Animal Model: Metabolic and Thermic Responses to Diet and Environment (4°C) in Obesity during Aging in the LA/Ntul//-cp Rat

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The aging represent the single most rapidly increasing segment of the population of Westernized countries and throughout much of the world [1, 2]. In the USA, obesity is the major nutritionally related health complication of adults and older Americans, where it has been variously reported to affect up to one in three or more of that population [3–5]. While obesity is a significant contributing risk factor in the pathophysiology of numerous metabolic diseases common in Westernized society, including non-insulin-dependent diabetes mellitus (NIDDM), hyperlipidemia, and other metabolic disorders, the precise mechanism or mechanisms through which it may contribute to an increased risk of premature morbidity and mortality have not been fully clarified [3, 4]. As nations become progressively more industrialized, the incidence of obesity and overweight conditions and their pathophysiologic sequelae have typically become increased, and along with those changes, there is a correspondingly greater dependence on the health care industry of those nations [5–8].

An animal model of aging and obesity has been developed in our laboratory in an attempt to gain insight into specific pathophysiologic mechanisms associated with aging and obesity [9]. The model shows marked obesity, impaired carbohydrate tolerance, hyperamylinemia, hypertriglyceridemia and hypercholesterolemia, and an impaired capacity for nonshivering thermogenesis (NST) and energy expenditure from an early age [9–12]. To determine the effects of obesity on metabolic and hormonal responses to aging and to the capacity for NST during aging, groups of lean and obese LA/Ntul//-cp rats were subjected to measurements
of VO\textsubscript{2} in young (3–6 months), middle-aged (12–16 months), old (24–30 months), and aged (32–36 months; lean only) states under conditions of thermal neutrality (30\textdegree C). The findings of the study indicated that aging in this unique animal model is associated with progressive declines in the normal dietary, metabolic, and hormonal responses to diet and environment, in a manner similar to that observed in man [1, 2]. Moreover, the effects of obesity further exacerbate those changes, with a corresponding negative impact on metabolic factors related to optimal health and longevity. A summary of the findings in this animal model follows below.

**Development and Biometric Characteristics of the LA/Ntul///-cp Strain**

The congenic LA/Ntul///-cp rat was derived from an original cross between the Koletsy rat and a congenic LA/N (Lister-Albany/NIH) strain of unknown origin at the National Institutes of Health, Bethesda, Md., USA (Fig. 1). Animals which carried the obesity (cp) trait were then backcrossed to the original LA/N strain until establishment of the congenic status was achieved in the new strain [13]. The animals were established in the Drexel University laboratory as the congenic LA/Ntul///-cp from offspring derived from the 12th backcross of the NIH strain, and are maintained in a closed environment as an SPF-VAF colony [9]. LA/Ntul///-cp rats from our laboratory have shown the greatest longevity of any obese rodent strain, with lean rats often surviving to over 4 years and obese rats to 30–36 months in conventional, geographically isolated housing with ad libitum access to rodent chow and house water [9].

The cp trait has also been established in other strains in a similar manner, including the SHR/Ntul///-cp, the WKY/N-cp, and others, resulting in the development of new strains with uniquely different metabolic characteristics including diabetes (NIDDM), atherosclerotic traits, renal dysfunction, and congestive heart failure [13–15]. Growth and adiposity data from LA/Ntul///-cp rats (Fig. 2, Table 1) show that male rats typically weigh about twice as much as similar aged...
Fig. 2. Body weights of rats. Growth curves of LA/Ntul/−cp rats. Body weights were obtained in approximately 600 fed rats between 8 and 11 a.m., with 10–20 rats for each individual data point. □ = Lean male; ○ = lean female; ■ = obese male; ● = obese female. Body weight of obese > lean in both sexes from 1 month of age (ANOVA).

Female rats in the lean phenotype, and that for any given age, weights of obese rats of either gender range between 2.5- to threefold more than normally fed lean littermates. Adiposity, computed as the sum of the dorsal and retroperitoneal fat pads over body weight (Table 1), indicates that obese female rats were substantially fatter than their lean littermates by 1–2 months of age, and that body fat content increased markedly from about the time of adolescence to adulthood, when it may represent 50% or more of the total body mass [9, 15, 16].

In normally lean animals in this and other studies, body weight became substantially stabilized by 5 months of age (Fig. 2, Table 1), with only gradual increases in body weight and energy intake (Table 1) and until 2 years of age. By 3 years of age, both energy intakes and body weights began to decline, while body fat content was preserved. In contrast, obese animals continued to gain weight and to increase in relative adiposity throughout the duration of this study, despite abundant reserves of interscapular brown adipose tissue (Table 1). The progressive increases in weight and adiposity in both phenotypes were associated with gradual decreases in energy efficiency, with the greatest efficiency observed in obese animals aged 2 years or more.

In contrast, serum thyroid hormone profiles during the same period changed markedly. Serum T3, expressed as a percentage of the serum T4 concentration, increased more than twofold in both sexes and phenotypes by 2–3 years of age – from 2.8% of the T4 concentration when 5 months of age to some 5.8% at 3 years of age in lean rats, and from 3% of the T4 at 5 months of age to over 7% of the T4
Table 1. Body weight and metabolic variables of aging rats

