Trafficking of dietary fat in obesity-prone and obesity-resistant rats

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1Department of Medicine, Division of Endocrinology, Metabolism, and Diabetes, University of Colorado at Denver and Health Sciences Center, Aurora, Colorado; 2Department of Pediatrics, Division of Pediatric Gastroenterology and Nutrition, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida; and 3Denver Health Medical Center, Aurora, Colorado

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Jackman, Matthew R., Robert E. Kramer, Paul S. MacLean, and Daniel H. Bessesen. Trafficking of dietary fat in obesity-prone and obesity-resistant rats. Am J Physiol Endocrinol Metab 291: E1083–E1091, 2006. First published June 27, 2006; doi:10.1152/ajpendo.00159.2006.—The trafficking of dietary fat was assessed in obesity-prone (OP) and obesity-resistant (OR) male and female rats. Test meals containing [1-14C]palmitate were delivered through gastric feeding tubes while rats consumed a high-carbohydrate diet (HCD) or after 5 days of HFD. Over the subsequent 24 h, the appearance of 14C was followed in the GI tract, skeletal muscles (SM), liver, adipose tissues (AT), and expired CO2. There was no difference in the production of 14CO2 between OP and OR rats consuming a HCD. However, after 5 days on HFD, OR rats produced significantly more 14CO2 after the test meal than OP rats (P < 0.001 females, P = 0.03 males). The differential oxidation of dietary fat between OP and OR rats on HFD was not due to differences in absorption but rather was associated with preferential disposition of tracer to AT in OP rats. Measurements of lipoprotein lipase in part explained increased tracer uptake by AT in OP rats but were not consistent with increased SM tracer uptake in OR rats. Surprisingly, female rats oxidized more tracer than male rats irrespective of phenotype or diet. These results are consistent with the notion that differences in the partitioning of dietary fat between storage in AT and oxidation in SM and liver that develop shortly after the introduction of a HFD may in part underlie the differential tendency for OR and OP rats to gain weight on this diet.

The following studies were designed to test the hypothesis that alterations in the partitioning of dietary fat are associated with obesity, labeled fat tracers have been used to follow the metabolic fate of dietary fat in vivo. Studies done in obese and reduced obese Zucker rats demonstrate less oxidation and greater adipose tissue (AT) storage of a dietary fat tracer compared with lean Zucker rats (5, 27). Lean Sprague-Dawley rats appear to preferentially traffic a dietary fat tracer to liver (L) and skeletal muscle (SM) away from AT, especially when studied in the fasted state (7). These studies support the notion that thinness is associated with greater partitioning of dietary fat toward SM and L, where it may be oxidized, and that obesity is associated with greater partitioning of dietary fat toward storage in AT.

Whether preferential fuel trafficking underlies the predisposition to become obese, however, requires that lipid trafficking be assessed prior to the development of obesity in a model that is more relevant to the human condition, namely one with a polygenic predisposition to become obese under environmental conditions that are similar to those that promote obesity in humans.

Such a model was developed by Levin and colleagues (24, 25), who used variability in weight gain following a high-fat diet (HFD) as a selective breeding tool. This approach yielded two strains of inbred Sprague-Dawley rats that have a similar genetic predisposition and diet composition affect dietary fat trafficking, OP and OR rats can be reliably identified prior to the development of excessive adiposity, allowing for the examination of fuel metabolism before and in the early process of weight gain. Finally, this model provides the opportunity to study a polygenic rodent model of thinness, potentially providing clues to adaptive mechanisms that protect against weight gain in the face of an obesogenic stimulus.

