Role of the central brain clock in the pathophysiology of insulin resistance

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Primary Objective: to determine the activity rhythm of the SCN in humans with progressive stages of insulin resistanceSecondary Objective(s): to determine the daily rhythm of the peripheral clock in buccal cells in humans with progressive stages of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON53722

Source
ToetsingOnline

Brief title
Brain Clock and Insulin Resistance

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Insulin resistance, prediabetes

Health condition

De perfusie/activiteit van de centrale hersenklok (SCN)

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Ministerie van OC&W,Vereniging Park Herstellingsoorden

Intervention

Keyword: fMRI, Insulin resistance, Suprachiasmatic nucleus, Type 2 diabetes mellitus

Outcome measures

Primary outcome

The daily rhythm in SCN activity. The primary outcomes are mean SCN activity,

the timing of the highest and lowest value of SCN activity, and the difference

between the highest and lowest value of SCN activity (i.e. the amplitude)

These outcomes will be assessed with:

• baseline SCN perfusion using Arterial Spin Labelling (non-invasive method),

• SCN functional connectivity using a seed-based analysis of resting state data

• the SCN response to light using the BOLD response

Secondary outcome

• behavioural sleep wake rhythms assessed with actigraphy

• sleep wake rhythm assessed with sleep wake diaries

• peripheral clock rhythms by non-invasive collection of buccal cells

• fasting plasma glucose and fasting plasma insulin at 6-month and

12-months follow up (this will only be assessed in groups 1 and 2)

Study description

Background summary

Diabetes mellitus (DM) has an increasing worldwide incidence with over 422 million affected individuals. Hyperglycemia in DM causes major morbidity and mortality due to its macrovascular and microvascular complications. Insulin resistance is a key pathophysiological process in the development of hyperglycemia in most patients with diabetes mellitus. Lifestyle interventions represent the initial treatment of insulin resistance, but they are frequently ineffective in clinical practice, possibly because they currently do not acknowledge the importance of meal timing and circadian synchrony.
Disruption of circadian synchrony leads to insulin resistance. Animal studies and post-mortem human brain studies suggest that the master brain clock in the hypothalamic suprachiasmatic nucleus (SCN) plays a role in the development of insulin resistance, but it is unknown if in vivo SCN rhythms are disturbed in patients with insulin resistance. In the present project we will therefore determine the SCN activity rhythm using advanced functional brain imaging.
The circadian timing system regulates daily rhythms in food intake, energy expenditure and glucose metabolism. The circadian timing system consists of the master clock in the SCN, and peripheral clocks in other tissues. The SCN regulates daily rhythms in energy expenditure and food intake. Peripheral clocks in metabolic tissues such as liver, muscle, and adipose tissue, regulate local insulin sensitivity and glucose metabolism. The SCN generates an endogenous rhythm of approximately 24 hours (that is, a circadian rhythm) and uses light input from the retina to synchronize this rhythm with the environment. The core molecular timekeeping process in the central and peripheral clocks is a transcriptional-translational feedback loop.
Circadian disruption is defined as disturbed synchrony between the daily rhythms of darkness/light, fasting/eating, sleep/wake, and the central and peripheral clock rhythms of the circadian timing system. Due to the ubiquitous availability of food and artificial light, nowadays the synchrony between the daily rhythms of food intake, physical activity, and the solar day is often disrupted in our 24-hour society. Evidence suggests that circadian disruption leads to insulin resistance, but most authors focus exclusively on the disturbed peripheral clock rhythms. For example, several studies showed evidence of disturbed peripheral clocks in insulin resistant patients.
We now hypothesize that also the central brain clock has an important role in the development of human insulin resistance. In support, in rodents electrical stimulation of the SCN causes hyperglycemia and SCN lesions induce insulin resistance. Furthermore, our group showed in 2019 in postmortem brains of patients with type 2 DM that the SCN contains reduced numbers of arginine vasopressin (AVP) and vasoactive intestinal polypeptide (VIP) neurons, which are the key timekeeping neurons in the SCN, compared to subjects with normal insulin sensitivity. In line, patients with type 2 DM, as well as type 1 DM have disturbed sleep-wake patterns. However, up to date no-one has investigated whether the in vivo activity rhythm of the SCN is affected in patients with insulin resistance. In the present project, we will use state-of-the-art

functional imaging of the SCN to determine the activity rhythm of the SCN in humans with progressive stages of insulin resistance.

