipid oxidation. Supporting this notion, overnight fasting increases circulating IL-6 plasma levels significantly in humans (29). Moreover, such rise in IL-6 concentration is accompanied by lower RQ (29). However, the impact of IL-6 on glucose homeostasis and insulin sensitivity remains unclear (2, 5). On one hand, increased IL-6 action may deteriorate (hepatic) insulin sensitivity and, thus, contribute to obesity-associated insulin resistance (2, 5, 19, 27). On the other hand, recent reports suggest a role for hepatic IL-6 signaling in limiting hepatic inflammation, thereby providing a protective mechanism against local and systemic insulin resistance (28).

In the present study, we hypothesized that fasting-mediated release of IL-6 stimulates FFA mobilization via activation of adipose tissue lipolysis, similar to IL-6 action during exercise, thereby supporting the fasting-induced metabolic switch from carbohydrate to lipid oxidation. To test this hypothesis, muscle IL-6 mRNA levels as well as circulating IL-6 and FFA concentrations were determined in fed versus fasted control mice and in IL-6-deficient mice. Our findings provide evidence for a novel role of IL-6 in energy supply during early fasting.

MATERIALS AND METHODS

Animals. Male C57BL/6J (C57BL/6JolaHsd)-mice were purchased from Harlan (AD Horst, The Netherlands), male IL-6 knockout (KO), and respective WT mice were obtained from Charles River Laboratories (Wilmington, MA). All mice were housed in a specific pathogen-free environment on a 12-h light-dark cycle (light on from 7 PM to 7 AM) and fed ad libitum with regular chow diet (Provisiom Kliba, Kaiseraugst, Switzerland) or high-fat diet (HFD) (D12331, Research Diets, New Brunswick, NJ). All protocols conformed to the

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Swiss animal protection laws and were approved by the Cantonal Veterinary Office in Zurich, Switzerland.

Intraperitoneal glucose tolerance tests. Glucose was injected intraperitoneally (2 mg/g body wt) in overnight-fasted mice (n = 6 mice per group). Blood glucose concentration was measured in blood from tail-tip bleedings using a glucometer (AccuCheck Aviva, Roche Diagnostics, Rotkreuz, Switzerland) as described (19).

Determination of plasma insulin, FFA, ketone body, IL-6, KC, and TNF-α levels. Plasma insulin and FFA levels were determined as described (11). Of note, FFA levels were analyzed in plasma sampled from heart blood. Plasma IL-6, KC (cytokine-induced neutrophil-attracting chemokine), and tumor necrosis factor factor (TNF-α) levels were measured with mouse LINCoplex kits from Linco Research (Labodia, Yens, Switzerland) and mouse Procarta Cytokine Assay Kit (Labodia). Blood ketone concentration was determined with the Precision Xtr ketone meter (Abbott Laboratories, Baar, Switzerland) allowing measurements with accuracy of one digit after the decimal point.

IL-6 neutralization. Neutralizing anti-IL-6 (0.5 mg) or an IgG control antibodies (R&D Systems) were injected intraperitoneally 1 h before the beginning of the fasting period (n = 8 or 10 mice per group).

Metabolic cage analysis. Food and water intake, O2 consumption, and CO2 production were determined for single-housed mice in a metabolic and behavioral monitoring system (PhenoMaster, TSE Systems, Bad Homburg, Germany). Mice were given at least 4 days to acclimate to single caging before experiments were started (n = 5 to 8 mice per group).

Activity analysis. To test the effects of food deprivation/removal on general activity, all animals were single housed in observation cages [type 3 clear-transparent plastic cages (425 mm × 266 mm × 155 mm)] without cage grids; animals were provided with unrestricted access to food and drinking water, sawdust bedding, one red mouse house as shelter (Indulab, Gams, Switzerland), and one Nestlet (5 cm × 5 cm) consisting of cotton fibers (Indulab) as nesting material for 3 days before observation. Behavior was digitally recorded on day 4. For recording of baseline activity, animals were fed ad libitum and observed for 24 h; subsequent on day 5 animals were observed for 24 h under the same conditions but without access to food (deprivation). The recorded 24-h video sequences were analyzed using EthovisionX software (Noldus, Wageningen, The Netherlands). As a parameter of activity, distance moved in centimeters was recorded (n = 8 mice per group).

