REVISTA NEUROCIÊNCIAS

Revisão Sistemática

Neuroprotective effect of physical exercise in a depression model in rodents: a meta-analysis

Efeito neuroprotetor do exercício físico em modelos de depressão em roedores: uma meta-análise

Efecto neuroprotector del ejercicio físico en un modelo de depresión en roedores: un meta-análisis

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Resumo

Introdução. Estudos na neurobiologia da depressão mostram uma desregulação de neurotransmissores em regiões cerebrais relacionadas à emoção, recompensa e funções executivas em indivíduos acometidos pela doença. A prática regular de exercício físico mostra-se como um importante aliado contra a depressão. **Método**. Buscou-se por meio de uma revisão sistemática, material bibliográfico de 2010 a 2021 que descrevesse o efeito neuroprotetor do exercício físico no tratamento da depressão. Utilizamos os descritores: Depressão, Neuroproteção e Exercício Físico nas bases de dados PubMed, LILACS, Science Direct, *Web of Science* e SCIELO. **Resultados**. Foram selecionados 04 artigos. O exercício físico regular promove alterações neurofisiológicas e neuroquímicas capazes de influenciar a doença, destacando-se o BDNF e o IGF-1 como fatores pró neurogênicos e alterações bioquímicas, somadas às alterações no eixo HPP durante o tratamento da depressão. Ressalta-se que o período de treinamento foi determinante para o efeito neuroprotetor. Tais evidências configuram o exercício físico como um excelente aliado no tratamento da depressão, principalmente a leve. **Conclusão**. Sugere-se pesquisas com duração de 09 semanas do protocolo de treinamento físico. Incentivamos mais pesquisas sobre os efeitos complexos induzidos pela inflamação do exercício. Além disso, podemos inferir que o estudo poderia ter resultados diferentes se o tempo para análise dessa neuroproteção fosse estendido ou se a

monitoração de LPS fosse adicionada para controlar níveis de LPS x tempo de exercício x melhora do quadro depressivo.
Unitermos. Neuroproteção; Exercício físico; Depressão; Enfermagem; Cuidados de saúde mental

Abstract

Introduction. Studies in the neurobiology of depression show a dysregulation of neurotransmitters in brain regions related to emotion, reward and executive functions in individuals affected by the disease. The regular practice of physical exercise is shown as an important ally against depression. **Method**. It was searched through a systematic review, bibliographic material from 2010 to 2021 that described the neuroprotective effect of physical exercise in the treatment of depression. We use the descriptors: Depression, Neuroprotective and Physical Exercise in the databases PubMed, LILACS, Science Direct, Web of Science and SCIELO. **Results**. 04 articles were selected. Regular physical exercise promotes neurophysiological and neurochemical changes capable of influencing the disease, with BDNF and IGF-1 being highlighted as pro neurogenic factors and biochemical changes, added to changes in the HPP axis during the treatment of depression. It is noteworthy that the training period was crucial for the neuroprotective effect. Such evidence configures physical exercise as an excellent ally in the treatment of depression, especially mild depression. **Conclusion**. It's suggested research with a duration of 09 weeks of the physical training protocol. We encourage further research into the complex inflammation-induced effects of exercise. Furthermore, we can infer that the study could have different results if the time for analysis of this neuroprotection were extended or LPS monitoring was added to control LPS levels x Exercise time x improvement in depressive condition.
Keywords. Neuroprotection; Physical exercise; Depression; Nursing; Mental Health Care

Resumen

Introducción. Los estudios en la neurobiología de la depresión muestran una desregulación de los neurotransmisores en las regiones del cerebro relacionadas con la emoción, la recompensa y las funciones ejecutivas en las personas afectadas por la enfermedad. La práctica regular de ejercicio físico se muestra como un importante aliado contra la depresión. **Método**. Se buscó a través de una revisión sistemática, material bibliográfico de 2010 a 2021 que describiera el efecto neuroprotector del ejercicio físico en el tratamiento de la depresión. Utilizamos los descriptores: Depresión, Neuroprotector y Ejercicio Físico en las bases de datos PubMed, LILACS, Science Direct, Web of Science y SCIELO. **Resultados**. Fueron seleccionados 04 artículos. El ejercicio físico regular promueve cambios neurofisiológicos y neuroquímicos capaces de influir en la enfermedad, destacándose el BDNF y el IGF-1 como factores pro neurogénicos y cambios bioquímicos, sumado a cambios en el eje HPP durante el tratamiento de la depresión. Es de destacar que el período de entrenamiento fue crucial para el efecto neuroprotector. Tal evidencia configura al ejercicio físico como un excelente aliado en el tratamiento de la depresión, especialmente la depresión leve. **Conclusión**. Se sugiere investigaciones con una duración de 09 semanas del protocolo de entrenamiento físico. Alentamos a que se realicen más investigaciones sobre los complejos efectos del ejercicio inducidos por la inflamación. Además, podemos inferir que el estudio podría tener resultados diferentes si se ampliara el tiempo de análisis de esta neuroprotección o se añadiera monitorización de LPS para controlar niveles de LPS x tiempo de ejercicio x mejora del estado depresivo.
Palabras clave. Neuroprotección; Ejercicio físico; Depresión; Enfermería; Cuidado de la salud mental

Research developed at Universidade do Estado do Rio Grande do Norte, Mossoró-RN, Brazil.

