Influence of dehydroepiandrosterone (DHEA) on the thyroid hormone status of BHE/cdb rats

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The effects of dehydroepiandrosterone treatment on the thyroid status of prediabetic, male BHE/cdb rats were investigated. Five-week old BHE/cdb rats fed a 65% glucose diet were injected intraperitoneally daily with either dehydroepiandrosterone (0.35 mol/kg body weight) or vehicle (1 mL/kg body weight) for 8 weeks. Organ weights, body composition, resting oxygen consumption, serum thyroxine, triiodothyronine, triglycerides, glucose and insulin, and thyroxine 5'-deiodinase activity in liver, brown adipose tissue, kidney, and pituitary were determined. Dehydroepiandrosterone-treated rats weighed significantly less at the end of the study than the control rats. Food intake was not different ($P \geq 0.05$) between groups. Dehydroepiandrosterone treatment decreased epididymal and retroperitoneal fat pad weights, carcass energy, total and free serum thyroxine levels, thyroxine:triiodothyronine ratios, and hepatic and pituitary 5'-deiodinase activities, and increased resting oxygen consumption, liver weights, liver protein, renal weights, and body ash. Dehydroepiandrosterone was without effect on the other parameters. These data suggest that dehydroepiandrosterone alters thyroid hormone status and in so doing, affects energy balance by increasing metabolic rate and decreasing fat stores.

Keywords: DHEA; thyroxine 5'-deiodinase; thyroxine; triiodothyronine; BHE/cdb rats

Introduction

The adrenal steroid dehydroepiandrosterone (DHEA) and the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), have been reported to promote energy expenditure and reduce body fat.[1,2] Clinically, thyroid hormones have been used not only for the treatment of hypothyroidism (ie, lack of sufficient T4) or euthyroid illness (ie, lack of sufficient T3), but also for the treatment of nonthyroidal illnesses such as obesity, hypercholesterolemia, and hyperlipidemia.[3,4] Triiodothyronine, the more biologically active thyroid hormone, is generated almost exclusively in non-thyroidal tissue (eg, liver, kidney, pituitary, brown adipose tissue, brain) by the enzyme T4-5'-deiodinase (5'-DI).[2,3] Below normal activity levels of 5'-DI have been observed in the liver, kidney, and brown adipose tissue (BAT) of obese mice and rats,[5-11] and this reduction in enzyme activity has been related to the decreased thermoregulatory capacity of these animals.[8-11] McIntosh et al.[5] demonstrated that the hepatic 5'-DI activity was one-fifth as active in obese Zucker rats as in lean Zucker rats. These obese rats also had reduced metabolic rates and serum levels of T3, as well as increased adiposity. Similarly, hyperlipemic, diabetes-prone BHE/cdb rats have less hepatic 5'-DI activity and serum T3, as well as higher levels of serum T4 than Sprague-Dawley rats.[5]

DHEA is similar in many respects to T3. In rats treated with DHEA there is a stimulation of metabolic rate, an increase in protein synthesis, and a decrease in body fat together with an increase in lipolysis and a decrease in lipogenesis.[12-28] Lardy et al.[15] have shown a synergistic effect of DHEA on T3 induction of hepatic sn-glycerol-3-phosphate dehydrogenase and

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malic enzyme activities in thyroidectomized rats. Foldes et al.[29] reported that humans with primary hypothyroidism have 60% less serum DHEA than euthyroid patients. These observations suggest that DHEA and thyroid hormone status may be related. Given the similarities of the effects of DHEA and thyroid hormone status in stimulating oxygen consumption, the question arises as to whether DHEA affects T4 levels and T3 genesis. If serum T4 levels are affected, then is 5′-DI activity affected? To answer these questions, we studied the activity of 5′-DI in non-thyroidal tissue and the serum levels of T3 and T4 in BHE/cdb rats treated with DHEA. We also determined a variety of other parameters relating to energy balance in these rats.

