

Neurobiological effects of forced swim exercise on the rodent hippocampus: a systematic review

Rodrigo Freire Oliveira, Karina Maia Paiva, Gabriel Sousa da Rocha, Marco Aurélio de Moura Freire, Dayane Pessoa de Araújo, Lucídio Cleberson de Oliveira, Fausto Pierdoná Guzen, Paulo Leonardo Araújo de Gois Morais* and José Rodolfo Lopes de Paiva Cavalcanti

Laboratory of Experimental Neurology, Department of Biomedical Sciences, University of the State of Rio Grande do Norte, Brazil

** Email: pauloleonardo87@hotmail.com*

Forced swimming is a common exercise method used for its low cost and easy management, as seen in studies with the hippocampus. Since it is applied for varied research purposes many protocols are available with diverse aspects of physical intensity, time and periodicity, which produces variable outcomes. In the present study, we performed a systematic review to stress the neurobiological effects of forced swim exercise on the rodent hippocampus. Behavior, antioxidant levels, neurotrophins and inflammatory markers were the main topics examined upon the swimming effects. Better results among these analyses were associated with forced exercise at moderate intensity with an adaptation period and the opposite for continuous exhausting exercises with no adaptation. On further consideration, a standard swimming protocol is necessary to reduce variability of results for each scenario investigated about the impact of the forced swimming on the hippocampus.

Key words: behavior, hippocampus, mice, rats, swimming

INTRODUCTION

The practice of regular physical exercise is well established as a restorative agent by its beneficial effects upon the physical and mental health (Ma, 2008; van Praag, 2009). Within the physical aspect it is commonly related with muscular development, cardiovascular maintenance (Tanaka, 2009) or overall physical fitness and regard the mental aspect it has a broad influence on the central nervous system (CNS), inducing better performance in cognitive functions (Kashihara et al., 2009; Cechella et al., 2014b). Moreover, it acts improving the morphophysiological characteristics in learning and memory processes (Aimone et al., 2014; Tutakhail et al., 2019), impacts on neural plasticity (Nunes et al., 2010), attenuates the dementia state caused by Alzheimer's disease (AD), decrease the oxidative stress (Abhijit et al., 2018; Belviranlı and Okudan, 2019) along with a crucial modulatory impact in the biochemical

course of hippocampal neuroprotection and neuroplasticity (Zhang et al., 2018).

Among the sorts of physical training with the cited benefits, swimming is considered a popular modality recommended for health promotion and physical conditioning due its practicality of execution and effectiveness in disease prevention (Tanaka, 2009). In scientific research swimming exercise is usually selected methods since it is possible to take advantage of the innate swimming skills in rodents.

As a forced exercise it consists in placing a single animal in a cylinder filled with water and no escape (Abel, 1993). Moreover it commonly aims to stimulate physical effort and energy expenditure able to influence physiological parameters. These are dependent from the species swimming pattern, protocol intensity and associated methods to generate better reliability and reproducibility in the outcomes (dos Reis et al., 2018). Additionally, a constant performance during training

session from the animal, suited for the physiological parameters evaluated and with excessive stress and fatigue avoided are points desired in most methods. For that many protocols were developed and adapted, perfecting these aspects, and promoting neurobiological effects in rodents.

When studying the consequences of this physical exercise, one of the brain structures most researched is the hippocampus. In rodents the hippocampus is an elongated C-shaped structure with a bilateral formation between the cerebral cortex and the thalamus (Amaral and Witter, 1989). It has a long or septotemporal axis that runs from the septal nucleus rostrally to the temporal cortex and works mainly for learning and consolidating memory (Amaral and Witter, 1989) and features key regions of neurogenic regulation that are affected in pathological conditions, leading to disturbances in behavior, as anxiety and depression (Mahajan et al., 2018). Likewise, swimming exercise stimulates biochemical changes such as increased expression of neurotrophins, neuroplasticity and inflammatory molecular markers, including brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), tyrosine kinase receptor TrkB, protein kinase B (Akt), phosphorylated Akt, ionized calcium-binding adapter molecule 1 (Iba-1), glial fibrillary acidic protein (GFAP) (Xu et al., 2013; Jiang et al., 2014; Niknazar et al., 2016; Souza et al., 2017; Cechella et al., 2018). These intracellular modifications, which are responsible for interfering with behavior in animals and triggering adaptation mechanisms to physical exercise, apparently depend on protocol and/or intervention characteristics employed. In the last decade, several research groups have been associating different techniques, protocols and substance tests with exercises, generating a rich and vast literature concerning the issue subject of the present review. In light of this, the present study aims to evaluate the global neurobiological effects of the forced swimming exercise in the rodent hippocampus, by systematically evaluating training protocols and its neurobiological findings by covering the years from 2009 to 2019.

