The effects of endocannabinoid system deficits induced by early-life stress on fear memory extinction

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21224

Source
NTR

Brief title
ELSCAN

Health condition

Early-life stressed people

Sponsors and support

Primary sponsor: Radboudumc, Nijmegen
Source(s) of monetary or material Support: China Council Scholarship

Intervention

Outcome measures

Primary outcome

1Autonomic nervous system indices of the fear response and its recovery after extinction. 2) Neuronal activity and connectivity of different regions involved in the fear expression and extinction learning.

Secondary outcome

1) Salivary levels of cortisol and blood level of endocannabinoid 2-arachidonoylglycerol (2-AG) and anandamide, also known as N-arachidonoylethanolamine (AEA), CB1 gene DNA-methylation and CB1 receptor. 2) Morphological differences between the two different groups.

Study description

Background summary

Early life stress (ELS) constitutes a major risk factor for the development and persistence of mental disorders, increasing rates of posttraumatic stress disorder (PTSD). A first-line and empirically validated approach to treat this disorder is Prolonged Exposure Therapy (PE), one component of which involves repeated exposure to fear-linked cues to produce ‘‘extinction’’ of fear and to prevent avoidance responses to these cues. However, a significant number of patients have incomplete responses or fail to sustain improvements over time, mainly due to the fact that extinction learning, which is the core mechanism underlying exposure-based therapy, is vulnerable to the return of pathological fear. A promising novel strategy is adding drug treatment to exposure therapy in a timed manner to improve the long-term outcome of exposure therapy. Recent findings indicate that hydrocortisone, a synthetic form of the endogenous stress hormone cortisol, may improve stress adaptation and enhance the extinction of fear memories. Critically, recent data from rodent models demonstrate that glucocorticoids exert their actions via recruitment of the endogenous cannabinoid (endocannabinoid) system. Pre-clinical studies moreover suggest that ELS causes disturbances in the endocannabinoid system which might render hydrocortisone ineffective as adjuvant treatment to exposure therapy. A striking and recurrent clinical observation is that a large percentage of PTSD patients, in particular those with a chronic course associated with ELS, uses cannabis as “self-medication” to alleviate their symptoms. Also, initial results from studies in healthy volunteers show that exogenous cannabinoids may strengthen extinction learning. We will investigate this in two separate studies. First, we will investigate the effect of hydrocortisone in enhancing extinction learning in healthy volunteers with and without ELS. Second, we will assess the efficacy of Δ9-tetrahydrocannabinol (THC; dronabinol), one of the active components of natural cannabis, in enhancing extinction learning in healthy volunteers with and without ELS. The goal of this study is to establish a proof of concept: namely, that cannabinoid and corticosteroid treatments have diverging effects on fear-related neural circuits and behaviors depending on ELS status.

Study objective

In the first of two substudies, we test the hypothesis that in healthy individuals without ELS, hydrocortisone will be effective in enhancing stress adaptation and extinction learning in an experimental model of exposure therapy, while it is not in in healthy individuals with ELS. In the second substudy, we test the hypothesis that THC, which directly targets the

endocannabinoid system, is effective in improving stress adaptation and extinction learning in an experimental model of exposure therapy in both healthy individuals with and without ELS.

Study design

one year

Intervention

In the first substudy: Hydrocortisone; In the second substudy: THC

Contacts

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Eligibility criteria

Inclusion criteria

In each substudy, in order to be eligible to participate in this study, a participant must meet all of the following criteria:

For both groups:

 Healthy volunteers between 18 and 45 years of age.
 For substudy 2 only: History of taking cannabis.

For ELS group:

 Meet the criteria for ELS as measured using the self-report questionnaire “Maltreatment and Abuse Chronology of Exposure Scale (MACE-X)”. There are 10 subscales in MACE-X, the criterion for each subscale is listed below.