The following studies were designed to test the hypothesis that the OR phenotype is associated with trafficking of dietary fat toward oxidation in L and SM and away from storage in AT compared with rats of the OP phenotype. To determine how genetic predisposition and diet composition affect dietary fat trafficking, OP and OR rats were studied while they consumed a HCD or after 5 days of HFD feeding. We specifically focused on this early time point to examine adaptive responses that arise before marked differences in body fat develop. Studies were performed in both male and female rats in an effort to see whether there were sex-based differences in the adaptive responses to the HFD. Measures of LPL in SM and AT were also obtained in an attempt to explain the differences in fat trafficking. These studies reveal differences across sex, as

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well as between OP and OR rats, in the oxidation of a dietary fat tracer, providing evidence that differences in the trafficking of dietary fat may play an important role in the predisposition or protection from the development of obesity following introduction of a HFD.

METHODS

Animals. A breeding colony of OP and OR rats was established from founder animals generously provided by Dr. Barry Levin (Veterans Affairs Medical Center, Orange, NJ, and the New Jersey Medical School). Animals were then continuously bred and maintained at the Surgical Research Facility at Denver Health Medical Center (DHMC). A total of 80 male and female OP rats and 80 male and female rats of the OR phenotype (total n = 160) were used for these studies: 120 for tracer studies and 40 for tissue LPL measurements. Protocols were approved by the Animal Care and Use Committees at the University of Colorado at Denver and Health Sciences Center and DHMC.

Surgery and [14C]palmitate meal studies. Before and immediately after surgery, rats had ad libitum access to a standard HCD (Lab Diet no. 5001: 28% protein, 12% fat, 60% carbohydrate). To facilitate the delivery of the dietary fat tracer, gastric feeding tubes were surgically implanted into the antrum of the stomach as previously described (9, 14). After a 24-h recovery period and on a daily basis thereafter, animals were weighed, and a 3-kcal liquid meal (Ensure, Ross Laboratories; 16% protein, 64% carbohydrate, 20% fat) was administered through the feeding tube to acclimate the rats to being handled and fed in this manner. Animals that lost more than 10% of their baseline weight and sustained this loss were excluded from further study.

On the third day after surgery, rats were randomly assigned to remain on the HCD or were switched to a HFD containing 21% protein, 39% carbohydrate, and 40% fat (33% each saturated, mono-, and polyunsaturated fats, Research Diets, no. D12147). Rats were allowed to consume these diets ad libitum for 5 days. All tracer experiments were performed in the morning after a dark cycle during which rats had ad libitum access to food (fed state). At 0800 the experiments were performed in the morning after a dark cycle during which rats had ad libitum access to food (fed state). At 0800 the experiments were performed in the morning after a dark cycle during which rats had ad libitum access to food (fed state). At 0800 the experiments were performed in the morning after a dark cycle during which rats had ad libitum access to food (fed state). At 0800 the experiments were performed in the morning after a dark cycle during which rats had ad libitum access to food (fed state).

After administration of the [14C]-labeled test meal, rats were placed in a sealed respiratory chamber. Room air was continually passed through the chamber at a flow rate of 1.0 l/min. Efluent CO2 from the chamber was collected over 30-min intervals in 3.0 ml aliquots of a 2:1 mixture of methanol and methylbenzethonium (hyamine) hydroxide (Sigma Chemical no. B2156). The [14C] content of these samples was then measured with a Beckman LS6500 scintillation counter. Background activity, determined by counting a sample containing only scintillation fluid and hyamine hydroxide, was subtracted from experimental values. All expired CO2 was collected in this manner for up to 6 h after tracer administration. Rats representing the 24-h time point were returned to their cages after 6 h, and a final 30-min sample of expired CO2 was collected from animals at 24 h.

