Glucose homeostasis in thyroxine-treated BHE/cdb rats fed corn oil or hydrogenated coconut oil

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Glucose turnover was assessed in BHE rats fed either a 6% corn or hydrogenated coconut oil diet and treated with 10 μg thyroxine (T_4/100 g body weight/day or untreated. Regardless of fat souce, measures of fractional irreversible glucose turnover and Cori cycle activity were higher in T_4-treated rats than in control rats. T_4 also increased the alanine to glucose conversion. Treatment with T_4 resulted in less muscle and hepatic glycogen. Lipogenesis was greatly increased in the rats fed hydrogenated coconut oil and this effect was potentiated by T_4 treatment. Blood glucose levels were also lower in this group, suggesting that this blood glucose lowering was due to a combination of treatment effects on glycogenolysis and lipogenesis. It would appear that the main effect of T_4 was to alter the sources of glucose in the total glucose pool in the body, and that the differences in glucose oxidation, synthesis, and recycling were a reflection of the body's adaptation to this reduction.

Keywords: glucose turnover; BHE/cdb rats; thyroxine; Cori cycle; hydrogenated coconut oil; lipogenesis

Introduction

Several investigators have reported that glucose turnover is affected by the thyroid hormones. Holness et al.[1–3] have shown that hyperthyroidism blocks glycogen synthesis and suppresses hepatic glucose output in starved-refed rats.[1] They have shown that hyperthyroidism contributes to the glucose intolerance noted in the starved rat.[2] When starved rats are glucose refed, administration of thyroxine (T_4) stimulated glycogenolysis, which in turn contributed to hepatic glucose output and the glucose intolerance noted in these rats. Decreased fatty acid levels in the blood and increased fatty acid synthesis were also reported in the T_4-treated starved-refed rats compared with nontreated rats.

Diabetes also affects glucose turnover. Smith et al.,[4] using obese hyperglycemic mice, infused doubly labeled glucose and measured glucose synthesis as well as the glucose recycling and glucose oxidation. They reported that in both the fed and fasted state the obese mice had higher blood glucose levels than their lean litter mates. They attributed this hyperglycemia to elevated rates of glucose synthesis and glucose-lactate recycling (Cori cycle). Although BHE rats are not hyperglycemic,[5] they do develop an impaired glucose tolerance as they age. Before this intolerance develops, they evidence significant elevations in hepatic lipogenesis and gluconeogenesis,[6,7] which can be further elevated by feeding sucrose and hydrogenated coconut oil.[8,9] These rats also have slower than normal hepatic mitochondrial respiration,[10] which is unresponsive vis à vis state 3 respiration to T_4 stimulation.[11,12] Yet these animals are otherwise responsive to hyperthyroidism.[11,12,13] They increase their whole body oxygen consumption,[13] increase their deiodenase activity,[14] and increase the activity of hepatic α glycerophosphate shuttle and $Ca^{++}Mg^{++}$ATPase.[11,13] In view of the work of Holness et al.[1–3] on the effect of T_4 on several important aspects of glucose metabolism and our earlier reports on the effects of feeding different fats[9] and T_4 treatment effects on gluconeogenesis,[13] we thought it might be useful to determine whether T_4 would affect glucose turnover in these diabetes-prone rats. In the earlier study[11] we reported that hyperthyroidism failed to stimulate state 3 hepatic mitochondrial respiration in corn oil-fed rats, yet in rats fed hydrogenated coconut oil (HCO), this treatment resulted in a partial loss of control of oxidative phosphorylation. Pryor et al.[15] reported that the looseness of control of oxidative phosphorylation negatively correlates with gluconeogenic rates. That is, the looser the control, the greater

Supported by Agricultural Experiment Station Project #H911 and the Bly Memorial Research Fund.
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Received June 27, 1991; accepted July 20, 1992.

the rate of glucose production. In our preceding paper, we suggested that abnormalities in hepatic mitochondrial metabolism might be related to abnormalities in the control of glucose homeostasis. We have shown an age-related decline in hepatic mitochondrial function[16] and an age-related development of impaired glucose tolerance.[17] Given that the combined HCO-T_4 treatment perturbed hepatic mitochondrial function in the preceding work, we decided to use this same treatment paradigm to determine whether we could manipulate glucose homeostasis. Using infusions of doubly labeled glucose, tritiated water, and labeled alanine, we monitored glucose disappearance, fatty acid synthesis, glycogen content, and alanine conversion to glucose.

