Further Studies on the Effects of Dehydroepiandrosterone on Hepatic Metabolism in BHE Rats[1,2] (42992)

CAROLYN D. BERDANIER[3] AND MICHAEL K. MCINTOSH

Department of Foods and Nutrition, The University of Georgia, Athens, Georgia 30602 and Department of Foods and Nutrition, University of Wisconsin-Stout, Menomonie, Wisconsin 54751

Abstract. **Two experiments were conducted to determine the effects of dehydroepiandrosterone (DHEA) on *de novo* fatty acid synthesis and oxygen consumption in BHE rats fed a 65% glucose diet. In Experiment 1, starved glucose-refed rats were injected ip with 120 mg of DHEA/kg body wt and hepatic *de novo* fatty acid synthesis was measured. DHEA-treated rats synthesized less fatty acid in response to starvation refeeding than nontreated rats. In Experiment 2, weanling rats were fed the glucose diet for 4 weeks. One-hundred twenty milligrams of DHEA/kg were injected daily for 3 weeks. Body weight gain, epididymal fat pad weight, and carcass lipid were less in the DHEA-treated rats than in the control rats. Mitochondrial respiration was less and liver size was greater in DHEA-treated rats compared with control rats. Whole body oxygen consumption was increased in DHEA-treated rats, suggesting that this steroid might be stimulating futile energy cycles involving lipid and protein turnover possibly through its effect on glucocorticoid and thyroid hormone function.** [P.S.E.B.M. 1989, Vol 192]

Considerable interest has developed in the steroid metabolite dehydroepiandrosterone (DHEA) due to its reported anti-obesity effects in genetically obese mice and rats (1–7). These effects have been thought to be mediated, in part, through an effect on glucose-6-phosphate dehydrogenase (G6PD, EC 1.1.1.49) because of the importance of this enzyme in fatty acid synthesis. DHEA-treated rats have lower G6PD activities and lower liver and carcass lipid levels than nontreated rats (8–11). Aside from the DHEA effect on lipid synthesis and accretion in genetically obese rodents, there are differences in response to this steroid among the different rat strains (10–12).

In an earlier publication, we reported that adrenalectomized BHE rats were more sensitive to this compound than intact BHE rats, and, indeed, responded quite differently than did Sprague-Dawley rats (10, 11). DHEA treatment of intact starved-refed Sprague-Dawley rats resulted in significantly lower hepatic lipid and G6PD activity than their nontreated cohorts. When adrenalectomized, the response to DHEA was even greater. This response was counteracted by glucocorticoid replacement. Similarly treated BHE rats did not evidence this counteractive effect of glucocorticoid on hepatic lipogenesis.

BHE rats are characterized by an age-related deterioration of glucose tolerance as well as by a fatty liver (13–20). Compared with Sprague-Dawley or Wistar rats, they have significantly greater G6PD activities and liver lipid levels when subjected to starvation-refeeding (11, 13), significantly greater hepatic lipogenic activity (13–16), and significantly less mitochondrial respiration (16–19). They also have larger adrenals (20) although circulating levels of adrenal steroids have not been determined. DHEA has been shown to suppress the lipogenic response to starvation-refeeding and has been shown to interact with glucocorticoid in this process (10, 11). Glucocorticoids determine the lipogenic response to starvation-refeeding (21–24), and there is a relationship of the glucocorticoids to mitochondrial respiration (25, 26). Given these observations and the observation that BHE rats are hyperlipogenic yet have less active mitochondria, we wanted to know whether DHEA would affect the large increase in *de novo* fatty

---

[1] Supported by a grant from Eli Lilly Research Laboratories and the Georgia Agricultural Experiment Station Project H-911.

[2] A preliminary report of some of these data was presented at the 18th Annual Steenbock Symposium, Madison, Wisconsin, June 1988.

[3] To whom correspondence should be addressed.

Received March 1, 1989. [P.S.E.B.M. 1989, Vol 192]
Accepted July 18, 1989.

