Qualitative regional differences in adipose tissue growth and cellularity in male Wistar rats fed ad libitum

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DiGirolamo, M., J. B. Fine, K. Tagra, and R. Rossmanith. Qualitative regional differences in adipose tissue growth and cellularity in male Wistar rats fed ad libitum. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R1460–R1467, 1998.—Adipose tissue grows primarily by a combination of increases in fat cell volume (hypertrophy) and in fat cell number (hyperplasia), but the regional growth pattern of white adipose tissue depots in animal species and in the human is still unclear. In this study we characterized fully the age-related changes in adipose tissue growth, composition, and cellularity of four fat depots of male Wistar rats that varied in age from 7 wk to 15 mo and in body weight from 178 to 808 g. Body weight and the weight of each of the four adipose depots studied (epididymal, mesenteric, subcutaneous inguinal, and retroperitoneal) increased progressively with age and ad libitum feeding. Comparison of the cellularity of the four adipose depots, however, showed remarkable and significant differences in the pattern of growth within the same animals. The cumulative growth of the two intra-abdominal fat depots (mesenteric and epididymal) was due mostly to hypertrophy (increases in cell volume of 83 and 64%, respectively), whereas the growth of the other two depots (retroperitoneal and inguinal) was due predominantly to hyperplasia (increases in cell number of 58 and 65%, respectively). These findings uncover major and unexpected regional differences in the modulation of adipose tissue growth within aging animals fed ad libitum and suggest local, region-specific regulatory controls of this growth.

MATERIALS AND METHODS

Animals and diet. Male Wistar rats were purchased, at 5 wk of age, from Charles River Laboratories. They were housed individually and fed ad libitum Purina Laboratory Rat Chow (5001) pellets placed in hoppers outside the cages. Water was available at all times.

The animals were studied from age 7 wk to 15 mo. They varied in body weight from 178 to 808 g. Body weight was recorded to the nearest gram every week between 9 and 11 AM. At intervals of ~2 mo, subsets of animals that had a mean body weight and variance similar to the surviving animals were killed for the purpose of harvesting selected white adipose depots. Six groups were formed according to body weight. Each group (A, B, C, D, E, F) contained seven animals with the exception of group F, which contained six rats. Before death, the animals were anesthetized with xylazine (13 mg/kg) and ketamine (87 mg/kg) mixed just before administration. The protocol of this study was approved by the Emory University Institutional Animal Care and Use Committee.

Tissue isolation and experimental procedure. Four regions of adipose tissue were carefully dissected: 1) the epididymal, by a horizontal cut above the epididymus; 2) the retroperitoneal, by first separating the perirenal fat and then dissecting the retroperitoneal pad in toto; 3) the mesenteric, by cutting the intestine below the duodenal–jejunal junction and stripping the fat by gently pulling the intestinal loops apart; 4) the inguinal subcutaneous, by carefully dissecting all fat in the inguinal region up to a horizontal line parallel to the xyphoid cartilage. The tissue was dissected of visible vessels, collected in warm saline, blotted, and weighed to the nearest milligram.

Several aliquots of each adipose depot were used for analysis of tissue composition and cellularity. Two aliquots (100–200 mg) were placed in chloroform-methanol (2:1) for extraction of lipids and determination of defatted dry residue (DDR) (26).
Morphological studies. The remaining tissue was minced with scissors and placed in Krebs-Ringer bicarbonate (KRB) with 4% BSA at 37°C for collagenase incubation (with 1.5 mg collagenase from Clostridium histolyticum/ml medium) for 45 min in a Dubnoff metabolic shaker.

At the end of the incubation, isolated adipocytes and tissue fragments were passed through a nylon mesh with holes of 250 µm in diameter. The collected cells were washed three times in KRB-4% BSA medium without collagenase by removal of the infranatant below the cells that floated by gravity or gentle centrifugation (1,000 g for 1 min), and resuspended. Details of the collagenase incubation and washing have been described previously (11).

