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Review article

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BRAIN DERIVED NEUROTROPHIC FACTOR, A LINK OF AEROBIC METABOLISM TO NEUROPLASTICITY

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Currently, literature has accumulated great knowledge over the effect of exercise on the neurotrophin named brain derived neurotrophic factor (BDNF) and its role in neuronal plasticity. However, there is no enough discussion about how the exercise is related to enrichment of BDNF in specific metabolic properties. This review provides the current evidences regarding aerobic metabolism relation to BDNF concentrations in healthy individuals. A PICOS strategy was applied considering the mesh terms for: P - healthy subjects; I - physical exercise; C - aerobic metabolism demands; O - BDNF concentrations; S - before and after aerobic exercise; on PubMed, Scopus and Medline databases. Studies presenting at least one session the exercise with reports of BDNF analysis before and after were included. Reviews, letters, case-reports, articles not written in English, non- published or involving non-healthy populations were excluded. Compiling results, it was possible to observe a close interaction between different aerobic energy demands from the exercise models and the responses of BDNF, suggesting thus that increases in BDNF concentrations are associated to the amount of aerobic energy required by exercise in a dose-dependent manner. Moreover, the dynamics of BDNF synthesis and reuptake resemble the functioning of the metabolic systems of aerobic energy generation, with which they share a co-transcriptional factor dependence.

Key words: *brain derived neurotrophic factor, aerobic metabolism, aerobic exercise, neuroplasticity, prolonged exercise, proliferator-activated receptor gamma co-activator 1-alpha*

CENTRAL NERVOUS SYSTEM. BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) AND EXERCISE - THE INCIDENCE OR COOPERATION?

Currently, exercise science has been turning its research to the positive changes provided in many aspects of nervous system functioning. Exercising has figured as a preventive medicine for those who seek for neuroprotection and cognitive improvement (1-3), being markedly studied within the scope of neurotrophic factors and related changes relevant for the brain's health (4-6).

It was shown that the metabolic changes evoked by exercise strongly reply on levels of brain derived neurotrophic factor (BDNF), the main growth factors of neural tissue (6-8). BDNF alteration associate to neurodegenerative mechanisms present in different pathological conditions (9), while elevated BDNF is associated with improvements in neuroplasticity, and also with lower ratios of cognitive decay in individuals under neuropathological disorders (10, 11).

This neuronal ability of creating new routes for the execution of a command when those of usage are no longer effective - a functional regeneration - is based on the construction and strengthening of connections between neurons that are supported by a number of factors among which BDNF displays of major importance (12-14). Further, BDNF is required for the proper development and survival of dopaminergic, GABA-ergic, cholinergic, and serotoninergic neurons (15), figuring thus as a biomarker for neuroplasticity (11, 16).

Regardless of the increasing number of studies approaching exercise and BDNF-related responses, the physiological and molecular mechanisms by which exercise affects BDNF gene expression to favor plasticity are not well discussed. Recently, Dinoff *et al*. (17) showed that BDNF concentrations are selectively responsive to the metabolic demands involved and revealed that the aerobic metabolism may play a role in this neurotrophin regulation. Regarding this, we collected all available data containing BDNF measures in aerobic exercise (AE), and discussed it on the bases of the mechanisms demonstrated by experimental physiology, the ultimate role of exercising on BDNF expression and neuroplasticity empowering.

A comprehensive search was ran up to the research date to access all published literature presenting AE interventions in healthy humans, with reports of BDNF analysis. For that, two independent reviewers applied for the PICOS strategy: P - patient/problem; I - Intervention; C - Comparison; O - Outcome; and S - Setting meaning: P - healthy subjects; I - physical exercise; C - aerobic metabolism demands; O - BDNF

concentrations; and S - before and after AE. Searches were conducted on PubMed, Scopus and Medline databases using the following combinations of terms:

