Attenuation of circadian rhythms of food intake and respiration in aging diabetes-prone BHE/Cdb rats

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OVER THE LAST 30 years we have studied the metabolic characteristics of the BHE/Cdb rat (3–9, 12, 13, 15–25). At first, these rats were quite heterogeneous, but through selective breeding, we developed a strain of rats that is quite uniform in its metabolic characteristics. Selection pressure was applied to the avoidance of obesity and the development of abnormal glucose tolerance at 300 days of age. Throughout this breeding program, we periodically determined their hyperlipogenic and glycemic characteristics, and these characteristics were never lost. The strain is now in its 86th generation as a closed colony. The BHE/Cdb rat typically has a twofold increase in de novo hepatic lipogenesis and a 40% increase in gluconeogenesis. These characteristics were first reported by Lakshmanan et al. (20) and Berdanier (5), respectively. These two features were responsive to dietary manipulation, in that high sugar feeding and/or the use of saturated fat, instead of corn oil, increased their activity. Mitochondrial activity was also observed to differ from that of a control strain, and it too was responsive to dietary manipulation (8, 9, 12, 13, 16, 25). The impaired glucose tolerance is age related. That is, as the animals age, glucose intolerance develops (4, 6, 7). This glucose intolerance is maternally inherited (21, 24) and diet responsive (4, 6, 7). In male animals fed an unrefined cereal-based diet, impaired glucose tolerance appears at 300 days of age. In rats fed sugar-rich and/or fat-rich diets, this impaired glucose tolerance appears much earlier. In some instances, it appears as early as 100 days of age (4, 6, 7). Despite all these metabolic differences due to strain and diet, the total daily food intake is very similar to that of control animals. Animals of the BHE/Cdb strain are not hyperphagic.

The rats of the BHE/Cdb strain have been found to have two homoplasmic mutations in the mitochondrial ATPase 6 gene as well as three heteroplasmic mutations in this same gene (23; C. Herrnsted, personal communication). These mutations have been found in all tissues tested (22). The genotype and the phenotype are maternally inherited (21, 22). As a result of these mutations, mitochondria isolated from these animals have been found to be slightly inefficient (8). This inefficiency is negatively correlated with its characteristically increased hepatic de novo lipogenic activity (12) and is also maternally inherited (21). The question that arises from these reports is how these animals manage to survive and reproduce. What accommodations do they make to continue life? BHE/Cdb rats are relatively short lived compared with Sprague-Dawley and Wistar rats. Their average life span is <600 days, whereas the life span of control rats is roughly double this.

The present report addresses the issue of how these animals accommodate their genetic mitochondrial mutation. We previously reported that, in part, their accommodation involves a difference in their choice of metabolic fuels (9, 16, 17). The present work monitored BHE/Cdb and Sprague-Dawley rats with respect to the circadian rhythms of respiration and food intake patterns as the animals aged. We hypothesized that, in part, the accommodation to their inherent mitochondrial defect could involve a shift in feeding behavior. To test this hypothesis, we conducted several experiments. Experiment 1 examined the daily feeding beh-

Mathews, Clayton E., Kathie Wickwire, Wiliam P. Flatt, and Carolyn D. Berdanier. Attenuation of circadian rhythms of food intake and respiration in aging diabetes-prone BHE/Cdb rats. Am J Physiol Regulatory Integrative Comp Physiol 279: R230–R238, 2000.—The hypothesis that BHE/Cdb rats with mutations in their mitochondrial genome might accommodate this mutation by changing their food intake patterns was tested. Four experiments were conducted. Experiments 1 and 2 examined food intake patterns of BHE/Cdb rats fed a stock diet or BHE/Cdb and Sprague-Dawley rats fed a high-fat diet from weaning. Experiment 3 examined the daily rhythms of respiration and heat production in these rats at 200 days of age. Experiment 4 examined the effects of diet composition on these measurements at 50-day intervals. The Sprague-Dawley rats, regardless of diet, had the typical day-night rhythms of feeding and respiration. In contrast, the BHE/Cdb rats fed the high-fat diet showed normal rhythms initially, but with age, these rhythms were attenuated. The changes in rhythms preceded the development of glucose intolerance.

heat production; mitochondrial diabetes; high-fat diet
Behavior of BHE/Cdb rats fed an unrefined cereal-based diet. Experiments 2 and 3 compared BHE/Cdb and Sprague-Dawley rats fed a high-fat diet until 200 days of age. In experiment 4, we studied rats at 50-day intervals from weaning until 250 days of age by measuring whole body respiration and studying feeding behavior. We found that young rats of both strains fed the stock diet or the low-fat purified diet had the usual day-night feeding behavior and respiratory patterns. As the BHE/Cdb rats aged, their feeding patterns shifted. In particular, the BHE/Cdb rats fed the high-fat diet shifted their feeding patterns and respiratory activity as they aged, such that the day-night pattern at 50 days of age was abolished by the time they were killed at 250 days of age.

