The effects of Acute Tryptophan Depletion in individuals with a history of depression with and without anger attacks

Published: 19-01-2009
Last updated: 06-05-2024

The aim of this project is to test the hypothesis that MDD patients with disturbances in anger/aggression regulation have more serotonin disturbances, as a trait marker for relapse, than MDD patients without disturbances in anger/aggression...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON32412

Source
ToetsingOnline

Brief title
Serotonin and depression

Condition

- Mood disorders and disturbances NEC

Synonym
depression; sad mood

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden

Source(s) of monetary or material Support: VENI (Dr. L. Booij); VICI (Prof. dr. W van der Does)

Intervention

Keyword: anger, cognition, depression, serotonin

Outcome measures

Primary outcome

The primary outcome measure is change in symptoms following ATD compared to

placebo (MADRS and Spielberger State anger as primary measures);

Secondary outcome

serotonin transporter and polymorphisms of the 5-Ht1A C(-1019)G gene and the

mineralocorticoid and glucocorticoid receptor-genes

Study description

Background summary

Symptoms of anger and aggression are very common in MDD patients, even though these are not part of the psychiatric taxonomies (Van Praag, 1990). Van Praag (2001) proposed a *subset of cases of depression* with anxiety and hostility as primary symptoms, and in which low mood is a latecomer. These patients were also thought to be more stress-vulnerable, have increased cortisol activity and more pronounced serotonergic disturbances (Van Praag, 2001). Disturbances in aggression regulation can be manifested inward (suicidal ideation, self-mutilation) or outward (irritability, anger attacks) (Van Praag et al., 1990). Fava (1998) characterized a subtype on a specific component of anger; i.e. the presence of anger attacks (Fava,Rosenbaum, 1998; Fava,Rosenbaum, 1999), which are *sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, hot flashes, and tightness of the chest which resembles panic attacks but without the predominant affects of fear and anxiety* (Fava,Rosenbaum, 1998). Using the *Anger Attacks Questionnaire* (a self-rating scale to assess the presence of anger-attacks (Fava, Rosenbaum, McCarthy, Pava, Steingard,Bless, 1991), rates of anger attacks in MDD outpatients have been reported around 40% (Fava, Nierenberg, Quitkin, Zisook, Pearlstein, Stone,Rosenbaum, 1997).

While the clinical behavioural profile for MDD can be heterogenous, the most consistent neurobiological finding is the association with impairments in the serotonin (5-HT) system, as shown by various direct and indirect markers of 5-HT function (Maes & Meltzer 1994; Belmaker and Agam 2008). Decreased 5-HT function is also still present in MDD patients in remission (Smith et al., 1997; Neumeister et al., 2002). High risk relatives have been shown to be more sensitive to 5-HT challenge procedures such as acute tryptophan depletion than individuals without a psychiatric family history (Benkelfat et al., 1994; Van der Veen et al. 2007), suggesting that impaired 5-HT function is not directly related to a depressive state, but signifies a biological risk factor (*trait*) for MDD.

There is some evidence that, within MDD samples, the largest 5-HT alterations are in those MDD patients that have disturbances in aggression regulation, e.g. suicidal patients and in MDD patients with anger attacks (Asberg et al., 1978; Fava et al. 2000). In addition, we previously observed in a recovered sample of MDD patients that the mood-lowering to Acute Tryptophan Depletion (ATD), an experimental 5-HT challenge procedure known to transiently alter central serotonin function, was largest in those former patients that had a history of suicidal ideation during their previous episode (Booij et al., 2002). In a sample of SSRI treated remitted depressed patients, depressed patients who had serious suicidal thoughts or had attempts during a previous episode also had a larger increase in anxiety, impulsivity, and reduced heart rate variability (HRV) following ATD as compared to patients who never have had suicidal ideation (Booij et al., 2006). Taken these findings together suggest that an endophenotype of depression may exist, consisting of patients who have problems with aggression regulation, and who have an increased reactivity to impaired serotonin function. Whether this increased 5HT vulnerability persists beyond a depressive episode and medication use, and thus represents a trait individual MDD vulnerability factor for relapse is not known.

Study objective

The aim of this project is to test the hypothesis that MDD patients with disturbances in anger/aggression regulation have more serotonin disturbances, as a trait marker for relapse, than MDD patients without disturbances in anger/aggression regulation, using the ATD method. To this end, we compare recovered MDD patients with and without a history of anger attacks during their previous episode(s) lifetime. It is expected that recovered MDD patients with a history of suicidal ideation have a greater serotonin vulnerability than recovered MDD patients without a history of suicidal ideation, reflected in the cognitive, physiological and behavioral response to ATD. Moreover, we expect that anger expression during their episode or beyond (as measured by the Spielberger trait anger scale) and suicidality during previous episodes will predict response to ATD. Secondary aims are to explore the influence of serotonergic genes (SERT; 5-Ht1A C(-1019)G) and MR / GR polymorphisms on ATD response and investigation of differences in cognitive markers between these

groups. The project is part of a larger VENI project aimed to investigate the neural, behavioural and cardiac mechanisms of anger and depression.

