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Strain Differences in the Dose–Response Curves of Adrenalectomized, Starved–Refed Rats to Dehydroepiandrosterone (DHEA)[1] (42657)

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Abstract. The effects of adrenalectomy and dehydroepiandrosterone (DHEA) doses (0, 15, 30, 60, 120 and 240 mg/kg/day ip) on hepatic enzyme activity and lipid content and on the amount of epididymal fat pad lipid were studied in starved–refed BHE and Sprague–Dawley rats. BHE rats had significantly greater relative liver size, glucose-6-phosphate dehydrogenase (G6PD) and malic enzyme (ME) activities, and percentage liver lipid but less epididymal fat pad lipid than Sprague–Dawley rats. Adrenalectomized (ADX) rats consumed significantly less food, gained less weight per day, and had less lipid in their livers and fat pads than intact rats. As the level of DHEA increased from 0 to 240 mg/kg/day there was a significant linear decrease in average daily weight gain, food intake, G6PD activity, and percentage liver lipid. At the 15 mg/kg/day dose, G6PD activity was significantly reduced without reductions in the other parameters measured. At the 120 mg/kg/day dose, however, weight gain, food intake, G6PD activity, and percentage liver lipid were significantly lower than that of the controls. At this dose DHEA treatment reduced food intake by 17% whereas it diminished average daily weight gain and G6PD activity by 30 and 56%, respectively. The 240 mg/kg/day dose of DHEA significantly reduced food intake, weight gain, liver lipid, G6PD activity, and ME activity. Intact and ADX BHE rats reduced their G6PD activity and liver lipid more rapidly than Sprague–Dawley rats as the level of DHEA administered increased. ADX Sprague–Dawley rats receiving DHEA had greater liver lipid content and enzyme activity than their intact counterparts whereas the reverse situation was true in BHE rats. These data indicate that the effect of DHEA on body weight gain, food intake, and hepatic and peripheral adiposity are dependent on the strain of rat, the adrenal status, and the DHEA dose.

Dehydroepiandrosterone (Δ5-androstene-3(β)-01-17-one, DHEA), a 17-ketosteroid synthesized primarily by the adrenal glands, has been shown to exhibit many antiobesity characteristics. Early reports (1, 2) suggested that DHEA may inhibit glucose-6-phosphate dehydrogenase (G6PD, EC 1.1.1.49) activity *in vitro*. Subsequently, it was shown that DHEA injected peripherally drastically reduced the G6PD overshoot in starved–refed rats (3) and in rats fed a high carbohydrate, low protein diet (4). Yen *et al.* (5) prevented the development of obesity in Avy/a mice by either parenteral or oral administration of DHEA. In this work, DHEA treatment did not suppress food intake and the effect on obesity was reversed following withdrawal of DHEA treatment.

More recently Cleary *et al.* (6–13), Tagliaferro *et al.* (14), and Casazza *et al.* (15) have shown an inhibitory effect of DHEA on enzyme activity, weight gain, and food intake which seemed to be dependent on the strain or species of animal used, the sex of the animal, the mode of administration, and the dose of the steroid given. Except for the work of Casazza, all of these studies were long-term studies which lasted for 3 to 29 weeks. In an earlier paper using the acute starvation–glucose refeeding technique which induces hepatic hyperlipogenesis we reported that the administration of DHEA acetate to Sprague–Dawley rats suppressed the large increase in G6PD activity induced by starvation–refeeding but had no effect on food intake. In a subsequent study (17) using the same ip dose of DHEA (240 mg/kg/day) and feeding paradigm but using adrenalectomized (ADX) BHE rats, we found that DHEA suppressed food intake to such an extent that the ablation of the usual enzyme overshoot response could be explained sim-

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ply on the basis of DHEA's effect on food consumption.