Materials and methods

Animals

Two groups of 10 male, 5-week old BHE/cdb rats obtained from the University of Georgia BHE/cdb colony were used. They were housed individually in hanging wire mesh cages in a room regulated for temperature (21 ± 2° C), humidity (45%–50%), and light (lights on 06:00–18:00). Animals were cared for in accordance with guidelines established by the Institute of Animal Resources of the National Research Council. Food and water were always available. The food intakes and body weights were determined weekly. The rats were fed a semi-purified diet consisting of (g/kg): glucose, 65; casein, 10; lactalbumin, 10; corn oil, 5; AIN-76 mineral mix, 5; cellulose (Alphacel), 4; and AIN-76 vitamin mix, 1. Diet ingredients were purchased from U.S. Biochemical Corp., Cleveland, OH. Test rats were injected i.p. each morning for 8 weeks with 0.35 mol/kg body weight DHEA (DHEA acetate, Sigma Chemical Co., St. Louis, MO) suspended in a 4:1 (vol/vol) saline: Emulphor mixture (GAF, New York, NY). Control rats were injected i.p. with vehicle alone (1 mL/kg body weight). Whole body respiration was determined in fasted rats 1 week prior to being killed in an airtight chamber of known volume containing a rack suspended over soda ash to adsorb CO_2. Oxygen consumption was determined manometrically following a 30-min acclimation period to chamber. An oral glucose tolerance test (OGTT) was conducted 4 days prior to being killed on rats fasted overnight. Tail blood was taken prior to a glucose challenge (13.8 mol/kg body weight) and at 30-, 60-, and 120-minutes post-challenge. All reagents were purchased from Sigma Chemical Co. unless otherwise indicated.

Sample collection and preparation

Rats were killed by decapitation, and trunk blood was collected in chilled tubes and allowed to clot. The sera was harvested after centrifugation (4° C, 1640*g*, 25 min) and dispensed into 250-μL aliquots and frozen at −20° C. The liver, subscapular BAT, pituitary, kidneys, epididymal, and retroperitoneal fat pads were quickly excised, weighed, and chilled. Pituitary, kidney, BAT, and 5 g of liver were homogenized in a 0.05 mol/L Tris-HCl, 0.25 mol/L sucrose, 0.01 mol/L dithiothreitol, and 1 mmol/L EDTA buffer. These tissues were prepared and subsequently frozen at −70° C for the determination of 5′-DI activity as previously described for liver.[5] The reaction conditions were similar for kidney, BAT, and pituitary. These tissues were prepared as follows: kidney (1 g: 3 mL ice cold buffer) was homogenized like the livers and then passed over one layer of gauze and dispensed in 2 mL aliquots; BAT (1 g: 5 mL cold buffer) was homogenized in 10 mL glass tubes for 15 sec at the 5.5 setting using a Brinkman Polytron (Brinkman Instruments, Westbury, NY) and dispensed in 0.5 mL aliquots; and pituitary (1 mg: 20 μL cold buffer) was homogenized in plastic 1.5 mL microtubes with plastic pestles (Kontes, Vineland, NJ) for 30 sec by hand turning and dispensed in 0.5 mL aliquots. The protein content of these tissues was determined by the method of Lowry et al.[30] using bovine serum albumin as the standard. The digestive contents of the gut were removed from the carcasses prior to freezing at −20° C.

Assays

Thawed sera were used for the radioimmunoassay of insulin (Cambridge Medical Technology, Billerica, MA) and total and free T4 and T3 (Amersham Corp., Arlington Hts., IL) as described in the kits purchased for these assays. Serum triglycerides were determined according to the procedure of Fletcher.[31] The 5′-DI assay previously described[5] was slightly modified, using column chromatography (Sephadex LH-20, Sigma Chemical Co.) instead of paper electrophoresis for the daily purification of [^{125}I]T4 (IM141, Amersham, Arlington Hts., IL). Preliminary 5′-DI kinetic studies were conducted in 0.1 mol/L phosphate buffer containing 1 mmol/L EDTA at 37° C on each tissue to establish the following ideal assay conditions: liver and kidney (10 μg protein, 1600 nmol/L T4, 10 mmol/L DTT, 20 min); BAT (40 μg protein, 10 nmol/L T4, 10 mmol/L DTT, 40 min); and pituitary (30 μg protein, 25 nmol/L T4, 20 mmol/L DTT, 30 min). The residential carcass (minus digestive contents, fat pads, liver, blood, kidneys, BAT, and pituitary) was analyzed for its fat, water, ash, and protein by gravimetric methods previously described.[12] The energy content of the residual carcass was determined in a bomb calorimeter. The significance ($P < 0.05$) of DHEA treatment on these parameters was determined using Student's *t* test.[32]