0037-9727/89/1923-0242$2.00/0

acid synthesis that occurs in BHE rats subjected to starvation-refeeding and whether DHEA would affect their hepatic mitochondrial respiration. The latter measures were made in an attempt to relate the hepatic response to that of the whole body when rats are treated with DHEA.

Materials and Methods

Two experiments were conducted using male BHE-cdb rats (UGA colony). The rats were housed individually in hanging wire mesh cages in a room controlled for temperature (21 ± 2°C), humidity (45–50%), and light (lights on, 0600–1800 hr). Unless otherwise noted, food and water were always available. In experiment 1, food intakes and body weights were determined daily. In experiment 2, they were determined weekly. The diet consisted of (w/w) glucose 65, casein 10, lactalbumin 10, corn oil 5, cellulose (alphacel) 4, AIN Mineral Mix 5, AIN Vitamin Mix 1. Diet ingredients were purchased from Nutritional Biochemicals, Cleveland, OH.

Experiment 1 examined the effects of DHEA and starvation-refeeding on the *de novo* synthesis of fatty acids by the liver. Four groups of five rats with an average initial weight of 200 g were used. Half of the rats were fed *ad libitum* a 65% glucose diet for 4 days while the remaining rats were starved for 48 hr and refed the glucose diet for 48 hr. One half of the *ad libitum*-fed (AL) and starved-refed (SR) rats were given daily ip injections of vehicle or DHEA (120 mg/kg) during the refeeding period. At the end of the 4-day experiment, hepatic *de novo* fatty acid synthesis using tritiated water (1 mCi [^{3}H]OH/100 g body wt ip) was determined. Rats were killed 60 min after injection of the label and the labeled hepatic fatty acids were determined using previously described methods (20). Significantly different means were identified by analysis of variance (24). When two means were compared, Student's *t* test was used.

Experiment 2 examined the effects of DHEA on hepatic mitochondrial respiration, whole body respiration, and body composition. Two groups of 10 male weanling BHE rats were fed the 65% glucose diet for 4 weeks. One group was injected daily with DHEA (120 mg/kg) while the control group was injected with vehicle only. The injections were begun 1 week after the rats had been started on the diet. Thus, they were treated with DHEA for 21 days prior to use. DHEA acetate (Sigma Chemical, St. Louis, MO) was suspended in an 80:20 saline:Emulphor (GAF, New York, NY) mixture. Whole body respiration was determined in conscious rats in a whole body respirometer the day before the rats were killed or after 20 days of DHEA treatment. The whole body respirometer consisted of an airtight container of known volume containing a rack suspended over soda ash to absorb CO_2. Oxygen consumption was determined manometrically.

The rats were killed by decapitation; the livers and epididymal fat pads were quickly excised, chilled, and weighed. Mitochondria were isolated by differential centrifugation according to the methods of Johnson and Lardy and quality was assured as described previously (16–19). Mitochondrial protein was determined by biuret with egg albumin as the standard. Oxygen consumption, with and without 0.16 m*M* ADP was determined using 10 m*M* pyruvate plus 1 m*M* malate, 10 m*M* β-hydroxybutyrate, or 10 m*M* succinate as substrates. The residual carcass minus gut contents, liver, and epididymal fat pads was used to determined percentage of water, percentage of fat, percentage of ash and percentage of protein. Percentage of fat was determined gravimetrically after lipid extraction, percentage of water determined after drying, percentage of ash after combustion in a muffle furnace, and percentage of protein by difference. The significance of DHEA treatments on these parameters was determined by Student's *t* test (27).

