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Acute changes in arginine vasopressin, sweat, urine and serum sodium concentrations in exercising humans: does a coordinated homeostatic relationship exist?

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Abstract

The parallel response of sweat rate and urine production to changes in plasma osmolality and volume support a role for arginine vasopressin (AVP) as the main endocrine regulator of both excretions. A maximal test to exhaustion and a steady-state run on a motorised treadmill were both completed by 10 moderately trained runners, 1 week apart. Sweat, urine and serum sodium concentrations ($[Na^+]$) were evaluated in association with the plasma concentrations of cytokines, neurohypophyseal and natriuretic peptides, and adrenal steroid hormones. When data from both the high-intensity and steady-state runs were combined, significant linear correlations were noted between: sweat $[Na^+]$ versus postexercise urine $[Na^+]$ ($r = 0.80$; $p < 0.001$), postexercise serum $[Na^+]$ versus both postexercise urine $[Na^+]$ ($r = 0.56$; $p < 0.05$) and sweat $[Na^+]$ ($r = 0.64$; $p < 0.01$) and postexercise urine $[Na^+]$ versus postexercise plasma arginine vasopressin concentration ($[AVP]_p$) ($r = 0.48$; $p < 0.05$). A significant positive correlation was noted between postexercise $[AVP]_p$ and sweat $[Na^+]$ during the steady-state condition only ($r = 0.66$; $p < 0.05$). These correlations suggest that changes in serum $[Na^+]$ during exercise may evoke corresponding changes in sweat and urine $[Na^+]$, which are likely regulated coordinately by changes in $[AVP]_p$ to preserve body fluid homeostasis.

Sweat glands play an active role in thermoregulation while the kidneys act to maintain fluid and solute homeostasis.¹ However, since antidiuresis and sodium retention are increased during physical activity performed above 50% VO_{2max} ,² sweat production predominates as the primary source of water and electrolyte loss during exercise. Ninety-two percent of all water³ and 87% of all sodium lost⁴ during exercise is derived from sweat, which establishes the potentially large impact that sweating may have on fluid and electrolyte balance under these circumstances. Despite functional and structural differences between kidney tubules and sweat glands, regulatory mechanisms which govern the concentration of sweat may serve important physiological roles in water and sodium balance when renal excretion is suppressed. The parallel changes of sweat rate and urine production in response to changes in plasma osmolality and volume at rest support arginine vasopressin (AVP) as a putative endocrine regulator of both excretions.⁵ Furthermore, the activation of transient receptor potential channel vanilloid 4 (TRPV4) by hypotonicity⁶ and inter-relationships with osmosensation,⁷ aquaporin-5⁸ and AVP secretion⁹ enhance the possibility for an integrative coordination of fluid and thermal balance via acute modification of sweat gland secretion at the molecular level.

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The aim of this study was to identify endocrine factors which may be associated with changes in sweat, urine and serum sodium concentration during high-intensity (HI) and steady-state running. The exploratory and descriptive nature of this investigation served as a stepping stone to launch future, more mechanistic, studies involving the endocrine regulation of sweat and urine composition in the coordinated maintenance of fluid balance during exercise. Preliminary data—measuring the same 15 endocrine and five fluid balance parameters—collected on a large cohort of runners participating in prolonged endurance exercise¹⁰ suggested that arginine vasopressin, oxytocin and corticosterone may be associated with changes in serum $[Na^+]$. Therefore, this laboratory sequel wished to clarify if these (and/or other) endocrine secretions held concomitant associations with sweat $[Na^+]$ and urine $[Na^+]$ during shorter duration exercise.

METHODS

Subjects

Ten trained endurance runners (five men and five women) were recruited and signed written informed consent for participation in this study, which was approved by both the Ethics Committee of the University of Cape Town and the Georgetown University Institutional Review Board.

Testing protocol

Each runner presented to the laboratory twice, 1 week apart, during the same part of the day to prevent individual diurnal variation between exercise tests. Each subject was asked to refrain from vigorous exercise 24 h before each test and to consume a similar diet. No food or fluid was allowed during either exercise test. Menstrual cycle phase was not controlled for in the female runners.

