Pharmacology Biochemistry and Behavior, Vol. 2, pp. 309–316. ANKHO International Inc., 1974. Printed in the U.S.A.

Effects of Cyproterone Acetate on Growth and Feeding in Rats[1]

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(Received 17 December 1973)

VILBERG, T. R., P. B. REVLAND, W. W. BEATTY AND L. A. FROHMAN. *Effects of cyproterone acetate on growth and feeding in rats.* PHARMAC. BIOCHEM. BEHAV. 2(3) 309–316, 1974. – Cyproterone acetate (CA) inhibited ponderal and linear growth and reduced food intake in juvenile male rats, but did not affect their water intake. CA reduced weight gain in young males that were unoperated, castrated, castrated and receiving testosterone propionate injections or adrenalectomized, but CA was not effective in inhibiting the already slow rate of growth in males that were both adrenalectomized and castrated. CA similarly failed to affect body weight in juvenile or old females, but it did inhibit weight gain following ovariectomy. In old males that were no longer gaining weight CA reduced food intake and caused a loss of body weight. Although food intake was reduced by CA treatment, pair feeding studies indicated that other factors must also be involved in the reduced rate of weight gain. CA failed to affect pituitary or plasma GH levels and treatment with bovine GH did not alter the effects of CA on ponderal or linear growth or food intake.

Cyproterone acetate Growth Food intake Body weight Growth hormone Androgens

CYPROTERONE acetate (CA) is an anti-androgen that competitively inhibits the growth promoting effects of testosterone on such classic target organs as the seminal vesicles (e.g., [12]). When exposed to this steroid prenatally, the male reproductive system of rodents fails to differentiate and the external genitalia are markedly feminized [11]. Moreover, the incidence of masculine sexual behavior in both male and female rodents is reduced by treatment with CA prenatally and during the early postnatal period [18,21]. Surprisingly, most behavioral studies in postpuberal rodents have failed to find significant effects of CA treatment on androgen-dependent behaviors. Thus, CA does not affect sexual behavior [1, 22, 23], aggression [5,14] or running wheel activity [17] in male rats, mice and gerbils or guinea pigs. Food intake and body weight are stimulated by endogenous or exogenous androgens (see [20] for a review), and recently Steinbeck and Neumann [16] reported that 55 days of CA treatment beginning at the age of 25 days caused a marked reduction in body weight that persisted for more than two months after cessation of the treatment. The present experiments examined the effects of CA treatment on linear and ponderal growth and feeding in relation to the age, sex, and endocrine status of the animals.

[1]Cyproterone acetate was generously supplied by Dr. P. Perlman of the Schering Corporation, Bloomfield, New Jersey and by Dr. F. Neumann, Schering AG, Berlin. Bovine growth hormone was supplied by Dr. A. E. Wilhelmi through the cooperation of the National Institute of Arthritis, Metabolism and Digestive Diseases. Plasma corticosterone assays were kindly performed by Dr. Robert E. Bowman and Mr. Robert Graf with the support of NIH Grant RR-00167 to the Wisconsin Regional Primate Research Center. Mrs. Ming Yi Chou performed the GH assays which were supported by Human Growth, Inc. Our thanks go to Dr. James Tilton for many helpful suggestions and to Dennis O'Briant, Wail Bengelloun and William Siders for assistance with the daily collection of data. We also thank Mr. O'Briant, Mr. Bengelloun, James Gange, James Ridley and Craig Kubick for their assistance in sacrificing the animals. Address reprint requests to William W. Beatty, Department of Psychology, North Dakota State University, Fargo, N. D. 58102.
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METHOD

Animals

Holtzman rats of both sexes were housed individually in an airconditioned animal room that was illuminated from 9 a.m. to 9 p.m. Young animals were obtained from the supplier at about 30 days of age and injected daily beginning on the 49th day of age. Older animals were either retired breeders obtained at 4–12 mos. of age or animals that previously served in behavioral experiments in our laboratory. Food (ground Purina rat chow in Experiments 1 and 2 or Purina rat chow pellets in the remaining experiments) and water were freely available except as indicated.

