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Effects of Different Exercise Protocols on the Oxidative Balance in the Cerebellum of Rodents: a Systematic Review

Jonata Henrique Santana[1]
https://orcid.org/0000-0002-6818-5545

Thaynan Raquel dos Prazeres Oliveira[1]
https://orcid.org/0000-0002-8243-3947

Thyago de Oliveira Rodrigues[1]
https://orcid.org/0000-0002-3973-9182

Mariana Pinheiro Fernandes[1,2]
https://orcid.org/0000-0002-9502-6355

Claudia Jacques Lagranhaa[1,2*]
orcid.org/0000-0001-6883-9476

[1]Universidade Federal de Pernambuco, Centro Acadêmico de Vitória, Vitória de Santo Antão, Pernambuco, Brasil; [2]Universidade Federal de Pernambuco, Centro Acadêmico de Vitória, Núcleo de Educação Física e ciências do Esporte, Vitória de Santo Antão, Pernambuco, Brasil.

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*Correspondence: claudia.lagranha@ufpe.br; Tel.: +55-81-2126-8000 (C.J.L.).

HIGHLIGHTS

- Moderate aerobic exercise and HIIT alters oxidative stress biomarkers.
- Antioxidant enzymes increase by different exercise protocols.
- Exercise as a strategy for prevention or treatment of neurodegenerative diseases.

Abstract: Physical exercise promotes numerous benefits in health promotion and disease prevention, that includes protection against oxidative damage in the cerebellum that has been associated with neurodegenerative diseases. However, exercise can be a potential therapeutic agent, but its response depends on individual and exercise factors such as type, intensity, and frequency of exercise. The aim of the review was to evaluate the effects of different exercise protocols on oxidative balance in the cerebellum. A literature search was performed using multiple literature databases (MEDLINE (PubMed), Web of Science, Scopus and Embase) in July 2024. In total, 329 articles were found and 11 studies that met the eligibility criteria were included in the review. The protocol was registered in PROSPERO (CRD42023411207), and we followed PRISMA (Preferred Reporting Items for Systematic Reviews) Checklist. The results found show that in most studies, exercise was able to modulate oxidative stress parameters, however, due to the differences in the evaluated parameters and methodological differences, it was not possible to highlight the best exercise protocol to improve oxidative balance in the cerebellum. Despite that, the review points to new perspectives on exercise strategies for prevention or treatment of diseases that are related to cerebellar oxidative stress that can potentially help health promotion.

Keywords: exercise; cerebellum; oxidative stress.

INTRODUCTION

According to the World Health Organization (WHO), physical activity is defined as any muscular contraction that leads to energy expenditure above the basal metabolic rate, while, while physical exercise is defined as an activity that is planned, systematized, with specific objectives and purposes, such as improving physical fitness and health [1]. According to WHO, the adult should practice 150-300 minutes of physical activity of moderate intensity or 75-150 minutes of vigorous intensity [1]. Several data in the literature already demonstrated benefits of regular physical exercise on various organs of the body such as skeletal muscle, liver, heart and brain [2-5].

In the brain, exercise promotes the release of neuroprotective molecules and antioxidant agents (i.e. Peroxisome proliferator-activated receptor gamma 1-alpha coactivator (PGC-1α), Superoxide dismutase (SOD) and Catalase (CAT)) that can prevent the accumulation of reactive oxygen species therefore decreasing oxidative stress or even block it [6-8]. The oxidative stress is considered a state of imbalance between the production of antioxidant agents and their removal by the antioxidant defense system and has been associated with the development of neurodegenerative diseases [9, 10].

Previous experimental studies have already demonstrated that moderate-intensity aerobic exercise is capable of increasing antioxidant capacity in prefrontal cortex and hippocampus [6, 11, 12]. Given this context, the brain that include the cerebellum, have been studied for its unique characteristics that make it vulnerable to oxidative damage: due to its high lipid concentration and high rates of oxygen consumption which contributes to greater production of reactive oxygen species (ROS) and [13-15]

The cerebellum is an important region of the brain that is located dorsal to the medulla and pons and rests on the cerebellar fossa of the occipital bone separated from the occipital lobe of the brain by an extension of the dura matter [16, 17]. The cerebellum that is involved in motor movement, regulation, balance control, cognitive and emotional processes present relation between neurodegenerative disease and oxidative stress [18-23].

