Early postweaning exercise improves central leptin sensitivity in offspring of rat dams fed high-fat diet during pregnancy and lactation

Bo Sun,¹,² Nu-Chu Liang,³ Erin R. Ewald,² Ryan H. Purell,² Gretha J. Boersma,² Jianqun Yan,¹ Timothy H. Moran,² and Kellie L. K. Tamashiro²

¹Department of Physiology and Pathophysiology, Xi’an Jiaotong University School of Medicine, Xi’an, Shaanxi, People’s Republic of China; and ²Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

Submitted 7 December 2012; accepted in final form 4 September 2013

THE INCIDENCE OF OBESITY in the developed and developing world has increased over the last decade (17, 27). The prevalence of childhood obesity is also increasing, suggesting that the obesity epidemic will continue to worsen (24, 33). Increasing evidence suggests that the early life environment can influence the development of obesity (15, 29). Maternal high-fat diet throughout gestation and suckling has been shown to have long-term consequences on the metabolic phenotype of the offspring. Here, we determined the effects of postweaning exercise in offspring of rat dams fed HF diet during gestation and lactation. Pregnant Sprague-Dawley rats were maintained on chow or HF diet throughout gestation and lactation. All pups were weaned onto chow diet on postnatal day (PND) 21. At 4 wk of age, male pups were given free access to running wheels (RW) or remained sedentary (SED) for 3 wk, after which all rats remained sedentary, resulting in four groups: CHOW-SED, CHOW-RW, HF-SED, and HF-RW. Male HF offspring gained more body weight by PND7 compared with CHOW pups and maintained this weight difference throughout the entire experiment. Three weeks of postweaning exercise did not affect body weight gain in either CHOW or HF offspring, but reduced adiposity in HF offspring. Plasma leptin was decreased at the end of the 3-wk running period in HF-RW rats but was not different from HF-SED 9 wk after the exercise period ended. At 14 wk of age, intracerebroventricular injection of leptin suppressed food intake in CHOW-SED, CHOW-RW, and HF-RW, while it did not affect food intake in HF-SED group. At death, HF-RW rats also had higher leptin-induced phospho-STAT3 level in the arcuate nucleus than HF-SED rats. Both maternal HF diet and postweaning exercise had effects on hypothalamic neuropeptide and receptor mRNA expression in adult offspring. Our data suggest that postweaning exercise improves central leptin sensitivity and signaling in this model.

Address for reprint requests and other correspondence: Corresponding author: K. L. K. Tamashiro, Dept. of Psychiatry and Behavioral Sciences, Johns Hopkins Univ. School of Medicine, 720 Rutland Ave., Ross 618, Baltimore, MD 21205, USA (e-mail: ktamashiro@jhmi.edu).

MATERIALS AND METHODS

Animals and Diet

Pregnant female Sprague-Dawley rats (Charles River, Kingston, NY) were received on gestation day 2. Animals were individually housed in conventional tub cages with access to food and water ad libitum. The room was maintained on a 12:12-h light-dark cycle with light onset at 0600. All animal procedures were approved by the Institutional Animal Care and Use Committee of the Johns Hopkins University School of Medicine.

Pregnant rats were divided into two groups and provided with one of two diets: standard chow diet (CHOW; LabDiet, 5001, 13.5% kcal from fat; n = 12) or high-fat diet (HF; Research Diets, D12492, 60% kcal from fat; n = 12). They remained on their respective diets from gestation day 2 throughout gestation and the suckling period. Dams’ body weight and food intake were measured daily throughout gestation. The day the dams gave birth was designated postnatal day (PND) 0. On PND 1, litters were culled to 10 pups each (5 males and 5 females). Pups and dams were weighed once a week on PND 1, 7, 14, and 21. Dams’ food intake was measured daily throughout the suckling period. On PND 21, all pups were weaned to standard chow diet. In all experiments, food spillage was recorded and accounted for in all food intake data presented.
Wheel Running