In view of the conflicting results (16, 17) from work with BHE and Sprague–Dawley rats using identical diets, feeding regimes, DHEA dose, and route of administration, the question arose as to whether the strains differed in their responsiveness to this steroid. Thus, this paper reports work designed to determine whether starved–refed Sprague–Dawley and BHE rats differed with respect to their hepatic enzyme activity, food intake, and body weight gain over different doses of DHEA. Adrenalectomized rats were used so as to limit the amount of endogenous DHEA and glucocorticoids produced. These were contrasted to intact rats. We found genetic differences in the dose–response curves and in the effect of this drug on the responses of rats to starvation–refeeding.

Materials and Methods. *Experimental design.* One-hundred eighty male BHE/cdb (University of Georgia, Athens, GA) and Sprague–Dawley (Harlan Sprague–Dawley, Indianapolis, IN) rats, approximately 9 weeks of age, were randomly allocated to 1 of 24 possible treatment combinations of eight rats each in this 2 × 2 × 6 factorial design. The factors and levels tested were strain (BHE, Sprague–Dawley), adrenal status (intact, ADX), and DHEA dose (0, 15, 30, 60, 120, or 240 mg/kg/day). DHEA acetate (Sigma Chemical Co., St. Louis, MO) was suspended in an 80:20 saline:Emulphor (GAF Corp., New York) mixture. Rats were injected twice daily at 12-hr intervals during the last 48 hr of the experiment with 7.5, 15, 30, 60, or 120 mg DHEA/kg body weight. Control rats were injected with vehicle only.

Animals. Rats were housed individually in wire mesh cages in a room controlled for temperature (21 + 2°C), humidity (45–50%), and light (lights on, 0600–1800 hr). Body weights and food intakes (FI, g food consumed/100 g body weight) were determined daily. Rats were bilaterally ADX 1 week prior to use and thereafter given a 0.9% NaCl solution for drinking water. Completeness of removal of the adrenals was ascertained at necropsy. Prior to use the rats were fed *ad libitum* a pelleted stock ration (Purina Laboratory Animal Chow, Ralston Purina, St. Louis, MO). After recovery from adrenalectomy, the rats were starved for 48 hr and refed a 65% glucose diet[3] for 48 hr. The rats were killed by decapitation and the livers were quickly excised, chilled, weighed, and used for the determination of G6PD (EC 1.1.1.49) and ME (EC 1.1.1.40) activities (18) and lipid (20). Enzyme activity was defined as that amount of enzyme needed to convert 1 μmole of substrate to product per minute under the conditions of the assay. The activity was expressed per 100 g body weight to compensate for possible treatment effects on liver weight that would not affect the amount of enzyme present. The justification for expressing enzyme activity in this manner has been discussed previously (18, 19). The epididymal fat pads were also excised, chilled, and weighed and their lipid content was determined gravimetrically (21).

Statistics. The means for each of the parameters were compared for significance using the least-squares analysis of variance for unequal numbers according to Harvey (22). Sources of variation included replication ($n = 2$), strain ($n = 2$), adrenal status ($n = 2$), and dose ($n = 6$). Where appropriate, means were compared for significance ($P < 0.05$) using the Student t test when preceded by a significant F test (23). For each variable an additional analysis was computed in which the treatment sum of squares for DHEA dose was subdivided into linear and quadratic response curves and tested for significance.

Results. Table I presents the least-squares ANOVA of the means of the various parameters measured. At the highest dose some of the rats died. The mortality of the ADX rats varied with strain and DHEA dose. Of the BHE rats, 75% died when given DHEA whereas 37% of the ADX Sprague–Dawley rats died when given this dose of DHEA. None of the other dose levels affected survival nor was survival affected at this dose level when the rats were intact. All three variables, strain, adrenalectomy, and DHEA dose, affected food intake, weight gain, liver

[3] Composition of diet (w/w): 65% glucose, 20% protein (1:1 casein:lactalbumin), 5% fiber (Alphacel, ICN Nutritional Biochemicals, Cleveland, OH), 1% AOAC vitamin mix, 4% AIN mineral mix, and 5% corn oil.

