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Original

Role of cardiorespiratory fitness on the associations between endocannabinoid system and depressive symptoms in adults diagnosed with depression: the SONRIE study

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ABSTRACT

Objective: Endocannabinoid system (ES) seems to be altered in patients with depression. Cardiorespiratory fitness (CRF) may be an interacting factor in the relationship between ES biomarkers and depressive symptoms in people diagnosed with depression. The aim was to study the role of CRF on the possible association between ES biomarkers and depressive symptoms in 73 adults diagnosed with depression.
Method: This study examine the outcomes of cardiorespiratory fitness and plasma levels of the lipid mediators; anandamide (AEA) and 2-arachidonoylglycerol (2-AG) sampled from 73 adults diagnosed with depression.
Results: Patients with high CRF level had significant and inverse association among depressive symptoms and 2-AG serum levels (β: -0.013; 95% CI: -0.262 to -0.000; R^2=22.6; P<0.001).
Conclusions: Higher CRF levels could have a protective role on depressive symptoms by increases in 2-AG.
Keywords: Depressive Disorder; Endocannabinoid System; Cardiorespiratory Fitness.

Papel de la capacidad cardiorrespiratoria en la asociación entre el sistema endocannabinoide y los síntomas depresivos en adultos diagnosticados de depresión: el estudio SONRIE

RESUMEN

Objetivo: El sistema endocannabinoide (SE) parece estar alterado en pacientes con depresión. La capacidad cardiorrespiratoria (CRF) puede ser un factor que interactúe en la relación entre los biomarcadores del SE y los síntomas depresivos en personas diagnosticadas de depresión. El objetivo de este trabajo es estudiar el papel del CRF en la posible asociación entre los biomarcadores de ES y los síntomas depresivos en 73 adultos diagnosticados de depresión.
Método: Este estudio examina los resultados de la aptitud cardiorrespiratoria y los niveles plasmáticos de los mediadores lipídicos; anandamida (AEA) y 2-araquidoilglicerol (2-AG) en 73 adultos diagnosticados de depresión.
Resultados: Los pacientes con alto nivel de CRF tuvieron una asociación significativa e inversa entre los síntomas depresivos y los niveles séricos de 2-AG (β: -0,013; IC 95%: -0,262 a -0,000; R^2=22,6; P<0,001).
Conclusiones: Los niveles más altos de CRF podrían tener un papel protector sobre los síntomas depresivos por el aumento de 2-AG.
Palabras clave: Trastorno depresivo; Sistema endocannabinoide; capacidad cardiorrespiratoria.

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O papel da capacidade cardiorrespiratória na associação entre o sistema endocanobinóido e os sintomas depressivos em adultos diagnostados com a depressão: o estudo SONRIE

RESUMO

Objetivo: O sistema endocannabinoide (ES) parece ser alterado em doentes com depressão. A aptidão cardiorrespiratória (CRF) pode ser um factor de interacção na relação entre os biomarcadores SE e os sintomas depressivos em pessoas diagnosticadas com depressão. O objetivo deste estudo foi estudar o papel da CRF na possível associação entre biomarcadores de ES e sintomas depressivos em 73 adultos diagnosticados com depressão.
Métodos: Este estudo examina resultados de aptidão cardiorrespiratória e níveis plasmáticos de mediadores lipídicos; anandamida (AEA) e 2-arachidonoylglycerol (2-AG) em 73 adultos diagnosticados com depressão.
Resultados: Os doentes com CRF elevado tinham uma associação inversa significativa entre sintomas depressivos e níveis séricos 2-AG (β: -0,013; 95% CI: -0,262 a -0,000; R^2=22,6; P<0,001).
Conclusões: Níveis mais elevados de CRF poderiam ter um papel protector nos sintomas depressivos, aumentando o 2-AG.
*Palavras-chave:*Desordem depressiva; Sistema endocannabinoide; Aptidão cardiorrespiratória.

