Effects of the norepinephrine reuptake inhibitor reboxetine on the exploitation-exploration trade-off

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

Summary

ID

NL-OMON31488

Source
ToetsingOnline

Brief title
Norepinephrine and exploitation/exploration

Condition

- Other condition

Synonym
normal explorative behaviour

Health condition

geen aandoeningen, onderzoek op gezonde vrijwilligers

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: exploitation, exploration, locus coeruleus, norepinephrine

Outcome measures

Primary outcome

The main study parameters are measures of performance on three cognitive tasks

designed to examine exploitative and explorative behavior.

Secondary outcome

Pharmacodynamics:

visual analogue scales (Bond & Lader)

pupilsize

adaptive tracking

saccadic eye movements

body sway

Pharmacokinetics:

Cmax of reboxetine

AUC (from zero to infinity) of reboxetine

Study description

Background summary

In daily life, people often have to choose between exploiting known sources of

reward and exploring new, and potentially better, contexts. This trade-off between exploitation and exploration is crucial for adaptive behavior, especially in changing environments. Recently, cognitive neuroscientists have addressed the question how the exploitation-exploration trade-off is regulated in the human brain (for an overview see Cohen, McClure, & Yu, 2007). Cell recording studies and model simulations have suggested that the locus coeruleus-norepinephrine (LC-NE) system plays an important role in the regulation of this trade-off (e.g. Aston-Jones et al., 2000; Usher et al., 1999; Yu & Dayan, 2005).

The nucleus locus coeruleus (LC) is situated in the brainstem and projects widely to all levels of the brain where it releases the neuromodulating substance norepinephrine (NE). There is widespread evidence that LC-mediated noradrenergic innervation leads to a temporary increase in the responsivity of efferent cortical neurons, which is thought to facilitate stimulus processing (reviewed in Berridge & Waterhouse, 2003). Although to date it has not been possible to directly measure the activation dynamics of the LC-NE system in humans, cell recordings in non-human primates have yielded a wealth of information regarding these dynamics. These studies have identified two components of LC activity: the spontaneous (baseline) activity, which is referred to as tonic activity, and the transient increase in activity in response to motivationally salient stimuli, which is referred to as phasic activity. The tonic and phasic LC activities interact, in such a way that intermediate tonic activity is associated with large phasic responses, whereas low or high tonic activity are associated with weak phasic responses (Aston-Jones et al., 2000). It has been found that when a monkey is performing well on a selective attention task, the monkey*s LC neurons exhibit intermediate tonic activity and strong phasic responses to target stimuli. This LC state has been referred to as the *phasic mode*. During periods of impaired attentional performance, on the other hand, the monkey*s LC neurons exhibit a high level of tonic activity but weak or absent phasic responses to target stimuli. This LC state has been referred to as the *tonic mode*. It has been suggested that the tonic and phasic LC activities play complementary roles in regulating the balance between exploitation and exploration (e.g., Aston-Jones et al.). In the phasic mode, norepinephrine is released specifically in response to task-relevant events, thereby facilitating the processing of those events which promotes exploitation. In the tonic mode, on the other hand, the sustained release of norepinephrine facilitates the processing of all events, regardless of their relevance for the current task, which promotes exploration. Computational modeling studies have provided support for a role of the LC-NE system in the regulation of the exploitation-exploration trade-off (Usher et al., 1999; Yu & Dayan, 2005). However, empirical studies testing these hypotheses in humans have not been conducted yet. One way to address this issue is to manipulate the LC-NE system pharmacologically. The proposed study will do this by using the selective norepinephrine reuptake inhibitor reboxetine. Reboxetine inhibits the reuptake of NE, which increases the availability of NE and thus shifts the LC towards the tonic mode. Based on the hypotheses of the role of the LC-NE system in the exploration-exploitation trade-off, the

expected effect of reboxetine is an increase in explorative behavior.
Besides its effect on the noradrenergic system, reboxetine also has a general effect on alertness. To control for this effect we will test a control group that receives the selective serotonin reuptake inhibitor citalopram. Citalopam is used as a positive control because it has a similar alerting effect as reboxetine, but does not affect the noradrenergic system. Citalopram does affect the serotonin system, but there is no evidence that this system is involved in the exploration-exploitation trade-off. Therefore, the differences in exploitative/explorative behavior between the reboxetine and citalopram group is likely to reflect the noradrenergic manipulation. Finally, we will also test a group of participants who receive a passive placebo.

Study objective

The objective of this study is to assess the effects of an increased NE level on the trade-off between exploitation and exploration. More specifically, this study will compare the exploitative/explorative behavior of participants who received either reboxetine, citalopram or a placebo in various cognitive tasks. Secondary objective is to evaluate the pharmacokinetics and pharmacodynamics of reboxetine.