Conflict of interest: no Received in: 01/10/2023 Acept in: 05/24/2023

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INTRODUCTION

Depression is currently highlighted as a public health problem due to its severity and its high rates of prevalence and social impact. According to the World Health Organization (WHO) there were 11 million people with depression in Brazil in 2015, corresponding to 5.8% of the country's total population[1].

The pathophysiology of Depression is associated with dysregulation of neurotransmitters, such as biogenic amines, Norepinephrine (NE) and serotonin (5-HT) that involve neurobehavioral systems, neural circuits and more complex neuroregulatory mechanisms[2,3]. Its appearance depends mainly on the neurobiology of each person, associated with environmental factors that lead to stress, which can be chronic or acute. Therefore, it is a severe, recurrent mental illness and its inadequate treatment can cause damage in the lives of individuals affected by Depression[4].

In general, adherence to antidepressant treatment is very difficult, due to factors such as the lack of acceptance of Depression as a disease, the stigma of using specific psychotropic drugs and the presence of drug side effects[5].

In addition to pharmacological treatments, there are non-pharmacological treatments such as regular physical exercise, from a neurochemical point of view, the practice of physical exercise is related to the stimulation of production and secretion of neurotransmitters such as serotonin, epinephrine, and endogenous opioids. During physical exercise there are changes in hormone release

(catecholamines, ACTH (adrenocorticotropic hormone or corticotropin) and vasopressin); in β-endorphin; in the release of serotonin, activation of specific receptors and decrease in blood viscosity, altering blood flow, therefore affecting the metabolism of the prefrontal cortex, hyperactivity of the subgenual prefrontal cortical region and increased glucose metabolism in various limbic regions[6]. In addition to pharmacological treatments, there are non-pharmacological treatments such as regular physical exercise, from the neurochemical point of view, the practice of physical exercise is related to the stimulation of production and secretion of neurotransmitters such as serotonin, epinephrine, and endogenous opioids. During physical exercise, changes occur in the release of hormones (catecholamines, ACTH and vasopressin); into β-endorphin; on the release of serotonin, activation of specific receptors and decreased blood viscosity, altering blood flow, therefore affecting the metabolism of the prefrontal cortex, hyperactivity of the subgenual region of the prefrontal cortex, and increased glucose metabolism in various regions limbic[6]. Promoting positive immunomodulation and antidepressant effects, being compared to the results obtained using antidepressants and cognitive-behavioral therapy in mild to moderate depression[7]. However, there are still no studies that show evidence of neuroprotection linked to physical exercise and depression[7,8].

Given the uncertainties and gaps in knowledge about the treatment of depression and the studies with conflicting

results about its relationship with neuroprotection and the practice of physical exercise, this study aims to understand the mechanisms involved in the neuroprotective effect of physical exercise and its contribution to the treatment of depression based on a systematic review.

METHOD

This is a systematic review, the protocol of this review was submitted to the platform International Prospective Register of Ongoing Systematic Reviews (PROSPERO) and accepted on November 13, 2020 (ID no. CRD42020157646).