The isolated fat cell preparation was stained with 0.1% methylene blue, and the diameter of 200–300 fat cells was measured with a Zeiss microscope equipped with a micrometer caliper. Details of the optical sizing have been described previously (13). From these measurements, mean diameter ± SD and volume could be calculated.

The total number of fat cells in the adipose pads were calculated as follows: weight of lipid contained in total pad/membrane fat on lipid content (mean volume × lipid density). The lipid density employed in these calculations was determined previously to be 0.915 (13).

Analytic techniques. The method of Folch et al. (17) was used for lipid extraction. Details of lipid extraction and measurements of lipid and defatted dry residue content of the tissue have been published previously (26).

Calculations. The following parameters were used for each adipose depot in each animal group to calculate the regional adipose tissue growth: the wet weight of the adipose pad(s); the relative and absolute tissue content of lipid, water, and DDR (a measure of protein content); the mean fat cell volume; and the mean fat cell number in the depot.

The water content was obtained by subtracting the weight of lipid and DDR from the wet weight of the pad. The data obtained from the individual animals were then averaged for each group. The contribution of the four tissue constituents (DDR, water, fat cell size, and fat cell number) to the growth of the pads from age 7 wk (group A) to any of the groups, or up to the largest rats of each group F, was then calculated individually for each group as percent of total weight increment of the pads and group means were obtained (12). The increments, from one group to the next, due to cell volume (hypertrophy) or cell number (hyperplasia) were then calculated and expressed relative to each other (total = 100).

Individual values were calculated to obtain a measure of variance when comparing one group to the average values of a previous one.

Statistical evaluation of data. Means, standard deviation, and standard error of the mean were estimated in the usual way. Unless indicated otherwise, the significance of differences between group means was determined by two-way ANOVA with repeated measures (SigmaStat software, Jandel Scientific). Differences among groups were considered statistically significant if P < 0.05. Post hoc comparisons of significant differences among groups were made using the Student-Newman-Keuls multiple-comparisons test.

RESULTS

Growth curve with age and ad libitum feeding. As seen previously (26), the animals’ body weights rose exponentially with age, reached a plateau around age 250–300 days, and then continued to increase at a lesser rate of growth for up to 450 days. Table 1 shows the mean body weights and the mean adipose depot weights for the animals in the different groups (A–F).

Growth of adipose pads in four distinct adipose regions. Figure 1 shows the progressive growth of the four individual adipose pads as the body weight increased with age and ad libitum feeding. Although the growth of all four depots correlated well with increases in body weight (r = 0.90 for mesenteric; 0.91 for epididymal and retroperitoneal; 0.88 for inguinal; P < 0.001 for each), distinct differences were apparent. The maximum weight of the inguinal subcutaneous depot was 55.6 g, whereas the retroperitoneal and the epididymal depots grew to a maximum of 21.8 and 18.8 g, respectively, with the mesenteric depot growing most slowly, to a maximum of 9.4 g. There was a significant group × depot interaction (P < 0.001) for the average weights of the four depots for the rats forming each of the six groups (see Table 1). The inguinal depot was significantly larger than the other three depots, and the epididymal and retroperitoneal depots were significantly larger than the mesenteric depot.

Adipose tissue composition in the different regions. Table 1 also shows the composition of the four depots for the rats in groups A–F. In these depots, namely retroperitoneal, epididymal, and mesenteric, there was a progressive increase in percent lipid and a progressive decline in DDR and water concomitantly with depot enlargement. The mesenteric tissue ap-

