GLUCOSE TURNOVER IN LEAN AND OBESE RATS OF
THE SHR/N-cp AND LA/N-cp STRAINS*

CAROLYN D. BERDANIER,†‡, JU-SHIN PAN,‡ DIANE K. HARTLE§ and O. E. MICHAELIS IV
†Department of Foods and Nutrition (Fax 706 542-5059); ‡Department of Pharmacology,
University of Georgia, Athens, GA 30602, U.S.A.; and §Carbohydrates Laboratory, ARS,
USDA, Beltsville, MD 30705, U.S.A.

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Abstract—1. The relationship between hypertension, obesity, non-insulin-dependent diabetes mellitus and
various parameters of glucose metabolism was studied. Lean and obese rats of the SHR/N-cp and
LA/N-cp congeneric strains were studied at four months of age.
2. Tritium and 14C-labeled glucoses were infused in one set of rats while tritiated water and 14C-labeled
alanine were infused in a second group.
3. Glucose oxidation, turnover, conversion to glycogen, fatty acid synthesis, and alanine conversion to
glucose were determined, as were blood pressure, pulse pressure and heart rate.
4. The presence of obesity influenced body weight, body fat, de novo fatty acid synthesis, organ weights,
glucose mass, glucose oxidation, glucose synthesis, glucose carbon turnover and pulse pressure.
5. It had no effect on glycogen synthesis, tissue glycogen levels, blood glucose, glucose space, or blood
pressure.
6. Strain differences were observed in final body weight, organ weights, blood pressure, pulse pressure,
hepatic fatty acid synthesis, glucose mass, glucose space, glucose synthesis, liver glycogen levels and
glucose conversion to muscle glycogen.
7. Strain–phenotype interaction effects were observed on glucose incorporation into hepatic glycogen,
Cori cycle activity, hepatic de novo fatty acid synthesis, final body weight, fat pad weight, heart weight,
and mean arterial pressure.
8. These results suggest that although obesity and hypertension are genetic traits in these rats, these
traits are independent in their influence on the metabolism of glucose and the development of
non-insulin-dependent diabetes mellitus.

INTRODUCTION

Recently it has been reported (Pollare et al., 1990) that hypertensive humans of normal body weight
subjected to the glucose clamp technique had a decreased sensitivity to insulin. If hypertensive
humans were obese, a further decrease in insulin sensitivity was observed. The normal weight subjects
were not hyperglycemic in the fasting unchallenged state; however, their blood lipid (cholesterol and
triglyceride) levels were elevated. If the subjects were overweight, both fasting blood glucose and lipids
were higher than found in normal weight normotensive subjects. Although the glucose clamp technique
used in the above study can provide information about whole body glucose use, it cannot provide
detailed information about specific tissues and their role in glucose disposal. For this information, one
must be able to sample individual tissues and track the activity of the various metabolic pathways
involved. Such a task is formidable in the human given the ethical constraints of such work. It is
possible in small laboratory animals provided that

the animal chosen for such work exemplifies the human whose metabolism is to be studied.

