Differential regulation of adrenal corticosteroids after restriction-induced drinking in rats

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Wotus, Cheryl, and William C. Engeland. Differential regulation of adrenal corticosteroids after restriction-induced drinking in rats. Am J Physiol Regul Integr Comp Physiol 284: R183–R191, 2003. First published October 3, 2002; 10.1152/ajpregu.00027.2002.—Water-restricted rats exhibit a rapid decrease in plasma corticosterone after drinking. The present study examined the effect of restriction-induced drinking on plasma aldosterone and plasma clearance of corticosterone. Rats were water restricted for 6–7 days and then killed before or 15 min after water administration; plasma and adrenal hormones were assayed. Plasma and adrenal corticosterone decreased after drinking without a change in plasma corticosteroid-binding globulin; plasma ACTH decreased or did not change. In contrast, plasma aldosterone did not change or increased after drinking; plasma renin activity was elevated by water restriction and increased further after drinking. In another experiment, rats were adrenalectomized, and corticosterone and aldosterone were replaced with pellets and osmotic minipumps, respectively. Rats were water restricted and killed. There was a small decrease in plasma corticosterone but no change in aldosterone after drinking in adrenalectomized animals. These data suggest that changes in plasma steroids after restriction-induced drinking result from zone-specific responses of the adrenal to known secretagogues, with minimal contribution from increased plasma clearance.

corticosterone; aldosterone; corticosteroid-binding globulin; steroid clearance; dehydration

THE RAT ADRENAL CORTEX is divided into two morphologically and functionally distinguishable steroidogenic zones. The inner zona fasciculata/reticularis produces corticosterone in response to its primary secretagogue, ACTH, which is released from the anterior pituitary. The outer zona glomerulosa produces the mineralocorticoid aldosterone in response to multiple factors, including ANG II, an end product of the renin-angiotensin system. Increased secretion of corticosterone and aldosterone represents a homeostatic response to stressful stimuli. In contrast to the response following stress, a marked reduction in plasma and adrenal corticosterone is observed immediately after water is presented to rats restricted to a limited amount of water each day (8, 18, 24, 31, 40). Although evidence suggests that this rapid decline in corticosterone may occur though mechanisms acting at the level of the adrenal cortex (8, 40), it is not known whether restriction-induced drinking affects aldosterone in a similar manner. Previous studies have shown increases in plasma aldosterone after deprivation-induced drinking in dogs (37) and sheep (3), whereas there were no changes in plasma aldosterone after drinking in dehydrated humans (15). However, rapid changes in corticosterone and aldosterone after drinking have not been investigated concurrently in the same animal model of dehydration. Moreover, there are inconsistencies concerning the effect of dehydration alone on aldosterone secretion in the rat (2, 11, 14, 19, 23, 26); therefore, predicting the outcome of restriction-induced drinking on aldosterone secretion in the rat, on the basis of studies in other species, is problematic.

It has also been suggested that the decrease in plasma corticosterone after restriction-induced drinking can be attributed, in part, to an increase in plasma clearance. The plasma half-life of corticosterone is ~20 min in rats (16); yet plasma corticosterone decreases by >50% within 10 min of restriction-induced drinking (18, 24, 40). An increase in plasma clearance, due to an increase in hepatic metabolism and/or a redistribution of corticosterone from the plasma into the extravascular space, could contribute to the rapid decline in plasma concentrations after drinking. In vitro bioasays have shown a small, but significant, increase in corticosterone metabolism by liver tissue from restricted animals after drinking (8); however, it has not been determined whether this increase in hepatic corticosterone metabolism after drinking can account for the decrease in corticosterone observed in vivo. Because the peripheral metabolism of corticosterone and aldosterone occurs through similar pathways (see Ref. 10 for review), it might be expected that increases in hepatic metabolism would result in parallel changes in both adrenal hormones. However, because the affinity for plasma binding proteins is lower for aldosterone than for corticosterone (6, 9), differential plasma clearance of these hormones could occur, through metabolism or redistribution, if changes in plasma binding proteins are induced by drinking.

The goal of the present study was to determine whether the mechanisms leading to the decrease in cor-
ticosterone after restriction-induced drinking are specific to the production of corticosterone or whether they also affect the production of aldosterone. Corticosteroid-binding globulin (CBG) was also measured before and after drinking to determine whether changes occur that could contribute to differential clearance of corticosterone and aldosterone. To further investigate whether plasma clearance contributes to changes in plasma steroids after drinking, adrenalectomies were performed and corticosterone and aldosterone were replaced with pellets and osmotic minipumps, respectively, before animals were placed on a water restriction schedule. Plasma steroid concentrations were then evaluated before and after restriction-induced drinking.