Abnormalities in the cerebellum are present in psychiatric discords as, schizophrenia, spectrum autism and attention deficit hyperactivity, but studies still investigate the specific link with emotional and cognitive regulation [24]. Parkison’s disease is associated with damage to the cerebellum, compromising its motor and cognitive functions [25]. In transgenic schizophrenia mouse model, the activity of the antioxidant Catalase was reduced in the cerebellum [26]. In other studies, using a model of Friedreich's ataxia and Alzheimer's disease, the ROS levels and lipid peroxidation were increased; and Catalase activity and reduced Glutathione (GSH) levels were decreased [27, 28].

Knowing that physical exercise can be an important tool in combating oxidative stress and acting as therapeutic agents in neurodegenerative diseases, this systematic review seeks to understand how physical exercise affects the oxidative balance in the cerebellum by comparing different exercise models.

MATERIAL AND METHODS

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023411207). The study followed the PRISMA (preferred reporting items for systematic Reviews and Meta-Analyses) guidelines presented in check list (supplementary 1).

Search strategy

The searches in the selected databases were carried out in July 2024. The electronic search strategy for this review was performed in the MEDLINE (PubMed), Web of Science, Scopus and Embase databases. Combination of MeSH descriptors and other input terms were used: Exercise, Physical exercise, oxidative stress, oxidative damage, reactive oxygen species, mitochondrial diseases, cerebellum and cerebellar.

Eligibility criteria

Experimental studies with: (a) rodent animals (rats and mice); (b) use of aerobic or resistance exercise protocols; (c) non-exercise comparison group; and (d) evaluation of the cerebellum: oxidative stress biomarkers, antioxidant enzymes, non-enzymatic antioxidants, gene and protein expression related to mitochondrial dynamics. There was no restriction on year of publication or language of the article.

Study selection

The search and selection of articles was carried out by two independent reviewers (SANTANA, J.H, RODRIGUES, T.O;). Initially, the duplicates were removed. Then, the titles and abstracts were screened for assessment of inclusion criteria. Rayyan tool was used during selection. Subsequently full-text screening was performed for selected studies with potential eligibility. Disagreements were resolved through discussions and consultations with the third reviewer (OLIVEIRA, T.R.P.). The kappa index was 0.819, which means that there was almost perfect agreement.

Data extraction

Data from eligible studies were extracted from texts and tables. The extraction was performed by two independent reviewers (SANTANA, J.H, RODRIGUES, T.O;). The key data were collected: (a) Species of animal; (b) Sex; (iii) age- (days or months) (c) exercise parameters (time of exercise intervention; frequency of exercise sessions; intensity of exercise) and (d) Parameters of oxidative stress in the cerebellum.

RESULTS

Study selection

The strategy used to select studies, following the phases of identification, screening, and inclusion of articles, is described in the flowchart (Figure 1). A total of 329 articles were found in the databases: PubMed (75), Scopus (87), Embase (91) and Web of Science (76). 152 articles were excluded because they were duplicates, leaving 176. After reading the title and abstract, 156 articles were excluded, 20 of which were selected for detailed reading of the text. Finally, 11 studies met the eligibility criteria and were selected in this review.

Study quality

Four of 11 studies did not mention randomization of animals [29-32], four studies on incomplete data results [30, 33-35] one on selective reporting [33], and other bias (stress by gavage) was detected. No studies reported on allocation concealment or blinding. In relationship to other parameters, the results are similar [35-37]. Following the results of the SYRCLE Risk of Bias tool, studies presented an unclear overall risk of bias (Table 1). There was not enough contrast between studies to perform sensitivity analysis according to study quality.

Description of the included studies

The Wistar rats was commonly used (n= 7), followed by Fisher rats (N= 1), Sprague-Dawley rats (N= 1), ICR mice (N= 1), and C57BJ/6 wild-type mice (N= 1). All studies used male animals. Regarding the age of the animals, the studies varied between 3 weeks to 25 weeks-old [31, 32, 38]. Eight of the 11 studies selected, were aerobic exercise protocol [30-32, 34-37, 39], two used endurance training [33, 38] and one used High Intensity Interval Training (HIIT) [29] . Other parameters of exercise session were mixed, as treadmill incline (0°-10°), speed (2-30 m/min), and intensity (50-100 % VO2max). Regarding the training protocol, the frequency of session was also diverse 2 [30], 3 [32], 4 [31, 35], 5 [11, 33, 34, 36, 38], 6 [29, 37] times per week], same as for total duration in weeks [4 [31, 34] ,6 [29, 33, 35, 36] , 8 [30, 37] 12 [32, 38, 39] weeks). The exercise program, each session lasted from 5 to 20 initial minutes and 30 to 90 in the final minutes (Table 2).