healthy subjects / aerobic exercise / brain derived neurotrophic factor

healthy subjects / aerobic exercise / BDNF

human / aerobic exercise / brain derived neurotrophic factor

human / aerobic exercise / BDNF

healthy subjects / aerobic metabolism / brain derived neurotrophic factor

healthy subjects / aerobic metabolism / BDNF

human / aerobic metabolism / brain derived neurotrophic factor

human / aerobic metabolism / BDNF

healthy subjects / VO_{2max} / brain derived neurotrophic factor

healthy subjects / VO_{2max} / BDNF

human / VO_{2max} / brain derived neurotrophic factor

human / VO_{2max} / BDNF

The inclusion criteria referred to studies with: healthy individuals, containing at least one controlled session of AE with reports of BDNF analyses before and after. Individuals from both sexes and up to 60 years old were acceptable. The searches were conducted from June 12 to August 28, 2016 and retrieved papers were referenced in Mendeley (version 1.17-dev1), with duplicates removed. All retrieved papers were initially screened based on their titles and abstracts for potential inclusion. Reviews, letters, case-reports, articles not written in English, and involving non-healthy populations were excluded. The eligibility of studies based on titles, abstracts, and full-text are summarized in *Fig. 1*. Participants, interventions, study appraisal and methods, and main findings of included studies are summarized in *Table 1*.

BRAIN DERIVED NEUROTROPHIC FACTOR AND NEUROPLASTICITY

BDNF is a highly conserved neurotrophin with pivotal role in neuronal survival, neurogenesis, synaptogenesis, and neuroplasticity (12, 14). It is synthesized as a pro-BDNF isoform then conversed into mature BDNF by post-translational cleavage, often during secretion (13). The expression of BDNF gene (*bdnf*) is closely linked to all aspects of neuronal functioning, including complex processes of cognition (1), and also to central and peripheral mechanisms of energy homeostasis (6).

Due to the complexity of BDNF signaling and receptor systems, exogenous overstimulation of BDNF has not shown safety results in animal (18, 19), often leading to some *bdnf* suppression in cell populations and affecting their normal development (20). Inversely, exercising triggers endogenous regulatory mechanisms that positively affect BDNF dynamics in local and systematic manners (2-4, 11, 16, 21), as it was observed throughout our study's results (*Table 1*).

This study gives a summary of the current knowledge upon aerobic catabolism relation to *bdnf* regulation and elucidates the known mechanisms believed to be involved. The exercise protocols comprised different protocols of aerobic exercise (AE) ranging from a single session to three months long programs, applied to individuals from both sexes aging from 15 to 30 years old (*Table 1*). Exercise protocols differ by duration and intensity, giving us the possibility to have a more complete analysis of how exercising physiologically affects BDNF response.

ACUTE EXERCISE AND BDNF RESPONSE

Acute protocols of exercise displayed of high intensity single bouts (above 80% of anaerobic threshold). Positive BDNF response were achieved in all studies reviewed, from the oldest, Vega *et al*. (22), through Heyman *et al*. (23) to newest, Saucedo Marquez *et al*. (24). Only in two cases, part of the sample had yielded no increase in BDNF concentration post-exercise (25, 26) - which is discussed below. The majority of studies was performed on males and a sex differences in BDNF response to exercise was present only in Schmidt-Kassow *et al*. (27). The influence of some other factors on exercise-dependent BDNF could be further observed through our retrieved studies.

Ferris *et al*. (28), confirmed that intensity is an important exercise factor for inducing BDNF changes. No BDNF response was detected in individuals after 30 min of exercising below the aerobic threshold, while either at intensity lightly above the aerobic threshold or at maximum effort, proportional increases in BDNF occurred (13% and 30%, respectively). The same positive intensity-dependence in BDNF release was observed in Schmidt-Kassow *et al*. (27), Schmolesky *et al*. (29) and Nofuji *et al*. (30) studies, where individuals of identical fitness conditions exposed to different exercise-intensities demonstrated distinct characters of BDNF response. Meanwhile, 30-min of moderate exercise did not provoke any change in BDNF of the young men of Seifert *et al*. (25) and Goda *et al*. (26) trails, and only partially did it to those of Tsai *et al*. (31), which suggests that low-intensity exercises do not consistently evoke changes in BDNF for young individuals.

A BDNF response dependence to the volume of exercise regarding the rule 'intensity + duration + frequency' was revealed after compiling data. Interestingly, when compared high-intensity interval with continuous intensity exercise in Saucedo Marquez *et al*. (24) it was shown that BDNF concentrations gradually increase over time in both models. The two models similarly request oxygen consumption provoking an accumulative response of BDNF to a point where both generate elevated post-exercise concentrations. However, in a time-efficiency perspective, high-intensity interval exercises evoke greater gains in VO_{2max} and for this reason they should provoke larger increases in BDNF (32, 33). Schmolesky *et al*. (29) in turn, confirmed that the intensity modulates BDNF response by showing that higher intensities of exercise evoke greater increases in BDNF and also revealed that lower-intensity exercises still can positively affect BDNF release if held up in greater volumes. Accordingly, individuals did yield increases in BDNF after both moderate (but yet above aerobic threshold) and prolonged exercise in Matthews *et al*. (34), with evidence for some time-increase effect as detected by Cho *et al*. (35).