Calculations and statistics. [14C] content of each tissue was calculated from the measured activity per gram of tissue multiplied by the total weight of the tissue. Serum [14C] content was calculated as the measured [14C] content/activity of serum × 0.0385 (%body mass accounted for by serum) × body mass (10). Total body SM [14C] content was calculated by multiplying the average [14C] activity per gram of the LG and MG by the percent SM of the entire carcass (38% of body weight) (10). Whole body AT [14C] content was estimated by multiplying the average [14C] activity per gram of individual fat pads (retroperitoneal and perigonadal) by the estimated whole body fat mass (%body fat × body weight). Percent body fat was estimated via regression equations that were determined from identical feeding experiments that examined changes in perigonadal and retroperitoneal fat pads relative to percent body fat as determined by whole carcass analyses (data not shown). Whole body AT LPL was estimated by multiplying the average AT LPL per gram times whole body fat content. All data are presented in graphic form as means ± SE. Comparisons of serum and tissue [14C] content were made across phenotype (OP and OR), sex, and time (3, 6, 24 h) (SigmaStat, Jandel Scientific). Differences in the cumulative production of [14C]CO2 (0–3 and 0–6 h after administration of the test meal) were evaluated with a three-way ANOVA (diet, phenotype, and sex). In the event of a significant difference, multiple comparison procedures were performed with Tukey’s test, and statistical significance was accepted at P < 0.05.
RESULTS

Animal characteristics pre- and post-diet and surgery. After surgery, body weights decreased in all groups (5–12 g); however, this decrease was transient, and all animals returned to and surpassed their presurgical weight by the end of the experiment. At the time of test meal administration, body weights were as follows (means ± SE): OR females 203 ± 3, OP females 235 ± 4, OR males 294 ± 4, and OP males 320 ± 4 g. As expected, male rats were heavier than female rats of the same phenotype, and both male and female rats of the OP phenotype were slightly heavier than OR rats (males *P < 0.001, females *P < 0.001). Within each group (sex and phenotype), body weights were not significantly different in rats consuming HFD compared with those consuming HCD.

Absorption of fatty acid tracer. The time course of 14C disappearance from the GI tract (stomach to rectum) is depicted in Fig. 1. Regardless of the phenotype or diet, female rats absorbed the tracer more rapidly than males, demonstrating lower 14C content within the GI tract at both 3 and 6 h (*P < 0.001 and *P = 0.004, respectively). Tracer absorption was also faster in rats fed the HFD, as GI 14C content was lower in these animals at both 6 and 24 h (*P = 0.032, *P = 0.003). A significant portion of the initial tracer load remained within the GI tract of all groups at 24 h (~10%), and less remained in female rats than in male rats (*P = 0.016; Fig. 2A). Although the absorption of the lipid tracer was influenced by both sex and diet composition, it did not appear to be affected by the genetic predisposition to become obese. In fact, no differences were observed between OP and OR rats at any time point.

Once absorbed from the GI tract, the lipid tracer enters the circulation in chylomicron TG. Serum 14C content was highest 3 h after test meal administration and decreased over time in all groups (see supplemental online table for complete data set). The rapid absorption of tracer in females was reflected by an elevated, albeit minor, increase in serum 14C content that was most apparent at 3 h compared with males. Interestingly, the
more rapid absorption of tracer in the HFD condition compared with the HCD condition was not accompanied by an increase in serum $^{14}$C at the 3-h time point. Rather, serum $^{14}$C content was significantly lower at 3 h in HFD-fed rats ($P < 0.029$), suggesting that faster absorption of the dietary fat tracer on the HFD was accompanied by more rapid clearance of the tracer by peripheral tissues. Twenty-four-hour $^{14}$C serum contents are depicted in Fig. 2B. A diet effect was observed in the OP rats at 24 h, and $^{14}$C contents after HFD were significantly lower compared with rats consuming the HCD ($P < 0.001, P < 0.001$). In contrast, OR rats were no different or elevated in the HFD condition compared with the HCD condition. This difference between OP and OR rats consuming the HFD at the 24-h time point was significant ($P < 0.001$) and is consistent with the idea that OP rats clear the tracer more rapidly from the plasma compartment.

