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ORIGINAL PAPER

Monoamines and cortisol as potential mediators of the relationship between exercise and depressive symptoms

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Abstract A randomized controlled trial was conducted to assess the effects of exercise plus pharmacotherapy on monoamine neurotransmitters (dopamine, noradrenaline, adrenaline, serotonin) and cortisol levels. A total of 26 women with clinical depression were randomly assigned to one of the two groups: aerobic exercise plus pharmacotherapy or only pharmacotherapy. The exercise program consisted of aerobic exercise, 45–50 min/session, three times/week, for 16 weeks. The biological parameters were measured before and after the exercise program. Adding exercise to pharmacotherapy had no additional effects on monoamines and cortisol plasma levels. These data are preliminary outcomes from a small sample and should be replicated.

Keywords Depression · Women · Aerobic exercise · Catecholamines · Cortisol

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Introduction

The contribution of exercise as an efficacious component of treatment for various mental disorders has been increasingly recognized [19]. Indeed, a high number of intervention studies have been conducted, which analyzed several factors that might moderate the antidepressant effect of exercise on depression [7]. However, there are no consistent conclusions about the underlying neurobiological explanation to the antidepressant effect of exercise in subjects with major depressive disorder [20]. Accordingly, the efficacy of exercise in depressive disorder is attributed to physiological changes in monoamine metabolism [22], hypothalamic–pituitary–adrenal (HPA) axis function [21], neurotrophic factors [23], neuroinflammation [10], and endocannabinoid system [8]. It is important to bear in mind that typical antidepressant medication for depression acutely blocks the reuptake or breakdown of the monoamines 5-hydroxytryptamine (5-HT or serotonin) and noradrenaline (NA), with 5-HT selective reuptake inhibitors (SSRIs) [6] representing the highest prescribed medication for depression. Nonetheless, depressive disorder is a multifactorial disease with changes in several biomarkers, which does not involve only monoamines [18]. Moreover, the cause of depression is far from being a simple deficiency of central monoamines [11]. This also explains why treatment with existing antidepressant drugs, most of which target monoamines, frequently does not show therapeutic response, or instead shows only a partial response [17]. Several systematic reviews described the influence of exercise on the serotonergic system [14, 15] and in the HPA axis function [20, 24], and had proposed that exercise might improve the efficiency of the monoamine system response and normalize HPA axis in depressive patients [13].

In order to identify possible biological mechanisms that might contribute to produce exercise effects on depressive disorder, we hypothesized that the exercise group (EG) would have a significant increase in monoamine levels (dopamine, DA; NA; adrenaline, AD; 5-HT) and a decrease in cortisol levels in comparison with the control group (CG). This is the first study developed in women with depressive disorder, which analyzed the influence of chronic exercise on monoamine responses and cortisol plasma levels.

Methods

Trial design

The HAPPY BRAIN trial was a two-armed randomized control trial (RCT), and a detailed description of the study has been previously published [2]. Randomization was implemented with sequentially numbered opaque, sealed envelopes. Patients had clinical depression according to International Classification of Diseases, 10th revision (ICD-10), diagnostic criteria (F32.1, F33.1, F34.1), and were diagnosed by psychiatrists. The sample was composed of 19 sedentary women, aged 18–65 years.

The patients, physical training teacher, general practitioners, psychiatrists, or researchers were not blinded regarding treatment allocation, except for the laboratory, which analyzed the blood samples.

The protocol respected the Declaration of Helsinki and was accepted by the Ethics Committee of Centro Hospitalar de São João with reference number 112/13 (March 11, 2013).

Exercise training protocol

Nine patients in the EG performed aerobic exercise, 45–50 min/session, three times/week, for 16 weeks. All sessions started with a 10-min low-intensity warm-up, followed by 30 min of aerobics and 5 min of low-intensity cooling down. The aerobic exercise involved traditional games, indoor/outdoor natural circuit workouts with resistance bands, jump ropes, fitness balls, brisk walking, and dancing. The target heart rate zone was calculated according to Karvonen et al. [9]. Exercise intensity was controlled with a heart rate monitor (Polar FT1, Finland). Average intensity for the 16 weeks was 72 % of the maximum heart rate. The rating of perceived exertion (RPE) scale [1] was used to assess training intensity at a moderate level (RPE = 12–13).

