Postprandial effects of a high salt meal on serum sodium, arterial stiffness, markers of nitric oxide production and markers of endothelial function.

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Funding source:

Supported by the Commonwealth Scientific and Industrial Research Organisation (CSIRO) and the National Health and Medical Research Council (NHMRC) grants (44102557) (1004380) (990156) (566947).

KMD is supported by Postgraduate Scholarships from the Faculty of Health Science, University of Adelaide and the (CSIRO)

PHRB is a NHMRC Senior Research Fellow; PMC is a NHMRC Principal Research Fellow, JBK is supported by a South Australian Cardiovascular Research Development Program Research Fellowship

Short Running Head: Salt and postprandial vascular function

Key words: sodium, arterial stiffness, nitric oxide

Abstract: 219

Total Word Count: 3784

Figures: 3

Tables: 2

This trial was registered with the Australian and New Zealand Clinical Trials Registry Unique Identifier: ACTRN12611000583943

http://www.anzctr.org.au/trial_view.aspx?ID=343019

Abstract

Aim: The aim of the study was to determine if a high salt meal containing 65mmol Na causes a rise in sodium concentrations and a reduction in plasma nitrate/nitrite concentrations (an index of nitric oxide production). Secondary aims were to determine the effects of a high salt meal on augmentation index (AIx) a measure of arterial stiffness and markers of endothelial function.

Methods and Results: In a randomised cross-over study 16 healthy normotensive adults consumed a low sodium soup containing 5mmol Na and a high sodium soup containing 65mmol Na. Sodium, plasma nitrate/nitrite, endothelin-1 (ET-1), C-reactive protein (CRP), vasopressin (AVP) and atrial natriuretic peptide (ANP) concentrations before and every 30 minutes after the soup for 2 hours. Blood pressure (BP) and AI were also measured at these time points.

There were significant increases in serum sodium, osmolality and chloride in response to the high sodium meal. However plasma nitrate/nitrite concentrations were not different between meals (meal p =0.812; time p=0.45; meal x time interaction p=0.50). Plasma ANP, AVP and ET-1 were not different between meals. AI was significantly increased following the high sodium meal (P=0.02) but there was no effect on BP.

Conclusions: A meal containing 65mmol Na increases serum sodium and arterial stiffness but does not alter postprandial nitrate/nitrite concentration in healthy normotensive individuals. Further research is needed to explore the mechanism by which salt affects vascular function in the postprandial period.

Introduction

There is substantial evidence of the adverse effects of high sodium intakes on blood pressure and cardiovascular health (1, 2). Accumulating evidence suggests that there are adverse effects of a high sodium intake on endothelial function that are independent of blood pressure (3). Endothelial dysfunction is regarded as an important initial event in atherogenesis and impaired nitric oxide (NO) production is thought to be a common pathway of endothelial injury and progression to clinical cardiovascular disease (CVD) (4, 5).

Endothelium dependent dilatation and endothelial NO production have been shown to be impaired by short term high salt intakes (6-8). We previously demonstrated that flow-mediated dilatation (FMD), a measure of endothelium dependent vasodilatation, is significantly impaired after a meal containing 65mmol Na compared with a meal containing 5mmol Na/day but whether NO concentrations are altered following a high salt meal had not been demonstrated (9).

Arterial stiffness, a predictor of cardiovascular risk and mortality has been shown to improve with salt reduction (10-12). However the postprandial effects of a high salt meal on measures of vascular stiffness as measured by augmentation index (AIx) it is unknown.

Elevated circulating levels of endothelin-1 (ET-1) are a hallmark of endothelial dysfunction. Chronic excess dietary sodium intake has been shown to increase ET-1 expression but it is not known if ET-1 is altered acutely by a high sodium meal (13). Studies also suggest that inflammatory markers such as C-reactive protein (CRP) are associated with higher dietary sodium intakes in hypertensive individuals but it is not known if CRP is altered in response to a high salt meal (14).

Both AVP and atrial natriuretic peptide (ANP) have vasoactive properties and may be altered acutely following a salt load, which may in part explain the effects observed on postprandial vascular function in response to salt loading (15, 16).

Our aim was to determine if a meal containing 65mmol Na, a sodium load which we have previously shown impairs flow-mediated dilatation (9) causes a reduction in plasma nitrate/nitrite concentrations (an index of nitric oxide production). We hypothesised sodium concentrations would increase and that nitrate/nitrite concentrations would decrease following a high salt meal. Secondary aims were to investigate the effects of the high salt meal on vascular function as measured by AIx and on plasma AVP, ANP, endothelin-1 and CRP.