Introduction

Depressive disorder is one of the leading causes of years lived with disability in the world.[1] Around 350 million people are estimated to be affected, with twice as many women as men[2,3] and it is also a major contributor to suicide deaths.[4] With the global burden of disease rising, there is an urgent need for the management and treatment of depressive disorder to be improved.[1,4]

Although is a common disease, its etiology remains largely unclear.[5] The latest studies suggested that depression is mainly caused by pathological plastic changes of the brain at the molecular and cellular levels resulting from external stimuli. In this way, recent studies have showed that the endocannabinoid system (ES) and depression occurrence are closely related.[5] ES is a lipid signaling system distributed throughout the body and involved in multiple intracellular signaling pathways.[6,7] ES components (receptors, ligands, synthesizing and degradative enzymes) have gained special interest due to their essential role in modulating the brain's reward functions, immunological processes, emotions, appetite, motivational behavior, and cognitive function.[8-10] Altered ES recapitulates the majority of measurable behavioral, endocrine and morphological changes that are seen in patients diagnosed with depression.[11] Specifically, the scientific literature reported lower endocannabinoids serum concentrations, such as anandamide (AEA) and 2-arachinodoil glycerol (2-AG), in patients with depression.[12-15]

Several studies found that physical exercise could increase endocannabinoids serum concentrations as an acute response.[16-20] However, there is no evidence if having a good physical fitness, expressed by cardiorespiratory fitness (CRF), could be an interacting factor in the relationships between ES concentrations and depressive symptoms.

Therefore, the aim of this study was to examine the role of CRF on the possible associations between SE biomarkers (2-AG and AEA) and depressive symptoms in adults with depression.

Methods

This study was a cross-sectional baseline data from the SONRIE study, performed in Psychiatric area in Puerto Real University Hospital, Cadiz, Spain.

Participants

A sample of 73 individuals (11 men) aged 25 to 65 years diagnosed with low-mild depression, recruited by their specialist psychologists at the Mental Health Center, participated in the present study. All participants gave written informed consent after receiving information regarding the nature and purpose of the study. The SONRIE protocolwas designed in accordance with the 2013 Declaration of Helsinki[21] and approved by the Ethics and Research Committee of the "Hospital Universitario de Puerta del Mar" (Cadiz, Spain)., written informed consent was given by all participants.

Inclusion criteria were:

- Aged between 25-65 years old;
- Diagnosed with low to moderated depressive disorder;
- Do not suffer any injury avoiding participants from doing physical activity;
- Be able to speak and write.

Exclusion criteria were:

- Severe depression;
- Acute or terminal disease;
- Unstable cardiovascular disease, medical history of ictus, epilepsy or brain cancer;
- Inability to perform physical activity.

Depressive symptoms

Depressive symptoms were assessed by Beck depression inventory (BDI).[22] The BDI comprised 21 items that assessed the severity of clinical anxiety symptoms experienced by patients in a previous month. Patients rate each symptom on a four-point Likert scale of increasing severity from 0 ("not at all") to 3 ("severe"). These items were further divided into somatic-affective (such a sadness, changes in sleeping pattern) and cognitive-psychological depressive symptoms (such a past failure, suicidal thoughts or wishes). The global score is an arithmetic summation of the ratings across all 21 symptoms scored on a scale of 0 to 63.

Endocannabinoid System Biomarkers

Anandamide (AEA) and 2-araquinodilglicerol (2-AG) were quantified by isotopic dilution, liquid chromatography/ electrospray ionization tandem mass spectrometry (LC-MS-MS).[23]

Cardiorespiratory Fitness (CRF)

Participants performed 6-minute walk test (6MWT), in which each patient was instructed to walk as quickly as possible without running for six minutes in 60 meters circuit. The final score computed as the maximum number of meters walked, was used in the analysis.

Statistical analysis

Participant characteristics were presented as means and standard deviations (SD) for continuous variables and frequencies for categorical variables. Multiple linear regression was used to estimate β coefficients and 95% confidence intervals (CI) for ES, i.e., AEA and 2-AG according to depressive symptoms variable.

The ES depression symptoms were assessed using three levels of adjustment. Model 1 was the unadjusted model; Model 2 as Model 1 plus age; and finally Model 3 as Model 2 plus CRF. No significant effect modification among exposure groups by sex were observed using likelihood ratio tests of nested models; therefore, results were presented pooled. Statistical analyses were performed using STATA version 14.1 (Stata Corp, College Station, TX, USA). Statistical significance was set at p< 0.05.

