Glucocorticoids inhibit sodium depletion-induced salt appetite in rat

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Abstract: Glucocorticoids, produced in adrenal cortex, exert potent natriuretic and diuretic actions in the kidney. Recently, it has been found that glucocorticoids could upregulate the expression of natriuretic peptide receptor A (NPR-A), the primary receptor of atrial natriuretic peptide, in the hypothalamus of the rat. Consequently, systemic administration of glucocorticoid could block dehydration-induced water intake by activation hypothalamic NPR-A. We describe here glucocorticoids could inhibit sodium intake when administrated systemically in conscious, salt-depleted rats; an effect which was strong and long-lasting. The study provided further evidence for the actions of glucocorticoids on central nervous system, which together with their established renal actions coordinated to normalize extracellular fluid volume.

Key words: glucocorticoids; salt appetite; natriuretic peptide receptor A;

Atrial natriuretic peptide (ANP), a peptide hormone secreted by the heart in response to volume expansion, provides a potent defensive mechanism counterbalancing the salt- and water-retaining actions of the renin–angiotensin–aldosterone system that predominates in terrestrial animals. Blood volume expansion acts not only directly on the heart by stretch of atrial myocytes to increase the release of ANP, but also on the hypothalamic ANP neuronal system through afferent inputs from baroreceptors . ANP and its primary receptor natriuretic peptide receptor A (NPR-A) are present in the kidney and hypothalamus, playing a pivotal role in body fluid control . Renal NPR-A activation induces potent diuresis and natriuresis, whereas hypothalamic NPR-A activation inhibits water and salt intake. They work in concert to prevent the body from fluid overload. In general, ANP release results in the elimination of excess extracellular fluid and normalization of fluid and electrolyte content of the blood. Previous evidences showed that glucocorticoids could upregulate ANP mRNA expression in the atrial myocytes and increase the ANP levels in the circulation . Recently, we demonstrated that glucocorticoids could inhibit dehydration-induced water intake by upregulating the expression of NPR-A in the hypothalamus . In addition to a hypothalamic action to inhibit drinking, it is possible that the natriuretic action of glucocorticoids in the kidney is matched physiologically by a central action of the glucocorticoids to reduce salt intake. Centrally, the ability of ANP to inhibit sodium-depletion induced salt appetite suggests such a role for glucocorticoids, since a role for glucocorticoids in the hypothalamic NPR-A expression has been indicated . We describe here the ability of systemic administration of glucocorticoid to inhibit salt appetite in sodium-depleted rats, an effect which was long-lasting.

Materials and methods.

Twenty intact Wistar rats were fed salt-free food for a week and were depleted of sodium by a single injection of furosemide (5 mg sc) for 24 hours to have sodium-depletion status . The sodium-depleted rats were, then, randomized to receive dexamethasone (Dex) or vehicle. Dex was pretreated with 1mg/kg 24 hours prior to free access to 0.3 mol/L sodium chloride and distilled water.

Statistical analysis

All the data were express as means ± standard error of mean (s.e.m). Data in sodium and water intakes were analyzed by two-way repeated measures ANOVA.

Results

Sodium intake

Sodium depletion induced a rapid and large sodium consumption in 15 min (1.80 ± 0.18 mmol in vehicle treated rats versus 0.89 ± 0.19 mmol in Dex treated rats, $P<0.01$). Dex pretreatment reduced almost 50% of sodium consumption compared with vehicle treatment. The inhibitory effect last at least for 12 hours (Fig 1).

Water intake

Associated with inhibition of sodium intake, Dex treatment also induced a dramatically long-lasting inhibition on water intake (Fig2).

Discussion

Every disturbance in the body evokes a stress response that serves to restore homeostasis. When exposing to stress, neurons in the paraventricular nucleus of the hypothalamus secrets corticotrophin releasing hormone and other neuropeptides that drive the activity of the sympatho-adrenomedullary and the hypothalamic-pituitary-adrenal systems . Of the two systems, the hypothalamic-pituitary-adrenal system involving corticosteroid hormone secreted by the adrenals is slower but more persistent in its actions. Therefore, glucocorticoid receptor (GR), a widely expressed corticosteroid hormone receptor, is essential for stress responses. In stress response, glucocorticoids are known to activate transcription in a number of systems possibly by association of the hormone-receptor complex with specific DNA sequences (i.e. glucocorticoid responsive element) . Our experimental results suggested that the potent volume-depleting effects induced by glucocorticoids be mediated by natriuretic peptide system involved body fluid control in two ways, i.e. to promote ANP production in the myocytes and upregulate NPR-A expression in the kidney and hypothalamus .

There is a widespread notion that glucocorticoids have sodium- and water-retention properties, because many publications documented that chronic administration of glucocorticoid attenuated renal water and sodium excretion . But it is difficult to explain the facts that acute administration of glucocorticoids could produce potent diuresis and natriuresis. Our recently findings provide a clear answer for this phenomenon. Acute glucocorticoid administration produces potent diuresis first by activating renal NPR-A, but their central inhibitory effects on water and sodium intakes have the body under systemic volume depletion. Systemic volume depletion, in turn, compromises the subsequent renal water and sodium excretion. Nevertheless, the cumulative effects of chronic glucocorticoid treatment on water and sodium intake produce a negative balance of both substances .