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Weight, g</th>
<th>Depot Weight, g</th>
<th>Relative Contribution of Each Component, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mes</td>
<td>Epi</td>
<td>Retro</td>
</tr>
<tr>
<td>A</td>
<td>245 ± 25</td>
<td>1.03 ± 0.2a</td>
<td>1.70 ± 0.4a</td>
</tr>
<tr>
<td>B</td>
<td>374 ± 15</td>
<td>2.44 ± 0.3b</td>
<td>3.98 ± 0.5c</td>
</tr>
<tr>
<td>C</td>
<td>489 ± 6</td>
<td>4.17 ± 0.2d</td>
<td>8.32 ± 0.5f</td>
</tr>
<tr>
<td>D</td>
<td>581 ± 14</td>
<td>5.34 ± 0.3e</td>
<td>10.19 ± 1.1d</td>
</tr>
<tr>
<td>E</td>
<td>648 ± 7</td>
<td>5.52 ± 0.3f</td>
<td>10.48 ± 0.5g</td>
</tr>
<tr>
<td>F</td>
<td>736 ± 20</td>
<td>7.49 ± 0.7a</td>
<td>15.13 ± 1.3c</td>
</tr>
</tbody>
</table>

Body weights and adipose depot weights are shown as means of each group ± SE. For each column, means without lowercase letters in common are significantly different (P < 0.05). Adipose tissue composition was measured in the harvested depots as percent lipid (triglyceride, TG), defatted dry residue (DDR), and water. Mes, mesenteric depot; Epi, epididymal depot; Retro, retroperitoneal depot; Ing, inguinal depot. Note progressive rise in lipid content and progressive decline in DDR and water content in all depots, except the inguinal depot, in which composition was stable.
peared to have lesser relative amounts of lipid and greater amounts of water than the other two depots. The subcutaneous inguinal depot showed a unique composition, in that the lipid (triglyceride) content was generally stable at 55–65%, the DDR at 4–6%, and the water content at 30–38%. This depot, in contrast to the others, did not appear to show the relative increase in lipid and decline in water content that was observed in the other three depots concomitantly with their expansion.

Absolute and relative changes in adipose tissue cellularity. Table 2 lists the mean (±SE) fat cell volume and number for each of the four depots in the different groups, A–F. In addition, for both cell volume and number, relative changes are shown from group A to the subsequent groups. There was a significant effect of group (P < 0.001) and of depot (P < 0.001) on mean fat cell volume over the duration of the study. The epididymal and retroperitoneal depots had larger absolute fat cell volumes than did the mesenteric and inguinal depots. There was also a significant group × depot interaction for the fat cell number (P < 0.001). Mean cell number was greatest for the inguinal depot, intermediate for the retroperitoneal and epididymal depots, and least for the mesenteric depot.

When the relative change in fat cell volume, from group A to group F, was analyzed, there was a significant effect of group (P < 0.001) and of depot (P < 0.001). The greatest degree of cumulative hypertrophy was seen for the mesenteric depot (569%) and the least for the inguinal depot (290%). Conversely, when the relative change in fat cell number was analyzed (significant group × depot interaction; P < 0.002), the inguinal and retroperitoneal depots had the greatest capacity for cellular hyperplasia (452 and 476%, respectively), the mesenteric depot had the least capacity (193%), and the epididymal depot was intermediate.

Relative contribution of depot components to cumulative adipose tissue growth in the four different regions. The data presented in Table 3 show that the relative growth (from the earliest, group A, to the largest, group F) varied from 7.27-fold in the mesenteric depot to 13.02-fold in the retroperitoneal depot. The DDR changes contributed 1% or less to the growth of three depots (mesenteric, epididymal, retroperitoneal), but 4.53% for the inguinal depot. Water content contrib-

![Fig. 1. Relationship between animals' body weight and individual depot weight for the 4 adipose regions studied (A–D). Correlation coefficient was r = 0.90 for mesenteric, 0.91 for epididymal and retroperitoneal, and 0.88 for inguinal. P < 0.001 for each.](http://ajpregu.physiology.org/).
Table 2. Absolute and relative changes in AT depot cellularity during growth and ad libitum feeding

