Molecular underpinning of light therapy in seasonal affective disorder

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Link inter-individual differences in light sensitivity (measured by melatonin suppression) to molecular pathways in primary fibroblasts in SAD patients and healthy controls and with light therapy succes in SAD patients and with gene variation in two...

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

Summary

ID

NL-OMON37640

Source
ToetsingOnline

Brief title
Light increases cellular excitability

Condition

- Other condition
- Mood disorders and disturbances NEC

Synonym
seasonal affective disorder, winterdepression

Health condition

circadiane ritme stoornissen, vermindering van celactiviteit nivo

Research involving
Human

Sponsors and support

Primary sponsor: Rijksuniversiteit Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cellular excitability, Light, Melatonin, Seasonal Affective Disorder

Outcome measures

Primary outcome

The effect of a 1.5 hour light pulse will be determined on the degree of melatonin suppression. The variance in individual responses in melatonin suppression (in vivo) will be compared within each individual with the variance in the degree of fibroblast cellular excitability (in vitro). Differences between healthy controls and SAD patients for this relationship will be determined. The variance in in vivo and in vitro measurements in SAD patients will be compared to light therapy success.

Secondary outcome

Analysis of inter-individual differences in non-visual light sensitivity measured as melatonin suppression in SAD patients and healthy controls and link individual characteristics of light sensitivity and the molecular pathways involved to light treatment efficiency in SAD patients. In addition gene variation in genes involved in light sensitivity (OPN4) and cellular excitability (adenylyl cyclase) will be related with the in vivo and in vitro measures.

Study description

Background summary

Depression is a prevalent and disabling disorder. Light therapy is effective in depressive disorders and especially well established in seasonal affective disorder (SAD). The mechanism by which light therapy is effective is only beginning to be elucidated and contains apparent contradictions. One of the hypotheses is that a change in light sensitivity is underlying winter depression. In a recent collaboration between the departments of chronobiology in Groningen and Zürich (Switzerland) we found a strong association between melatonin suppression (often used as a marker of light sensitivity) measured in healthy humans and cellular excitability (CREB induction) measured in fibroblasts collected from these same individuals. This finding shows that the degree of cellular excitability is individually determined and probably similar throughout several parts in the body (central and peripheral). Melatonin production might not only be determined by stimulatory or inhibitory (light exposure) signals but also by cellular degree of excitability. From this finding we hypothesize that SAD patients have lowered cellular excitability in general and this results in lowered serotonin levels, which contribute to the development of depression. Light therapy is hypothesized to be effective by compensating for this subsensitivity in cellular excitability levels. We aim to link the molecular study of human fibroblasts in vitro with measures of melatonin suppression in vivo in both SAD patients and healthy controls to test this hypothesis. Recently some indications have been found that a missense variation in a gene coding for melanopsin may be involved in seasonal affective disorder and in light sensitivity. Since we are also interested in the background of light sensitivity we propose to analyse gene variation in this OPN4 gene. In addition another gene, thought to be involved in cellular excitabitilty, adenelyl cyclase, is know in various forms, and we hypothesize that differences between individuals in the cellular excitability may be explained by differences in this gene.

Study objective

Link inter-individual differences in light sensitivity (measured by melatonin suppression) to molecular pathways in primary fibroblasts in SAD patients and healthy controls and with light therapy succes in SAD patients and with gene variation in two candidate genes involved in these processes.

Study design

The data collection will take place in the winter of 2011-2012 and will continue in the winter of 2012-2013.
Each subject will be asked to give two 2 mm skin biopsies for fibroblast

collection. A drop of blood that will be available because of this procedure will be collected to obtain serum. The fibroblasts and serum will be send anonymously to the Institute for Pharmacology and Toxicology, of the University of Zurich, for further analysis. Subjects will stay one night in the lab.
Timing of measurements will depend on an individual's sleep timing. Each half hour, starting at habitual sleep onset, saliva samples will be collected for melatonin analysis. Subjects will stay in dim light from one hour before habitual sleep onset until bedtime and from 2.5 hours after habitual sleep onset until the end. During these periods subjects are allowed to sleep. Acute melatonin suppression will be determined by exposing subject to a light pulse of 1.5 hours starting one hour after habitual sleep onset. During this period subjects have to stay awake. Subjects are asked to give one extra saliva sample in the beginning of the night for candidate gene analysis. The effect of light therapy will be measured by SIGH SAD ratings immediately prior to the start of light therapy, immediately following the last light therapy, and 1 week later.

Study burden and risks

Subjects will have two small skin biopsies (2 mm) taken for dermal/fibroblast cell sampling. A drop of blood that accompany this procedure will be collected to obtain serum. This will be performed by a doctor experienced with the procedure and subjects are free to ask for anaesthetics. The biopsy may leave a small scar on their buttocks or upper arm. No extra burden is necessary to obtain serum.
Healthy and SAD subjects will be brought into our time-isolation facility once to measure melatonin suppression in response to a light pulse of 1.5 hours (600 lx) and to collect one saliva sample for gene variation analysis. Subjects will arrive at 1.5 hours before habitual sleep onset and will be brought to their own room where they will stay in dim light starting half an hour later. Subjects are asked to go to bed at habitual bedtime and lights will be turned off during sleep. From habitual bedtime till 5 hours later each half hour saliva samples for melatonin analyses will be collected, by chewing a cotton swab. Subjects are restricted in the timing and type of food and drinks that are allowed: eating and drinking is not allowed during 30 min prior to saliva sample, no coffee, black tea, alcohol, bananas, chocolate, and toothpaste are allowed during the entire sampling period of saliva. Because saliva will be collected each half hour, subjects are only allowed to drink water starting at half an hour before the first sample. One hour after habitual sleep onset subjects are woken up for a period of 1.5 hours during which they stay in medium intensity full spectrum light (600 lux). During this period acute melatonin suppression will be determined. Half hour saliva collections will continue for a period of 2.5 hours after the light pulse to measure the timing and level of the recurrence of melatonin production. Subjects are asked to go back to sleep during this period, although they will be briefly woken up for the collection of saliva. After the last collection subjects are allowed to sleep further until they naturally wake up.
There are no specific risks associated with participation. Patients will

receive regular light treatment as usual, which will be evaluated during three interviews. The in vivo measurements have to be scheduled prior to the start of the light treatment. This may result in a slight delay of the start of the light treatment with a maximum of one week.

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

SAD patients and healthy sex/age matched controls

Exclusion criteria

Healthy control group: Symptoms of possible sleep disorder, time zone transmeridian flights (or more) one month prior to taking part in the study, Shift work during the last 3 months, Colour blindness, Eye diseases, Somatic and psychiatric diseases (no indications of depressed mood), History of chronic diseases, Excessive daily amount of caffeinated drinks, Alcohol and drug problems, Regular medication during past 3 months. Large to moderate seasonal fluctuations in social behaviour, sleep and food intake, any indication of seasonal variation in mood.
Patients group: Other AS-I disorders on DSM-IV than for the inclusion selection, Risk of committing suicide, Use of mood changing or photic sensitizing medication, Eye diseases, colour blindness, shift workers, recent travels across two time zones or more, large changes in daily light expose (no travelling to sunny areas, use of any artificial sun/tanning machines) other than for the treatment of winter depression

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-01-2012
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	06-12-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL38299.042.11