METHODS AND MATERIALS

Animals and diets. Male weanling BHE/Cdb (University of Georgia colony) and Sprague-Dawley (Harlan Sprague Dawley, Indianapolis, IN) rats were used. In experiments 1–3, group size was six. In experiment 4, group size was 12. The rats were offered an unrefined cereal-based diet (Diet 5012, PMI Feeds, St. Louis, MO), a 48% sucrose-18.5% corn oil diet, or a 65% sucrose-5% corn oil diet (Table 1). These diets are designated the stock diet, the high-fat diet, and the low-fat diet. The low-fat diet had the same percent distribution of carbohydrate, fat, and protein as the stock diet.

The animals were housed individually in hanging wire mesh cages in a room regulated for light (lights on 0600–1800), temperature (21 ± 1°C), and relative humidity (40–50%). Animal care followed the recommendations set forth in the Guide for the Care and Use of Laboratory Animals (DHHS Publ. (NIH) 85-23, 1985). The animal care facility is under the supervision of a licensed veterinarian. Specific pathogen-free conditions were maintained and ensured through the monthly monitoring of sentinel animals for the presence of common pathogens. Food and water were always available, except as noted below. The food was stored at 4°C until provided to the animals. Except when the animals were in the respiration chambers, food intakes and body weights were measured weekly. Food intake was expressed as grams of food consumed per 100 g body wt. This adjustment allowed for the comparison of food consumed among animals of different body weights.

Indirect calorimetry. Animals were placed in individual open-circuit respiration chambers at 200 days of age (experiment 3) or at 50, 100, 150, 200, and 250 days of age (experiment 4). The gas exchange was measured at 16.5-min intervals over a 48-h period. The carbon dioxide concentration was measured using an infrared analyzer, the oxygen concentration was determined using an Oxymax oxygen sensor battery (Columbus Instrument, Columbus, OH), and the results of these analyses were used to calculate heat production as well as the respiratory quotient (RQ). Airflow was measured and regulated by a mass flow controller. Water consumption (licks/min) and feeding activity were also recorded automatically.

Table 1. Diet composition

<table>
<thead>
<tr>
<th>Component</th>
<th>High-Fat Diet</th>
<th>Low-Fat Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose</td>
<td>48.3</td>
<td>65</td>
</tr>
<tr>
<td>Corn oil</td>
<td>18.5</td>
<td>5</td>
</tr>
<tr>
<td>Casein</td>
<td>11.6</td>
<td>10</td>
</tr>
<tr>
<td>Lactalbumin</td>
<td>11.6</td>
<td>10</td>
</tr>
<tr>
<td>AIN mineral mix</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Cellufil</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>AIN vitamin mix</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Values are expressed as percentages.

Other measurements. In experiment 4, fasting (16 h without food) and nonfasting blood glucose (glucose oxidase, kit 510, Sigma Chemical, St. Louis, MO) and free glycerol and triglycerides (kit 360, Sigma Chemical) were determined. The fasting determinations were performed in the morning (8–9 AM), and the nonfasting measurements were made at 2 PM. This time was selected to coincide with the maximum difference in indirect calorimetry between the strains at the time of measurement. Glucose tolerance was determined after an overnight fast (14–16 h without food) at 50, 200, and 250 days of age in experiment 4. Glucose tolerance testing consisted of measuring the blood glucose level before and at 30, 60, and 120 min after a glucose challenge of 1 g/100 g body wt administered per os as a 25% solution.

Statistical analysis. Statistical significance was determined using Super ANOVA for the Macintosh (Abacus Systems, Berkeley, CA). Experiments 1 and 2 were 1 × 4 experiments and were analyzed statistically using a one-way ANOVA. Experiment 3 utilized regression analysis, and experiment 4 was analyzed using ANOVA for this 2 × 3 × 5 experiment. The ANOVA on experiments 1–3 was followed by Fisher’s least-significant difference test to determine P values. The ANOVA used for experiment 4 was followed by Duncan’s new multiple-range test to identify significantly different means. Age, as a variable in these experiments, was not evaluated separately. P < 0.05 was considered significant.