Results

Body weight and composition, food intake, and resting oxygen consumption

DHEA treatment reduced body weight gain (*Table 1*). The DHEA-treated rats weighed 283 ± 3 g at the end of the experiment, whereas the control rats weighed 345 ± 7 g. Significant differences in body weight became apparent after the fourth week of treatment (*Figure 1*). Relative food intake (g/100 g body weight) was not affected by DHEA treatment (*Table 1*). DHEA treatment reduced the efficiency of food conversion to body weight gain (*Table 1*). DHEA-treated rats had heavier livers and kidneys and lighter epididymal and retroperitoneal fat pads than control rats (*Table 1*). The composition of the residual carcass, which lacked its major fat pads, was minimally affected by DHEA treatment (*Table 2*). Nonetheless, the residual carcasses of DHEA-treated rats contained less energy and more ash than did the carcasses of control rats. Liver protein was significantly greater in the DHEA-treated rats than in the control rats. The levels of protein in the other tissues of DHEA-treated rats were not statistically different from the control rats. Resting oxygen consumption was greater in the DHEA-treated rats than in the control rats (*Table 2*).

Table 1 The effects of DHEA treatment on body, organ, and tissue weights in male BHE/cdb rats

Tissue	DHEA	Control
Initial body weight (g)	61 ± 2	64 ± 2
Final body weight (g)	283 ± 3[a,b]	345 ± 7
Average daily weight gain (g/d)	4.1 ± 0.1[b]	5.0 ± 0.2
Relative daily food intake (g/100 g body weight)	10.0 ± 0.9	9.4 ± 0.8
Food conversion efficiency[c]	4.2 ± 1[b]	3.7 ± .1
Liver (g)[d]	15.2 ± 0.5[b]	12.8 ± 0.5
Brown adipose tissue (g)[d]	0.93 ± 0.05	0.95 ± 0.06
Kidneys (g)[d]	3.1 ± 0.1[b]	2.7 ± 0.1
Pituitary (mg)[d]	7.7 ± 0.4	8.0 ± 0.4
Epididymal fat pad (g)[d]	2.4 ± 0.2[b]	3.7 ± 0.2
Retroperitoneal fat pad (g)[d]	3.6 ± 0.3[b]	5.3 ± 0.3

[a] Mean ± SEM, n = 10
[b] Effect of DHEA treatment is significant ($P < 0.05$) as determined by the Student's *t* test
[c] Grams of food consumed per grams of weight gained during the entire study
[d] Wet weight

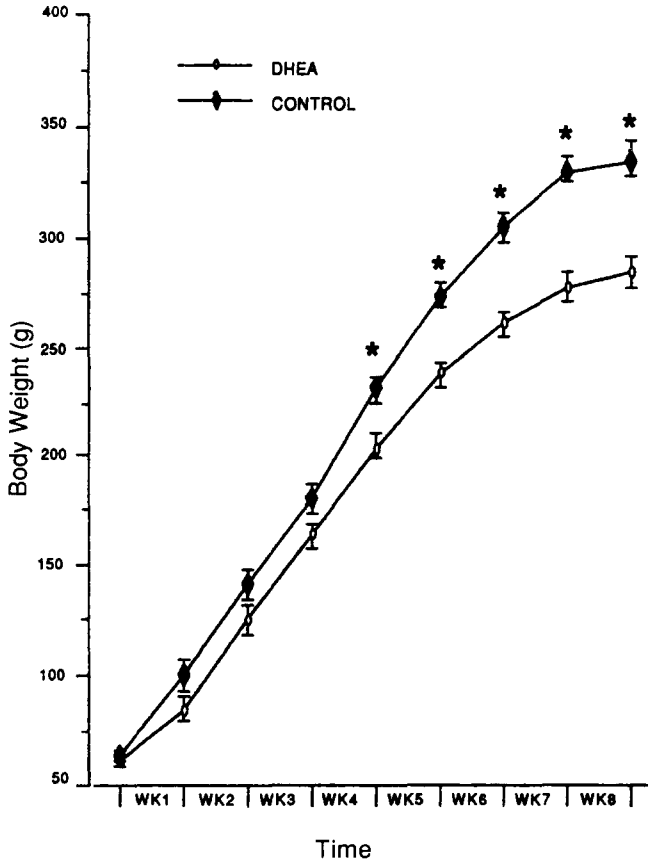

Figure 1 The effects of DHEA treatment on body weight gain in BHE/cdb rats. Significant differences ($P < 0.05$) due to DHEA treatment are indicated by *.