Materials and Methods

Two groups of 20 weanling (40–45 g body weight) BHE/cdb rats were used. They were fed a diet consisting of 64% (wt/wt) sucrose, 10% casein, 10% lactalbumin, 6% corn oil (CO), or HCO, 5% fiber, 4% American Institute of Nutrition (AIN) mineral mix, 1% AIN vitamin mix. Diet ingredients were purchased from ICN Nutritional Biochemicals (Irvine, CA USA). During the fourth week one group was made hyperthyroid through the daily injection of 10 μg T_4/100 g body weight. The control group was injected with vehicle only. The T_4 (Sigma Chemical, St. Louis, MO USA) was dissolved in a 0.005 N NaOH and the solution was prepared fresh each day.

The rats were obtained from the UGA colony and were housed individually in hanging wire mesh cages. Food and water were always available. The environment was controlled for lights (lights on, 0600–1800) temperature (20 ± 1° C) and humidity (45–50%). Body weight and food intake were monitored weekly. The rats were cared for in accordance with the standards of humane care set forth by USDA, NAS, and the Association of Laboratory Animal Caretakers.

After 1 week of T_4 treatment, the groups were subdivided into weight-matched pairs. One-half of each pair was used to determine glucose turnover using two isotopically labeled glucoses, 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 measurements were made between 9 and 11 a.m. in nonfasted rats.

The rats were anesthetized with a combination of nembutal (12 mg/kg, i.p.) and ketamine (45 mg/kg i.m.) and 10 μCi [U^{14}C] glucose and 100 μCi [6-^{3}H] glucose/100 g body weight in isotonic saline were infused into the femoral vein. The tritiated glucose was purchased from Amersham International, (Amersham, UK) and the tritiated water, carbon-labeled glucose, and carbon-labeled alanine came from ICN Radiochemicals (Irvine, CA USA). Blood samples (~ 0.3 mL) were drawn from the cut tip of the tail. The samples were collected every 15 minutes in heparinized tubes for a total of 105 minutes, centrifuged (350 rpm, 10 min, 4°), 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.[18] The remaining 2 mL of eluate was evaporated to dryness to remove ^{3}HOH. The ^{3}H/^{14}C radioactivity of the dried eluates was determined after reconstitution in 1 mL HOH and the addition of 20 mL toluene/Triton X-100 (3:1, vol/vol) containing 5 g of PPO (2,5-diphenyloxazole) plus 250 mg of POPOP (1,4-bis(5-phenyloxazole-2-yl)-benzene/liter 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 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 glycogen was purified by the method of Cowgill and Pardee.[19] The specific activity of the glycogen was determined by determining the specific activity of its constituent glucose molecules. Glycogen content of liver and muscle was determined using samples (~ 1 g) that were digested with 2.0 mL of 40% (wt/vol) KOH at 100° C. Aliquots of the hydrolysate were used for the determination of glucose using glucose oxidase and radioactivity as described above. Glycogen levels in the tissues are reported as μmoles glucose/g tissue rather than μmoles glycogen because a glycogen molecule can vary in its glucose content.

Glucose turnover rates were calculated from semilogarithmic plots of ^{14}C and ^{3}H glucose in the plasma versus time, using the methods validated by Smith et al.[4] Observed radioactivity was corrected for background, sample size, and dilution during deproteinization. The radioactivity of each isotope was expressed as the fraction of the dose injected (per 100 g body weight) remaining in 1 μmol of plasma glucose at the time of sampling (fractional residual radioactivity). The glucose turnover rate (μmol mg/min/100 g body weight) was estimated from a semi-long plot of plasma glucose specific activity versus time. The plot yielded a straight line represented by the exponential equation $S = S_o e^{kt}$ where S is specific activity (dpm/μmol) of glucose in a blood sample. S_o 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 2.303 × slope of the decay curve. A straight line was obtained that suggested that glucose turned over in an instantaneously mixing pool during the 105 minutes of observation *(Figure 1)*.

The glucose synthesis or production rate was calculated from the equation R (μmol/min/100 g body weight) = Mk, where M is the blood glucose pool size (μmol/100 g body weight), and could be determined by M = injected radioactivity (dpm/100 g body weight), S_o. The glucose pool size is the product of glucose concentration, C (μmol/mL, averaged from seven time points) and the space occupied by the glucose pool (the pool space, V, mL/100 g body weight), 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 ^{14}C-labeled glucose is recycled, whereas the ^{3}H of carbon 6 of glucose is presumed to be lost (irreversible glucose turnover) during glycolysis lipogenesis and gluconeogenesis and does not reappear in the blood glucose.[20,21] We validated this assumption through the measurement of the appearance in the blood of labeled glucose in rats infused with labeled alanine *(Figure 2)*.