Procedure

Typically, animals received a series of 21 daily injections, although in Experiment 3 only 17 injections were given because supplies of CA were temporarily exhausted. Young rats of both sexes received 10 mg/day cyproterone acetate (6-chloro-17-acetoxy-1α, 2α-methylene-4, 6-pregnadiene-3,20-dione) dissloved in a mixture of 20% sesame oil and 80% benzyl benzoate (v/v). Control animals received an equivalent volume (0.10 cc) of the vehicle.

Larger rats received greater amounts of CA as indicated. Since the injection concentration was always the same, they received injections of proportionately greater volume. All injections were subcutaneous. Approximately 24 hr after the last injection the rats were sacrificed with an overdose of ether or by decapitation. At this time measurements of body length and the wet weight of various organs were obtained. In some experiments blood was collected and the plasma frozen for later corticosterone or growth hormone assay.

EXPERIMENT 1

This experiment examined the effects of CA on the growth of male rats that were castrated and received exogenous injections of testosterone propionate (TP).

Method

Twenty-one young male rats were castrated at 35 days of age and assigned to one of 3 groups of 7 rats each that were matched in terms of body weight and food intake over the last 6 pre-injection days. Group TP received 1 mg TP/day dissolved in the oil-benzyl benzoate mixture. Group TP-CA received a combination of 1 mg TP and 10 mg CA while Group V received the vehicle only. Daily measurements of food and water intake and body weight were recorded.

Results

As seen in Fig. 1, CA caused a profound reduction in the rate of body weight gain in rats given exogenous TP. Analysis of variance revealed a significant effect of injection treatment, $F(2,18) = 28.85$, $p<0.001$, and a significant treatment × blocks interaction, $F(12,108) = 28.66$, $p<0.001$. Subsequent t tests indicated that each group differed significantly from every other group.

A similar pattern of effects was seen in the food intake data. Again, analysis of variance revealed a significant main effect of injection treatment, $F(2,18) = 14.93$, $p<0.001$. Subsequent t tests indicated that Group TP-CA differed from both other groups; the difference between the TP and V groups just missed significance ($p<0.10$). There was no drug injection effect on water intake.

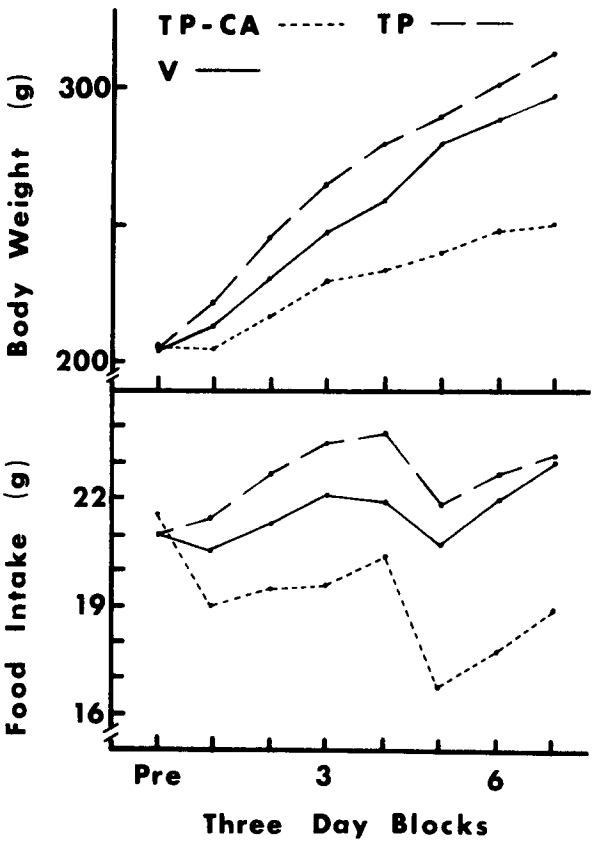

FIG. 1. Mean body weight and food intake of gonadectomized male rats that received TP, TP and CA or V in Experiment 1.

Table 1 summarizes the results of the postmortem measures. CA antagonized the action of TP on the seminal vesicles, but the inhibition as judged by this measure was incomplete, as each group differed significantly from every other group on the seminal vesicle weight measure (all $p<0.001$). Rats that received TP-CA treatment were significantly shorter than other animals ($p<0.01$). They also had heavier livers, but lighter adrenal glands than rats in the other groups ($p<0.001$). TP alone slightly increased nose-anus length, reduced adrenal weight, but did not affect liver weight. Spleens of the TP-CA group were lighter than those of the V groups but did not differ in weight from spleens of the TP group. There was no effect of the drug treatments on thyroid weight.

