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Research Article

Osmoreceptor-Response to Acute Water-Loading in Salt-Sensitive Normotensive Subjects

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SUMMARY
Objective: Salt-sensitivity may be determined by salt taste threshold (STT). We decided to evaluate the role of STT in osmoreceptor-response to acute water-loading (AWL) in normotensive subjects.
Methods: Forty-seven normotensive healthy young adults (age 21.3±0.3yrs) participated in this study after giving informed consent. Salt taste threshold was detected by asking subjects to taste increasing concentrations of NaCl (15mmol/l-105mmol/l). They were then divided into Low Salt Taste Threshold (STT) if their STT was <60 mmol/L and High STT if >60 mmol/L. The subjects were water-loaded with 1000ml in 5 minutes. Cardiovascular parameters, urine electrolytes, plasma electrolytes, osmolality (POsm) and arginine vasopressin (AVP) levels were measured before and 60 minutes after the water-load exercise. Data were analysed with GraphPad software and expressed as Mean±SEM. Level of significance was set at $p<0.05$.
Results: Following the STT test, 36(76%) subjects had low STT while 11(24%) had high STT. Following AWL, there was a significant increase ($p<0.02$) in Diastolic Blood pressure (DBP) among high STT while subjects with low STT recorded no significant difference in BP. There was also a significant increase ($p<0.002$) in the heart rate of high STT subjects. There was no significant difference in POsm in subjects with high STT but the POsm decreased significantly ($p=0.0011$) in subjects with low STT following AWL. There was a slight increase in plasma AVP among both groups.
Conclusion: We conclude that salt-sensitive subjects (high STT) elicited a greater response to an acute water-load than salt-resistant subjects (low STT).

INTRODUCTION

The level of salt intake is a nutritional behaviour influenced by a multitude of factors. Cultural and socioeconomic factors in conjunction with intrinsic characteristics play important roles in pleasure derived from eating. This influence can be intermediated by the salt taste sensitivity resulting in modulation of the amount of salt intake.[1] In most industrialized societies, salt intake is in excess of the upper limit of <87 mmol Na/day (<5 g NaCl/day) to prevent chronic diseases, set by World Health Organization.[2,3] Increased dietary salt intake has been linked time and again to an increase in blood pressure [4-6] though most of the studies into the link of salt as a causative agent for hypertension have revealed only a weak relationship between sodium intake/excretion and blood pressure in the general population.[7] Some individuals however do manifest large blood pressure changes in response to acute or chronic ingestion of salt or to salt restriction. These individuals are termed "salt sensitive".[8,9] Salt sensitivity has been described among Nigerians, normotensive and hypertensives alike[6] and the phenomenon has been associated with increased morbidity and mortality irrespective of the blood pressure status of the individual.[8,10]

Sodium chloride (NaCl), the prototypical stimulus that elicits salty taste, is a commonly-used food ingredient which provides many technological functions such as flavour enhancement, preservation and texture modification.[11] Sodium also performs several vital roles in the body including maintaining the volume of extracellular fluid, osmotic pressure, acid-base balance and transmission of nerves impulses.[12] It is the most abundant electrolyte in the extracellular fluid and has the greatest influence on the osmolality.[13] Thus, an increase in sodium concentration leads to an increase in the plasma osmolality in the body which then stimulates the osmoreceptors.

Plasma osmolality represents one of the most highly-regulated parameters of body physiology. Osmoreceptor-response is accomplished through an integration of thirst which controls water drinking behaviour, arginine vasopressin (AVP) secretion, and renal responsiveness to arginine vasopressin.[14] It has been demonstrated in both human subjects and other mammals that when the plasma osmolality, usually within the range of 280-294mosm/KgH_2O[15] is increased experimentally as a result of increasing the concentration of solutes such as NaCl, the osmoreceptors get stimulated.[16]] Vasopressin is the main hormone involved in mammalian osmoregulation; it affects

the kidney's excretion of water under physiological conditions.[17]