In the situation where one wishes to ask the question of whether hypertension is part of the
syndrome characterized by abnormalities of glucose and lipid metabolism independent of the presence of
obesity, there are two new congenic rat strains available for use. One is the SHR/N-cp corpulent rat and
the other is the LA/N-cp corpulent rat. The SHR/
N-cp is a rodent model for non-insulin-dependent diabetes mellitus that has been developed by Hansen
at the National Institutes of Health (Hansen, 1988; Michaelis et al., 1984, 1985, 1986; Tulp et al., 1986;
Turley and Hansen, 1986; Carswell et al., 1989; Bhathena et al., 1989; Baly et al., 1989; Velasquez et al., 1989). This strain resulted from the matings of Koletsky rats (which are obese) and SHR rats (which
are hypertensive). The resultant progeny are either lean or obese and either mildly or markedly hyper-
tensive. The homozygous (cp/cp) rat is obese and mildly hypertensive while the heterozygous (cp/+ )
and homozygous (+/+ ) lean littermates are hypertensive. One substrain of SHR/N-cp rats (SHHF/
Mcc-cp) evidence congestive heart failure and edema at an early age in both lean and obese phenotypes
(McCune, 1989).
The LA/N-cp rat strain also carries the recessive \( cp \) gene and when homozygous for the \( cp \) trait is obese and lipemic (Michaelis et al., 1983; Tulp and Shields, 1984; Tulp et al., 1984; Bhathena et al., 1986; Michaelis et al., 1986; Tulp and Buck, 1986; Russell and Amy, 1986; Dolphin et al., 1987; Tulp and James, 1987; DeBowno et al., 1989; Schnitzer-Polokoff et al., 1989; Dolphin et al., 1990; Russell et al., 1991). This lipemia is particularly responsive to dietary sucrose in that feeding this carbohydrate results in increased serum triglyceride and modestly increased cholesterol levels in the blood. The development of lipemia is dependent on the development of obesity. Obese animals have higher levels of fasting insulin yet are normoglycemic or mildly hyperglycemic when compared to the lean littersmates. One colony of LA/N-cp (JCR:La/N-cp) rats has been reported to have significant cardiovascular disease (Dolphin et al., 1990; Russell et al., 1991). In this substrain there is no correlation between lipemia and the development of cardiovascular disease.

To date there have been no reports of studies of glucose turnover in either the SHR/N-cp or the LA/N-cp rats. In view of the importance of these studies to our understanding of the relationships between hypertension, obesity, cardiovascular disease and non-insulin-dependent diabetes mellitus (NIDDM) in man, it was decided to infuse \( 3\text{H} \) and \( 14\text{C} \)-glucose, \( 3\text{HOH} \), and \( 14\text{C} \)-alanine so as to be able to determine how glucose metabolism in these rats is affected by obesity, hypertension and NIDDM. Glucose oxidation, turnover, conversion to glycogen, \( de\ novo \) fatty acid synthesis, and alanine conversion to glucose were determined and compared in obese and lean phenotypes of these two strains. Because these rats are difficult to produce and obtain in large quantities, the group sizes were small. Nonetheless, significant strain and phenotype differences in many of these measurements were observed.

**MATERIALS AND METHODS**

Four groups of male rats were used. The rats were provided by Carl Hansen of the NIH Animal Resource Center and were obese and lean phenotypes of the SHR/N-cp and LA/N-cp strains. There were nine SHR/N obese rats, seven SHR/N lean rats and five each of the lean and obese LA/N-cp rats. The animals were maintained on the 54% sucrose diet devised by O. E. Michaelis (1984, 1985). This diet has been reported previously and contains, in addition to the sucrose, 10% casein, 10% lactalbumin, 3.1% AIN mineral mix, 5.9% fiber (alphacel), 1% AOAC Vitamin mix, 4% beef tallow, 4% lard, 4% corn oil and 4% hydrogenated coconut oil. The rats were housed individually in hanging wire mesh cages. Food and water were always available. The environment was controlled for light (on-off: 0600–1800) temperature (20 ± 1°C) and humidity (45–50%). Body weight and food intake were monitored weekly. After three months, the groups were subdivided into weight-matched pairs within strain and phenotype. One half of each pair was used to determine glucose turnover using two isotopically labeled glucooses while the other half of the pair was used to determine body water, \( de\ novo \) fatty acid synthesis, and alanine conversion to glucose. All the animals were used for the determination of body composition using gravimetric methods and of blood pressure and heart rate. The latter measures were made just prior to the infusion of the various labeled compounds. All the measurements of glucose and fatty acid synthesis and of blood pressure and heart rate were made between 9 and 11 a.m. in non-fasted rats.