When comparing high-intensity with maximum effort, Brunelli *et al*. (36) it was possible to observed that the models elevate BDNF and pronounce different shapes of recover. Whereas after a high-intensity the elevated BDNF remains stable until recovery; post maximal effort BDNF levels may decrease to a point lower than baseline during recovery, especially for well-conditioned individuals. So, the individual fitness condition is another factor that influence on BDNF response, also confirmed by Tang *et al*. (37) study where highly trained subjects tended to yield higher BDNF response and faster recovery throughout the experiment.

Along with the fact that lower or even lack of BDNF response to low-intensity exercise were evidenced in sedentary individuals in Goda *et al*. (26), Schmolesky *et al*. (29) and Nofuji *et al*. (30), it is understandable that greater adaptations in BDNF signaling are found in individuals with better fitness conditions. This could be an explanation because increased BDNF production - which can be detected in higher basal levels of BDNF - positively regulates *bdnf* expression (38). BDNF signaling itself can recruit MAPK-cascade as a cross-talk to phosphatidylinositol-3 kinase (PI-3K)/Akt activating pathway making a positive loop of BDNF auto-stimulation (38). Another explanation is related to the BDNF specific receptor. BDNF modulates survival, differentiation, and activity of neurons by binding to its high affinity receptor

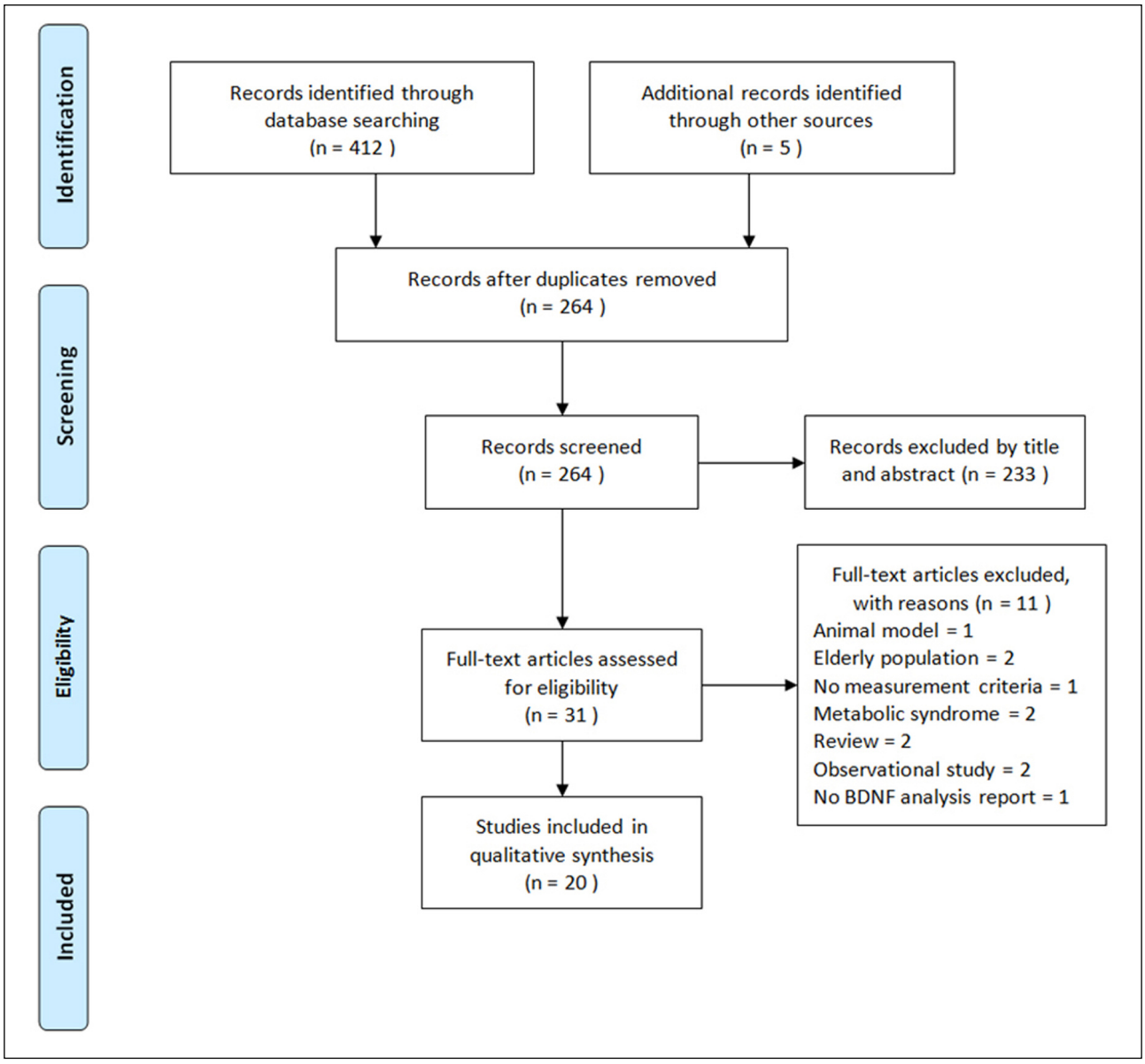

Fig. 1. Included studies selection strategy.

tropomyosin kinase B (TrkB) at the cell surface, leading to initiation of intracellular signaling cascades and different biological responses. The disposal of TrkB receptors on BDNF target cells is thus positively regulated by BDNF stimulation (38, 39). Therefore, well-trained individuals even yielding larger amounts of exercise-dependent BDNF, also carry a more efficient BDNF-TrkB binding and signaling system, which should explain why their post-exercise concentrations of BDNF rapidly decrease during recovery.