Search procedure and study characteristics

The present study comprises a systematic review of the literature which was structured following four steps: search, identification, selection and eligibility of published articles related to the issue investigated.

After screening the articles were submitted to methodological quality assessment to compose the final review, based on modifications for animal models from Ainge et al. (2011) on the Downs and Black Qual-

ity Index (Downs and Black, 1998). There is a total of 14 questions: 6 to evaluate the quality of reporting; 7 to address the internal validity and 1 to appraise the power of the work (Table 1). Each published work was after grouped in quality levels based on their previous score: high quality as having 8 points or higher; regular quality as ranging from 7 to 5 points; low quality from 4 or lower. Only high-quality studies were selected to be included in the final review.

After search in the selected databases 56 papers met the inclusion criteria therefore included in this review.

From the 56 studies listed, 87.5% works used rats and 12.5% used mice, in which 80% of them utilized male and 20% female. The average body weight for rats were 180-400 g and for mice 30-40 g with the adult life stage the most used in exercise. Groups of rodents submitted to swimming exercise were considered regardless of their intensity, frequency, presence of added load weight and model of diseases or supplements studied. The main strains used were those of Wistar rats (66%), Sprague-Dawley rats (17%), albino Swiss mice (7%), among other strains (10%). 62.5% of the

Table 1. Methodological quality assessment questions.

General	
1.	Is the hypothesis or objectives precisely described in the introduction?
2.	Is the ethical permission or guide stated in the methods?
Animal characteristics	
3.	Is the animal species/strain/genetic modification or pathology identified?
4.	Is the animal age in the start of study declared?
5.	Is the animal average weight age in the start of study specified?
6.	Is the animal housing described?
Design and outcomes	
7.	Are the interventions well detailed?
8.	Is the drug/ supplementation routine used detailed?
9.	Are the animal groups plainly reported?
10.	Is any detrimental event from the intervention execution addressed?
11.	Are the animals randomly distributed among groups?
Internal validity – bias	
Bias	
12.	Are the researchers blind to the main outcomes?
Confounding	
13.	Is any animal loss or death during the intervention informed?
Power	
14.	Is the p value <0.05?

Methodological quality assessment questions modified from (Ainge et al., 2011) and (Downs and Black, 1998).

studies described incorporated swimming with nutritional or pharmacological intervention and 30.3% studied pathological states such as hypertension (Cheng et al., 2018; Cardoso et al., 2019), neurodegeneration (Souza et al., 2013; 2017; Nasehi et al., 2014; Zhong et al., 2016; Joukar et al., 2017; Wu et al., 2018; Belviranlı and Okudan, 2019), multiple sclerosis (Jin et al., 2014), aging (Kou et al., 2017), depression (Sigwalt et al., 2011), focal cerebral infarction (Song et al., 2012), toxicity or stress (Liu et al., 2010; 2018; Basha and Sujitha, 2012; Dief et al., 2015).

In studies that combined nutritional interventions and exercise were applied variable doses of grape seed polyphenols (Abhijit et al., 2018), naringenin (August et al., 2018), caffeine (Cechella et al., 2014b), diphenyl diselenide (Cechella et al., 2014c; 2014a), organoselenium enriched-diet (Cechella et al., 2018), low-soybean-oil enriched-diet (Teixeira et al., 2011; Cheng et al., 2018), vitamin B1 (Dief et al., 2015), fish oil (dos Santos et al., 2018), curcumin (Feizolahi et al., 2019), genistein (Habibi et al., 2017), *Decalepis hamiltonii* extract (Ravikiran et al., 2016) and ginsenoside (Xu et al., 2013). Likewise, for pharmacological interventions in association with exercise testosterone-enanthate (Joksimovic et al., 2017a; 2017b; 2019), nandrolone decanoate (Selakovic et al., 2017), sildenafil (Ozbeyli et al., 2015) were analyzed.