TABLE I. THE LEAST-SQUARES ANOVA TABLE OF THE MAIN EXPERIMENTAL EFFECTS AND THEIR RESPECTIVE INTERACTIONS

Sources of variation	Levels	Final weight (g)	ADG (g/day)	Food intake (g/100 g body wt)	RLS	Enzyme activity G6PD (units/100 g body wt)	Enzyme activity ME (units/100 g body wt)	Liver lipid (%)	Fat pad lipid (g)
Main effects									
Strain(s)									
BHE		213 ± 2	9.3 ± 0.4	7.4 ± 0.2	5.5 ± 0.1[a]	34.3 ± 1.4[a]	25.7 ± 1.0[a]	6.6 ± 0.2[a]	0.6 ± 0.03[a]
SD		210 ± 2	9.4 ± 0.4	7.4 ± 0.1	4.8 ± 0.1	23.4 ± 1.3	18.2 ± 0.9	4.6 ± 0.2	0.8 ± 0.03
Adrenals (A)									
ADX		211 ± 2	7.8 ± 0.4[b]	6.8 ± 0.2[b]	5.2 ± 0.1	28.0 ± 1.5	21.7 ± 1.0	5.1 ± 0.2[b]	0.4 ± 0.03[b]
Intact		212 ± 2	10.9 ± 0.3	7.9 ± 0.1	5.2 ± 0.1	29.7 ± 1.2	22.2 ± 0.8	6.1 ± 0.1	1.0 ± 0.02
Dose (D)	0	218 ± 3[c]	12.3 ± 0.6[c]	8.8 ± 0.2[c]	5.4 ± 0.1[c]	44.9 ± 2.1[c]	25.5 ± 1.5[c,d]	6.2 ± 0.6[c]	0.7 ± 0.04[c]
	15	218 ± 3[c]	12.3 ± 0.6[c]	8.5 ± 0.2[c,d]	5.1 ± 0.1[c]	35.0 ± 2.2[d]	22.4 ± 1.5[d]	6.0 ± 0.3[c]	0.8 ± 0.04[c]
	30	214 ± 3[c,d]	10.7 ± 0.6[c]	8.0 ± 0.2[d]	5.3 ± 0.1[c]	29.7 ± 2.1[d]	21.4 ± 1.5[d]	5.7 ± 0.3[c,d]	0.7 ± 0.04[c]
	60	219 ± 3[c]	11.9 ± 0.6[c]	8.2 ± 0.2[c,d]	5.5 ± 0.1[c]	32.6 ± 2.0[d]	29.2 ± 1.5[c]	6.3 ± 0.3[c]	0.8 ± 0.04[c]
	120	210 ± 3[d]	8.6 ± 0.6[d]	7.3 ± 0.2[e]	5.3 ± 0.1[c]	20.5 ± 2.2[e]	22.3 ± 1.5[d]	5.3 ± 0.3[d]	0.7 ± 0.04[c]
	240[i]	191 ± 4[e]	0.2 ± 0.8[e]	3.6 ± 0.3[f]	4.3 ± 0.2[d]	10.4 ± 2.9[f]	10.8 ± 2.0[e]	4.2 ± 0.3[e]	0.5 ± 0.06[d]
Replication[j]	2	NS	NS	**	NS	NS	NS	NS	**
S × A	4	NS	**	**	**	**	**	**	NS
S × D	12	NS	NS	NS	**	**	**	•	NS
A × D	12	NS	**	**	**	**	**	NS	NS
S × A × D	24	NS	NS	**	**	NS	NS	NS	NS
D linear	6	**	**	**	**	**	**	**	NS
D quadratic	6	**	**	**	**	NS	**	**	•

Note. Abbreviations used: ADG, average daily weight gain during last 48 hr of experiment; G6PD, glucose-6-phosphate dehydrogenase; ME, malic enzyme; RLS, (liver weight × 100)/body weight; SD, Sprague–Dawley; ADX, adrenalectomized.

[a] Least-squares means ± SEM within the same strain column having different superscripts are significantly ($P < 0.05$) different.