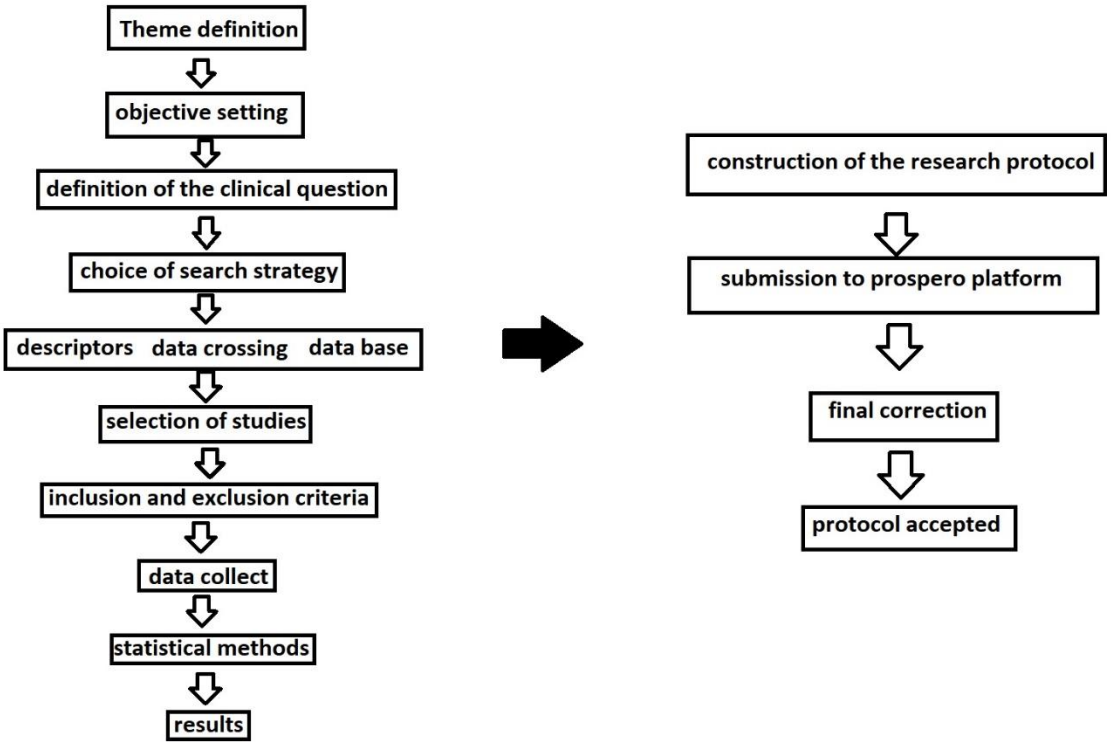
The searches were built using the terms standardized by Medical Subject Heading (MeSH) and the Descriptors in Health Sciences (DeCS). The descriptor Neuroprotective was combined using the boolean operator AND with the descriptors Physical Exercise and Depression were adapted and translated for each of the selected databases: Cochrane Library (Wiley); Embase (Elsevier); Portal BVS; Medical Literature Analysis and Retrieval System Online (MEDLINE, PubMed).

Studies that involved physical exercise as a study in the neuroprotection of depression in rodents were considered as an eligibility criterion. In addition, for the inclusion of studies, they met the following criteria: (1) know the main mechanisms studied in the neuroprotection of physical exercise, (2) evaluate how physical exercise can change the neurobiology of depression, (3) evaluate the samples of pre-

clinical studies concerning sedentary people and practitioners of regular physical exercise.

For each article, a record was made with some elements considered basic: research question/problem, objectives, theoretical framework, methodological procedures for data collection and analysis and main results as can be seen in the steps of the research protocol detailed in Figure 1.

Figure 1. Steps in the construction of the research protocol.

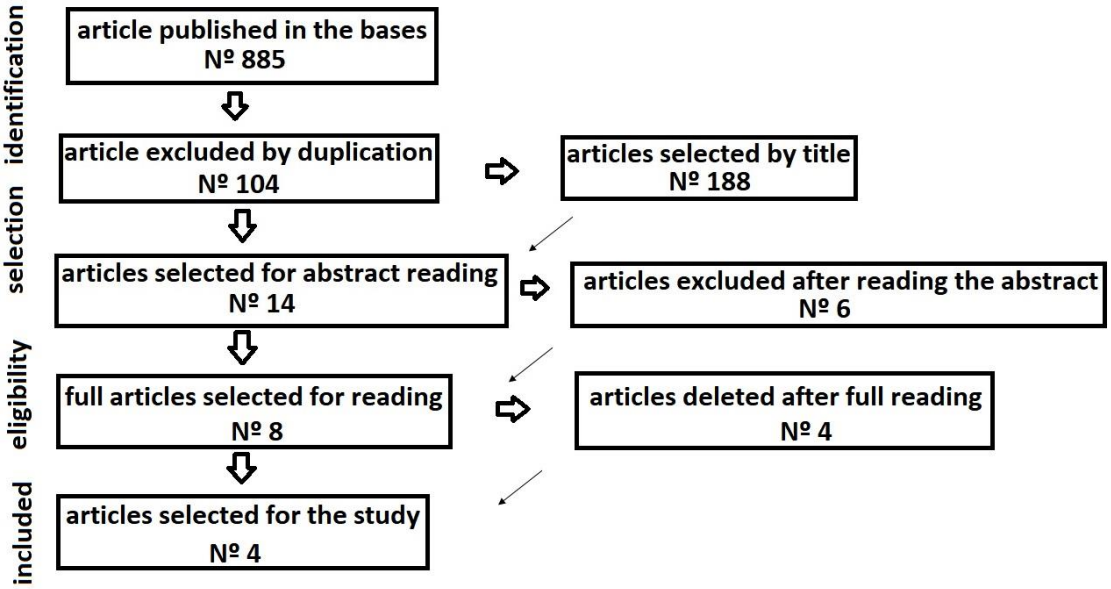


It is noteworthy that articles with an inadequate description of the conclusion factors and sample characteristics will be excluded, absence of adjusted analysis for conclusion factors and articles not available in full. The

time frame between the years 2010 to 2021 was used. All other articles found and available that fit in the present study were analyzed.

