The functional consequences of the 57 kb deletion for the TRPV1-receptor in cystinosis patients

Published: 14-05-2013
Last updated: 24-04-2024

(i) To compare the DBF response to capsaicin between cystinosis patients, homozygous and heterozygous for the 57-kb deletion, and matched controls.(ii) To compare the skin sensitivity response after capsaicin application between cystinosis patients,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON39916

Source
ToetsingOnline

Brief title
Functioning of TRPV1 in cystinosis patients

Condition

- Renal and urinary tract disorders congenital

Synonym
Fanconi syndrome, kidney disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: KULeuven

Intervention

Keyword: 57 kb deletion, Capsaicin, Cystinosis, TRPV1

Outcome measures

Primary outcome

1. Change in dermal blood flow in respons to topical applied capsaicin over

time.

2. Difference in skin sensitivity (pain- and sensitivitythreshold) after

application of capsaicin between cystinosis patients,homozygous and

heterozygous for the 57-kb deletion, and controls.

3. Difference in temperature sensitivity between cystinosis patients,homozygous

and heterozygous for the 57-kb deletion, and controls.

Secondary outcome

not applicable

Study description

Background summary

Cystinosis is a rare autosomal recessive disorder, characterized by the abnormal accumulation of cystine in the lysosomes. This accumulation occurs in almost all cells and tissues, including the conjunctivae, corneas, liver, spleen, lymph nodes, intestines, brain and kidneys.1 The most common and severe form is infantile nephropathic cystinosis. Patients are usually asymptomatic at birth, but at the age of 6 months they present with failure to thrive, vomiting, constipation, polyuria, excessive thirst, dehydratation and sometimes rickets. Cystinosis is mostly caused by mutations in the cystinosin gene (CTNS). The major mutation, which is present in almost 50% of the cystinosis patients, is a 57-kb deletion. This deletion removes the first 9 exons and a part of exon 10 of the CTNS gene. Exon 10 of the CTNS gene is a upstream 5* region that encodes for the CARKL gene and also for the first two noncoding exons of the transient receptor potential channel, vanilloid subfamily member 1 (TRPV1) gene.3

TRPV1 belongs to the transient receptor potential (TRP) superfamily of cation channels. TRPV1 is primarily expressed in sensory nerves and is activated by heating (>43°C) and a wide range of chemical stimuli. One of these chemical stimuli is capsaicin, the pungent ingredient in hot chilli peppers.4 This receptor is expressed on a subpopulation of primary sensory neurons consisting of A*- and C-fibre nociceptors. Though several putative endogenous ligands of the TRPV1 receptor have been identified, their physiological and pathophysiological effects in and outside the sensory nervous system remain unclear.5 In contrast, the effect of binding of the exogenous ligand capsaicin with the TRPV1 receptor is well known to provoke the release of a number of bioactive substances including calcitonin gene-related peptide (CGRP).6,7 These substances, in turn, act on target cells in the surrounding tissue such as mast cells, immune cells and vascular smooth muscle cells. The resulting response is characterized by redness and warmth (secondary to vasodilatation), swelling (secondary to plasma extravasation) and allodynia (i.e. hypersensitivity to heat and touch secondary to alterations in the excitability of primary sensory neurons). Collectively, these changes are referred to as *neurogenic inflammation*, that is, inflammatory symptoms resulting from the release of substances from the afferent fibres of primary sensory neurons.

The present study wants to test the following hypotheses:

(i) The DBF response to topical applied capsaicin is decreased in cystinosis patients, compared to matched control subjects.

(ii) The skin sensitivity response after topical applied capsaicin is decreased in cystinosis patients, compared to matched control subjects.

(iii) The temperature sensitivity is decreased in cystinosis patients, compared to matched control subjects.

Study objective

(i) To compare the DBF response to capsaicin between cystinosis patients, homozygous and heterozygous for the 57-kb deletion, and matched controls.
(ii) To compare the skin sensitivity response after capsaicin application between cystinosis patients,homozygous and heterozygous for the 57-kb deletio,n and matched controls.
(iii) To compare the temperature sensitivity between cystinosis patients,homozygous and heterozygous for the 57-kb deletion, and matched controls.

Study design

This is a single-blinde study, consisting of 1 visit of approximately 2 hours. During this study visit, the following tests will be performed:

1. The capsaicin test
During this test, 3 rubber O-shape rings will be placed on the volar surface of the forearm. In the 2 most proximal rings, 1000µg/20µL capsaicin (adults) or 300µg/20µl (<18 years old) will be applied. In the most distal ring, placebo will be applied. Thereafter, the change in dermal blood flow will be measured with the use of Laser Doppler Perfusion Imaging on baseling (i.e. 30 minutes after acclimatization) and on 10,20,30 and 40 minutes after capsaicine/placebo application in each ring.
2. The Von Frey test
During this test, the skin sensitivity will be tested, 40 minutes after capsaicin application, with the use of Von Frey filaments. These filaments are standarised fine-gauge metal wires, to test skin sensititivity to pinch and mechanical stimuli.
3. Temperature test
Temperature sensitivity will be tested by applying gradual increasing and decreasing temperatures to determine the temperature sensitivity threshold.

Study burden and risks

1. Topical application of capsaicin can cause temporarily redness, irritation, warmth and hypersensitivity of the skin.
2. Subjects can experience hypersensitivity of the skin during the Von Frey test and temperature test.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grote plein zuid 8
Nijmegen 6500 HB
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grote plein zuid 8
Nijmegen 6500 HB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- White (Caucasian) male or female subjects, aged >8 year.
-Subject is capable and willing to give informed consent.

Exclusion criteria

- Any abnormality of the skin which may interfere with the study assessments.
- Excessive hair growth on the volar surface of the forearm.
- Excessive tanning (any exposure to sunlight or a tanning bed which would cause a sunburn reaction) throughout the study and incapable to cover the forearms for 24 hours prior to the study period.
- Subject using topical treatments on the forearm.
- History of sensitivity to the fruits of capsicum plants (e.g. chilli peppers).
- Any situation that can compromise the study, including a predictable lack of cooperation from the volunteer.
- Female subject is pregnant or breastfeeding

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-01-2014
Enrollment:	13
Type:	Actual

Ethics review

Approved WMO

Date:	14-05-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL42764.091.12