By comparing the turnover rates obtained with U-^{14}C-glucose with those obtained using ^{3}H-glucose, the rate of glucose carbon recycling from extra hepatic tissue to liver, i.e., Cori cycle, was calculated. This recycling is represented

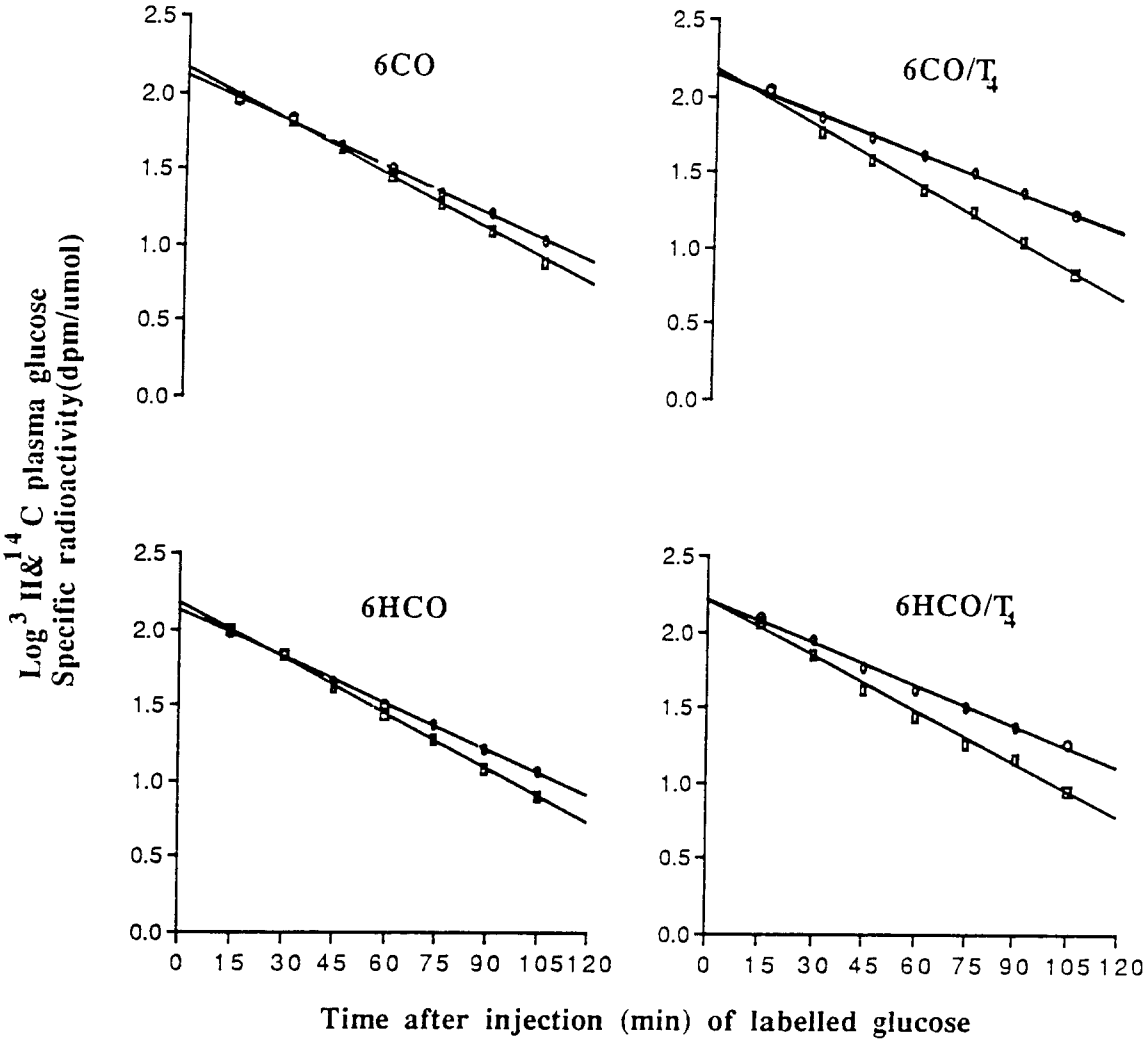

Figure 1 Semi-logarithmic plot of plasma glucose specific radioactivity in different fat-fed and T_4-treated rats injected with D-[6-^{3} H]/[U-^{14}C]-glucose at zero time. (○) refers to [^{14}C]-glucose; (□) to [^{3}H]-glucose. The dose of radioactivity is normalized to 100,000 dpm/100 g body weight for each isotope. HCO, hydrogenated coconut oil; CO, corn oil. The values shown are means of five rats with a standard deviation of ± 0.0001.

by $(R_{6H}-R_C)/R_{6H}$ and its percentage contribution to the blood glucose turnover is $100 \times (R_{6H}-R_C)/R_{6H}$ where R_{6H} and R_C represent the turnover rates calculated with the use of tritiated and ^{14}C-labeled glucoses, respectively.

