EFFECTS OF DIETARY SODIUM INTAKE ON VASCULAR FUNCTION

A thesis submitted by

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DECLARATION OF ORIGINALITY

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Kacie Dickinson

DESCRIPTION OF THESIS

All of the studies have either been published (Chapter 3 and Chapter 4) or have been submitted for publication (Chapter 2) prior to completion of this thesis. Therefore the thesis was prepared in a Thesis by Publication style. Each chapter is formatted to conform to the style of the journal to which it was submitted. The methodologies are included within the relevant chapters. Author contribution statements are at the beginning of each chapter.

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ABSTRACT

Background

Increased dietary salt (sodium chloride) intake may increase the risk of cardiovascular disease independently of the effects on blood pressure by altering vascular endothelial function. It has previously been shown that reducing dietary salt intake can improve endothelial function after a short period of time however the effects of chronic moderate salt reduction and acute effects of a high salt meal on vascular function are not well studied in controlled trials. The thesis presents studies exploring the effects of manipulating dietary salt intake on endothelial function in normotensive overweight and obese and healthy adults.

Aims

To assess the effects of 1) longer term moderate salt reduction on vascular function in overweight and obese adults 2) a high salt meal on post-prandial vascular function in healthy adults and 3) explore potential mechanisms underlying effects of acute and chronic modification of salt intake on vascular function.

Results

In the first study overweight and obese adults (n=25) with normal blood pressure followed a moderately reduced salt diet (100mmol Na/day) and a usual salt diet (150mmol Na/day) for six weeks each in a randomised cross-over design. Following the reduced salt diet flow-mediated dilatation (FMD) was improved and endothelin-1 (a biomarker of endothelial function) improved significantly compared with the usual salt diet. The change in FMD occurred after two days, was sustained at 6 weeks and was significantly related to the change in 24hr urinary sodium to creatinine ratio. There were no changes in other markers of vascular stiffness (pulse wave velocity, augmentation index), plasma

nitrate/nitrite, asymmetric dimethylarginine, renin, aldosterone or blood pressure between treatments.

Population salt intakes are in excess of recommendations and published data suggest it may be common to consume in excess of 6g salt in a single meal. In the second study we tested the hypothesis that a high salt meal has adverse effects of vascular function in the postprandial period. The results showed that compared with a low salt meal (5mmol Na), the high salt meal (65mmol Na) impaired postprandial FMD and that the FMD response was not related to changes in blood pressure.

In the third study, the mechanisms underlying the effects on endothelial function observed following the high salt meal in Study 2 were investigated. The results showed that augmentation index (a measure of arterial stiffness), serum sodium and osmolality increase significantly in response to the high salt meal (65mmol Na) compared with the low salt meal (5mmol Na). No differences in plasma nitrate/nitrite, vasopressin, atrial natriuretic peptide or blood pressure were observed between treatments.

The main findings in of this thesis are that a modest reduction in dietary salt intake (3g/day) improves FMD rapidly after 2 days, which persists after 6 weeks, which may be explained by a fall in endothelin-1. Second, a single high salt meal has acute adverse effects on post-prandial arterial stiffness that is not accounted for by changes in plasma nitrate/nitrite or other vasoactive hormones. These results suggest mealtime sodium intakes as well as total daily salt intake may have implications for cardiovascular disease risk through altering endothelial function. Further work should be done to define the underlying short and long-term mechanisms by which salt affects endothelial function and long-term cardiovascular disease risk.

PUBLICATIONS ARISING FROM THIS THESIS

Peer Review articles

Dickinson KM, Clifton PM, Keogh JB. A reduction of 3g/day from a usual 9g/day salt diet improves endothelial function and decreases endothelin-1 in a randomised cross-over study in normotensive overweight and obese subjects
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Dickinson KM, Clifton PM, Burrell LB, Barrett PHR, Keogh JB. Postprandial effects of a high salt meal on serum sodium, arterial stiffness, markers of nitric oxide production and markers of endothelial function.
(Accepted 31/10/13 Atherosclerosis)

Dickinson KM, Clifton PM, Keogh JB. Endothelial function is impaired after a high salt meal in healthy subjects, *American Journal of Clinical Nutrition*, 2011; 93; 500-505.

Published Abstracts

Dickinson KM, Clifton PM, Keogh JB; The effects of modest dietary salt reduction on vascular function and blood pressure in overweight and obese adults, Hypertension, 2012; 60(30); A1-A667

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OTHER PUBLICATIONS DURING CANDIDATURE

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Willoughby SR, **Dickinson KM,** Schultz CD, Clifton PM, Keogh JB, Worthley MI, Lau DH, Sanders P; Effect of obesity on arterial stiffness in subjects with and without atrial fibrillation, Heart Lung and Circulation, 2012; 21; S13-S14.