Control group

The CG involved ten patients who carried on with their usual pharmacological therapy, but did not exercise.

Outcome measures

All patients were assessed to blood analysis at baseline and at the end of the exercise intervention.

Table 1 Outcome measure scores at baseline and 16 weeks, with differences (p value) and effect size ($\eta^2 p$) for the differences

Catecholamine's	Exercise ($N = 9$)	Control ($N = 10$)	Time × group	
			p value	$\eta^2 p$
Dopamine (ng/mL)				
Baseline	15.82 ± 5.75	20.29 ± 5.55	0.028	0.254
16 weeks	15.03 ± 6.14	13.29 ± 2.28		
Noradrenaline (pg/mL)				
Baseline	253.66 ± 95.26	260.54 ± 135.56	0.536	0.023
16 weeks	394.75 ± 127.85	364.89 ± 147.18		
Adrenaline (pg/dL)				
Baseline	15.51 ± 24.27	23.27 ± 7.95	0.347	0.052
16 weeks	19.18 ± 11.36	23.46 ± 9.49		
Serotonin (ng/mL)				
Baseline	17.04 ± 13.52	38.83 ± 37.90	0.252	0.076
16 weeks	12.32 ± 8.86	51.32 ± 31.53		
Cortisol (µg/dL)				
Baseline	15.11 ± 3.95	11.90 ± 6.38	0.207	0.092
16 weeks	10.22 ± 3.60	10.20 ± 4.89		

Blood analyses

Blood sampling and preparation

Peripheral levels of monoamines were assessed at baseline and after the exercise intervention. The length of time between the last exercise session and the laboratory staff performing the blood analyses was approximately 18 h post-training. Blood samples were taken in tubes with a stabilization solution prepared exactly according to the instruction manual for the HPLC analysis of catecholamines in plasma from Chromsystems (Grafelfing, Germany).

Monoamines and cortisol quantification in plasma

Samples were prepared using the Reagent kit 5000 catecholamines in plasma, for HPLC analysis, from Chromsystems (Grafelfing, Germany).

Cortisol in plasma was measured using the chemiluminescent ADVIA Centaur Cortisol immunoassay. Measurements were performed in an ADVIA Centaur XP Immunoassay System (Siemens, Germany).

Statistical analysis

Results were expressed by descriptive statistics (mean and standard deviation). All dependent variables were tested for normality according to the Shapiro–Wilks method before performing analyses. Potential group differences in baseline measures were evaluated by independent sample *t* tests for all variables. Repeated measures ANOVA with assumed sphericity were used to analyze the time × treatment interactions for all outcome variables at baseline and 16 weeks. We analyzed data with IBM SPSS statistics software (version 21.0). A p value of <0.05 was taken as significant. The effect size partial eta-squared ($\eta^2 p$) was computed and reported for repeated measures ANOVA, which was provided with statistical software packages SPSS. Cohen [3] provides benchmarks to define small ($\eta^2 = 0.01$), medium ($\eta^2 = 0.06$), and large ($\eta^2 = 0.14$) effects (Table 1).