Results

Consistent with previous reports (8–10, 18–21) rats subjected to starvation-refeeding without DHEA treatment weighed less and had larger livers than *ad libitum*-fed control rats (14.21 ± 0.69 vs 11.89 ± 0.39) (Table I). SR rats also synthesized more fatty acids than *ad libitum*-fed rats and again this was expected. The treatment of SR rats with DHEA resulted in a decrease in *de novo* hepatic fatty acid synthesis; however, DHEA treatment of AL-fed rats had the reverse effect. *De novo* fatty acid synthesis was increased in the DHEA-treated

Table I. Effects of DHEA on Body Weight, Liver Weight, and Hepatic Fatty Acid Synthesis in *Ad Libitum*-Fed and Starved-Refed BHE Rats (Experiment 1)

Group	Final body weight (g)	Liver weight (g)	Tritium incorporation into fatty acids (μmol acetyl units/g tissue/hr)
Control, *ad libitum*	254 ± 3a	11.89 ± 0.39a	0.30 ± 0.18a
DHEA, *ad libitum*	210 ± 22b	13.08 ± 1.53a	1.82 ± 0.80b
Control, starved-refed	227 ± 3b	14.21 ± 0.69b	12.95 ± 4.3c
DHEA, starved-refed	222 ± 4b	13.68 ± 0.80a	4.97 ± 1.45d

Note. Mean ± SE; $n = 5$ means having unlike letters are significantly different ($P < 0.05$).

AL-fed rats compared with their nontreated AL-fed counterparts. DHEA had no effect on body weight in SR rats but reduced body weight in AL-fed rats. This was somewhat unexpected since Yen *et al.* (1) reported that DHEA treatment of A^{vy}/a mice synthesized and accumulated less lipid than their nontreated controls. However, the difference in the AL-fed rats of the present work was not as striking as the difference between the two groups of SR rats or between the *ad libitum*-fed and SR groups. In the DHEA-treated rats, SR resulted in more than a 2-fold increase in *de novo* fatty acid synthesis whereas in the nontreated rats, SR elicited more than a 40-fold increase above that of the AL-fed rats. There was considerable variation around the mean for the AL-fed rats. This suggests that although the difference between the two groups was statistically significant, it probably was biologically unimportant.

Table II. Effects of Daily DHEA Injections on Food Intake, Body Weight Gain, Oxygen Consumption, and Body Composition of BHE Rats (Experiment 2)

Parameter	Control	DHEA
Food intake (g/100 g body wt/day)	7.3 ± 0.2a	6.8 ± 0.2a
Body weight gain (g)	142 ± 5a	97 ± 4b
Liver weight (g)	11.6 ± 0.4a	14.0 ± 0.6b
Relative liver size[a]	3.76 ± 0.31a	5.85 ± 0.15b
Epididymal fat pad weight (g)	2.96 ± 0.13a	2.01 ± 0.11b
% Lipid, carcass[b]	10.1 ± 0.6a	8.4 ± 0.4b
% Ash, carcass	2.55 ± 0.09a	2.86 ± 0.10b
% Protein, carcass	21.8 ± 0.2a	21.6 ± 0.2a
% Water, carcass	65.5 ± 0.8a	67.2 ± 0.5a
Whole body oxygen consumption (ml O_2/min/100 g $W^{.725}$)	2.00 ± 0.01a	2.62 ± 0.22b

Note. Mean ± SE; $n = 10$ for the control group; $N = 9$ for the DHEA group. Means having different letters are significantly different ($P < 0.05$).

[a] Relative liver size = liver weight/body weight × 100.

[b] Carcass = whole body − gastrointestinal tract contents − liver − epididymal fat pads.

Food intake was not affected by DHEA but was increased by SR. *Ad libitum*-fed DHEA and control rats consumed 8 ± 1 g/100 g body wt whereas SR control and DHEA-treated rats consumed 8 ± 1 g/100 g body wt. These values were not significantly different.