A HI exercise test was performed during the first experimental session. This consisted of a maximal running test to volitional exhaustion on a motorised treadmill (Quinton type BA-1 treadmill, Bothwell, WA, USA). Each athlete was allowed to warm-up on the treadmill at a self-selected speed for 5 min. After completion of the warm-up, a heart-rate monitor (Polar Heart Rate Monitor, Lake Success, NY, USA) was fitted around each runner's chest and a mask tightly secured over the nose and mouth to prevent air from escaping through the boundary of the mask. Oxygen uptake was measured continuously using an Oxycon Alpha Analyzer (Jaeger, Netherlands) with maximal oxygen consumption (Vo_{2max}) defined as the highest value obtained in each subject before volitional exhaustion. The exercise protocol utilised was a peak treadmill running test, during which each runner ran for 1 min at a speed of 7.5 km/h. Thereafter, the speed was increased by 0.5 km/h every 30 s until the subject could no longer keep pace with the treadmill.¹¹ The last 30 s stage that was completed was designated as each athlete's peak treadmill running speed. A steady-state treadmill test (SS) was performed 1 week later. Each subject ran for 60 min on the treadmill at a speed that corresponded to 60% of the peak speed reached during the HI test.

Sample collection and measurements

Immediately before each exercise test, bodyweight was obtained on a calibrated Adamlab JPS electronic scale (Scales, Brackenfell, South Africa) in running attire and without shoes after the subject voided. A urine sample was obtained from this prerace void. Venous blood was obtained with each subject in a seated position. Ten millilitres of venous blood was collected into chilled lithium heparin tubes and immediately centrifuged for 10 min at 3000 rpm. The separated plasma was immediately frozen at $-80^{\circ}C$ until further analysis could be performed. A central area on the back, between the shoulder blades, was cleansed with

distilled water and one 5 cm×5 cm piece of sterile gauze was secured with a sheet of plastic wrap and tape for sweat collection, similar to the method described by Ikai *et al.*¹²

Within 1 min of completing each exercise test, all subjects returned to the seated position, and 10 ml of venous blood was collected into chilled lithium heparin tubes, centrifuged, separated and frozen. Sweat was collected from the sterile gauze and transferred into an Eppendorf tube. The subject voided, and the urine was collected. The sweat and urine samples were immediately frozen and stored at –80°C until further analysis could be performed. A postexercise bodyweight was then obtained.

Analytical measurements

Changes in plasma volume were estimated by comparing prerace and postrace measurements of plasma protein using a clinical refractometer (Schuco Clinical Refractometer 5711–2020, Japan). Serum, urine and sweat sodium ($[Na^+]$) and potassium ($[K^+]$) concentrations were measured using ion-selective electrodes (Beckman Synchron EI-ISE, Fullerton, California, USA). Osmolality was measured using a vapor pressure osmometer (VAPRO 5520, WESCOR, Logan, Utah, USA)

Hormone measurements

Plasma concentrations of arginine vasopressin ($[AVP]_p$) and oxytocin ($[OT]_p$) were measured by specific radioimmunoassay following acetone–ether extraction as described previously.¹³ The standard curve for AVP is linear between 0.5 and 10.0 pg/tube with the use of a synthetic AVP standard (PerkinElmer Life Sciences, Boston, Massachusetts, USA). The minimum detectable concentration of AVP in extracted plasma was 0.5 pg/ml. The AVP antiserum (R-4) displays <1% cross-reactivity with OT. The standard curve of the OT assay is linear between 0.25 and 5.0 pg/tube with the use of a synthetic OT standard (PerkinElmer Life Sciences). The minimum detectable concentration of OT in extracted plasma is 0.25 pg/ml. The OT antiserum (Pitt-Ab2) displays <1% cross-reactivity with AVP.

Eleven adrenal steroid hormones (cortisol, 11-deoxycortisol, aldosterone, corticosterone, DHEA, DHEAS, testosterone, androstenedione, 17-hydroxyprogesterone, progesterone and 25-hydroxyvitamin D3) were measured using a liquid chromatography-tandem mass spectrometer, in conjunction with an atmospheric pressure photoionisation source, using methodology described recently.¹⁴

Brain natriuretic peptide concentrations were assessed with measurement of the more stable cleaved inactive fragment, N-terminal pro-brain natriuretic peptide (NT-proBNP), using the automated Dade RxL Dimension as previously described.¹⁵ Interleukin 6 (IL6) was measured by chemiluminescence (Immulite 1000 Diagnostic Product, Los Angeles, California, USA)

Statistical analysis

All data were analysed using STATISTICA V.7.0 software (StatSoft, Tulsa, OK, USA). Data are presented as means (SEM), together with the range of values. The change (Δ) represents postexercise minus pre-exercise measurement. Statistical significance was accepted when $p < 0.05$.