The rats were anesthetized with a combination of Nembutal (12 mg/kg, i.p.) and ketamine (45 mg/kg i.m.). A catheter was placed in the carotid artery for the measurement of heart rate and systolic and diastolic blood pressure using an Electromed MS20 Physiological Pressure transducer and a Gould (RS3200) Recorder with processor preamplifier. The blood pressure recording equipment was calibrated each day using a mercury manometer. Following the measurements of heart rate and blood pressure, 10 mCi [U-\( ^{14}\text{C} \)] glucose and 100 mCi [6-\( ^{3}\text{H} \)] glucose/100 g body wt in isotonic saline were infused into the femoral vein. The tritiated glucose was purchased from Amersham International (Amersham, U.K.) and the tritiated water, carbon-labeled glucose, and alanine came from ICN Radiochemicals (Irvine, CA). Blood samples (~0.3 ml) were drawn from the catheter in the carotid, which remained patent throughout the procedure. The samples were collected after 15 min and then at 15 min-intervals in heparinized tubes, centrifuged (3500 rpm, 10 min, 4°C) and the plasma used for the determination of the specific activity of the glucose. After perchlorate deproteinization, the supernatant was applied to the top of a mixed-bed ion-exchange column (0.5 Amberlite CG-120-Na\(^+\) above 0.5 g Amberlite CG400 formate). The columns were eluted with 2.5 ml HOH. Of this eluate, 0.5 ml was analyzed for glucose by the glucose oxidase method of Krebs et al. (1963). The remaining 2 ml of eluate was evaporated to dryness in order to remove \( ^{3}\text{H} \)HOH. The \( ^{3}\text{H} /^{14}\text{C} \) radioactivity of the dried eluates was determined after reconstitution in 1 ml HOH and the addition of 10 ml toluene/Triton X-100 (3:1, V/V) containing 5 g of PPO (2,5-diphenyloxazole) plus 250 mg of POPOP (1,4-bis(5-phenyloxazole-2-yl)-benzene)/l as a scintillant. Radioactivity was determined in a liquid scintillation spectrometer (Beckman model 9200, Palo Alto, CA) using the channels ratio method.

At the end of the 105-min blood collection period, the rats were killed by pneumothorax. Liver, gastrocnemius muscles and epididymal fat pads were quickly excised, weighed, and flash-frozen in liquid nitrogen. Liver and muscle were used for the determination of glycogen. Liver and fat pads were used for the determination of fatty acids. The specific activity
Glucose turnover in SHR/N-cp and LA/N-cp rats

of the glycogen was determined. Liver and muscle samples (~1 g) were digested with 2.0 ml of 40% (w/v) KOH at 100°C. The glycogen was purified by the method of Cowgill and Pardee (1957). The glycogen was washed three times with alcohol. It was then hydrolyzed to glucose with 1 M H2SO4 for 2 hr at 100°C and samples of the hydrolysate were used for the determination of glucose by glucose oxidase and radioactivity as described earlier.

Glucose turnover rates were calculated from semi-logarithmic plots of 14C- and 3H-glucose in the plasma vs time, using the methods validated by Smith et al. (1986). The radioactivity of each isotope was expressed as the fraction of the dose injected (per 100 g body wt) remaining in 1 mmol plasma glucose at the time of sampling (fractional residual radioactivity). The glucose turnover rate (mg/min/100 g body wt) was estimated from a semi-log plot of plasma glucose specific activity vs time. The plot yielded a straight line represented by the exponential equation \[ S = S_0 e^{-kt} \] where \( S \) is the specific activity (dpm/mmol) of glucose in a blood sample. \( S_0 \) is the extrapolated glucose value at zero time and \( k \) is the first order rate constant or the fractional turnover rate (min\(^{-1}\)). This is 2.303x slope of the decay curve. A straight line was obtained which suggested that glucose turned over in an instantaneously mixing pool during the 105 min of observation (Fig. 1).

The glucose synthesis or production rate was calculated from the equation: \( R = \frac{M k}{C} \), where \( M \) is the blood glucose pool size (mmol/100 g body wt) and could be determined by \( M = \frac{\text{injected radioactivity} \ (\text{dpm}/100 \text{ g body wt})}{S_0} \). The glucose pool size is the product of glucose concentration, \( C \) (mmol/ml, average from seven time points) and the space occupied by the glucose pool (the pool space, \( V \), ml/100 g body wt), then \( R = kCV \).

