The vasoactive role of TRPV1, TRPA1 and TRPM3 in human dermal arteries

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In this study the primary objective is to investigate whether activation of TRPV1, TRPA1 and TRPM3 by selective channel agonists induces vasodilation in human dermal arteries. If the primary objective is achieved, the secondary objective is to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Maternal complications of pregnancy
Study type	Observational invasive

Summary

ID

NL-OMON48401

Source
ToetsingOnline

Brief title
Dermal TRP study

Condition

- Maternal complications of pregnancy
- Obstetric and gynaecological therapeutic procedures
- Vascular hypertensive disorders

Synonym
pre-eclamspia

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Artery, Pharmacology, Pre-eclampsia, Subcutaneous fat

Outcome measures

Primary outcome

Endpoints:

- Contractions and relaxations induced by the agonists studied.

- Inhibition of these contractions and relaxations by the antagonists studied.

With the current in vitro study, we hope to substantiate these target engagement biomarker models as some scientific questions remain unanswered:

1) Which vasodilatory mediators are released upon activation of TRPV1 and TRPA1 with capsaicin and cinnamaldehyde, respectively?

2) Does activation of TRPM3 by pregnenolone sulfate and/or CIM0216 induce vasodilation and if so, which mediators are involved in this response?

In an attempt to answer these questions, we want to evaluate the effect of capsaicin, cinnamaldehyde, pregnenolone sulfate and CIM0216 on human dermal arteries, the vessels targeted in the biomarker models in vivo. Different experimental conditions will be applied, e.g. in the presence or absence of specific channel antagonists as well as antagonists of possible mediators involved (e.g. CGRP-, NK1-, COX-inhibitors*).

Secondary outcome

In addition, as an exploratory objective, we want to compare the vasodilatory responses resulting from TRPV1, TRPA1 and TRPM3 activation between dermal arteries obtained from both normotensive pregnant women and preeclamptic women

undergoing a caesarean section. TRPV1 has recently been pointed out as one of the receptors dysregulated in preeclampsia [5]. Furthermore, calcitonin-gene related peptide (CGRP), a potent vasodilatory peptide and possible mediator released upon TRP activation, has been suggested to play a role in the vascular tone of the placenta.

Study description

Background summary

Transient receptor potential (TRP) ion channels are expressed in almost all mammalian cell types, where they contribute to a variety of physiological functions including vision, hearing, taste perception and thermosensation. In addition, several members of the TRP ion channel family have been implicated in nociception and are believed to play a role in different chronic pain conditions including neuropathic pain and migraine, making them appealing drug targets. Of particular interest are TRP Vanilloid 1 (TRPV1), Ankyrin 1 (TRPA1) and Melastin 3 (TRPM3), all pursued to develop novel analgesics [4,8].
To get a better understanding of the (patho)physiological role of these channels in human, in vivo target engagement biomarker models can be developed. The principle behind these models is that the topical application of a selective agonist will activate the specific TRP channel of interest and subsequently result in the release of vasoactive neuropeptides, producing a measurable increase in dermal blood flow. Such target engagement biomarker models have been developed for TRPV1, using capsaicin as a selective agonist [6] and for TRPA1, using cinnamaldehyde [1]. In the future, we plan to set up a similar model for TRPM3 using pregnenolone sulfate and the synthetic compound CIM0216 as chemical agonists [3,7].

We have ample experience in studying human arteries in our laboratory with myograph experiments, including subcutaneous fat arteries obtained from pregnancies [e.g., 9].

References:

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Study objective

In this study the primary objective is to investigate whether activation of TRPV1, TRPA1 and TRPM3 by selective channel agonists induces vasodilation in human dermal arteries. If the primary objective is achieved, the secondary objective is to examine the mediators involved in this response. As an additional objective, the functionality of TRPV1, TRPA1 and TRPM3 will be compared between normotensive and preeclamptic pregnant women.

Study design

After arrival at the laboratory, segments of the dermal arteries will be mounted in organ baths for isometric contraction measurements. The tromboxane A2 analogue U46619 will be administered to the segments as internal standard for the contractile force developed by the segment. Also the endothelial quality will be studied by assessing relaxations to bradykinin/substance P. We will study vasodilation to selective TRPV1 (capsaicin), TRPA1 (cinnamaldehyde) and TRPM3 (pregnenolone sulfate and CIM0216) agonists in the presence or absence of a precontraction induced by a threshold concentration of U46619, as well as after addition of specific TRPV1 (capsazepine), TRPA1 (HC030031) and TRPM3 (isosakuranetin) channel antagonists and antagonists of possible mediators involved (CGRP, COX, NK1*).

Study burden and risks

We expect no (or minimal) risks associated with participation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Both, normotensive and preeclamptic subjects must meet the following inclusion criteria:

- Women >= 18 years old
- Capable of understanding the purpose and (minimal) risks of the study, fully informed and given written informed consent (signed Informed Consent Form had

been obtained)
- Subjects undergoing elective caesarean section

Moreover, at least 1.5 cm of tissue of both, normotensive and preeclamptic subjects, should be available for our study.

Exclusion criteria

A potential normotensive subject who meets any of the following criteria will be excluded from participation in this study:
- Admission to an Intensive Care Unit (ICU) for any reason
- Subjects undergoing an emergency caesarean section

A potential preeclamptic subject who meets any of the following criteria will be excluded from participation in this study:
- Admission to an Intensive Care Unit (ICU) for any reason
- Subjects diagnosed with the HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets)
- Subjects undergoing an emergency caesarean section

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-07-2020
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	04-07-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL68891.078.19