EXPERIMENT 2

This experiment examined the effects of CA treatment in food intake and weight gain in castrated male rats.

Method

Twenty-two male rats were castrated at 35 days of age and assigned to one of 3 groups matched in weight and food intake over the 5 days before the start of injections. Group CA received daily injections of CA (N = 7) while Group V (N = 7) received comparable injections of the

TABLE 1

MEAN ORGAN WEIGHTS AND BODY LENGTH

Group / Organ*	TP	V	TP–CA
Seminal Vesicles (mg)	233.9 ± 27.08	6.5 ± 1.92	96.3 ± 15.58
Adrenals (mg)	15.1 ± 4.82	18.7 ± 1.75	8.4 ± 1.80
Liver (g)	4.07 ± 0.31	4.02 ± 0.30	5.58 ± 0.59
Thyroid (mg)	3.77 ± 1.11	3.72 ± 0.47	4.24 ± 1.02
Spleen (mg)	238.8 ± 45.14	270.0 ± 28.92	213.7 ± 12.54
Nose-Anus Length (cm)	22.1 ± 0.52	21.7 ± 0.58	20.4 ± 0.21

*Organ Weights are expressed as mg or g/100 g Body Weight. All values are ± Se.

TABLE 2

MEAN WEIGHT GAIN, FOOD INTAKE AND ORGAN WEIGHT IN EXPERIMENT 2

Group	CA	V	NI
Weight Gain in 21 days (g)	62.3 ± 14.78	105.7 ± 11.01	104.4 ± 12.66
Daily Food Intake (g)	18.99 ± 1.28	20.44 ± 0.91	19.94 ± 1.22
Adrenal Weight* (mg)	10.19 ± 0.97	21.16 ± 2.24	18.40 ± 2.43
Liver Weight* (g)	5.258 ± 0.29	3.744 ± 0.18	3.814 ± 0.19

*Organ Weights are expressed as g or mg/100 g Body Weight. All values are ± Se.

vehicle. Since benzyl benzoate is a skin irritant, a third group (Group NI, N = 8) that was not injected was included to assess the possibility of a vehicle effect. Food intake and body weight were measured as in Experiment 1; water intake was not recorded in this or any subsequent experiment since no differences were found in Experiment 1.

Results

Table 2 summarizes the results of the experiment. Groups V and NI did not differ on any measure except adrenal weight. As might be expected, the adrenals of the vehicle group were heavier than those of non-injected animals ($p<0.05$). Otherwise, the effects of CA in young male castrates were quite similar to the effects seen in castrates receiving TP. In the present experiment CA reduced weight gain ($p<0.01$), food intake ($p<0.05$), adrenal weight ($p<0.001$), but increased liver weight ($p<0.001$).

EXPERIMENT 3

This experiment examined the effects of CA on growth in male rats that were intact, adrenalectomized, or adrenalectomized and castrated and in females.

Method

The animals were 47 male and 16 female rats obtained from the supplier at 30 days of age. Sixteen ADX males were adrenalectomized at 35 days of age while 19 ADX-GX males were adrenalectomized at 35 days of age and castrated 3 days later.

The remaining 12 males and all females were left intact, but they were food deprived at the time surgery was performed on the operated groups. Otherwise, the rats had free access to food and fluid throughout the experiment. Adrenalectomized rats were given 1% saline solution; the other animals drank tap water. Injections began at 49 days of age and continued for 17 days. It was necessary to terminate the experiment at this point because a shipment of CA was delayed. At the time of sacrifice all rats were given a 1 mA shock for 1 min. Five minutes later the rat was etherized and blood was withdrawn from the right ventricle, centri-

fuged and frozen for later corticosterone assay by the method of Murphy [10] as modified by Bowman and Deluna [2]. At this time organ weights were also obtained.

Results

Vehicle-treated rats were considered completely adrenalectomized only if they had less than 0.5 μg % of plasma corticosterone which is the sensitivity limit of the assay (R. E. Bowman, personal communication, 1973). On the basis of this criterion 2 rats were discarded from the ADX-V group and 1 from the ADX-GX-V group. Since CA depressed corticosterone levels to negligible amounts in intact males (Mean = 0.0 μg %), it was not possible to use the corticosterone criterion and all animals in the adrenalectomized groups that received CA were retained.