MATERIALS AND METHODS

Materials

The following supplies and chemicals were purchased: corticosterone RIA kits from ICN Biochemical (Costa Mesa, CA); aldosterone RIA kits from Diagnostic Products (Los Angeles, CA); \(^{125}\)I-labeled ACTH from Diantor (Stillwater, MN); ANG I RIA kits from NEN Life Sciences Products (Boston, MA); \(^{3}\)H-labeled corticosterone from Perkin Elmer (Boston, MA); corticosterone from Roussel Uclaf (Romainville, France); charcoal, dextran, gelatin, cholesterol, and propylene glycol from Sigma Chemical (St. Louis, MO); aldosterone from Steraloids (Newport, RI); and Alzet osmotic minipumps (0.5 μl/h, 14 days) from Alza (Palo Alto, CA).

Animals

Male Sprague-Dawley rats (Charles River, Wilmington, MA) weighing 175—200 g were housed two per cage under a 12:12-h light-dark cycle (lights on 0600—1800); food and water were available ad libitum before initiation of the water restriction schedule. Experiments were initiated 2—3 days after arrival. Animals were maintained and cared for in accordance with National Institutes of Health guidelines. Experimental procedures were approved by the University of Minnesota Animal Care Committee.

Experimental Protocols

Experiment 1. To determine the effect of restriction-induced drinking on plasma aldosterone, rats (n = 6/group) received water each day for 30 min beginning at 1730 (water restricted; WR) or ad libitum (AL); both groups had access to food at all times. After 7 days, rats were killed by decapitation in the afternoon (Post), water was presented to the WR group. Trunk blood was collected for assay of plasma hormones and measurement of CBG by a binding assay; in addition, plasma osmolality was measured by vapor pressure osmometry. Adrenals were collected for assay of corticosterone content as described for experiment 1.

Experiment 2. To determine whether changes in adrenal steroids after restriction-induced drinking, rats (n = 6 in each group in each experiment) were anesthetized with pentobarbital sodium (65 mg/kg) and underwent sham (Sham) or bilateral adrenalectomy (ADX) by the dorsal approach. Sham animals were implanted subcutaneously with 100-mg cholesterol pellets and osmotic minipumps containing propylene glycol; ADX animals received 100-mg corticosterone pellets (in cholesterol, wt/wt) (1) and osmotic minipumps containing aldosterone (in propylene glycol) (30, 33, 38). Experiment 3 was repeated three times as follows: 25% corticosterone and 16 μg/day aldosterone (treatment I), 50% corticosterone and 5.3 μg/day aldosterone (treatment II), and 75% corticosterone and 2.7 μg/day aldosterone (treatment III). Rats were allowed to recover for 3—4 days after surgery and placed on the afternoon water restriction schedule as described in experiment 1. After 6 days, rats were killed by decapitation in the afternoon, before or 15 min after water was presented to the WR group. Trunk blood was collected for assay of plasma hormones as described above. Thymuses were removed, cleaned, and weighed.

Analytic Methods

RIA. Plasma ACTH was determined by RIA as described previously (20). Adrenals were homogenized in 20% ethanol in saline and then centrifuged at 1,200 g for 5 min. Supernatants were assayed for corticosterone; aldosterone in supernatants could not be measured because of nonspecific interference in the RIA. Plasma and adrenal corticosterone and plasma aldosterone and PRA levels were determined by RIA kits. The interassay coefficients of variation for corticosterone, aldosterone, and ANG I were 13.3, 21.8, and 6.28%, respectively. Steroid content was expressed relative to adrenal weight.

CBG assay. CBG assay was performed as described by Marti et al. (27) with a few modifications. Briefly, plasma samples (40 μl) were stripped of endogenous corticosterone by incubation with a dextran-coated charcoal solution (2 ml) consisting of 1% dextran T70 and 1% charcoal in phosphate-gelatin buffer (PGB: 0.01 M PBS with 0.1% gelatin, pH 8.2) for 30 min at room temperature with constant shaking. Tubes were then centrifuged for 15 min at 4°C, and the supernatants were diluted with PGB (1:2) for use in the binding assay. Total binding was determined by incubating diluted stripped plasma (200 μl) with \(^{3}\)H)corticosterone (20 nM in PGB, specific activity 70 Ci/mmol) in a final volume of 500 μl for 30 min at 37°C and then for 15 min at 4°C. Cold dextran-coated charcoal (500 μl) was added, and after 10 min, tubes were centrifuged for 15 min at 4°C. Supernatants were added to scintillation fluid and counted in a beta counter. Nonspecific binding was determined by adding corticosterone (20 μM in PGB) to a separate set of tubes for each sample; specific binding was calculated by subtracting nonspecific binding from total binding.