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
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<tbody>
<tr>
<td></td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>224±9</td>
<td>247±6</td>
</tr>
<tr>
<td>Relative adiposity</td>
<td>1.2±0.1</td>
<td>1.4±0.2</td>
</tr>
<tr>
<td>Energy intake, kcal/day</td>
<td>53±3</td>
<td>55±2</td>
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<tr>
<td>Fluid intake, ml/day</td>
<td>23±2</td>
<td>28±2</td>
</tr>
<tr>
<td>Caloric efficiency, kcal/kg BW/day</td>
<td>0.24±0.03</td>
<td>0.23±0.02</td>
</tr>
<tr>
<td>RMR, ml O₂/BW·0.75</td>
<td>13.6±0.9</td>
<td>14.3±0.6</td>
</tr>
<tr>
<td>VO₂ in cold at 45 min</td>
<td>24.9±2.9</td>
<td>25.9±1.0</td>
</tr>
<tr>
<td>VO₂ + NE, 100 μg/kg BW³</td>
<td>19.3±1.1</td>
<td>18.8±0.8</td>
</tr>
<tr>
<td>Serum T3</td>
<td>1.2±0.1</td>
<td>1.4±0.1</td>
</tr>
<tr>
<td>Serum T4</td>
<td>42.6±3.5</td>
<td>31.7±1.6</td>
</tr>
<tr>
<td>Fasting serum insulin, μIU/ml</td>
<td>30±6</td>
<td>35±6</td>
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<tr>
<td>Fasting serum glucose, mM</td>
<td>5.4±0.2</td>
<td>4.6±0.4</td>
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Data are mean ± 1 SEM, n = 10 rats/group. n.d. = Measurement not done; RMR = resting metabolic rate; NE = norepinephrine.

³ Measures taken 30 min after injection.
content by 2 years of age in obese rats. These increases in the percent and total concentration of T3 were found to be associated with gradual decreases in T4 concentrations and in a delayed clearance in vivo of both thyroid hormones (T3 and T4) in the obese phenotype [17]. When the thyroidal kinetics are considered in the light of the resting metabolic rate (RMR) and energy efficiency data, the conclusions are consistent with an age-related refractoriness to thyroid hormones, particularly T3 in aging obese rats.

In other studies, the rate of T3 neogenesis from T4 in several tissues was also found to be lower in pre-obese than lean animals of this strain [18], consistent with a decreased rate of thyroidal monodeiodination in peripheral tissues, and with a gradual decrease in thyroid hormone-mediated components of energy metabolism in the obese phenotype. Impaired serum thryoxine monodeiodination was also noted in other obese, hyperinsulinemic models, including both obese-diabetic (NIDDM) SHR/Ntul//cp rats [19] and obese Zucker rats [20], suggestive of a possible role for insulin resistance in mediating the impairments in thyroid hormone metabolism which were observed in this study.

Thus the results of this study are consistent with an improved economy of energy utilization and storage in association with aging, an economy that is further enhanced in the obese phenotype. Measures of resting metabolism (summarized in Table 1) reflected a gradual decline in RMR in both phenotypes, but the magnitude of the decline in energy expenditure was more pronounced in the obese than the lean phenotype. In aging LA/Ntul//cp rats, the VO₂ of lean rats was greater than of obese rats, and decreased progressively in both phenotypes at each age studied (Table 1). In addition, the thermic responses to norepinephrine (100 μg NE/kg body weight, s.c.), feeding, and acute cold exposure (2–4°C) also decreased progressively with age, such that at the oldest ages the thermic responses to variables of diet and environment were no longer statistically significant. The food and fluid intake data are consistent with a greater proportion of lipid utilization with progressive aging in both phenotypes, in concert with the age-related thyroidal responses noted above. The thermic and cold responses to carbohydrate feeding also declined with progressive aging in both phenotypes (data not shown). Fasting insulin and glucose concentrations of lean rats remained euglycemic throughout the study (Table 1), while in obese animals, the fasting insulin and the insulin to glucose ratios were markedly increased throughout the study, consistent with moderate insulin resistance and glucose intolerance of long-standing duration in the obese phenotype. Glucose uptake and incorporation into muscle glycogen was also impaired [11], and both the glucose and the insulin area following an oral glucose tolerance became increased from 2 months of age [10, 21], also indicating long-standing insulin resistance in the obese phenotype. Insulin resistance has been reported by several investigators to play a significant role in the impaired thermic responses to diet and environment in animal models [9, 15, 21–25], and is presumed to be a contributing factor in the impaired thermic responses and other chronic metabolic sequelae of the present study.
Summary

The results of this study indicate that aging is associated with progressive declines in the normal dietary and metabolic responses to diet and environment in this animal model. The normal thermic and hormonal responses to diet and environment are thought to contribute to the fine regulation of energy balance by modulation of the efficiency of energy utilization or storage [25]. In the obese phenotype, the declines in the above variables may be further complicated by the presence of long-standing insulin resistance, and by perturbations in the normal metabolism and action of thyroid hormones, particularly T3. These may further contribute, individually or in combination with other factors, to an enhancement of energy storage and thereby contribute to maintaining the obese state. Moreover, the effects of progressive increases in obesity further exacerbate the decline in the economy of energy utilization and storage. Thus the impact of these physiologic changes of aging and obesity may impart significant alterations on the efficiency of energy metabolism, which in turn may contribute to some of the pathophysiologic changes associated with longevity, and could influence nutritional indices in affected individuals. As nations become progressively more industrialized, the incidence of overweight conditions – including obesity, NIDDM, and related metabolic disorders – has been shown to become increased and, along with those changes, the metabolic and pathophysiologic sequelae related to those disorders become more common [6–8]. A greater understanding of mechanisms of impaired energy metabolism and energy balance in aging may provide new insight into the nutritional factors that may contribute to obesity in aging, their modulation, and the emergence of a longer, healthier lifestyle.

Acknowledgements

We wish to thank Ms. Jacomina Winters and Ms. Amy Parkman for contributions to manuscript preparation. Support was provided from grants-in-aid from the American Diabetes Association, the American Dietetic Association, and institutional support.

References