The number of works found can be seen in Figure 2, which presents a diagram with the main phases of collection.

Figure 2. Studies selection diagram for the systematic review.



The research was constructed using the PRISMA 2009 reporting guideline. The results were described from a qualitative analysis extracted data for further quantitative evaluation through meta-analysis. The study selection process was performed by two independent reviewers and any disagreements were resolved by a third reviewer. The selection of studies was carried out in two stages. In the first stage, the titles and abstracts of the references were

evaluated identified through the search strategy and potentially eligible studies were pre-selected. In the second stage, the full text of the pre-selected studies was evaluated to confirm eligibility. The selection process was carried out through the platform Rayyan (https://rayyan.qcri.org). After selecting the studies, the risk of bias analysis of each study was performed the application was used the module Metaview from the computer program Review Manager® (RevMan, 2000). The selection process flowchart is shown in Figure 1. After the selection process, 04 studies were included.

RESULTS

Each study was independently evaluated by two reviewers and the decision on the inclusion of studies was made by consensus between them, considering the established criteria. For better understanding, the data from the analyzed articles were divided into tables and figures, as shown below.

Table 1 shows the main results of the studies, we can observe the diversity of investigations about physical exercise in the neuroprotection of depression, the emphasis on the type of aerobic exercise is notorious.

When analyzing Table 2, we can observe the singularities present in each study, these being the number of animals per study and experimental group and age of the samples. In Table 3 we have the methods that were used to induce depressive behavior, methods used to assess

depressive symptoms and results obtained in each test. The most used method of inducing depression, as shown in Table 3, is through the administration of dexamethasone, used in two studies.

Table 1. Main results of the analyzed articles.

Article identification	Main Findings
Martin 2014[9]	Data from the studies indicate the sensitivity of the antidepressant and neuroprotective effects of aerobic exercise to the inflammatory stimulus lipopolysaccharide (LPS) used.
Yau 2014[10]	The study demonstrates that the antidepressant effects of physical exercise are partially mediated by the induction of adiponectin production, which in turn promotes hippocampal neurogenesis.
Dahlin 2019[11]	Prolonged running for 21 days did not improve synaptic plasticity in adolescent Wistar rats, but it did decrease synaptic efficacy. Aerobic exercise increases Long Term Potentiation (LTP) in the dentate gyrus. Exercise does not increase LTP in CA1 (region of the hippocampus - known as the Sommer). Surprisingly, prematurely administered dexamethasone increased synaptic plasticity in the dentate gyrus.
Sigwalt 2011[12]	Study results showed an antidepressant response in animals chronically exposed to dexamethasone, after performing training in intensity below the anaerobic threshold (MLSS) after three weeks of training.

Table 2. Experimental groups used in the studies.

Article identification	Experimental groups
Martin 2014[9]	80 C57BL/6J male mice, 40 with 4 months of age (young), experience 1 and 40 at 19 months of age (elderly), experience 2. Mice were housed with a running wheel (Voluntary Wheel Running, VWR) or no wheel (Standard) for 30 days (young adult mice) or 70 days (aged mice), after which they were intraperitoneally injected with LPS (young adult mice: 0.83 mg/kg; aged mice: 0.33 mg/kg) or saline.
Yau 2014[10]	Eight- to nine-week-old male WT C57BL/6J mice or adiponectin knockout (adipo−/−) mice with the same genetic background.
Dahlin 2019[11]	Pregnant Wistar rats were injected in the nape of the neck with dexamethasone (150 µg kg 1) or saline once every day for the last five days of gestation. Offspring was used. 64 animals, Adolescent male Wistar rats (37 animals) and adults (27 animals). Were submitted 10- or 21-day running experiment.
Sigwalt 2011[12]	60 adult male Wistar rats (200-250g). The animals received daily subcutaneous injections of dexamethasone (1.5mg/Kg) or saline. As a control, an experiment with the classic antidepressant, fluoxetine, was carried out in parallel, in which the animals were divided into 2 groups, fluoxetine (10mg/Kg via gavage) and dexamethasone + fluoxetine. The animals were submitted or not to physical exercise for three weeks

Table 3. Methods for induction and assessment of depression used in the analyzed studies.

Article identification	Depression induction protocol result
Martin 2014[9]	LPS increased immobilization in tail suspension test and decreased sucrose preference compared to baseline.
Yau 2014[10]	Adiponectin knockout model produces a depression-like behavior. There was a loss of preference for sucrose, which suggests Anhedonia.
Dahlin 2019[11]	It resulted in anhedonia and lower offspring weight at birth.
Sigwalt 2011[12]	Reduction in body mass from the sixth day of dexamethasone administration; imbalance in the hypothalamic-pituitary-adrenal axis (HPA) through reduction in endogenous corticosterone synthesis; decrease in glucose tolerance.

It is noteworthy that in one study dexamethasone was administered to pregnant rats to induce depression in the offspring. And the most used test for evaluating depressive behavior was sucrose preference.