The second half of each group was injected via the femoral vein with 4 μCi L-[U-^{14}C] alanine/100 g body weight and 1 mCi ^{3}HOH/100 g body weight. Again, tail blood samples were drawn at 15 minute intervals for a total of 45 minutes, 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 (as described above) and total body water. The value obtained for total body water was used in the calculation of the glucose pool space under the assumption that the glucose, as a water soluble substance, would be distributed within the total body water compartment. Blood plasma, liver, and fat pads were used for the determination of tritiated fatty acids.[22-25] Radioactive lipids were extracted using the Dole and Meinertz technique.[22] Tritium incorporation was determined as described by Lowenstein[23] and Fain and Scow.[24] According to Jungas[25] the ^{3}HOH method yields an average of 0.87 atom of ^{3}H incorporated per carbon atom incorporated into long-chain fatty acid. Results are expressed as micromoles of acetyl units incorporated per gram wet weight of tissue per hour. Liver and muscle were used for the determination of ^{14}C-glycogen glucose as previously described. The appearance of ^{14}C 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 (ANOVA) (SAS, Inc. Cary, NC USA) with groups of unequal size.

Results

Although the initial body weights and the food intakes for all four groups did not differ, final body weights were affected by both the diet and the T_4 treatments *(Table 1)*. The HCO diet was deficient in essential fatty acids, yet the duration of the experiment was such that it was unlikely that these rats were devoid of these essential fatty acids in their tissues. However,

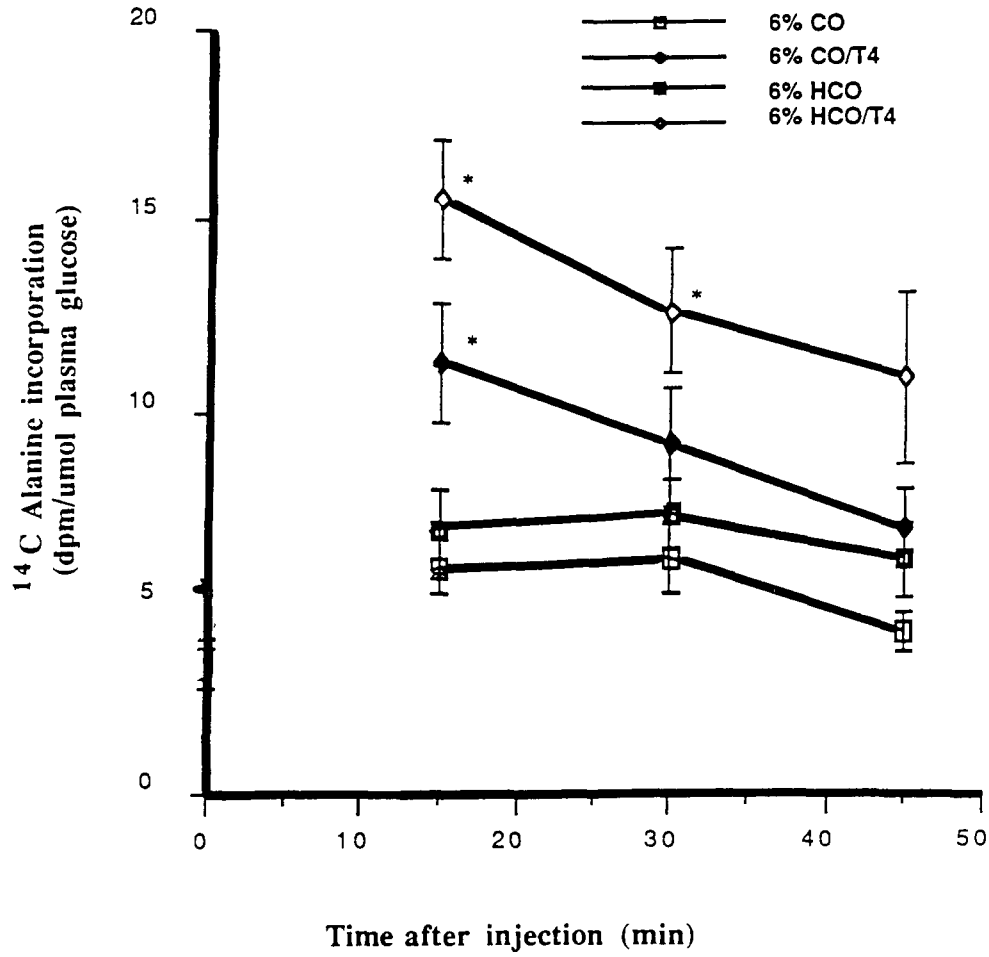

Figure 2 Time-course of incorporation of ^{14}C from L-[^{14}C] alanine into plasma glucose. The L-[^{14}C]-alanine (4 mCi/100 g body wt.) was administered by intravenous injection at zero time. *indicates the effect of T_4 within the same dietary treatment at the same time point was significant ($P < 0.05$). HCO, hydrogenated coconut oil; CO, corn oil.