Nevertheless, diverse metabolic pathways differently modulate the muscle content of BDNF and its low affinity receptor p75 - a member of tumor necrosis factor family of receptors - which binds to the pro-BDNF isoform to activate apoptotic cascades (40, 41). Pro-BDNF increases in similar way in progressive and continuous intensity exercise, whereas the levels of p75 receptor increase following the intensity as it was shown in Brunelli *et al*. (36). Therefore, elevated expression of p75 receptor after a maximal effort represent a negative feedback from which excessive aerobic energy consumption impact on the pro-BDNF/BDNF ratio, contributing to a rapid breakdown of BDNF concentrations (42).

It is believed that the age might influence on the relation exercise-intensity/BDNF response, when small volumes of exercise pronounce BDNF increase in younger individuals which are attributed to enhanced proteolytic systems, like the plasmin/plasmogenin that may act on pro-BDNF processing (43). It is needed to remark that the main source of BDNF-induced exercise is the brain and not skeletal muscles, as shown by Matthews *et al*. (34) and Rasmussen *et al*. (44).

In general, low-intensity exercise did not affect levels of BDNF in active or sedentary individuals, while both moderate and high-intensity exercise pronounced increase in BDNF in these groups, with higher response in well-trained people and magnitudes of effect following the oxygen consumption intensity.

PROLONGED EXERCISE AND BDNF RESPONSE

The energy request of an exercise bout is based on two factors: intensity (meaning the quantity of oxygen processed in time) and duration. Additionally, the total volume of exercise can

Table 1. Included studies summary.

