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

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Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON21224

Bron
NTR

Verkorte titel
ELSCAN

Aandoening

Early-life stressed people

Ondersteuning

Primaire sponsor: Radboudumc, Nijmegen
Overige ondersteuning: China Council Scholarship

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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.

Onderzoeksopzet

one year

Onderzoeksproduct en/of interventie

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

Contactpersonen

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-09-2019
Aantal proefpersonen:	48
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Ja

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

Ethische beoordeling

Positief advies

Datum:	10-01-2020
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 50765
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

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

Resultaten

Samenvatting resultaten
N.A.