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Continuous Infusion of Aldosterone: Correlates of Body Weight Gain[1]

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DEVENPORT, L. D., K. G. GOODWIN AND P. M. HOPKINS. *Continuous infusion of aldosterone: Correlates of body weight gain.* PHARMACOL BIOCHEM BEHAV 22(5) 707–709, 1985.—Aldosterone stimulated body weight gain in adrenalectomized male rats across all but the highest of seven doses delivered by continuous infusion. Gains were especially strong in the latter part of the 12-day infusion period peaking at values twice those of adrenalectomized rats given only glucocorticoid replacement or sham infusions. The gains were not related to skeletal growth, and hematocrit and percent tissue water were only modestly and inversely related to weight gain (rs=−.24). In contrast, epididymal fat pad mass correlated strongly (r=.72), indicating that the gains were partly or wholly attributal to adipose tissue hypertrophy.

Aldosterone Corticosterone Body fat Dose-response Body water Skeletal growth

MINERALOCORTICOIDS (mCORTs) possess actions that are distinctly different from their influence on sodium and potassium [2]. Aldosterone (Aldo) and deoxycorticosterone (DOC) stimulate feeding and weight gain, and the effect is not exclusively or even primarily behavioral: Weights rise at an accelerated rate even when intake is strictly controlled [4,5]. Similar in many respects to the changes that follow ovariectomy [10], we have shown that the actions of mCORTs are nevertheless independent of estrogen and progesterone [4]. Likewise, mCORTs act independently of glucocorticoids (gCORTs) [2]. Apart from this, little is known concerning the nature of the weight gain instigated by mCORTs.

The present work extends the investigation of mCORT to male rats, ascribes much of the gain to adipose tissue, and describes the day by day Aldo dose effects using continuous infusion devices.

METHOD

Male albino rats (Sprague-Dawley derived) reared in our colony were adrenalectomized and implanted with continuous infusion devices at age 44 days (mean±SEM body weight=190±2.82). This involved pretreatment with atropine sulfate (2 mg/kg, IP) followed by ether anesthesia. Bilateral dorsolateral incisions of about 1 cm in length permitted complete removal of the adrenal glands. The body wall was closed with surgical gut and the skin reunited with wound clips. From a single small incision located anterodorsally, a subcutaneous pocket was prepared by blunt dissection. This nuchal pocket received the hormone infusion device ("mini-pump," model 2002, Alza Corp. sterilized with 70% ethanol) and was closed with a single wound clip. The mini-pumps were coded by number and the rats were ear-punched. In this way the assignment of each animal was concealed so that measurements could be taken without bias.

The mini-pumps delivered about 11 μl/24 hr vehicle for the duration of the experiment. They were filled with a sterile (heated to 100°C for 4 min) solution of corticosterone (Cort) dissolved in polyethelene glycol. Corticosterone dose was set at 500 μg/24 hr (about 2 mg/kg), a dose that was close to the maximum concentration soluble in the vehicle. Added to this constant gCORT replacement regimen were concentrations of Aldo adjusted to doses of 15.6 (n=10), 31.2 (n=8), 45 (n=7), 62.5 (n=7), 93.7 (n=7), 125 (n=7), or 250 (n=7) μg infused over a 24 hr period. (These doses ranged from approximately 62.5–1000 μg/kg body weight/day). Other groups of rats (ns=11) were infused with Cort-only or were implanted with blank pumps, and thus received no steroid replacement whatsoever.

Following adrenalectomy (ADX) and pump implantation the rats were housed in pairs in heated recovery units for 24 hr. Food and water were freely available. The next day the animals were reweighed (providing the baseline body weight measurement) and housed in individual hanging steel cages with continuous supplies of saline (2% NaCl, w/v) and tap water. Purina rodent chow (Formula 5008) was always available and was supplied fresh every other day when body weights were regularly determined. This routine lasted 12 days. The autopsy which followed involved a final body weight determination, recording of body length (nose-anus), and a thorough visual inspection for adrenal regeneration. Evidence of regeneration led to elimination of the subject from the study. Also eliminated were rats whose pump reservoirs upon inspection, indicated a delivery failure. Duplicate hematocrit samples were centrifuged, and diaphragm tissue (about 45 mg) was removed, blotted, and weighed to