	Study	Demographic characteristics	Exercise procedures.	Main Findings
Acute BDNF responses	Rojas Vega *et al*., 2006 (20)	8 individuals, male, mean age 24 years, mean height 178 cm, mean weight 73 kg; VO_{2max} 56.6 ± 8.6 mL/kg/min	Subjects were submitted to an incremental cycling bout and has blood analyzed at baseline, during and after exercise.	Serum BDNF concentration significantly increased during the incremental exercise to exhaustion.
	Ferris *et al*., 2007 (26)	15 individuals, 11 male, mean age 25 years, mean height 174 cm, mean weight 71 kg; VO_{2max} 46.8 ± 2.7 mL/kg/min.	Subjects performed a 30-min cycling at the constant power of either anaerobic threshold plus 10% or minus 20%, with blood analyses performed before and after.	BDNF concentrations were significantly greater at the higher intensity relative to the lower.
	Tang *et al*., 2008 (35)	16 individuals, 8 male, Age 19 – 30 years, Weight 45 – 68 kg.	Subjects performed 15-min step-exercise with heart rates recorded. Blood analyses were performed at baseline, and at min 0, 25 and 50 after exercise start.	The 15-min exercise significantly increased BDNF levels, with these returning to pre-exercise values. Results raised the possibility that regular exercise facilitates the metabolization of BDNF after a maximal effort.
	Matthews *et al*., 2009 (32)	8 individuals, male, mean age 25 years, mean height 181 cm, mean weight 82 kg.	Subjects performed 120 min of cycling exercise at 60% of VO_{2max} and had muscle biopsy samples collected for analyses before and after exercise, plus 3, 5, 8, 24, 48 and 72 h into recovery.	BDNF increased immediately after exercise and returned to its baseline after 60 min. An increase in serum BDNF during exercise is not supplied by skeletal muscles.
	Rasmussen *et* al., 2009 (42)	8 individuals, male, mean age 30 years, mean height 188 cm, mean weight 84 kg, VO_{2max} 57.1 ± 6.2 mL/kg/min.	Subjects accomplished a 4-h ergometer rowing at 10 – 15% below the anaerobic threshold. Jugular vein and brachial arterial blood were analyzed before, within 2, 4 hours and after 1 h of recovery.	Jugular venous and arterial BDNF concentrations significantly increased during prolonged exercise and returned to basal levels after 60 min of rest. Venous concentrations of BDNF are higher than arterial's, both at exercise and rest.
	Brunelli *et al*., 2012 (34)	10 individuals, male, mean age 22 years, mean height 177 cm, mean weight 76 kg.	Subjects completed a GXT on a bicycle with blood analyses taken before and every 3-min, plus 1 min into active recovery. Also, a 30-min cycling at anaerobic threshold intensity was performed with blood collected before, 5-min from the end, 30 and 60 min after.	After the GXT, increases in BDNF concentration were significant within 30 minutes and remained elevated at 30 min recovery, whereas for the anaerobic intensity, the value reached statistical significance only in 60 min. BDNF and p75 receptor are differently modulated depending on the intensity of exercise.
	Cho *et al*., 2012 (33)	18 individuals, male, mean age 19 years, mean height 173 cm, mean weight 78 kg, VO_{2max} 52.23 ± 6.43 mL/kg/min.	Subjects performed GXT and with blood analyses before and after.	Highlighted the inverse correlation between basal circulating BDNF levels and cardiorespiratory fitness levels and positive for BDNF exercise response. There was also a positive correlation between the running time and the changes in serum and plasma BDNF pre-post exercise.
	Heyman *et al*., 2012 (21)	11 subjects, male, mean age 23 years, mean height 183 cm, mean weight 77 kg.	Subjects underwent a GXT on a cycloergometer to determine the intensities of 55% and 75% of maximal power for the experimental cycling. They had blood analyzed at rest, post-exercise and after 15 min of recovery.	Exercise had a pronounced effect on plasma BDNF level which rose significantly during exercise and decreased to basal levels after 15 min of recovery. BDNF dynamics correlates with endocannabinoids
	Schmidt-Kassow *et al*., 2012 (25)	40 individuals, 20 male, mean age 23 years, mean weight 69 kg.	Subjects completed two sessions of 30-min continuous ergometric cycling in different intensities and had blood analyses before and after.	Increases in BDNF were more pronounced during the higher-intensity than the low-intensity exercise. The increase in the BDNF concentration during the exercise phase was more pronounced in men than in women.
	Nofuji *et al*., 2012 (28)	16 individuals, female, mean age 22 years, mean height 159 cm, mean weight 50 kg. Sedentary subjects VO_{2max} 34.7 ± 4.0 mL/kg/min, Active VO_{2max} 42.3 ± 4.5 mL/kg/min	Active and sedentary subjects participated in 3 exercise sessions with different intensities, i.e. maximal, moderate and low, and had blood analyses ran at baseline, plus 30 and 60 min after each.	Circulating BDNF responses to acute maximal exercise were different between active and sedentary groups with a positive exercise time effect. Moderate-exercise also showed an effect of time for BDNF in both groups, while low-intensity exercise had no effect on BDNF concentrations.
	Goda *et al*., 2013 (24)	33 subjects, male, mean age 24 years, mean height 170 cm, mean weight 64 kg, VO_{2max} 37.2 ± 6.5 mL/kg/min.	Subjects performed 30-min of exercise at 60% of VO_{2max} on a stationary bicycle and had their blood analyzed before and after.	Serum BDNF increased relatively to baseline in 18 of 33 healthy young sedentary men exposed to 30 minutes of moderate exercise.
	Schmolesky *et al*., 2013 (27)	45 individuals, male, mean age 22 years	Subjects were assigned to one of the 4 cycling conditions, *i.e.* 80% or 60% intensity, and 20 or 40 min duration. Blood analyses were conducted before and after sessions.	Subjects who exercised at vigorous intensities were more likely to show a significant BDNF increase than moderate intensity exercisers. And subjects who remained sedentary were not likely to show significantly increased BDNF levels.
	Tsai *et al*., 2014 (29)	60 individuals, male, mean age 23 years, lower fitness VO_{2max} 36.04± 3.64 mL/kg/min, higher fitness VO2max 58.04± 6.67 mL/kg/min.	Subjects speared by higher, lower fitness, and control groups completed a 30-min treadmill session at 60% VO_2max with blood analyses before and after.	BDNF levels rose after an acute session of moderate AE for both fitness (VO2max) profile groups.
	Saucedo Marquez *et al*., 2015 (22)	29 individuals, male, mean age 27 years, VO_{2max} 56.6 ± 2 mL/kg/min.	Subjects were divided into high intensity interval and continuous moderate exercise and had blood analyses collected in multiple times.	Larger increases in BDNF levels were observed in high-intensity interval exercise compared to moderate continuous exercise.