In Table 4, we can see the exercise protocol performed, all studies used aerobic training, the training period and on the studies that made available we have a description of the activity performed. The hippocampal region, especially the CA1 was the most investigated. the studies mostly analyzed BDNF, IGF-1, IL-10. Furthermore, it is possible to observe two studies that brought swimming as an exercise to the experiment (Table 5).

Given the quantitative analysis of the evaluated studies, it was possible to observe the various forms of induction and experiments for behavioral and laboratory analysis to confirm depressed mood. In the study by Martin 2014[9] different doses of Liposaccharide (LPS) were administered and according to the age of the samples there was a

difference in dosage. In the Yau 2014[10] 2 µl of adenovirus expressing adiponectin (ADN) was administered. In the study by Dahlin 2019[11] depression was prematurely induced in pregnant rats within 5 days for birth. And finally, the study by Sigwalt 2011[12] used dexamethasone to induce depressive behavior (Figure 3).

Table 4. Physical exercise protocol of the analyzed studies.

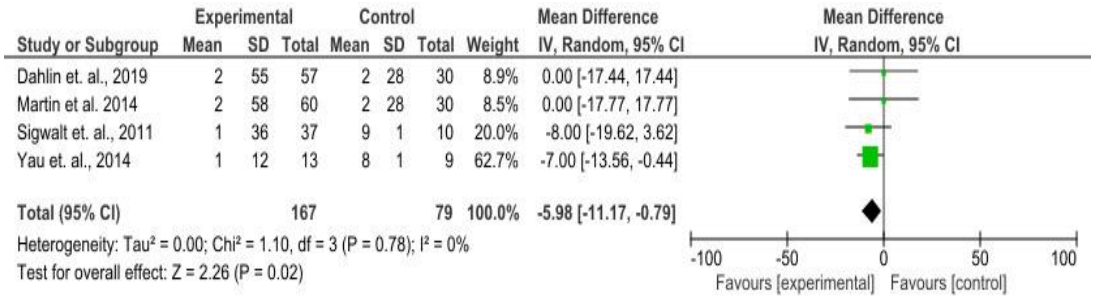
Article identification	Exercise protocol
Martin 2014[9]	The animals were submitted to voluntary wheel running training (VWR). Young people underwent 30 days of training, the elderly 70 days. To assess VWR-induced training adaptations, we measured fatigue strength from forced exercise on day 26 of the 30-day VWR intervention and on day 65 of the 70-day VWR intervention. Young (Y) and old (O) mice ran to exhaustion on a treadmill monitored at 5% incline at gradually increasing the speed of Y: 10 a 26m/min; O: 6 a 21m/min. The training protocol lasted Y: 30 days; lasted O: 70 days.
Yau 2014[10]	14-day voluntary wheel running training (VWR).
Dahlin 2019[11]	Treadmill test period from 10 to 21 days voluntary wheel running training (VWR).
Sigwalt 2011[12]	The training consisted of swimming exercises (1h/day, 5 days/week) for 3 weeks, overweight corresponding to 5% of the animal's body mass at moderate intensity, just below the anaerobic threshold.

Table 5. Neurochemical/Electrophysiological/Immunohistochemical assessment.

Article identification	Neurochemical/Electrophysiological/Immunohistochemical evaluation
Martin 2014[9]	LPS reduced brain BDNF. Prolonged voluntary exercise in mice does not effect on the neuroinflammatory and behavioral response to LPS.
Yau 2014[10]	Analysis with ADN-specific immunoassays showed an increase in IGF-1 and BDNF factor.
Dahlin 2019[11]	Physical exercise (10 days) was able to alter long-term potentiation (LTP) induction in the AA dentate gyrus; Prenatal dexamethasone and 10 days physical exercise did not alter synaptic transmission or LTP in CA1 hippocampus in AJ. physical exercise to exhaustion* was associated with decreased synaptic efficacy probably induced by stress.
Sigwalt 2011[12]	Increased BDNF immunoreactivity (pro and mature) in the CA1 region of the hippocampus. Increased BDNF and IL-10 in animals chronically exposed to dex; The physical exercise protocol was able to induce an increase in IL-10 expression, but without modifying BDNF expression in animals treated with dex; A 5% body mass overload-induced a significant increase in testosterone.

*After little stimulation the animals were unable to continue training.

Figure 3 - Results of the types of induction of depressive behavior.



DISCUSSION

After the induction of depression performed in Wistar rats, it was possible to verify the symptoms presented in the clinical condition of depression. For the analysis of mood depression, all used the Test of sucrose preference, as the main anhedonia factor. But they also used the tail suspension test and blood sample to analyze corticosterone concentrations.