RESULTS

Food intake. Table 2 shows the food intake adjusted for body weight of BHE/Cdb rats fed the stock diet from 40 to 190 days of age (experiment 1). With age, there was a progressive change in food consumed that is accounted for by the changing needs of the animal with maturation. There was a change in feeding pattern as well. In these rats, there were shifts in feeding, such that the usual day-night pattern was suppressed as the animals matured. At 40 days of age, the rats consumed 67% of their food during the dark phase of the lighting cycle. By 140 days of age, the rats consumed 56% of their food during the dark phase, and by 200 days of age, this had fallen to 49% of their total food intake. Table 2 provides the results of the ANOVA of these data. Age and time period had significant effects on food intake.

In experiment 2, we compared BHE/Cdb and Sprague-Dawley rats fed a 48% sucrose-18% corn oil diet from weaning until 190 days of age (Fig. 1). As in experiment 1, we observed the usual day-night food intake pattern that characterizes a nocturnal animal such as the young rat. However, the strains differed...
with age in their feeding patterns. Just as we noted a steady shift toward light phase feeding in the BHE/Cdb rats fed the stock diet in experiment 1, this shift also occurred in these rats when fed the high-sugar–high-fat diet. In contrast, the Sprague-Dawley rats did not show as marked a shift. Yes, there was an age-related change in feeding (the animals ate progressively less per 100 g body wt as they aged), but the Sprague-Dawley rats continued to consume the majority of their food during the dark phase of the lighting cycle, whereas the BHE/Cdb rats did not. These differences due to age and strain in light phase feeding were significant.

Because we wanted to confirm these strain differences in feeding behavior, we repeated these feeding measurements with animals of both strains fed the stock diet, the high-fat diet, or the low-fat diet (experiment 4). In this experiment, we observed the feeding patterns at 50-day intervals from weaning to 250 days of age. Thus our period of observation was longer than that used in the earlier experiments. Furthermore, we expanded the experiment so that we could make simultaneous measurements of rats fed one of three diets. The stock and the high-fat diets were the same as those used in experiments 1–3, and we added a third diet, a low-fat diet, which replicated the proximate composition of the stock diet but used the same ingredients used in the high-fat diet. This repeat of the earlier experiments was made possible through the expansion of the indirect calorimetry facility.

Figure 2 shows the food intake patterns of both strains of rats fed these three diets as they aged from 50 to 250 days of age. The intervening ages are not shown to save space. The results of the ANOVA of these data are shown in Table 3. There were significant strain, diet, and interacting effects on daily food intake as the animals aged from 50 to 250 days of age. These results confirm those found in experiments 1 and 2, in that we observed a shift in the day-night feeding patterns of the BHE/Cdb rats, whereas the Sprague-Dawley rats retained their nocturnal feeding pattern. Age and diet affected the feeding pattern, such that the BHE/Cdb rats shifted to more daytime feeding when given the high-fat diet at an earlier age than the rats fed the stock diet. Rats fed the low-fat diet shifted at an earlier age than those fed the stock diet but not as early as those fed the high-fat diet.