Tracer oxidation/$^{14}$CO$_2$ production. Dietary fat tracer taken up by peripheral tissues could be oxidized, stored as TG, or resecreted. The 6-h time course of $^{14}$CO$_2$ production by male and female OP and OR rats under HCD and HFD conditions is depicted in Fig. 3. In all groups, $^{14}$CO$_2$ production peaked or reached a plateau by 3 h. Regardless of diet or phenotype, females demonstrated a more rapid increase in $^{14}$CO$_2$ production and overall significantly higher levels of postprandial oxidation of the dietary fat tracer within the first 6 h following test meal administration. In contrast, males exhibit a slower rise in $^{14}$CO$_2$ production that was maintained relatively constant. The cumulative production of $^{14}$CO$_2$ (0–6 h) was similar between OP and OR rats under HCD conditions (Fig. 4A). In contrast, after HFD feeding, the OR rats produced significantly more $^{14}$CO$_2$ than OP rats over the 6 h following test meal administration. This was true for both female ($P < 0.001$) and male rats ($P = 0.03$). The difference in tracer oxidation seen in the HFD condition was largely due to divergent responses to the introduction of the HFD in OP compared with OR rats. Specifically, $^{14}$CO$_2$ production was reduced in OP rats consuming the HFD, whereas $^{14}$CO$_2$ production was unchanged or modestly increased in OR rats in the HFD condition compared with the HCD condition.
with the HCD condition. In the following, it appears that
greater oxidation of the dietary fat tracer in OR rats is associ-
ated with, and perhaps causally related to, resistance to weight
gain on a HFD.

In comparison, female rats had significantly higher levels of
$^{14}$CO$_2$ production relative to males ($P < 0.001$) irrespective of
phenotype or diet condition. This sex-based difference may be
explained in part by more rapid absorption of the tracer from
the GI tract but is also likely a reflection of differences in the
partitioning of the tracer between $L$, SM, and AT.

**Tracer and TG content in L and SM.** Higher levels of tracer
oxidation in female and OR rats could be the result of greater
disposition of tracer to L and SM or a greater capacity for fat
oxidation in these tissues. In an effort to explore these possi-
bilities, tracer content in L and SM was measured at 3, 6, and
24 h. TG content in SM and L was also measured at these time
points. Hepatic $^{14}$C tracer content was highest immediately
after ingestion of the labeled meal and declined by 24 h in all
groups (see supplemental online table). No significant differ-
ences in hepatic $^{14}$C content were observed between OP and
OR rats at any time point. In both male and female rats,
exposure to the HFD resulted in a significant increase in liver
TG content compared with TG content in rats consuming a
HCD ($P < 0.001$; Table 1). The increase in hepatic TG content
in the HFD condition was significantly greater in OP than in
OR rats ($P = 0.003$) and may reflect either increased storage or
a reduced capacity to oxidize dietary fat in the L of OP rats.

The other tissue that likely makes a substantial contribution
to whole body dietary fat oxidation is SM. In an effort to
examine the effects of fiber type on tracer disposition, SM $^{14}$C
content was measured in the LG and MG muscle (see supple-
mental online table) and soleus (Sol). Across all groups, the
$^{14}$C content within different SM types paralleled their oxidative
capacity, with the $^{14}$C content in Sol being greater than that in
LG, which was in turn greater than that in MG. The time course
of $^{14}$C appearance in Sol following HCD and HFD feeding is
prese as mentioned in Fig. 5. Content of $^{14}$C in Sol was consistently and
significantly higher in females than in males (3 h $P < 0.001$,
6 h $P < 0.001$, 24 h $P = 0.008$). Contents were significantly
lower at the 24-h time point in both male ($P < 0.001$) and
female ($P = 0.005$) rats consuming the HFD compared with
rats consuming the HCD, which could be a result of greater
tracer disposition to AT in the HFD condition.