METHODS

Subjects

Sixteen men and women aged between 18-70 years were recruited by advertisement at the local university and hospital and from the Commonwealth Scientific and Industrial Research Organisation (CSIRO) Food and Nutritional Sciences Adelaide. Inclusion criteria were body mass index (BMI) $\geq$18kg/m^2 and $\leq$27 kg/m^2, systolic blood pressure (SBP) < 130mmHg, diastolic blood pressure (DBP) <90mmHg, weight stable in the preceding 6 months, no use of anti-hypertensive medication, systemic steroids, folate supplementation or non-steroidal anti-inflammatory drugs. Participants were not excluded if they were taking other vitamin or mineral supplements provided their dosage and frequency remained unchanged for the duration of the study. Sixteen participants met the selection criteria, including two women taking oral contraceptives and one woman who waspost-menopausal. The study was approved by the CSIRO Human Research Ethics Committee (HREC11/05) and the University of Adelaide Human Research Ethics Committee (H-033-2011). All participants gave written informed consent. This trial was registered with the Australian and New Zealand Clinical Trials Registry (Unique Identifier: ACTRN12611000583943). URL http://www.anzctr.org.au/trial_view.aspx?ID=343019

Study Methodology

In a randomised cross-over design, participants attended the clinical research unit on two mornings separated by at least one full day and consumed a high sodium meal (HSM) containing 65mmol Na or a control meal (LSM) containing 5mmol Na. Both meals contained 130mg potassium (3.3mmol). Subjects were randomly assigned to treatment order by using a numbered random-allocation sequence generated by a

person independent to the study (CLINSTAT software; Martin Bland, York, United Kingdom). Participants were required to fast from 10pm the night before (no food, water only) and refrain from alcohol, smoking, vigorous exercise and caffeine in the 24hours prior to each study. On arrival, body height was measured at baseline to the nearest 0.1 cm with a stadiometer (SECA, Hamburg, Germany) while the participants were barefoot. Body weight was measured to the nearest 0.05 kg with calibrated electronic digital scales (AMZ 14; Mercury, Tokyo, Japan) while the participants were wearing light clothing and no footwear.

Blood pressure and vascular measurements

Seated blood pressure (BP) was measured with an automated sphygmomanometer (SureSigns V3; Philips, North Ryde, Australia) while fasting at Visit 1 and 2. After 5 minutes of rest four consecutive BP measurements were taken 1 minute apart. The first reading was discarded, and the mean of the next 3 consecutive readings with SBP readings within 10 mm Hg and DBP readings within 5 mm Hg of each other were taken as the fasting measurement. Additional measurements were made if required. The AIx was estimated by radial applanation tonometry using the SphygmoCor blood pressure analysis system (AtCor Medical, Sydney, Australia) as previously described (17). Three consecutive measurements were performed. The intraobserver CV for AIx in our hands was 12.8% on the basis of data for healthy individuals (n = 12) who were tested on 2 separate occasions (3). A fasting venous blood sample was taken for measurement of serum electrolytes, plasma osmolality and plasma nitrate/nitrite, ET-1, CRP, ANP and AVP. Fasting baseline parameters were assessed between 0800 and 0845 after which participants consumed 250ml soup within 5 minutes. Subsequent blood sampling (seated), BP and AIx and thirst were assessed at 30, 60, 90, 120

minutes after consuming the soup meal. Participants were not allowed to drink during the 2.5hour study protocol.

Serum electrolytes and plasma hormones

Blood for serum was collected in vacutainer tubes with no additives, kept at room temperature and sent to a certified commercial laboratory (IMVS, Adelaide, South Australia) for measurement of electrolytes, osmolality and CRP. Blood for plasma was collected in vacutainer tubes with EDTA for nitrate/nitrite, ET-1 and ANP and lithium heparin for AVP, stored on ice and centrifuged within 15 minutes of collection at 3000rpm for 10 minutes at 4 ^{o}C. The spun plasma was then stored at -80 ^{o}C. Nitrate/nitrite, ANP and AVP were measured after the completion of the study. ANP samples were analysed by a commercial laboratory (ProSearch International Australia Pty Ltd, PO Box 515, Malvern, Victoria, Australia). Plasma AVP was measured by radioimmunoassay as previously described (18, 19). The inter-assay and intra-assay coefficients of variation were less than 8% and the limit of detection was approximately 1 pmol/l. Plasma nitrate/nitrite levels were measured in duplicate using a commercially available enzyme immunoassay kit (Nitrate/nitrite Colorimetric Assay Kit, Cayman Chemical Company Ann Arbor, MI). After filtration using 30-kD microfuge ultrafilters (Nanosep 30k Omega Centrifugal Device, PALL Life sciences Ann Arbor, MI, USA), 40 µL of plasma was diluted with 200 µL assay buffer and mixed with 10µL enzyme cofactor and 10µL nitrate reductase After the plasma had been kept at room temperature for 3 hours to convert nitrate to nitrite, total nitrate was measured at 540 nm absorbance following reaction with Griess reagent (sulfanilamide and naphthalene– ethylene diamine dihydrochloride). The intra-assay CV was 2.7% and the inter-assay CV 3.4% and the limit of detection was approximately 2.5µM. Plasma ET-1 levels were measured in duplicate using a commercially available