RESULTS

Descriptive fitness, demographic and training characteristics of the subjects are presented in table 1. There were no significant differences between female versus male runners with regard to any characteristic except for: NT-proBNP Δ after the HI run (54.6 vs 12.4 pg/ml;

$p < 0.01$) and testosterone concentrations ($p < 0.001$) after both the HI (pre: 18.2 vs 413 ng/ml; post: 25.6 vs 586.2 ng/ml; Δ : 7.4 vs 172.4 ng/ml), and steady-state runs (pre: 17.6 vs 423.2 ng/ml; post: 23.6 vs 528.0 ng/ml; Δ : 6.0 vs 104.8 ng/ml). Therefore, all data for male and female were analysed collectively.

For HI exercise, significant prerun to postrun differences were noted in the plasma concentrations of AVP (3.3 (0.5 pg/ml) vs 15.8 (4.6 pg/ml); $p < 0.01$), OT (1.3 (0.1 pg/ml) vs 2.9 (0.5 pg/ml); $p < 0.01$) and aldosterone (5.4 (0.7 ng/ml) vs 12.6 (1.3 ng/ml); $p < 0.01$). For steady-state exercise, significant prerun to postrun differences were noted in OT (1.0 (0.2 pg/ml) vs 1.5 (0.1 pg/ml); $p < 0.05$) and aldosterone (6.0 (1.3 ng/ml) vs 20.3 (3.4 ng/ml); $p < 0.01$).

With regard to the physiological markers of fluid balance, for HI exercise, the pretest to post-test increase in serum $[\text{Na}^+]$ (137.6 (0.6 mmol/l) to 140.4 (0.7 mmol/l); $p < 0.01$) and plasma osmolality (294.1 (2.2 mOsm/kg H_2O) to 306.7 (2.2 mOsm/kg H_2O); $p < 0.001$) were significantly different, while for steady-state exercise, only the pretest to post-test increase in serum $[\text{Na}^+]$ was significant (138.1 (0.6 mmol/l) to 140.2 (0.5 mmol/l); $p < 0.05$).

When data from both the HI and steady-state runs were combined, significant positive linear correlations were noted between the following parameters: sweat $[\text{Na}^+]$ versus posturine $[\text{Na}^+]$ (fig 1a), sweat $[\text{Na}^+]$ versus postserum $[\text{Na}^+]$ (fig 1b), posturine $[\text{Na}^+]$ versus postserum $[\text{Na}^+]$ ($r = 0.56$; $p < 0.05$), posturine $[\text{Na}^+]$ versus post-[AVP]_p ($r = 0.48$; $p < 0.05$), post-urine osmolality versus posturine $[\text{Na}^+]$ (fig 2a) and sweat osmolality versus sweat $[\text{Na}^+]$ (fig 2b). Sweat osmolality was positively correlated with post-[AVP]_p after both HI and steady-state exercise (fig 3a). When data from only the steady-state running condition were considered, there were significant relations between post-[AVP]_p versus both post urine and sweat $[\text{Na}^+]$ (fig 3b) and between post-[AVP]_p versus urine osmolality ($r = 0.66$; $p < 0.05$). No other measured endocrine parameter was significantly correlated with sweat, urine or serum $[\text{Na}^+]$.

Sweat samples were obtained in only six runners after the HI test and in all 10 runners after the SS run. After the HI run, the sweat $[\text{K}^+] = 7.7$ (0.5 mmol/l), $[\text{Na}^+] = 69.7$ (8.5 mmol/l), and osmolality = 170.7 (14.2 mOsm/kg H_2O). After the SS run, the sweat $[\text{K}^+] = 4.8$ (0.4 mmol/l), $[\text{Na}^+] = 76.9$ (7.7 mmol/l) and osmolality = 172.2 (13.6 mOsm/kg H_2O).

DISCUSSION

This is the first study to document significant linear relationships among sweat, urine and serum $[\text{Na}^+]$ during exercise in humans (fig 1a and b). The urine and sweat sodium concentrations represent aggregate samples that were collected immediately after HI and SS running. Therefore, whether or not the observed changes in urine and sweat $[\text{Na}^+]$ are primarily due to an increase in sodium excretion, a decrease in sweat water excretion, or both, cannot be ascertained by these data, as these relationships only reflect a snapshot rather than changes over time.