RNA extraction and quantitative reverse transcription-PCR. Total RNA from quadriceps muscle, epidydimyal white adipose tissue, liver, and brain was extracted with the RNeasy lipid tissue mini kit (Qiagen, Basel, Switzerland). RNA was reverse transcribed with Superscript III Reverse Transcriptase (Invitrogen, Basel, Switzerland) using random hexamer primer (Invitrogen). Tagman system (Applied Biosystems, Rotkreuz, Switzerland) was used for real-time PCR amplification. Relative gene expression was obtained after normalization to 18S RNA (Applied Biosystems), using the formula 2^ΔΔCt (18). The gene expression assays used were the following: IL-6, Mm00446190_m1; CPT-1, Mm00550438_m1; and PGC-1α, Mm01208835_m1 (Applied Biosystems).

Muscle glycogen assay. Skeletal muscle of 10–20 mg was placed in duplicates in microfuge tubes with 500 μl M HCl. Tubes were boiled for 2 h and reconstituted to original volume with ddH2O. Five hundred microliters of 2 M NaOH were added for neutralization of the acid. Tubes were vortexed to break up muscle tissue. One hundred microliters of standard (Sigma, Buchs, Switzerland), ddH2O (blank), or sample were mixed with 1 ml of hexokinase reagent (Sigma) and incubated for 10 min at room temperature. Samples and standards were finally read in a spectrophotometer at 340 nm (n = 10 Chow-fed and n = 3 HFD-fed mice per group).

Western blot. Tissues were lysed and Western blots were performed as previously described (27). Membranes were blocked for 1 h in 5% nonfat dry milk (Bio-Rad) and incubated overnight at 4°C on a rocking platform with respective primary antibodies diluted 1:1,000. Primary antibodies used were the following: anti-phospho-p38, anti-phospho-HSL (Ser660) (both from Cell Signaling, Danvers, MA), and anti-actin (Millipore, Zug, Switzerland).

Data analysis. Data are presented as means ± SE and were analyzed by unpaired Student’s t-test or ANOVA with Bonferroni-corrected post hoc tests. Log transformation was performed to obtain normally distributed data where necessary.

Fig. 1. Increased circulating IL-6 levels after 6 h of fasting. Chow-fed C57BL6J mice were either fasted starting at 8.00 AM or fed ad libitum, and blood was sampled by tail tip bleeding at indicated time points. Shown are values for ketone bodies (β-hydroxybutyrate) (A), blood glucose (B), IL-6 (C), and plasma insulin (D). Results are means ± SE; n = 4–6 mice. Measured parameters were significantly different between the groups for time (B: P < 0.001, C: P < 0.01 and D: P < 0.05), and there were time × group interactions (B: P < 0.001, C: P = 0.07 and D: P < 0.001) (ANOVA). *P < 0.05, **P < 0.01, ***P < 0.001 (Bonferroni-corrected post hoc tests). Of note, data for ketone body measurements (A) were not normally distributed (probably due to measurement accuracy; see MATERIALS AND METHODS), and, hence, ANOVA could not be performed.
RESULTS

Plasma IL-6 levels are increased upon fasting in chow-fed C57BL/6J mice. To examine the potential role of IL-6 in metabolic adaptation to fasting, circulating IL-6 levels were assessed in mice after food withdrawal. Three-month-old C57BL/6J mice were either randomly fed or fasted for 24 h (starting at 8 am), and blood was sampled after 6, 12, and 24 h. As expected, fasting induced an increase in blood ketone levels, with an increase already after fasting for 6 h, whereas blood glucose levels were only significantly different after 24 h of fasting (Fig. 1B). In parallel, plasma IL-6 levels increased 3-fold after 6 h and 4.5-fold after 12 h of fasting (Fig. 1C). In contrast, there was no fasting-induced increase in the concentration of other circulating cytokines such as keratinocyte chemoattractant (KC, the mouse homologue of interleukin-8) and TNF-α (data not shown), suggesting that the elevation in circulating IL-6 in response to fasting does not indicate activation of classical pro-inflammatory cytokine cascades. Of note, circulating insulin levels were not significantly different between mice fasted for 6 h and random fed mice, whereas they were more than fivefold decreased in mice fasted for 12 h (Fig. 1D). Since insulin is a major regulator of circulating FFA
levels by inhibiting lipolysis, which results in decreased FFA concentrations, we focused our additional studies on mice fasted for 6 h, which does not significantly affect blood insulin levels. To further investigate whether 6 h of fasting affect metabolism in lean mice, FFA levels were analyzed. As shown in Fig. 2A, plasma FFA levels were significantly increased in mice fasted for 6 h. Consistently, phosphorylation of HSL was significantly increased in white adipose tissue of fasted mice (Fig. 2B), indicating increased lipolysis. Moreover, 6 h of fasting led to a significant reduction in the RQ, suggesting increased fat oxidation (Fig. 2C). In agreement, mRNA expression of carnitine palmitoyltransferase 1 (CPT-1) and peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) [two enzymes involved in fat oxidation (21)] were significantly increased in skeletal muscle of fasted mice (Fig. 2D). Of note, body weight was similar in fed and fasted mice (27.6 ± 0.8 g vs. 27.1 ± 0.9 g) and randomly fed mice ate on average 0.3 ± 0.1 g during the 6-h period.