There are five distinct taste perceptions that have been identified in human indicating specific coding mechanism for each. Also, it is believed that each of these taste types (sweet, umami, bitter, salty, sour) is mediated by specific taste receptors.[18] Sodium and lithium are known to elicit a pure salty taste, other minerals such as potassium, can elicit some salt taste often mixed with metallic or bitter flavours.[19] However, for some reason, humans prefer the salt taste from sodium. A sodium-specific epithelial sodium channel (ENaC) is believed to be responsible for the appetitive nature of sodium in foods.[20] It is thought that the ion channels for salt taste are not located on the apical surface of the taste cell, but rather on the paracellular region between taste cells.[21] As the concentration of salt increases, a level will be reached when an individual will be able to discriminate from water but unable to identify the taste quality. This is the detection or taste threshold.[22] Taste identification occurs when the concentration of salt is enough to not only activate the taste receptors but produce an electrical impulse which can be carried via afferent fibers to the brain where it is decoded and the taste quality identified. This is known as recognition threshold.[22,23] Thus the amount of salt ingested by any subject is related to his conscious and unconscious ability to recognize the taste. Salt taste threshold is higher in salt sensitive individuals and they are likely to ingest higher concentrations of salt before they can perceive the salt taste which is also important for palatability of food. The reduction in ability to recognize the salt taste would drive individuals to consume more salt until a salt concentration identified as pleasant is reached.[1]

Osmoreceptors respond to changes in osmolality; even the smallest change in salt level in the blood will affect osmolality. We postulate that salt-sensitive individuals, determined in this study by salt taste threshold ≥60 mmol/L,[1] will have a greater response to osmoreceptor challenge compared to their salt-resistant (STT < 60 mmol/L) counterparts. This study was therefore designed to determine the influence that variation in salt taste threshold, an index of salt sensitivity, has on the subjects' response to a water-load.

MATERIALS AND METHODS

Forty-seven (47) healthy individuals aged 18 to 30 years were randomly selected from a group of LASUCOM student volunteers. Ethical approval was obtained from the Lagos State University College of Medicine (LASUCOM) Research and Ethics Committee. All subjects gave written informed consent. The tests were carried out in line with the Helsinki Declaration and they were well tolerated by the subjects.

Inclusion Criteria

To be included in this study, subjects had to be healthy, normotensive with systolic blood pressure ≤140/90 mmHg [24] and not suffering from any cardio-respiratory abnormality.[16]

Exclusion Criteria

Subjects with history of major illness altering the taste sensation like facial nerve palsy, diabetes mellitus, and stomatitis, were excluded. Also, subjects with history of alcohol intake, smoking, and tobacco chewing were excluded. Participants with long duration of intake of drugs like Captopril® and Metronidazole were also excluded.[1]

Baseline Measurements

Subjects' body weight was measured to the nearest 0.1kg using a bathroom scale. The height was measured with the aid of a wall- mounted stadiometer to the nearest 0.01m while the subjects stood in an upright position. Body mass index (BMI) was calculated from the weight (w) and height (h).

Measurement of Cardiovascular Parameters

After allowing 10 minutes of rest in the laboratory, baseline blood pressure (mmHg) and heart rate (beats/min) were determined with the subject in a sitting position at normal room temperature. Blood pressure was measured by means of the auscultatory method using a standard sphygmomanometer (Accoson). The Phase I Korotkoff sounds was taken as the systolic blood pressure while the Phase V sound was taken as the diastolic blood pressure. The average of two blood pressure readings was recorded. Heart rate was calculated from Lead II of the ECG. Mean arterial blood pressure (MABP) was calculated from DBP + Pulse Pressure/3 (mmHg).[1]

24-Hour Urine Collection

In the twenty-four hours prior to the test, participants were asked to complete a 24-hour urine collection. A five-litre plastic keg containing 3.0 ml of toluene as preservative was given to each participant; in addition to which a funnel was supplied to the female participants to prevent loss of volume. The subjects were asked to void and discard the urine at 7.00 am on the day of collection. They were then to void all urine into the keg provided. The subjects were asked to void the last urine volume at 7.00am of the following morning (morning of experiment) whether they felt the need to or not. The urine volume was measured with a measuring cylinder. Urinary electrolytes (Na^+, K^+), urea and creatinine were determined from 10ml aliquots of the 24-hour urine sample which were refrigerated till analysis.