Oxidative stress biomarkers

Moderate aerobic/endurance [33, 35, 37, 38], and HIIT [29] exercise protocols promotes alteration in oxidative stress biomarkers. Eight studies that evaluated Malondialdehyde (MDA) levels, three demonstrated decrease [35, 37, 38] and three increase [29, 33, 39]. The carbonyls levels were reduced in two of the three studies [37, 38]. The lipid hydroperoxide also evaluated and observed an increase [32] while the 4-hydroxy-alkenes (4HDA) levels no change were found [34] (Table 2 and 3).

Enzymatic antioxidant defense

Studies with moderate aerobic/endurance [32, 33, 35, 37-39], and HIIT [29] exercise protocols evaluated the activity of the enzyme Superoxide dismutase (SOD), and demonstrated an increase [29, 39], two decrease [35, 37] or no changes [32, 33, 38]. Of the four studies that evaluated Catalase (CAT) activity, two studies showed an increase[33, 39], and one study demonstrated decreased [37]. The moderate aerobic/endurance exercise protocols reduced[35] or no altered[33] the glutathione Peroxidase activity (Gpx) and did not change the Glutathione Reductase (GR) activity [33, 35] (Table 2 and 3).

Non-enzymatic antioxidant defense

The Glutathione (GSH) was evaluated by 4 studies [33-35, 39] with moderate aerobic/endurance exercise protocols and showed increase in only one[33]. The oxidized glutathione levels (GSSG) were also assessed and did not observe differences [35, 39]. The HIIT increase total antioxidant capacity[29] whereas moderate aerobic exercise protocols did not alter [32]. Three studies also with moderate aerobic exercise protocols evaluated total thiol levels [30, 32, 38] and only one study demonstrated increase [32] (Table 2 and 3).

Secondary outcomes

The moderate aerobic/endurance exercise protocols increase Peroxisome proliferator-activated receptor gamma 1-alpha coactivator (PGC-1α) mRNA expression in two studies [36, 37] and did not promoted changes in protein expression [38]. The increase of the Sirtuins was observed to (SIRT1) mRNA expression [36, 37], activity [31] and protein expression of SIRT3 [38]. Marques-Aleixo et al. (2015) [38] also observed an increase in mitochondrial Uncoupling protein 2 (UCP2) (Table 2).