Statistical analysis. Data are presented as means ± SE. Before analysis, nonhomogeneous data were subjected to
logarithmic or square-root transformation. Differences in body weights and water intake from experiment 1 were assessed by one-way ANOVA with repeated measures; body weights from experiment 3 were assessed by two-way ANOVA. Differences in hormone and CBG concentrations and in thymus weights were also assessed by two-way ANOVA. When ANOVA showed a significant difference within an experiment, Fisher’s post hoc analysis was used to determine differences between groups. Differences were considered statistically significant when the test yielded $P < 0.05$.

**RESULTS**

**Experiment 1**

WR rats ($n = 2$/cage) increased their daily water intake over the 6-day experimental period; however, the amount consumed in 30 min was ~42% less than that consumed by AL controls (Table 1). Whereas AL rats gained weight over the course of the experiment, WR rats lost weight over the first 4 days of water restriction. Over the last 3 days of the experiment, body weights of WR rats increased but remained significantly lower than those of AL rats.

Water restriction for 7 days resulted in an increased hematocrit in WR rats compared with AL controls (Fig. 1A). Although there was no significant decrease in hematocrit after restriction-induced drinking (WR-Pre vs. WR-Post), values were not different between WR-Post animals and either AL-Pre or AL-Post controls.

Water restriction alone had no effect on plasma ACTH or corticosterone (WR-Pre vs. AL-Pre, Fig. 2, A and B). Plasma ACTH and corticosterone were increased in AL rats 15 min after water was presented to WR rats, likely because of an increase in activity in the animal room at the time of death. In contrast, plasma ACTH and corticosterone were significantly decreased in WR rats 15 min after restriction-induced drinking. Adrenal corticosterone content was decreased by water restriction alone (WR-Pre vs. AL-Pre) and, similar to plasma ACTH and corticosterone, was lowered further by restriction-induced drinking (Fig. 2C).

PRA was elevated by water restriction alone (WR-Pre vs. AL-Pre) and was increased further by drinking (Fig. 2D). Plasma aldosterone was not different between any groups (Fig. 2E).

**Experiment 2**

Plasma osmolality was elevated by 6 days of water restriction and was reduced back to control levels 15 min after restriction-induced drinking (Fig. 1B).

As in experiment 1, water restriction alone had no effect on plasma ACTH or corticosterone (WR-Pre vs. AL-Pre, Fig. 3, A and B). Also, plasma and adrenal corticosterone were significantly decreased in WR rats after restriction-induced drinking. However, unlike ex-

**Table 1. Water intake and body weights of control and water-restricted rats: experiment 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Day of Restriction</th>
<th>Water intake, ml/cage</th>
<th>Body weight, g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>AL</td>
<td>78 ± 1.2</td>
<td>82 ± 2.1</td>
<td>83 ± 2.4</td>
</tr>
<tr>
<td>WR</td>
<td>21 ± 0.7*</td>
<td>28 ± 0.9†</td>
<td>31 ± 0.8†</td>
</tr>
<tr>
<td>AL</td>
<td>199 ± 2.02</td>
<td>237 ± 2.29†</td>
<td>266 ± 3.75†</td>
</tr>
<tr>
<td>WR</td>
<td>201 ± 1.50</td>
<td>190 ± 1.63†</td>
<td>207 ± 1.81†</td>
</tr>
</tbody>
</table>

Values are means ± SE ($n = 12$). WR, water-restricted rats; AL, rats allowed ad libitum access to water. WR water intake on day 7 is volume consumed during 15 min before animals were killed ($n = 6$). *$P < 0.05$ vs. AL at the same time point. †$P < 0.05$ vs. previous time point within group.
Experiment 1, plasma ACTH did not change in AL or WR rats 15 min after water was presented to WR rats. Again, PRA was elevated by water restriction alone (WR-Pre vs. AL-Pre), but PRA did not change in WR rats after drinking (Fig. 3D). Aldosterone was not affected by water restriction; however, unlike experiment 1, plasma aldosterone was increased in WR rats after drinking (Fig. 3E).