The results of the body weight measures are seen in Table 3. Comparable data from Experiments 1 and 2 are shown for comparison. Because body weight levels of the adrenalectomized males were significantly below those of intact controls at the start of injections, the principal dependent variable was the amount of weight gained during the injection period. As can be seen, CA reduced weight gain in intact or adrenalectomized males, but it was not effective in males that were adrenalectomized and castrated or in females. Indeed, CA reduced weight gain of all male groups to values that were not significantly different from the growth rates of females on this measure. CA produced changes in liver, spleen, and adrenal weight that were similar to those observed previously. These changes were observed in all groups including females and are therefore independent of changes in weight gain. In females CA reduced uterine weight ($p<0.01$), but did not affect ovarian weight.

TABLE 3

MEAN WEIGHT GAIN DURING 15 DAYS (g)*

Sex/Surgical Treatment	Injection Treatment	
	CA	V
M/Intact	26.2 ± 13.6 (6)	85.7 ± 5.6 (6)
M/Adx	42.0 ± 11.4 (9)	65.6 ± 12.0 (5)
M/Adx + Gx	46.0 ± 8.0 (10)	51.9 ± 18.8 (8)
M/Gx + TP (Exp. 1)	35.8 ± 9.5 (7)	91.6 ± 5.1 (7)
M/Gx (Exp. 2)	42.0 ± 11.0 (7)	75.4 ± 9.0 (7)
F/Intact	34.8 ± 6.0 (8)	32.4 ± 2.1 (8)

*All values are expressed ± Se. Numbers in parentheses are the Ns per group.

EXPERIMENT 4

The failure of CA to affect weight gain in females or in adrenalectomized and castrated males is consistent with the view advanced by Steinbeck and Neumann [16] that CA inhibits weight gain and other aspects of growth by competitively inhibiting androgens, whose facilitative action on growth is well established (see [20]). The negative findings with intact females, while consistent with this view, are amenable to another interpretation. CA is a powerful progestrogen and progesterone is known to increase body weight in intact females [7,13]. The failure of CA to affect weight gain in females might therefore have arisen because of cancelling effects of the drug on weight gain. To test this possibility, the effects of CA on growth of ovariectomized females was studied, since it is known that progesterone does not alter the weight gain that follows ovariectomy [7, 13, 24].

Method

Forty-one retired breeder females that weighed 300–400 g at the start of the experiment were divided into 4 groups: CA Control (N = 10), CA Ovariectomy (N = 11), Vehicle Control (N = 9), Vehicle Ovariectomy (N = 11). About half the controls were sham-operated; the others were merely anesthetized. All of the rats had received active avoidance training about 1 mo before the present experiment.

All animals were fed Lab Chow pellets and water ad lib. Baseline body weights were established for 8 days preoperatively; injections began on the 6th postoperative day and continued for 21 days. CA animals received 15 mg/day subcutaneously while controls were injected with a like volume (0.15 cc) of the vehicle.

Results

As seen in Fig. 2, CA reduced the rate of weight gain following ovariectomy, although the inhibition was not complete. Thus, ovariectomized CA-treated females gained more weight than either intact group, but less than the ovariectomized vehicle group. CA again failed to affect weight of intact females, extending the earlier observation to older females whose weight levels were stable over the treatment period.

CA produced similar changes in liver and adrenal weight in both intact and ovariectomized females that were comparable to those observed previously. CA reduced uterine weight of intact females, but caused a moderate increase in the weight of the uterus of OVX rats.

EXPERIMENT 5

Recently, Lakshman and Isaac [8] reported that CA injections reduced the number of alpha acidophils in the anterior pituitary. This finding raised the possibility that CA might reduce growth by inhibiting the production or release of GH. The present experiment examined body weight and food intake changes following CA treatment in old male rats that had achieved stable pretreatment body weight levels. Pituitary and plasma GH levels were also measured.