given that the HCO rats consumed ~8.5 ± 0.4 g food/100 g body weight/day compared with 8 ± 0.3 g food/100 g body weight/day consumed by the CO rats, yet weighed slightly less, one should assume that they were mildly deficient with regard to their essential fatty acid status. Decreased feed efficiency is characteristic of this state. The HCO rats weighed less than the CO rats and the T_4 rats weighed less than their nontreated cohorts. In the HCO rats, liver weight was not affected by T_4 treatments nor was the glucose space or glucose mass. In the CO rats, T_4 treatment resulted in a decrease in liver weight. T_4 did not affect glucose pool size and glucose space. T_4 treatment increased the fractional irreversible glucose turnover (glucose oxidation and glucose conversion to fatty acids) and diet had no effect on this measurement. The fractional glucose carbon recycling (the Cori cycle) was unaffected by diet but was increased by T_4 treatment and there was a significant diet–T_4 interaction effect. Neither diet nor T_4 affected the appearance of glucose in the blood (the so called absolute glucose synthesis rate.) However, this measurement assesses the appearance of newly synthesized and newly released glucose, so it is a combination measure of gluconeogenesis and glycogenolysis. As can be noted, T_4 treatment markedly increased glycogenolysis. Almost no glycogen was detected in the livers of the T_4-treated rats even though these rats were examined in the fed state. These findings are consistent with the report of Okajima and Ui.[20] This T_4 effect on hepatic glycogen overwhelmed the small effect diet might have had on this metabolite. The HCO rats had less (150 ± 34 versus 205 ± 18) glycogen than did the CO rats, but this difference was not identified by ANOVA and N was too small to provide significant degrees of freedom to show a difference with a simple *t* test.

Muscle glycogen was significantly less in the T_4-treated rats than in the nontreated rats and diet was without effect on this measurement. Because there was so little hepatic glycogen in the T_4-treated rats we could not determine its specific activity. However, the specific activity of the muscle glycogen regardless of which isotopically labeled glucose was assessed, was significantly less in the T_4-treated groups. Again diet, was without effect on this measurement.

Diet did, however, strongly affect fatty acid synthe-

sis. The HCO rats synthesized significantly more fatty acids than the CO rats. This is consistent with our earlier report on hepatic lipogenesis in 2-day-starved–2-day-HCO-refed rats.[26] This effect was observed in both liver and fat pads and was apparent regardless of which tracer was used to assess fatty acid synthesis from glucose. The measured hepatic lipogenic rates were greater in the HCO groups than in the CO groups and were affected (increased) by T_4. In the adipose tissue both diet and T_4 treatment affected synthesis, but the effects were not always significant. The choice of label determined whether a significant effect on the incorporation of tritium from the tritiated glucose into fatty acids; however, when the ^{14}C label (from glucose) in the fatty acids was determined, T_4 treatment increased the incorporation of ^{14}C label into fatty acids. When tritiated water was used, a T_4 effect was observed in the CO rats, but not in the HCO rats. HCO rats incorporated more tritiated label from water into fatty acids in the adipose tissue than CO rats. T_4 also increased the appearance of the ^{14}C label from alanine in the blood glucose *(Figure 2)*. This indicates a T_4 effect on gluconeogenesis and the alanine cycle.

Discussion

The results of the present work are consistent with previous reports with respect to lipogenesis in BHE/cdb rats fed HCO. As shown in *Table 1*, both hepatic and adipocyte lipogenesis were markedly increased in the HCO rats. Further, it was apparent that T_4 potentiated the HCO effect in the liver. Liver lipogenesis was increased in the rats fed HCO and further increased when the rats were treated with T_4. Likely, the T_4 effect also affected fatty acid elongation and fatty acid oxidation as suggested by Landriscina et al.,[27] Stakkstead and Brenner,[28] and Reed and Tarver.[29] However, fatty acid oxidation and elongation was not measured. Landriscina et al.[29] reported that T_4 treatment increases hepatic microsomal fatty acid chain

Table 1 Glucose turnover and use in BHE rats fed corn or hydrogenated coconut oil and treated with thyroxine (T_4) or saline