Serum hormones and metabolites and tissue 5'-DI activities

DHEA was without effect on oral glucose tolerance and on the non-fasted serum levels of triglycerides and insulin (data not shown). Serum levels of T4, both total and free, and the T4:T3 ratios were lower in the DHEA-treated rats than in the control rats (*Table 3*). Because serum T3 was unchanged but T4 was lower, the T4:T3 ratio was lower in the DHEA-treated rats. The 5'-DI activities in liver and pituitary were also lower in DHEA-treated rats compared with control rts (*Table 3*). BAT and renal 5'-DI activities were not affected by DHEA treatment.

Discussion

As shown in *Table 3*, DHEA treatment resulted in a decrease in the activity of hepatic and pituitary deiodinase activity and a reduction in the level of serum T4 levels. This result was unexpected because we also observed, as have others, a reduction in body weight gain and an increase in resting metabolic rate. However, if one views these responses as indicators of an effect of DHEA on thyroid hormone function, the results are understandable. These data suggest that the DHEA treatment potentiated the effects of thyroid hormone on metabolism such that metabolic rate was increased. In so doing, DHEA treatment stimulated the feedback loop for thyroid hormone control. Less T4 was released from the thyroid gland and less T4 was converted to T3 in the liver and pituitary. The pituitary is the key to this explanation of DHEA action. The pituitary has feedback control on the thyroid gland via thyroid stimulating hormone (TSH). A decrease in pituitary 5'-DI activity is associated with a decrease in TSH release.[33,34] With a decrease in TSH, one would expect a decrease in T4 levels and that is what we observed. With less T4 available as substrate, there would be less stimulus for the hepatic 5'-DI activity, again that is what we observed: hepatic 5'-DI activity was less in DHEA-treated rats than in control rats. Despite these effects of DHEA on 5'-DI and serum T4, serum T3 levels were not affected yet resting metabolic rate was increased. Again, this supports the hypothesis that DHEA potentiated the action of T3 on metabolism vis-à-vis oxygen consumption and feed efficiency. Lardy et al.[15] have also shown a potentiating effect of DHEA on T3's stimulation of thermogenesis via the hepatic enzymes sn-glycerol-3-phosphate dehydrogenase and malic enzyme. Hepatic malic en-

Table 2 The effects of DHEA treatment on resting oxygen consumption, body composition, and on the protein content of various tissues in male BHE/cdb rats.

Measurements	DHEA	Control
Resting oxygen consumption [mL/(min × $kg^{.75}$)]	37.3 ± 1.5[a,b]	29.5 ± 1.5
Residual body composition (g/100 g)[c]		
Fat	12.3 ± 0.5	12.4 ± 0.5
Ash	3.1 ± 0.1[b]	2.5 ± 0.2
Protein	19.1 ± 0.3	18.8 ± 0.3
Water	65.7 ± 0.5	66.4 ± 0.5
Residual carcass energy (Kcal/100 g)[c]	204 ± 3.2[b]	222 ± 3.2[b]
Tissue protein		
Liver (mg)	1852 ± 62[b]	1663 ± 68
Kidney (mg)	407 ± 14	376 ± 16
Brown adipose tissue (mg)	94 ± 7	91 ± 7
Pituitary (μg)	1228 ± 81	1168 ± 89

[a] Mean ± SEM, n = 10
[b] Effect of DHEA treatment is significant ($P < 0.05$) as determined by the Student's *t* test.
[c] Wet weight residual carcass = carcass − (liver + kidneys + pituitary + retroperitoneal fat pads + epididymal fat pads + brown adipose tissue + ingesta)

Table 3 The effects of DHEA treatment on serum hormone levels and thyroxine 5'-deiodinase activity in liver, kidney, brown adipose tissue, and pituitary in male BHE/cdb rats