The method for calculating glucose turnover as described above is based on the assumption that newly synthesized glucose is unlabeled and is released into the circulation at a steady rate. The validity of this assumption depends on the choice of isotope used to label the blood glucose. Some of the 14C-labeled glucose is recycled whereas the 3H of carbon 6 of glucose is presumed to be lost during glycolysis and gluconeogenesis and thus is less likely to reappear in the blood glucose (Smith et al., 1986; Vernon and Walker, 1974; Dunn et al., 1967). We validated this assumption through the measurement of the appearance in the blood of labeled glucose.
in rats infused with labeled alanine (described below).

By comparing the turnover rates obtained with U-14C-glucose with those obtained using 3H-glucose, the rate of glucose carbon recycling from extra hepatic tissue to liver, i.e. Cori cycle, was calculated. This recycling is represented by \( R_{6R}R_C \) and its percentage contribution to the blood glucose turnover is \( 100 \times (R_{6R}R_C)/R_{glc} \) where \( R_{6R} \) and \( R_C \) represent the tritiated and 14C labeled glucose, respectively.

The second half of each group was injected, again via the femoral vein, with 4 \( \mu \)Ci U-[U-14C] alanine/100 g body weight and 1 mCi3HOH/100 g body wt. Again, carotid blood samples were drawn at 15-min intervals for a total of 45 min, at which time heart blood was drawn followed by rapid excision of liver, gastrocnemius muscle and epididymal fat pads. The blood plasma was used to determine radioactive glucose and total body water as described above. Blood plasma, liver and fat pads were used for the determination of tritiated fatty acids (Dole and Meinertz, 1960; Lowenstein, 1971; Fain and Scow, 1966; Jungas, 1986). The appearance of 14C glucose in the blood over time was taken as a measure of the rate of gluconeogenesis via the alanine cycle. Means for all four groups for each measurement were compared using Analysis of Variance (SAS procedures) with groups of unequal size.

**RESULTS**

Table 1 presents a summary of the physical characteristics of the rats used. No differences in food intake, corrected for body size, were observed. As expected, the obese rats of each strain weighed more, had heavier livers and lighter muscles than their lean counterparts. Within the strains and between the strains there were also differences in a number of the measurements. The obese animals of each strain were similar in initial body weight; the lean rats were not. The lean SHR/N-cp rats weighed more than the lean LA/N-cp rats. The liver weight was greater in the obese SHR/N-cp rats than in the obese LA/N-cp rats. In turn, the liver weight was greater in the lean SHR/N-cp rats than in the lean LA/N-cp rats. The gactrocnemius muscles weight comparison was SHR/N-cp obese rats < LA/N-cp obese rats < SHR/N-cp lean rats < LA/N-cp lean rats. Lean and obese SHR/N-cp rats had similar fat pad weights which were less than the fat pad weights of the obese LA/N-cp rats and more than the fat pad weights of the lean LA/N-cp rats. The strain and phenotype comparison for the heart was obese SHR/N-cp = lean SHR/N-cp < obese LA/N-cp < lean LA/N-cp; kidney weights were larger in the obese SHR/N-cp than in the lean SHR/N-cp rats. The obese LA/N-cp rats were not different from either obese or lean SHR/N-cp rats. The lean LA/N-cp rats were lighter in kidney weight than any of the other groups.

In normotensive Sprague-Dawley rats, the usual mean arterial pressure is less than 140 mm Hg. As shown in Table 1, all four groups had values in excess of normal. Hence all must be considered hypertensive. However, the lean and obese LA/N-cp rats were less hypertensive than the lean and obese SHR/N-cp rats. Within the SHR/N-cp strain, the obese rats were less hypertensive than the lean rats. All four groups differed in pulse pressure. The comparisons were as follows: obese SHR/N-cp < lean SHR/N-cp < obese LA/N-cp < lean LA/N-cp. The heart rate did not differ among the four groups. Analysis of variance of these data revealed significant strain effects on final body weight, liver weight, muscle weight, heart weight, kidney weight, mean arterial pressure and pulse pressure. Significant phenotype effects were observed on all parameters except food intake, mean arterial pressure and heart rate. Significant strain–phenotype interaction effects were noted on final body weight, fat pad weight, heart weight, and mean arterial blood pressure.