The positive association between serum and urine $[\text{Na}^+]$ is largely expected, as osmotically induced AVP secretion generally induces a linear increase in urine $[\text{Na}^+]$ and osmolality as a result of water reabsorption through aquaporin 2 (AQP2) water channels.¹⁶ The positive relationships between sweat $[\text{Na}^+]$ versus both urine $[\text{Na}^+]$ (fig 1a) and serum $[\text{Na}^+]$ (fig 1b) are largely unexpected, however. A similar increase in sweat $[\text{Na}^+]$ in response to dehydration-induced hypernatraemia has been previously documented in one study involving eight cyclists riding for 2 h in the heat.¹⁷ Since these collections also represent aggregated samples, the underlying mechanism(s) for the observed changes in sweat $[\text{Na}^+]$ remain uncertain.

The strong correlations between urine osmolality versus urine $[\text{Na}^+]$ (fig 2a) and between sweat osmolality versus sweat $[\text{Na}^+]$ (fig 2b) suggest that the changes in $[\text{Na}^+]$ are mainly due to a concentrating mechanism of water reabsorption rather than from a hormonally mediated alteration in sodium excretion, since no endocrine variable other than $[\text{AVP}]_p$ correlated significantly with urine or sweat $[\text{Na}^+]$. During the steady-state condition only, there were positive linear correlations noted between $[\text{AVP}]_p$ post with both urine and sweat $[\text{Na}^+]$ post (fig 3b). Although the sample size is small, and the significant correlation between $[\text{AVP}]_p$ and sweat $[\text{Na}^+]$ during steady-state exercise (fig 3b) and between $[\text{AVP}]_p$ and sweat osmolality during the HI condition (fig 3a) appears to be driven by a single outlier, the physiological possibility that AVP may promote water conservation in both urine and sweat production seems intuitive and worthy of more stringent scientific investigation.

Sweat glands possess all of the essential elements required for acute fluid and sodium regulation including aquaporins (AQP5),¹⁸ Na^+/H^+ exchangers,¹⁹ adrenergic nerve terminals, β -adrenergic receptors, and cAMP regulatory components that activate or inactivate CFTR-Cl channels within the sweat duct.²⁰ Sweat sodium concentration is neither constant over time nor identical over different regions of the body,²¹ with significant intersubject and intrasubject variability¹ supporting a plausible role for sweat glands in fluid and electrolyte balance. Although the activation,^{11,22} anatomy¹¹⁹ and function¹²³ of the sweat glands are morphologically and functionally distinct from those of the renal tubules, similar responses to perturbations in both salt intake^{23–25} and plasma chloride concentration (as a surrogate for NaCl)²⁶ suggest that they may perform similar and complementary functions in the acute regulation of serum $[\text{Na}^+]$ and plasma osmolality.

AVP may affect sweat rate and composition via two possible mechanisms: (1) vasoconstriction of cutaneous blood flow (via AVP V_{1A} receptors) or (2) water reabsorption (via AVP V_2 receptors). Injections of either Pitressin or Octapressin provide evidence against vasoconstriction (V_{1A}) as the principle mechanism affecting sweat output. Fifty milliunits of Octapressin contains 2.5-fold the amount of pressor activity as 20 mU of Pitressin; yet sweat rates remain indistinguishable when the two analogues are compared.²⁷ Furthermore, local injections of bradykinin have similar effects on sweating rate as local injections of AVP, even though bradykinin stimulates vasodilation, not vasoconstriction, of skin blood flow.²⁸ Dissociations between $[\text{AVP}]_p$ and skin blood flow²⁹ plus documentation that sweat production continues after arterial occlusion³⁰ also suggest that changes in cutaneous blood flow contribute minimally to changes in sweat rate or composition.

Plasma AVP concentrations are not positively correlated with sweat $[\text{Na}^+]$ when data from both the HI and SS trials are combined. When the data are separated, however, significant correlations are evident between post- $[\text{AVP}]_p$ versus sweat osmolality after both the HI and SS conditions (fig 3a) and between post- $[\text{AVP}]_p$ versus sweat $[\text{Na}^+]$ after the SS condition only (fig 3b). This disparity may be due to both the duration and the intensity of the running trials, as the number of activated sweat glands increase rapidly during the first 8 min after the onset of sweating.³¹ Furthermore, because exercise delays the onset of thermoregulatory sweating due to an increase in plasma osmolality,³² it is also expected that the onset of sweating would be most delayed after HI running because changes in plasma osmolality are greatest after maximal intensity exercise.³³ Thus, the large variability in postexercise $[\text{AVP}]_p$ combined with our inability to collect adequate sweat samples in 40% of our runners after ~10 min of maximal exercise to exhaustion further supports the possibility that a relation between sweat $[\text{Na}^+]$ and $[\text{AVP}]_p$ lacked sufficient time to materialise during the HI condition.