Regarding exercise, 68% of the protocols used pre-training as an adaptive measure and others added a weight load attached to the animal's body based on the percentage of their own body weight, ranging from 1-3% (Souza et al., 2013; 2017; Cechella et al., 2014a; 2014b; 2014c; 2018, Ravikiran et al., 2016; Zhong et al., 2016; Abhijit et al., 2018), 5-8 % (Sigwalt et al., 2011; Gegentonglaga et al., 2013; Xu et al., 2013; Joukar et al., 2017; dos Santos et al., 2018; Belviranlı and Okudan 2019; Cardoso et al., 2019) or until 15% in high intensity sessions (Joukar et al., 2017). Intensity levels and duration varied based on research focus, with or without adaptive period or pharmacological/nutritional intervention, with a 7 days duration in high intensity training (Xu et al., 2013) to 120 days for long term effects (Abhijit et al., 2018).

Among the main findings, 42 articles analyzed behavior aspects and in 23.8% of them the subjects had better performance in spatial memory tests better performance in spatial memory tests (Teixeira et al., 2011; Drumond et al., 2012; Kim et al., 2013; Cechella et al., 2014a; 2014c; Diegues et al., 2014; Dief et al., 2015; dos Santos et al., 2018; Belviranlı and Okudan, 2019; Feizolahi et al., 2019), 23.8% better results in short- and long-term memory tests (Drumond et al., 2012; Kim et al., 2012; 2013; Alomari et al., 2013; Khabour et al., 2013; Souza et al., 2013; Cechella et al., 2014a; 2014c;

2014b; Jin et al., 2014; Marcelino et al., 2016), in 21.4% anxiolytic-like activity (Liu et al., 2010; Teixeira et al., 2011; Dief et al., 2015; Ozbeyli et al., 2015; Zhong et al., 2016; Selakovic et al., 2017; Souza et al., 2017; Faria et al., 2018; Joksimovic et al., 2019), 9.5% reduction in depressive-like behavior (Sigwalt et al., 2011; Joksimovic et al., 2017b; Souza et al., 2017; Liu et al., 2018), 7.1% of learning improvement and general cognitive features associated with the hippocampus (Basha and Sujitha, 2012; Alomari et al., 2013; Khabour et al., 2013). However, some studies reported opposite reactions (4.7%) (Niknazar et al., 2016; Joksimovic et al., 2019) and impairment in memory and cognition operations (7.1%) (Cechella et al., 2014b; Kou et al., 2017; dos Santos et al., 2018).

Swimming exercise protocols can affect the expression of key molecular markers participants in the hippocampus features. 54 articles observed neurochemical and molecular alterations in the tissue, including affected neuroprotective and cellular neurogenesis mechanisms (Sigwalt et al., 2011; Alomari et al., 2013; 2016; Khabour et al., 2013; Kim et al., 2013; Jiang et al., 2014; Dief et al., 2015; Niknazar et al., 2016; Badowska-Szalewska et al., 2017; Habibi et al., 2017; Joksimovic et al., 2017b; 2019; Souza et al., 2017; Cechella et al., 2018; dos Santos et al., 2018; Liu et al., 2018; Zhang et al., 2018; Belviranlı and Okudan, 2019; Feizolahi et al., 2019), improved neuroplasticity (Drumond et al., 2012; Kim et al., 2012; 2013; Xu et al., 2013; Cechella et al., 2014a; 2014c; 2014b; Diegues et al., 2014; Habibi et al., 2017; Selakovic et al., 2017; Liu et al., 2018; Wu et al., 2018; Zhang et al., 2018), improvement of antioxidant defense system (Liu et al., 2010; Song et al., 2012; Marcelino et al., 2013; Souza et al., 2013; Chen and Xiao, 2014; Ozbeyli et al., 2015; Stone et al., 2015; Ravikiran et al., 2016; Joksimovic et al., 2017a; Joukar et al., 2017; Kou et al., 2017; Abhijit et al., 2018; August et al., 2018; Wu et al., 2018; Belviranlı and Okudan, 2019; Cardoso et al., 2019), reduced inflammation process (Sigwalt et al., 2011; Kim et al., 2012; Souza et al., 2013; 2017; Jiang et al., 2014; Jin et al., 2014; Mourão et al., 2014; Ozbeyli et al., 2015; Cechella et al., 2018; Wu et al., 2018; Zhang et al., 2018), altered neurotransmitters synthesis (Baganz et al., 2010; He et al., 2012; Xu et al., 2013; Dief et al., 2015; Cardoso et al., 2019), ameliorated Alzheimer's disease symptoms (Diegues et al., 2014; Souza et al., 2017; Wu et al., 2018; Belviranlı and Okudan, 2019) and mitochondrial activity (Kou et al., 2017; Klein et al., 2019).