Table 1. **TG content and LPL activity in peripheral tissues**

<table>
<thead>
<tr>
<th>Tissue TG</th>
<th>OR Female</th>
<th>OR Male</th>
<th>OP Female</th>
<th>OP Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCD</td>
<td>HPD</td>
<td>HCD</td>
<td>HPD</td>
</tr>
<tr>
<td>LG</td>
<td>3.56±0.73</td>
<td>1.72±0.12</td>
<td>3.11±0.64</td>
<td>2.59±0.20</td>
</tr>
<tr>
<td>MG$_{a,b}$</td>
<td>3.34±0.68</td>
<td>4.72±0.92</td>
<td>5.68±1.08</td>
<td>7.66±2.32</td>
</tr>
<tr>
<td>Soleus$_a$</td>
<td>4.09±0.55</td>
<td>8.64±1.84</td>
<td>6.86±0.48</td>
<td>8.72±1.68</td>
</tr>
<tr>
<td>Liver$_{a,b}$</td>
<td>3.85±0.34</td>
<td>6.01±0.51</td>
<td>5.08±0.70</td>
<td>8.63±0.66</td>
</tr>
<tr>
<td>Muscle LPL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LG</td>
<td>2.16±0.46</td>
<td>3.89±1.01</td>
<td>4.78±0.34</td>
<td>2.79±0.80</td>
</tr>
<tr>
<td>MG$_a$</td>
<td>2.28±0.66</td>
<td>4.85±1.41</td>
<td>5.55±0.42</td>
<td>2.60±0.68</td>
</tr>
<tr>
<td>Soleus$_{a,b}$</td>
<td>22.5±2.9</td>
<td>21.0±3.3</td>
<td>24.3±2.1</td>
<td>11.1±2.6</td>
</tr>
<tr>
<td>Total body muscle$_c$</td>
<td>209±43</td>
<td>320±67</td>
<td>509±35</td>
<td>287±65</td>
</tr>
<tr>
<td>Adipose LPL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perigonadal$_{a,b}$</td>
<td>11.9±4.5</td>
<td>43.7±5.6</td>
<td>16.7±1.4</td>
<td>19.3±9.7</td>
</tr>
<tr>
<td>Retroperitoneal$_{a,b}$</td>
<td>19.6±5.9</td>
<td>39.8±7.0</td>
<td>21.8±5.9</td>
<td>20.7±9.4</td>
</tr>
<tr>
<td>Total body adipose$_{a,b}$</td>
<td>206±54</td>
<td>668±92</td>
<td>580±162</td>
<td>1.13±454</td>
</tr>
</tbody>
</table>

Values are means ± SE, n = 5/group. OP, obesity prone; OR, obesity resistant; HFD, high-fat diet; HCD, high-carbohydrate diet. Triglyceride (TG) content within individual lateral gastrocnemius (LG), medial gastrocnemius (MG), soleus muscle, and liver are expressed in mmol/g wet wt. Lipoprotein lipase (LPL) activity in 3 skeletal muscles and 2 adipose tissue depots is expressed in mmol FA/g$^{-1}$-min$^{-1}$ as individual and total body estimates. A significant difference was accepted at $P < 0.05$; superscripts denote significance for $^a$diet, $^b$phenotype, and $^c$sex. For clarity, significant interactions and results of multiple comparison procedures are identified in the text.
Increased deposition of $^{14}$C tracer within the OP rats is consistent with the idea that the OP phenotype is associated with greater storage of dietary fat in AT compared with OR rats.

**LPL activity in SM and AT.** LPL has been viewed as the rate-limiting step in the uptake of TG-derived fatty acids into SM and AT. The levels of heparin-releasable LPL in AT and SM obtained from rats in this study are shown in Table 1. Regardless of diet, whole body AT LPL was higher in OP than in OR rats. This was true for both male ($P < 0.001$) and female rats ($P = 0.024$). In general, the introduction of a HFD resulted in an increase in AT LPL activity; however, this change was significant only in female rats ($P = 0.008$). Interestingly, AT LPL decreased in OP males after the introduction of a HFD. In general, these results are consistent with an increased tendency to store dietary fat in OP rats both on HCD and HFD. As has been previously shown, SM LPL is more abundant in Sol than in MG or LG. The effects of sex and diet on SM LPL levels were inconsistent, and it does not appear that changes in this enzyme in SM explain the differences seen in tracer oxidation between groups.