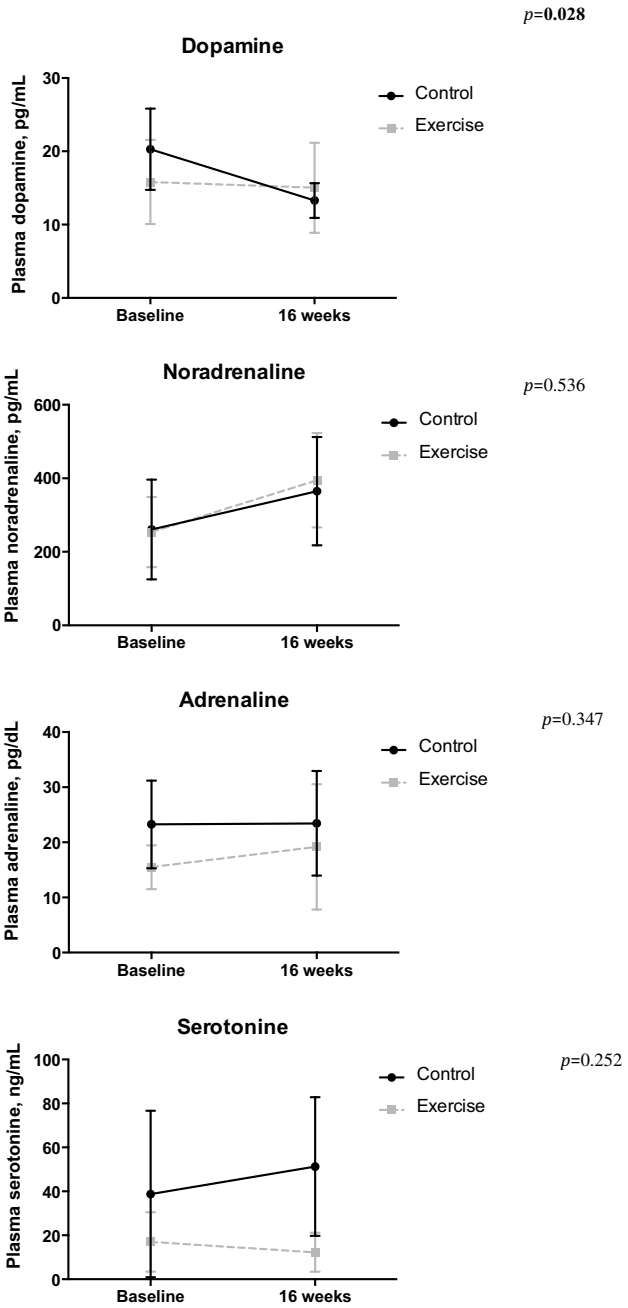

Fig. 1 Catecholamines response to aerobic exercise in depressed patients and controls. Baseline refers to mean basal value of plasma catecholamines assessed before exercise; 16 weeks refers to mean plasma catecholamines value assessed after 16 weeks of exercise

Results

Pre-exercise monoamines and cortisol blood plasma levels

The mean and standard deviation plasma levels of hormones measured at baseline in the EG and CG were 15.82 ± 5.75 and 20.29 ± 5.55 pg/mL for DA, 253.66 ± 95.26 and 260.54 ± 135.56 pg/mL for NA, 15.51 ± 3.98 and 23.27 ± 7.95 pg/dL for AD, 17.04 ± 13.52 and 38.83 ± 37.90 ng/mL for 5-HT, and 15.11 ± 3.95 and 11.90 ± 6.38 µg/dL for cortisol. Comparisons between groups revealed no significant differences with respect to DA, NA, AD, 5-HT, and cortisol.

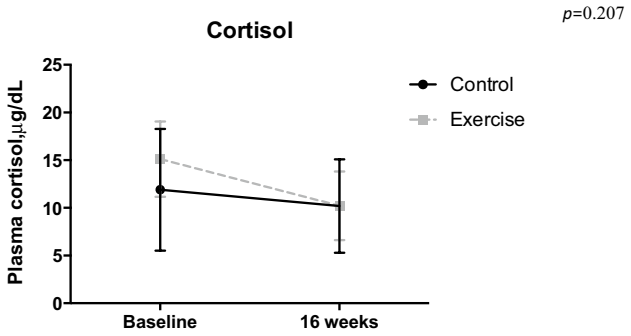

Fig. 2 Cortisol response to aerobic exercise in depressed patients and controls. Baseline refers to mean basal value of plasma cortisol assessed before exercise; 16 weeks refers to mean plasma catecholamines value assessed after 16 weeks of exercise