Behavioral assessment on the hippocampus

Aerobic swimming exercise can improve cognitive functioning with the change of behavioral and mo-

lecular parameters, including improved metabolism, antioxidant action and other molecular mechanisms, such as neuroplasticity and neuroprotection (Basha and Sujitha, 2012; Belviranlı and Okudan, 2019). Many of the studies listed in this review used a heterogeneous methodological approach, which, in turn, made it difficult to compare results and, consequently, to perform a meta-analysis.

Most studies had methodologies that addressed the predictive assessment of memory, learning and anxiety through behavioral tests. These data reflect the direct hippocampal influence on the emotional regulatory mechanisms of the exercised animals (Belviranlı and Okudan, 2019; Rosa et al., 2019). Swimming is able to stimulate memory consolidation and learning through different mechanisms, such as the maintenance of Long-term potentiation (LTP) in the hippocampus, the reduction of oxidative stress, promoting an increase in spatial memory, short and long term memory, of work, reducing the anhedonia in the animals, influence the expression of BDNF, GDNF, insulin-like growth factor 1 (IGF-1), TrkB, neurotrophin-3 (NT-3), inflammation, cell proliferation and other markers.

Chemical neuroplastic factors expressed in the hippocampus are responsible for positively control anxiety, depression, memory, attenuate neurological neurodegeneration as in Alzheimer's disease (Wu et al., 2018; Amani et al., 2019), improve cellular energy metabolism (Pedersen et al., 2009) and therefore have a direct influence on behavioral development. Liu et al. (2018) observed that swimming enabled a passive struggle reaction in chronically stressed animals and that was followed by an increase in the expression of plasticity proteins in the hippocampus, which indicates a correlation of neuroplastic capacity and anxiolytic effect in response to exercise. It is a common concept that depressive behavior in rodents is measured by an inert floating posture during the evaluation time, but when this is applied as a depressive behavior parameter that floating behavior is adaptive predisposition as coping in a stressful context (Molendijk and de Kloet, 2019). It should be taken in consideration when analyzing rodents familiar to forced swimming as an exercise. In the reviewed behavioral evaluations, only 2 works (Sigwalt et al., 2011; Liu et al., 2018) used depressive behavior assessment forced swimming test with mice and rats. Forced swimming test is better suited for mice as they are aquaphobic and show a more precise response and less adaptive behavior to swimming than rats.

The reduction of anxiogenic behavior as seen in the performance of the open field (OF) test, elevated plus maze (EPM), tail suspension test and sucrose

preference test (SPT) in the evaluated studies, denotes swimming as capable of chemically altering the brain, reflecting in behavioral changes to animals. The OF test, as well as EPM, are used to verify possible stimulating or sedative effects of antidepressant drugs and non-pharmacological antidepressant strategies, being also considered an effective tool to track general anxiolytic properties (Prut and Belzung, 2003) such as those of the exercise.

The neurochemical and behavioral changes presented in these studies from the evaluation of memory by the Morris water maze and object recognition test may be associated with regulation of some neurotransmitters important to memory and emotions, such as GABA and with increased BDNF levels in cells, since it is shown that alteration in the expression of this marker prolongs the life span of hippocampal cells, especially in the CA3 and dentate gyrus regions (Alo-mari et al., 2013; Belviranlı and Okudan, 2019). Several brain functions related to cognition are influenced by neurotrophins, especially those regulating information processing, such as those of hippocampus. This correlation is responsible for mediating, for example, axonal and dendritic remodeling of key cells in memory mechanisms, cell synaptogenesis, increased synaptic efficacy and neuronal survival (Greenberg et al., 2009; Autry and Monteggia, 2012).

Swimming exercise as a neurological strategy

Among practices employed to stimulate regular physical activity, the aerobic swimming has advantage of exercise low cost and easy execution with the physiological and energetic stimulus regarded as favorable to the brain (Seo et al., 2014).

This systematic analysis of swimming protocols applied in the studies showed a preference for a pre-training period before the main training, within a maximum period of one week but varying intensity and weight load. This practice reduces stress from aquatic environment without inducing the noticeable physiological changes from training. It helps prevent fatigue, levels physical performance among animals and promotes muscular adaptation for continuity of intermittent training (Liu et al., 2018).