After confirmation of symptoms like depression, the physical exercise training protocol comes into play to obtain the neuroprotective response of the clinical condition. During the analysis, it was observed that the predominance in physical training programs was about 10 weeks, with the longest period of physical training being the study by Martin 2014[9] with two groups of 4 to 10 weeks; the study by Yau 2014[10] with 14 days of physical training, Dahlin 2019[11] with 10 to 21 days of training and the study by Sigwalt 2011[12] which took place during 21 days of physical training.

Still, we can observe that the type of training used in the analyzed studies was the aerobic exercise, being different only the study by Sigwalt 2011[12] which brought an overload of 5% of the body mass and a stimulus made by touching the animals on the treadmill during the training protocol induced beneficial effects on depression such as an increase in IL-10.

Thus, it is understood that the intensity of the training protocol in depressed patients should be self-selected. The perception of effort and adjust the load according to the participant's understanding of the effort made, therefore, can make the exercise session more pleasant and pleasurable contributing to the development of the benefits of exercise in depression[13,14].

The four studies bring characteristics that relate physical exercise as an important ally for the prevention and treatment of depression. However, some singularities need to be considered. Most studies have shown neuroprotective effects of exercise on depression.

In this sense, when analyzing the studies, we listed points that stood out as important factors for the neuroprotection of physical exercise in depression in rodents, for a better understanding of the findings in some points, they are: a) Neurophysiological and neurochemical alterations of physical exercise in depression in rodents, subdivided into: BDNF and IGF-1 as pro neurogenic factors and Biochemical and HPA axis changes; B) Role of adiponectin; C) Effects of short-term vs. long-term exercise.

Neurophysiological and neurochemical changes of physical exercise in depression

The term neuroprotection refers to the control and strategies used to protect neurons against injuries suffered by diseases that affect the Central Nervous System, such as depression. Psychiatric illness can be influenced by multiple neural circuits. Thus, the search for neuroprotective agents, such as physical exercise, for the prevention and treatment of depression is of paramount importance[7,11].

Most evidence about the effects of exercise on the brain suggests that the basic neurobiological mechanisms associated with exercise may occur at two levels: at the extracellular level, exercise induces angiogenesis from pre-existing vessels. At the intracellular level, exercise has been associated with hippocampal neurogenesis. The functional meaning of this effect is still uncertain, but some studies propose that newly formed neurons can be fully integrated into the neural network, making them functional[15].

Furthermore, studies show the ability of physical exercise to induce the growth of new synapses (synaptogenesis). Through changes in molecular growth factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-type (IGF-1), proteins with a crucial role in neuroplasticity, neuroprotection, and neurogenesis[16].

The practice of physical exercise can change the metabolism of monoamine oxidase, with increased levels of serotonin in the CNS, as well as decreased levels of cortisol

and cytokines, which may mediate the effects of physical exercise on depression, thus, the wide range of other structural changes and metabolic changes, such as improved synaptic plasticity and neurogenesis[17].

In this sense, when analyzing the studies, we listed two points that stand out as important factors for neuroprotection related to physical exercise: they are the role of BNDF IGF-1 and ADN.

BDNF and IGF-1 as pro neurogenic factors

The neurotrophic hypothesis is one of the hypotheses formulated to explain depression. Previous studies reveal that brain-derived neurotrophic factor (BDNF) was found in reduced concentrations in the hippocampus of animals subjected to stress. BDNF is a neurotrophin responsible for stimulating the neural regeneration process in several brain areas. Neurotrophin acts as a mediator of synaptic efficacy, increasing connectivity between neurons and thus favoring neuroplasticity. It is understood that circulating BDNF can be produced by both the central nervous system and the peripheral nervous system as well as by vascular endothelial cells and the immune system[18,19].

Increased production of neurotrophic factors such as BDNF has also been indicated as one of the potential mechanisms of action of exercise in depression, mainly due to its effects on neuroplasticity[20]. BDNF and IGF-1 are known to be pro neurogenic factors mediating the effect of running on neurogenesis[21].

The impact of exercise on cerebral blood flow should also be considered an important mechanism with beneficial results on depressive symptoms. Thus, increasing oxygen and other energy substrates, it can improve blood circulation in the brain, thereby changing the scheme and degradation of neurotransmitters. This is considered the direct effect of physical activity on improving cognitive processing speed. Thus, when analyzing the studies, we can observe that in other studies[8,22,23] showing that there is an increase in BDNF production in specific areas of the brain during exercise, but it is not the only source of BDNF production during exercise, making it an effective therapeutic option for the treatment of mild to moderate depression[24] .Therefore, we can emphasize the increased production of neurotrophic factors, with BDNF being indicated as one of the potential mechanisms of action of exercise in depression, mainly because of its effects on neuroplasticity, along with proteins essential for neuronal survival, proliferation and maturation, which are also activated and synthesized during acute exercise. They also relate the increase in BDNF levels with type 1 insulin-like growth factor (IGF-1) after exercise[21].

