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

Kacie M. Dickinson [a,b,c], Peter M. Clifton [b,c,d], Louise M. Burrell [e], P. Hugh R. Barrett [f], Jennifer B. Keogh [d,*]

[a] Commonwealth Scientific and Industrial Research Organisation, Animal, Food and Health Science, Adelaide, South Australia, Australia
[b] Discipline of Physiology, Faculty of Health Science, University of Adelaide, South Australia, Australia
[c] The National Health and Medical Research Council of Australia Centre of Clinical Research Excellence in Nutritional Physiology, Interventions and Outcomes, Adelaide, South Australia, Australia
[d] School of Pharmacy and Medical Sciences, Division of Health Sciences, University of South Australia, Adelaide, South Australia 5000, Australia
[e] Departments of Medicine and Cardiology, Austin Health, University of Melbourne, Victoria, Australia
[f] Metabolic Research Centre, School of Medicine & Pharmacology & Faculty of Engineering, Computing and Mathematics, University of Western Australia, Perth, Western Australia, Australia

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ABSTRACT

Aim: The aim of the study was to determine if a high salt meal containing 65 mmol 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 5 mmol Na and a high sodium soup containing 65 mmol 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 min after the soup for 2 h. 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 × 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 65 mmol 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.
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.

1. 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 65 mmol Na

* Corresponding author. Tel.: +61 8 8302 2579; fax: +61 8 8302 2389.
E-mail address: jennifer.keogh@unisa.edu.au (J.B. Keogh).

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compared with a meal containing 5 mmol 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 65 mmol 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.

2. Methods

2.1. Subjects

Sixteen men and women aged between 18 and 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$18 kg/m^2 and $\leq$27 kg/m^2, systolic blood pressure (SBP) <130 mmHg, diastolic blood pressure (DBP) <90 mmHg, 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.

2.2. 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 65 mmol Na or a control meal (LSM) containing 5 mmol Na. Both meals contained 130 mg potassium (3.3 mmol). 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 24 h 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.

2.3. 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 min of rest four consecutive BP measurements were taken 1 min 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 250 ml soup within 5 min. Subsequent blood sampling (seated), BP and AIx and thirst were assessed at 30, 60, 90, 120 min after consuming the soup meal. Participants were not allowed to drink during the 2.5 h study protocol.

2.4. 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 min of collection at 3000 rpm for 10 min at 4 °C. The spun plasma was then stored at −80 °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 10 μL enzyme cofactor and 10 μL nitrate reductase After the plasma had been kept at room temperature for 3 h 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 2.5 μM. 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