Exercised animals can easily adapt to aquatic environment, since swimming is an innate ability in rodents. Then, it is recommended a weight load attached during protocol execution, based on body weight plus intensity intended, like in high intensity exercises where a 15% body weight load can be used (Joukar et al., 2017). Also, the weight added should match the physical characteristics found in each animal

strain/species and accordingly to the goal designed. In studies where pre-training is present, anxious and depression-like behavior from training stress are reduced. Besides, continuous exercise without adaptation raises plasmatic corticosterone release and lowers serotonin content in rodents (Baganz et al., 2010). This negatively alters behavioral and neuroprotection parameters, were in the hippocampus contain glucocorticoid receptors, which when activated inhibit the hypothalamic-pituitary-adrenal (HPA) axis activity, limiting defense against deleterious consequences induced by stress from exercise (Joca et al., 2003).

An additional feature is that the common swimming protocol duration range from 4 to 8 weeks. This show better cognitive improvements when compared with lower duration protocols. In studies with 8 or more weeks, the results about behavior are unsatisfactory or not evaluated. A superior protocol time may be required for the substance investigated exert its metabolic effects (Chen and Xiao, 2014; Abhijit et al., 2018; Belviranlı and Okudan, 2019). Also both swimming modalities, forced or voluntary, increase the cognitive functions, where the memory formation along with learning process is favored by higher hippocampal plasticity, a larger volume in the dentate gyrus and blood flow (Pereira et al., 2007; Alomari et al., 2016). In addition to metabolic improvements, the outcomes in rodents shares resemblances in physiological human findings (Gobatto et al., 2001; Voltarelli et al., 2002; Gomes-Osman et al., 2018). These similarities make this methodology a helpful broad strategy to elucidate molecular mechanisms related to behavior and neuroplasticity in the hippocampus.

Antioxidant system assessment on the hippocampus

The main markers used were the measurement of glutathione peroxidase (GPx) activity (Marcelino et al., 2013; Souza et al., 2013; Stone et al., 2015; Ravikiran et al., 2016; Abhijit et al., 2018; August et al., 2018), catalase (CAT) activity (Marcelino et al., 2013; Souza et al., 2013; Stone et al., 2015; Ravikiran et al., 2016; Abhijit et al., 2018; August et al., 2018), superoxide dismutase (SOD) activity (Song et al., 2012; Marcelino et al., 2013; Souza et al., 2013; Stone et al., 2015; Ravikiran et al., 2016; Joksimovic et al., 2017a; Kou et al., 2017; August et al., 2018; Wu et al., 2018; Belviranlı and Okudan, 2019) and lipid peroxidation through malondialdehyde (MDA) measurement (Song et al., 2012; Ozbeyli et al., 2015; Ravikiran et al., 2016; Joksimovic et al., 2017a; Joukar et al., 2017; Kou et al., 2017; Abhijit et al., 2018; August et al., 2018; Wu et al., 2018; Belviranlı and

Okudan, 2019) and glutathione (GSH) measurement (Stone et al., 2015; Joksimovic et al., 2017a; Abhijit et al., 2018; Belviranlı and Okudan, 2019).

It seems that the varied outcomes reflect different stimulus from each protocol with interaction from duration, intensity and type used (Ravikiran et al., 2016). No consensus from these studies could be drawn once these variations affect measurements but it is possible to see a positive influence towards the redox balance.

The increased production of reactive oxygen species (ROS) and nitrogen species (RNS) by exercise generates, as response, metabolic adjustments. This is associated with the hormetic theory, where low doses/exposure of stressor induces physiological adaptations in the body, with an improved later state (Souza et al., 2013). According to this, in exercise (stressor), acute exposure induces oxidative stress and so longer (chronic) exposure would be required for the upregulation of antioxidant defenses.

Free radicals and exercise may lead to increased expression of antioxidant response elements (ARE) with higher transcription of antioxidant response genes such as glutathione reductase, GPx, peroxiredoxin, thioredoxin, thioredoxin reductase, CAT, and Cu/Zn-SOD (Marcelino et al., 2013; Ravikiran et al., 2016). For that signaling pathways are activated, like those mediated by mitogen-activated protein kinases (MAPKs) (p38 and extracellular signal-related kinase, ERK1/ERK2), the redox-sensitive nuclear factor κ B (NF κ B), nuclear erythroid 2 p45-related factor 2 (Nrf2), and peroxisome-proliferator-activated receptor-c coactivator-1a (PGC-1a) (Marcelino et al., 2013; Souza et al., 2013). This generates decreased levels of DNA damage, oxidized proteins, activity of the proteasome complex and lipid peroxidation (Song et al., 2012). Also, can explain reduced MDA levels, one of the products found in lipid peroxidation and protect GSH levels.