At weaning, two male pups per litter were individually housed in running-wheel cages (Mini Mitter, Bend, OR) with locked running wheels. One week later, at 4 wk of age, the running wheel for one male pup per litter was unlocked, while the second one remained locked. The pups were given free access to running wheels (RW) or remained sedentary (SED) for 3 wk, after which the running wheels were removed and rats remained sedentary. A separate group of rats (controls) or leptin (10 μg/kg, i.c.v.) was given at weaning. Because 3 of the 24 rats drank less than 5 ml water, they were not used in the food intake experiment. Because 3 of the 24 rats drank less than 5 ml water, they were not used in the food intake experiment. Because 3 of the 24 rats drank less than 5 ml water, they were not used in the food intake experiment. Because 3 of the 24 rats drank less than 5 ml water, they were not used in the food intake experiment.

Experiment 1

Glucose tolerance test and endocrine assays. At 7 wk (right after 3 wk running) or 10 wk (3 wk running + 3 wk sedentary) of age, rats were food-deprived overnight for 16 h with only water available. A baseline blood sample (~200 μl blood) was taken via a small tail nick for determination of plasma insulin. Baseline fasted blood glucose was determined at the same time by a hand-held glucose meter (Freestyle; TheraSense, Alameda, CA). Glucose (2.0 g/kg body wt, 20% glucose in sterile water solution) was then administered by oral gavage. Blood samples were collected at 15, 30, 45, 60, and 120 min after glucose gavage to determine plasma insulin levels. Blood glucose was determined at each time point using the glucometer. Plasma hormone concentrations were determined by commercially available radioimmunoassay kits for leptin and insulin (both for rats; Millipore, Billerica, MA).

Cannulation surgery. At 11 wk of age, rats were implanted with cannulas into right lateral ventricle. The coordinates described in Ref. 31.

Leptin effects on food intake. Four days after the ANG II test (at 14 wk of age), food was removed 2 h prior to dark onset (1200). At dark onset (1400), all rats received intracerebroventricular injection of either 2 μl saline or leptin (A. F. Parlow, National Hormone and Peptide Program, Torrance, CA; 10 μg in 2 μl) in a counter-balanced manner. Food was returned, and food intake was measured at 4 and 22 h after injection. There was short day rest between the two injections.

Leptin responsiveness. Seven days after the last injection (at 17 wk of age), rats were fasted overnight. At dark onset, rats received intracerebroventricular injection of either 2 μl saline or leptin (10 μg in 2 μl; n = 3 per group). Three hours later, rats were killed by decapitation. Brains were removed and immediately frozen on powdered dry ice and stored at −80°C. The paraventricular nucleus (PVN), ARC, ventromedial nucleus (VMN), dorsomedial hypothalamic nucleus (DMN), and lateral hypothalamus (LH) were punched from four 600-μm-thick frozen coronal sections using a blunt 16-gauge stainless-steel needle (inner diameter = 1.65 mm) based on the coordinates described in Ref. 31.

Western blotting. ARC samples were homogenized in lysis buffer (Sigma, St. Louis, MO) with protease inhibitor cocktail (Roche) and phosphatase inhibitor cocktail (Roche). After lysis on ice for 2 h, samples were centrifuged at 12,000 rpm at 4°C for 15 min. Protein concentration was determined using a protein assay kit (Thermo Scientific, Waltham, MA). Proteins (30 μg) were run on a 3–8% Tris-acetate gel and transferred onto PVDF membranes. Blots were blocked with 5% nonfat dry milk for 2 h. Phospho-STAT3 and STAT3 were determined using corresponding antibodies from Cell Signaling (Beverly, MA). Targeted proteins were revealed using SuperSignal West Pico Chemiluminescent Substrate (Thermo Scientific) and exposed to film (GE Healthcare, New York, NY). The intensity of bands was quantified using Scion Image Software (Scion, Frederick, MD). The ratio of the intensity of pSTAT3 to STAT3 was calculated to represent the level of phosphorylation. β-actin (Sigma, St. Louis, MO) was used as the loading control.