enzyme immunoassay kit (Human Endothelin-1 Immunoassay Kit, R&D System, Inc Minneapolis, MN) according to the manufacturer's instructions. The intra-assay CV was 4.6% and the inter-assay CV 6.5% and the limit of detection was approximately 1.0pg/ml.

Thirst visual analogue scale

Thirst was assessed at the time of blood sampling using a well-validated 10cm visual analogue scale as previously described (20). Participants were asked the question "*How thirsty do you feel?"* and asked to indicate a vertical line on the scale between *"no thirst"* at 0cm and *"very severe thirst"* at 10cm to represent their thirst. The thirst rating was defined as the distance (in mm) of the subject's mark from 'no thirst' at 0cm.

Statistical Analyses

Based on a previously study of sodium loading we had 80% power ($\alpha = 0.05$) to detect a mean difference in serum sodium of 2.1 mmol/l in a cross-over design with 16 participants (21). Preliminary analyses were conducted to assess normality using the Kolmogorov-Smirnov test and inspection of histograms and Q-Q plots. Paired samples t-test was used to compare fasting variables at baseline between treatments. Repeated measures ANOVA (with meal and time as within-subject variables) were used to assess the effect of intervention on outcomes over time. Gender was included as a between subject factor because of the possible influence of menstrual cycle status in women on ANP and AVP. Pearson's correlation was used to assess association between variables. Analyses were performed with IBM SPSS Statistics (version 20) for Windows (SPSS Inc, Chicago, IL) A Hill function was used to describe the AIx data generated during each 120-minute meal study (22). For each set of AIx data, "population" parameter values for the Hill function were computed using an iterative

two-stage method based on using the population mean at each iteration as a prior for improving the individual parameter estimates (23). Population kinetic analysis takes into consideration inter-subject variability to estimate kinetic parameters for a group or population of individuals. The PopKinetics software (The Epsilon Group, Charlottesville, VA, USA) was used to fit the Hill function to the AIx data:

$$AIx = a + b\frac{t^n}{t^n + k^n}$$

where a is the baseline AIx, $a + b$ is the maximum AIx, t is time, k is the value of t where the function is 50% of its maximal value, and n, the Hill coefficient, determines the slope of the Hill function at k. Significance was set at $P < 0.05$. All data are Mean±SD unless otherwise stated.

RESULTS

Subjects

Sixteen participants completed the protocol. There were no significant differences between any fasting clinical and biochemical variables between treatments (Table 1).

Biochemical parameters

The high sodium meal increased serum sodium concentration within 60minutes compared with the low sodium meal (HSM 141±1.3 mmol; LSM 139.6±1.3 meal x time interaction p=0.008). Serum chloride (HSM 106.7±2.7mmol; LSM 104.3±1.8 mmol; meal x time interaction p=0.002) and osmolality (HSM 294±3.9mOsmol/kg; LSM 291±4.2mOsmol/kg; meal x time interaction p=0.046) were increased within 90 minutes compared with the low salt control meal (Figure 1). Potassium concentration increased in response to both meals with no significant difference between treatments (meal x time interaction p=0.253) (Figure 2).

Plasma nitrate and nitrite concentration was not significantly different between meals (meal effect p =0.81; time effect p=0.45; meal x time interaction p=0.50). Plasma ANP and AVP were not significantly different between treatments (Figure 2). This did not change when gender was added into the model as a between subject factor. There were no significant differences between treatments for ET-1 (meal effect P=0.64; time P=0.29; meal x time interaction P=0.45) or CRP (meal effect P=0.35; time P=0.2; meal x time interaction P=0.36).

There was no significant correlation between plasma nitrate/nitrite and any other electrolyte, osmolality or BP variables (p>0.05). There was no significant correlation observed between change in any blood pressure variables from baseline and change in sodium, potassium, chloride or osmolality from baseline.