Another important part of the antioxidant response is the thiol (-SH) levels, especially GSH, as they constitute the major portion of the total body antioxidants. Low levels by usage indicate oxidative stress. Since GPx inactivates hydrogen and lipid peroxides using GSH it is essential the maintenance of GSH levels, catalyzed by glutathione reductase (GR) (Souza et al., 2013; Ravikiran et al., 2016).

Swimming interaction with other interventions on the antioxidant system

Physical exercise had an overall good impact towards minimize oxidative stress common in the patho-

logical models (Song et al., 2012; Souza et al., 2013; Joksimovic et al., 2017a; Joukar et al., 2017; Kou et al., 2017; Wu et al., 2018; Belviranlı and Okudan, 2019) but not fully restoring antioxidant markers to control status and had additive interaction with other interventions (Ravikiran et al., 2016; Abhijit et al., 2018).

Abhijit et al. (2018) showed that middle-aged naturally had more MDA than the adult animals and an increased GSH levels from swimming stimulus and/or GSPE supplementation. Also Ravikiran et al. (2016) found similar findings with *Decalepis hamiltonii* in combined interventions. The combination of maternal exercise and naringin supplementation was found to block each other effects when combined (August et al., 2018). Song et al. (2012) showed that acetyl-L-carnitine (ALC) with exercise was helpful to improve antioxidant defenses, probably due less ROS formation from lactic acidosis and reducing glutamate neurotransmission toxic effects.

For the AD models (Souza et al., 2013; Wu et al., 2018; Belviranlı and Okudan, 2019), they induce oxidative stress and produce neuroinflammation, neuronal apoptosis and gliosis (Wu et al., 2018). These models showed increased oxidation markers and some antioxidant defense markers too, probably as response to stress. Swimming exercise attenuated both changes in modalities of voluntary, involuntary and forced exercises showed by (Belviranlı and Okudan, 2019).

Animals that received nandrolone decanoate (Joukar et al., 2017) or chronic testosterone enanthate administration (Joksimovic et al., 2017a) showed that high doses of androgenic anabolic steroids are neurotoxic. Both studies showed better parameters with exercise and (Joukar et al., 2017) found heavy exercise to recover healthy cells. Likewise, the protective effects of sildenafil with chronic exercise against stress exposure were possibly by interference in nitric oxide levels (Ozbeyli et al., 2015).

Neurotrophins assessment on the hippocampus

The main marker used for the neurotrophins measurement was BDNF, found in 20 studies (Sigwalt et al., 2011; Alomari et al., 2013; 2016; Khabour et al., 2013; Kim et al., 2013; Jiang et al., 2014; Dief et al., 2015; Marcelino et al., 2016; Niknazar et al., 2016; Badowska-Szalewska et al., 2017; Habibi et al., 2017; Souza et al., 2017; Cechella et al., 2018; Cheng et al., 2018; dos Santos et al., 2018; Liu et al., 2018; Zhang et al., 2018; Belviranlı and Okudan, 2019; Feizolahi et al., 2019; Klein et al., 2019).

The variation in BDNF levels can be influenced by animals' age, species/strain or gender, by exercise type

applied, its duration and frequency and other methodological particularities such as animal sample size, the time of sacrifice, the methods used for BDNF detection and what form is being analyzed (Badowska-Szalewska et al., 2017; Belviranlı and Okudan, 2019). All the differences come together to generate unconformity among the results. Even so, the majority authors argue that swimming exercise exerts a positive effect on the neurotrophin levels. All the mechanisms involved are varied and not exactly fully understood.

It is known that BDNF is largely involved in cognitive brain functions. It is most evident in the hippocampus, where improvements in learning and memory are correlated with higher levels as it can induce axonal and dendritic remodeling, synaptogenesis, and raise synaptic efficacy, effects that contribute to LTP (Alomari et al., 2016; Cheng et al., 2018). Also important is the form levels of BDNF, since they have divergent actions (Marcelino et al., 2016).

Mature form affects neuronal differentiation, synaptic plasticity, and regulation of complex behaviors and pro form participates in neuronal cell death and impaired synaptic plasticity (Sigwalt et al., 2011, Marcelino et al., 2016, Cechella et al., 2018). BDNF begins as the pro form, later cleaved to the mature form which binds to the TrkB to exert its effects (Sigwalt et al., 2011). The BDNF/TrkB signaling pathway act downstream activating phosphatidylinositol 3-kinase (PI3-K)/Akt signal cascades which in turn contribute to the maintenance of LTP with improved N-methyl-D-aspartate receptors (NMDAR) activity (Cheng et al., 2018).