Experiment 2

Hypothalamic neuropeptide and receptor mRNA assays by real-time PCR. At 14 wk of age (second cohort), rats were fasted 4 h (0900–1300) and were killed by decapitation at 1300. Brains were removed and immediately frozen on powdered dry ice and stored at −80°C. The paraventricular nucleus (PVN), ARC, ventromedial nucleus (VMN), dorsomedial hypothalamic nucleus (DMN), and lateral hypothalamus (LH) were punched from four 600-μm-thick frozen coronal sections using a blunt 16-gauge stainless-steel needle (inner diameter = 1.65 mm) based on the coordinates described in Refs. 14 and 31. Punches of PVN, ARC, VMN, DMN, and LH were put into QIAzol lysis reagent (Qiagen, Valencia, CA) and homogenized immediately with a sterile pipet tip. RNA was extracted with the RNeasy Mini Kit (Qiagen). For each individual sample, 500 ng of total RNA was used in reverse transcription using the Quantitect reverse transcription kit (Qiagen). Expression of target genes was determined by real-time PCR using gene-specific TaqMan probes (Applied Biosystems, Foster City, CA) with TaqMan Gene Expression Master Mix (Applied Biosystems) on the ABI 7900HT Fast real-time PCR system set for 40 PCR cycles. Probes used for RT-PCR are listed in Table 1. To determine relative expression values, the ∆ΔCt method (Applied Biosystems) was used, where triplicate Ct values for each sample were averaged and subtracted from those derived from the housekeeping gene Actb.

Statistical analysis. Data were analyzed by ANOVA, repeated-measures ANOVA, or Student’s t-tests for independent samples as appropriate, using SPSS (SPSS 13.0; SPSS, Chicago, IL). Subsequent comparisons between groups used Newman-Keuls procedures. Data are presented as the means ± SE.

RESULTS

Dams’ body weight and food intake during gestation and male pups’ body weight before weaning. There were no significant differences in maternal body weight between the two dietary groups during the gestation period (Fig. 1A). HF dams
had higher caloric intake during the first and second week of gestation than CHOW dams ($P < 0.05$) (Fig. 1B). By PND 7, male HF offspring were significantly heavier than those with maternal chow diet, and this difference persisted through weaning on PND 21 ($P < 0.05$) (Fig. 1C). Effects of maternal HF diet and postweaning exercise on body weight, food intake, body composition, leptin concentration, and glucose tolerance.

At 4 wk of age, HF pups were ~24% heavier than CHOW pups (Fig. 2A). There was no difference in daily running revolution between the two dietary groups during 3 wk of running (Fig. 2C). There was no effect of exercise on body weight in either CHOW or HF rats (Fig. 2A). During the 21-day running period, HF rats consumed more food than CHOW rats ($P < 0.05$) (Fig. 2B). In the last week of running, exercised rats had greater food intake than sedentary rats in both CHOW and HF groups ($P < 0.05$), and this persisted until 1 wk after running (Fig. 2B).

At 14 wk of age, HF rats had more subcutaneous and retroperitoneal fat than CHOW rats (Fig. 3, A and B). Three weeks of postweaning exercise had no effect on adipose depots in CHOW rats, while it decreased both subcutaneous and
Differing from HF-SED rats, HF-RW rats had greater body weight and adiposity, impaired glucose tolerance, and altered hypothalamic neuropeptide and receptor mRNA expression. At 14 wk of age, HF-RW rats had 50% higher mRNA expression of PVN MC4R (P < 0.034) compared with CHOW-SED rats. Male HF offspring that were sedentary (HF-SED) had a 30% increase (P = 0.001) in ARC NPY mRNA expression compared with CHOW-SED rats, while postweaning exercise (HF-RW) resulted in a 40% decrease in ARC NPY mRNA expression compared with HF-SED rats. Rats in CHOW-RW and HF-RW groups both had 30% lower (P = 0.043) mRNA expression of ARC POMC compared with CHOW-SED rats. HF-SED had a 20% decrease (P = 0.044) in VMN leptin receptor-b mRNA expression compared with CHOW-SED rats. Rats in CHOW-RW, HF-SED, and HF-RW groups all had lower mRNA expression of LH orexin (P = 0.001) and melanin-concentrating hormone (MCH; P = 0.001) compared with CHOW-SED group. There were no other significant differences in other genes assessed among these groups.