### Table 2. Relative 6-h food intakes in BHE/Cdb rats fed a stock diet at 50, 130, 210, and 250 days of age

<table>
<thead>
<tr>
<th>Age, days</th>
<th>n</th>
<th>Body Wt, g</th>
<th>0600–1200</th>
<th>1200–1800</th>
<th>1800–2400</th>
<th>2400–0600</th>
<th>Treatment</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>6</td>
<td>203 ± 7a</td>
<td>1.2 ± 0.2a</td>
<td>2.7 ± 0.2b</td>
<td>4.9 ± 0.5d</td>
<td>3.5 ± 0.2c</td>
<td>Age</td>
<td>0.0001</td>
</tr>
<tr>
<td>130</td>
<td>6</td>
<td>447 ± 18b</td>
<td>1.0 ± 0.2a</td>
<td>1.9 ± 0.2c</td>
<td>2.2 ± 0.1a</td>
<td>1.9 ± 0.2c</td>
<td>Quarter</td>
<td>0.0001</td>
</tr>
<tr>
<td>210</td>
<td>5</td>
<td>497 ± 23c</td>
<td>1.0 ± 0.1a</td>
<td>1.4 ± 0.2c</td>
<td>1.9 ± 0.2c</td>
<td>1.6 ± 0.2c</td>
<td>Age × quarter</td>
<td>0.0001</td>
</tr>
<tr>
<td>250</td>
<td>6</td>
<td>507 ± 21d</td>
<td>1.5 ± 0.4a</td>
<td>1.4 ± 0.2c</td>
<td>1.8 ± 0.1c</td>
<td>1.6 ± 0.2c</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. Relative food intake = food intake (g) ÷ 100 g body wt. Lights on from 0600 to 1800. Different superscripts (a–g) in the same column denote statistical difference (P < 0.05).
**Indirect calorimetry.** Figures 3 and 4 show the light-dark variation in RQ of the BHE/Cdb and Sprague-Dawley rats (*experiment 3*). In Fig. 3, a time-dependent change in RQ was observed in rats fed the stock diet. These rats were 200 days of age at the time of observation. Although strain differences in RQ were observed, the differences were not as marked as those shown in Fig. 4. These rats also were 200 days of age, but instead of the stock diet, they were fed the high-fat diet. The Sprague-Dawley rats had high RQs during the dark phase of the lighting cycle and low RQs during the light phase. Differences in RQs were smaller throughout the 24-h light-dark cycle in the BHE/Cdb rats. The RQs of the BHE/Cdb rats were higher during the light phase and lower during the dark phase than those of the Sprague-Dawley rats. The times at which there were significant strain differences are noted on Figs. 3 and 4. The 24-h RQ patterns for the 50- and 250-day-old rats fed the stock diet, the low-fat diet, or the high-fat diet (*experiment 4*) are shown in Figs. 5 and 6. Consistent with the results shown for *experiment 3*, there was a diet- and strain-dependent shift in RQ rhythm. The high-fat diet strain difference is particularly noticeable.

Table 4 gives the values for gross heat production (kJ/24 h) and heat production adjusted for metabolic body size (kJ/kg^{0.75}) in the animals at 50 and 250 days of age. Although we made these measurements at 50-day intervals, the intervening observations are not reported to save space. Although no differences in heat production were observed in the 50-day-old rats, by 250 days of age, strain and diet differences were found. The 250-day-old Sprague-Dawley rats fed the low-fat diet produced less heat than their Sprague-Dawley cohorts fed the high-fat or the stock diet. In contrast, the BHE/Cdb rats at this age produced more heat when fed the high-fat diet than when fed either of the other two diets. ANOVA of these data revealed significant diet, strain, and diet-strain interaction effects. When heat production was adjusted for metabolic body size, again there were no significant differences at 50 days of age. At 250 days of age, the Sprague-Dawley rats fed the high-fat or low-fat diet produced less heat than their stock diet-fed cohorts and than the BHE/Cdb rats fed any of the diets. ANOVA of these data revealed significant diet, strain, and diet-strain interaction effects.

**Other measurements.** Consistent with previous reports (3, 4, 10), strain and diet differences were observed in the triglyceride and free glycerol levels in the fasting and nonfasting blood (Figs. 7 and 8). In the fasting state, BHE/Cdb rats had higher levels of triglycerides and glycerol than the Sprague-Dawley rats,
Fig. 4. Circadian rhythm of the RQ of 200-day-old BHE/Cdb and Sprague-Dawley rats fed a high-fat diet; \( n = 6 \). *Significant \((P < 0.05)\) differences at specific time points.

Fig. 5. Circadian rhythms of the RQ of 50-day-old BHE/Cdb (●) and Sprague-Dawley (■) rats fed a stock diet (A), a low-fat diet (B), or a high-fat diet (C). *Significant \((P < 0.05)\) strain differences at specific time points; \( n = 12 \).