Results

Descriptive characteristics of the study population according to sex are shown in Table 1. Non-significant differences were found between any variable studied for male and female.

Linear regression analysis (Table 2) revealed that 2- AG was inversely associated (β: -0.013 and 95% CI: -0.262 to -0.000; p< 0.001) with depressive symptoms after adjustment for age and CRF. Specifically, a 1 ng/mL increase in 2-AG was inversely associated (p< 0.001) with a decrease of 0.013 (95% CI: -0.262 to -0.000) depressive symptoms. The percentage of variance (R2) explained was 22.6%. No significant relationship was found between depression and AEA (Table 2).

Table 1. Descriptive characteristics of the study sample.

	All (n=73)	Female (n=62)	Male (n= 11)	P-value
Age (years)	49.04 ± 9.96	48.35 ± 9.91	52.92 ± 9.79	0.16
BDI (Score,0-63)	33.14 ± 9.53	33.48 ± 9.69	31.18 ± 8.70	0.46
AEA (ng/mL)	0.25 ± 0.09	0.25 ± 0.10	0.24 ± 0.08	0.75
2-AG (ng/mL)	2.77 ± 1.70	2.74 ±1.69	2.97 ± 1.80	0.68
6-MWT (meters)	539 ± 79.16	532.88 ± 79.79	573.45 ± 68.89	0.12

Values are presented as mean ± standard deviation. Differences between sexes were examined by independent t test. BDI, Beck Depression Inventory; AE, Anandamide; 2-AG, 2-Arachinodoil glycerol.

Table 2. Association between 2-AG and depression symptoms.

	β [95% LCI-UCI]	R^2	R^2adj
DS			
Model 1	-0.014 [-0.03 to 0.00]	0.053	0.039
Model 2	-0.012 [-0.025 to 0.002]**	0.255	0.002
Model 3	-0.013 [-0.26 to 0.000]***	0.226	0.193

Data are presented for all sample as standardized coefficient (β), r squared (R2) and adjusted r squared (R2adj). **p<0.01; ***p<0.001
Model 1 was unadjusted.
Model 2 was adjusted for age.
Model 3 was adjusted for age and CRF.

Discussion

This study aimed to examine the role of CRF on the possible associations between SE biomarkers (2-AG and AEA) and depressive symptoms in adults diagnosed with depression. The main finding of the present study was that the inverse association between SE and depressive symptoms was independent of CRF.

Our findings are in line with previous studies showing that 2-AG, but not AEA, was associated with depressive symptoms.[24] Those study reported that ES seems to be an expansive neuromodulatory network that regulates synaptic excitability and neurotransmitter release. Moreover, that system looked to be involved in diverse psychological processes such as reward and emotional regulation, memory, nociception and cognitive functions.[14] Overall, it is known that exercise may improve mood states and wellbeing in healthy and depressive adults.[24] Moreover, exercise appears to be as effective in treating depression as antidepressant medications and other accepted behavioral therapies.[25-27] However, our study found no strong evidence for a mediation effect by CRF for the association between SE and depressive symptoms, as β coefficients remained relatively similar following additional adjustment for CRF. This was the first study designed to analyze the role of CRF on those associations therefore, we did not find evidence to support such a mediating role.

This study has several limitations. Although an extensive medical examination was performed, findings of our study may also have been affected by residual confounding from undetected subclinical disease. However, a sensitivity analysis excluding participants with self-reported history of diabetes and cardiovascular illness (n=51 participants) did not change the results.

The main strength of the present study was that it´s the first study analyzing physical fitness (CRF) on the association between DS and ES.

Future studies analyzing deeper the role of CRF on ES and depressive symptoms in adults are needed.

Therefore, we concluded by stating that 2-AG is associated of depressive symptoms in adults diagnosed by depression. The association is not mediated by CRF. However, our work highlighted the lack of knowledge about the influence of physical fitness on SE biomarkers in people with depression.

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