The role of the vascular wall in the salt and blood pressure homeostasis

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24712

Source
NTR

Brief title
SALT study

Health condition

salt
NaCl
sodium
sodium -and volume balance
blood pressure
extracellular volume
endothelial surface layer
glycocalyx
natrium
zout
bloeddruk
zout-en volume huishouding

Sponsors and support

Primary sponsor: Academic Medical Center
Source(s) of monetary or material Support: ZonMW, Nederlandse Nierstichting (Dutch Kidney Foundation)

Intervention

Outcome measures

Primary outcome

Primary endpoint will be the ECV as represented by the BP and Body Weight (BW) in response to a acute and chronic salt load, studied in healthy volunteers.

Secondary outcome

ESL will be assessed by three different (indirect) methods in association with different salt-conditions:

- Volume of microvascular ESL (by Sidestream Darkfield (SDF) imaging as described in the methods section)

- Transcapillary Escape Rate (TER-Alb) for measuring vascular permeability and determination of ESL function

- ESL shedding products (heparan sulphate, hyalorunan, syndecan-1, hyloranudase activity)

- GFR (determined with ioxehol)

Study description

Background summary

Rationale: Sodium (Na+) plays a key role in maintaining volume homeostasis and blood pressure (BP). The difference between Na+ intake and excretion, the Na+ balance, is regulated by the kidney. Regulation of the Na+ balance by the kidney is believed to be the main determinant of extracellular fluid volume (ECV). Recent studies have revealed that the Na+ balance is not only regulated by the kidney, but also in the interstitium of the skin. Here, binding of Na+ to glycosaminoglycans (GAGs) allows non-osmotic handling of Na+, thereby acting as a Na+ buffer. Based on these findings, we hypothesize that the endothelial surface layer (ESL), representing a complex sugar layer principally composed of negative-charged GAGs lining the endothelium, is an important determinant of volume homeostasis and BP by its ability to act as an immediate non-osmotic Na+ buffer. Furthermore, a perturbed ESL might lead to an increased ECV and BP response after a salt load. The volume of the ESL varies highly between individuals (0.5-2.3 L) and is know to be smaller in specific patient groups like diabetes type 1 and patients with chronic kidney disease. Due to its function in vascular physiology, including mechanotransduction, hemostasis, and blood cell-vessel wall interactions, the ESL is instrumental for vascular permeability, which might also be influenced

by the Na+ buffering capacity of ESL.
The putative non-osmotic buffer capacity of the endothelial GAGs without commensurate water retention has only been limitedly studied yet, but seems particularly relevant in clinical conditions characterized by volume overload (e.g., heart failure, hypertension, chronic kidney disease). If the endothelial GAGs are involved in non-osmotic Na+ storage, treatment strategies directed to restoration of the ESL would lead to improved BP and ECV control and, conceivably, to better cardiovascular outcome. This study focuses on a novel function of the ESL, namely the capacity to store Na+ non-osmotically.

Objective: In this study we will identify the role of the endothelial GAGs in Na+ and volume homeostasis. Is there a link between the ESL and an individual its susceptibility to Na+-excess?

Study design: In this project, we plan to conduct an experimental interventional cross-over study to investigate the Na+ storing capacity of the endothelial GAGs. For this, different Na+ conditions and the effect on ESL, ECV and BP, will be studied in healthy subjects.

Study population: Patients are 12 healthy non-smoking male subjects with non-treated normal (office) blood pressure (<140/90 mmHg).

Main study parameters/endpoints: We will study primarily the effects of a salt load on the haemodynamics and ECV in healthy subjects with a presumed normal ESL. Primary endpoint will be the ECV as represented by body weight and BP. Furthermore, the golden standard for ECV measurement will be performed. Other study paramaters consist of indirect measurements of the ESL dynamics and function as assessed with intravital microscopy of the sublingual microvasculature and transcapillary escape rate (TER). We will study the kidney function as represented by the glomerular filtration rate (GFR), fractional Na+ excretion, albuminuria and proteinuria. Finally, skin biopsies will allow study of the role of interstitial GAGs and macrophage influx in response to a salt load.

