Characterization of 2-AG as a potential biomarker

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON26589

Source
Nationaal Trial Register

Brief title
CHDR2019

Health condition

Neuropsychiatric diseases

Sponsors and support

Primary sponsor: CHDR
Source(s) of monetary or material Support: CHDR

Intervention

Outcome measures

Primary outcome

• CSF and plasma 2-AG
• CSF and plasma 1-AG

Secondary outcome

• CSF and plasma 2-AG and 1-AG
• CSF BDNF
• plasma ACTH
• serum cortisol
• serum prolactin
• sleep duration, sleep onset and time to wake
• sleep cycles: deep, light, REM phases
• BMI
• total body fat

Study description

Background summary

The endocannabinoid (eCB) system is an intricate and well conserved biological system located both the central nervous system (CNS) and peripherally. As a result, it has been implicated in a vast array of physiological processes such as emotion regulation, feeding behavior, pain sensation, reward behaviour, glucose metabolism, memory, and sleep.
The endocannabinoid system is comprised of the G-protein coupled receptors (GPCRs) cannabinoid receptor type 1 (CB1R) and cannabinoid receptor type 2 (CB2R), their endogenous ligands 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamine (AEA or anandamide), as well as the enzymes responsible for the synthesis and degradation of these molecules. AEA and 2-AG are two endocannabinoids whose role has been extensively investigated in the context of CNS disorder and they are synthesized from membrane-derived lipid precursors coupled to their release, while degradation occurs via fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. CB1R and CB2R are G-protein-coupled receptors and are found in almost every major system throughout the body. Specifically, CB1R is highly expressed in the CNS, particularly in cortex, hippocampus, amygdala, basal ganglia and cerebellum, whereas CB2R is mostly present on immune cells. Also, the eCB system plays critical modulatory role in synaptic plasticity and homeostasis, and has been implicated in learning, memory formation and mood regulation.
In fact, accumulating evidence supports cross-talk between eCB signaling and the synaptic growth factor brain derived neurotrophic factor (BDNF) which is recognized as a key player in brain neurogenesis and synaptic plasticity. Together, several lines of research support targeting the eCB system in the treatment of neuropsychiatric disease in general, and particularly so for affective disorders such as anxiety and depression.
Agonists, antagonists or inverse agonists, that indiscriminately or/and potently activate or inhibit the function of CB1Rs, can interfere with normal endocannabinoid-mediated function in non-target cells, with untoward clinical effects as a result. As opposed to targeting CB1Rs directly, selective inhibition of the degradation enzymes FAAH or MAGL are expected to increase endocannabinoid concentrations, which may enable more subtle modulation of the eCB system. Noteworthy, FAAH and MAGL inhibition are dependent upon 2 different mechanisms. 2-AG, the major substrate for MAGL, is present in significantly greater concentrations (i.e., 2 orders of magnitude higher) in the brain as compared to anandamide;

notably, 2-AG is the most abundant endogenous agonist of cannabinoid receptors in the body. JNJ-69095897 is a selective, reversible, centrally active, non-competitive inhibitor of MAGL
currently in preclinical development. Several clinical studies are currently being planned in different human populations.
Pharmacodynamic biomarkers are crucial in first-in-human (FIH) studies since they can guide dose selection and safety decisions based on demonstration of target engagement. However, methodological and technical issues related to the biomarker may unknowingly influence its validity. For example, circadian rhythm or external factors such as sleep, or diet may act as confounders by influencing biomarker concentrations. Such challenges are also faced when considering 2-AG as a pharmacological biomarker for use in future early phase clinical trials with JNJ-69095897. First, 2-AG and AEA, and possibly related endogenous substances arachidonic acid (AA) and prostaglandin E2 (PGE2) levels demonstrate circadian changes in plasma, and might show a similar profile in the cerebrospinal fluid (CSF) but this is currently not known. Second, since CSF is the source of 2-AG most proximal to the intended target of MAGL inhibitors, it is expected to provide the most relevant information on 2-AG as a pharmacological biomarker.
However, obtaining CSF involves a relatively invasive procedure that requires placement of intrathecal catheter at lumbar site and serial CSF sampling[21]. Thus, the most optimal CSF sampling schedule is required to minimize burden to research subjects. Third, is not certain that peripheral 2-AG actually reflects 2-AG in the CSF, and it is unclear whether circadian variation is similarly prominent in the CSF. Fourth, 2-AG is chemically unstable in vitro, and therefore prone to molecular rearrangement to a thermodynamically more stable isomer 1-AG after. Fourth, the intimate relationship between the eCB system and neurovegetative functions such as sleep and stress on the one hand, and homeostasis and neuroplasticity on the other hand, makes it important to interpret 2-AG in the context of neuroendocrine and/or growth factors which form part of the orchestrated circadian oscillation.
Although rigorous laboratory measures such as predefined mealtimes and sleep times are put in place, it remains crucial to characterize hypothalamus-pituitary-adrenal (HPA) axis activity and growth factor activity to adequately validate 2-AG as a pharmacological biomarker for MAGL inhibitors.
In summary, thorough investigation characterizing 2-AG and its possible influencers is warranted before 2-AG can considered a valid
and reliable pharmacological biomarker for MAGL inhibition. The current study is therefore intended to characterize 2-AG in both central and peripheral compartments as a potential pharmacological biomarker in healthy human subjects, to inform thus our future clinical proof of concept trials with the central MAGL inhibitor JNJ-69095897.