In the dentate gyrus, in the hippocampus, new neurons cluster close to blood vessels and proliferate in response to vascular factors, IGF-1, and vascular endothelial growth factor (VEGF) elevated in WT rats after running[21] compared to animals that were not administered adiponectin whose neurogenesis remained unchanged. This led to the hypothesis that neural progenitor cells are associated with a

vascular niche and that neurogenesis and angiogenesis are closely related[10].

From a neurofunctional point of view, it is known that, throughout life, new neurons are continuously added to the dentate gyrus of an adult brain. Studies in the field of neurogenesis point to it as a possible path to the remission of depression[25].

The study by Dahlin 2019[11] concluded that after 10 (ten) days of training there was an influence on the dentate turn, thus the study demonstrates that running facilitates the long-term potentiation of the dentate gyrus in adult animals that corroborate with another research that verified the proliferation of new neurons in rodents and after 7 (seven) days from the start of the race, these increases were evident, sustained by the duration of the exercise[3]. And yet, circuit remodeling has increased, increased neurogenesis in the dentate gyrus and reduced the context of fear memory when Wistar rats were tested 6 (six) weeks later.

IGF-1 levels throughout the hippocampus of mice subjected to non-runner ADN were lower than in the Wistar counterparts of runners, regardless of hippocampal neurogenesis and depressive state. Reducing IGF-1 levels can decrease neurogenesis which can be improved in running. Whether the reduction reflects the potential interaction between IGF-1 and adiponectin deserves further investigation[11].

The long-term effects of exercise appear to result from different responses and adaptations compared to the effects

of acute exercise. Among all the effects of physical activity on the brain, neurogenesis is the neurochemical phenomenon most associated with the impact of exercise on the central nervous system. Increased hippocampal neurogenesis is a robust and clearly evidenced phenomenon[26].

Thus, the duration of the physical exercise training protocol is an important variable identified as the main moderator of the effects on depression. Studies have shown that a program of at least 9 weeks is related to a large reduction in depression symptoms[27].

In the study by Sigwalt 2011[12] used dexamethasone to induce depression, dysregulation of the hypothalamic-pituitary-adrenal axis caused an exacerbated increase in IL-10 expression in the hippocampus, cytokine that can be considered a predictor of cell death. One of the main mechanisms responsible for the beneficial effects of exercise can be attributed to the increase in testosterone and BDNF neurotrophin.

Furthermore, systemic inflammation increases inflammation in the CNS and is associated with cognitive decline. It is noteworthy that exercise reduces all peripheral risk factors, improving cardiovascular capacity, lipid-cholesterol balance, energy metabolism, glucose utilization, insulin sensitivity and inflammation[28].

The effects of exercise on central and peripheral IGF-1 signaling are an example. Studies show that the presence of pro-inflammatory cytokines impairs IGF-1 signal

transduction and is a mechanism of insulin resistance and impair IGF-1 signal transduction in neurons. Peripheral IGF-1 is essential for glucose metabolism, tissue maintenance, cerebrovascular function and, it was also observed that a low level of IGF-1 brings risks of cognitive impairment[28].

Biochemical and HPA axis changes

Activation of the hypothalamic-pituitary-adrenal (HPA) axis, involved in the regulation of stress hormones, such as cortisol, seems to play a fundamental role in the effect of exercise on the brain. When stimulated, the hypothalamus releases corticotrophin-releasing hormone (CRH), which in turn stimulates the pituitary gland to synthesize adrenocorticotropic hormone. The latter interacts with the adrenal gland promoting the synthesis of cortisol (corticosterone in animals)[29].

The study by Sigwalt 2011[12] demonstrates that dysregulation of the HPA axis caused an exacerbated increase in the expression of IL-10 in the hippocampus, cytokine that can be considered a predictor of cell death and that indicates that exercise improves the brain's immune status by reducing IL-10[16].

Some hypotheses suggest that alterations in the activity of the HPA axis, such as greater density and efficiency of mineralocorticoid receptors, lower cortisol levels and inhibition of cortisol synthesis may represent efficient negative feedback mechanisms[30].

The result of the analysis of the studies demonstrated that the acute exercise protocol increases the serum concentration of BDNF but is not able to promote neurogenesis[31]. However, the chronic exercise protocol has a neuroprotective effect. Furthermore, studies show that animals undergoing a chronic physical exercise protocol have lower levels of cortisol at rest or in response to a stressor.

The Role of Adiponectin in Depression

Adiponectin (ADN) is a well-known insulin sensitizer with multiple metabolic activities, including the promotion of glucose uptake and induction of fatty acid oxidation in liver and skeletal muscle and inhibition of hepatic glucose production via AMPK activation[32].

In obese individuals, circulating levels of adiponectin and its mRNA expression in adipose tissue are reduced compared to healthy individuals. Possibly because hypoxia and inflammatory cytokines suppress adiponectin gene expression in enlarged adipocytes. Exercise has been shown to improve adiponectin production by reducing fat mass and inflammation in obese/diabetic patients[33].