<table>
<thead>
<tr>
<th>Group</th>
<th>Mes</th>
<th>Epi</th>
<th>Retro</th>
<th>Ing</th>
<th>Mes</th>
<th>Epi</th>
<th>Retro</th>
<th>Ing</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>47.5a</td>
<td>89.4a</td>
<td>91.1a</td>
<td>77.2a</td>
<td>100a</td>
<td>100a</td>
<td>100a</td>
<td>100a</td>
</tr>
<tr>
<td></td>
<td>±10.4</td>
<td>±12.4</td>
<td>±16.9</td>
<td>±10.7</td>
<td>±14.2</td>
<td>±14.2</td>
<td>±14.2</td>
<td>±14.2</td>
</tr>
<tr>
<td>B</td>
<td>93.6b</td>
<td>140.4b</td>
<td>139.8b</td>
<td>93.5b</td>
<td>197b</td>
<td>157b</td>
<td>153b</td>
<td>121b</td>
</tr>
<tr>
<td></td>
<td>±8.9</td>
<td>±15.1</td>
<td>±11.6</td>
<td>±8.5</td>
<td>±19.7</td>
<td>±17.3</td>
<td>±13.1</td>
<td>±11.1</td>
</tr>
<tr>
<td>C</td>
<td>150.0c</td>
<td>256.2c</td>
<td>201.7b</td>
<td>165.0c</td>
<td>316c</td>
<td>287c</td>
<td>221b</td>
<td>214b</td>
</tr>
<tr>
<td></td>
<td>±10.9</td>
<td>±14.1</td>
<td>±17.5</td>
<td>±39.1</td>
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<td>±16.9</td>
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<td>D</td>
<td>192.9f</td>
<td>301.0cd</td>
<td>245.0f</td>
<td>169.8f</td>
<td>406d</td>
<td>337cd</td>
<td>269d</td>
<td>220d</td>
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<tr>
<td></td>
<td>±23.5</td>
<td>±18.4</td>
<td>±11.9</td>
<td>±32.5</td>
<td>±50.2</td>
<td>±21.3</td>
<td>±13</td>
<td>±4</td>
</tr>
<tr>
<td>E</td>
<td>191.2c</td>
<td>328.5d</td>
<td>282.1b</td>
<td>233.4c</td>
<td>402d</td>
<td>368cd</td>
<td>310pc</td>
<td>302b</td>
</tr>
<tr>
<td></td>
<td>±28.1</td>
<td>±39.6</td>
<td>±57.2</td>
<td>±41.3</td>
<td>±59.4</td>
<td>±44.6</td>
<td>±63</td>
<td>±53</td>
</tr>
<tr>
<td>F</td>
<td>270.2d</td>
<td>364.9d</td>
<td>334.6d</td>
<td>223.5b</td>
<td>569e</td>
<td>408d</td>
<td>367c</td>
<td>290c</td>
</tr>
<tr>
<td></td>
<td>±36.0</td>
<td>±45.2</td>
<td>±34.1</td>
<td>±23.0</td>
<td>±76.5</td>
<td>±51.7</td>
<td>±37</td>
<td>±30</td>
</tr>
</tbody>
</table>

Values for fat cell volume (FCV) and cell number (FCN) are means ± SE for 6 or 7 animals in each group. A to F (see body weights in Table 1). Relative changes in fat cell volume and cell number were calculated, respectively, from the depots of group A (values = 100) as percent increment averaged for the group (B to F). In each column of 4 tissues (mean FCV, relative changes in FCV, mean FCN, relative changes in FCN), values without a superscript in common indicate a significant difference (P < 0.05). AT, adipose tissue.