The results of Experiment 2 in which rats were treated for 3 weeks with 120 mg/kg/day with DHEA are presented in Tables II and III. Food intake was not affected by DHEA; however, body weight gain was significantly less in the treated group compared with the control group. Thus, there was a decreased feed efficiency associated with DHEA. Liver weight, relative liver size, carcass ash, and whole body oxygen consumption were greater whereas carcass lipid and epididymal fat pad weights were less in DHEA-treated rats compared with the control rats. The increase in whole body oxygen consumption with DHEA is consistent with the decreased feed efficiency observed in this group. The observations of decreased weight gain and carcass lipid are consistent with the reports of others on the effects of DHEA on weight gain (1–7). Carcass protein and carcass water were not significantly affected by DHEA.

Isolated hepatic mitochondria from DHEA-treated rats consumed significantly less oxygen in state 3 than mitochondria from control rats when pyruvate, succinate, or β-hydroxybutyrate were used to support respiration. In state 4, DHEA treatment significantly lowered pyruvate- and β-hydroxybutyrate-supported respiration. The respiratory control (RC) ratio is a calculated value that uses the oxygen consumption in the presence and absence of ADP as the numerator and denominator, respectively (28). The RC values serve as indicators of the quality of the mitochondrial preparations. Intact actively respiring mitochondria should have RC values between 2 and 10. Values less than 2 indicate a large percentage of dead mitochondria or mitochondria unable to respond to ADP addition by

Table III. Effect of DHEA on Hepatic Mitochondrial Respiration in BHE Rats (Experiment 2)

Substrate	ADP Addition[a]	Oxygen consumed	
		Control	DHEA
		(μmol O_2/mg protein/min)	
Pyruvate	−	5.60 ± 0.34a	4.06 ± 0.31b
	+	16.81 ± 0.80a	14.82 ± 0.75b
	RC[3]	3.04 ± 0.13a	3.61 ± 0.21b
β-hydroxybutyrate	−	7.09 ± 0.43a	5.37 ± 0.52b
	+	25.94 ± 1.28a	20.48 ± 1.16b
	RC	3.74 ± 0.24a	3.95 ± 0.27a
Succinate	−	19.18 ± 1.22a	15.06 ± 1.45b
	+	71.5 ± 2.15a	54.57 ± 2.18b
	RC	3.71 ± 0.26a	3.82 ± 2.18a

Note. Mean ± SEM. Ten rats in the control group; eight rats in the DHEA-treated group. Means having different letters are significantly different ($P < 0.05$).

[a] Successive additions of 0.16 mM ADP were added and oxygen consumption measured before and after each addition. State 3 respiratory conditions were simulated by the addition of ADP; state 4 was presumed to occur when the oxygen consumption rate returned to its pre ADD addition state.

[b] RC = mean oxygen consumption state 3 (+ADP)/mean oxygen consumption/state 4 (−ADP).

increasing their oxygen consumption. Values higher than 12 suggest that a degree of uncoupling or uncontrolled respiration has occurred; that there is a dissociation of oxygen consumption and ATP synthesis. DHEA treatment resulted in a significant increase in the RC for pyruvate-supported respiration but had little effect on the RC for β-hydroxybutyrate- or succinate-supported respiration.

Discussion

The question asked in Experiment 1 was whether DHEA would affect lipogenesis in the BHE rat as assessed by tritium incorporation into fatty acids. This question was answered in the affirmative. As expected, in BHE rats subjected to the hyperlipogenic treatment of starvation-glucose refeeding, hepatic *de novo* fatty acid synthesis was decreased by 60% by DHEA. This short-term result was supported by the results of the longer term second experiment which indicated a decreased weight gain and decreased carcass fat in DHEA-treated rats.