 In the emotional neglect subscale, the cut-off is 2 items out of 5.
 In the parental non-verbal abuse subscale, the cut-off is 4 out of 6.
 In the parental physical maltreatment subscale, the cut-off is 4 items.
 In the parental verbal abuse subscale, the cut-off is 3 items out of 4.
 In the sexual abuse subscale, the cut-off is 2 items out of 7.
 In the witnessing interparental violence subscale, the cut-off is 2 items out of 5.
 In the peer verbal abuse subscale, the cut-off is 4 items out of 5.
 In the peer physical bullying subscale, the cut-off is 2 items out of 5.
 In the physical neglect, the cut-off is 2 items out of 5.
 In the witnessing violence to siblings subscale, the cut-off is 1 items out of 4.
We will include people a) who meet the criterion on any single subscale, while only counting items under age of ten, or b) who meet the criteria on multiple subscales regardless of age, when the sum of percentages of the cut-offs reached below the age of ten for each of these subscales equals or exceeds 100. For instance, if a potential participant scores 2 item on the sexual abuse subscale, of which 1 is below the age of 10, and scores 5 on the verbal abuse subscale, of which 3 are below the age of ten, then this participant would be included because (1/2) *100 + (3/4) *100 = 125.
 For Non-ELS group: We aim to recruit participants in the control group with no experiences of ELS. The MACE-X has six subscales which are indicate severe childhood maltreatment: Emotional Neglect, Parental Nonverbal Emotional Abuse, Parental Physical Maltreatment, Parental Verbal Abuse, Sexual Abuse, or Witnessing Interparental Violence. The criterion for each of these subscales is listed below.
 In the emotional neglect subscale, the cut-off is 2 items out of 5.
 In the parental non-verbal abuse subscale, the cut-off is 4 out of 6.
 In the parental physical maltreatment subscale, the cut-off is 4 items.
 In the parental verbal abuse subscale, the cut-off is 3 items out of 4.
 In the sexual abuse subscale, the cut-off is 2 items out of 7.
 In the witnessing interparental violence subscale, the cut-off is 2 items out of 5.
And four subscales which are less relevant to severe childhood maltreatment. The criterion for each of these subscales is listed below.
 In the peer verbal abuse subscale, the cut-off is 4 items out of 5.
 In the peer physical bullying subscale, the cut-off is 2 items out of 5.
 In the physical neglect, the cut-off is 2 items out of 5.
 In the witnessing violence to siblings subscale, the cut-off is 1 items out of 4
We will include people into the control group who a) score 0 on the six subscales most relevant to severe childhood maltreatment (SCM) listed above, and b) score below the cut-off on the other four subscales less relevant to severe childhood maltreatment, and c) do not score any item on these four subscales below the age of ten.

Exclusion criteria

In each study, a potential subject who meets any of the following criteria will be excluded from participation in this study:

For both groups:

 Body mass index lower than 18.5 or higher than 30.
 Abnormal hearing or (uncorrected) vision.
 Average use of psychotropic medication or recreational drugs weekly or more.
 Habitual smoking, i.e. more than a package of cigarettes per week and a self-reported inability or unease to cease smoking for 24 hours prior to testing.
 Use of psychotropic medication, or of recreational drugs over a period of one week prior to each test session, and use of alcohol within the last 24 hours before each measurement.
 Regular use of corticosteroids.
 Current psychiatric treatment. (e.g., severe depression, anorexia nervosa, severe mood disorders, mania, schizophrenia or borderline personality disorder)
 Current neurological treatment.
 Current endocrine treatment. (e.g., phechromocytoma, hyperthyroidism, Cushing's syndrome)
 Contraindication for systemic hydrocortisone (e.g., ulcus ventriculi, ulcus duodeni, certain infections, and eye problems that point toward a risk (closed-angle) glaucoma).
 History of repeated (more than once) of autonomic failure (e.g., vasovagal reflex syncope).
 Contraindications for MRI scanning (e.g., pacemaker, implanted metal parts, deep brain stimulation, claustrophobia)
 Metal objects in or around the body (braces, pacemaker, metal fragments, hearing devices).
 Use of medication that may interact with hydrocortisone (study 1) or THC (study 2). E.g., for Hydrocortisone, e.g., taking taking mifepristone within one week before and during the study period is reason for exclusion. For THC, taking rifampicin, ketoconazole, and omeprazole will not be allowed within one week before and during the study period.
 Cognitive impairment (MMSE < 26)
 Pregnancy
 Night shift work
 Known enhanced risk of using THC or hydrocortisone

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2019
Enrollment:	48
Type:	Actual

IPD sharing statement

Plan to share IPD: Yes

Plan description
Data will be shared via the institutional data repository (Donders Repository) upon request and in agreement with privacy regulations.

Ethics review

Positive opinion

Date:	10-01-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 50765
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8326
CCMO	NL62274.091.18
OMON	NL-OMON50765

Study results

Summary results
N.A.