Augmentation Index

AIx increased following both meals. The change in AIx was significantly greater following the HSM compared with the LSM (HSM 4.5 % ±1.0 vs. LSM 2.3% ± 0.8 p=0.012). There was no significant difference between other parameters in the model (Table 2)

Blood pressure

There was no significant difference in SBP, DBP, MAP or HR at baseline (Table 1). A significant effect for time was observed for DBP and HR (DBP: P =0.034; HR: P=0.009). No significant effect of meal or meal x time interaction was observed for any BP variable (SBP: meal effect p=0.15; meal x time interaction p=0.37; DBP: meal effect p=0.15; meal x time interaction p=0.68; MAP: meal effect p=0.59; meal x time interaction p=0.41; HR: meal effect p=0.18; meal x time interaction p=0.51).

Thirst

Thirst was significantly greater with the high sodium meal over time compared with the low sodium meal (meal x time interaction p=0.003) (Figure 3). There was no significant correlation between change in AVP and change in thirst (HSM r = -0.38 p =0.15; LSM r = 0.14 p = 0.61)

DISCUSSION

This study demonstrated that a meal containing 65mmol sodium raised postprandial sodium by 1.5mmol/l in a group of healthy normotensive adults. We have previously shown that administration of an similar sodium load in a group of healthy normotensive individuals impaired postprandial flow-mediated dilatation, a nitric oxide-dependant response, within 60 minutes (9). We hypothesised that the mechanism responsible for this observation would be a rise in postprandial serum sodium and a concomitant decrease in NO production. Studies in vitro have suggested this as a physiologically plausible mechanism in the postprandial state (24, 25). A number of studies have shown that chronic sodium loading decreases NO bioavailability among patients who were hypertensive or sodium sensitive (7, 26). The dietary sodium load in these studies was substantially higher than in the present study. It may be the sodium load was not sufficient to induce alterations in plasma nitrate/nitrite within the 2-hour postprandial period. Two in-vitro studies have demonstrated a significant reduction in nitric oxide bioavailability and nitric oxide synthase activity when plasma sodium was increased (25, 26). The magnitude of change in sodium in these studies was in the range of 5-10mmol/l, which is greater than the maximum change observed in the current study.

However, concentrations of nitrate/nitrite did not change after the high sodium meal despite the significant rise in serum sodium observed in the present study suggesting that other mechanisms are involved. Other investigators observed a similar rise in serum sodium concentration and osmolality following a meal containing 100mmol of sodium (21). They also observed a rise in BP which was not replicated in the present study.

We found that arterial stiffness, as measured by augmentation index , was increased to a greater extent (approximately 2% greater increase) following the high sodium meal. Previous longer term studies have shown that arterial stiffness is higher with increased sodium intakes but to our knowledge this is the first time augmentation index responses have been described after a high sodium meal (10). Contrary to our hypothesis these changes are not explained by changes in nitric oxide bioavailability as nitrate/nitrite was not different between treatments, despite the association between nitric oxide, sodium and endothelial cell stiffness demonstrated in vivo (25). Other possible mechanisms that may explain these effects could be endothelium-independent alterations in vascular smooth muscle cells caused by a higher sodium intake which were not examined in the current study (27). The renin-angiotensin-aldosterone system is suppressed by a high sodium intake (28). In a study in athletes aldosterone concentration decreased by 36.5% after ingestion of sodium citrate with no change in renin (29). In our study vascular compliance as assessed by augmentation index was worse after the high salt meal with no effect on BP. However we did not analyse renin and aldosterone in the study but a reduction in aldosterone would not be expected to account for the vascular changes. There were no significant differences in plasma ET-1 following the meals. These results contrast with previous findings of chronic high sodium intake that demonstrate increased aortic ET-1 expression suggesting that ET-1 does not change acutely (13). Compensatory mechanisms stimulated when serum sodium is raised and osmolality increases include fluid movement from the intracellular to the extracellular intravascular space, which if large enough may be accompanied by an increase in BP. However we did not observe any differences in BP in response to the meals, nor was there any correlation between BP and nitrate/nitrite concentration. This is in contrast

to a recent sodium loading study that reported a 1mmol increase in plasma sodium which was associated with an increase in SBP of 1.91mmHg over a 4hour postprandial period (21).

We also studied the response of vasoactive hormones to the high and low sodium meals as a potential mechanism for the conduit vessel vasodilatation we reported previously (9). Following meal ingestion we observed a parallel decrease in ANP that occurred within 30 minutes following both meals with no significant differences between meals. ANP concentrations returned to fasting levels within the 2-hour period. Previous studies have also shown ANP levels to be unaffected by oral sodium-loading or intravenous saline infusion (15). One study showed a transient, but significant increase in plasma ANP at 30minutes following a 100mmol sodium load compared with 5mmol sodium control meal, but levels returned to fasting values within 60 minutes (30).