**DISCUSSION**

The results of this study support the hypothesis that the OR phenotype is associated with greater oxidation and less storage of dietary fat than the OP phenotype. This difference in the handling of dietary fat did not appear to be present when rats consumed a HCD but became apparent after the introduction of a HFD. Differences in the handling of dietary fat developed within just a few days of exposure to the HFD. Although the design of these experiments does not provide definitive information on tissue uptake or turnover rates, the data are consistent with the idea that a shift of dietary fat disposition into L and SM in OR rats and into AT in OP rats underlies the observed differences in tracer oxidation. Finally, the magnitude of the difference between male and female rats was unexpected and deserves further consideration in future studies. A summary of the differences between the OP and OR phenotypes, as well as males and females, is depicted in Table 2.

A number of researchers have suggested that reduced oxidation of fat predisposes to weight gain (1, 30, 46), and a growing number of studies suggest that insulin resistance and obesity are associated with a lower SM oxidative capacity (23, 43). One paradigm to study this issue is the weight-reduced state, which is known to have a strong metabolic propensity for weight gain. Preferential use of carbohydrates for energy needs is thought to result in an energetically efficient deposition of excess calories, and a number of studies in both humans and rodents have shown that the weight-reduced state is accompanied by a reduction in the capacity for fat oxidation (2–4, 6, 16, 28, 29, 38, 39). From this perspective, a lower capacity for fat oxidation appears to be a compensatory adaptation to weight reduction that contributes to the high incidence of relapse to the obese state. In contrast, it has been more difficult to demonstrate that a reduced capacity for fat oxidation contributes to the initial development of obesity. One of the primary challenges in addressing this issue is in the identification of subjects with a strong predisposition for weight gain prior to their actually becoming overweight or obese. To address this difficulty, one group of researchers examined nonobese relatives of those with a strong familial predisposition for obesity,
reporting a reduced level of fat oxidation in these subjects (17). Another group observed that the ratio of carbohydrate to lipid being oxidized over a 24-h period was predictive of future weight gain (46). Although both of these studies demonstrate a reduction in fat oxidation in those individuals predisposed to obesity, it was not possible to determine whether the limitation was in the oxidation of endogenous or dietary fat. In support of the latter possibility, Ji and Friedman (21) found that a reduced ability to oxidize a dietary fat tracer is associated with weight gain in outbred Sprague-Dawley rats.

Although numerous studies have examined the relationship between alterations in fat oxidation and weight gain, the present study has a number of unique features. First, to develop a more complete view of the movement of dietary fat over time, measurements of tracer disposition were made in a number of relevant tissues over 24 h following test meal administration. Second, OP and OR phenotypes were compared on a HCD and early in their exposure to a HFD to determine the relative roles of preexisting differences and the early adaptive responses to a HFD. Finally, to our knowledge, this is the first study to directly compare the dietary fat oxidation following the introduction of a HFD in both male and female rats, a variable that appears to be quite important in determining the overall rate of dietary fat oxidation in the rat.

The studies presented were performed after a relatively brief exposure to a HFD. In contrast, numerous studies in this model and others have been done following long-term exposure to a HFD, resulting in the development of an obese phenotype (25, 29). Although studies using long-term exposure to an HFD can provide important insights into the physiology associated with obesity, initial adaptive responses that promote or protect against weight gain may be diminished or absent by this time. To be effective in maintaining body weight, adaptive responses to a change in diet or energy imbalance likely need to occur quickly. In support of this view, recent studies by Ricci and Levin have shown that leptin resistance appears to develop in OP rats within 3 days of exposure to a high-energy diet (40), and Rossetti and coworkers have shown that insulin and leptin resistance develop within 3–7 days of HFD feeding (Pocai et al. (37), Wang et al. (45)). Similarly, our observations indicate that 5 days of HFD feeding is long enough to result in differences in the oxidation of diet-derived fatty acids within OP and OR rats. Future studies might even be done in the first 1–2 days of exposure to a HFD. Although the non-steady-state nature of this period poses substantial experimental challenges, this may be a critical period in determining the mechanisms that underlie HFD-induced weight gain.