Plasma electrolytes, urea, creatinine

Venous blood was collected from a peripheral vein into lithium heparin bottles. Plasma Na^+ and K^+ were determined by means of a Corning 4010 flame photometer. Urea was determined by the Berthelot method while creatinine was determined by the picric acid method in an Airone autoanalyzer.

Blood glucose and Plasma osmolality

Random blood glucose level (mg/dl) was determined using a model-GC ACCU-CHEK glucometer machine. The blood glucose in mg/dl was converted to mmol/l using the formula: mmol/l = $mgdl^{-1}$ divided by 18. Thereafter, plasma osmolality (Posm) was calculated using the standard formula: Posm = $2(Na^+ + K^+)$ + Urea + Glucose.[16] All values were in mmol/1.

Determination of Salt Taste Threshold

Salt solutions of different concentrations were used for the determination of salt taste recognition, using a modified

procedure previously described by the American Society for Testing and Materials (ASTM E679) and by the International Organization for Standardization (ISO 13301).[25] Sodium chloride (Lobacheme, Mumbai, India) was used to prepare increasing concentrations (15, 30, 45, 60, 75, 90 and 105 mmol/l) of NaCl solution. The experiments were carried out in the morning. The subjects were asked to observe an overnight fast because of the water-loading test that was to be carried out after the determination of the salt taste threshold.[1]

Subjects were blinded to the NaCl solutions. They were only informed that the test solutions were of various tastes such as water, sucrose, urea (bitter) and sour but not salty to avoid speculation.[1] Different concentrations of the solutions were tasted by asking the subjects to drop sterile cotton wool swab into the solutions of different concentrations and place it on the anterior two-third of the tongue.[1] The subjects were instructed to indicate the taste perceived using Placard Method by pointing to the card on which different taste sensations are written.[26] The subjects were asked to rinse the tongue with distilled water after each test. Beginning with the 15 mmol/L solution, subjects were given increasing concentrations of NaCl solutions to taste, until they identified the salt taste. Following correct identification of NaCl solution, the procedure was continued to the next higher concentration of NaCl to ensure the subject could identify the taste as stronger. The first NaCl concentration in which the salt taste was identified was recorded as the salt taste threshold (STT) for the subject. Subjects were then grouped on the basis of their salt taste threshold into Low STT and High STT using 60mmol/l as the cut-off point for grouping [1,27]:

i. High salt taste threshold - subjects that tasted salt at or above 60mmol/l
ii. Low salt taste threshold- subjects that tasted salt below 60mmol/l

Water-loading Test

The subjects were given 1litre of water over five minutes duration; the water was at room temperature.[28] The automated sphygmomanometer (Citizen Micro HumanTech CH-453; Tokyo Japan) was used to measure the blood pressure and heart rate before and at 60 minutes after the water-loading test. Spot urine was also collected at 60 minutes after the test for determination of urine electrolytes, urea and creatinine. Collection of blood samples was also repeated at 60 minutes after the test. Plasma and urine electrolytes were measured by flame photometry.

