Effects of leptin therapy on hypothalamic structure and function in congenital lipodystrophy

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Aim of the studyIn addition to the aims of the compassionate use protocol.To study:1. hypothalamic structure before and during leptin therapy2. hypothalamic function before and during leptin therapy

Ethical review	Approved WMO
Status	Pending
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Observational non invasive

Summary

ID

NL-OMON32723

Source
ToetsingOnline

Brief title
Hypothalamic effects of leptin

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
congenital lypodystrophy

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: eigen afdelingsfonds

Intervention

Keyword: hypothalamus, leptin, lipodystrophy

Outcome measures

Primary outcome

The hypothalamic BOLD signal before and during leptine therapy.

Hypothalamic structure before and afduring leptine therapy (7 Tesla MRI)

Secondary outcome

none

Study description

Background summary

Congenital lipodystrophy is a rare disorder, characterized by the absence of adipocytes, resulting in accumulation of triglycerides in the liver and muscles. Severe steatosis of the liver develops in childhood followed by insulin resistance, diabetes and severe hypertriglyceridemia. Treatment with antidiabetic drugs, insulin and triglyceride-lowering drugs is usually insufficient to control this metabolic disorder. Due to the absence of adipocytes plasma leptin levels are low. Supplementation with leptin may effectively improve the diabetes and hypertriglyceridemia, by reducing the accumulation and production of triglycerides by the liver. Liver fat content and liver size may subside significantly.
Leptin has several specific effects:
1. Stimulates T3,T4, IGF-1, reproductive hormones and fatty acid oxidation in muscle cells.
2. Inhibits fatty acid synthesis, triglyceride storage and VLDL production in the liver
3. Inhibits bone formation via ventromed neurons of hypothalamus, autonomous CS and Beta-adrenergic receptors of the osteoblast.
In leptin deficiency bone density may therefore be increased.
4. Stimulates angiogenesis in adipose tissues
5. Reduces insuline resistance
Leptin suppresses apetite through activation of pro-opiomelanocortine (POMC) neurons. In turn these neurons activate the melanocortin-4 receptor resulting

in activation of α-melanocyte stimulating hormon.[2] Energy expenditure will increase. Agouti-related protein (AgRP) and neuropeptide-Y (NPY)-producing cells of the arcuate nucleus is inhibited by leptine. The inhibitory effects of AgRP and NPY on POMC neurons and α-MSH are impaired by leptin. Without leptin the NPY/AgRP systeem is active and suppresses POMC neurons resulting in stimulation of the appetite.
Moreover stimulation by leptin of the histamin H1-receptor in the hypothalamus increases sympathic activity, which stimulates energy expenditure.

We hypothesize that longstanding leptin deficiency may alter hypothalamic function and structure. At present new MRI technology is available to study function and structure of the hypothalamus.
Recently it was found with functional MRI (3 Tesla) that hypothalamic activity in patients with diabetes is reduced after an oral glucose load in comparison with healthy controls.

Aim of the study
In addition to the aims of the standard protocol.

To study:
1. hypothalamic structure before and during leptin therapy
2. hypothalamic function before and during leptin therapy

Study objective

Aim of the study
In addition to the aims of the compassionate use protocol.

To study:
1. hypothalamic structure before and during leptin therapy
2. hypothalamic function before and during leptin therapy

Study design

fMRI (3 Tesla): hypothalamic function, before and during standard oral glucose tolerance test

at visit 1,2 and 5 (day 1, week 1 and month 3)

MRI (7Tesla): hypothalamic structure at visit 1 and visit 5 (day 7 and month 3)

Oral glucose tolerance test:

Subjects ingest a glucose solution through an oral tube, 7 min. after the start of the fMRI scan. The glucose solution consists of 75 gram of glucose dissolved in 296 ml water, which is similar to the normal standardized OGTT.
fMRI is a non-invasive method, which detects transient haemodynamic changes in the brain, using blood oxygen level dependent (BOLD) signal differences in response to external or internal stimuli. BOLD signal differences (contrasts) measured with T2* weighted fMRI imaging sequences are dependent on local and global oxygen content, blood volume, perfusion and/or tissue metabolism. These factors potentially influence the oxy-to-deoxyhaemoglobin ratio, and hence result in variation in the fMRI signal. We will employ this technique to examine hypothalamic neuronal activity in response to glucose ingestion at all three time points.
The hypothalamic BOLD signal will be recorded for 43 minutes, starting from 7 minutes before ingestion of glucose solution. Depending on the time subjects need for ingestion, the BOLD signal will be measured for approximately 27-32 after ingestion. fMRI will be performed on a 3.0 Tesla scanner (Philips Achieva, Philips Medical Systems, Best, The Netherlands).
Scanparameters:T2*-weighted echo-planar imaging (EPI) sequence with TR/TE/flip angle=120ms/ 30 ms/ 30°, image matrix = 256 x 231, field of view = 208 x 208 mm, slice thickness =14mm. midsagittal slice. A T1-weighted anatomical scan will be made of the same slice (repetition time = 550 ms, echo time = 10 ms, field of view = 208 x 208 mm).

Study burden and risks

The MRS technique is noninvasive involving no catheterizations or introduction of exogenous tracers. Numerous human subjects have undergone magnetic resonance studies without apparent harmful consequences. Radiofrequency power levels and gradient switching times used in these studies are within the FDA approved ranges. Contraindications to MRI studies are:
1. presence of a pacemaker or a subcutaneous defibrillator;
2. presence of metal clips in cerebral blood vessels, metal splinters in eye or non-removable piercings,
3. presence of a non-removable hearing aid, a neurostimulator or a hydrocephalus pump,
4. presence of denture kept in place by a magnet or metal wire behind the teeth (crowns, dental fillings and removable braces are allowed).
5. claustrophobia is a relative contraindication. If individuals become claustrophobic while inside the device, the study will be terminated immediately at the subject's request.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

>5 years of age
Negative pregnancy test
appropriate birth control
confirmed congenital lipodystrophy
diabetes
hypertriglyceridemia
If >18 years of age: able to read, understand and sign Informed consent form

Exclusion criteria

HIV
liverinfection
allergy to E.coli-derived proteins

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2008
Enrollment:	5
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL24676.058.08