Secretion of AVP, primarily stimulated by increased plasma osmolality, acts as a vasoconstrictor at high concentrations and is also stimulated by thirst. Despite the observed increase in osmolality with the high sodium meal we did not observe a rise in AVP nor was there a significant difference in AVP between the two meals over time. Participants were fasted, which may account for a higher AVP concentration at the time of baseline assessments. We also measured thirst, using a validated visual analogue scale which was significantly increased with the high sodium meal (20). However, there was no relationship between the change in thirst and change in AVP. This study used an amount of sodium-chloride typical of that in current foods and single meals consumed in developed countries (31). However, to produce a change in serum sodium concentration of the magnitude observed in vitro studies it may not be physiologically possible with oral sodium loading alone, without adverse effects (e.g.

nausea and vomiting). We did not attempt to control dietary sodium or nitrate intake during the wash-out period, as we believed that the randomised design of the study would account for differences in habitual food intake.

Limitations of the study include the number of subjects although more than adequate for serum sodium and osmolality was relatively low for the vascular measures. The measurement period of 2 hours was relatively short and a longer collection period would have provided more information on serum sodium and osmolality. Dietary sodium or nitrate intakes were not controlled during the wash-out period which may have influenced the outcome. Participants were asked to replicate their food intake prior to the second study day referring to a 24hr recall which was taken on the first study day.

In conclusion, our results demonstrate that postprandial serum sodium and augmentation index are significantly increased after a meal containing 65mmol Na, which may, in part, explain increased cardiovascular disease with increased dietary salt intake. A rise in serum sodium of this magnitude does not appear to have any effect on nitrate/nitrite concentration over a 2-hour postprandial period in normotensive adults. ANP and AVP did not change in response to oral salt loading so they may not play a role in postprandial vascular responses. Therefore, the mechanism of the effects of salt loading on postprandial vascular function in healthy normotensive adults warrants further investigation.

Author Responsibilities

KMD designed the protocol, conducted the study, analysed the data and wrote the manuscript. PMC and JBK designed the study, contributed to interpretation of the data and critically reviewed the manuscript. LMB contributed to study design, interpretation of the data and critically reviewed the manuscript. PHRB contributed to statistical analysis, interpretation of the data and critically reviewed the manuscript.

Acknowledgments

We would like to acknowledge Vanessa Russell who contributed to the nitrate/nitrite analysis, Carlee Schultz who performed the endothelin-1 analysis and Kirsty Turner who assisted with the vascular measurements.

Disclosures

None of the authors had any conflict of interest in relation to this manuscript.

Table 1:

Fasting variables between treatments

	Low Salt Meal	High Salt Meal	p
Weight (kg)	71±3	72±3	0.10
SBP (mmHg)	116±3	113±3	0.17
DBP (mmHg)	73±2	71±2	0.11
MAP (mmHg)	87±2	85±2	0.14
HR (bpm)	59±2	58±2	0.13
Augmentation Index (%)	26±3	25±4	0.40
Plasma nitrate/nitrite (µmol/l)	19.6±2.0	22.2±3.0	0.51
Plasma ANP (pmol/l)	18.4±4.9	19.1±6.5	0.50
Plasma AVP (pmol/l)	2.3±0.4	2.6±0.3	0.32
Plasma Endothelin-1 (pg/ml)	1.1±0.1	1.3±0.2	0.37
Serum sodium (mmol/l)	139.6±0.3	139.5±0.4	0.84
Serum potassium (mmol/l)	4.4±0.1	4.4±0.1	0.95
Serum chloride (mmol/l)	104.7±0.6	105.0±0.6	0.53
Serum osmolality (mosmol/l)	291.0±1.1	291.1±1.0	0.91
Serum CRP (mg/dl)	1.1±0.5	0.7±0.3	0.34

Data are Mean±SEM

n=16 (9 female, 7 male)

Abbreviations

ANP, atrial natriuretic peptide; *AVP*, vasopressin, *CRP*, *C-reactive protein*, *DBP*, diastolic blood pressure; *HR*, heart rate*; MAP*, mean arterial pressure*; SBP*, systolic blood pressure

Table 2

Model to describe the postprandial changes to Augmentation Index following a high salt meal and a low salt meal

	High Salt Meal	**Low Salt Meal**	**P value**
Baseline AIx (%)	24.53 (3.37)	25.42 (2.93)	0.33
Change in AIx (%) over time	4.45 (1.04)	2.34 (0.84)	0.012
[4]Time (min) at which maximum change in AIx (%) observed	65.50 (3.69)	59.94 (6.12)	0.28
The Hill coefficient (a measure of the rate of change in AIx at time k)	10.95	11.68	N

Data are Mean±SEM

Figure legends

Figure 1. Mean (±SEM) serum electrolyte concentration at fasting and in response to consumption of low salt meal (--♦--) and high salt meal (–□–)