Figures and Tables

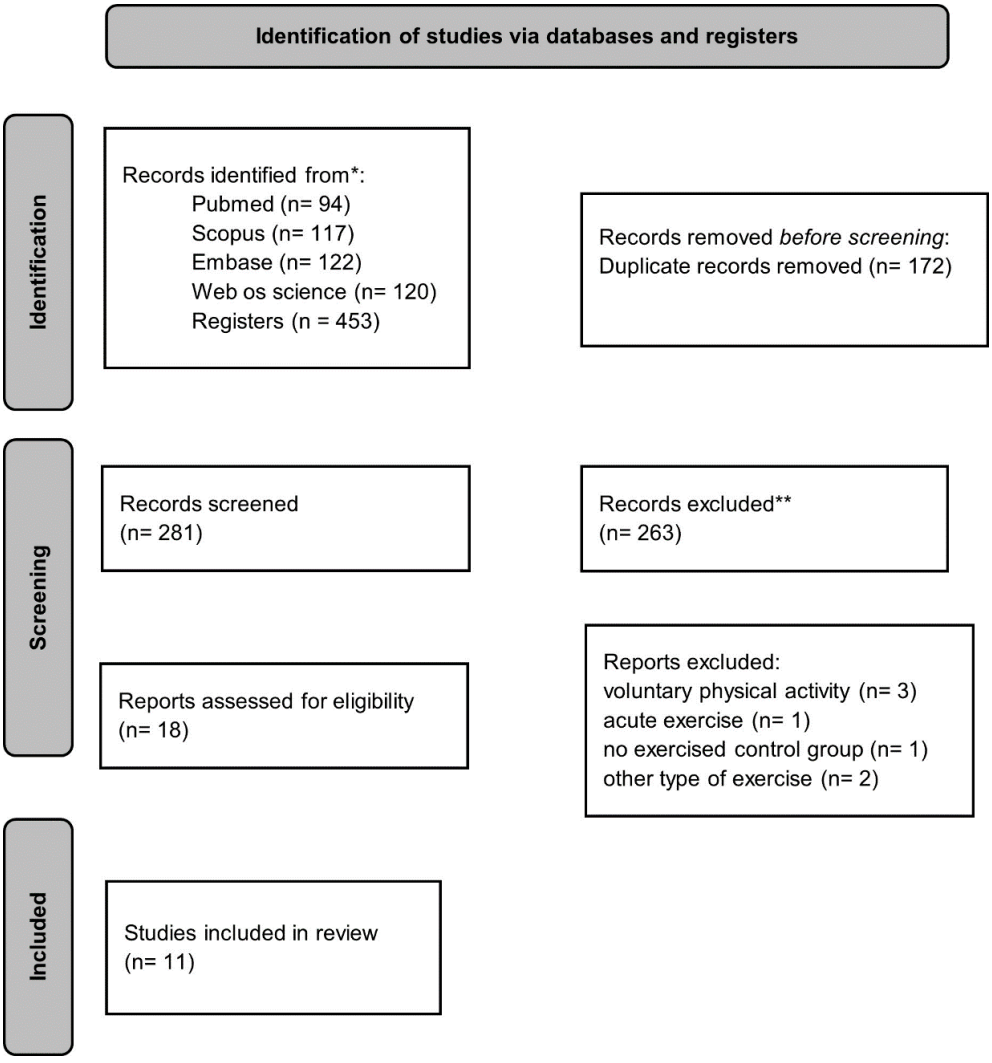

Figure 1. Flow chart for study selection

Table 1. Risk of bias evaluated by SYCLE's Rob tool

Items of the tool	Somani, 1997 [35]	Marton et al, 2010 [31]	Steiner et al, 2011[36]	Casuso et al, 2015 [37]	Chalimoniuk et al, 2015 [33]	Marques-Aleixo et al, 2015 [38]	Freitas et al, 2019 [29]	Lamarão-Vieira et al, 2019 [34]	Hoepers et al, 2020 [30]	Silveira et al, 2020 [32]	De Souza et al, 2020 [39]
Random sequence generation (selection bias)	+	-	+	+	+	+	-	+	-	-	+
Groups similar at baseline (selection bias)	+	+	+	+	+	+	+	+	+	+	+
Blinded group allocation (selection bias)	-	-	-	-	-	-	-	-	-	-	-
Randon housing (performance)	?	?	?	?	?	?	?	?	?	?	?
Blinding of participants and personnel (performance bias)	-	-	-	-	-	-	-	-	-	-	-
Randon outcome assessment (detection)	?	?	?	?	?	?	?	?	?	?	?
Blinding of outcome assessment (detection bias)	+	+	+	+	+	+	+	+	+	+	+
Incomplete outcome data (attrition bias)	-	+	+	+	-	+	+	-	?	+	+
Selective reporting (reporting bias)	+	+	+	+	-	+	+	+	+	+	+
Other bias	+	+	+	+	+	+	+	-	+	+	+

+ = low risk of bias; - = high risk of bias; ? = item not reported.

Table 2. Characteristics of the included studies.

Authors/year	Animal	Age*	Sex	(n) group£	Exercise model	Protocol
Somani, 1997 [35]	Fisher rats	Not mentioned	Male	Ex group (n-6) SE group (n-6)	Aerobic exercise (Treadmil)	4 times a week during 6 weeks at an angle of 6°; Duration 5 - 30 min; Speed 8.2 - 19.3 m/min.
Marton et al, 2010 [31]	Wistar rats	25 weeks	Male	Ex group (n-6) SE group (n-6)	Aerobic exercise (treadmill)	4 times a week during 4 weeks at 60% of VO2max. Duration 20- 40 min.
Steiner et al, 2011 [36]	ICR mice	8 weeks	Male	Ex group (n-19) SE group (n-16)	Aerobic exercise (treadmill)	5 times a week during 6 weeks at an angle of 10°; Duration 20 -80 min.
Casuso et al, 2015 [37]	Wistar rats	6 weeks	Male	Ex group (n-8) SE group (n-9)	Aerobic exercise (treadmill)	6 times a week during 8 weeks at 5% incline; Duration of 60 min.
Chalimoniuk et al, 2015 [33]	Wistar rats	6 weeks	Male	Ex group (n-18) SE group (n-18)	Endurance training (treadmill)	5 times a week during 6 weeks at 0° incline; Duration 40 - 60 min; Speed 16 - 28 m/min.
Marques-Aleixo et al, 2015 [38]	Sprague-Dawley rats	3 weeks	Male	Ex group (n-6) SE group (n-6)	Endurance training (treadmill)	5 times a week during 12 weeks at 0° incline; Duration 60 min/day; Speed 18 - 30 m/min.
Freitas et al, 2019 [29]	Wistar rats	8 weeks	Male	Ex group (n-13) SE group (n-13)	High-intensity interval training (HIIT) (treadmill)	6 times a week during 6 weeks at a 10° incline, for 1 min at 85–100% VO2max interspersed with 2 min of active recovery (60% of VO2max); Duration 30 - 45 min.
Lamarão-Vieira et al, 2019 [34]	Wistar rats	4 weeks	Male	Ex group (n-10) SE group (n-10)	Aerobic exercise (treadmill)	5 times a week during 4 weeks without an incline; Duration 5- 10 min; Speed 2 - 15 m/min.
Hoepers et al, 2020 [30]	C57BJ/6 wild-type mice	4 Weeks	Male	Ex group (n-15) SE group (n-15)	Aerobic exercise (treadmill)	2 times a week during 8 weeks without an incline; Duration of 30 min.
Silveira et al, 2020 [32]	Wistar rats	12 weeks	Male	Ex group (n-12) SE group (n-12)	Aerobic exercise (treadmill)	3 times a week during 12 weeks at 0° incline; Duration of 30 min; Speed 2 - 8 m/min.
De Souza et al, 2020 [39]	Wistar rats	8 weeks	Male	Ex group (n-8) SE group (n-8)	Aerobic exercise (treadmill)	5 times a week during 12 weeks at 50-70 % VO2max; Duration 10 - 90 min.