be defined by the number of exercise bouts in a certain period of time and may determinate long-term adaptations. Six of our study's results referred to long-term exercise programs with two to three months duration, and different patterns of access.

Aerobic catabolism refers to the conversion of carbohydrates, proteins and fatty acids into energy out of oxygen consumption in which mitochondria plays a major regulatory role (45). This ability can be improved through exercises according to physiological stimuli in order to guarantee the global and local energetic homeostasis of individuals (8). Data accumulation revealed a dose-dependence between aerobic energy expense and BDNF local and systemic responses. For

Long-term BDNF changes.	Zoladz *et al*., 2008 (44)	13 individuals, male, mean age 22 years, mean height 180 cm, mean weight 77 kg, VO2max 45.29 ± 0.93 mL/kg/min	Subjects accomplished five weeks of exercising and were tested for GXT before and after it. BDNF analyses were performed before and after both tests.	Endurance training at a moderate intensity has a bimodal influence on BDNF, increasing both basal and post-exercise concentrations in young healthy men.
	Seifert *et al*., 2010 (23)	20 individuals, male, mean age 29 years, mean height 181 cm, mean weight 90 kg, VO_{2max} below 45 mL/kg/min.	Subjects completed 3 months of daily exercise and had analyses from jugular vein and brachial artery performed at baseline and after 5, 10, and 15 min of a cycling session at 70% HR_{max}; as well as at every 4 min bout of an incremental cycling test.	Individuals increased 25% in VO_{2max} and presented higher levels of jugular venous BDNF at rest, as well as higher releases during exercise. Arterial levels of BDNF also increased pre-post exercise tests before and after training, with no changes in resting levels. Training increased the exercise-induced response of jugular BDNF to higher levels than those of not trained subjects.
	Griffin *et al*., 2011 (46)	47 individuals, male, mean age 22 years, mean height 180 cm, mean weight 82 kg, VO_{2max} 44.69 ± 10.36 mL/kg/min.	Subjects performed a GXT with blood analyzed at rest, at min 30 (post-test), 60, and 90 (recovering). Same protocol was repeated after 3 and 5 weeks of exercising on a stationary bicycle at 60% VO_{2max} 60min.	Three weeks and five weeks of AE training may respectively alter the serum BDNF acute and temporal profile responses to maximal acute exercise. There was an effect of exercise volume on BDNF levels with a significant positive interaction between BDNF and exercise time-exposure.
	Jeon & Ha, 2015 (45)	20 individuals, male, mean age 15 years, mean height 162 cm, mean weight 56 kg.	Subjects accomplished a 3-times week treadmill at 40% to 60% VO_2max for 8 weeks with blood analyses conducted 2 days before and after this period.	Basal levels of BDNF significantly increased in young inactive subjects after 2 months of regular AE.
	Murawska-Cialowicz et al., 2015 (47)	12 individuals, 7 male, mean age 26 yr, mean height 177 cm, mean weight 79 kg, VO2max 38.71± 5.67 mL/kg/min.	Subjects underwent a CrossFit exercising 2-times a week at 85-95% HRmax for 3 months. They performed a 30-second Wingate and a GXT protocols both before and after the CrossFit. Blood analyses were ran before and after the program.	Resting levels of BDNF increased in three months of intense regular exercise for young adults. BDNF concentrations were significantly higher after the GXT compared to the Wingate.
	Wagner *et al*., 2015 (48)	17 individuals, male, mean age 25 years, VO_{2max} 45.9 ± 4.7 mL/kg/min.	Subjects were submitted to 6-week exercising. Sessions included 50-min working at 85% VO_{2max}.	Exercise-induced BDNF concentration significantly decreased after the intervention for the exercise group only. Changes in exercise-induced BDNF increases were positively correlated with changes in the workload at the individual anaerobic threshold in the exercise group. The exercise-induced changes in BDNF levels significantly correlated with changes in hippocampal subfield volumes.