Figure 2. Mean (±SEM) Plasma nitrate/nitrite, ANP and AVP concentration at fasting and in response to consumption of low salt meal (--♦--) and high salt meal (–□–)

Figure 3. Mean (±SEM) thirst at fasting and in response to consumption of low salt meal (--♦--) and high salt meal (–□–)

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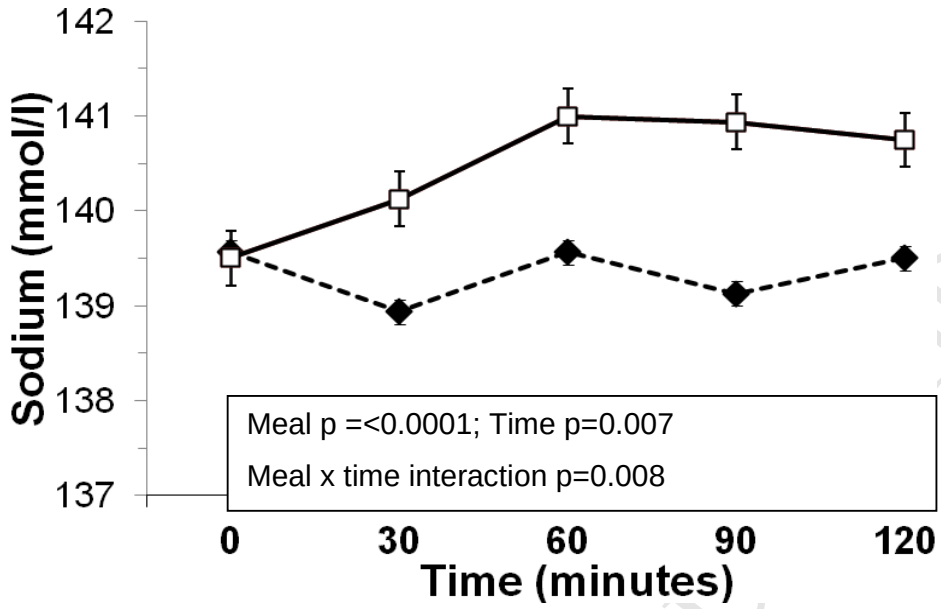
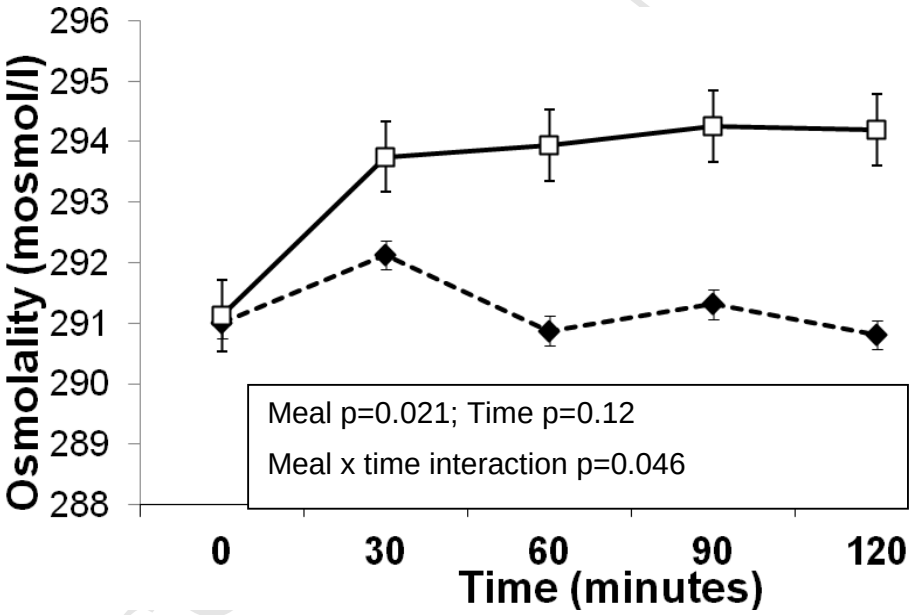
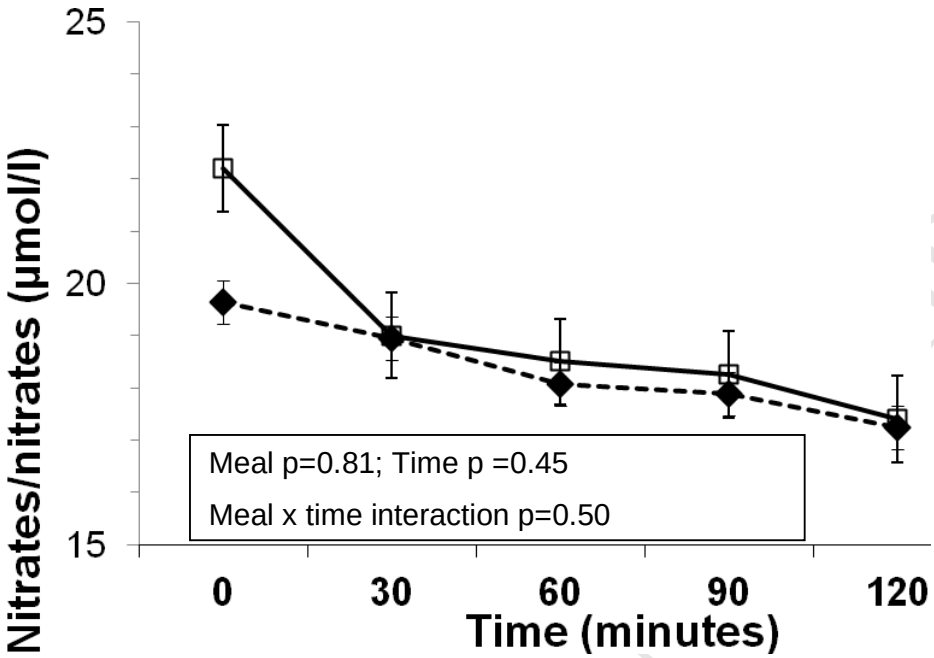
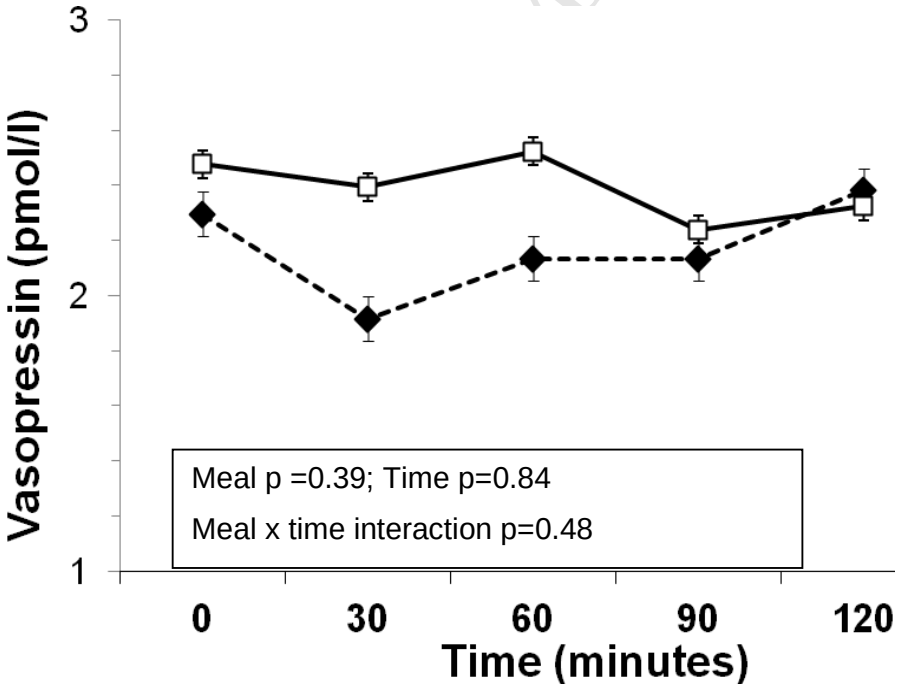
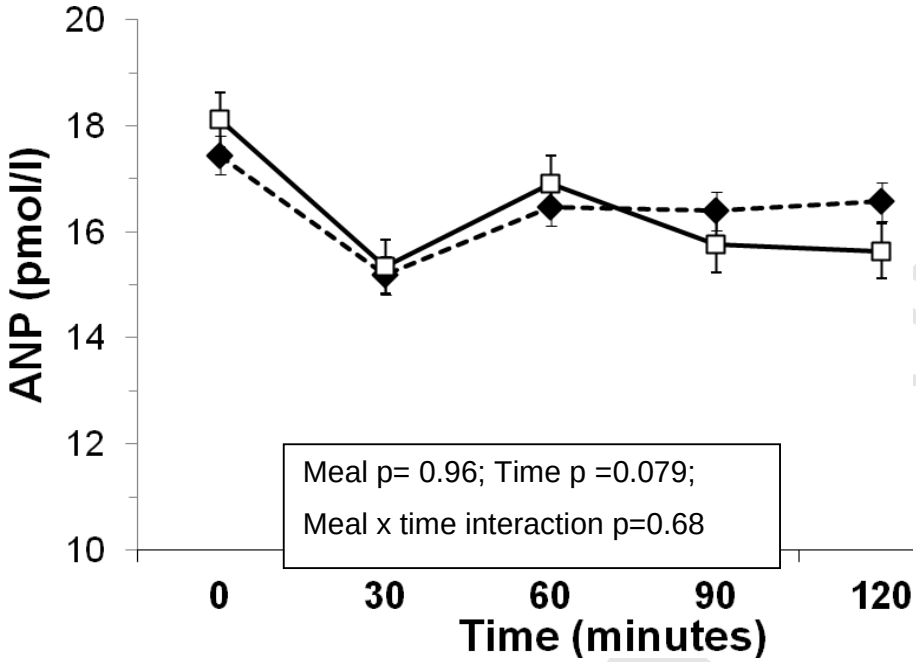
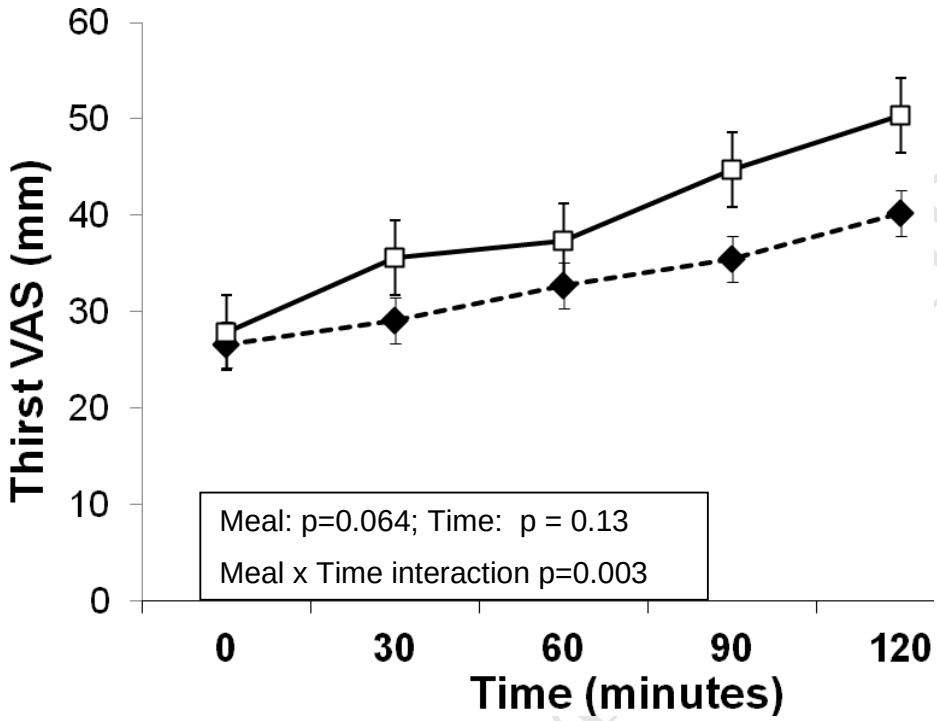