Study objective

• Characterize the plasma and Cerebrospinal Fluid (CSF) time concentration profile of 2-AG, 1-arachidonoylglycero (1-AG) over 24h
and 16h period, respectively.
• Determine the optimal sampling frequency of 2-AG, 1-AG for future studies.
• Establish whether 2-AG and 1-AG in CSF demonstrate a diurnal rhythm.

Study design

Day -28(screening) till EOS

Intervention

N.A.

Contacts

Public
Centre for Human Drug Research
G. Jacobs

+31 71 5246 400
Scientific
Centre for Human Drug Research
G. Jacobs

+31 71 5246 400

Eligibility criteria

Inclusion criteria

- Healthy, male and female subjects between 25 and 65 years of age, inclusive.
- Female participants must be postmenopausal or must be on hormonal contraception for at least 6 months regulating the menstrual cycle.
- Subjects must have a BMI between > 18.0 and 30.0 kg/m2, inclusive (BMI = weight/height2).
- Subject must be healthy based on physical examination, medical history, vital signs, and 12-lead Electrocardiogram (ECG). Minor abnormalities in ECG, which are not considered to be of clinical significance by the investigator, are acceptable.
- Subjects must be healthy based on clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities to be not clinically significant. This determination must be recorded in the subject's source documents and initialed by the sub investigator.
- Subjects must be willing to adhere to the prohibitions and restrictions specified in the protocol.
- Each subject must sign an informed consent form (ICF) indicating that he or she

understands the purpose and procedures required for the study and are willing to participate in the study.
- Subjects must be willing to undergo intrathecal insertion of the spinal catheter for 16 hours ±2.
- Agree to avoid any strenuous exercise from screening until the last day at the clinical research unit.

Exclusion criteria

- Pregnant woman.
- Past or present history of any clinically relevant psychiatric disorder as classified according to DSM-IV or DSM 5, mood, anxiety and psychotic disorders in particular.
- Subject has a history of drug or alcohol use disorder according to DSM-IV or DSM 5 within 12 months before screening or has a positive test result(s) for alcohol and/or drugs of abuse (including but not limited to: opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, and benzodiazepines) at screening or admission to the clinical unit.
- Significant coagulation abnormality (e.g. hemophilia, platelet counts less than the lower limit of normal or clinically significant elevation in PT or PTT at screening), or has a medical condition requiring treatment with an anticoagulant (e.g. warfarin) or with two or more antiplatelet agents. Platelet counts between 125,000 and 150,000/microliter are permissible as long as the investigator confirms there is no evidence of current bleeding diathesis or coagulopathy.
- Subject has abnormalities upon fundoscopy indicating an increased Intracranial Pressure (ICP), unless assessed as safe by principal investigator when no further evidence is present indicating ICP.
- History of clinically significant back pathology and/or back injury (e.g. degenerative disease, spinal deformity, or spinal surgery) that may predispose to complications or technical difficulty with the spinal catheter.
- Subject smokes cigarettes (or equivalent) and/or has used nicotine-based products within 3 months prior to spinal catheter insertion ; positive cotinine test at screening and admission.
- Subject has a history of heparin allergy.
- Subject has undergone major lifestyle changes in the previous 6 months: significant weight loss > 5kg or started a specific diet which could potentially result in weight loss.
- Vulnerable subjects (e.g., a person kept in detention or a person under guardianship).
- Subject is unable to read and understand the consent forms, complete study-related procedures, and/or communicate with the study staff.
- Unsuitable veins for cannulation and/or repeated venepuncture.
- Diagnosis or suspicions of any sleep disorder in the last 6 months or current complaints of sleep disturbance, irregular sleep schedule or shift work; habitual daytime naps; travel across time zones in the last 4 weeks or daytime symptoms attributable to unsatisfactory sleep.
- Use of a prescription medicine and or over-the-counter medicine influencing the sleeping habits (such as benzodiazepines, melatonin) or occasional use (last 6 months) of cannabis (in all its forms including the use of cannabidiol (CBD)).

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-05-2021
Enrollment:	18
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Plan description
N.A.

Ethics review

Positive opinion

Date:	06-10-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 50921
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL9774
CCMO	NL75602.056.20
OMON	NL-OMON50921

Study results

Summary results
N.A.