Study design

The study is a double-blind placebo-controlled intervention study, using a between-subjects design. We will test three experimental groups, each comprised of 16 participants. Participants in group 1 receive a single oral dose of 4 mg reboxetine. Participants in group 2 receive a single oral dose of 30 mg citalopram. Participants in group 3 receive a placebo. All experimental treatments will be administered in identical capsules.
Participants will take part in one experimental session taking approximately 6 hours. The protocol will start with a medical screening. On the study day, participants will be administered 2 mg of granisetron, to prevent potential nausea as a side effect of the citalopram. Sixty minutes after administration of the granisetron, the experimental treatment (reboxetine, citalopram or placebo) will be administered. Participants then wait for 90 minutes before they are tested on the three experimental tasks. The total duration of the tasks is approximately 60 minutes.
After completion of the last cognitive task, participants will perform a simple reaction time task which lasts for approximately 1 minute. The mean reaction times on this task will provide an objective measurement of the participants* alertness.
Before administration of the experimental treatment, in between the experimental treatment and the first cognitive task, and after each cognitive task, participants fill in 16 Bond-Lader visual analogue scales measuring alertness, calmness and contentment (Bond & Lader, 1974).
Upon completing the experimental tasks, participants are kept under supervision

of a physician until the end of the six-hour session. Participants* blood pressure, pulse, ECG will be measured at regular tine points as well as pupilsize, saccadic eye movements, body sway, adaptive tracking, cortisol, ACTH, prolactine, en reboxetine plasma levels.

Intervention

One experimental group will receive a single oral dose of 4 mg reboxetine. Reboxetine is a selective norepinephrine reuptake inhibitor. The second experimental group will receive a single oral dose of 30 mg citalopram. Citalopram is a selective serotonin reuptake inhibitor. Because citalopram*s alerting effects are comparable to those of atomoxetine citalopram is used as a positive control. The third experimental group will receive a placebo (lactose).

Study burden and risks

Risks associated with reboxetine intake: Reboxetine is used as a drug for the treatment of depression. It is well tolerated in man for doses up to 10 mg daily.

Risks associated with citalopram intake: Citalopram is used as an antidepressant drug. It is well tolerated in doses of 20 to 60 mg/day. Previous studies have found that a single dose of citalopram does not have disruptive effects on psychomotor performance (Lader et al., 1986), does not affect heart rate and blood pressure (Penttillä et al., 2001), and does not have serious side effects, apart from a mild feeling of sedation and a dry mouth (Lader et al., 1986).

Risks associated with the cognitive tasks: there are no risks associated with the cognitive tasks, except the possibility of some frustration with poor performance or fatigue.

Benefit of the study: the proposed study is expected to make an important contribution to our understanding of the role of the noradrenergic system in the exploitation-exploration trade-off. The importance of the scientific contribution outweighs the minimal risks involved.

Contacts

Public
Centre for Human Drug Research

Zernikedreef 10

2333 CL Leiden
Nederland
Scientific
Centre for Human Drug Research

Zernikedreef 10
2333 CL Leiden
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Healthy volunteers between 18 and 25 years of age.
Volunteers are willing to give written informed consent to participate in the study and to comply with the study procedures.
Participants should speak Dutch fluently.
Normal or corrected-to-normal vision.

Exclusion criteria

Clinically significant abnormal values for clinical chemistry, haematology or urinalysis at screening.
Clinically significant abnormal physical examination, vital signs or 12-lead ECG at screening.
Clinically significant (history of) psychiatric illness.
Clinically significant (history of) major internal or neurological illness.
Use of psychotropic medication.
Alcohol or substance abuse.
Pregnancy or breast feeding.
Positive urine screen for drugs of abuse.
Clinically significant acute illness within 7 days prior to study drug administration.

Clinically significant history of food and/or drug allergies.
Serology positive for hepatitis B surface antigen, hepatitis C antibodies or HIV antibodies.
Have received an experimental drug or used an experimental medical device within 90 days before the planned start of treatment.
Psychological and/or emotional problems which would render the informed consent invalid, or limit the ability of the subject to comply with the study requirements.
Donation of 1 or more units (approximately 450 ml) of blood or acute blood loss of an equivalent amount of blood within 90 days before the planned treatment.
Exposure to any medication, including over-the-counter medication (not including paracetamol), within 2 weeks prior to treatment.
Subject not able to refrain from alcohol from 10 PM the night prior to the experimental session until end of the study day.
Subject not able to refrain from smoking from 10 PM the night prior to the experimental session until end of the study day.
Subject not able to refrain from xanthine intake from 10 PM the night prior to the experimental session until end of the study day.
Subject not able to refrain from grapefruit intake from 14 days prior to the experimental session until end of the study day.
Subject not able to refrain from heavy physical exertion from 24 hours prior to the experimental session until end of the study day.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-01-2009
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Citalopram
Generic name:	citalopram
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Edronax
Generic name:	reboxetine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	kytril
Generic name:	granisetron
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-11-2008
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-01-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-01-2009
Application type:	Amendment
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
EudraCT	EUCTR2007-006772-10-NL
CCMO	NL20821.058.08