Fig. 6. Circadian rhythms of the RQ of 250-day-old BHE/Cdb (●) and Sprague-Dawley (■) rats fed a stock diet (A), a low-fat diet (B), or a high-fat diet (C). *Significant \((P < 0.05)\) strain differences within each diet comparison at specific time points; \( n = 12 \).
and these differences were diet and age dependent (Table 5). As the BHE/Cdb rats aged from 50 to 250 days of age, their blood triglycerides and free glycerol levels rose, whereas these measures in the Sprague-Dawley rats were unchanged as the animals aged. Feeding the purified diets to the BHE/Cdb rats resulted in increases in triglycerides and glycerol, whereas these diets had little effect on these measures in the Sprague-Dawley rats. The strain differences in serum triglycerides and glycerol were more pronounced in the nonfasted rats (Fig. 8), and this was probably due to the differences in feeding patterns between the strains. The BHE/Cdb rats had far higher nonfasting values, probably because they were eating substantially more during the light phase than were the Sprague-Dawley rats. ANOVA of the triglyceride and glycerol data showed that diet and strain had significant effects on these measurements (Table 5).

Glucose tolerance, measured at 50 and 250 days of age, was affected by age and strain (Fig. 9). Figure 9A shows that at 50 days of age all the rats returned to their prechallenge blood glucose level. There were no strain or diet differences. However, by 250 days of age (Fig. 9B), rats of the BHE/Cdb strain, regardless of diet, failed to return to their prechallenge blood glucose levels, whereas rats of the Sprague-Dawley strain, except those fed the high-fat diet, did. The Sprague-Dawley rats fed the high-fat diet did not have as high a 30-min postchallenge glucose level as the BHE/Cdb rats fed the same diet, yet the strains did not differ at 120 min. ANOVA of the fasting blood glucose and the area under the curve showed significant diet, strain, and diet-strain interaction effects at 250 days of age (Table 5). A diet-strain interaction effect on fasting blood glucose was found at 50 days of age, but no other effects were observed at this age.

**DISCUSSION**

The results of the present work raise some important questions about the nature of the cues that influence (or fail to influence) metabolism. Examination of the data from the Sprague-Dawley rats gives clear indica-
tion that the lighting regimen cues feeding and that this feeding influences intermediary metabolism as assessed by indirect calorimetry. The food intake during the dark phase of the lighting cycle cues the oxidation of carbohydrate, which, in turn, is reflected by the elevations in RQ in the periods that follow. The stock diet is rich in complex carbohydrates from cereal grains, and this carbohydrate has a longer residence time in the intestinal tract than the low-fat diet, which has the same proximate composition but contains sugar as the carbohydrate source. This carbohydrate is readily absorbed and thus, when used as the metabolic fuel, will result in an RQ close to 1. When the diet is richer in fat (with smaller amounts of sugar), this too cues the RQ, but the excursions are broader than when the stock diet is consumed. This too is probably due to the nature of the diet consumed. This diet has a combination of sugar (as the carbohydrate source) and corn

Table 5. ANOVA for serum triglycerides, glycerol, fasting glucose, and area under the curve for glucose tolerance

<table>
<thead>
<tr>
<th>Measurement</th>
<th>50 days of age</th>
<th>250 days of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diet</td>
<td>Strain</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.05</td>
<td>0.001</td>
</tr>
<tr>
<td>Glycerol</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Area under curve</td>
<td>NS</td>
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</tr>
</tbody>
</table>

Fig. 8. Nonfasting triglyceride (A) and glycerol (B) levels in BHE/Cdb and Sprague-Dawley rats fed a stock diet, a low-fat diet, or a high-fat diet from weaning until 250 days of age; n = 12.

Fig. 9. Glucose tolerance of 50- (A) and 250-day-old (B) BHE/Cdb and Sprague-Dawley rats fed a stock diet, a low-fat diet, or a high-fat diet from weaning to 250 days of age; n = 12.
oil as the fat source. The sugar will disappear relatively quickly from the intestinal tract and will be used as a metabolic fuel. An elevated RQ is characteristic of this oxidation state. The fat, with its longer residence time in the intestinal tract and slower rate of use as fuel, will result in a lower RQ when it serves as the metabolic fuel. Indeed, in the Sprague-Dawley rats, this is what we observed. These rats, when fed the stock diet or the low-fat diet, had larger excursions in RQ between the light and dark periods, yet differences between light and dark periods of feeding were smaller when the Sprague-Dawley rats were offered the high-fat diet. This diet effect was also observed in the BHE/Cdb rats, but the peaks and nadirs in the RQ were far closer in this strain than in the Sprague-Dawley rats fed the high-fat diet. The circadian rhythms of feeding and RQ were muted to a greater extent than in the Sprague-Dawley rats. When the low-fat or stock diet was offered, the RQs were, in general, higher in the BHE/Cdb rats than in similarly fed Sprague-Dawley rats. As the BHE/Cdb rats aged, they shifted their feeding and RQ patterns, whereas the Sprague-Dawley rats did not.