Body composition and de novo fatty acid synthesis is shown in Table 2. As expected, the obese phenotypes of each strain had more body fat and less body

<table>
<thead>
<tr>
<th>Genotype phenotype</th>
<th>SHR/N</th>
<th>LA/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese (9)</td>
<td>Lean (7)</td>
<td>Obese (5)</td>
</tr>
<tr>
<td>Food intake (g/100 g)</td>
<td>5.4 ± 0.2*</td>
<td>5.1 ± 0.2*</td>
</tr>
<tr>
<td>body weight/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial weight (g)</td>
<td>132 ± 7*</td>
<td>113 ± 8*</td>
</tr>
<tr>
<td>Final body weight (g)</td>
<td>658 ± 18</td>
<td>448 ± 10</td>
</tr>
<tr>
<td>Liver weight (g)</td>
<td>25.5 ± 1.8</td>
<td>15.1 ± 0.4</td>
</tr>
<tr>
<td>Gastro. muscles (g)</td>
<td>3.14 ± 0.13*</td>
<td>4.82 ± 0.08b</td>
</tr>
<tr>
<td>Epididymal fat pads (g)</td>
<td>10.62 ± 0.48</td>
<td>10.54 ± 0.13a</td>
</tr>
<tr>
<td>Heart (g)</td>
<td>1.86 ± 0.05*</td>
<td>1.78 ± 0.04*</td>
</tr>
<tr>
<td>Kidneys (g)</td>
<td>3.16 ± 0.13a</td>
<td>2.78 ± 0.07b</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>185 ± 4</td>
<td>212 ± 3</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>88 ± 3*</td>
<td>79 ± 2b</td>
</tr>
<tr>
<td>Heart rate</td>
<td>392 ± 11*</td>
<td>384 ± 13*</td>
</tr>
</tbody>
</table>

*Mean ± SEM; N in parentheses at top of column. Means having unlike letter superscripts are significantly different (P < 0.05).
†ANOVA, Analysis of variance. Significant strain, phenotype and strain X phenotype interaction effects are shown as the P value for each effect. NS indicates no significant effect.
water than the lean phenotypes. The strains did not differ. Also, as expected, de novo fatty acid synthesis in liver and adipose tissue was greater in the obese phenotypes than in the lean phenotypes. Again, there were no strain differences. Analysis of variance of these data revealed a significant strain effect on hepatic de novo fatty acid synthesis and a significant strain–phenotype interaction effect. All the other measurements were affected by phenotype only.

The various aspects of glucose turnover are presented in Table 3. Hyperglycemia was observed in all four groups. These blood glucose values were in excess of what one would expect in normal (Sprague–Dawley) non-fasting rats of this age and sex. Glucose mass was affected by both strain and phenotype as indicated by analysis of variance. The SHR/N-cp rats had a greater mass than the LA/N-cp rats and, within strain, the obese rats exceeded the lean rats. Glucose space is the same as the percent body water as determined gravimetrically as well as by the determination of the volume of distribution of the infused tritiated water. The obese phenotypes had a smaller percent body water than the lean phenotypes of both strains. The measurements of glucose turnover were made in ad libitum fed rats under conditions where ample dietary carbohydrate was present in the gastrointestinal tract and where there was an ample stimulus for glycogen and fatty acid synthesis. As shown in earlier work on BHE rats (Kim et al., 1989, 1993; Pan and Berdanier, 1990) and ob/ob mice (Smith et al., 1986), semi-logarithmic plots of the decay of 3H-glucose and 14C-glucose in the blood over time were linear (Fig. 1). This allowed for the calculation of glucose pool size and glucose turnover. Glucose pool size was similar in the lean SHR/N-cp, and the lean and obese LA/N-cp and less than that observed in the obese SHR/N-cp rats. Analysis of variance of these data showed a significant strain effect on glucose pool size. Irreversible glucose turnover or the percentage of glucose that was oxidized per unit of time, was greater in the obese SHR/N-cp than in the lean SHR/N-cp rats but was not different in the lean and obese LA/N-cp rats. Analysis of variance showed a significant phenotype effect but no strain effect. Absolute glucose synthesis rates were different in all four groups. Synthesis was greatest in the obese SHR/N-cp rats followed by obese LA/N-cp, lean SHR/N-cp and lean LA/N-cp rats. As expected, analysis of variance showed significant phenotype and strain effects on this measurement. Finally, Cori cycle activity or the fractional glucose carbon recycling percentage, was affected by obesity in the LA/N-cp rats but not in the SHR/N-cp rats. The lean LA/N-cp rats had greater Cori cycle