Measurement of Arginine Vasopressin

Arginine vasopressin (AVP) was measured using an Enzyme-linked immunosorbent assay (ELISA) kit (Sunlong, Biotech, China) following the manufacturer's direction. Briefly, 2.0ml of blood collected in the chilled heparin tube for arginine vasopressin was centrifuged in a refrigerated centrifuge. Platelets contain a certain amount of AVP. The blood was centrifuged for 20 minutes at 2,000 rpm, and care was taken when collecting the supernatant to leave the platelets and the RBCs intact. The assay sensitivity was 0.5pg/ml plasma. Since AVP level varies according to osmotic stimulations, it was compared with plasma osmolality measures at the same time.[29]

Statistical Analyses

All statistical analysis of data was carried out using GraphPad Statistical software, Version 5 for Windows (GraphPad Software, San Diego, California, USA). The data were expressed as mean ± standard error of mean (SEM). Variations before and after water-loading exercise were analysed using Student paired t-test while variations between low salt taste threshold and high salt taste threshold were analysed using Student unpaired t-test. Statistical significance was accepted at $p < 0.05$ level.

RESULTS

Mean values of Age, Weight, Body Mass Index (BMI), Blood Pressure and Heart Rate parameters are shown in Table 1.

Effect of Water-loading on Cardiovascular Parameters

Blood Pressure: Following ingestion of the acute water-load, SBP decreased marginally from baseline value to 113 ±1mmHg ($p = 0.07$) while DBP increased slightly to 74 ± 1mmHg ($p = 0.3$) as shown in Figure 1. The pulse pressure decreased significantly to 39 ± 2mmHg ($p = 0.04$) while MABP increased slightly from 88 ± 1 mmHg ($p = 0.70$) as shown in Figure 1.

Heart rate: Figure 2 shows that the heart rate rose significantly to 82 ± 2 beats/min ($p = 0.003$) following the acute water-loading.

Table 1: Baseline data of subjects

Parameters	Value
Age (years)	21.30 ± 0.38
Weight (kg)	65.13 ±1.25
Height (m)	1.74 ± 0.01
BMI (kg/m^2)	22.13 ± 0.32
SBP (mmHg)	116 ± 1
DBP (mmHg)	73 ± 1
PP (mmHg)	43 ± 1
MABP (mmHg)	87 ± 1

n = 47

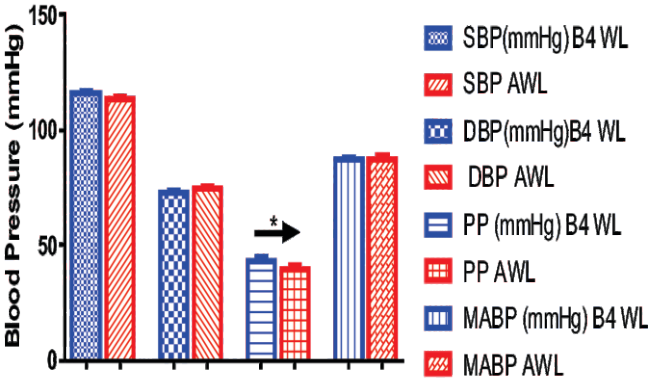

Figure 1: Effect of water-loading on blood pressure
*$p<0.05$ PP B4WL versus AWL; n = 47

Key: SBP= systolic blood pressure; DBP= diastolic blood pressure; PP= pulse pressure; MABP= Mean arterial blood pressure; B4 WL= before water-load; AWL= after water-load

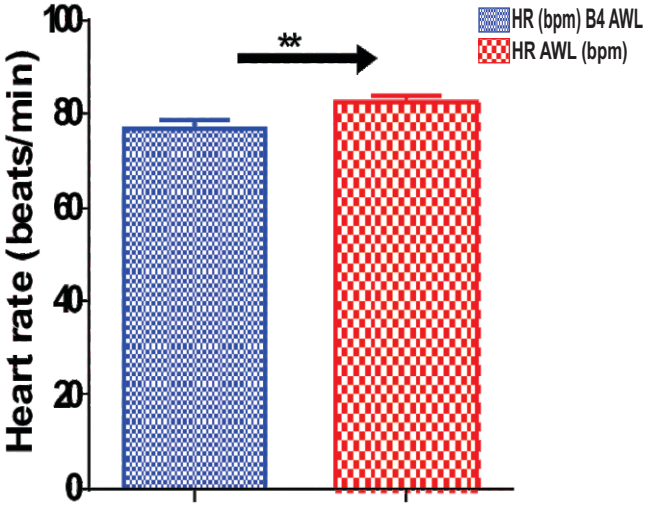

Figure 2: Effect of water-loading on heart rate
*p<0.001 HR B4 AWL versus HR AWL; n = 47