**DISCUSSION**

We previously found that maternal HF diet can increase body weight and adiposity, impair glucose tolerance, and alter hypothalamic neuropeptide and receptor mRNA expression. We measured leptin injection significantly increased p-STAT3 level in ARC in all four groups (P < 0.05) (Fig. 6B). However, leptin-induced significantly less p-STAT3 in the ARC of HF-SED rats compared with that induced in CHOW-SED rats (P < 0.05), indicating that maternal HF diet reduces leptin-induced activation of STAT3 in adult offspring. There was no difference in leptin-induced p-STAT3 between CHOW-SED and CHOW-RW groups, while rats in HF-RW group had higher p-STAT3 level after leptin challenge compared with HF-SED group (P < 0.05), demonstrating that postweaning exercise improves leptin-induced activation of STAT3 in HF rats.

**Effects of maternal HF diet and postweaning exercise on hypothalamic neuropeptide and receptor mRNA expression.** We measured leptin injection significantly increased p-STAT3 level in ARC in all four groups (P < 0.05) (Fig. 6B). However, leptin induced significantly less p-STAT3 in the ARC of HF-SED rats compared with that induced in CHOW-SED rats (P < 0.05), indicating that maternal HF diet reduces leptin-induced activation of STAT3 in adult offspring. There was no difference in leptin-induced p-STAT3 between CHOW-SED and CHOW-RW groups, while rats in HF-RW group had higher p-STAT3 level after leptin challenge compared with HF-SED group (P < 0.05), demonstrating that postweaning exercise improves leptin-induced activation of STAT3 in HF rats.

**DISCUSSION**

We previously found that maternal HF diet can increase body weight and adiposity, impair glucose tolerance, and alter hypothalamic neuropeptide and receptor mRNA expression. We measured leptin injection significantly increased p-STAT3 level in ARC in all four groups (P < 0.05) (Fig. 6B). However, leptin induced significantly less p-STAT3 in the ARC of HF-SED rats compared with that induced in CHOW-SED rats (P < 0.05), indicating that maternal HF diet reduces leptin-induced activation of STAT3 in adult offspring. There was no difference in leptin-induced p-STAT3 between CHOW-SED and CHOW-RW groups, while rats in HF-RW group had higher p-STAT3 level after leptin challenge compared with HF-SED group (P < 0.05), demonstrating that postweaning exercise improves leptin-induced activation of STAT3 in HF rats.

**DISCUSSION**

We previously found that maternal HF diet can increase body weight and adiposity, impair glucose tolerance, and alter hypothalamic neuropeptide and receptor mRNA expression. We measured leptin injection significantly increased p-STAT3 level in ARC in all four groups (P < 0.05) (Fig. 6B). However, leptin induced significantly less p-STAT3 in the ARC of HF-SED rats compared with that induced in CHOW-SED rats (P < 0.05), indicating that maternal HF diet reduces leptin-induced activation of STAT3 in adult offspring. There was no difference in leptin-induced p-STAT3 between CHOW-SED and CHOW-RW groups, while rats in HF-RW group had higher p-STAT3 level after leptin challenge compared with HF-SED group (P < 0.05), demonstrating that postweaning exercise improves leptin-induced activation of STAT3 in HF rats.

**DISCUSSION**

We previously found that maternal HF diet can increase body weight and adiposity, impair glucose tolerance, and alter hypothalamic neuropeptide and receptor mRNA expression. We measured leptin injection significantly increased p-STAT3 level in ARC in all four groups (P < 0.05) (Fig. 6B). However, leptin induced significantly less p-STAT3 in the ARC of HF-SED rats compared with that induced in CHOW-SED rats (P < 0.05), indicating that maternal HF diet reduces leptin-induced activation of STAT3 in adult offspring. There was no difference in leptin-induced p-STAT3 between CHOW-SED and CHOW-RW groups, while rats in HF-RW group had higher p-STAT3 level after leptin challenge compared with HF-SED group (P < 0.05), demonstrating that postweaning exercise improves leptin-induced activation of STAT3 in HF rats.