### Table 2. *De novo* fatty acid synthesis in obese and lean rats of the SHR/N and LA/N strains

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SHR/N</th>
<th>LA/N</th>
<th>Analysis of variance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body fat (%)</td>
<td>48 ± 2.0a</td>
<td>29 ± 2.6a</td>
<td>45 ± 1.4b</td>
</tr>
<tr>
<td>Body water (%)</td>
<td>59 ± 2.0a</td>
<td>59 ± 2.0a</td>
<td>36 ± 1.9b</td>
</tr>
<tr>
<td>Liver (^3)H→FA (μmol acetyl units/hr g)</td>
<td>14.9 ± 0.34a</td>
<td>2.55 ± 0.42a</td>
<td>18.75 ± 3.37a</td>
</tr>
<tr>
<td>Adipose (^3)H→FA (μmol acetyl units/hr g)</td>
<td>0.3 ± 0.1a</td>
<td>NV</td>
<td>0.06 ± 0.06a</td>
</tr>
</tbody>
</table>

*Mean ± SEM; N = 4 for the SHR/N rats; N = 2 for the LA/N rats. Means having unlike letter superscripts are significantly different (P < 0.05).

### Table 3. Influence of strain and phenotype on various measurements of glucose use

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SHR/N-cp</th>
<th>LA/N-cp</th>
<th>Analysis of variance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose (mg/dl/μmol/ml)</td>
<td>199 ± 10.4a</td>
<td>195 ± 5.0a</td>
<td>211 ± 27a</td>
</tr>
<tr>
<td>Glucose mass (μmol/100 g b.w.)</td>
<td>1102 ± 67a</td>
<td>925 ± 63a</td>
<td>1171 ± 1.51a</td>
</tr>
<tr>
<td>Glucose space (ml/100 g b.w.)</td>
<td>33 ± 2a</td>
<td>59 ± 2a</td>
<td>36 ± 1a</td>
</tr>
<tr>
<td>Glucose pool size (μmol/100 g b.w.)</td>
<td>102 ± 9.6a</td>
<td>86.6 ± 6.6b</td>
<td>71.8 ± 4.7a</td>
</tr>
<tr>
<td>Irreversible fractional glucose turnover (μmol/min/g b.w.)</td>
<td>9.73 ± 0.49a</td>
<td>6.69 ± 0.32b</td>
<td>9.60 ± 0.58b</td>
</tr>
<tr>
<td>Absolute glucose synthesis rate (μmol/min/100g b.w.)</td>
<td>106.3 ± 4.7a</td>
<td>62.3 ± 3.8b</td>
<td>80.9 ± 9.9a</td>
</tr>
<tr>
<td>Fractional glucose carbon recycling (Cori cycle) (%)</td>
<td>30.2 ± 1.8c</td>
<td>34.1 ± 1.5c</td>
<td>25.9 ± 2.8c</td>
</tr>
</tbody>
</table>

*Number of rats per group. 
†Mean ± SEM. Means having unlike letter superscripts are significantly different (P < 0.05). 
‡b.w., body weight. 
§Significant effects for strain, phenotype and phenotype–strain interactions are given as the P value for each effect.
activities than the obese LA/N-cp rats. Within the SHR/N-cp strain there was a trend towards greater Cori cycle activity in the lean rats, but the difference between lean and obese rats was not significantly different. Analysis of variance of these data revealed a significant phenotype effect and a significant strain-phenotype interaction effect.