[b] Least-squares means ± SEM within the same adrenal column having different superscripts are significantly ($P < 0.05$) different.

[c–h] Least-squares means ± SEM within the same dose column having different superscripts are significantly ($P < 0.05$) different.

[i] At the 240 dose level 75% of the ADX BHE rats died and 37% of the ADX Sprague-Dawley rats died. No other treatments had this effect.

[j] **, •, or NS, replication interactions and the linear and quadratic response curves are significant at the $P < 0.01$ level, significant at the $P < 0.05$ level, or nonsignificant, respectively.

lipid, G6PD activity, ME activity, and fat pad lipid. BHE rats had significantly larger livers relative to their body weights (RLS), greater G6PD and ME activities, and more liver lipid and less epididymal fat pad lipid than Sprague–Dawley rats. No strain differences in final body weight, average daily weight gain, or food intake (G/100 g body weight) were detected. ADX rats consumed significantly less food, gained less weight per day, and had less lipid in their livers and fat pads than intact rats. Based on the linear response curve no significant differences in enzyme activity were observed between intact and ADX rats. There was a significant linear decrease in body weight gain, food intake, enzyme activity, and liver lipid as the level of DHEA administered increased from 0 to 240 mg/kg/day. At the 15 mg/kg/day dose, only G6PD activity was significantly reduced. At the 120 mg/kg/day dose, however, average daily gain, food intake, G6PD activity, and liver lipid were significantly lower when compared with control rats. At this dose DHEA treatment reduced food intake by 17% whereas it decreased average daily gain and G6PD activity by 30 and 56%, respectively. In the 240 mg/kg/day dose of DHEA, all of the parameters measured were significantly reduced.

Individual strain and adrenal status responses to the doses of DHEA given are presented in Figs. 1–3. These figures represent the mean values for each of the parameters and were computer generated and statistically compared. Intact BHE rats consistently gained more weight and consumed more food (Fig. 1) and had greater enzyme activities (Fig. 2) and more liver lipid (Fig. 3) than the other three groups of rats over all of the DHEA doses tested. ADX Sprague–Dawley rats receiving DHEA had greater liver lipid

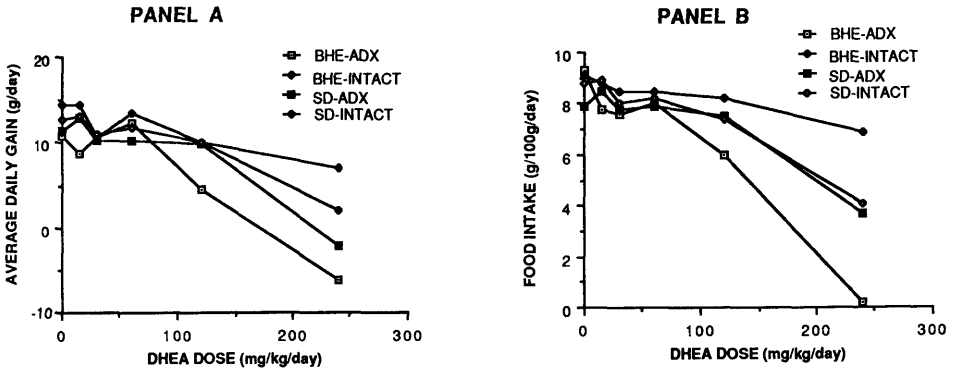

FIG. 1. The effect of dehydroepiandrosterone (DHEA) dose on the average daily weight gain (A) and food intake (B) in intact and adrenalectomized (ADX) BHE and Sprague–Dawley (SD) rats.

content (Fig. 3) and enzyme activities (Fig. 2) than their intact counterparts, whereas DHEA treatment of ADX BHE rats reduced these responses below those of the intact BHE rats.