Table 3. Relative contributions of AT depot components to cumulative AT depot growth

<table>
<thead>
<tr>
<th>AT Depot</th>
<th>Cumulative Growth</th>
<th>DDR %</th>
<th>H2O %</th>
<th>FCV %</th>
<th>FCN %</th>
<th>FCV vs. FCN, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenteric</td>
<td>7.27</td>
<td>10.2</td>
<td>18.6</td>
<td>66.9</td>
<td>13.3</td>
<td>83.38</td>
</tr>
<tr>
<td>Epididymal</td>
<td>8.90</td>
<td>0.86</td>
<td>11.6</td>
<td>56.4</td>
<td>31.1</td>
<td>64.47</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>13.02</td>
<td>0.61</td>
<td>10.8</td>
<td>36.2</td>
<td>51.7</td>
<td>47.59</td>
</tr>
<tr>
<td>Inguinal</td>
<td>10.69</td>
<td>4.53</td>
<td>30.4</td>
<td>22.7</td>
<td>42.2</td>
<td>39.01</td>
</tr>
</tbody>
</table>

Adipose depots of group F (the last group) and group A (the first group) were used to determine the cumulative growth of each depot and the components of the growth increment expressed as percent of total. In the last 2 columns, the increment in lipid content of the depots was expressed as the relative increase in FCV vs. that in FCN. Note that mesenteric and epididymal depots grew mostly by cellular hypertrophy, in contrast to the retroperitoneal and inguinal depots that grew mostly by cellular hyperplasia.

The mesenteric depot, in Fig. 3A, showed a pattern of growth that is mostly due to cell hypertrophy (maximum 83%), with a much lower contribution to this growth by hyperplasia (~17%).

The epididymal depot, in Fig. 3B, showed an approximately equal contribution of cell hyperplasia and hypertrophy to the growth from group A to B. Subsequently, cumulative growth was due predominantly to cell hypertrophy (64–72%) rather than to cell hyperplasia (28–36%).

In contrast, the retroperitoneal depot (Fig. 3C) showed a growth pattern due mostly to cellular hyperplasia.
(58–63%), with cell hypertrophy contributing around 40%.

The inguinal depot (Fig. 3D) showed an overall growth due to predominant cellular hyperplasia reaching 65% and an hypertrophy of 35%, but the pattern showed an intermediate stage (groups A–C) during which hypertrophy predominated for a while.

**DISCUSSION**

The results of this study confirm and amplify the notion that marked and distinct regional differences exist in the composition and cellularity of adipose tissue that, in turn, determine the amplitude and modality of its expansion with age and ad libitum feeding. Novel data are presented that use quantification of these region-specific changes and reveal site-dependent patterns of adipose tissue growth within the same animals. Specifically, whereas cellular hypertrophy appears to be the major mode of expansion of two intra-abdominal depots (mesenteric and epididymal), cellular hyperplasia predominates in the growth of the two other depots studied (retroperitoneal and inguinal). These data suggest that, in addition to systemic factors (e.g., hormones such as insulin and other growth factors), local region-specific regulatory control exists that may modulate regional growth of adipose tissue.

Several investigators have previously reported differential regional growth of adipose depots in rodents and other animal species, including humans, under physiological or manipulated conditions (2, 4, 19, 27), but a clear, comprehensive picture of regional adipose growth has not yet emerged. For example, it is known that the retroperitoneal fat depots of rodents proliferate to a greater extent than do the epididymal fat depots (3, 27, 30). Investigations of lean and obese Zucker rats, Osborne-Mendel rats, and mice rendered obese by a high-fat diet have shown region-specific differential growth in the onset and development of obesity (16, 21, 25).

Ultimately, and despite the intense interest in and scrutiny of regional adipose depot differences, the relative contributions of cellular hypertrophy and hyperplasia to the normal growth and development of adipose tissue within an individual animal and the possible perturbations of these parameters during the development of obesity have not been established in any
species. The data presented in Tables 1–3 and Figs. 1–3 advance the existing notions on regional adipose depot differences and highlight unique features of each of the four depots studied in this model of aging rats fed ad libitum (26).