Study objective

Primary Objective: to determine the activity rhythm of the SCN in humans with progressive stages of insulin resistance
Secondary Objective(s): to determine the daily rhythm of the peripheral clock in buccal cells in humans with progressive stages of insulin resistance

Study design

This is an observational cohort study with a duration of two weeks. For group 1 (obese people with normal insulin sensitivity) and group 2 (obese people with insulin resistance) we will also assess fasting plasma glucose and insulin at 6-month and 12-month follow-up, to assess potential correlations within these groups between SCN dysfunction and the development of insulin resistance or type 2 diabetes.The study will be performed at Amsterdam UMC, location AMC, with imaging performed at the Spinoza Institute for neuroimaging.

Study burden and risks

Participants will fill in a food diary, a sleep-wake diary for two weeks, and participants will wear an actigraphy unit.
Subsequently, they will be admitted to our research unit for 24 hr. They will be allowed to adhere to their regular sleep wake cycle except for a 60-min awakening for SCN imaging.
An average Zeitgeber time (ZT) 0:00 will be calculated for each participant based on the baseline MCTQ questionnaire and sleep-wake dairy. Zeitgeber time 0:00 represents the average wake-up time of the individual subject. At 4 time-points across the diurnal cycle (ZT 2:00, 08:00, 14:00, and 20:00), we will image baseline SCN perfusion using fMRI.
In addition to the fMRI measurements, we will assess peripheral clock rhythms by non-invasive collection of buccal cells at 4 timepoints across the diurnal cycle followed by qPCR of the clock genes PER1, PER2, PER3, CRY, and ARNTL.
For group 3 (obese people with type 2 diabetes) we will assess glucose levels using a finger stick blood test at the same 4 time points across the diurnal cycle.

There is a small chance that the MRI scan shows an incidental finding. In that case, Spinoza Neuroimaging center procedure is that the MRI scan is forwarded to an Amsterdam UMC radiologist to check this finding. If the radiologist confirms a finding for which medical treatment may be necessary, this information will be passed on to the participant and the participant*s general practitioner by the researcher. This information is also included in the patient information and informed consent.

There is a chance that patients with insulin resistance at baseline will be diagnosed with DM2 during follow-up. This information will be shared with the participant and the participant*s general practitioner, as stated in the informed consent form. The general practitioner will treat participants with newly diagnosed type 2 diabetes or the general practitioner will refer these participants to a specialist in internal medicine, if necessary.

Participant* sleep will be interrupted for one hour to obtain fMRI images at ZT 20:00. Therefore, for safety reasons, subjects will be instructed not to participate in traffic and to have someone accompany them when leaving the research unit after the 24-hour admission.

Patients with type 2 DM will be instructed to stop metformin treatment from three days prior to imaging and to resume metformin treatment after imaging (4 days in total). This may cause a temporary elevation of plasma glucose but has no long term risks. Patients with type 2 diabetes will be instructed to measure their blood glucose once in the morning prior to the MRI sessions, using a finger stick blood glucose test. We will determine the blood glucose to determine the increase of fasting plasma glucose after temporarily stopping metformin treatment, and to perform correlation analyses of increased glucose on SCN activity.

Participants are not allowed to wear a face mask during fMRI imaging, as a face mask may alter the BOLD signal. Scanning operators will wear a face mask.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Group 1: obese people with normal insulin sensitivity
• age 25-65 years
• BMI>30
• fasting plasma insulin <=62 pmol/L
• fasting plasma glucose <5.6 mmol/L
• HOMA-IR <= 4.5
Group 2: obese people with insulin resistance
• age 25-65 years
• BMI>30
• fasting plasma insulin >62 pmol/L
• fasting plasma glucose >=5.6 mmol/L
• not fulfilling the ADA criteria for type 2 DM
Group 3: obese subjects with overt type 2 DM
• age 25-65 years
• BMI>30
• diagnosis type 2 DM according to ADA criteria

Exclusion criteria

• An extreme chronotype (midpoint of sleep on free days (MSFsc) before 2:00 or after 6:00).
• Active psychiatric disorder (including circadian rhythm sleep disorder) as defined in DSM 5
• Disorders of the central nervous system (Early-onset dementia, stroke, epilepsy, Parkinson*s disease, brain tumour)
• Severe visual impairment (WHO classification)
• Shift workers
• Crossing > 2 time zones in the 3 months before the study
• Patients with type 2 DM receiving insulin treatment or GLP-1 agonists
• MRI safety and contraindications
o The presence of MRI-incompatible metal implants or devices:
o Claustrophobia

o Pregnancy
o Waist circumference or shoulder circumference >155 cm
o Body weight > 200 kg
o Inability to walk up a staircase independently

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-01-2023
Enrollment:	30
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	31-01-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2022
Application type:	Amendment

Review commission: METC Amsterdam UMC

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	NL79698.018.21