It is indicated that regular exercise can increase BDNF mRNA expression within few days (Alomari et al., 2016). In this process, metabolic byproducts from skeletal muscle contraction elevates norepinephrine level in brain regions (Alomari et al., 2013). Activated adrenergic receptors starts a signaling cascade that induces BDNF mRNA expression in the hippocampus. Some mediators of this pathway are protein-dependent kinase-1, phosphatidylinositol 3-kinase, phospho-thr308-Akt, phospho-ser473-Akt, phospho-glycogen synthase kinase-3 β , and cyclic-AMP response element binding protein (CREB) (Alomari et al., 2013).

Accordingly, Zhang et al. (2018) found boosted expression and activation of the ERK-CREB-BDNF signaling pathway after swimming. ERK and CREB are upstream regulators of BDNF production. The ERK signaling translates growth factor signals into regulation of gene expression, where synaptic plasticity and learning are affected, mediated by a Ca²⁺-dependent NMDAR-mediated response (Zhang et al., 2018).

A more recent influence discovered is the participation of microRNAs in the nervous cell inner workings. As RNA segments edited at the post-transcriptional

level, they may interfere with many of cell activities including developmental patterning, apoptosis, cell proliferation, and metabolism (Habibi et al., 2017). The microRNA-132 is associated with neuroprotection and its expression is stimulated by BDNF (Habibi et al., 2017). As indicated by Habibi et al. (2017), exercise can increase expressions of BDNF and IGF-1 by also increasing the expression of microRNA-132. Related to that, IGF-1, a growth factor structurally associated with proinsulin, can also increase BDNF mRNA in the brain.

The BDNF pathway can explain some changes related with neurogenesis and cognitive function attributed to exercise (Alomari et al., 2013). Some of these neurological changes can reflect changes in behavior. It is proposed that the BDNF effects on hippocampal synaptic plasticity may influence depressive states, where the upregulation from swimming can have antidepressant effects (Jiang et al., 2014). As indicated by Jiang et al. (2014) exercise, in the neurotrophic hypothesis of depression, can raise BDNF and its downstream neurotrophic peptides, neuropeptide Y (NPY) and nerve growth factor inducible (VGF), leading to neuronal synaptic remodeling. Another influential pathway is the cAMP-CREB cascade by BDNF signaling. This pathway also can interfere with depressive behavior and stress and correlates with increase in the AKT/glycogen synthase kinase-3 β (GSK-3 β) pathway, a participant mechanism in the antidepressant effects of lithium and ketamine (Liu et al., 2018).

Additionally, intensity and workload can influence inflammation status, oxidative stress and cortisol levels which impact the BDNF production (Alomari et al., 2016). Stress stimulus activates the HPA axis with increased secretion of glucocorticoids and via glucocorticoids receptors, which affects hippocampal pyramidal neurons activation pattern (Badowska-Szalewska et al., 2017). For female rodents, stress hormones adrenocorticotrophic hormone (ACTH) and corticosterone are more impactful once they have a higher release and for a longer time if compared to males (Niknazar et al., 2016).

Besides, corticotropin-releasing factor (CRF) gene expression is sensible to estrogen and androgen hormones, as seen in the paraventricular nucleus (PVN), where estrogen increases CRF expression and androgen does the opposite (Niknazar et al., 2016). As consequence, BDNF gene is affected, with higher methylation levels less is expressed leading to gene silencing and it is related with negative cognitive performance, such as memory and depressive behavior (Niknazar et al., 2016). Yet, if stimulus is repeated long enough a phenomenon called habituation occurs, attenuating stress-related measures (Alomari et al., 2013).

The opposing results about stress, neuroprotection and behavior raise a point of debate in whether

voluntary exercise or forced exercise could have different or similar beneficial effects. Forced exercise is associated with more stress. Chronic stress can lessen spatial memory function and hippocampal BDNF as well (Dief et al., 2015). In some studies, forced swimming exercise can do the opposite (Dief et al., 2015). For that it is possible to say that even stressful, this modality shares many biochemical beneficial mechanisms with the voluntary form and the habituation effect allow further amelioration to the CNS and body (Alomari et al., 2013; 2016; Jiang et al., 2014; Dief et al., 2015; Badowska-Szalewska et al., 2017; dos Santos et al., 2018; Belviranlı and Okudan, 2019). It is important to indicate though this may not be applied to (very) high intensity exercises since the damage done can be greater than the body's ability to adapt with the physiological stress (Alomari et al., 2013; 2016; dos Santos et al., 2018).