Method

Fourteen retired breeder males were divided equally into CA or Vehicle groups so that preoperative weight and food intake were well matched. When body weights were stable for all rats, the animals received 21 daily injections of CA

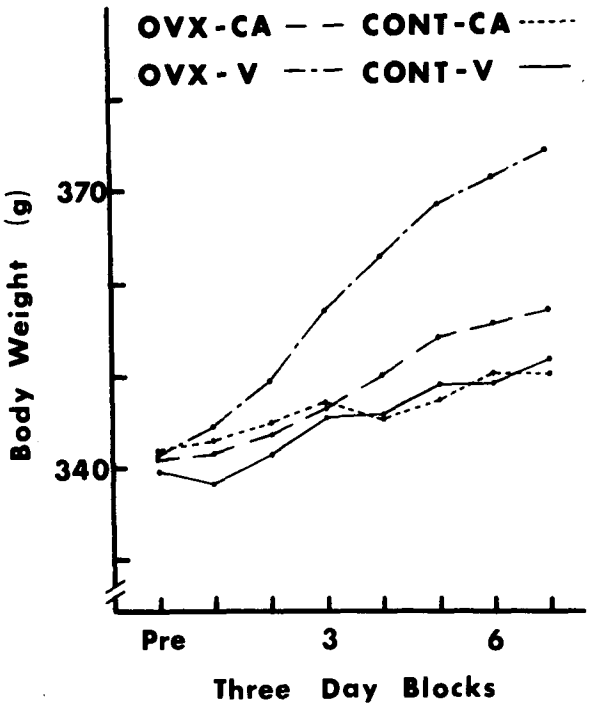

FIG. 2. Mean body weight of ovariectomized or control females that received CA or V in Experiment 4.

(20 mg/day) or an equal volume of vehicle (0.20 cc). Approximately 24 hr after the last injection the animals were killed by decapitation. At the time of sacrifice heparinized plasma and pituitaries were obtained and frozen for GH assay by the double antibody radio-immunoassay method [6]. Other organs were weighed as described before.

Results

As seen in Fig. 3, CA caused changes in food intake and body weight in these old males that were similar to those observed earlier in younger males. In the present experiment weight levels of the vehicle controls remained fairly constant while the CA group steadily lost weight throughout the treatment period. The weight loss was paralleled by a significant reduction in food intake in the CA group. Despite these changes in feeding and body weight, we were unable to demonstrate significant changes in either pituitary or plasma GH levels resulting from CA treatment (see Table 4). There was also no effect of CA on pituitary weight, but the usual effects on liver, adrenal, and seminal vesicle weight were obtained.

EXPERIMENT 6

In this experiment we attempted to prevent the reduction in weight gain, food intake and linear growth following CA with exogenous injections of GH.

Method

Seventeen young male rats were divided into 3 groups: Group GH-CA (N = 6) received daily injections of bovine growth hormone (NIH-GH-B17, 1 mg/day) and CA

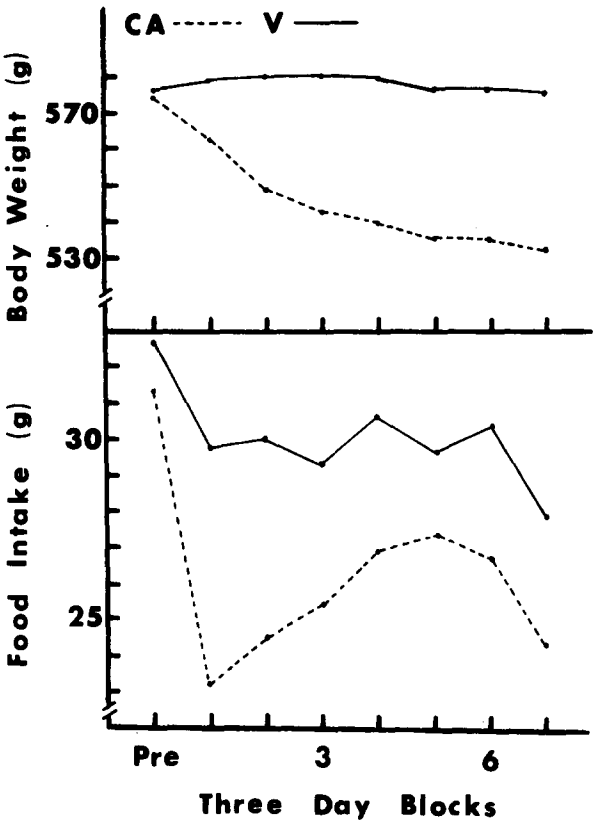

FIG. 3. Mean body weight and food intake of intact male rats that received CA or V in Experiment 5.