To determine the source of IL-6 production during fasting, its mRNA expression was assessed in white adipose tissue and skeletal muscle, the two major sources of circulating IL-6 levels (5, 14) as well as in the liver and brain. As depicted in Fig. 3A, 6 h of fasting upregulated IL-6 mRNA expression in skeletal muscle, but not in white adipose tissue. Of note, IL-6 transcription was decreased by 6 h of fasting in the liver and brain (Fig. 3A). It was previously suggested that intramuscular glycogen content is an important enhancer of IL-6 mRNA expression in skeletal muscle during exercise (14). We therefore hypothesized that a fasting-induced decrease in muscle glycogen content might trigger IL-6 expression in skeletal muscle. As shown in Fig. 3B, 6 h of fasting reduced glycogen levels by ∼25% in skeletal muscle of chow-fed C57BL/6J mice paralleling the rise in muscle IL-6 mRNA levels (Fig. 3A). In addition, fasting increased phosphorylation of the p38 mitogen-activated protein kinase (p38 MAPK) in skeletal muscle (Fig. 3C), a stress kinase involved in skeletal muscle IL-6 expression (16). Of note, the decrease in skeletal muscle glycogen content could not be attributed to increased locomotor activity in response to fasting (Fig. 3D). This finding suggests that the observed increase in IL-6 mRNA levels upon fasting was not due to increased physical activity/muscle contraction as part of increased food-seeking behavior, and thus, differs from IL-6 induction in muscle in response to exercise.

Loss of fasting-induced regulation of IL-6 and FFA levels in HFD-fed mice. Obese and glucose-intolerant mice have a blunted metabolic adaptation to fasting (24). To investigate whether fasting-induced IL-6 is disrupted in mice with impaired metabolic flexibility, C57BL/6J mice were fed a high-fat diet (HFD) for 6 wk. As expected, HFD increased body weight (28.4 ± 0.4 g chow-fed vs. 32.6 ± 0.4 g HFD,  P < 0.01), impaired glucose tolerance (Fig. 4A), and induced insulin resistance [fasting insulin levels: 76.0 ± 4.4 pmol/l chow-fed vs. 487.8 ± 78.9 pmol/l HFD,  P < 0.01]. Of note, HFD-fed mice were either fasted (open bars) starting at 8.00 AM or fed ad libitum (closed bars) for 6 h. Shown are plasma IL-6 levels in high-fat diet-fed mice. IL-6 plasma levels in high-fat diet-fed mice were significantly different between the groups for time ( P < 0.001), and there was a time×group interaction ( P < 0.001; ANOVA). * P < 0.05, ** P < 0.01, *** P < 0.001 Bonferroni-corrected post hoc tests.