Fig. 2. Plasma ACTH, corticosterone, renin activity (PRA), and aldosterone and adrenal corticosterone content from AL and WR rats before and 15 min after drinking (experiment 1). Values are means ± SE. *P < 0.05 vs. Pre of the same treatment group (AL or WR). #P < 0.05 vs. AL-Pre.

Fig. 3. Plasma ACTH, corticosterone, PRA, and aldosterone and adrenal corticosterone content from AL and WR rats before and 15 min after drinking (experiment 2). Values are means ± SE. *P < 0.05 vs. Pre of the same treatment group (AL or WR). #P < 0.05 vs. AL-Pre.
Plasma CBG was decreased by water restriction alone but did not change after restriction-induced drinking (Fig. 4).

**Experiment 3**

Body and thymus weight and plasma ACTH and PRA were measured to determine the effectiveness of steroid replacement in ADX rats (Fig. 5). Over the course of the three repeated experiments, the replacement doses of corticosterone and aldosterone were adjusted to minimize differences between ADX and Sham rats. Rats were subjected to treatment I, II, or III. After 6 days of water restriction, body weight was maintained in ADX animals with treatment II compared with Sham animals, whereas body weight was decreased in ADX rats with treatments I and III (Fig. 5A). Thymus weight, a specific index of physiological corticosterone replacement, was normalized in ADX rats with treatment II but was increased in ADX animals with treatment I and decreased with treatment III compared with Sham animals (Fig. 5B). Plasma ACTH was normalized by corticosterone replacement with treatments II and III but was increased in ADX animals with treatment I (Fig. 5C). PRA, an index of physiological aldosterone replacement, was normalized with treatments II and III but was decreased in ADX animals relative to Sham animals with treatment I (Fig. 5D). On the basis of all physiological indicators, the optimal corticosterone and aldosterone replacement occurred in ADX rats receiving treatment II.

Plasma corticosterone decreased consistently after restriction-induced drinking in Sham animals (Fig. 6, A and E). In ADX animals, increased doses of corticosterone administered as pellets increased plasma corticosterone; however, plasma concentrations were significantly lower than in Sham animals. There was no difference in plasma corticosterone between ADX-Pre and ADX-Post groups with 25% and 75% corticosterone pellets (Fig. 6A and E); however, a small but significant reduction in plasma corticosterone occurred after drinking in ADX animals treated with 50% corticosterone pellets (Fig. 6C).

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**Fig. 4.** Plasma corticosteroid-binding globulin (CBG) from AL and WR rats before and 15 min after drinking. Values are means ± SE. #P < 0.05 vs. AL-Pre.

**Fig. 5.** Body and thymus weight and plasma ACTH and PRA from Sham and ADX rats treated with 25% corticosterone pellet and 16 μg/day aldosterone (treatment I), 50% corticosterone pellet and 5.3 μg/day aldosterone (treatment II), and 75% corticosterone pellet and 2.7 μg/day aldosterone (treatment III) before drinking. Values are means ± SE. *P < 0.05 vs. Sham within the same experimental session.
With two of the three experimental treatments, plasma aldosterone was not different between Sham-Pre and Sham-Post groups (Fig. 6, D and F); however, with treatment I, plasma aldosterone increased in Sham animals after drinking (Fig. 6B). In ADX animals, higher doses of aldosterone (16 and 5.3 μg/day) resulted in elevated plasma aldosterone levels than in Sham controls (Fig. 6, B and D). However, there was no change in plasma aldosterone in ADX animals after drinking.

**DISCUSSION**

A major goal of the present study was to determine whether water restriction-induced drinking reduces plasma aldosterone in parallel with plasma corticosterone. In five independent experiments, plasma corticosterone was markedly decreased 15 min after restriction-induced drinking, as shown previously (8, 18, 24); in contrast, plasma aldosterone did not change or was increased. The finding that aldosterone did not decrease clearly suggests that aldosterone and corticosterone are influenced by different factors after restriction-induced drinking.

Plasma ACTH and PRA, an index of circulating plasma ANG II, were measured to determine whether the differential changes in corticosterone and aldosterone after drinking were paralleled by similar responses of their primary secretagogues. Although corticosterone was decreased by >50% after drinking in both experiments, ACTH was reduced only in experiment 1. These findings are consistent with earlier results concerning the ACTH response to restriction-induced drinking. Whereas some have shown concomitant decreases in ACTH and corticosterone (31), others have shown temporal disparities between changes in ACTH and corticosterone, even when extensive time courses of the response were examined (8, 40). These disparities have led to the hypothesis that changes in adrenal sensitivity to ACTH contribute to the decline in corticosterone. Therefore, it is conceivable that a combination of declining plasma ACTH and reduced adrenal responsiveness to ACTH contributes to the decline of corticosterone after restriction-induced drinking.