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Keogh JB; **Dickinson KM**; Clifton PM. Salt Intake and Flow Mediated Dilatation, Obesity Facts 2009; 2 (Suppl.2):214-256

PRESENTATIONS ARISING FROM THIS THESIS

Oral presentations

Dickinson KM, Clifton PM, Keogh JB (2012) Long term effects of modest salt reduction on vascular function in overweight and obese subjects; *Nutrition Society of Australia Annual Scientific Meeting*, Wollongong, NSW, Australia, 27 -30 November [Oral]

Dickinson KM, Clifton PM, Keogh JB (2012) Effects of a high salt meal on postprandial sodium and nitric oxide concentration; *Australian Society of Medical Research SA Branch*, Adelaide, Australia, 6 June. [Oral]

Dickinson KM, Clifton PM, Keogh JB (2011) Long term effects of modest salt reduction on vascular function in overweight and obese subjects; *Nutrition Society of Australia and New Zealand Joint Annual Scientific Meeting*, Queenstown New Zealand, 29 November – 2 December. [Oral]

Dickinson KM, Keogh JB, Clifton PM (2010) The effects of a high salt meal on flow-mediated dilatation; *Nutrition Society of Australia Annual Scientific Meeting*, Perth Australia, 30 November – 3 December. [Oral]

Dickinson KM, Keogh JB, Clifton PM (2010) The effects of a high salt meal on flow-mediated dilatation; *Australian Atherosclerosis Society Annual Scientific Meeting*, Cairns Australia, 26-29 October. [Oral]

Dickinson KM, Keogh JB, Clifton PM (2010) The effects of a high salt meal on flow-mediated dilatation; *Nutrition Society of Australia Annual Scientific Meeting*, Perth Australia, 30 November – 3 December. [Oral]

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Poster Presentations

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Dickinson KM, Clifton PM, Keogh JB; (2012) Postprandial sodium and nitric oxide in response to a high salt meal, *International Society of Hypertension Meeting*, Sydney, Australia 30 Sept-4 Oct [Poster]

Dickinson KM, Clifton PM, Keogh JB (2012); Postprandial sodium and nitric oxide in response to a high salt meal, *American Heart Association High Blood Pressure Research Sessions*, Washington DC, USA, 19-22 September [Poster]

Dickinson KM, Clifton PM, Keogh JB (2012); Postprandial sodium and nitric oxide in response to a high salt meal, *The 34th Meeting of the European Society for Clinical Nutrition and Metabolism*, Barcelona, Spain, 8-11 September [Poster]

Dickinson KM, Clifton PM, Keogh JB (2011) The effects of a high salt meal on post-prandial sodium concentration and arterial stiffness; *Nutrition Society of Australia and New Zealand Joint Annual Scientific Meeting*, Queenstown New Zealand, 29 November – 2 December [Poster]

Dickinson KM, Clifton PM, Keogh JB (2011) The effects of a high salt meal on post-prandial sodium concentration and arterial stiffness; *Australian Atherosclerosis Society Annual Scientific Meeting*, Adelaide Australia, 19 October – 21 October.[Poster]

Dickinson KM, Clifton PM, Keogh JB (2011); A pilot study of modest salt reduction in obesity- effects on vascular function; *Australian and New Zealand Obesity Society Conference (ANZOS),* Adelaide Australia, 20-22 October [Poster]

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Dickinson KM, Keogh JB, Clifton PM (2009) Salt Intake and Flow Mediated Dilatation; *Australian Society for Medical Research Annual Scientific Meeting (SA branch)*, Adelaide Australia, 2 June. [Poster]

Dickinson KM, Keogh JB, Clifton PM (2009) University of Adelaide Faculty of Health Sciences Postgraduate Symposium "Salt intake and flow-mediated dilatation"

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2012

University of Adelaide Faculty of Health Sciences International Travel Award

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International Society of Hypertension Special Travel Grant Award

Foundation for High Blood Pressure Research Young Investigator Travel Grant

Nutrition Society of Australia Early Career Research Award

National Heart Foundation Postgraduate International Travel Award

University of Adelaide, Discipline of Physiology Travel Award

Faculty Finalist (Health Science) University of Adelaide 3-Minute Thesis Competition

Finalist Ross Wishart Memorial Award Australian Society of Medical Research

2011

University of Adelaide, Discipline of Physiology Publication Award

Nestle and Nutrition Society of Australia Student Travel Grant

2010

Nutrition Society of Australia Student Travel Award

Australian Atherosclerosis Society Student Travel Award

ABBREVIATIONS

AI	Adequate intake
ANOVA	Analysis of variance
ADH	Anti-diuretic hormone
AUC	Area under the curve
ADMA	Asymmetric dimethyl arginine
ANP	Atrial natriuretic peptide
AVP	Arginine vasopressin
AIx	Augmentation index
BP	Blood pressure
BMI	Body mass index
CVD	Cardiovascular disease
CRP	C-reactive protein
CV	Coefficient of variation
DBP	Diastolic blood pressure
ET-1	Endothelin-1
FMD	Flow-mediated dilatation
HSM	High salt meal
HR	Heart rate
ICAM-1	Intracellular adhesion molecule - 1
kJ	Kilojoule
LSM	Low salt meal
K	Potassium
MAP	Mean arterial pressure
NO	Nitric oxide

NRV	Nutrient reference value
PAT	Peripheral arterial tonometry
PWV	Pulse wave velocity
RHI	Reactive hyperaemia index
RAAS	Renin angiotensin aldosterone system
Na	Sodium
NaCl	Sodium chloride
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of the mean
UL	Upper limit
UNa	Urinary sodium
UNa:C	Urinary sodium creatinine ratio
UNa:K	Urinary sodium: potassium ratio
VAS	Visual analogue scale
VCAM-1	Vascular cellular adhesion molecule – 1