Dissecting the mechanisms of fear formation: a pharmacological study with healthy volunteers

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• To elucidate the role of noradrenaline in the mechanisms involved in human memory consolidation• Evaluate the levels of cortisol and 3-methoxy-4-hydroxyphenylglycol in the various points of a memory consolidation window• Define pharmacological...

Ethical review	Approved WMO
Status	Pending
Health condition type	Anxiety disorders and symptoms
Study type	Interventional

Summary

ID

NL-OMON38140

Source
ToetsingOnline

Brief title
camf

Condition

- Anxiety disorders and symptoms

Synonym
post-traumatic stress disorder, PTSD

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: atomoxetine, fear conditioning, memory consolidation, propranolol

Outcome measures

Primary outcome

• Skin conduction response and/or eye blink response as a measure of differential acquisition of memory for each group.

• Comparison of fear response measures between the different drug groups and placebo will allow to determine what is the roles of noradrenaline enhancement or blockage in fear memory consolidation. Enhancement or weakening of memory with any of the drugs will allow confirmations of assumptions on the specific effects of noradrenaline in the postlearning consolidation processes.

Secondary outcome

Heart rate data will be used as an auxiliary measure.

Study description

Background summary

Traumatic events such as military combat, car accidents, or sexual assault can lead to debilitating psychological disturbances, including posttraumatic stress disorder (PTSD), a common and often chronic and disabling disorder. Its uniqueness among psychiatric disorders resides in the fact that its etiology can be pinpointed to a precise moment. This raises the possibility that prevention of PTSD might be achieved through intervention in the consolidation phase of the traumatic memory. In recent years, due to the advances in neuroscience, namely with the extraordinary possibilities opened by molecular genetics in animal models, knowledge of the mechanisms of memory formation has progressed at a rapid pace. Fear conditioning plays a pivotal role in these studies, as fear is well conserved throughout evolution, making it a near-ideal model system to study the interplay between genetic factors, operating brain

circuits and behavior that modulate learning and memory besides presenting itself as a reliable model of PTSD. Furthermore, decades of human psychological studies conducted in normal and brain lesioned patients have provided unique insights into the areas involved in the processing of each memory subtype.
Also, the progresses in clinical psychopharmacological drug discovery that revolutionized modern-day Psychiatry have yielded a number of compounds that can be used as psychopharmacological tools in order to probe the abovementioned memory formation mechanisms.
We intend to capitalize on the knowledge and possibilities offered by these 3 areas for providing clues of what could be the appropriate pharmacological interventions in the aftermath of a traumatic situation and also as a way to probe and pharmacologically dissect the differential neurotransmitter and circuitry underlying human memory formation. As a step towards these goals, a study design is therefore proposed in order to address the influence of pharmacological interventions in primary memory formation through the use of CS-US (mild electrical shock) with SCR and startle response as fear measurement. In order to probe the mechanisms of memory formation and the putative pharmacological prevention strategies we propose the use of a specific set of clinical drugs targeting the mechanisms known to be involved in memory consolidation. Single clinically relevant oral doses of atomoxetine (the most selective NA agonist), propranolol (a selective Beta-blocker) and placebo will be used for targeting the effects of Noradrenaline in the mechanism of memory consolidation. The safety of the proposed pharmacological interventions is consubstantiated by its extensive use in the clinical setting as well as in previous studies in healthy subjects, both in a single dose and multiple dose interventions.
This will be achieved through the use of visual and auditory conditioned stimulus (CS) paired with mild electrical shocks as unconditioned stimuli (US) with skin conductance response and eye startle reflex as fear measures in memory reassessment. A double-blind parallel-groups design will be used where each group of participants will receive a psychopharmacological intervention following CS-US pairing, thus acting upon the memory consolidation phase. The fact that the pharmacological manipulations will be administered after learning eliminates bias posed by any possible influence on attentional or motivational processes occurring during encoding. By influencing in a precise way the formation of non-subjective memories whose strength can be accessed reliably and accurately, it is expected that insights into the mechanisms of memory formation will be obtained and novel strategies for the prophylaxis of PTSD can be developed.

Study objective

• To elucidate the role of noradrenaline in the mechanisms involved in human memory consolidation

• Evaluate the levels of cortisol and 3-methoxy-4-hydroxyphenylglycol in the various points of a memory consolidation window

• Define pharmacological strategies for preventing fear formation

Study design

The study will develop in a randomized placebo controled double blind design. The present study will employ a between-subject rather than within-subject design, in order to avoid bias related to previous conditioning and practice effects on neuropsychological tests that can make interpretation difficult in studies employing cross-over designs.

Intervention

In this study we will make use of the pharmacological agents atomoxetine, propranolol and placebo in a randomized double blind design in order to probe the effects of the differential neurotransmitters in the mechanisms of memory formation.

Study burden and risks

Participants will have to undergo fear conditioning; like often used in comparable experiments with human participants, the volunteers will receive mild shocks during the fear conditioning. Like often used in comparable experiments with human participants, the volunteers will receive mild shocks during the fear conditioning. Also, at unexpected moments during these experiments participants can receive mild but painless shocks to the wrist, noises of high intensities through headphones and/or fear-relevant images on a computer screen.
Venous punction will be performed on three occasions (3x10 ml).
The pharmacological compounds in a single dose administration at the intended dosage may cause the following side effects: A) Atomoxetine: GI symptoms, namely nausea, abdominal discomfort and dyspepsia. Somnolence and dizziness have been reported to occur in fewer than 4 % of the subjects. B) Propranolol: GI symptoms, namely nausea, abdominal discomfort and dyspepsia Dizziness and hypotension are also reported to occur. Psychomotor disturbances such as somnolence and agitation have been reported in less than 2% of the subjects.
Total duration of the experiment is about 5 hours (four hours on day 1 plus one hour on day 2)
Overall there are negligible risks associated with this study.

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

The subjects must be in good mental and physical health (as established by first contact and health questionnaire). Participants with a past or present psychiatric,or respiratory (including asthma) will be excluded from the study. Background of high blood pressure or cardiovascular diseases will also be an exclusion criterion. Testing days for female subjects will demand that they are in the end of the follicular phase in order to standardize the influence of gonadal hormones. Participants must be drug and alcohol free from at least 48 hrs before time of testing and should refrain from caffeine and cigarette smoking from 3 hours before testing. Age should be comprised between 18 and 40 years.

Exclusion criteria

Uncorrected vision disturbances, pregnancy, use of oral contraceptives or lactation, any neurological and psychiatric diseases past and present, including manic and suicidal depression.History of seizures, respiratory disease (including asthma), cardiovascular illness or head trauma with loss of consciousness, abnormal blood pressure, glaucoma or abnormal clinical laboratory tests. Subjects will also be excluded when they cannot understand the Dutch and English languages sufficiently to understand the purposes and implications of the

experiment.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2012
Enrollment:	120
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Placebo capsule
Generic name:	Placebo capsule
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Placebo tablet
Generic name:	Placebo tablet
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Propranolol
Generic name:	Propranolol
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Strattera
Generic name:	Atomoxetine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-06-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EudraCT	EUCTR2011-002838-40-NL
CCMO	NL36746.078.11