Lastly, tissue glycogen levels, as well as the incorporation of labeled glucose into glycogen, are presented in Table 4. Liver glycogen levels were higher in the lean and obese rats of the LA/N-cp strain than in the lean and obese rats of the SHR/N-cp strain. Furthermore, the obese rats of the SHR/N-cp strain had higher glycogen levels than their lean counterparts. Differences between the lean and obese LA/N-cp rats were not observed. The incorporation of labeled glucose into this glycogen did not follow the same pattern. Whereas in the LA/N-cp strain the tissue glycogen levels were similar, the incorporation of labeled glucose was 10 times greater in the obese rats as in the lean rats. In the SHR/N-cp rats, the lean and obese rats were not statistically different. The incorporation of glucose into muscle glycogen was greater in the obese SHR/N-cp rats than in the lean SHR/N-cp rats and greater in these rats than in either the obese or lean LA/N-cp rats. Neither strain nor phenotype affected muscle glycogen levels. Analysis of variance of all the above data revealed a significant strain effect on liver glycogen levels and on the incorporation of labeled glucose into muscle glycogen. No significant phenotype effects were found. A significant strain-phenotype interaction effect was observed on the incorporation of glucose into liver glycogen. With respect to the conversion of alanine to glucose, no strain or phenotype differences were observed (data not shown).

**DISCUSSION**

The results of this detailed comparison of the fate of radiolabeled glucose in two strains of rats which evidence varying degrees of an inappropriate glucose-insulin relationship, obesity and hypertension, together with cardiovascular disease, are of interest because these groups of rats closely replicate similar conditions in man. Pollare et al. (1990) posed the question in his study of hypertensive obese and non-obese humans of whether hypertension is characterized by insulin resistance. Using obese and lean rats of the LA/N-cp and SHR/N-cp strains we were able to answer this question as well as approach the question of how the animal manages to survive given these various abnormalities. All of the animals were hypertensive compared to what one would expect for normal rats. Yet not all were obese nor were they all equally hypertensive. There did not seem to be a relationship between obesity per se and the degree of hypertension. However, there was a relationship between the degree of hypertension and glucose disposal that was modified by the presence or absence of obesity. The various aspects of glucose disposal in Tables 2–4 clearly show this. The rate of glucose oxidation (irreversible glucose turnover) was appreciably less in the most hypertensive group, the SHR/N-cp lean rats. Obese rats of both strains have been reported to be hyperinsulinemic, hyperglycemic-insulin resistant and have fewer insulin receptors than their lean counterparts (Hansen, 1988; Michaelis et al., 1984; Bhathena et al., 1986, 1989; Baly et al., 1989; Ellwood et al. 1985). In the SHR/N-cp rats, obesity could be regarded as a response to hyperglycemia since hypertension-induced peripheral insulin resistance (if such exists) might have interfered with the down-regulation of lipolysis by insulin. The hypertension was less in the obese rats and these were the rats that were the most lipogenic. Their rates of de novo lipogenesis were considerably higher than their lean cohorts and one might also assume that their rates of lipolysis and fatty acid oxidation were also lower than those in their lean counterparts. The lean LA/N-cp rats not only oxidized more glucose to CO₂, they also had more hepatic glycogen than did the lean and obese SHR/N-cp rats. Within the SHR/N-cp genotype, the obese rats oxidized more glucose and had more liver glycogen than did their lean cohorts. These differences in tissue glycogen stores were not related to rates of glycogen synthesis, however. The group that had the highest

**Table 4. Glycogen levels and synthesis by liver and muscle in lean and obese rats of the SHR/N-cp and LA/N-cp strains**