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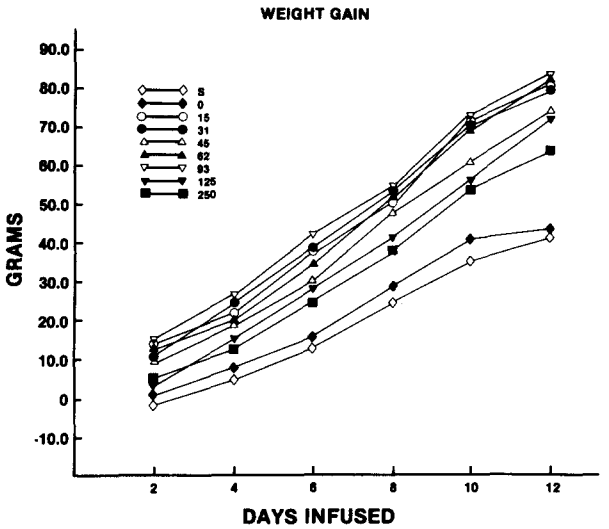

FIG. 1. Mean body weight gains during the 12 days of aldosterone infusion at the doses (in μg/24 hr) indicated; O=no aldosterone (corticosterone-only), S=sham pump (adrenalectomy-only, no infusion).

the nearest 0.1 mg on an analytical balance. After 72 hr desiccation in a convection oven, the dry weight of this muscle was recorded. The epididymal fat pads were also removed bilaterally, blotted, and weighed together.

RESULTS AND DISCUSSION

Figure 1 illustrates the cumulative body weight gains observed across the 12 experimental days. Aldo boosted weights generally, $F(8,66)=4.82$, $p<0.001$, and became increasingly effective across successive days, $F(40,330)=2.92$, $p<0.001$, relative to the control groups. As a whole, the Aldo-infused rats displayed an unabating increase in body weight, while Cort-only and ADX-only groups slowed with the passage of time. These latter groups did not differ from each other, $t(20)=0.10$, $p>0.05$. Only one other dose effect was observed, and that concerned the highest dose which was less effective than the others. While elevated, it did not differ significantly from the Cort-only dose, $t(16)=1.75$, $p>0.05$. All other doses significantly accelerated gains beyond the Cort-only group, $ps<0.02$–0.001. Skeletal growth, as represented by body length, was unaffected by the steroid treatment, $F(8,66)=1.36$, $p>0.05$.

Of the weight gain correlates depicted in Fig. 2, only one, fat pad mass, served to account for the effects of Aldo. Animals that gained the most weight possessed the heaviest fat pads. Hematocrit held a slightly positive relationship with body weight that suggested a modest trend toward increased expansion of the extracellular fluid space (ECF) in heavier animals. This was not unexpected in view of Aldo's well known promotion of sodium retention. That the effect is so small, especially at the highest dose, indicates the possible operation of a renal "escape" response [1]. In any event, the effect on body weight was negligible, amounting to no more than 0.75 ml between the most extreme groups (based on regression equations given by Kutscher [6]). An association of identical strength but of negative value was observed for percent tissue water. Thus, in terms of the intracellular compartment (ICF), the heavier animals were mildly dehydrated. Moreover, as the ICF is the larger of the fluid compartments,