Key: HR = Heart rate (bpm); B4 WL = Before water-load; AWL = After water-load

Effect of Salt Taste Threshold status on Blood Pressure and Heart Rate Response to Acute Water-loading

Thirty-six (77%) subjects salt taste threshold ≥60mmol/l and were classified as high STTs while 11 (23%) subjects that had slat taste threshold <60 mmol/l were classified as low STTs.

The SBP decreased slightly ($p > 0.05$) among subjects with low STT and high STT as shown in Figure 3. The DBP increased marginally from 73 ± 2mmHg to 74 ± 2 mmHg ($p = 0.64$) as shown in Figure 3a but increased significantly ($p = 0.02$) among subjects with high STT as shown in Figure 3b. The STT status also did not affect the PP or MABP significantly among the subjects.

As shown in Figure 4, heart rate increased significantly ($p = 0.002$) among the subjects with low STT while there was no significant change in the heart rate of subjects with High STT following the acute water-loading.

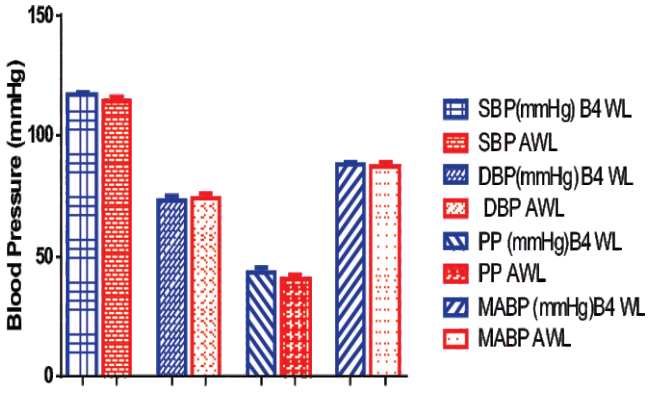

Figure 3a: Effect of water-loading on blood pressure among low salt tasters (n = 36)

Key: SBP= systolic blood pressure; DBP= diastolic blood pressure (mmHg); PP= pulse pressure (mmHg); MABP= Mean arterial blood pressure (mmHg); B4 WL= before water-load; AWL= after water-load

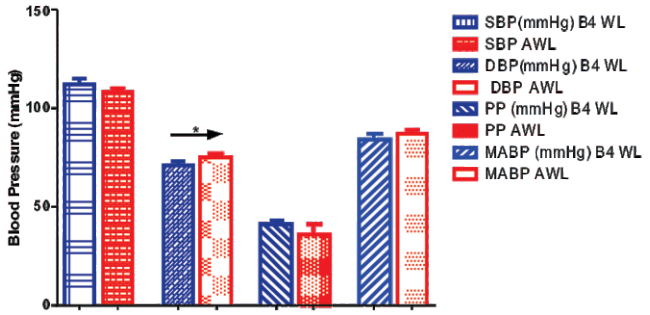

Figure 3b: Effect of water-loading on blood pressure among high salt tasters (n = 11)

Key: SBP= systolic blood pressure (mmHg); DBP= diastolic blood pressure; B4 WL= before water-load; AWL= after water-load

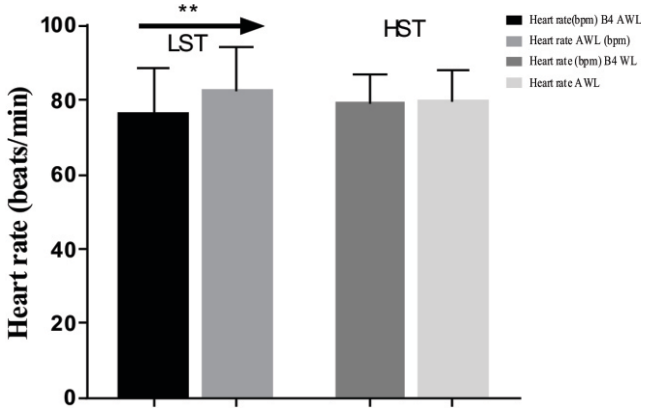

Figure 4: Effect of water-loading on heart rate in subjects with Low and High Salt Taste Threshold
**p = 0.002; (n = 36 LST; n = 11 HST)