	Diet				Analysis of variance		
	Corn oil		Hydrogenated coconut oil				
	$-T_4$	$+T_4$*	$-T_4$	$+T_4$*	Diet	T_4	Interaction
Number of rats	10	10	10	10			
Body weight, g†	236 ± 7†	22 ± 4	210 ± 3	200 ± 4	.01	.05	NS
Liver weight, g†	10.5 ± 0.4	9.2 ± 0.2	9.3 ± 0.3	8.9 ± 0.5	NS	NS	NS
Plasma glucose mmol/L†	8.1 ± 0.3	7.2 ± 0.2	7.6 ± 0.3	6.3 ± 0.3	NS	.01	NS
Glucose mass μmol/100 g B.W.	854 ± 119‡	656 ± 112	824 ± 166	622 ± 122	NS	NS	NS
Glucose pool size μmol/100 g B.W.	120 ± 16	97 ± 12	112 ± 23	107 ± 21	NS	NS	NS
Glucose space, v, mL	142 ± 4	133 ± 2	126 ± 2	120 ± 2	NS	NS	NS
mL/100 g B.W.	60 ± 2	60 ± 1	60 ± 1	60 ± 1	NS	NS	NS
Fractional irreversible glucose turnover % min^{-1}	2.54 ± 0.18	3.35 ± 0.47	2.87 ± 0.12	3.49 ± 0.36	NS	.05	NS
Fractional glucose carbon recycling, % (Cori cycle)	11.01 ± 1.01	34.83 ± 1.78	15.89 ± 2.02	24.35 ± 1.43	NS	.01	.01
Glucose release into circulation, μmol/min/100 g B.W.	24.74 ± 5.36	19.13 ± 1.32	22.87 ± 0.78	20.88 ± 4.49	NS	NS	NS
Liver glycogen, μmol/glucose/g	205 ± 18	<0.01	150 ± 34	<0.05	NS	.01	NS
Muscle glycogen, mmol/glucose/g	18 ± 1	11 ± 1	16 ± 1	9 ± 3	NS	.01	NS
Specific activity in muscle glycogen dpm/μmol glucose							
^3H glucose	5409 ± 1300	619 ± 79	3606 ± 862	1687 ± 378	NS	.01	NS
^{14}C glucose	809 ± 193	146 ± 26	474 ± 119	327 ± 79	NS	.05	NS
Hepatic fatty acid synthesis, μmol acetyl units/g/hr							
^3H glucose	1.12 ± 0.18	3.25 ± 0.55	6.58 ± 0.71	11.08 ± 2.71	.01	NS	NS
^{14}C glucose	2.08 ± 0.33	3.38 ± 0.78	6.12 ± 1.45	12.59 ± 2.37	.01	.05	NS
^3H HOH	3.00 ± 0.30	10.4 ± 3.00	18.90 ± 3.00	33.40 ± 5.00	.01	.01	NS
Epididymal fat pad, μmol acetyl units/g/hr							
^3H glucose	6.02 ± 1.10	13.13 ± 2.23	12.05 ± 1.87	12.72 ± 1.98	.05	NS	NS
^{14}C glucose	5.60 ± 1.23	8.36 ± 2.40	13.49 ± 3.09	11.35 ± 1.47	.05	NS	NS
^3HOH	0.30 ± 0.20	1.10 ± 0.30	2.00 ± 1.00	2.00 ± 1.00	.05	NS	NS

*10 mg T_4/100 g body weight/day.
†Mean ± SEM. The values from 10 rats contributed to this mean.
‡Mean ± SEM. The values from five rats contributed to the means reported for this and each subsequent measurement. In instances where multiple sampling from each rat contributed to the mean value for each rat, only the mean value was used to calculate the mean and SEM of the group mean value.

elongation. Stakkestad and Bremer[28] showed that similar treatment resulted in increased fatty acid oxidation, and Reed and Tarver[29] showed that the T_4 effect on lipogenesis was dependent on the dietary fat intake.

The T_4-treated rats had very little hepatic glycogen regardless of diet. The rats were killed in the fed state and as can be seen in the control rats, the liver glycogen level should have been substantial. Likely, T_4 increased glycogenolysis in these rats and, likely, glycogenesis was minimized as well, with the net result of very low hepatic glycogen levels. These assumptions about glycogen are consistent with those of Holness and Sugden.[1]