*The ages of the animals were converted to weeks and considered at the beginning of the training protocol.
£ Ex- Exercise / SE- Sedentary.

Table 3. Effects of physical exercise on markers of oxidative stress and antioxidant system in the cerebellum.

Author, Year	Oxidative Stress Biomarkers	Enzymatic Antioxidants Outcomes	Non -Enzymatic Antioxidants Outcomes	Secondary outcomes
Somani, 1997 [35]	↓ MDA	↓ SOD and GPx ↔ CAT and GR	↔ GSH and GSSG	—
Marton et al, 2010 [31]	—	—	—	↑ SIRT1 activity
Steiner et al, 2011 [36]	—	—	—	mRNA expression: ↑ PGC-1α and SIRT1
Casuso et al, 2015 [37]	↓ MDA and Carbonyls	↓ SOD and CAT	—	mRNA expression: ↑ PGC-1α and SIRT1
Chalimoniuk et al, 2015 [33]	↑ MDA	↑ CAT ↔ SOD, GPx and GR	↑ GSH	—
Marques-Aleixo et al, 2015 [38]	↓ MDA and Carbonyls	↔ SOD	↔ Total thiol levels	Protein expression: ↑ SIRT3 and UCP2 ↔ PGC-1α
Freitas et al, 2019 [29]	↑ MDA	↑ SOD	↑ TAC	—
Lamarão-Vieira et al, 2019 [34]	↔ MDA and 4HDA	—	↔ GSH	—
Hoepers et al, 2020 [30]	↔ MDA and Carbonyls	—	↔ Total thiol levels	—
Silveira et al, 2020 [32]	↑ lipid hydroperoxide	↔ SOD	↑ Total thiols ↔ TAC	—
De Souza et al, 2020 [39]	↑ MDA	↑ SOD and CAT	↔ GSH and GSSG	—

DISCUSSION

Our study sought to investigate the effects of different exercise protocols on oxidative balance in the cerebellum. Of the 11 studies that were selected in this review, nine observed changes in some aspects of the oxidative balance by exercise. In general, the selected studies presented variations exercise protocols and individuals parameters as age and strain of rodent.

In relation of oxidative stress biomarkers, the studies included in this review demonstrated that exercise produced different results on lipid peroxidation markers (MDA, 4HDA and lipid hydroperoxide), demonstrating a reduction [35, 37, 38] or an increase [29, 33, 39]. The exercise also promoted reduction in carbonyl levels, a protein oxidation marker [37, 38]. The oxidative stress biomarkers can be used to evaluate the oxidative damage caused by ROS in biomolecules such as lipids, proteins, and nucleic acids [40-42]. The discrepancy in the results in this review may reflect differences in the intensity of exercise programs, which mainly include the parameters of VO2max, duration and inclination. In previous studies in which the hippocampus and prefrontal cortex were analyzed, moderate-intensity aerobic exercise models reduced markers of oxidative stress, while high volumes of exercise were associated with greater ROS production [43, 44]. Interestingly, one of studies included in the review compared a moderate volume protocol [10-30 min] with a high-volume protocol [10-90 min], and found that high exercise volume increased MDA levels in the cerebellum [39].