Monoamines and cortisol blood plasma levels in response to exercise

Regarding DA, the response to exercise was statistically significant in the EG compared to the CG in the interaction between time × group. Observed F value was statistically significant in the DA variable in relation to the interaction [$F(1,17) = 5.789$, $p = 0.028$, $\eta^2 p = 0.254$]. Likewise, the NA response to chronic exercise has not differed significantly [$F(1,17) = 0.400$, $p = 0.536$, $\eta^2 p = 0.023$] when considering the interaction between time × group. Furthermore, the AD response to exercise did not differ significantly in the interaction between time × group [$F(1,17) = 0.934$, $p = 0.347$, $\eta^2 p = 0.052$]. Moreover, the 5-HT response to exercise has not differed significantly in the interaction between time × group [$F(1,17) = 1.407$, $p = 0.252$, $\eta^2 p = 0.076$] (Fig. 1). The cortisol response to exercise did not differ when we observed the interaction between time × group [$F(1,17) = 1.724$, $p = 0.207$, $\eta^2 p = 0.092$] (Fig. 2).

Discussion

This RCT was conducted in conjunction with the HAPPY BRAIN study [2], which has showed that aerobic exercise training was an adjuvant therapy for treating women who suffered from depression, as it reduced the severity of depressive symptomatology and improved physical fitness.

However, in this study the comparison of plasma hormone concentration of monoamines (DA, NA, AD, and 5-HT) and cortisol at baseline and after 16 weeks between groups revealed statistically significant differences between groups over time with a large effect size in DA levels. Yet, changes were different from our expectations. Indeed, while the EG showed a weak decrease in DA levels, the CG showed a greater decrease. These results might be explained by changes in NA and AD synthesis. In fact, the synthesis of NA and AD depends directly on the activity of its rate-limiting enzyme, dopamine-b-hydroxylase (converts DA into NA) and phenylethanolamine *N*-methyltransferase (converts NA into AD). Regarding that DA is the precursor of NA, and that NA levels increased in both groups, it could be speculated that the weak decrease in plasma DA levels in the EG could be explained by an increase in NA and AD levels. Nonetheless, we do not have sufficient data to reach this conclusion.

In relation to 5-HT plasma levels, the results have shown a decrease in the EG, which seems contradictory to the hypothesis that exercise would be beneficial for depressive symptoms through an increase in 5-HT plasma levels. Researches involving animal and human beings suggested that the antidepressant effect of exercise is attributable to an increase of 5-HT [5, 12, 16]. These results contradict our findings and should be interpreted with caution. According to the literature, chronic exercise leads to a reduction in serum cortisol levels [4], which is similar to the trend observed in our study.

The strength of this study is the sample randomization. Furthermore, all biomarkers were measured in plasma, which increased generalizability and comparability across studies.

The major limitations are the small sample size; patients' large age range (18–65 years), which could contribute to a greater result variability; the inclusion of patients diagnosed with different subtypes of depressive pathology; and the presence of other sicknesses (arterial hypertension and hyperthyroidism) that can interfere with catecholamine responses.

Conclusion

This RCT does not provide evidence for a biologically mediated effect of exercise in women with depressive disorder. The lack of response to exercise could be related to the moderate intensity or training level. Indeed, it can be hypothesized that exercise may potentially have a differential effect depending on exercise characteristics, training status, and gender.

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Author contributions Lara S. F. Carneiro carried out the literature search and statistical analysis, and wrote the first draft of the manuscript under the supervision of authors Professor José Vasconcelos-Raposo and Professor Maria Paula Mota. Author Professor Maria Augusta Vieira-Coelho conducted the clinical assessment of screened patients and coordinated sample, processed, and prepared it for analysis. Author Professor Rita C. Alves wrote the performed experiments. Author Professor António Manuel Fonseca provided the manuscript critical input. All authors contributed and approved the final manuscript.

Compliance with ethical standards

Conflict of interest All authors report no conflict of interest.