Key: LST = Low Salt Taste Threshold; HST = High Salt Taste Threshold; B4 WL = Before water-load; AWL = After water-load; bpm = beats per minute

A comparison of the magnitude of Change in Cardiovascular parameters to Acute Water-Loading among subjects with Low Salt Taste Threshold and High Salt Taste Threshold

To determine further whether Salt Taste Threshold (STT) status affected the subjects' response to acute water-loading, we calculated the actual magnitude of the responses shown by means of the percentage difference.

The magnitude of change in SBP among low STT was -1.67 ± 1.6% and it was similar ($p = 0.63$) to the -3.21 ± 2.36% recorded among high STT. Similarly, the magnitude of change in DBP among low STT was 2.58 ± 2.9% and this did not differ significantly ($p = 0.42$) from the 7.08 ± 2.6% among high STT. These are shown in Figure 5.

The magnitude of change in PP among low STT was -1.23 ± 6.5% and it was only slightly higher ($p = 0.12$) than the -20.41 ± 6.0% recorded among high STT. However, the magnitude of change in MABP among low STTs was 0.42 ± 2.0 % and it was higher ($p < 0.0001$) than the -31.14 ± 3.3% recorded in subjects with high STT (Figure 5).

Also, the magnitude of change in the HR among low STTs was 10.19 ± 3.0% and it was lower ($p=0.17$) than the 2.03 ± 4.1% recorded among high STTs (Figure 6).

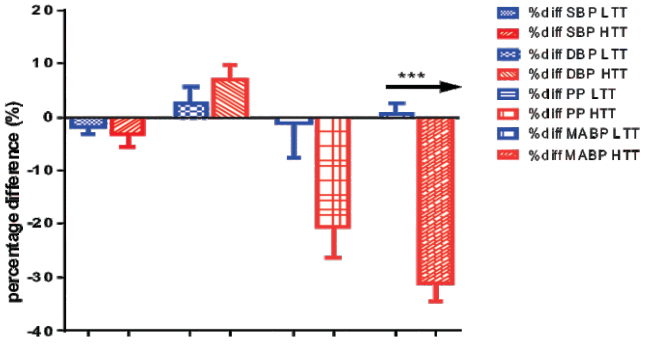

Figure 5: A comparison of magnitude of change in blood pressure-response to Water-loading among subjects with Low Salt Taste Threshold and High Salt Taste Threshold

***=p<0.0001 (n = 36 LST; n = 11 HST)

Key: SBP= systolic blood pressure; DBP= diastolic blood pressure; PP= pulse pressure; MABP= mean arterial blood pressure; AWL= after water-load

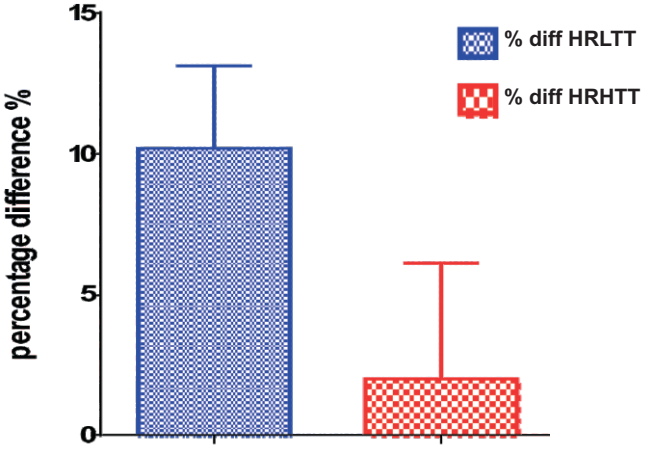

Figure 6: Effect of water-loading on Heart Rate in subjects (n = 36 LST; n = 11 HST)