In our review, the studies included used animals of 3-weeks – 25-weeks-old [32, 35, 38]. Age is an important parameter that may be associated with the response to training by influencing the oxidative balance [45, 46]. In other studies, older animals have a higher rate of oxidative stress markers than younger animals [47, 48]. In this study, moderate aerobic exercise protocols that showed similarities [4-6 weeks; 4-5 times/week; 30 minutes; 15-19 m/min] [34, 35], the MDA was not changed in youngest animals with 4-weeks-old [34], while in study with 25-weeks-old animals, the reduction was observed[35]. Suggesting a greater resistance of younger animals to oxidative imbalance.

Interestingly, one of the studies included in this review, that used animals with 6-month-old animals submitted to moderate aerobic exercise protocol [4 weeks, 4 times, 60% VO2max, 20-40 minutes], found an increase of the SIRT1 activity [31]. Sirtuin 1 (SIRT1) is a NAD-dependent deacetylase that plays a neuroprotective role against oxidative stress through the deacetylation of FOXO (Forkhead box O), which stimulates the production of new antioxidant enzymes such as SOD and CAT [49-52]. Although Marton and coauthors (2010) [31] study did not evaluate biomarkers of oxidative stress, it is tempting to suggest that the increase in SIRT1 may be related to a potentiation of the antioxidant system, combating ROS and reducing markers of oxidative damage.

Antioxidant enzymes form an important defense system against damage caused by ROS, acting on the removal pro-oxidant molecules, preventing oxidative damage [53, 54]. For example, the SOD enzyme catalyzes the conversion of superoxide anion (O2•) into hydrogen peroxide (H2O2) [55]; while CAT and Gpx have a joint action in the removal of H2O2. Gpx uses the conversion of a GSH to GSSG, and for the recovery of GSH, GR catalyzes this reaction [55]. The data from this review, demonstrated that SOD and CAT activity increased in three studies [29, 33, 39], and reduced in other two studies [35, 37]. The protocols, age or specie of the studies mentioned above presented similarities suggesting that other factors may be involved, and additional analysis might need be done to understand the effects of exercise on the stimulation of antioxidant enzymes. Regarding non-enzymatic antioxidant, the most studies did not observe alteration in GSH, GSSG and total thiols [30, 32-35, 38, 39]

Thus, the antioxidant defense system was also modulated by physical exercise in most studies, however, with a certain divergence between the results, which may suggest a greater susceptibility to the enzymatic antioxidant system. One of the explanations for this may be the fact that a series of proteins are associated with enzymatic antioxidant activity, such as UCPs, SIRTs and PGC1-α. In two studies that evaluated the expression of SIRT1, the aerobic running protocols (6-8 weeks/ 20-80 minutes) showed an increase in expression de SIRT1 [36, 37]. These same studies [36, 37], also showed an increase in the mRNA expression of PGC1-α, which is a master regulator of ROS scavenging enzymes, including Gpx, SOD, CAT and UCP2 [7, 56-58].

Interestingly, the protein expression of UCP2 was evaluated in one study [38] and it was observed that the moderate aerobic exercise protocol (12 week/ 60min/ 18-30 m/min) increased its expression in the cerebellum [38]. In this same study also showed an increase in the expression of SIRT3, which is associated with protection against oxidative damage by activating antioxidant enzymes such as SOD and CAT [59-61]. Uncoupling proteins (UCPs) also has a role in the elimination of ROS, as uncoupling decreases ROS production [62]. In other studies not included in this review, the UCP2 protein provides protection against oxidative stress [63-65] and that exercise increases its expression [66, 67]. Curiously, the study included in this review that observed changes in protein expression of the SIRT3 and UCP2 observed no changes in

antioxidant enzymes [36-38], although data showed that UCP protein are closely linked to the enhancement of the enzymatic antioxidant system [7, 8]. This fact suggests that the increase in gene expression may not necessarily reflect an increase in functional protein.

CONCLUSION

This systematic review observed that physical exercise can modulate oxidative parameters in the cerebellum, altering markers of oxidative stress, with little impact on non-enzymatic antioxidants system. In general, our review does not highlight the best exercise protocol to improve oxidative balance in the cerebellum. However, it points out that volume of exercise and age are some of the factors that should be considered in future investigations and the therapeutical potential of physical exercise in the prevention or treatment of diseases related to cerebellar oxidative stress.

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