Differences in serotonin synthesis between patients with major depression and healthy controls, measured with [11C]5-HTP PET

Published: 25-06-2012
Last updated: 27-04-2024

Primary: a) To asses whether there is a difference in patients with major depression and healthy controls in serotonin synthesis rates. Secondary: a) Do these rates correlate with severity of depression? b) Does serotonin synthesis correlate with...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Mood disorders and disturbances NEC
Study type	Observational invasive

Summary

ID

NL-OMON39051

Source
ToetsingOnline

Brief title
Serotonin synthesis in depression

Condition

- Mood disorders and disturbances NEC

Synonym
Affective disorder, Depression

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

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

Intervention

Keyword: [11C]5-HTP, kinetic modelling, PET, Serotonin synthesis

Outcome measures

Primary outcome

The primary parameter is the constant accumulation Kacc or Patlak rate (similar parameters resembling serotonin synthesis rate) in the brains, along with the scores on the IDS-SR. In addition, the k3, resembling AADC activity, will be measured.

The difference (IDS-SR, Kacc, k3 or Patlak rate) between patients and healthy volunteers is shown as absolute values**. In addition, the Patlak Kacc and the scores on the IDS-SR correlated.

Secondary outcome

Secondary parameters are the ratio between tryptophan levels in plasma and other large amino acids and polymorphisms for several serotonin-related genes like the serotonin transporter, the 5-HT1A receptor, and tryptophan hydroxylase. In addition, the outcomes of the personality questionnaires are compared between the two groups and aspects like neuroticism and copings style are correlated to Kacc and Patlak rates. Also the outcome of the fMRI tasks and the MRS are related to Kacc and Patlak rates.

Study description

Background summary

In literature, depressive symptoms and antidepressant effects are often related to serotonin (5-HT) neurotransmission in the brain. In addition, a possible reason for the moderate effectiveness of antidepressants may be related to serotonin synthesis rates. A reduction in serotonin synthesis could reduce serotonin stores, resulting in insufficient availability of serotonin for release. There are indications that serotonin synthesis is decreased in the brain of depressed patients.
The measurement of serotonin synthesis in the brain is possible with positron emission tomography (PET) and by using the tracer [11C]5-HTP. Previous studies show, that the uptake of this tracer is reduced in depressed patients. Although, actual synthesis rates have never been looked at, which can be calculated by kinetic modeling. Therefore in this study, we look at the difference in synthesis rate between healthy volunteers and depressed patients.

Study objective

Primary: a) To asses whether there is a difference in patients with major depression and healthy controls in serotonin synthesis rates.
Secondary: a) Do these rates correlate with severity of depression? b) Does serotonin synthesis correlate with other factors like neuroticism or coping style? c) Or is there a relation with glutamate levels or performance in fMRI tasks?

Study design

The study design is a case-control study where we compare patients with major depression with healthy controls, to see if they differ in baseline 5-HT synthesis rates. Depressed patients will be recruited via the University Medical Center Groningen (UMCG), via their treating physician, or through Roden, GGZ Drenthe, and healthy controls will be recruited through advertisement and distribution of flyers (E3_flyer_5-HTP). Only drug-naïve patients are included in the study.
Patients will be asked by their physician whether they are interested to be informed about the study. Next, they receive verbal and written information (E1_informatie Vrijwilligers/patienten) from the investigator. They will be asked whether they are interested to participate in the imaging study, during which they will undergo a PET scan and a MRI scan. In addition, they are told they will have to fill in a few questionnaires about personality traits and coping style.
When the subjects received the information for participants, they have two weeks to decide whether they want to participate in the study. When the subject agrees, he can sign the informed consent and make an appointment with the investigator which will subsequently fill in the informed consent.
All participants will receive a medical examination including: anamnesis and physical examination. The medical examination together with a MINI-plus and a questionnaire about their medical history (F1_medische vragenlijst) is

performed by the research psychiatrist to determine if the subject meets the inclusion and exclusion criteria. If not, they wiil be excluded from the study and their information will be discarded.

First, 5 healthy subjects and 5 depressed patients undergo a baseline scan to validate the tracer for the use in our facilities and assess whether there is an initial difference between the groups. When through power analysis it becomes apparent that significant differences in serotonin synthesis rates will be obtained between groups, another 2 x 5 subjects are included. A significant difference would indicate a physiological condition that could contribute to the pathophysiology of depression, but more importantly it suggests an important target for antidepressants. When the scans are not like we expected (low resolution, failure kinetic modeling), the study is not continued. A low resolution would result in high variability between subjects, which we can check in controls. The scans are analyzed by kinetic modeling, where a curve is fitted through the activity data. By visual inspection of the curve fit one can if this fit is appropriate for data analysis.