The increased whole body oxygen consumption by the rats injected with DHEA suggested that this compound might be acting via the thyroid gland and the nonthyroidal conversion of thyroxine to triiodothyronine. This conversion has been reported to be less active in the hepatic, but not pituitary tissue of BHE rats than in Sprague-Dawley rats (29). The activity of hepatic deiodinase was negatively correlated with hepatic lipogenesis. That is, hepatic lipogenesis was higher in animals with inherently less active hepatic deiodinase activity. This suggests that in the present work, DHEA might have stimulated deiodinase and inhibited hepatic lipogenesis as well as stimulated peripheral metabolism with the net result of an increase in whole body oxygen consumption. MacEwen *et al.* (30) recently reported a 40% reduction in circulating thyroxine levels in DHEA-treated lean and obese dogs. This supports the hypothesis that DHEA stimulates the conversion of thyroxine to triiodothyronine with the result of a higher turnover rate of the active hormone in the tissue which stimulates respiration. In addition, Foldes *et al.* (31) reported significantly lower circulating sulfate conjugated and free DHEA in hypothyroid patients than in normal patients. Thus, there seems to be a link between DHEA, thyroid status, and obesity.

In DHEA-treated animals having an increase in whole body oxygen consumption and a decrease in carcass lipid, we also observed a larger liver and a decreased hepatic mitochondrial respiration. Although mitochondrial respiration in the DHEA-treated rats was ~80% that observed in the control rats, the 20% larger livers with presumably more mitochondria probably compensated for this decrease. Oxygen consumption was calculated on a per milligram protein basis, so on a whole organ basis the livers from the DHEA-treated rats presumably consumed more oxygen than livers from the control rats.

Mohan and Cleary (32) reported that 3- or 7-day treatment of Zucker lean and obese rats also resulted in an increased liver weight relative to body weight but no change, due to DHEA, in respiration regardless of substrate when expressed per milligram of mitochondrial protein. When they expressed their results per gram liver or per liver, a DHEA effect (increase) was shown when succinate supported the respiration. The present experiment with BHE rats used a longer (21 days) DHEA treatment period and a decrease in mitochondrial respiration expressed on a milligram protein basis was shown.

Mohan and Cleary (32) also suggested that one of the reasons why DHEA has an anti-obesity effect is that it might potentiate the activity of a fatty acid deacylation-reacylation futile cycle. The energy wasted by this futile cycle would be, however, quite small compared with the loss in energy or rather the lack of energy gained as fat. Thus, there must be some other mode of action for DHEA.

One possibility is a decrease in energetic efficiency created when mitochondrial coupling is less tight. Mitochondrial respiration and coupling to ADP synthesis is a very well-controlled metabolic scheme. It must be well controlled to ensure survival. We observed in this study a decreased feed efficiency and an increased respiratory ratio when pyruvate supported respiration. Presumably this was due to "looser" coupling. This suggests that DHEA might be interfering with the action of glucocorticoid in the regulation of ATP export from the mitochondria via the calcium accumulation scheme of Kimura and Rasmusson (25).

However, looser coupling was not observed when the other substrates were used to support respiration, thus a DHEA effect on mitochondrial energetic efficiency must be discarded. Our earlier studies of the interaction of DHEA and glucocorticoid (10, 11) suggested that these hormones might be competitive for the same intracellular receptor. Their molecular structures are quite similar so it might be reasonable to suggest that DHEA might be an antiglucocorticoid and vice versa. Glucocorticoid is quite important to the regulation of hepatic lipogenesis (21–24) as well as the regulation of several anabolic and catabolic pathways important in energy balance. Lamontagne *et al.* (33) have shown that single functional group modifications of glucocorticoid can result in antiglucocorticoid activity. If DHEA is an antiglucocorticoid and was administered ip once daily, there might be a glucocorticoid-antiglucocorticoid cycle which could result in energy wastage. Both steroids have a relatively short half-life. When DHEA was present, competition for the cytosolic receptor could interfere with the glucocorticoid effect on lipogenesis and lipolysis might be stimulated. After this exogenous DHEA was degraded the endogenous glucocorticoid would prevail and lipogenesis stimulated. Thus, a futile cycle of lipogenesis-lipolysis might be established and energy lost. This would be consistent with the hypothesis of Mohan and Cleary (32) of fatty acid deacylation-reacylation and would include fatty acid oxidation and synthesis as well as protein degradation and resynthesis. Glucocorticoids have long been known to affect these processes as well. If such futile cycling does occur, then such would explain the significant increase in whole body oxygen consumption.