Adiponectin deficiency alone does not affect neurogenesis, but it causes attenuation in a race-induced proliferation of hippocampal progenitor cells in rodents[10]. The trimeric and hexameric forms of adiponectin can cross the hematoencephalic barrier entering the brain through the blood[34].

Thus, peripheral adipose tissues are probably the main source of adiponectin in the central nervous system. Interestingly, we observed an increase in adiponectin in the hippocampus without a concomitant increase in the blood of running rodents. This could reflect that the two-week training is insufficient to produce a substantial elevation of circulating adiponectin or that it potentially facilitates the transport of circulating adiponectin in the brain[35].

The distribution of ADNR1 is primarily detected in the mood regulatory regions (eg., medial prefrontal cortex, hippocampus, and amygdala) appearing to be the possible candidate to mediate the antidepressant effects of physical exercise likely to increase adiponectin in the hippocampus, induced by physical exercise, maybe the facilitating step in the antidepressant process[36].

Although the reduction of receptors in vitro may not be adequate to obtain the result, reflect the response of hippocampal neurons in vivo, it shows that ADNR1 has a high affinity with LMW (low molecular weight) adiponectin and is highly expressed in the hippocampus[34].

Future work in primary progenitor cell cultures with virus shRNA mediated delivery against ADNR1 or Wistar mice with specific hippocampus a decrease in ADNR1 is needed to reinforce the important role of ADNR1 in mediating the proliferative effect induced by adiponectin[21].

Regarding the role of adiponectin, as mentioned by the authors Yau 2014[10]. Non-pharmacological interventions to elevate endogenous adiponectin, how the regular practice of

physical exercise with a training protocol using pre-exhaustion strength can represent an effective strategy for the treatment or prevention of depression.

Effects of the short x long term physical exercise

In the study by Yau 2014[10] it was observed that in the dentate gyrus, in the hippocampus, new neurons cluster near the blood vessels and proliferate in response to vascular factors such as type 1 insulin-like growth factor (IGF-1) and elevated vascular endothelial growth factor (VEGF) in Wistar rats after running (acute)[21]. Compared to animals that were not administered adiponectin runners whose neurogenesis remained unchanged. This led to the hypothesis that neural progenitor cells are associated with a vascular niche and that neurogenesis and angiogenesis are closely related.

The long-term effects of exercise appear to result from different responses and adaptations compared to the effects of acute exercise. Among all the effects of long-term physical activity on the brain, neurogenesis is the neurochemical phenomenon most associated with the impact of exercise on the CNS. Increased hippocampal neurogenesis is a robust and evidenced phenomenon[26]. Thus, it is understood that future study protocols involving the theme, interventions should be regular and lasting longer, as it is noticed better responses to treatment about training with longer duration.

The study by Yau 2014[10] demonstrates that the trimeric and hexameric forms of adiponectin can cross the

hematoencephalic barrier, entering the brain through the blood[34].

Thus, peripheral adipose tissues are probably the main source of adiponectin in the central nervous system. Interestingly, we observed an increase in adiponectin in the hippocampus without a concomitant increase in the blood of Wistar runners. This could reflect that the two-week training is insufficient to produce a substantial elevation of circulating adiponectin or that it potentially facilitates the transport of circulating adiponectin in the brain[35].

Therefore, the findings of the present study corroborate concerning the training program with nine weeks or more seems to obtain more significant results[37]. As well as the maintenance of training frequency has a greater positive influence, while high-intensity exercises did not have such significant benefits.

CONCLUSION

This review based on experimental studies with rodents provides evidence of the neuroprotective effect of physical exercise on depression since the neurochemical and neurophysiological changes caused by depression can be influenced by the regular practice of aerobic physical exercise.

We identified the necessity for a greater number of studies correlating neurochemical change and improvement in depressive symptoms and duration of the physical training

protocol. We, therefore, suggest research with a duration of 09 weeks of the physical training protocol.

Furthermore, it is observed that the neuroprotective effects of physical exercise are sensitive to lipopolysaccharide-induced depression, to encourage further research into the complex inflammation-induced effects of exercise. Furthermore, we can infer that the study could have different results if the time for analysis of this neuroprotection were extended, or lipopolysaccharide monitoring was added to control lipopolysaccharide levels x Exercise time x improvement in depressive condition.

This study has limitations regarding the induction of depression, the studies used drugs to induce depression, which we see as a factor that alters the analysis and consequently the result. Still, we infer the importance of classifying depression presented by the samples, as it is necessary to differentiate the degree of depression presented and its respective treatment.

Such evidence configures physical exercise as an excellent ally in the treatment of depression. Undoubtedly, physical exercise added to pharmacological treatment and psychotherapy is a determining factor for the integral improvement of the clinical picture presented. It is expected that future research correlating clinical research may better elucidate the mechanisms by which aerobic exercise can be used as an intervention to prevent/treat depression.

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