<table>
<thead>
<tr>
<th></th>
<th>Obese (5)*</th>
<th>Lean (3)</th>
<th>Obese (3)</th>
<th>Lean (3)</th>
<th>Strain</th>
<th>Analysis of variance</th>
<th>Phenotype</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver glycogen</td>
<td>366 ± 56†</td>
<td>106 ± 32</td>
<td>1158 ± 340</td>
<td>1320 ± 370</td>
<td>0.0011</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>(μmoles glucose/g liver)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>l4C glucose — glycogen</td>
<td>2.87 ± 0.64</td>
<td>5.63 ± 1.83</td>
<td>5.27 ± 0.23</td>
<td>0.57 ± 0.12</td>
<td>NS</td>
<td>NS</td>
<td>0.0024</td>
<td>NS</td>
</tr>
<tr>
<td>(dpm/μmoles glucose/105 min)</td>
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<tr>
<td>Muscle glycogen</td>
<td>252 ± 18</td>
<td>203 ± 4</td>
<td>189 ± 38</td>
<td>216 ± 53</td>
<td>NS</td>
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<td>(μmoles glucose/g muscle)</td>
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<tr>
<td>l4C glucose — glycogen</td>
<td>203 ± 44</td>
<td>108 ± 14</td>
<td>59 ± 25</td>
<td>75 ± 27</td>
<td>0.0422</td>
<td>NS</td>
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<td>(dpm/μmoles glucose/105 min)</td>
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*Number of rats in each group given in parenthesis.
†Mean ± SEM.
‡Analysis of variance. P values are given for those effects that are significant; non-significant effects are indicated as NS.
amount of hepatic glycogen was the group that synthesized the least glycogen. Clearly this group (lean LA/N-cp) had a slower rate of glycogen use. When coupled to the observation of increased fractional glucose carbon recycling, one is led to suggest that the reason these animals are lean is that they are able to both recycle their glucose carbon quicker and that which can be stored as glycogen is left in storage. This provides a mechanism for reducing the blood glucose to near normal levels.

Lastly, one should note the consistencies and inconsistencies of these observations to those published previously using other rodent models with NIDDM. The BHE/cdb rat strain evidences an age-related deterioration in glucose tolerance (Berdanier, 1991). When fed a 6% hydrogenated coconut oil/64% sucrose diet (Kim et al., 1989, 1993), irreversible glucose turnover is increased as is hepatic fatty acid synthesis. The fractional glucose carbon turnover exceeds that observed in corn oil-fed rats. Muscle glycogen synthesis is decreased, as is the muscle glycogen level. In the non-fasted state, these rats are mildly hyperglycemic but not different from their corn oil-fed cohorts. The hyperglycemia of non-fasted BHE/cdb is not as great as seen in the lean and obese SHR/N-cp and LA/N-cp rats of the present study. Further, the BHE/cdb rat has neither the obese trait nor the hypertension trait. These traits seem to be independent modifiers of the diabetic trait with respect to tissue-specific differences in glucose use. The results found in the BHE/cdb rat were consistent with those of Okajima and Ui (1979) with respect to glucose mass and glucose pool size. The glucose mass in the lean SHR/N-cp and the obese LA/N-cp rats was similar to that of the BHE/cdb rats, the rats used by Okajima and Ui and that of the lean mice used by Smith et al. (1986).

The glucose pool sizes in the present study were smaller than those in BHE/cdb rats and normal rats. However, the pool size of the lean LA/N-cp rats was similar to that of the lean ob/ob mice (Smith et al., 1986). In the fed animal, the glucose that enters the circulation is contributed by the diet and by the liver and other tissues that synthesize glucose de novo or produce it via glycogenolysis. Glucose carbon recycling is therefore a major component of the system which regulates the blood glucose level. As noted, all four groups had blood glucose levels well above normal (~6 mmole/ml). Perusal of the glucose carbon recycling data suggests that this hyperglycermia was due, in part, to a very active recycling system. The values herein reported are two to three times greater than those reported by others (Smith et al., 1986; Kim et al., 1989; Okajima and Ui, 1979). The difference cannot be related to the presence of obesity since the lean rats in each strain had higher percentages of recycling glucose carbon than did the obese rats. Was recycling rate related to hypertension alone in these rats? Probably not. The lean and obese LA/N-cp rats had similar blood pressure but had differences in recycling. However, the LA/N-cp rats differed from the SHR/N-cp rats with respect to their diabetic tendencies.

How else can one explain this large recycling of the glucose carbon? It is probably due to a combination of the peripheral resistance to insulin that is a feature of the diabetes in these rats and their hypertension. If one could lower their blood pressure through drugs one might then determine how the glucose recycling would be affected. Future work is needed to tease out those factors responsible for glucose intolerance and to segregate these factors from those responsible for hypertension.

REFERENCES


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