142
141
140
139
138
137
Sodium (mmol/l)
Meal p =<0.0001; Time p=0.007
Meal x time interaction p=0.008
0
30
60
90
120
Time (minutes)


296
295
294
293
292
291
290
289
288
Osmolality (mosmol/l)
Meal p=0.021; Time p=0.12
Meal x time interaction p=0.046
0
30
60
90
120
Time (minutes)


25
20
15
Nitrates/nitrates (µmol/l)
Meal p=0.81; Time p =0.45
Meal x time interaction p=0.50
0
30
60
90
120
Time (minutes)


3
2
1
Vasopressin (pmol/l)
Meal p =0.39; Time p=0.84
Meal x time interaction p=0.48
0
30
60
90
120
Time (minutes)





Postprandial effects of a high salt meal on serum sodium, arterial stiffness, and markers of nitric oxide production and endothelial function ATH_ATH-D-13-00829

Highlights

- 65 mmol Na causes a rise in serum sodium and osmolality
- Arterial stiffness was significantly increased after the high sodium meal
- Plasma nitrate/nitrite concentrations were not changed by the high sodium meal

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Title:
Postprandial effects of a high salt meal on serum sodium, arterial stiffness, markers of nitric oxide production and markers of endothelial function

Date:
2014-01-01

Citation:
Dickinson, K. M., Clifton, P. M., Burrell, L. M., Barrett, P. H. R. & Keogh, J. B. (2014). Postprandial effects of a high salt meal on serum sodium, arterial stiffness, markers of nitric oxide production and markers of endothelial function. ATHEROSCLEROSIS, 232 (1), pp.211-216. https://doi.org/10.1016/j.atherosclerosis.2013.10.032.

Publication Status:
Accepted manuscript