Increased turnover of protein would also increase oxygen use. Tagliaferro *et al.* (34) reported an increase in resting metabolic rate and the relative protein content of male and female Sprague-Dawley rats treated with DHEA compared with that of control rats. Given the high energy cost of protein synthesis and degradation, the observed changes in body composition could account for a portion of the energy lost associated with DHEA treatment. Although we did not observe a significant change in carcass protein, our study was not as long as the 11-week study of Tagliaferro *et al.* (34). Whole body substrate cycling will have to be determined before such an hypothesis can be found acceptable.

---

1. Yen TT, Allan JA, Pearson DV, Acton JM, Greenberg MM. Prevention of obesity in A^{vy}/a mice by dehydroepiandrosterone. Lipids **12**:409–413, 1977.
2. Coleman DL, Leiter EH, Schwizer RW. Therapeutic effects of dehydroepiandrosterone (DHEA) in diabetic mice. Diabetes **31**:830–833, 1982.
3. Cleary MP, Shepherd A, Jenks B. Effect of dehydroepiandrosterone on growth in lean and obese Zucker rats. J Nutr **114**:1242–1251, 1984.
4. Coleman DL, Schwizer RW, Leiter EH. Effect of genetic background on the therapeutic effects of dehydroepiandrosterone (DHEA) in diabetes-obesity mutants and in aged normal mice. Diabetes **33**:26–32, 1984.
5. Shepherd A, Cleary MP. Metabolic alterations after dehydroepiandrosterone treatment in Zucker rats. Am J Physiol **246**:E123–E128, 1984.
6. Cleary MP, Fox N, Lazin B, Billheimer JT. A comparison of the effects of dehydroepiandrosterone treatment to ad libitum and pair feeding in the obese Zucker rat. Nutr Res **5**:1247–1257, 1985.
7. Cleary MP, Zisk JF. Anti obesity effect of two different levels of dehydroepiandrosterone in lean and obese middle aged female Zucker rats. Int J Obesity **10**:193–204, 1986.
8. Willmer JS, Foster TS. The influence of dehydroepiandrosterone and pregnenolone upon adaptation of hepatic glucose 6 phosphate dehydrogenase to refeeding a high glucose diet after fasting. Can J Biochem **43**:1375–1377, 1965.
9. Tepperman HM, De La Garza S, Tepperman J. Effects of dehydroepiandrosterone and diet protein on liver enzymes and lipogenesis. Am J Physiol **214**:1126–1132, 1968.
10. McIntosh MK, Berdanier CD. Strain differences in the dose response curves of adrenalectomized, starved-refed rats to dehydroepiandrosterone (DHEA). Proc Soc Exp Biol Med **187**:216–222, 1988.
11. McIntosh MK, Berdanier CD. Differential effects of adrenalectomy and starvation-refeeding on hepatic lipogenic responses to dehydroepiandrosterone and glucocorticoid in BHE and Sprague-Dawley rats. J Nutr **118**:1011–1017, 1988.
12. Berdanier CD, McIntosh MK. Lessons learned from genotypic differences in response to dehydroepiandrosterone treatment. In: Shafrir E, Renold A, Eds. Frontiers in Diebetes Research. Lessons from Animal Diabetes. London: John Libby & Co., pp356–361, 1988.
13. Berdanier CD, Venable L. Strain differences in response to starvation-refeeding. Nutr Rep Int **26**:955–960, 1982.
14. Berdanier CD. Metabolic characteristics of the carbohydrate sensitive BHE strain of rats. J Nutr **104**:1246–1256, 1974.
15. Lakshmanan MR, Berdanier CD, Veech RL. Comparative studies on lipogenesis and cholesterogenesis in lipemic BHE rats and normal Wistar rats. Arch Biochem Biophys **183**:355–360, 1977.