One of the more striking findings of this study was the marked sex difference in $^{14}$CO$_2$ production. Previous investigations of dietary fat trafficking in rats did not provide a direct comparison of male and female rats, and the dramatic sex differences observed in this study were surprising. Increased levels of tracer oxidation were seen in females of both the OR and OP phenotypes compared with their male counterparts. One important consideration is that, regardless of body weight,
all rats were administered the same dietary tracer meal. OR rats were slightly smaller than OP rats, and males were larger than females. Correcting for total body weight or lean body mass (where tracer oxidation likely takes place) only increases the magnitude and statistical significance of the differences seen. Greater tracer content was also observed within individual muscles and in the estimated whole body SM tracer content of female rats at all time points. In contrast, a greater fraction of the tracer label was retained in total body AT of male rats. Our current observations are consistent with our previous study, using limb balance methodology, in which we found that women had greater uptake of a dietary fat tracer by SM than men (20); however, no differences in the postmeal generation of $^{14}$CO$_2$ were seen in that study. Other investigators have not found sex differences in the oxidation of a dietary fat tracer or found greater oxidation in males (34, 41). It has been known for some time, though, that women have a smaller postmeal serum TG excursion compared with men (11), and it is possible that differential trafficking of dietary fat may in part underlie this difference. It is also possible that the rat is not a good model for studying sex differences in dietary fat metabolism as they relate to humans. However, it seems at this time that it is not entirely clear what the sex-based differences in trafficking of dietary fat are in humans, and at a minimum the important effect of sex on dietary fat oxidation identified in this study should be considered in future studies using rat models of obesity.

There are a number of important limitations to this study. The dietary fat tracer was administered intragastrically, and $^{14}$CO$_2$ production was measured in breath. There are clearly a large number of steps between these two points, and it is therefore difficult to make definitive conclusions about the cause of the observed differences in $^{14}$CO$_2$ production. Perhaps more importantly, at the time studies were performed in the HCD condition, male rats were consuming more food than female rats. In studies conducted in the HFD condition, not only were male rats consuming more food than female rats, OP rats of both sexes were consuming more food than OR rats. In addition, tissue lipid pools were larger in OP rats than in OR rats at the time tracer studies were done in the HFD condition. It is not clear from the present studies what specific mechanisms are responsible for the observed differences in tracer oxidation. It is possible that differences in food intake and tissue lipid content played an important role. Despite these limitations, however, this method has been used in rats and humans by a number of investigators (26, 33, 41, 44) to derive useful information about the handling of dietary fat at the whole body level. Data from studies such as this one complement studies that focus more on specific tissues. The fact that tracer recovery in CO$_2$ between groups paralleled SM complement studies that focus more on specific tissues. The metabolism of the whole body level. Data from studies such as this one suggest that, although important, variations in the menstrual cycle do not substantially alter the trafficking of dietary fat (44).

In summary, within a few days following the introduction of an HFD, OR rats appear to oxidize more dietary fat than OP rats. OP rats, in turn, have a greater tendency to store dietary fat. This difference did not appear to be present prior to the introduction of the HFD. This difference in the trafficking of dietary fat was associated with maintenance of a thin phenotype in OR rats. Future studies should examine both the relative importance that changes in food intake and energy expenditure play in the development of obesity in this model and the ways in which changes in nutrient metabolism, food intake, and energy expenditure relate to each other.

GRANTS

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