TABLE 4

MEAN GH LEVELS IN EXPERIMENT 5*

Group	Pituitary GH Content (μg)	Pituitary GH Concentration (μg/mg)	Plasma GH (ng/ml)
CA	284 ± 21	21.5 ± 2.1	90 ± 40
V	352 ± 32	27.0 ± 3.5	32 ± 13

*Values are expressed as mean ± Se.

(10 mg/day); Group HOH-CA (N = 6) received daily injections of the GH vehicle (0.30 cc water for injection) and CA (10 mg/day); Group GH-V received daily injections of GH (1 mg/day) and of the CA vehicle (0.10 cc/day of benzyl benzoate-oil). Injections began at 49 days of age and continued for 21 days; body length was measured 1 day before the start of injections and at sacrifice.

Results

Growth hormone injections failed to remedy the de-

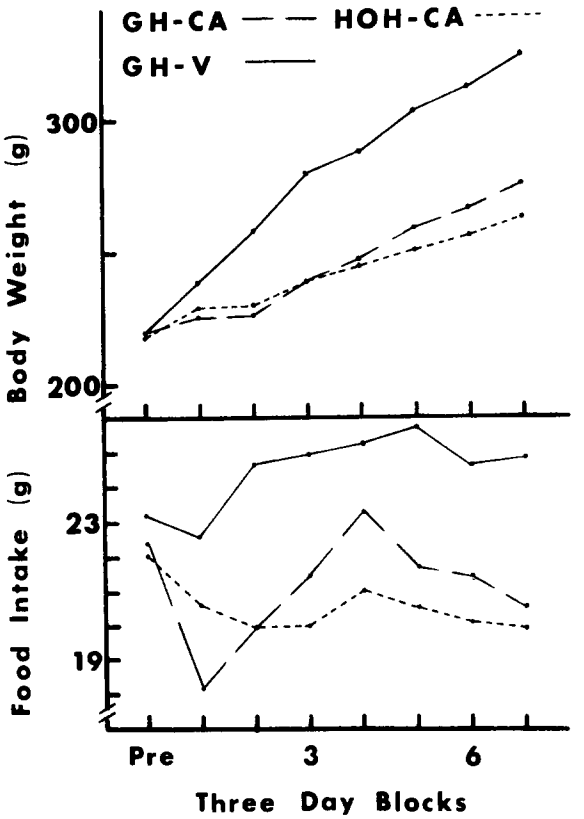

FIG. 4. Mean body weight and food intake of intact male rats that received GH and V, GH and CA or water (HOH) and CA in Experiment 6.

pressed rate of body weight gain or food intake that resulted from CA treatment (see Fig. 4). Group GH-V grew at rates similar to intact animals in previous studies, but faster than animals that received CA regardless of whether or not they also received GH injections. GH also failed to repair the depressed rate of linear growth or affect any of the changes in organ weights following CA treatment.

EXPERIMENT 7a

Previous studies demonstrated that CA reduces food intake and body weight. The next two experiments sought to determine whether the reduction in feeding could completely account for the changes in body weight.

Method

Sixteen male rats that weighed 325–450 g at the start of the experiment were equally divided into CA and V groups so that the pretreatment weights of the groups were matched. After baseline weights were established the rats were deprived of both food and water for 48 hr. During this time they received 2 daily injections of either CA (15 mg/day) or vehicle (0.15 cc) spaced 24 hr apart. Following this treatment the rats were returned to ad lib feeding and watering. Body weights were recorded daily for the next 30 days, but no injections were given.

Results

During the 2-day deprivation period CA-treated rats lost weight more rapidly than controls (Mean = 66.3 g for CA vs 55.4 g for controls, U = 1, $p<0.01$). CA rats also recovered body weight more slowly than controls, when free access to food and water was restored. Controls regained pretreatment weight levels in an average of 2.0 days, while CA rats required a mean of 8.8 days to reach their preinjection baseline (U = 0, $p<0.01$). Controls continued to gain weight more rapidly than CA-treated rats for the first two weeks after termination of injection and the difference in body weight between the groups reached a maximum of 33.6 g on post-injection days 7–9. Thereafter, CA animals grew more rapidly than controls and the difference in weight was only 10 g by the end of the experiment.