References

1. Borg GA (1974) Perceived exertion. Exerc Sport Sci Rev 2:131–153
2. Carneiro LS, Fonseca AM, Vieira-Coelho MA, Mota MP, Vasconcelos-Raposo J (2015) Effects of structured exercise and pharmacotherapy vs. pharmacotherapy for adults with depressive symptoms: a randomized clinical trial. J Psychiatr Res 71:48–55
3. Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Lawrence Erlbaum Associates, Hillsdale
4. Corazza DI, Sebastiao E, Pedroso RV, Andreatto CAA, Coelho FGD, Gobbi S, Teodorov E, Santos-Galduroz RF (2014) Influence of chronic exercise on serum cortisol levels in older adults. Eur Rev Aging Phys A 11:25–34
5. Dey S, Singh RH, Dey PK (1992) Exercise training: significance of regional alterations in serotonin metabolism of rat brain in relation to antidepressant effect of exercise. Physiol Behav 52:1095–1099
6. Duman RS, Voleti B (2012) Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. Trends Neurosci 35:47–56
7. Helmich I, Latini A, Sigwalt A, Carta MG, Machado S, Velasques B, Ribeiro P, Budde H (2010) Neurobiological alterations induced by exercise and their impact on depressive disorders. Clin Pract Epidemiol Ment Health 6:115–125
8. Heyman E, Gamelin FX, Goekint M, Piscitelli F, Roelands B, Leclair E, Di Marzo V, Meeusen R (2012) Intense exercise increases circulating endocannabinoid and bdnf levels in humans—possible implications for reward and depression. Psychoneuroendocrinology 37:844–851
9. Karvonen MJ, Kentala E, Mustala O (1957) The effects of training on heart rate: a longitudinal study. Ann Med Exp Biol Fenn 35:307–315
10. Kohut ML, McCann DA, Russell DW, Konopka DN, Cunnick JE, Franke WD, Castillo MC, Reighard AE, Vanderah E (2006) Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. Brain Behav Immun 20:201–209
11. Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. Nature 455:894–902
12. Lee H, Ohno M, Ohta S, Mikami T (2013) Regular moderate or intense exercise prevents depression-like behavior without change of hippocampal tryptophan content in chronically tryptophan-deficient and stressed mice. PLoS ONE 8:e66996
13. Meeusen R (2005) Exercise and the brain: insight in new therapeutic modalities. Ann Transplant 10:49–51
14. Meeusen R, De Meirleir K (1995) Exercise and brain neurotransmission. Sports Med 20:160–188
15. Meeusen R, Piacentini MF, De Meirleir K (2001) Brain microdialysis in exercise research. Sports Med 31:965–983
16. Melancon MO, Lorrain D, Dionne IJ (2014) Changes in markers of brain serotonin activity in response to chronic exercise in senior men. Appl Physiol Nutr Metab 39:1250–1256
17. Nemeroff CB (2007) Prevalence and management of treatment-resistant depression. J Clin Psychiatry 68(Suppl 8):17–25
18. Pålhagen S, Qi H, Mårtensson B, Wålinder J, Granérus A-K, Svenningsson P (2010) Monoamines, BDNF, IL-6 and corticosterone in CSF in patients with Parkinson's disease and major depression. J Neurol 257:524–532
19. Rosenbaum S, Tiedemann A, Stanton R, Parker A, Waterreus A, Curtis J, Ward PB (2016) Implementing evidence-based physical activity interventions for people with mental illness: an Australian perspective. Australas Psychiatry 24:49–54
20. Schuch FB, Deslandes AC, Stubbs B, Gosmann NP, Silva CT, Fleck MP (2015) Neurobiological effects of exercise on major depressive disorder: a systematic review. Neurosci Biobehav Rev 61:1–11
21. Sousa e Silva T, Longui CA, Rocha MN, Faria CDC, Melo MR, Faria TG, de Souza JA, Rizzo LV (2010) Prolonged physical training decreases mrna levels of glucocorticoid receptor and inflammatory genes. Horm Res Paediatr 74:6–14
22. Stenman E, Lilja A (2013) Increased monoaminergic neurotransmission improves compliance with physical activity recommendations in depressed patients with fatigue. Med Hypotheses 80:47–49
23. Szuhany KL, Bugatti M, Otto MW (2015) A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. J Psychiatr Res 60:56–64
24. Wegner M, Helmich I, Machado S, Nardi AE, Arias-Carrion O, Budde H (2014) Effects of exercise on anxiety and depression disorders: review of meta-analyses and neurobiological mechanisms. CNS Neurol Disord Drug Targets 13:1002–1014