**DISCUSSION**

We previously found that maternal HF diet can increase body weight and adiposity, impair glucose tolerance, and alter hypothalamic neuropeptide and receptor mRNA expression. We measured leptin injection significantly increased p-STAT3 level in ARC in all four groups (P < 0.05) (Fig. 6B). However, leptin induced significantly less p-STAT3 in the ARC of HF-SED rats compared with that induced in CHOW-SED rats (P < 0.05), indicating that maternal HF diet reduces leptin-induced activation of STAT3 in adult offspring. There was no difference in leptin-induced p-STAT3 between CHOW-SED and CHOW-RW groups, while rats in HF-RW group had higher p-STAT3 level after leptin challenge compared with HF-SED group (P < 0.05), demonstrating that postweaning exercise improves leptin-induced activation of STAT3 in HF rats.

**DISCUSSION**

We previously found that maternal HF diet can increase body weight and adiposity, impair glucose tolerance, and alter hypothalamic neuropeptide and receptor mRNA expression. We measured leptin injection significantly increased p-STAT3 level in ARC in all four groups (P < 0.05) (Fig. 6B). However, leptin induced significantly less p-STAT3 in the ARC of HF-SED rats compared with that induced in CHOW-SED rats (P < 0.05), indicating that maternal HF diet reduces leptin-induced activation of STAT3 in adult offspring. There was no difference in leptin-induced p-STAT3 between CHOW-SED and CHOW-RW groups, while rats in HF-RW group had higher p-STAT3 level after leptin challenge compared with HF-SED group (P < 0.05), demonstrating that postweaning exercise improves leptin-induced activation of STAT3 in HF rats.

**DISCUSSION**

We previously found that maternal HF diet can increase body weight and adiposity, impair glucose tolerance, and alter hypothalamic neuropeptide and receptor mRNA expression. We measured leptin injection significantly increased p-STAT3 level in ARC in all four groups (P < 0.05) (Fig. 6B). However, leptin induced significantly less p-STAT3 in the ARC of HF-SED rats compared with that induced in CHOW-SED rats (P < 0.05), indicating that maternal HF diet reduces leptin-induced activation of STAT3 in adult offspring. There was no difference in leptin-induced p-STAT3 between CHOW-SED and CHOW-RW groups, while rats in HF-RW group had higher p-STAT3 level after leptin challenge compared with HF-SED group (P < 0.05), demonstrating that postweaning exercise improves leptin-induced activation of STAT3 in HF rats.
leptin sensitivity in neonatal rats (40). Exercise is often considered to be an effective treatment for obesity. Previous studies have shown that 3 wk of early-onset exercise in DIO rats prolongs obesity resistance and increases central leptin sensitivity and signaling (28, 30). In this study, we used a different obese model-obese offspring from dams fed HF diet during gestation and lactation to determine whether early-onset exercise can reduce body weight or improve central leptin sensitivity in these rats. Our data suggest that postweaning exercise improves central leptin sensitivity and signaling without affecting body weight in male HF offspring.

Consistent with previous studies using HF diet only during gestation, those dams fed the HF diet consumed more calories during gestation and lactation, but body weight did not differ significantly between the dietary groups throughout the experiment, perhaps suggesting that the HF-fed dams may have increased their energy expenditure during this time (1). These data are also consistent with our previous studies (39, 40), which also showed similar results.

The offspring from HF dams in this study were heavier than that of chow-fed dams at weaning, and the difference persisted through adulthood after being weaned on a chow diet. This is in contrast with our previous study (40), in which body weight of HF offspring was higher at weaning, but was not different from CHOW offspring in adulthood when weaned on chow diet. Only those pups that were weaned on HF diet were heavier than control pups, suggesting that HF offspring were more susceptible to diet-induced obesity. The chow diet used in this study (LabDiet 5001) contains sugars (4.22%), while the diet used previously did not. HF offspring were hyperphagic on the LabDiet 5001 in this study, while those on Harlan Teklad 2018 in our previous study were not. Thus, the difference in body weight outcomes in this study compared with our previous study may be due to greater palatability of the chow diet used. Others have demonstrated deficits in the dopamine and opioid reward systems of HF offspring (41), and this is a possibility in our study but remains to be tested directly.

