ADRA2B polymorphism as a putative biomarker for the acquisition of anxiety based on inadequate storage of emotional memories

Published: 10-07-2008
Last updated: 11-05-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Anxiety disorders and symptoms
Study type	Observational non invasive

Summary

ID

NL-OMON35676

Source
ToetsingOnline

Brief title
Is there a genetic risk for developing anxiety?

Condition

- Anxiety disorders and symptoms

Synonym
anxiety

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: ADRA2B polymorphism, anxiety

Outcome measures

Primary outcome

This is a one-time intervention evaluating the proportions of individuals with

the ADRA2B polymorphism between both groups as well as differences in (sub)

scores on the DAS, VAG and IES questionnaires

Secondary outcome

not applicable

Study description

Background summary

Why is one person plagued by memories of traumatic events years after the fact, while another hardly has any problems? Findings in the field of molecular biology have indicated that how events are stored in a more emotionally laden manner is influenced by genetic factors (de Quervain, Kolassa, Ertl, Onyut, Neuner, Elbert & Papassotiropoulosm, 2007). One of the genes involved in the regulation of the stress response system is ADRA2B, the gene coding for the a2b adrenergic receptor. An estimated 30 percent of people carry the 12Glu9 variant of this gene. This deletion variant codes for a receptor in which 3 glutamic acid residues (301-303) are missing from its third intracellular loop. This modification changes a number of essential receptor functions, such as receptor desensitisation. In a recent study, researchers showed 435 subjects with and without the deletion variant a variety of images: images with negative emotional associations (e.g. bloody operation), with positive emotional associations (e.g. cute children) and neutral images (e.g. someone making a phone call). People with the deletion variant remembered the emotional photographs in particular; 78% of the images they remembered had an emotional association, compared with 43% in people without the deletion variant of the ADRA2B gene. The researchers wondered whether people with this genetic variant also ran a higher risk of developing post traumatic stress disorder (PTSD). In order to test this theory, the genetic profile of 202 Rwandan refugees was

determined. This revealed that refugees with PTSD more frequently carried the deletion variant of the ADRA2B gene than refugees without PTSD (and without a history of the condition). They also found that the seriousness of reliving differed significantly between the two groups suggesting that the deletion variant acts primarily as a loss-of-function polymorphism of the a2b-adrenergic receptor in the regulation of emotional memory (de Quervain et al., 2007, p. 1139).
The results of this study provide a biomolecular aetiological explanation for anxiety disorders. For example, people with the deletion variant of the ADRA2B gene may run an elevated risk for deregulation of the HPA axis, making them more vulnerable to stressful impressions and potentially increasing their chances of developing anxiety.
Dentistry is a particularly suitable context for testing this hypothesis. This is because dental treatment is experienced as more or less stressful by the majority of individuals, and there is a significant correlation between nature and frequency of unpleasant dental experiences and anxiety about dental treatment (De Jongh, Muris, Ter Horst and Duyx, 1995). There are also large individual differences in how people react to the same treatment. In a recent trial, 34 people underwent a certain maxillary surgery (removal of an M3 in the lower jaw; De Jongh et al, submitted for publication). About 27% of them showed higher disposition anxiety four weeks after the treatment than they did before the treatment, while anxiety remained the same or decreased in the rest of the group. It may be that the memories of the intervention have been stored as more emotionally laden events in the brains of these individuals, and that this is caused by a less adequate stress response based on the ADRA2B polymorphism.

Study objective

The objective of the proposed research is to gain insight into the circumstances under which anxiety and avoidance behaviour can develop. More precisely, the goal of the current trial is to determine whether a genetic basis exists for the individual difference in stress responsiveness and susceptibility to developing phobic anxiety about dental treatment. To determine whether the deletion variant of ADRA2B is involved, answers to the following questions will be sought.

1. Is the deletion variant of ADRA2B more common in individuals being treated for their extreme anxiety about dental treatment (and who also meet the DSM IV criteria for a specific phobia, and score > 15 on the Dental Anxiety Scale) than people without this anxiety?

2. Do people with this variant of ADRA2B have more emotionally laden memories of previous dental interventions, and do they suffer more from them than people without this variant?

3. If we expose people to a standard dental experience, do individuals with this variant respond with more intrusive memories and/or with an increase of

the existing anxiety level than people without this variant?

Study design

The study is a pre-test and post-test with control group design and takes place according to the criteria set out in the Declaration of Helsinki. Potential study subjects are approached and asked to participate in the study. The nature and goal of the study is explained to the them, and if they agree to participate, they are asked to sign an informed consent form. Subjects are informed that research data will be collected anonymously, that their name and other personal details cannot in any way be traced back to individual findings, and that all collected data will be destroyed after being interpreted.
Subjects will receive an envelope with a number of questionnaires, a test tube with a fixative liquid and a cotton swap prior to a standard dental treatment (anaesthesia, preparation and application of a filling). They are asked to collect cheek mucosa with the cotton swab and place it in the appropriate test tube. They then receive an envelope containing a number of questionnaires, namely the:
* Dental Anxiety Scale (DAS), to measure the level of disposition anxiety for the dental treatment;
* Level of Exposure Questionnaire (Vragenlijst angstwekkende gebeurtenissen, VAG), to measure the frequency of previous unpleasant/shocking events, both dental and otherwise;
* Impact of Events Scale, Revised (IES-R), to measure trauma symptoms (reliving, avoidance, hyperarousal);
Also included is a brief questionnaire with items about the overall number of memories, the number of positive and negative memories about past dental treatment. Subjects are asked to determine the intensity of the most representative memory, to recall the clarity of the memory, the feeling of *nowness* and the degree to which this memory influences the respondent*s daily life (VAS).
After completing the questionnaires, they are offered dental treatment, and the dentist is asked to describe the technical details of the procedure on a separate form.
Once treatment is complete, participants are once again asked to complete a short questionnaire asking them about anxiety and tension during treatment, how they experienced pain, and the intensity of the memory of the treatment.
Subsequently a final discussion takes place, and the completed forms and test tube with cheek mucosa are placed back in the envelope and sealed. If they wish, people may speak to a psychologist.

Study burden and risks

not applicable

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

Score on Dental Anxiety Scale (DAS) >15

Exclusion criteria

people with psychobiological disorders, behavioral disorders, an age below 18 or above 65 or people with a cognitive impairment.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2008
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	10-07-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-11-2010
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	NL20561.029.07