There was no clear correlation between plasma aldosterone and PRA in either experiment: plasma aldosterone did not change after drinking in experiment 1 (Fig. 2) and increased after drinking in experiment 2 (Fig. 3), whereas PRA increased in experiment 1 and did not change in experiment 2. Moreover, PRA was elevated but aldosterone was not affected by dehydration alone (WR-Pre vs. AL-Pre). Similar dissociations between PRA and aldosterone during dehydration and after drinking have been documented in the dog (37), sheep (3), and rat (19, 23). Although ANG II is believed to be a primary secretagogue of aldosterone, it has been suggested that plasma sodium concentrations may have a stronger influence over the regulation of aldosterone.

**Fig. 6.** Plasma corticosterone and aldosterone from Sham and ADX rats before and 15 min after drinking with experimental treatments I (A and B), II (C and D), and III (E and F). Values are means ± SE. *P < 0.05 vs. Pre within the same treatment group (Sham or ADX). #P < 0.05 vs. Sham-Pre.
sterone secretion during dehydration and rehydration (37). This influence may occur by direct effects on aldosterone secretion by glomerulosa cells (41) or by effects on adrenal sensitivity to ANG II (29, 34). Therefore, although dehydration creates a state of hypovolemia, which is a potent stimulus for renin release, the resulting elevation of plasma sodium may act to inhibit aldosterone secretion to defend osmotic homeostasis. Conversely, rapid rehydration can lower plasma sodium, thus stimulating aldosterone secretion. This scenario could explain the data obtained in the present study. Water restriction-induced dehydration produced hypovolemia, as reflected by elevated hematocrit, resulting in elevated plasma osmolality, likely due in large part to increased plasma sodium (22), and plasma aldosterone did not change. After drinking, plasma osmolality decreased rapidly to control levels (Fig. 1), which should result in increased aldosterone secretion. Plasma aldosterone increased in experiment 2 (Fig. 3) but not in experiment 1 (Fig. 2). It is possible that aldosterone did not increase after drinking in experiment 1 because of the concomitant decrease in plasma ACTH, a potent secretagogue for aldosterone secretion (4, 17). The results of the present experiments support earlier work demonstrating the complexity of control mechanisms mediating aldosterone secretion during dehydration and rehydration.

The finding that adrenal corticosterone content is decreased after drinking has also been shown previously (40) and is consistent with the hypothesis that declining plasma levels of corticosterone are due to an inhibition of adrenal corticosterone production. However, because the half-life of corticosterone is ~20 min in rats (16), it is unlikely that even a complete suppression of adrenal corticosterone production alone could account for the observed 70% decrease in corticosterone after drinking. Therefore, an experiment was performed to determine whether increased clearance contributes to the reduction of adrenal steroids in the plasma after drinking.

Animals were adrenalectomized, and corticosterone and aldosterone were replaced with pellets and osmotic minipumps, respectively, to clamp corticosterone and aldosterone at constant plasma levels. Different dose combinations of corticosterone and aldosterone were used in each of three experiments with the goal of achieving plasma concentrations that were physiologically similar to those observed in Sham animals. Body and thymus weights and plasma ACTH concentrations were measured as physiological indicators of corticosterone activity (1). Also, PRA was measured as an indicator of aldosterone activity, because optimal replacement of aldosterone would be expected to maintain blood volume and osmolality, which in turn limits renin secretion (32). These physiological indicators were normalized in ADX animals replaced with 50% corticosterone pellets and 5.3 μg/day aldosterone; therefore, this replacement regimen was viewed as optimal to achieve physiological levels of corticosterone and aldosterone. A small but significant reduction in plasma corticosterone occurred after drinking in ADX animals receiving 50% corticosterone pellets. However, there were no differences between plasma aldosterone concentrations before and after drinking in ADX animals with any of the three steroid treatments. These data suggest that when adrenal steroids are within the physiological range, an increase in clearance accounts for a small fraction of the decrease in plasma corticosterone observed after restriction-induced drinking but does not contribute to changes in plasma aldosterone under the same conditions.

