The effect of hypothalamic temperature setpoint inhibition at a central and peripheral level on exertional elevations of core body temperature.

Published: 23-01-2014
Last updated: 23-04-2024

To determine changes in core body temperature under simultaneous inhibition of prostaglandin E2 synthesis at a central and peripheral level (paracetamol + ibuprofen) compared to a control condition (no inhibition of PGE2 synthesis) and with…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON38258

Source
ToetsingOnline

Brief title
Setpoint inhibition and exertional elevations of core body temperature.

Condition

- Other condition

Synonym
Exertional hyperthermia, overheating during exercise

Health condition

Systemisch: thermoregulatie

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Exercise, Hyperthermia, Setpoint, Thermoregulation

Outcome measures

Primary outcome

- Core body temperature.

Secondary outcome

- Skin Temperature

- Interleukin-1*

- Interleukin-6

- Heart rate

- Body Weight

- Rating of Perceived Exertion (BORG-score)

- Thermal Comfort score

- Thermal sensation score

Study description

Background summary

Core body temperature (CBT) is normally strictly regulated by the body*s natural thermostat, localized in the hypothalamus. This thermostat compares the measured core body temperature with the hypothalamic temperature setpoint, which is set between 36.0 * 37.5°C in physiological situations. If the CBT becomes too high, the hypothalamus initiates several adaptational mechanisms

(e.g. peripheral vasodilatation, sweating and behaviour adaptations) in order to pass on the excess heat to the environment, allowing the CBT to return to its normal values. Physical exercise almost always results in an elevated CBT, and current concepts state that this is solely the result of metabolic heat production due to muscle labour whilst the temperature setpoint remains unchanged. Another (non-exertional) mechanism that leads to an elevated CBT is the elevation of the hypothalamic temperature setpoint itself. Several processes are activated by this mechanism, resulting in an increased CBT. An elevated hypothalamic temperature setpoint is typically caused by pro-inflammatory cytokines such as IL-1* or IL-6 which are released during infection or inflammation. These cytokines stimulate the enzyme cyclo-oxygenase (COX) to produce the mediator prostaglandin E2 (PGE2), and it is this mediator that increases the temperature setpoint in the hypothalamus. The most important antipyretic medications act through inhibition of COX on a central level (paracetamol/acetaminophen) or peripherally (NSAIDs). Whilst it is postulated that the CBT rise during physical exercise is solely the result of metabolic heat production, it has also been described that several pro-inflammatory cytokines are released during exercise. It is therefore also possible that the hypothalamic setpoint becomes elevated during exercise, and this would partly explain the CBT rise if this is indeed the case. Gaining a better insight into this mechanism is important, since a better understanding of thermoregulation during exercise could lead to new points of action in the prevention of hyperthermia and could hence also lead to better prevention of heat-related disorders. Recently, a few studies were published that substantiate that an altered temperature setpoint during exercise may play a role, however these studies were methodologically limited by inhibiting COX at only one level. In the present study, we want to test the hypothesis that the CBT rise during exercise is partly due to an elevated hypothalamic temperature setpoint. We will test this hypothesis by inhibiting PGE2 synthesis at both a central and a peripheral level in healthy subjects, after which they will perform submaximal treadmill exercise for 60 minutes whilst CBT will be continuously measured. By blocking PGE2 synthesis at both a central and a peripheral level, we will surpass the methodological limitations of previous studies that inhibited PGE2 synthesis at only a single level. In addition to inhibiting COX centrally and peripherally, we will also inhibit PGE2 synthesis as a third condition in order to compare our findings with previous studies.

Study objective

To determine changes in core body temperature under simultaneous inhibition of prostaglandin E2 synthesis at a central and peripheral level (paracetamol + ibuprofen) compared to a control condition (no inhibition of PGE2 synthesis) and with inhibition of PGE2 synthesis at only a central level (paracetamol) during 60 minutes of submaximal treadmill exercise.

Study design

Randomised controlled trial with crossover design.

Intervention

Subjects will all perform submaximal treadmill exercise. Before every exercise test, one of the following interventions will be applied in random order 45 minutes prior to the start of exercise:
A: Central and peripheral COX-inhibition: Paracetamol 1000mg dissolved in 100mL water + ibuprofen 400mg dissolved in 100mL water.
B: Central COX-inhibition: Paracetamol 1000mg dissolved in 100mL water + 100mL water (as control for ibuprofen).
C: No COX-inhibition: Two times 100mL water (control for paracetamol and ibuprofen).

Study burden and risks

Maximal exercise tests are safe and are not associated with substantial health risks. A potential risk of maximal exercise tests is the development of an acute coronary syndrome. In subjects of 40 years and younger, sudden cardiac death is mainly ascribed to congenital cardiac disorders, whilst in subjects older than 40 years sudden cardiac death is mainly ascribed to cardiovascular disease. It should be emphasized that these potential complications are rare. Submaximal exercise tests are also safe and are not associated with substantial health risks. Moreover, this type of exercise is performed by millions of recreational athletes without the occurrence of (serious) health problems. The potential risks of submaximal exercise tests are similar to those of maximal exercise tests, however the risk is lower due to the submaximal aspect of these tests. All test locations are equipped with an emergency kit containing emergency medication. This kit is compiled and checked by the institutional pharmacy of the Radboudumc. Furthermore, an Automatic External Defibrillator (AED) is present at all test locations. Furthermore, a venipuncture will be performed at a total of 6 time points throughout the study in order to draw a blood sample in which IL-1* and IL-6 will assessed. A complication that may occur after a venipuncture is the occurrence of a haematoma. This haematoma is self-limiting and will heal without any significant health risks.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Philips van Leydenlaan 15
Nijmegen 6525 EX
NL

Scientific
Universitair Medisch Centrum Sint Radboud

Philips van Leydenlaan 15
Nijmegen 6525 EX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age <=> 18 years
- Willing to participate in all parts of the present study, and willing to confirm this by signing an informed consent.
- Trained in running (performs running exercise <=>1.5 hours/week on average)

Exclusion criteria

- A history of any hypersensitivity reactions or idiosyncratic reactions in response to paracetamol (acetaminophen) or ibuprofen.
- A history of or ongoing obstructive/inflammatory bowel disease or surgery to the gastro-intestinal tract (not contraindicated: appendectomy or cholecystectomy).
- The presence of an implanted electric (medical) device, such as an ICD or pacemaker.
- Expected to undergo an MRI scan within 5 days after one of the submaximal exercise tests.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-03-2014
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO

Date:	23-01-2014
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	NL47201.091.13

Study results

Date completed:	12-01-2016
Actual enrolment:	16