5'-DI activity	DHEA	Control
T4, total (nmol/L)	29 ± 2[a,b]	43 ± 2
T4, free (pmol/L)	21 ± 1[b]	35 ± 2
T3, total (nmol/L)	0.90 ± 0.05	0.96 ± 0.05
T3, free (pmol/L)	2.4 ± 0.2	2.8 ± 0.2
T4/T3	30 ± 2[b]	44 ± 2
Liver, specific [pmol/(hr × mg protein)]	105 ± 10[b]	173 ± 11
Liver, total (nmol/hr)	198 ± 22[b]	289 ± 25
BAT, specific [fmol/(hr × mg protein)]	76 ± 7.4	77 ± 8
BAT, total (fmol/hr)	6935 ± 707	6929 ± 774
Kidney, specific [pmol/(hr × mg protein)]	162 ± 7.6	154 ± 8.3
Kidney, total (nmol/hr)	66 ± 3.5	58 ± 3.9
Pituitary, specific [pmol/(hr × mg protein)]	593 ± 44[b]	990 ± 46
Pituitary, total (nmol/hr)	721 ± 101[b]	1171 ± 106

[a] Mean ± SEM, n = 10
[b] Effect of DHEA treatment is significant ($P < 0.05$) as determined by the Student's *t* test.
Abbreviations: 5'-DI, thyroxine 5'-deiodinase; T4, thyroxine; T3, triiodothyronine; BAT, brown adipose tissue

zyme, an indicator of thyroid hormone status, has been reported to be elevated by DHEA treatment in a number of studies.

In addition to its supposed effect on T3 action, DHEA might also affect other oxygen-using processes that likewise are responsive to changes in thyroid status. Kaiser et al.[35] demonstrated that administration of a hypolipidemic agent and peroxisome proliferator, nafenopin, to euthyroid rats lowered liver 5'-DI activity and reduced serum total and free T4 concentrations by 32% and 62%, respectively, without changing serum T3 concentrations. They reported that the plasma clearance rate of T4 was doubled and that of T3 was reduced by 30% in nafenopin-treated rats compared with control rats. The significant reduction in serum T4 levels obtained in the present study may therefore be attributable to an increased rate of T4 turnover. Unfortunately, T4 plasma clearance rates were not determined in the present study. The use of T4 by other metabolically active tissue such as muscle would increase T4 plasma clearance rates and decrease T4 levels. Our observations of a DHEA effect on T4 levels are consistent with those reported by Mohan et al,[23] but not consistent with their reports of a lowering effect of DHEA on T3. Mohan et al.[23] used Sprague-Dawley rats for their studies. Genetic differences in response to DHEA have been previously reported,[1,17,19,21-26] so this inconsistency is not surprising.

Since DHEA, T4, T3, and nafenopin have been demonstrated to enhance peroxisomal activity, it may be possible that these agents promote energy expenditure by increasing peroxisomal beta oxidation of fatty acids. Since peroxisomes do not contain an electron transport chain or a TCA cycle, beta oxidation is not directly coupled to adenosine triphosphate synthesis. Thus any agent that stimulates peroxisomal activity will promote energy wastage. DHEA's effects on increasing whole body oxygen consumption found in

this and other studies[12,13] may therefore be due to enhanced oxidation of fatty acids in the peroxisomal system. This may also explain the reductions in body fat stores and carcass energy in DHEA-treated rats. Giacobino et al.[36] demonstrated that the peroxisomal capacity of BAT was dependent on the thyroid hormone status of rats. Song et al.[37] have shown that the induction of malic enzyme, which is a potential source of reducing equivalents in the peroxisomal reduction of hydrogen peroxide, by DHEA, requires thyroid hormone. Frenkel et al.[38] found that DHEA treatment in rodents promoted hepatic peroxisome proliferation and enzymes associated with beta oxidation. Mohan et al.[23] reported that DHEA treatment increased peroxisomal beta-oxidation and carnitine acetyl transferase activity. Leighton et al.[39] demonstrated a 10-fold increase in the activity of fatty acyl-CoA oxidase in peroxisomes of DHEA-treated rats. The energy lost as heat at this step in beta oxidation contributed, in part, to the reduction in body weight gain and food conversion efficiency. These observations in the present work suggest that DHEA potentiates the action of the thyroid hormones that in turn promote metabolic energy wastage by reducing energy storage as fat. One possible mode of action is through the promotion of peroxisomal activities that consume oxygen and reducing equivalents. One possible mode of action is through the promotion of peroxisomal activities that consume oxygen and reducing equivalents but are not coupled to oxidative phosphorylation. Further study is needed to confirm this hypothesis.

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