In this experiment, we found no significant difference in body weight between the SED group and RW group, suggesting that the exercise provided no protection against gains in body mass. Patterson et al.’s 2007 study found that 3 wk of early-onset exercise can decrease body weight gain in DIO rats (30); Bi et al. (6) also have shown that voluntary running activity beginning at 8 wk of age normalized body weight in Otsuka Long-Evans Tokushima fatty (OLETF) rats. However, several other studies have also reported access to a running wheel had little impact on body mass (9, 16, 18, 21). Studies with varying experimental factors, including strain, duration, and type of exercise, dietary fat content, and palatability,
reported that exercise is associated with increased (26), decreased (19), or no change (22) in food intake. In our experiment, exercise did not affect food intake in the first 2 wk, and increased food intake in the last week of running. One possible explanation for this phenomenon is that the offspring were only 4 wk of age when exercise started, and they were in the period of rapid growth. In this case, exercise did not reduce food intake in these animals.

Although 3 wk postweaning exercise provided no protection against gains in body weight in our experiment, we found that exercise reduced both subcutaneous and retroperitoneal fat in adult HF rats. Schroeder et al. (35) showed that postweaning voluntary exercise reduced inguinal and retroperitoneal fat in male OLETF rats. Patterson et al. (30) also found that postweaning exercise reduced fat depot in DIO rats. A similar study by Rajia et al. (32) showed that voluntary postweaning exercise reduced fat mass in female offspring of HF dams. Patterson et al. (30) also found that postweaning exercise reduced fat depot in DIO rats. A similar study by Rajia et al. (32) showed that voluntary postweaning exercise reduced fat mass in female offspring of HF dams. Patterson et al. (30) also found that postweaning exercise reduced fat depot in DIO rats.

Many previous studies showed that wheel running increased leptin signaling in several brain regions (28, 34, 37) and changed hypothalamic neuropeptide expression involved in the regulation of energy balance (6, 25, 30). Although exercise provided no protection against gains in body mass in our experiment, we found that 3 wk of postweaning exercise improved central leptin sensitivity and signaling in HF offspring. Our previous study showed that maternal HF diet during gestation and suckling altered offspring leptin sensitivity prior to weaning (39). In this study, maternal HF diet throughout gestation and suckling continues to reduce central leptin sensitivity in adulthood, even after weaned onto a chow diet, consistent with the study by Ferezou-Viala et al. (13). Patterson et al. (28) showed that 3 wk of postweaning exercise in DIO rats increased the anorectic effect of leptin at 4 wk after exercise cessation, while neither the previously exercised, nor
the continuously sedentary rats responded to leptin by reducing their food intake by 10 wk after exercise cessation. Our results show that 3 wk of postweaning exercise increases the anorectic effect of leptin at 7 wk after exercise cessation (14 wk of age) in HF offspring. There are several differences between these two studies: First, the DIO rats that Patterson used were weaned onto the HF diet, which may cause leptin resistance after prolonged exposure, while our HF offspring were weaned onto a chow diet; Second, the leptin challenge used was an intraperitoneal injection in Patterson’s study, in which leptin resistance may be due to reduced leptin transport across the blood-brain barrier (BBB) associated with the development of obesity on an HF diet in DIO rats (23), while the leptin challenge used was an intracerebroventricular injection in our study. The increased anorectic effect of leptin is consistent with increased central leptin signaling in ARC in our experiment.

