SALT-2 study: Role of endothelial surface layer in regulating the sodium balance and extracellular fluid volume

Gepubliceerd: 12-09-2014 Laatst bijgewerkt: 15-05-2024

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Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON28711

Bron
NTR

Verkorte titel
SALT-2

Aandoening

endothelial surface layer
sodium
extracellular volume
blood pressure

Ondersteuning

Primaire sponsor: Academic Medical Center, Amsterdam
Overige ondersteuning: ZON-MW, The Netherlands Organization for Health Research and Development

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

We will primarily study the effects of a salt load on the haemodynamics, ECV and ESL in patients with acquired and congenital loss of the ESL. Primary endpoint will be the ECV as represented by body weight, BP and iohexol measurements.

Toelichting onderzoek

Achtergrond van het onderzoek

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. A perturbed ESL might therefore lead to an increase in ECV and BP after a salt load. The volume of the ESL varies highly between individuals (0.5-2.3 L) and is known to be smaller in specific patient groups such as diabetic patients and patients with chronic kidney disease. 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 of the study:
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 individual 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, the effect of different

Na+ conditions on ESL, ECV and BP, will be studied in diabetic and hereditary multiple exostosis (HME) patients.

Study population:
Patients are 12 non-smoking male type 1 diabetes patients (DM1) with microalbuminuria (model for acquired loss of ESL) and 12 male patients with HME (model for genetic loss of ESL through a defect in GAG polymerization).

Intervention:
High salt diet (>200 mmol Na+ daily) for 1 week, and low salt diet (<50 mmol Na+ daily) for one week, each in random order. Furthermore, all subjects will receive a hypertonic salt infusion at day 8 of the low salt diet to study the effects of an acute salt load.

Primary study parameters/outcome of the study:
We will primarily study the effects of a salt load on the haemodynamics, ECV and ESL in patients with acquired and congenital loss of the ESL. Primary endpoint will be the ECV as represented by body weight, BP and iohexol measurements.

Secundary study parameters/outcome of the study:
Other study paramaters consist of indirect measurements of the ESL dynamics and function assessed by imaging of the sublingual microvasculature, measurement of ESL shedding products and determination of the transcapillary escape rate (TER) of I125-albumine. The kidney function will be studied by estimating the glomerular filtration rate (eGFR) and measurement of the fractional Na+ excretion and albuminuria. Finally, skin biopsies will allow studying the role of interstitial GAGs and macrophage influx in response to a salt load.

Doel van het onderzoek

Until recently, it was believed that the sodium (Na+) balance is only regulated by the kidney. 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, the hypothesis will be 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. Based on the hypothesis that a perturbed ESL might lead to an increased ECV and BP response after a salt load, this study focuses on a novel function of the ESL, namely the capacity to store Na+ non-osmotically. If the ESL is involved in non-osmotic Na+ storage, treatment strategies directed to restoration of the ESL would lead to improved BP and ECV

control.

Onderzoeksopzet

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Onderzoeksproduct en/of interventie

High salt diet (>200 mmol Na+ daily) for 1 week, and low salt diet (<50 mmol Na+ daily) for one week, each in random order. Furthermore, all subjects will receive a hypertonic salt infusion at day 8 of the low salt diet to study the effects of an acute salt load.

Contactpersonen

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen

(Inclusiecriteria)

1. Diabetic patients (n=12)

- Male between 18 and 40 years old

- Known with Diabetes Mellitus - type 1

- Microalbuminuria defined as either albuminuria 20-200 mg/L in a morning urine sample or albuminuria 30-300 mg/24 hrs collected in a 24-hours urine collection or albumin-to-creatinin ratio 2,5-25 mg/mmol in a morning urine sample.

- Stable renal function (creatine clearance > 60 ml/min and < 6 ml/min per year decline) on stable therapy with RAAS inhibiting agents - HbA1c levels between 6.0 and 10.0% (42-86 mmol/mol) during the 6 months preceding the study

- Multiple injections of insulin a day

- Able to provide written informed consent and to comply with the requirements and restrictions listed in the informed consent form

2. HME patients (n=12)

- Male between 18 and 40 years old - Documented Hereditary Multiple Exostoses

- Stable renal function (creatinin clearance > 60 ml/min and < 6 ml/min per year decline, no proteinuria)

- Able to provide written informed consent and to comply with the requirements and restrictions listed in the informed consent form

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- 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

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

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd

Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	27-06-2014
Aantal proefpersonen:	24
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	12-09-2014
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 46844
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL4645
NTR-old	NTR4788
CCMO	NL48278.018.14
OMON	NL-OMON46844

Resultaten

Samenvatting resultaten
none