Gluconeogenesis and glucose oxidation were also affected by T_4. Both glucose oxidation, as represented by the fractional irreversible glucose turnover rate, and gluconeogenesis, as represented by the appearance of ^{14}C-glucose in the blood from ^{14}C-alanine were greater in the T_4-treated rats than in the control rats. An effect of T_4 on alanine conversion to glucose by isolated hepatocytes from 40-hr starved rats was shown to be less than that in hepatocytes from nontreated starved rats.[7] These rats had been fed a nonpurified control diet and starved so the results of the present work and the in vitro work are not comparable because of the differences in diet and nutritional state. However, a subsequent study of gluconeogenesis by hepatocytes from starved HCO-fed rats indicated that gluconeogenesis was elevated in these rats compared with hepatocytes isolated from starved CO-fed rats.[9] Unfortunately, T_4 treatment was not included in the latter study. All of these effects of T_4 on glucose turnover occurred in rats fed either of the diets, yet there were clear diet differences as well. The effect of T_4 was statistically significant in several of the measurements, whereas in the HCO rats T_4 was without effect. The exception to this within diet group-T_4 effect, was the effect of T_4 on blood glucose. Only in the HCO group did T_4 lower the blood glucose. The difference was due to T_4 in blood glucose between the CO groups and the HCO groups and might have been due to the differential effect T_4 had on glucose use. In the HCO groups there was less glucose recycling (Cori cycle) in the T_4 rats than in the non-T_4 rats (24.35 ± 1.43 versus 15.89 ± 2.02). There was very little glycogen (a source for glucose) and there was a significant increase in fatty acid synthesis (a sink for glucose). Altogether these actions had the net effect of lowering blood glucose, despite the combined effect of HCO and T_4 on gluconeogenesis. Note that the rate of glucose release into the circulation (which includes both gluconeogenesis and glycogenolysis) was not affected by either the diet treatment or the hormone treatment.

The results of the present study were dissimilar in some respects to our previous work with BHE/cdb rats fed menhaden oil.[12,30] We had shown that T_4 was without effect on hepatic mitochondrial state 3 respiration, yet improved the energetic efficiency (amount of ATP produced per mole oxygen consumed) of this tissue.[12] T_4-treated menhaden oil-fed rats had a greater glucose mass, greater absolute glucose synthesis rate, less hepatic and muscle glycogen, and greater rates of lipogenesis than their nontreated cohorts. There were no differences in blood glucose. In the present study using HCO, the T_4 effects were different. T_4 lowered blood glucose and increased the fractional recycling, but had no effect on glucose release into the circulation. We report in the companion study that T_4 also failed to stimulate hepatic state 3 respiration supported by TCA cycle intermediates.[11] These two sets of observations may be related. Pryor et al.[15] reported that in the liver when respiratory efficiency is decreased, gluconeogenesis is increased. In the present study, the appearance of glucose ^{14}C in the blood when ^{14}C alanine was given increased in the T_4-treated HCO-fed rats, yet the glucose release into the circulation was not different. The latter measurement includes, however, the glucose released from glycogenolysis. The T_4-induced increase in glucose recycling, which was less in the HCO rats than in the CO rats, might be related to the less efficient (in the HCO rats) regulation of mitochondrial metabolism.[11] However, this suggestion has not been fully substantiated. Nonetheless, it is apparent that the T_4 effects on glucose metabolism are dependent on the type of dietary fat fed which, in turn, can have an influence on the regulation of glucose homeostasis.

References

1 Holness, M.J. and Sugden, M.C. (1987). Hepatic carbon flux after refeeding. *Biochem. J.* **247**, 627–634

2 Holness, M.J. and Sugden, M.C. (1987). Continued glucose output after refeeding contributes to glucose intolerance in hyperthyroidism. *Biochem. J.* **247**, 801–804

3 Holness, M.J. French, T.J. Schofield, P.S., and Sugden, M.C. (1987). The relationship between fat synthesis and oxidation in the liver after refeeding and its regulation by thyroid hormone. *Biochem. J.* **247**, 621–626

4 Smith, S.A., Cawthorne, M.A. and Simson, D.L. (1986). Glucose metabolism in the obese hyperglycemic (C57B1/6ob/ob) mouse: The effects of fasting on glucose turnover rates. *Diabetes Res.* **3**, 83–86

5 Berdanier, C.D. (1991). The BHE rat: An animal model for the study of non insulin dependent diabetes mellitus. *FASEB J* **5**, 2139–2144

6 Lakshmanan, M.R., Berdanier, C.D. and Veech, R.L. (1977). Comparative studies on lipogenesis and cholesterogenesis in lipemic BHE rats and normal Wistar rats. *Arch. Biochem. Biophys.* **183**, 355–360

7 Berdanier, C.D. (1982). Rat strain differences in gluconeogenesis by isolated hepatocytes. *Proc. Soc. Exp. Biol. Med.* **169**, 74–79