Key: HR = heart rate, LTT = low salt taste threshold; HT - high salt taste threshold

Plasma Electrolyte, Urea and Creatinine Concentration among Subjects with Low Salt Taste Threshold and High Salt Taste Threshold

The plasma [Na^+] among low STTs was significantly higher (p = 0.02) than that among high STTs. The plasma [K^+], urea and creatinine were however similar among the two groups (Table 2). Also, following the acute water-load, plasma [Na^+] increased significantly among the Low STTs whereas the plasma [K^+], urea and creatinine did not change significantly (p > 0.05) among both the Low STTs and the High STTs (Table 2).

Effect of Salt Taste Threshold on Plasma Osmolality and Arginine Vasopressin-response to Water-loading Test

Plasma osmolality was lower among high STTs (p = 0.08) compared to the low STTs prior to water-loading. Following the acute water-load, plasma osmolality decreased significantly (p = 0.001) among the low STTs but only slightly (p = 0.57) among the high STTs (Table 2).

Plasma arginine vasopressin (AVP) was lower (p = 0.5) among high STTs before the acute water-loading. The acute water-load led to a slight increase among the two groups (Table 2).

Effect of Acute Water-Loading on Urine Electrolyte, Urea and Creatinine Concentrations among Low and High Salt Taste Threshold Subjects

Before the water-load, urine [Na^+] was similar among the Low STTs and the High STTs. The water-load led to significant change in [Na^+]levels only among Low STT and in creatinine levels among both groups (Table 3).

Table 2: Effect of Acute Water-loading on plasma electrolytes among Low Salt Taste Threshold and High Salt Taste Threshold Subjects

	Low STT Before AWL	Low STT After AWL	High STT Before AWL	High STT After AWL
Na^+ (mmol/l)	132.1 ± 0.7	128.5±0.8[a]	128.7 ± 1.0[b]	126.9 ± 1.3
K^+ (mmol/l)	3.6± 0.3	3.5 ± 0.3	4.6 ± 0.8	5.4 ± 0.4
Urea (mmol/l)	6.4± 0.2	6.42±0.3	5.82 ± 0.40	5.96 ± 3.2
Creatinine (µmol/l)	88.5 ±2.8	91.4 ± 3.0	82.00± 3.3	85.20 ± 5.2
Plasma Osmolality (mosm/kg)	286.2 ± 1.3	278.0 ± 1.6[c]	281.0 ± 3.0	278.7 ± 2.3
AVP pg/ml	23.3 ± 6.3	33.5 ± 12.3	14.5 ± 2.9	17.01 ± 8.9

[a]p = 0.002vs Before AWL; [b]p = 0.02vs Low STT; [c]p=0.001vs Before AWL; (n = 36 LST; n = 11 HST)
KEY: STT, salt taste threshold; AWL, after water-loading; AVP = Arginine vasopressin

Table 3: Urine Electrolytes, Urea and Creatinine among Low Salt Taste Threshold and High Salt Taste Threshold

	Low STT Before AWL	Low STT After AWL	High STT Before AWL	High STT After AWL
Na^+ (mmol/l)1	33.6 ± 0.7	126.8 ± 7.2	132.5 ± 1.7	100.2 ± 7.7[a]
K^+ (mmol/l)	32.86 ± 0.9	35.70 ± 2.1	33.13 ± 0.9	31.4 ± 3.8
Urea (mmol/l)	2.4±± 0.2	2.8± 0.2	2.2± 0.4	2.9 ± 0.5
Creatinine (mmol/l)	12200 ± 924.3	16693.00 ± 167.4[b]	1284.00± 888.4	20333.00± 202.1[c]