One possible criticism of the interpretation of data from the present study could be that the calculations used to derive the data are too simplistic. Specifically, we separated adipose tissue into three simple compositional compartments (lipid, DDR, water), we may have overlooked the obvious overlap between them. For example, fat cells contain water and DDR contains not only stromal-vascular cells, but also fat cell membranes and cytoplasm (14). For our purposes, however, these overlaps are limited in magnitude and should not unduly influence either the calculations or their interpretation. Specifically, the water content of isolated adipocytes is ~1–2% of the total fat cell volume after the cells reach a volume of 100 µl (14) and the DDR seldom exceeds 3–4% of total adipose depot weight, excepting the subcutaneous inguinal tissue. The incremental changes in lipid accumulation of expanding fat depots can only derive from an increase in fat cell number, fat cell volume, or their combination. Thus we believe that these methodological limitations are unlikely to affect our data or interpretations to a significant degree.

The current method of expressing progressive and cumulative adipose depot growth facilitates the study of the variable contributions of cellular hypertrophy and hyperplasia under physiological conditions. It also could provide the basis for studying the qualitative and quantitative effects of nutritional, hormonal, or other interventions. It has to be recognized, however, that there are region-specific, partial and temporal modalities of growth that may not correspond to the overall cumulative growth pattern; therefore, investigators should take care not to interpret too quickly the consequences of initial changes in cellularity patterns brought about by powerful interventions conducted for a limited period of time. The overall, region-specific adipose depot growth patterns appeared to be established relatively early in development (see Fig. 3), with the exception of the inguinal subcutaneous depot that had an intermediate phase of reversal from hyperplasia to hypertrophy.

The finding that such striking region-specific patterns of adipose depot growth exist within individual animals indicates that there is a strong, local regulation of adipose tissue growth underlying these differences. The precise mechanisms that would produce these growth patterns are, however, mostly unknown. The contributions of systemic factors that may affect overall growth or availability of nutrients and metabolic substrates cannot be excluded, and regional differences in sensitivity and/or responsiveness to humoral or hormonal factors must also be considered. Some evidence has accumulated recently for the existence of region-specific modulators of adipose tissue growth, such as tissue perfusion and neural and genetic influences; they will be discussed here individually and in Perspectives in an integrated fashion.

Local, region-specific modulation of adipose tissue vascular growth and perfusion has been reported (9, 10) under basal conditions and with dietary manipulation. Crandall et al. (10) reported a higher blood flow rate per fat cell in the mesenteric compared with the other fat depots studied. More recently, Kowalski et al. (24) found significant differences (~9-fold) among adipose depots of rats studied in the fed state. These differences were further augmented with starvation. Whereas, in the fasted state, the mesenteric and epididymal depots showed three- to fourfold increases in blood flow, the inguinal and retroperitoneal depots showed relatively minimal to modest increases, respectively.

Direct innervation of white adipose tissue depots by the sympathetic nervous system may also play an important regulatory role in regional growth via modulation of metabolic processes, such as lipolysis, and the proliferative capacity of adipose tissue (2a, 8). Catecholamines are known to inhibit the proliferation of adipocytes in vitro (22), and catecholamine removal (denervation) stimulates adipose tissue proliferation in vivo (2a, 8). Rebuffé-Schaebe (28) used histofluorescence and confocal microscopy to quantify the density of catecholamine innervation of four white adipose depots. This investigator found that the mesenteric depot was the most richly innervated, in contrast to the inguinal depot, which had the least dense catecholamine innervation. Thus it appears that the more dense the catecholamine innervation of a given adipose region, the higher the lipolytic rate and the lower the rate of adipocyte proliferation. This is in accordance with the findings in the present study that, whereas the mesenteric depot was resistant to proliferation, the inguinal depot grew mostly by cellular hyperplasia (see also Table 4). There also are regional differences in catecholamine turnover in white adipose depots. Youngstrom and Bartness (35) found this parameter to be higher in epididymal versus inguinal adipose tissue. This suggests a greater suppression of cellular proliferation in the epididymal depot than in the inguinal depot and is in agreement with the data from this study (see also Table 4).