**Fig. 4.** Loss of fasting-induced increase in IL-6 plasma levels in high-fat diet-fed mice. A: intraperitoneal glucose tolerance tests in chow-fed and HFD-fed C57BL/6J mice. Chow-fed mice were the same animals as used for blood sampling in Fig. 1. n = 6 mice. HFD-fed mice were either fasted (open bars) starting at 8.00 AM or fed ad libitum (closed bars) for 6 h. Shown are plasma IL-6 concentrations (n = 6 mice) (B), skeletal muscle IL-6 mRNA expression (n = 4 mice) (C), skeletal muscle glycogen (n = 3 mice) (D), and plasma FFA levels (n = 4–5 mice) (E). All results are means ± SE. Glucose excursion (A) was significantly different between the groups for time ( P < 0.001), and there was a time×group interaction ( P < 0.001; ANOVA). * P < 0.05, ** P < 0.01, *** P < 0.001 Bonferroni-corrected post hoc tests.
Fed vs. 151.5 ± 19.7 pmol/l HFD, *P < 0.01; homeostatic model assessment of insulin resistance (HOMA-IR): 2.2 ± 0.2 in Chow-fed vs. 5.5 ± 0.7 HFD, *P < 0.01) compared with Chow-fed mice that showed elevated IL-6 levels upon fasting (Fig. 1). Interestingly, 6 h of fasting had no impact on circulating IL-6 levels in HFD-fed mice (Fig. 4B). Consistent with similar circulating IL-6 levels in fed and fasting HFD mice, IL-6 mRNA expression in skeletal muscle (Fig. 4C) as well as skeletal muscle glycogen levels (Fig. 4D) were not different between fed and fasted mice under HFD. Concomitantly, there was no increase in fasting-induced FFA concentration in obese and glucose-intolerant mice (Fig. 4E). Of note, FFA levels were markedly higher than in lean Chow-fed mice (Fig. 2B). Thus IL-6 may contribute to early fasting-induced metabolic adaptations in lean but not obese, glucose-intolerant mice.

Fasting-induced increase in FFA levels is reduced in lean IL-6 KO mice and in lean mice injected with neutralizing IL-6 antibody. IL-6 KO mice were used to further assess a causative contribution of IL-6 in fasting-induced increase in circulating FFA levels. Glucose tolerance was not different in 3-mo-old Chow-fed IL-6 KO and WT mice (Fig. 5A), confirming previous findings in young IL-6 KO mice (6). In addition, there was no difference in blood glucose levels between the two groups in fed and fasted mice (Fig. 5B). Importantly, fasting-induced increase in FFA levels was significantly blunted in IL-6 KO mice compared with WT mice (Fig. 5C), whereas no difference in plasma insulin levels was observed (Fig. 5D).

Since the absence of IL-6 during development might have led to (metabolic) (mal)adaptation in IL-6 KO mice, a second approach was used to study the potential role of acute IL-6 depletion in early FFA mobilization. Chow-fed C57BL/6J mice were treated either with a neutralizing IL-6 (nIL-6) or an isotype control (IgG) antibody and subsequently fasted for 6 h. While there was no difference in blood glucose concentration between the two groups after 6 h of fasting (Fig. 6A), FFA levels were significantly lower in mice injected with nIL-6 antibody compared with IgG-injected mice (Fig. 6B). Of note, white adipose tissue of fasted mice treated with nIL-6 antibody revealed significantly reduced phosphorylation of HSL, suggesting blunted lipolysis (Fig. 6C). Importantly, insulin levels were similar in the two fasted groups (Fig. 6D). Moreover, neutralization of IL-6 did not alter RQ and mRNA expression of CPT-1 and PGC-1α in skeletal muscle (Fig. 6, E and F) suggesting that muscle lipid oxidation is not affected by IL-6 neutralization. In summary, experiments in IL-6-depleted mice further confirm the notion that the fasting-induced rise in circulating FFA levels is IL-6 dependent.

DISCUSSION

In the present study we identified a role for IL-6 in the fasting-induced increase in circulating FFA levels. The major findings of this study supporting this proposition are 1) fasting increases circulating IL-6 levels in lean mice; 2) depletion of IL-6 (either by IL-6 KO or by neutralization of circulating IL-6) blunts the fasting-induced rise in circulating FFA levels in lean mice; and 3) obese and glucose-intolerant mice lack the fasting-induced increase in circulating IL-6 and FFA levels.