Previous studies have provided conflicting results regarding the influence of exogenous AVP administration on sweat rate and sweat $[\text{Na}^+]$. Investigations that have supported a

positive relationship between AVP administration and sweat $[Na^+]$ primarily have utilised local injections of Pitressin.²⁷²⁸ In contrast, investigations that document either an increase⁵³⁴³⁵ or no change³⁶³⁷ in sweat rate and composition have utilised subcutaneous or intramuscular injections of Pitressin. The only study to evaluate the relation between endogenous $[AVP]_p$ and sweat $[Na^+]$ failed to collect sweat and blood samples on the same testing day.³⁸

We acknowledge that it is clearly documented that sweat $[Na^+]$ increases with increasing sweat rate.³⁹⁴⁰ However, possible hormonal interactions affecting the reabsorption/excretion of sweat sodium (and possibly potassium) via aldosterone⁴¹ in conjunction with potential changes in sweat water reabsorption via arginine vasopressin may help explain some of the deviations noted between sweat rate versus sweat sodium excretion.⁴²

Limitations

We acknowledge that our method of sweat sodium collection may not be reflective of the whole body sweat $[Na^+]$. However, our procedure was standardised between individuals and across trials. The mean sweat $[Na^+]$ of our subjects was 69.9 and 76.9 mmol/l after the HI and steady-state runs, respectively. These concentrations are comparable to the mean values obtained in exercising subjects reported by Ikai *et al* (75.8 mmol/l), whose procedure we replicated.¹² Furthermore, the sweat potassium concentration during steady-state exercise was near the physiological range (4.8 mmol/l) as to reflect true changes in sweat sodium concentration without significant leaching of electrolytes from the stratum corneum.⁴³

CONCLUSION

Changes in serum $[Na^+]$ during exercise are correlated with corresponding changes in sweat and urine $[Na^+]$. Furthermore, these changes in both sweat and urine $[Na^+]$ appear to be associated with water reabsorption, as suggested by the strong linear relations between $[Na^+]$ and osmolality with regard to these two variables. Associations between sweat and urine $[Na^+]$ with $[AVP]_p$ after steady-state exercise would allow for speculation that AVP-mediated water absorption in both urine and sweat may occur in response to dynamic increases in serum $[Na^+]$ to preserve body fluid homeostasis during exercise. More detailed investigations are thus necessary to establish if the maintenance of fluid, sodium and thermoregulatory balance are regulated coordinately by subtle changes in pituitary AVP secretion.

Practical implications

The hypothesis that sweat sodium secretion may be regulated by acute and subtle changes in $[AVP]_p$ has clinical relevance regarding current recommendations to ingest supplemental sodium during exercise.⁴⁴ Calculations which assume that sweat sodium concentration are “fixed”⁴⁵ support the belief that sodium supplementation is not only necessary, but a mandatory practise for all athletes participating in endurance exercise to prevent the development of life-threatening exercise-associated hyponatraemia.⁴⁶ Evidence which may support the acute regulation of sweat sodium secretion via AVP-mediated water reabsorption in the kidney *and sweat gland* in response to subtle changes in plasma osmolality would likely revive interest in the “primitive” sweat gland as perhaps an integral regulator of fluid and sodium balance during exercise.

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Figure 1.

(A) Sweat sodium concentration versus urine sodium concentration immediately following both high-intensity (HI) and steady-state running. (B) Sweat sodium concentration versus serum sodium concentration immediately after both high-intensity and steady-state running.

Figure 2.

(A) Urine sodium concentration versus urine osmolality immediately after both HI and steady-state running. (b) Sweat sodium concentration versus sweat osmolality immediately after both HI and steady-state running.

Figure 3.

(A) Sweat osmolality versus [AVP]_P immediately after both HI and steady-state running.

(B) Both urine and sweat sodium concentration versus [AVP]_P immediately after steady-state running only.

Table 1

Physiological and training parameters of subjects participating in high-intensity and steady-state laboratory trials (n = 10: five women and five men)

Variable	Mean (SEM)	Minimum	Maximum
Vo ₂ maximum (ml/kg/min)	56.1 (3.2)	34.0	70.8
Time to VO ₂ max (min)	10.4 (0.9)	5.5	15.0
Peak running speed (km/h)	16.7 (0.8)	12.5	21.5
Maximum heart rate (beats per minute)	175.7 (4.9)	141	194
Training distance (km/week)	57.3 (6.8)	36	100
Years running	10.9 (2.7)	1	30
Age (years)	40.4 (3.4)	25	53
Body Mass Index (kg/cm ²)	22.3 (0.7)	17.9	25.4