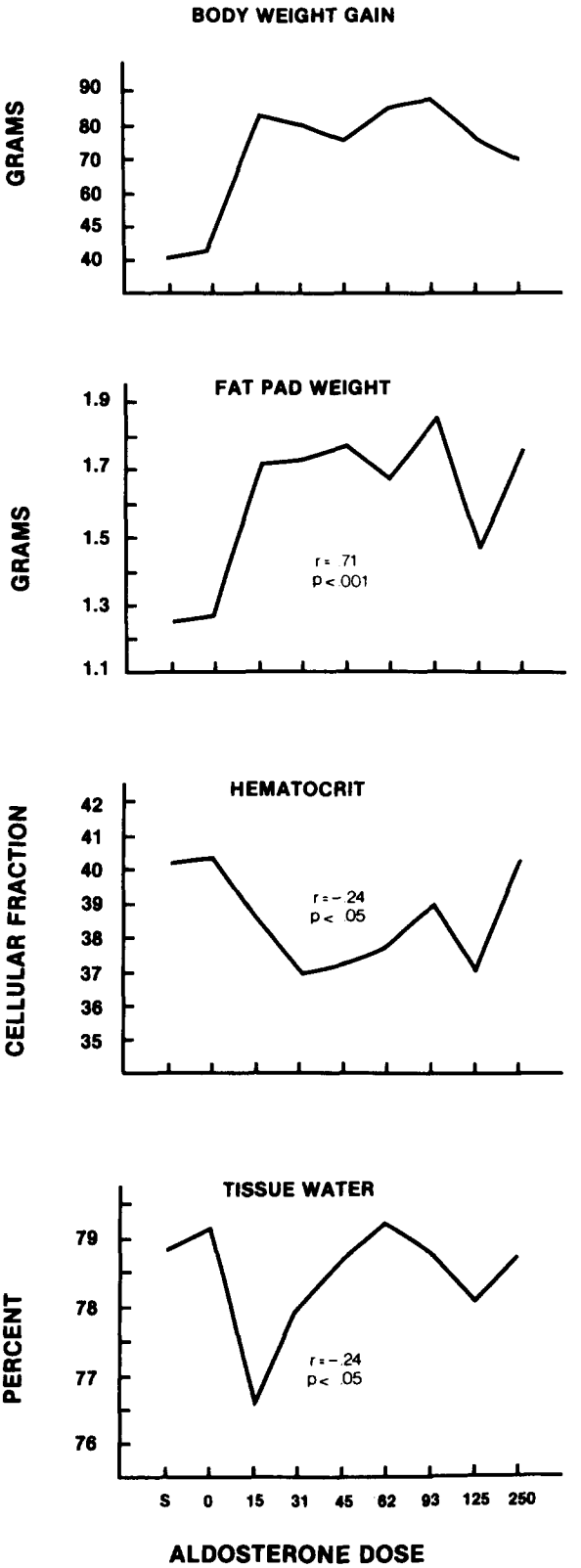

FIG. 2. Mean body weight gain, epididymal fat pad mass, hematocrit, and percent diaphragm water content at autopsy (infusion day 12) for each aldosterone dose. Correlations (Pearson coefficients) with body weight and two-tailed probability values are indicated. Abbreviations as in Fig. 1.

and as the diaphragm tissue sample reflects the combined percent water in both ICF and ECF spaces, hydrational differences can confidently be eliminated as contributing to the Aldo-stimulated weight gain. Gains occurred in spite of a slight overall water loss.

Aldosterone stimulates weight gain across a surprisingly broad range. The relatively flat dose-response curve suggests that we have not yet found the lower limits of Aldo's effectiveness. On the other hand, these results may reflect a "permissive" action of Aldo that requires only a minimal presence of the hormone for its effect to appear. Although nothing can be said with certainty without serum Aldo assays, we can at least conclude that the Aldo effect is obtained at low near-physiological doses. Indeed, the effect is not obtained with very high doses.

Chronic infusion does not diminish Aldo's potency. On the contrary, gains become more, not less, pronounced with successive days. Whether this result springs from some cumulative effect of continued hormone exposure or simply maturational changes that render the animal more responsive to the steroid remains to be seen. In any case, the results with males compare favorably with female rats [2, 4, 5] and imply that the Aldo effect is not sex-dimorphic. And as we have observed previously with females, the weight gain cannot be accounted for in terms of volume expansion owing to water retention. Similarly, skeletal growth is not stimulated or retarded by Aldo.

A strong association was found for weight gain and fat pad mass. While the epididymal fat pads cannot stand for all body fat depots, an increase in overall adiposity now becomes a likely explanation for the effect of Aldo. Carcass composition studies presently underway will settle this matter and further determine if protein anabolism was promoted by Aldo as well.

It might be thought that one account of the Aldo effect has been overlooked. This involves the possibility of a general improvement in health conferred by Aldo replacement. A similar interpretation has been put forth for the feeding and weight gain stimulated by progesterone in ADX subjects [9]. There are three reasons why this explanation is not tenable in the present case. First, a source of sodium was continuously available. We have previously shown [5] that saline is avidly consumed by ADX rats that receive no Aldo replacement, assuring that they and the present subjects were replete in sodium. (This precaution alone eliminated the progesterone effect mentioned above [9].) Moreover, all animals, except for the ADX-only group, were continuously infused with Cort, which provided for the calorigenic and other glucocorticoid actions that were lost with adrenalectomy. Finally, and most convincing to us is the result of a recent terminal deprivation study [3]. Aldosterone-infused rats were dramatically intolerant to starvation. Their endurance was only about half as long as ADX-only, ADX + Cort, or sham-operated rats. This is not an indication of good health. Rather, it was an inability to lose weight that was the major impairment. Accordingly, we think that Aldo may accelerate the deposition of ingested calories as fat and inhibit their mobilization even under the severe condition of starvation. This, rather than nonspecific health factors would account for ADX-induced weight gain as well as its lethality in the face of starvation.

In many respects a dual role for Aldo in mineral and energy metabolism may seem incongruous. However, both are anabolic or retentive functions. In most instances, the simultaneous conservation of calories and sodium is physiologically appropriate. One case has already been reported in the literature: repeated food deprivation has been found to elevate Aldo titers between successive episodes of privation [11]. This serves to expand ECF [11] and might augment fat stores, both of which are challenged by food deprivation. Whatever future research holds for Aldo this much at least seems clear: the weight loss that is known to accompany adrenalectomy [7], and that cannot be restored by gCORT replacement [8] may now be firmly ascribed to mCORTs.

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