The only interventions are a [11C]5-HTP PET scans and a MRI scan. This tracer is already produced in the department of Nuclear Medicine and Molecular Imaging for the visualization of neuro-endocrine tumours, so we are familiar with the procedure.
For kinetic modeling an arterial input function is needed, obtained by continuous arterial blood sampling during the PET scan (185 ml). In addition, blood samples for measurements of metabolites, tryptophan/ amino acid ratios, and genetic polymorphisms are determined (5 ml). Prior to the scan, patients and healthy controls will complete the IDS-RS questionnaire to assess severity of depressive symptoms, the NEO-PI-R for personality traits, and the Utrechtse Coping Lijst for coping style.

In total, there are two groups needed:
1) 10 Healthy controls
2) 10 Depressed patients

Intervention

Patients: randomized treatment with a SSRI or CBT and 2 PET scans before and after 8 weeks of treatment + 1 MRI; healthy controls: 1 PET scan + 1 MRI.

Study burden and risks

The risks in this study are limited as no new drug is being tested and all procedures have been performed in human before. The PET scan procedure is being performed at the department of Nuclear Medicine and Molecular Imaging on a regular base by trained and skilled technicians. According to the International Commission on Radiological Protection (ICRP62) the radiation level of 2 times

1.45 mSv (for 400 MBq, see IMPD of [11C]-5-HTP) is within category IIb (1-10 mSv, minor to moderate risk).
However, some of the procedures like arterial canulation are invasive and possibly uncomfortable. This burden is in proportion with the potential value of this study, because the outcome can be of great medical importance. The mechanisms underlying depressive symptoms are unknown. In addition, there is no fast acting antidepressant on the market, and differences in serotonin synthesis rate at baseline or changes due to treatment may be associated with therapeutic efficacy. Therefore, it is of great importance to know the difference in 5-HT synthesis rate between healthy controls and depressive patients at baseline levels, as hereafter we can investigate the effect of antidepressant drugs on 5-HT synthesis.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients
- Out-patients
- Age 18-55.
- Major depressive disorder, single or recurrent episode according to DSM IV.
- Severity: >22 IDS-SR
- No psychotic features
- No intention to commit suicide, or a history of a seroious suicide attempt
- No proven non-response to CBT during the current or a previous episode
- No current or recent (< 3 months) alcohol or substance use disorder (smoking is allowed).
- Declared somatically healthy after medical examination.
- No current or recent (<1 month) pharmacological treatment (antidepressant, antipsychotic, lithium, anticonvulsant, benzodiazepine)
- Understanding Dutch language and judged capable to participate
- Willing to cooperate and sign the informed consent form.;Healthy volunteers
- Matched for gender and age
- Age 18-55.
- No lifetime major psychiatric disorders (e.g. psychosis, mood disorder, anxiety disorder, somatoform disorder, eating disorder)
- No lifetime treatment with an antidepressant, antipsychotic, lithium or anticonvulsant
- No long-term treatment (>1 month) and no current (<1 month) with a benzodiazepine
- No current or recent (< 3 months) alcohol or substance abuse and no lifetime alcohol or substance dependence (smoking is allowed)
- Declared somatically healthy after medical examination.
- Willing to cooperate and sign the informed consent form.

Exclusion criteria

Similar for patients and healthy controls
- Indication of medical/somatic illness that could interfere with study results or constitutes a risk factor when participating in the study and undergoing treatment.
- Cardiovascular abnormalities that may be a risk factor when participating in the study.
- Neurological damage or previous severe head injury
- Consumption of chocolate, caffeinated products or tabacco within 24 hours of the scan.
- Pregnancy or the intention to become pregnant during the estimated time course of the study.
- Radiation exposure (for diagnostic reasons) as a radiological worker or during medical trial in the previous year.
- Claustrophobia
- Presence of materials in the body that can be magnetized, like:
i. A pacemaker
ii. Metal fragments
iii. Shunts

iv. Artificial heart valves
v. Vascular clips
vi. Fixed hearing aid
vii. Tattoos containing metal
viii. Hair implants
ix. Artificial dentures

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:	Will not start
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO Date:	25-06-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	20-08-2013
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	NL34502.042.11