8 Berdanier, C.D., and Baltzell, J.K. (1986). Comparative studies of the responses of two strains of rats to an essential fatty acid deficient diet. *Comp. Biochem. Physiol.* **85**, 725–727

9 Wander, R.C. and Berdanier, C.D. (1986). Effects of type of dietary fat and carbohydrate on gluconeogenesis in isolated hepatocytes from BHE rats. *J. Nutr.* **116**, 1156–1164

10 Berdanier, C.D, Tobin, R.B. and DeVore, V. (1979). Studies on the control of lipogenesis: strain differences in hepatic metabolism. *J. Nutr.* **109**, 247–260

11 Kim, M.-J.C. and Berdanier, C.D. (1992). Hyperthyroidism in BHE/cdb rats does not induce an increase in mitochondrial respiration. *J. Nutr. Biochem.* (in press)

12 Kim, M.-J.C. and Berdanier, C.E. (1989). Influence of menhaden oil on mitochondrial respiration in BHE rats. *Proc. Soc. Exp. Biol. Med.* **192**, 172–176

13 Berdanier, C.D. and Shubeck, D. (1981). Effects of thyroid hormone on mitochondrial activity in lipemic BHE rats. *Proc. Soc. Exp. Bio. Med.* **166**, 348–354

14 McIntosh, M.K., Berdanier, C.D., and Kates, A.-L. (1989). Studies of 5'deiodinase activity in rats differing in hepatic lipogenic activity. *FASEB J.* **3**, 1734–1740

15 Pryor, J.H., Smyth, J.E.,, Quinlan, P.T., and Halestrap A.P. (1987). Evidence that the flux control coefficient of the respiratory chain is high during gluconeogenesis from lactate in hepatocytes from starved rats. *Biochem. J.* **247**, 449–457

16 Berdanier, C.D. and McNamara, S. (1980). Aging and mitochondrial activity in BHE and rats. *Exp. Gerontol.* **15**, 519–525

17 Berdanier, C.D. (1991). The BHE rat: An animal model for the study of non insulin dependent diabetes mellitus. *FASEB J* **5**, 2139–2144

18 Krebs, H.A., Bennett, D.A.H., deGasquet, P. Gascoyne, T., and Oshita, T. (1963). Renal gluconeogenesis: The effects of diet on the gluconeogenic capacity of rat kidney cortex slices. *Biochem. J.* **86**, 22–27

19 Cowgill, R.W. and Pardee, A.B. (1957). *Experiments in Biochemical Research Techniques,* p. 158, John Wiley, New York, NY USA

20 Okajima, T. and Ui, M. (1979). Metabolism of glucose in hyper and hypothyroid rats in vivo. Glucose turnover values and futile cycle activities obtained with ^{14}C and ^{3}H labeled glucose. *Biochem. J.* **182**, 565–575; 577–584

21 Dunn, A., Chenoweth, M., and Schaffer, L.D. (1967). Estimation of glucose turnover and the Cori cycle using glucose 6 ^{14}C. *Biochem. J.* **6**, 6–11

22 Dole, V.P. and Meinertz, H. (1960). Microdetermination of long chain fatty acids in plasma and tissue. *J. Biol. Chem.* **235**, 2595–2599

23 Lowenstein, J.M. (1971). Effect of (-) hydroxycitrate on fatty acid synthesis in vivo. *J. Biol. Chem.* **246**, 629–632

24 Fain, J.N. and Scow, R.O. (1966). Fatty acid synthesis in vivo in maternal and fetal tissues in the rat. *Am. J. Physiol.* **210**, 19–25

25 Jungas, R.L. (1968). Fatty acid synthesis in adipose tissue incubated with tritiated water. *Biochem. J.* **7**, 3708–3717

26 Baltzell, J.K. and Berdanier, C.D. (1985). Effect of the interaction of dietary carbohydrate and fat on the responses of rats to starvation-refeeding *J. Nutr.* **158,** 104–110

27 Landriscina, C., Gnoni, G.V., and Quagliariello, E. (1976). Effect of thyroid hormones on microsomal fatty acid elongation synthesis in rat liver. *Eur. J. Biochem.* **71**, 135–143

28 Stakkestad, J.A. and Bremer, J. (1982). The metabolism of fatty acids in hepatocytes isolated from triiodothyronine-treated rats. *Biochem. Biophys. Acta* **711**, 90–100

29 Reed, E.B. and Tarver, H. (1976). Influence of diet on the lipogenic response to thyroxine in rat liver. *Life Sci.* **17**, 1785–1798

30 Pan, J.-S. and Berdanier, C.D. (1990). Thyroxine effects on parameters of glucose turnover in BHE rats fed menhaden oil. *J. Nutr. Biochem.* **1,** 244–248