Collectively, in addition to their actions in the periphery to assist in the normalization of extracellular fluid volume by renal actions , glucocorticoids can act centrally to inhibit dehydration-induced water intake, and, as we demonstrated here, sodium-depletion induced saline intake. The result of such diverse actions appears to be the coordinated action on control of fluid volume.

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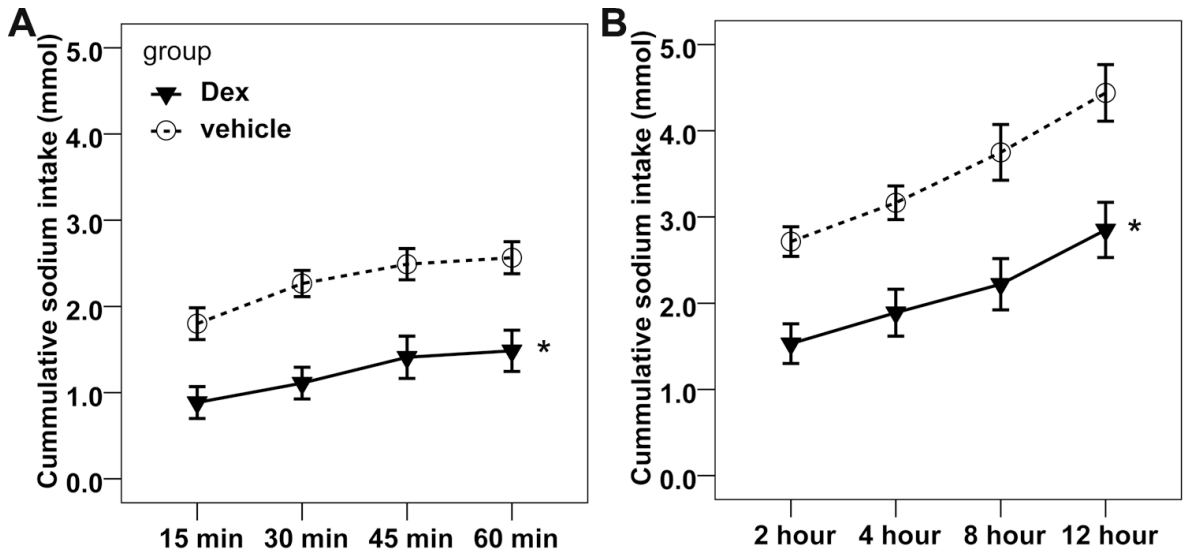

Figure 1. The effect of glucocorticoids on sodium intake in rats with sodium depletion.

[A] Effect of glucocorticoids on sodium intake in rats with sodium depletion in 60 minutes; n = 10 for each group; data were analyzed by two-way repeated measures ANOVA; # <0.01 compared with rats treated with vehicle. **[B]** Effect of glucocorticoids on sodium intake in rats with sodium depletion in 12 hours; n = 10 for each group; data were analyzed by two-way repeated measures ANOVA; # <0.01 compared with rats treated with vehicle.

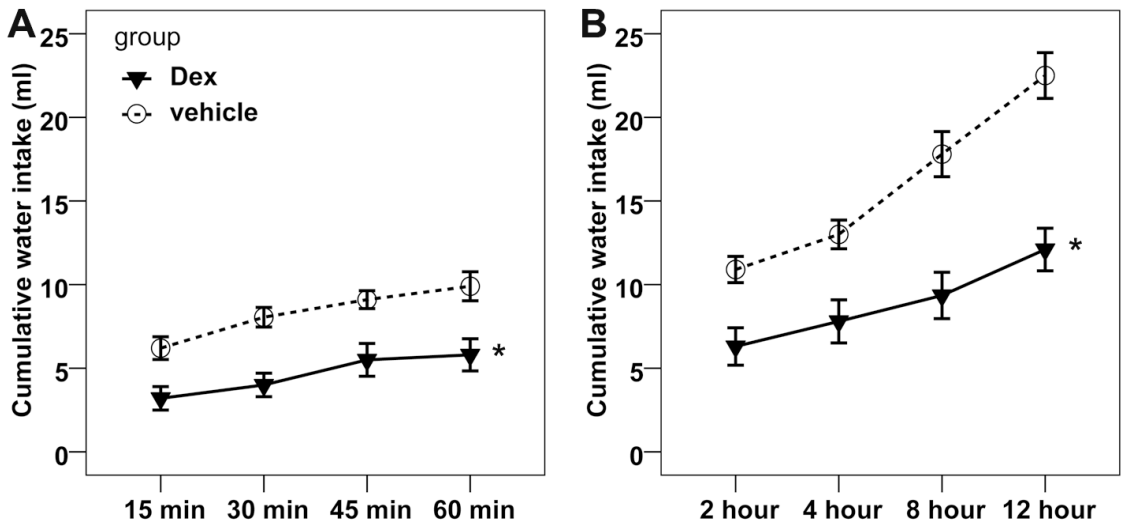

Figure 1. The effect of glucocorticoids on water intake in rats with sodium depletion.

[A] Effect of glucocorticoids on water intake in rats with sodium depletion in 60 minutes; n = 10 for each group; data were analyzed by two-way repeated measures ANOVA; # <0.01 compared with rats treated with vehicle. **[B]** Effect of glucocorticoids on water intake in rats with sodium depletion in 12 hours; n = 10 for each group; data were analyzed by two-way repeated measures ANOVA; # <0.01 compared with rats treated with vehicle.