The 15 mg/kg/day level of DHEA significantly reduced G6PD activity in BHE rats, whereas DHEA treatment did not significantly decrease G6PD activity in Sprague–Dawley rats until the 120 mg/kg/day dose (Fig. 2). In fact, up to the 120 mg/kg/day level of DHEA, intact and ADX BHE rats had consistently lower food intakes and average daily weight gains (Fig. 1), smaller enzyme activities (Fig. 2), and less liver and fat pad lipid (Fig. 3) than Sprague–Dawley rats when expressed as percentages of their respective controls. Furthermore, consistent with reports by others using intact rats (7, 14), ADX Sprague–Dawley rats receiving either 15, 30, 60, or 120 mg/kg/day DHEA had from 30 to 50% greater ME activity (Fig. 2) and from 20 to 33% more liver lipid (Fig. 3) than the control ADX Sprague–Dawley rats. At the 60 mg/kg/day dose of DHEA, there was a significant positive departure from the linear depression in performance, especially in ADX BHE rats.

Surviving ADX BHE rats injected with 240 mg/kg/day drastically reduced their food intake, weight gain (Fig. 1), tissue lipid (Fig. 2), and enzyme activity (Fig. 3). These reductions were far greater than those observed in Sprague–Dawley rats. Conversely, the average daily gain and food intake (Fig. 1), enzyme activities (Fig. 2), and liver lipid

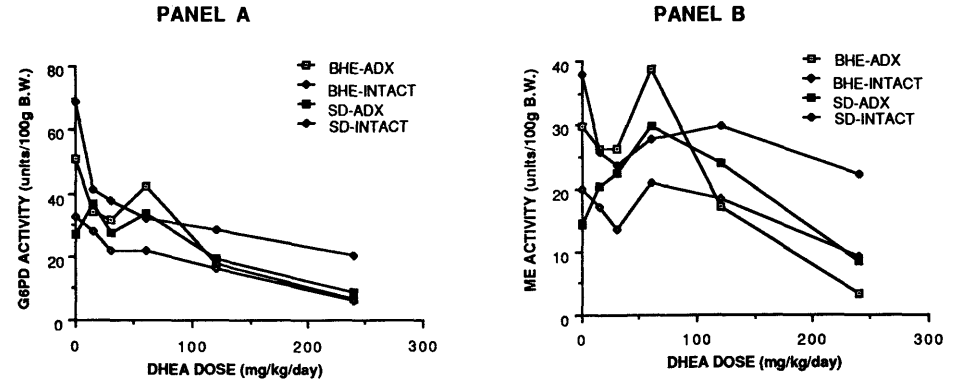

FIG. 2. The effect of dehydroepiandrosterone (DHEA) dose on glucose-6-phosphate dehydrogenase (G6PD) (A) and malic enzyme (ME) (B) activity in intact and adrenalectomized (ADX) BHE and Sprague–Dawley (SD) rats.

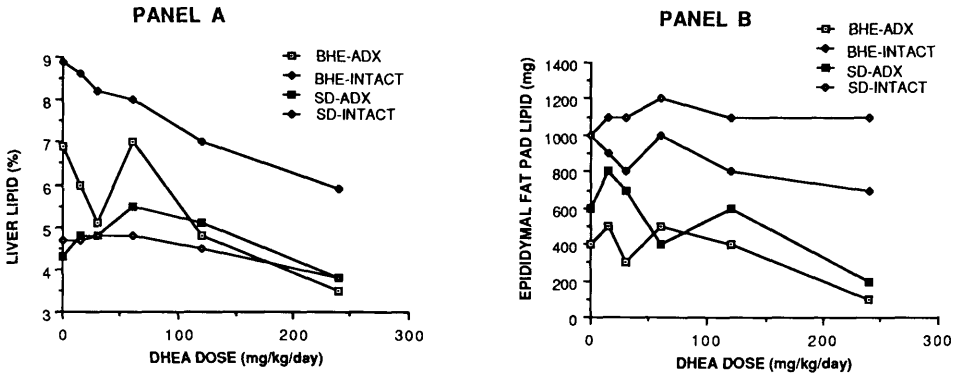

FIG. 3. The effect of dehydroepiandrosterone (DHEA) dose on liver lipid content (A) and epididymal fat pad lipid (B) in intact and adrenalectomized (ADX) BHE and Sprague–Dawley (SD) rats.

content (Fig. 3) of the intact BHE rats were greater than those of the intact Sprague–Dawley rats when both were given DHEA at the 240 mg/kg/day dose.