Swimming interaction with other interventions on neurotrophins

5 works with nutritional/pharmacological interventions had a positive increase in BDNF markers (Khabour et al., 2013; Alomari et al., 2016; Cechella et al., 2018; Cheng et al., 2018; Belviranlı and Okudan, 2019), and 2 others (Sigwalt et al., 2011; Habibi et al., 2017) detected no particular changes and in 4 (Souza et al., 2017; dos Santos et al., 2018; Feizollahi et al., 2019; Klein et al., 2019) more reduced levels were discovered.

Alomari et al. (2016) showed that BDNF levels were increased only with voluntary exercise although other parameters were similarly affected by forced training, where restricted diet alone had no impact. Khabour et al. (2013) had similar results, where the exercise had more influence in the parameters than the dietary restriction or the combined intervention. Contrary to Alomari et al. (2016), forced exercise applied did raised BDNF levels. Complementary to this, in dos Santos et al. (2018) the effects of high intensity exercise protocol combined with fish oil supplementation lowered BDNF levels.

Organoselenium dietary plus exercise could increase BDNF levels in old rats with no statistical difference from exercise group (Cechella et al., 2018). Contrary to this, the short-term combination of curcumin and swimming exercise showed to increase BDNF expression in binge ethanol drinking model. This was attributed with synergistic effects on antioxidant defense and BDNF levels (Feizollahi et al., 2019). In Cheng et al. (2018) forced swimming up regulated the expression of BDNF and NMDAR1 suppressed

by a low-fat diet alone. The composition of fatty acids in the oil could be the reason for the impairment in synaptic plasticity. For Habibi et al. (2017) all the ovariectomized groups had lowered BDNF expression. But the combined genistein treatment made the levels increase near the sham control, explained by antioxidant effects and estrogens-like neuroprotective action. In Sigwalt et al. (2011) the dexamethasone increased pro-form BDNF levels, associated with loss of neuroplastic effects, where exercise could normalize the increase content.

For AD models, (Belviranlı and Okudan, 2019) discussed that the voluntary, involuntary, and forced exercise trainings were almost equal neuroprotective in AD interventions, but the forced swimming group had more BDNF. And Klein et al. (2019) BDNF levels in offspring were reduced by A β O $_s$ injection and maternal exercise during pregnancy did not prevent reduction, where in Souza et al. (2017) exercise raised BDNF levels in the disease group near sedentary sham control.

Swimming interaction with other interventions on the inflammatory process

Some nutritional/pharmacological interventions interacted with swimming exercise regarding IL-10 (Sigwalt et al., 2011; Souza et al., 2013; Wu et al., 2018).

In a depression model induced by dexamethasone, exercise could prevent IL-10 increase in the dexamethasone group, correlated with impairment in BDNF cleavage of pro to mature form (Sigwalt et al., 2011). The authors associated that with immune dysregulation (Sigwalt et al., 2011).

In the AD models, both with Ab_{1–40} peptide (Souza et al., 2013) or streptozotocin (Wu et al., 2018), exercise could normalize IL-10 levels and prevent decrease. It is known that neuroinflammation is a fundamental in the pathogenesis of AD (Souza et al., 2013; Wu et al., 2018). Exercise may have increased release of anti-inflammatory cytokines from contracting skeletal muscle, such as IL-10 (Souza et al., 2013). IL-10 downregulate effects of proinflammatory cytokines such as TNF- α and IL-1 β . So, the anti-inflammatory actions can impair complications like apoptosis and raise cell survival, protecting neurons in the hippocampus (Souza et al., 2013; Wu et al., 2018).

CONCLUSION

The present review brought the neurobiological effects of forced swimming exercise applied in many protocols, with or without nutritional/pharmacological

interventions. Our systematic evaluation of the theme revealed that the main impacts on the CNS were mainly associated to behavior, antioxidant system, neurotrophins and inflammatory markers. However, the results were derived from highly variable models, which somehow compromise more ratifying conclusions regarding the impact of forced swimming. It is noticeable that the lack of standardized protocols accounted for divergent outcomes in the same area of research. Even so, most authors agreed that moderate intensity in forced swimming with an adaptation period was linked to more beneficial outcomes, with 4 to 8 weeks duration. Future studies focusing on the problem could contribute with a better draw of this picture, by comparing distinct protocols and developing better models with larger sample sizes.

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