[a]p = 0.002vs Before AWL; [b]p = 0.02vs Before AWL; [c]p = 0.01vs Before AWL; (n = 36 LST; n = 11 HST)
KEY: STT, salt taste threshold; AWL, after water-loading

DISCUSSION

It is believed that individuals with high salt taste threshold (STT) will generally tend towards more salt in their diet which will put them at a higher risk of developing hypertension compared with those with a low STT. However, there are still some controversies regarding this. Whereas some researchers have reported an elevated STT among hypertensive subjects, Azinge *et al*.[27] did not find any difference between the blood pressures of low STT and high STT group.

In this study, the water-loading had a slight effect on the blood pressure of subjects with low STT as the SBP and pulse pressure decreased while the DBP and the MABP increased. The same effect was seen in subjects with high STT but the increase in DBP was significant. Although the effects of the water-loading were similar in both groups of subjects, the subjects with high STT had a greater response to water-loading than subjects with low STT. The decrease observed in the SBP among both groups of subjects did not vary from previous findings.[28] The increase in DBP and MABP can be explained on the basis that higher salt taste threshold is linked to involuntary excess salt consumption. The amount of salt ingested by any subject is related in some way to his/her conscious or unconscious ability to recognize the taste. Reduced salt sensitivity would drive individuals to consume more salt until a salt concentration identified as pleasant and suitable is reached.[1] This is recognized as the bliss point, at which the effect of salt on food flavour is optimal.[30] The subjects with high STT are also at a risk of developing hypertension which happens to be a similar interpretation to previous works by other researchers.[1,27,31]

The results of this study show that subjects with low STT had a greater decrease in the plasma Na^+ which indicates that the osmoreceptors were stimulated more in them. The plasma K^+ increased which was not in variance with other studies [28] while the urea and creatinine increased slightly. The subjects with high STT recorded a slight decrease in the plasma Na^+, increase in the K^+, urea and creatinine concentrations.

Results of this study also shows that subjects with a low STT had a significant decrease in plasma osmolality at 60 minutes after the water-load test. This indicates that the plasma osmolality was restored to its normal range by the osmoregulatory mechanism. The subjects with high STT recorded a slight decrease in the plasma osmolality, which could be as a result of the fact that these subjects have the tendency to have a higher sodium concentration in their blood due to increased consumption of salt.[1]

It has been reported that hyperosmolality of the extracellular fluid (ECF) triggers the release of arginine vasopressin, AVP.[32] The AVP acts on the kidneys and causes increased sodium excretion and thirst. After water-loading, AVP level is expected to reduce and also reduce the sodium excretion so as to maintain the osmolality range.[32] The subjects were made to undergo an overnight fast which resulted in the increase in plasma osmolality and plasma AVP recorded. After the water-loading, the plasma osmolality decreased significantly in subjects with low STT while it reduced slightly in subjects with high STT. The plasma AVP levels increased in both low STT and high STT which did not vary with findings from previous research works.[29] This might have been as a result the fact that the blood samples were withdrawn at 60 minutes after the water-loading test which means the result may be a response to the water-load rather than the acute phase response. Previous studies show that there is a significant decrease in the urine Na^+ following water-loading test in healthy individuals [28] and in normotensive and hypertensive subjects.[33] The result of the present study shows that subjects with low STT recorded a marginal decrease in the Na^+, a slight increase in the K^+, urea and creatinine. The subjects with high STT recorded a significant decrease in the Na^+ at 60 minutes after the water-loading which is similar to previous findings.[28] This indicates that the subjects with high STT have a greater urine electrolyte response to water-loading test. They also recorded a slight increase in the K^+, urea and creatinine levels.

CONCLUSION

The results of this study have shown that the salt taste threshold of individuals enhanced their cardiovascular response to an acute osmoreceptor challenge. However, further work will be required to identify the phase of the response recorded especially with regard to AVP.

Conflict of interest

The authors report no conflict of interest and are responsible for the content and writing of the manuscript.

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