EXPERIMENT 7b

The previous experiment suggested that reduced food intake could not account entirely for the reduced rate of weight gain following CA treatment. The present experiment confirmed this suggestion by demonstrating that CA-treated rats gain weight more slowly than pair-fed controls.

Method

Twenty-one male rats were assigned to one of 3 treatment groups of 7 rats each. Group CA was fed ad lib and injected daily with 10 mg of CA. Group Val was fed ad lib and injected daily with an equivalent volume of vehicle (0.10 cc). Group Vpf were matched in weight and food intake to individual rats in the CA group on the basis of measurements collected for 3 days before the start of injections. During the 21 day injection period rats in Group Vpf were fed an amount equal to that consumed by their paired mate in the CA group on the previous day. For the CA group and half of the Val group injections began at 49 days of age; for the remaining rats, injections began at 50 days of age. Water was freely available at all times. At the conclusion of the experiment the animals were sacrificed by decapitation. Blood plasma and pituitaries were prepared for GH assay as described above. Organ weights were also obtained.

Results

As seen in Fig. 5, rats given CA treatment gained weight more slowly than animals in both vehicle groups. Each of the rats in Group Vpf gained more weight during the 21 day injection period than its CA paired mate, demonstrating that the reduced food intake following CA injections does not explain entirely the reduced weight gain following CA treatment, although obviously it is a contributing factor. CA treatment significantly reduced food intake (compared to vehicle controls fed ad lib) ($p<0.05$), replicating earlier results. Again, CA failed to affect pituitary or plasma GH levels (Table 5). The usual effects of CA on liver and adrenal weight were observed.

GENERAL DISCUSSION

The present findings confirm earlier work [15, 16, 23] showing that CA treatment reduces both ponderal and linear growth rate in young male rats and depresses adrenal weight and blood corticosterone levels [3]. In older male

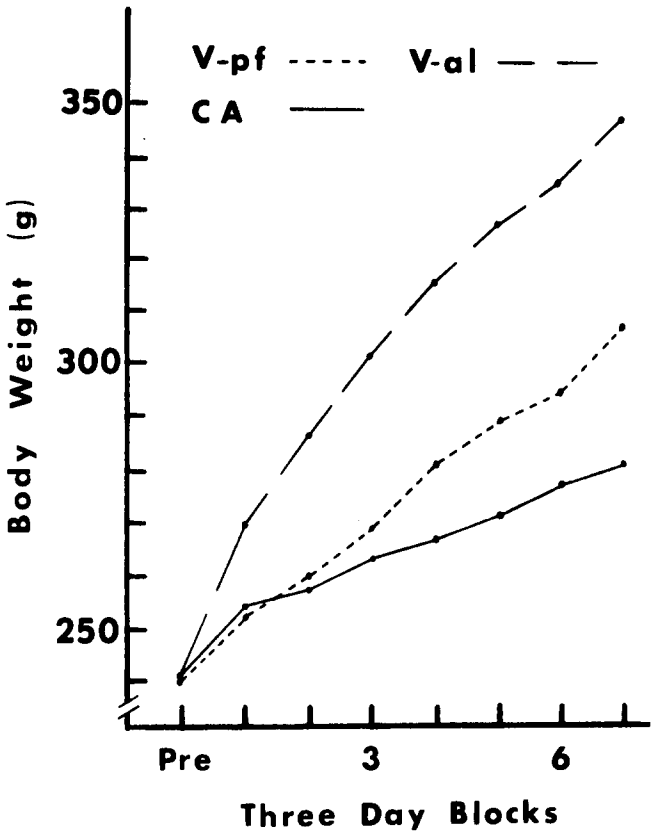

FIG. 5. Mean body weight of intact male rats that received CA or V in Experiment 7b. Group Val had unrestricted access to food. Group Vpf were pair-fed and given only as much food as their matched mates in Group CA.

TABLE 5

MEAN GH LEVELS IN EXPERIMENT 7b*

Group	Pituitary GH Content (μg)	Pituitary GH Concentration (μg/mg)	Plasma GH (ng/ml)
CA	500.4 ± 130.5	56.7 ± 14.9	48 ± 21
Val	643.7 ± 68.7	65.2 ± 6.3	95 ± 34
Vpf	594.1 ± 107.5	66.7 ± 11.4	103 ± 38

*Values are expressed as mean ± Se.

rats that were no longer gaining weight, CA treatment produced weight loss. Regardless of the age of the animals CA treatment caused a slight reduction in the food intake of male rats, but two lines of evidence indicate that reduced food intake is only a partial explanation of the retarded growth rate. First, rats without access to food or water lost greater amounts of weight when given CA than did comparable vehicle-injected controls. Second, vehicle-treated controls whose food intake was restricted to the level of rats injected with CA gained weight more rapidly than the CA-treated animals.