Study design

After a screening procedure to confirm final eligibility, two experimental sessions will be carried out. This involves the ingestion of a tryptophan-free (ATD) and a tryptophan-containing balanced mixture (placebo) under double blind, counterbalanced conditions, with a minimum of 7 days apart. All sessions including the screening procedure will take place at Leiden University Medical center, at the dept of Psychiatry. A double-blind crossover design is used, which means that participants as well as researchers and research-assistants will be blind to the order in which the two sessions will be conducted.

Intervention

The day before the session, all subjects will be instructed to fast from midnight. The ATD mixture is similar to the one in Young et al. (1985), known to decrease tryptophan levels by by 70 to 90% within about 6 hours after intake (Young et al., 1985). It consists of the following amino acids: L-alanine 5.5 g, L-arginine 4.9 g, L-cysteine 2.7 g, glycine 3.2 g, L-histidine 3.2 g, L-isoleucine 8 g, L-leucine 13.5 g, L-lysine monohydrochloride 11 g, L-methionine 3 g, L-phenylalanine 5.7 g, L-proline 12.2 g, L-serine 6.9 g, L-threonine 6.9 g, L-tyrosine 6.9 g, L-valine 8.9 g. The balanced (placebo) mixture contains the same amino acids plus 2.3 g L-tryptophan (Young et al., 1985). Because women weigh on average 16.7% less then men, the mixture will be adjusted accordingly (Ellenbogen et al.1999). Because of the unpleasant taste of L-methionine, L-cysteine, and L-arginine, these amino acids will be given in capsules. The remaining amino acid mixtures are prepared just before oral administration by mixing the powdered amino acids with about 200 ml water, 100 ml chocolate syrup, and 1.1 g of cyclamate (fake sugar). The amino acids will be mixed with 200 ml orange juice for those who do not like chocolate. Participants are asked to swallow the suspension in as short a time as possible because of its somewhat unpalatable taste. After intake of the mixture, participants spend the day in a private research room and are allowed to watch neutral videos and to read neutral material. Sleeping is not allowed. About 3 hours after the protein mixture, subjects will be offered some low protein snacks, incl. low protein cookies and/or low protein bread(@Loprofin), herb bouillon and/or apple sauce.

Study burden and risks

To date, the ATD procedure has been carried out in more than 4200 subjects of various diagnostic categories including depression, anxiety disorders, eating disorders, schizophrenia and in healthy volunteers with and without a family history of psychopathology. No major side effects have been reported. Both ATD

and the placebo procedure can produce transient nausea 1-2 hours after ingestion of the mixture, and in a few cases vomiting. We previously conducted four ATD studies in patients (three in remitted MDD patients, 1 in symptomatic patients, about 70 patients total), and no serious side effects have been observed. It is expected that ATD will lead to a transient mood-lowering in about 60% of the patients (van der Does 2001; Booij et al., 2003; 2005a). Previous studies in our own lab and in other labs showed that the mood-lowering effect is transient (i.e. occur 5h after the ATD mixture, lasting for 3 hours maximum), and a symptom exacerbation of similar magnitude as seen in naturalistic relapse is rare (Booij et al., 2005).
There is no direct benefit from participating in the study. However, a more systematic evaluation in remitted depressed patients that took part in a similar experiment showed that the participants experienced increased insight into their current and past functioning as a result of taking part in an ATD study as an advantage (Booij et al., 2005).

Contacts

Public
Universiteit Leiden

Wassenaarseweg 52
2333 AK Leiden
NL
Scientific
Universiteit Leiden

Wassenaarseweg 52
2333 AK Leiden
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

- Age between 18 and 65 years; - Meeting DSM-IV criteria for past depression as a primary diagnosis; - Having at least 2 episodes of past depression OR having at least one first-degree relative with recurrent MDD; - A Hamilton depression rating scale (HDRS)-score lower than 10 OF MADRS < 12; - Depression in remission for at least 3 months; - Free of antidepressant medication for at least 1 month or for more than 5 elimination half-lives of the drug, whichever is more.

Exclusion criteria

- Major physical illness; - Substance abuse within the last 3 months; - Lactation
- Pregnancy; - History or current Psychotic Disorder or Bipolar Disorder; - Using medication likely to affect CNS function, incl. benzodiazepines

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2009
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	19-01-2009
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	NL23761.058.08