Discussion. The results of the present work clearly show that BHE and Sprague–Dawley rats differ in their sensitivity to the steroid DHEA. This sensitivity was increased when the endogenous supply of DHEA and glucocorticoid was removed as in adrenalectomy. Using the acute diet-induced increase in hepatic G6PD as the indicator of hepatic hyperlipogenesis we found that BHE rats consistently had 30% more enzyme activity and liver lipid than did Sprague–Dawley rats. At the same time, these BHE rats had significantly less fat pad lipid than the Sprague–Dawley rats. This is consistent with earlier reports (9, 17, 24) on BHE rats and indicates that this rat has an increased capacity for hepatic lipogenesis without the concomitant obesity observed in the Zucker rats.

In contrast to the long-term study of Berdanier and Burrell (25), but consistent with our earlier report (17), this acute study showed that ADX reduced hepatic and peripheral lipid levels by 17 and 60% in BHE rats. ADX Sprague–Dawley rats also had reduced tissue lipid levels. In part, this was due to a reduced food intake but, in part, this was due to the deficiency of glucocorticoid which has a critical role in the induction of the G6PD overshoot and liver lipid response to starvation–refeeding (19, 26–28). This hormone also is essential to the hyperphagia of genetically obese rodents as well as to rats made obese by hypothalamic lesions (29–33). However, glucocorticoid does not seem to play a role in food intake by normal rats except in the realimentation of rats after starvation (19, 26–28). ADX rats frequently are difficult to realiment after 48 hr of starvation.

Removing the endogenous supply of DHEA and glucocorticoid through adrenalectomy potentiated the genetically determined differences in sensitivity to exogenous DHEA. This was shown by the strain and ADX differences in the dose–response curves. Regardless of the parameter measured, the genetic differences in response to DHEA were apparent.

Others have reported genetic differences in response to DHEA. Cleary and associates compared lean and obese Zucker rats (8, 10–13), mice (6), and BHE (9) and Sprague–Dawley rats (7) and found that those rodents with a genetic tendency toward hepatic hyperlipogenesis were more responsive to DHEA than normal rodents. All of Cleary's work used a long feeding period (10 to 21 weeks) and DHEA was incorporated into the diet at 0.6 g/100 g diet. No dose–response studies have been reported.

The question of why strains should differ in their sensitivity to DHEA is an intriguing one. Since DHEA is a normal steroid metabolite, one question is whether this metabolite is an important *in vivo* factor in the regulation of energy balance. The genetically obese and lipemic animals are more sensitive to exogenous DHEA than are normal animals.

Does this mean that these genotypes further metabolize DHEA via a pathway different than that used by normal genotypes? Or, does it mean that the genetically determined increased sensitivity is due to genetically determined hormonal imbalances? Hyperinsulinism is a feature of these genotypes; could this be involved? Normal ADX rats are particularly sensitive to insulin (28) since they lack glucocorticoid one of the insulin counterregulatory hormones. ADX rats evidence large swings in blood glucose levels and when starved or given exogenous insulin may die in hypoglycemic shock. Their ability to regulate the glucose–insulin relationship is compromised as is their ability to "turn on" glucogenolysis and gluconeogenesis. When hyperinsulinemic BHE rats are ADX they do not seem to be as labile (25). They are able to maintain normal blood glucose levels when starved, yet in the present work, they were far more sensitive to DHEA. In fact, 75% of those ADX BHE rats given the 240 mg dose of DHEA died whereas none of the intact BHE rats given this much DHEA died. This suggests that some other hormone may be involved. The thyroid hormones, insulin, and glucocorticoid all have been implicated in G6PD regulation (34–36). Thus, future work on the mechanism of action of DHEA on G6PD in the different genotypes should focus on these three hormones.

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