These observations suggest that CA interferes with some other factor related to growth or energy balance, but the identity of this factor remains obscure at present. An alteration in activity seems unlikely in view of the work of Stern and Murphy [17] who failed to find an effect of CA on androgen-dependent running wheel activity. Reduced growth hormone output could account for the impairments in growth we have observed as well as for the findings of Lakshman and Isaac [8] who reported that CA reduces the number of alpha acidophils in the anterior pituitary, but in two different experiments we were unable to find evidence of significant reductions in pituitary or plasma GH levels. Moreover, treatment with bovine GH was not effective in preventing reductions in ponderal or linear growth or food intake that accompany CA treatment. It has been shown that CA inhibits bone growth and maturation [15], which may partially explain its depressing effect on ponderal and linear growth. However, it is not clear to what extent the effects of CA on bone growth are related to its effects on food intake.

Steinbeck and Neumann [16] suggested that the effects of CA on growth could in part be accounted for by its action as an antianabolic agent, a property which is consistent with its capacity to competitively inhibit endogenous androgens. By-and-large, the present data are amenable to such an interpretation. We observed that CA treatment was effective in reducing the rate of body weight gain in intact males, castrated males, adrenalectomized males, and in castrated males that received exogenous TP, but CA did not reduce weight gain in males that were both gonadectomized and adrenalectomized. Moreover, the rate of weight gain of CA-treated animals was relatively independent of their endocrine status and approximated that of males which were both adrenalectomized and castrated. Further, CA had no effect on body weight in young or old intact females. These observations are all consistent with Steinbeck and Neumann's hypothesis, but the finding that CA reduced, but did not eliminate, weight gain following ovariectomy raises certain difficulties. One interpretation of this latter finding is that in intact females, CA has two equal but opposite effects on body weight: a weight-depressing action which is cancelled by a weight-promoting influence which arises from its progestational properties. Since progesterone has little or no weight-increasing effect in the ovariectomized rat, the weight-depressing influence of CA is primarily expressed in this preparation. This analysis is not necessarily inconsistent with Steinbeck and Neumann's proposal, but since it does not depend on the anti-androgenic properties of CA, it raises the possibility of a different mechanism to account for the weight-inhibiting effects of CA. While this may indeed be the case, recent work by Mook and his colleagues offers the possibility of incorporating our observations on the effects of CA on growth in ovariectomized females within the framework of a mechanism which accounts for growth inhibition by CA principally in terms of its anti-androgenic action and which is otherwise supported by our data. Mook and his colleagues [9] have observed that the weight gain that normally follows ovariectomy can be prevented or arrested and reversed by adrenalectomy. Thus, the integrity of the adrenals is essential to the increased eating and growth that

accompany ovariectomy. While it is not yet clear which of the many adrenal hormones contribute to the increase in growth that follows ovariectomy, recent work indicates that corticosterone, the principal glucocorticoid in the rat, is capable of restoring growth in ovariectomized-adrenalectomized female rats [19]. The present data, as well as earlier work [3], clearly demonstrate that CA causes marked inhibition of corticosterone output. This depression of adrenocortical function most likely results from a direct inhibition of ACTH output by CA [4]. Thus, it is reasonable to suspect that both androgenic antagonism and inhibition of adrenocortical function contribute to the depressed growth following CA treatment.

At the same time it is possible to argue that CA is acting like a weak estrogen, and indeed, nearly all of the effects on feeding and growth that we have observed following CA treatment also result from estrogen injections [20]. We prefer the interpretation outlined above because it is consistent with the actions of CA which have been most directly demonstrated. However, the present data certainly are compatible with an estrogenic hypothesis and such an interpretation should not be dismissed prematurely.

Clearly hormone antagonists such as CA have complex actions which vary in their importance depending upon the behavioral or physiological response being studied. Labelling such agents anti-androgens can sometimes be quite misleading.

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