16. Berdanier CD, Tobin RB, DeVore V. Studies on the control of lipogenesis: Strain differences in hepatic metabolism. J Nutr **109**:247–260, 1979.
17. Berdanier CD, McNamara S. Aging and mitochondrial activity in BHE and Wistar strains of rats. Exp Gerontol **15**:519–525, 1980.
18. McCusker RH, Deaver OE Jr., Berdanier CD. Effect of sucrose or starch feeding on the hepatic mitochondrial activity of BHE and Wistar rats. J Nutr **113**:1327–1334, 1983.
19. Wander RC, Berdanier CD. Effects of dietary carbohydrate on mitochondrial composition and function in two strains of rats. J Nutr **115**:190–199, 1985.
20. Marshall MW, Durand AMA, Adams M. Different characteristics of rat strains: Lipid metabolism and response to diet. Defining the Laboratory Animal. National Academy of Science, Washington, DC: pp383–412, 1971.
21. Wurdeman R, Berdanier CD, Tobin RB. Enzyme overshoot in starved-refed rats: Role of the adrenal glucocorticoid. J Nutr **108**:1457–1461, 1978.
22. Berdanier CD, Shubeck D. Interaction of glucocorticoid and insulin in the response of rats to starvation-refeeding. J Nutr **109**:1766–1771, 1979.
23. Bouillon DJ, Berdanier CD. Role of glucocorticoid in adaptive hyperlipogenesis in the rat. J Nutr **110**:286–297, 1980.
24. Nessmith S, Baltzell J, Berdanier CD. Interaction of glucocorticoid and thyroxine in the responses of rats to starvation-refeeding. J Nutr **113**:2260–2265, 1983.
25. Kimura S, Rasmussen H. Adrenal glucocorticoids, adenine nucleotide translocation and mitochondrial calcium accumulation. J Biol Chem **252**:1217–1225, 1977.
26. Allan EA, Chisholm AB, Titheradge MA. The stimulation of hepatic oxidative phosphorylation following dexamethasone treatment of rats. Biochim Biophys Acta **725**:71–76, 1983.
27. Steele RG, Torrie J. Principles and Procedures of Statistics, 2nd ed. New York: McGraw-Hill, pp348–361, 1980.
28. Chance B, Williams GR. The respiratory chain and oxidative phosphorylation. In: Nord FF, Ed. Advances in Enzymology. New York: Academic Press, Vol **17**: pp65–70, 1956.
29. McIntosh MK, Berdanier CD, Cates A-L. Studies on 5′-deiodinase activity in rats differing in hepatic lipogenic capacity. FASEB J **3**:1734–1740, 1989.
30. MacEwen E, Kurzman I, Haffa A. Antiobesity and hypocholesterolemic activity of dehydroepiandrosterone (DHEA) in the dog. In: Lardy H, Stratman F, Eds. Hormones, Thermogenesis and Obesity. New York: Elsevier, pp399–404, 1989.
31. Foldes J, Feher T, Feher K, Kouin E, Bodrogi L. Dehydroepiandrosterone sulphate (DS), dehydroepiandrosterone (D) and "free" dehydroepiandrosterone (FD) in the plasma of patients with thyroid disease. Horm Metab Res **15**:623–624, 1983.
32. Mohan PF, Cleary MP. Effect of short term DHEA administration on liver metabolism of lean and obese rats. Am J Physiol

255:E1–E8, 1988.

33. Lamontagne N, Mercier L, Pons M, Thompson EB, Simons SS Jr. Glucocorticoid versus antiglucocorticoid activity: Can a single functional group modification of glucocorticoid steroids always convey antiglucocorticoid activity? Endocrinology **114**:2252–2263, 1984.
34. Tagliaferro A, Davis J, Truchon S, Van Hamont N. Effects of dehydroepiandrosterone acetate on metabolism, body weight and composition of male and female rats. J Nutr **116**:1977–1983, 1986.