Study objective

Sodium (Na+) plays a key role in maintaining volume homeostasis and blood pressure (BP). The difference between Na+ intake and excretion, the Na+ balance, is regulated by the kidney. Regulation of the Na+ balance by the kidney is believed to be the main determinant of extracellular fluid volume (ECV). Recent studies have revealed that the Na+ balance is not only regulated by the kidney, but also in the interstitium of the skin. Here, binding of Na+ to glycosaminoglycans (GAGs) allows non-osmotic handling of Na+, thereby acting as a Na+ buffer. Based on these findings, we hypothesize that the endothelial surface layer (ESL),

representing a complex sugar layer principally composed of negative-charged GAGs lining the endothelium, is an important determinant of volume homeostasis and BP by its ability to act as an immediate non-osmotic Na+ buffer. Furthermore, a perturbed ESL might lead to an increased ECV and BP response after a salt load. The volume of the ESL varies highly between individuals (0.5-2.3 L) and is know to be smaller in specific patient groups like diabetes type 1 and patients with chronic kidney disease. Due to its function in vascular physiology, including mechanotransduction, hemostasis, and blood cell-vessel wall interactions, the ESL is instrumental for vascular permeability, which might also be influenced by the Na+ buffering capacity of ESL.
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Study design

day 8 of low sodium diet and day 8 and 9 of high sodium diet.

- extracellualr volume with tracer ioxehol

- BP and haemodynamic parameters with semi-automatc devices (Omron), Nexfin and Sphygmocor

- assessment of endothelial surfasce layer with Sidestream Darkfield Imaging, transcapillary escape rate (with labeled albumin) and assessment of ESL shedding products in blood

- divers blood and urine samples (endocrinology, chemistry, hematology, ESL shedding products) on different time points

Intervention

dietary intervention:

subjects will asked to adhere in random order for one week a low sodium diet (50 mmol Na/day) and for one week a high sodium diet (200 mmol Na/day)

At study visit concerning low sodium diet

- acute salt load with 500 ml NaCl 3%

At study visit concerning high sodium diet

- infusion with Lipopolysacharadie (LPS)

Contacts

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Eligibility criteria

Inclusion criteria

Healthy subjects (n=12)

- Male between 18 and 40 years of age

- Healthy, as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination (PE) and laboratory tests carried out in the screening visit.

- Non-treated office blood pressure ¡Ü 140/90 mmHg

- Capable of giving written informed consent and able to comply with the requirements and restrictions listed in the informed consent form

Exclusion criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study:

- An office blood pressure >140/90 mmHg

- A body mass index > 30 kg/m2

- A major illness in the past 3 months or any significant chronic medical illness that the Investigator would deem unfavourable for enrolment, including chronic inflammatory diseases

- A history of any type of malignancy within the past 5 years with the exception of successfully treated basal cell cancer of the skin

- A history of any renal disease

- A history of cardiovascular disease (in the past 6 months) defined as documented coronary artery disease including myocardial infarction, (un-)stable angina pectoris or acute coronary syndrome, precutenaous transluminal coronary angioplasty, coronary artery bypass grafting, cerebrovascular disease including ischemic and hemorrhagic stroke or a subarachnodial bleeding, or peripheral artery disease including aortic aneurysmata

- A history of coagulation disorders

- A history of primary hyperlipoproteinemias

- A history of hypersensitivity or allergy to iodium or to shell fish

- A history, within 3 years, of drug abuse (including benzodiazepines, opioids, amphetamine, cocaine, THC, methamphetamine)

- A history of alcoholism and/or is drinking more than 3 units of alcohol per day. Alcoholism is defined as an average weekly intake of >21 units for males. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits

- Difficulty in donating blood or limited accessibility of a vein in left and right arm

- Subject has donated blood in last 3 months

- Use of tobacco products

- Any other issue that, in the opinion of the Investigator, could be harmful to the subject or compromise interpretation of the data

- Prior participation in a trial where the subject received intravenous endotoxin (LPS) infusion

- Any clinically relevant abnormality noted on the 12-lead ECG as judged by the Investigator or an average QTcB or QTcF > 450 millisec

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2013
Enrollment:	12
Type:	Anticipated

Ethics review

Positive opinion

Date:	29-07-2013
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 40170
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL3933
NTR-old	NTR4095
CCMO	NL42890.018.13
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON40170

Study results

Summary results
N/A