A genetic basis for the observed regional differences in modality of adipose tissue growth has been reported by Warden et al. (34). These investigators used a

<table>
<thead>
<tr>
<th>Table 4. Regional differences</th>
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<tbody>
<tr>
<td>Blood Flow Pro-</td>
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<tr>
<td>Fed</td>
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<tr>
<td>Mesenteric</td>
</tr>
<tr>
<td>Epididymal</td>
</tr>
<tr>
<td>Retroperitoneal</td>
</tr>
<tr>
<td>Subcutaneous</td>
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</table>

Schematic representative of regional differences in growth modality, proliferative capacity, perfusion, and innervation density. See RESULTS for details and for reference to supporting work. Scores from + to +++ represent a semiquantitative expression of the information available. See DISCUSSION for details.
complete linkage map approach to identify loci contributing to the growth (assessed by weight) of four different fat depots, residing on mouse chromosomes 6, 7, 12, and 15. Furthermore, there is evidence that site-specific proliferative capacities of adipose depots in vitro mimic the in vivo patterns; several investigators (15, 33) have found that region-specific rates of proliferation of clonal adipocyte colonies derived from rodent adipose tissue are preserved through a number of generations. Thus there is the potential for interaction between genetics, local factors (e.g., interleukin growth factor 1, leptin), systemic factors (nutrition, etc.), vascularization, and degree of innervation by the sympathetic nervous system to produce site-specific normal or pathological growth of adipose tissue.

In summary, we have provided evidence for, and new methods to express, significant and marked regional differences in the growth and cellular development of adipose tissue in ad libitum-fed male Wistar rats. We have shown, for the first time, that, whereas two intra-abdominal adipose regions (epididymal and mesenteric) grow mostly by hypertrophy of adipocytes, two other regions (subcutaneous inguinal and retroperitoneal) grow mostly by cellular hyperplasia. We also have shown that individual regions do not proceed in parallel growth, but express site-specific temporal growth patterns; this is typified by the late hyperplastic growth of subcutaneous adipose tissue. Definition of regional growth under baseline conditions of ad libitum feeding is a prerequisite for a better understanding of the variations produced by nutritional, hormonal, or other interventions in individual species.

Perspectives

This work represents the first instance that the contribution of hyperplasia and hypertrophy to fat depot enlargement has been thoroughly examined in any animal model. The broad implications of this study are as follows.

Within a given animal species, different adipose regions develop at rates and with cellular modalities that are region specific. This notion needs to be expanded to studies of animals of both genders, to other species, and to strains of a given species with different genetic or abnormal conditions.

The existence of local, interacting, regulatory control probably influences region-specific adipose tissue growth. Table 4 offers a semiquantitative summary of the information available and its possible integration.

It is apparent that a high perfusion capacity in a depot, such as the mesenteric adipose depot, is associated with greater innervation density, a low-proliferative capacity, and a cumulative growth due predominantly to cellular hypertrophy. Conversely, a low blood flow, such as seen in the inguinal adipose depot from both fed and fasted animals, is associated with a low-innervation density and a high cellular proliferative capacity. The precise mechanisms of these associations are not clear, and could reflect differential genetic expression. More research needs to be conducted with respect to each of these controlling mechanisms and their possible interactions.

Given this new information, it may be possible to devise strategies of intervention to affect regional adipose tissue growth differentially. Interventions could be nutritional in nature (quality and quantity of the diet), behavioral (i.e., exercise, etc.), pharmacological, or other. For instance, it would be highly desirable to find ways to reduce the visceral fat accumulation and thus reduce the associated health risks (5–7, 23). The present study uncovers a unique capacity of mesenteric adipose tissue for cellular hypertrophy with minimal hyperplasia. This could set the stage for specific interventions that reduce adipocyte enlargement in this region.

The importance of the present work resides in the demonstrated ability to characterize modalities of growth in different adipose regions. An important challenge for the future of this field will be a reevaluation of regional adipose tissue growth among species and of the factors that modulate this growth under physiological or abnormal conditions.

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