One possible explanation for changed central leptin sensitivity and signaling is alterations in the central pathways involved in the regulation of energy balance. In this experiment, maternal HF diet increased ARC NPY expression, while postweaning exercise lowered ARC NPY expression in these rats. Kozak et al. (20) similarly found that HF offspring tended to have higher ARC NPY concentration in adulthood. Patterson et al. (30) showed that postweaning exercise had no effect on ARC NPY expression in DIO rats. The NPY expression in DMN had a similar trend with ARC NPY, but there was no significant difference. In contrast with other studies (30), we found RW rats had a decreased ARC POMC expression. If it were associated with a decreased release of the anorectic peptide α-MSH, it could increase food intake in RW rats, which was consistent with our food intake result—RW rats had more food intake than SED rats in the last week of running, and this persisted 1 wk after running. Further research will be done to see whether there is a change of ARC POMC expression right after running. There was no difference in the long form leptin receptor (LepRb) expression in ARC, while HF offspring had lower VMN LepRb expression, which may be a reason for reduced central leptin sensitivity. Many studies have shown that brain-derived neurotrophic factor (BDNF) in PVN and VMN reduces energy intake and increases energy expenditure (42–45), which may work through interacting with MC4R (48). We did not see any change in PVN BDNF, VMN BDNF, or VMN MC4R expression, while RW rats tended to have higher PVN MC4R, which may increase energy expenditure in RW rats even after running. LH orexin and MCH have been shown to be involved in both homeostatic and reward-based food intake (10, 12), and what we found in this experiment was that both maternal HF diet and postweaning exercise decreased LH orexin and MCH expression, although the reason for this decrease is unclear. However, changes in mRNA expression are not necessarily representative of parallel changes in peptide release or receptor function. Further research will be done at the protein level.

Finally, it is interesting to see that in HF offspring, postweaning exercise improved central leptin sensitivity and signaling, and it changed mRNA expression of hypothalamic neuropeptide and receptor, which are involved in energy balance, while it provided no protection against gains in body mass. One possible explanation is that HF offspring have impaired BBB transport (2–5), and postweaning exercise did not improve it. Therefore, although HF-RW rats have normal central leptin sensitivity and signaling, peripheral leptin cannot pass through the BBB to activate the leptin receptor. Further studies with peripheral leptin injection may be helpful in understanding this. Another consideration is that all offspring were weaned on a standard chow diet. Weaning on a HF diet may reveal the protective effects of exercise in HF offspring against weight gain compared with those that remain sedentary. Although postweaning exercise provided no protection against gains in body weight, it reduced adipose depots in HF offspring, which may have a relationship with improved central leptin sensitivity and changed hypothalamic neuropeptide expression (36, 47).

**Perspectives and Significance**

Early life environment can influence the development of obesity, and a growing body of evidence suggests that maternal HF diet during gestation and suckling has long-term consequences on offspring’s metabolic phenotype. We demonstrate here that 3 wk of early postweaning exercise improved central leptin sensitivity and signaling, changed hypothalamic mRNA expression, and reduced fat depots in HF offspring, while it had no effect on body weight. Further studies are needed to elucidate these mechanisms, including BBB transport of leptin, HF diet challenge after weaning, measurement of energy expenditure, and so on. These data provide a better understanding for how maternal HF diet

**Fig. 6.** At 17 wk of age, after overnight fast, rats received intracerebroventricular injection of saline ($n=3$) or 10 µg leptin ($n=3$) at dark onset and were decapitated 3 h later. p-STAT3 and t-STAT3 were measured in ARC by Western blot. A: band for p-STAT3. B: p-STAT3/t-STAT3 ratio (compared with leptin-injected rats in CHOW-SED group). *$P<0.05$. 

**AJP-Regul Integr Comp Physiol • doi:10.1152/ajpregu.00566.2012 • www.ajpregu.org**
affects adult offspring’s metabolic phenotype and how early life exercise can partially moderate it.

ACKNOWLEDGMENTS

We thank Dr. Su Gao (Scripps Institute, Jupiter, FL) for technical assistance.

GRANTS

This study was supported by National Institutes of Health grant HD-055030 and DK-077623. Bo Sun was supported by an Exchanging Scholarship from the China Scholarship Council of the Ministry of Education of China.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

REFERENCES