An increase in corticosterone clearance from the plasma could result from an increase in peripheral metabolism and/or volume of distribution. Hepatic tissue collected from water-restricted animals 5 min after drinking exhibited a 5% increase in corticosterone metabolism compared with tissue taken from animals before drinking (8). It seems unlikely that a change of this magnitude alone could account for the >30% decrease in plasma corticosterone observed in experiment 3. Moreover, if corticosterone and aldosterone are metabolized through similar hepatic pathways (for review see Ref. 10), an increase in hepatic metabolism also should result in a decrease in plasma aldosterone concentration; however, decreases in plasma aldosterone were not observed. An increase in volume of distribution, caused by shifts in body fluid after drinking induced by water restriction (28), could rapidly change plasma hormone concentrations. This possibility also seems to be an unlikely mechanism to explain the decline in plasma corticosterone in the absence of declining plasma aldosterone. Because affinity for plasma binding proteins is lower for aldosterone than for corticosterone (6, 9), aldosterone should be more susceptible to movement out of the plasma compartment. However, a decrease in CBG after drinking could explain a preferential increase in the plasma clearance of corticosterone over aldosterone. Increased binding of corticosterone to CBG has been associated with a decrease in its volume of distribution (5, 35, 36). Therefore, a decrease in CBG after drinking could facilitate corticosterone diffusion from the plasma compartment, allowing for increased metabolism in the periphery. Moreover, rapid decreases in plasma CBG have been observed after insulin injection in humans (12). Because feeding resumes on rehydration (39; unpublished observations), it is likely that plasma insulin increases soon after presentation of water to restricted rats. Increases in plasma insulin may be sufficient to decrease plasma CBG levels and, thereby, promote corticosterone clearance from the plasma. Consistent with this hypothesis is the finding that rapid decreases in corticosterone also occur after food presentation alone in animals that have been food and water restricted (24).

Plasma CBG was measured in experiment 2, and although it was reduced by water restriction alone, there was no change after drinking in WR rats. It is possible that the decrease in CBG induced by water restriction is a result of elevations in corticosterone that occur during the first 2 days of the water restriction protocol (unpublished observations), because it
has been shown that corticosterone has a negative regulatory effect on CBG levels (13, 21). These data do not support the hypothesis that acute changes in CBG account for the preferential clearance of corticosterone over aldosterone after drinking. However, the finding that CBG is decreased by 6 days of water restriction, without a change in total plasma corticosterone, suggests that the amount of unbound, or free, corticosterone is elevated in WR rats compared with AL rats before drinking. Unbound corticosterone is more susceptible to movement out of the plasma and, therefore, to metabolism by peripheral tissues (5, 35, 36). However, drinking-induced changes in plasma corticosterone without changes in aldosterone cannot occur without a mechanism that differentially affects corticosterone clearance. A possible mechanism is increased metabolism by 11ß-hydroxysteroid dehydrogenase type 2 (25), an enzyme found in peripheral tissues, including the kidney, that inactivates corticosterone, but not aldosterone. Rapid clearance of corticosterone from the plasma could occur without changes in plasma aldosterone if drinking increases metabolism of corticosterone by 11ß-hydroxysteroid dehydrogenase type 2. Therefore, the relatively small increase in corticosterone clearance observed in the present study could be due to a combination of factors, including a restriction-induced decrease in plasma CBG followed by a drinking-induced increase in peripheral metabolism.

**Perspectives**

The data obtained in the present study support the hypothesis that a reduction in plasma corticosterone after restriction-induced drinking is due to an inhibition of adrenal corticosterone production, as well as a small increase in corticosterone clearance. The inhibition of corticosterone production may be a response to declining plasma ACTH and/or may be due to changes in adrenal sensitivity to ACTH. Aldosterone also may be affected by declining ACTH levels after drinking, but this response is likely to be offset by simultaneously decreasing plasma sodium and/or increasing ANG II concentrations. Maintenance of aldosterone concentrations after restriction-induced drinking likely aids in the restoration of plasma osmolality and volume through sodium retention (37). Conversely, because feeding resums on rehydration, decreasing corticosterone concentrations after drinking could play a beneficial role in shifting the body from a catabolic to an anabolic state (7). The signals leading to the decrease in ACTH and/or adrenal sensitivity to ACTH and, therefore, a decrease in corticosterone production have not been clearly defined. However, the remarkably rapid timing of the corticosterone response and the absence of a rise in corticosterone before drinking suggest that neurally mediated mechanisms (40) acting independently of corticosterone negative feedback may be involved.

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