The question that arises is why this should occur. The central integrator of these rhythms clearly is of environmental and genetic origin. In a recent, thought-provoking article, Sassone-Corsi (26) described self-sustaining clocks that master time by gene regulation. In the present instance of rats having a normal or an abnormal base sequence in their mitochondrial genome and provided diets that differed in composition, we found an interactive effect of genetics and nutrition on these internal clocks. In fact, we provide evidence of these interactive effects that alter the shifts in time-related biological functions, and we suspect that these shifts are related to life span as well as disease development. Our previous studies of longevity of BHE/Cdb rats showed that when they were fed high-fat diets, life span was decreased and the time frame for degenerative change in the pancreatic islets and the kidneys was compressed. The shifts in feeding pattern and corresponding shifts in intermediary metabolism as described here might thus have relevance to life span and the time course of degenerative disease development.

It is known that rats of the BHE/Cdb strain have a mutated mitochondrial genome and a tendency to develop age-related glucose intolerance (4, 6, 7, 21–24). We have also shown that the composition of the diet influences the age at which this intolerance occurs (6, 7). The results of the present study suggest that shifts in the circadian rhythms of feeding occur as the animal attempts to regulate its metabolism so as to forestall abnormal glucose homeostasis. These rats have a twofold increase in de novo fatty acid synthesis when fed a low-fat or stock diet compared with rats of other strains. They also have an increase in lipolytic rate (10), which suggests that fatty acids are choice metabolic fuels. The high rate of fatty acid synthesis could artificially elevate the RQ. However, the high-fat diet should suppress de novo fatty acid synthesis, and the RQ should fall as a result (Figs. 5C and 6C). Although elevated fatty acid synthesis can explain in part the RQ, one should also realize that glucose carbon recycling also occurs to a greater extent in the BHE/Cdb rat than in the normal rat. Increased gluconeogenesis and increased glycogen turnover as well as glucose oxidation could influence the RQ pattern. Glucose turnover is likewise influenced by diet composition. Altogether, these observations suggest that the genomic mutation has subtle effects on metabolic flux that, in turn, influence the feeding pattern and the RQ. Indeed, it is conceivable that the BHE/Cdb rats adapt to their mutation (5), such that these aberrant metabolic patterns suppress the normal day-night feeding and respiratory patterns. The age- and diet-related increases in serum triglycerides and glycerol that characterize this rat strain indicate a greater dependence on fatty acid recycling. This too would influence the circadian rhythms of feeding and respiration. As the BHE/Cdb rats fed the high-fat diet began to lose control of glucose homeostasis and rely more on fatty acids as metabolic fuel, they shifted their feeding pattern, and this resulted in a shift in their RQ rhythm. These rats were responding to some internal cue that abolished the day-night circadian rhythm in feeding that is usually observed in rodents. We suspect that this cue might originate with the mitochondrial defect that reduces ATP synthesis efficiency (8). That a reduction in ATP synthesis efficiency could occur can be deduced from the RQs and from the heat production that rises as the animal ages. An increase in heat production due to some sort of mitochondrial slippage would be expected, and indeed we observed this to occur.

Perspectives

How relevant are these observations to the human? Recently, several reports appeared in the literature documenting mutations in the mitochondrial genome that associate with non-insulin-dependent diabetes mellitus (1, 2, 21). Many years ago, Jarrett and others (11, 14, 15, 27) reported that the normal diurnal rhythm in glucose tolerance was lost as humans progress toward non-insulin-dependent diabetes mellitus. These changes in rhythm were associated with losses in the rhythms of blood glucose, insulin sensitivity, growth hormone, and fatty acids, suggesting that prediabetic humans, like the BHE/Cdb rats, adjust their metabolic patterns in an effort to retain some control of glucose homeostasis. The humans studied by Jarrett and colleagues were not genetically screened, so we do not know whether the rat-human comparison is valid. However, given our present knowledge of the incidence of mitochondrial DNA defects and diabetes, perhaps the comparison has some merit. Further studies of prediabetic humans with mitochondrial defects should be conducted to determine whether such shifts do occur and are relevant to our understanding of how the body accommodates its aberrant mitochondrial metabolism when such metabolism is abnormal.
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