What is the source of the fasting-induced increase in circulating IL-6 levels? IL-6 mRNA expression was increased in skeletal muscle but not in white adipose tissue, liver, and brain 6 h after fasting. Since both skeletal muscle and adipose tissue contribute significantly to circulating IL-6 levels at rest (5, 14), our data suggest that skeletal muscle is the main contributor to increased circulating IL-6 levels during early fasting. Compatible with such notion, fasting increased phosphorylation of p38 MAPK in skeletal muscle, which was previously found to contribute to IL-6 transcription and secretion (16). Although the link is only associative, IL-6 transcription may be triggered by decreased muscle glycogen levels, as was previously shown for physical activity (14). However, in contrast to physical activity, decreased glycogen levels during fasting does not

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**Fig. 5.** Fasting-induced increase in FFA levels is reduced in IL-6 KO mice. A: intraperitoneal glucose tolerance tests in Chow-fed WT (○) and IL-6 KO (●) mice. n = 5–6 mice. Chow-fed WT and IL-6 KO mice were either fasted (open bars) starting at 8.00 AM or fed ad libitum (closed bars) for 6 h. Shown are blood glucose (n = 5 mice) (B), plasma FFA (n = 4–5) (C), and plasma insulin levels (n = 4–5 mice) (D). All results are means ± SE. *P < 0.05, **P < 0.01 (Student’s t-test).
IL-6-mediated release of free fatty acids in early fasting

Fig. 6. Fasting-induced increase in FFA levels is reduced in mice treated with neutralizing IL-6 antibody. Chow-fed WT mice were treated with either neutralizing IL-6 (hatched bars) or control IgG (open bars) antibody and fasted for 6 h starting at 8.00 AM. Shown are blood glucose levels (n = 4 mice) (A) and plasma FFA levels (n = 8–10 mice) (B) after 6 h of fasting. C: representative Western blots of epididymal adipose tissue of fasted mice. Graph depicts results of 3 mice per group. D: plasma insulin levels (n = 8–10 mice) after 6 h of fasting. E: respiratory quotient (RQ) was determined in metabolic cages in mice fed ad libitum or in mice fasted for 6 h. Shown are average RQ data recorded during the last hour of the experiment (n = 5–7 mice). F: skeletal muscle mRNA expression of CPT-1 and PGC-1α was analyzed in fed and fasted mice and normalized to 18S RNA. All results are means ± SE; n = 4–6 mice. *P < 0.05, **P < 0.01 (Student’s t-test).

IL-6 levels may depend on time of day, duration, as well as the pattern of fasting (single bout vs. intermittent).

The finding of decreased IL-6 expression in brain and liver not only demonstrates the unique role of skeletal muscle IL-6 in metabolic adaptation, but also highlights a possible regulatory role for IL-6 in the adaptation to short-term fasting also in these tissues: IL-6 was shown to have anorexigenic effects in the brain (22) and thus decreased local IL-6 production during fasting would support food-seeking behavior. Complementarily, IL-6 decreases hepatic gluconeogenesis (10). Therefore, its decreased hepatic expression would support the required upregulation of hepatic glucose production during fasting.

Insulin is a major regulator of circulating FFA levels by inhibiting lipolysis in white adipose tissue. As pointed out, we focused our studies on mice fasted for 6 h, which did not significantly affect blood insulin levels. Nevertheless, the observed slight reduction in circulating insulin levels upon 6 h of fasting may still have affected circulating FFA levels in lean WT mice. However, circulating insulin levels were not increased in fasted IL-6 KO mice and in mice treated with nIL-6 antibody compared with their respective fasted control mice. Such result would suggest that decreased circulating FFA levels in IL-6-depleted mice after 6 h of fasting were not dependent on increased circulating insulin levels. In addition, decreased phosphorylation...
of HSL in white adipose tissue of IL-6-depleted mice upon fasting suggests that IL-6 induces lipolysis in adipose tissue and thereby contributes to the fasting-induced increase in circulating FFA levels. Our data are in agreement with a previous study reporting a lipidic effect of IL-6 in adipocytes (17).

Obese and glucose-intolerant mice have a blunted metabolic adaptation to fasting (24). Such impaired metabolic flexibility, recently recognized as a potentially highly clinically relevant early characteristic of individuals suffering from obesity or glucose intolerance, may in fact be due to a failure to mount the normal rise in IL-6 levels in response to fasting.

Perspectives and Significance

Our results indicate a novel physiological role for IL-6 in early fasting-induced increase in circulating FFA levels and, thus, metabolic adaptation. Moreover, they suggest that an impaired rise of IL-6 in response to fasting may contribute to constrained metabolic flexibility characteristic for obesity-associated glucose intolerance.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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