# Nutrient sensing in response to starvation in obese and lean individuals.

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We hypothesize that the molecular and systemic response to calorie restriction is more explicit in obese compared to normal weight individuals to explain there propensity to grow obese.

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

## Samenvatting

#### ID

NL-OMON29226

Bron NTR

#### Aandoening

obesity

## Ondersteuning

**Primaire sponsor:** Leiden University Medical Center **Overige ondersteuning:** CMSB

#### **Onderzoeksproduct en/of interventie**

#### Uitkomstmaten

#### Primaire uitkomstmaten

The primary outcome are biochemical parameters (eg AMPK, Sirtuins) measured in muscle biopsies.<br>

These will be obtained before and after 60 hours of starvation and for the obese group after the weight loss intervention as well.

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# **Toelichting onderzoek**

#### Achtergrond van het onderzoek

Supply of fuel is of critical importance for survival. AMP activated protein kinase (AMPK) plays a pivotal role at the cellular level. It is activated by nutrient deprivation via a reduced intracellular ADP/AMP ratio and a variety of endocrine cues (including insulin and leptin) and controls energy balance by shutting off energy consuming processes while activating the machinery to produce ATP (1). The sirtuins are a family of highly conserved nicotinamide adenosine dinucleotide (NAD)+ dependent deacetylases that play similar roles by histone modification of genes encoding proteins involved in energy metabolism (2). Energy sensing neurons in the brain employ the same molecular machinery (AMPK in particular) to sense the body's energy status and coordinate a multifaceted systemic neuroendocrine and behavioural response to nutrient deprivation. Most of these neurons are located in the hypothalamus and the nucleus of the solitary tract in the brain stem. They (in)directly control autonomic nervous system activity and pituitary hormone release to adapt metabolism, and higher cortical neural circuits to regulate appetite (3). Within this framework, the hypothalamus-pituitary-adrenal (HPA) and -thyroid (HPT) axes are particularly important for the control of energy balance and metabolism. Obesity is marked by an altered setting of energy balance. It is extremely difficult to lose weight on a long term basis, as evidenced by the very disappointing results of virtually every weight loss strategy that has been developed in the last 50 years or so. Indeed, even after bariatric surgery almost no obese patient ends up with a normal bodyweight (although considerable amounts of weight are lost after these procedures). The above-mentioned energy sensing system probably underlies this difficulty. We propose that the setting of this system is different in obese humans. We specifically hypothesize that the molecular and systemic response to calorie restriction is more explicit in obese compared to normal weight individuals to explain there propensity to grow obese. To test this hypothesis we will map the integrated molecular and neuroendocrine response to fasting in obese vs normal weight humans. Muscle and brain are exquisitely sensitive to fuel deprivation. Therefore, we will study the (molecular) physiology of calorie restriction in these tissues. As endocrine systems are dynamic by nature, multiple sequential blood samples will be drawn to evaluate the status of the pituitary adrenal- and thyroid axes as pivotal components of the systemic neuroendocrine response.

#### Doel van het onderzoek

We hypothesize that the molecular and systemic response to calorie restriction is more explicit in obese compared to normal weight individuals to explain there propensity to grow obese.

#### Onderzoeksopzet

N/A

#### **Onderzoeksproduct en/of interventie**

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In this study a group of 12 obese individuals and a group of 12 lean individuals (control group) will be exposed to 60 hours of starvation. Before and after this intervention we will obtain muscle biopsies, perform a fMRI scan, indirect calorimetry and obtain blood samples.

After this intervention, obese individuals will be asked to participate in part 2 of the study (after signing the informed consent for part 2). In this part of the study, participants will use a very-low-calorie-diet in order to lose weight. After 8 weeks on this diet all measurements will be repeated.

# Contactpersonen

#### **Publiek**

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## Wetenschappelijk

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## **Deelname eisen**

## Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- 1. Healthy males and females;
- 2. Age 19-60 yrs;
- 3. Obese subjects: BMI >30 kg/m2;
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- 4. Lean controls: BMI 19-25 kg/m2;
- 5. Stable weight for the last 3 months;
- 6. Caucasian;
- 7. FPG < 6 mmol/L;
- 8. Well-controlled blood pressure < 150/95 mmHg);
- 9. Creatinine <100 umol/l;
- 10. Hb > 7.5 mmol/l;
- 11. Negative family history (first degree) of DM2.

### Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Use of medication known to affect glucose metabolism (for example prednisone) or lipid metabolism;

2. History of genetic or psychiatric disease (e.g. fragile X syndrome, major depression) that affects the brain;

- 3. Significant chronic disease;
- 4. Renal or hepatic disease;
- 5. Pregnancy;
- 6. Smoking (current);
- 7. Alcohol consumption of more than 14 units per week at present or in the past;
- 8. Difficult accessible veins for insertion of an intravenous catheter;
- 9. Recent blood donation (within the last 3 months);

10. Recent participation in other research projects (within the last 3 months), participation in 2 or more projects in one year;

- 11. Contra-indication to MRI scanning:
- A. Claustrophobia;

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- B. Pacemakers and defibrillators;
- C. Nerve stimulators;
- D. Intracranial clips;
- E. Intraorbital or intraocular metallic fragments;
- F. Cochlear implants;
- G. Ferromagnetic implants.

## Onderzoeksopzet

#### Opzet

Туре:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

#### Deelname

Nederland	
Status:	Werving gestart
(Verwachte) startdatum:	05-06-2010
Aantal proefpersonen:	24
Туре:	Verwachte startdatum

# **Ethische beoordeling**

Positief advies Datum: Soort:

01-07-2010 Eerste indiening

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# Registraties

## **Opgevolgd door onderstaande (mogelijk meer actuele) registratie**

Geen registraties gevonden.

## Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

#### In overige registers

Register	ID
NTR-new	NL2275
NTR-old	NTR2401
Ander register	Ethical Committee, Leiden University Medical Center : P10.035
ISRCTN	ISRCTN wordt niet meer aangevraagd.

# Resultaten

Samenvatting resultaten N/A