Abbreviations: AE, aerobic exercise; BDNF, brain derived neurotrophic factor; VO_{2max}, maximum rate of oxygen consumption; GXT, graded exercise test.

instance, a significant effect of training on BDNF response was perceived in Zoladz *et al*. (46) study, when subjects yielded higher levels of BDNF at post-GXT, along with increase in VO_{2max}, after training.

The exercise volume also had a special influence on basal levels of BDNF, that appears to be modulated by intensity. Exercising individuals in Seifert *et al*. (25) study showed no changes in basal BDNF after three months of moderate exercise sessions, even though these levels would elevate during the sessions. Further, it was still possible to detect an increase in basal concentrations of individual's BDNF in brain. Such evidence implies that increases of BDNF release in response to exercise occur in distinct scales between central to peripheral systems. Brain release of BDNF is greater and rises in larger magnitude during exercise than peripheral's, starring as the primary source of circulating BDNF (44). Nevertheless, for the sedentary adolescents in Jeon & Ha (47) study, even two months of low-intensity exercise was enough to increase the basal levels of BDNF.

Griffin *et al*. (48) study demonstrated the effect of the exercise volume on BDNF by a time-exposure interaction found between BDNF levels and exercise. It was detected that individuals exposed to 5-weeks exercise yielded higher post-exercise BDNF response than those exposed to 3-weeks. Accordingly, individuals of Murawska-Cialowicz *et al*. (49) study did show increases in BDNF within the same 3-months exercise as in Seifert *et al*.'s (25), but a lower volume (sessions) and higher intensity. It is assumable by these, that higher demands of aerobic energy evoke more adaptive changes from aerobic metabolism together with more consistent BDNF outcomes.

Wagner *et al*. (50) study confirms that exercise-dependent increases in BDNF associate with the energy demands involved by showing that individuals display of smaller BDNF responses to the same exercise conditions as they held higher fitness states. Such decay in BDNF response is expected for well-trained individuals as a reflect of the acquired capability of generating energy more efficiently (51). Moreover, individuals with better fitness conditions hold larger potential to produce BDNF through exercise in time, as they have a more specialized system for processing metabolic byproducts. Correspondently, individuals who exercised for longer periods showed post-exercise BDNF increases that sustained longer during recovery (48).

Great volumes of exercise such as 3 or 5-months and moderate to high-intensity have been reported to induce changes in basal levels of BDNF gathered even in older individuals with cognitive disturbances (9, 52, 53). Different exercise scopes require different shapes of energy supply and so different physiologic adaptations. The exercise volume is determinant for the consistency of the metabolic changes in an individual as much as the amplitude of adaptive responses to exercise mainly depend on the mitochondrial adjustments - in number and function - together with their associated protein expression. We suggest that there must be a specific mechanism by which exercise causes different BDNF responses corresponding to the degrees of adaptation of aerobic metabolism, as observed throughout the studies.

BRAIN DERIVED NEUROTROPHIC FACTOR AND AEROBIC METABOLISM CROSSTALK

BDNF expression stimulation by catabolic signaling was detected previously (6, 7), along with its association to reactive oxygen species (ROS) production by cells (54, 55). Relatively recently BDNF was identified as an exercise-induced cytokine in skeletal muscles along with an increase of its gene expression in hippocampus (56) and other brain parts according to animal models (57). Then, a modulatory effect of exercising on a peptide

fibronectin type III domain-containing protein 5 (FNDC5) and BDNF, whereof expression is induced by peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α) activation under energy imbalance conditions, was found in muscle (58). Later on, it was revealed that both BDNF and FNDC5 genes are regulated by PGC-1α in neurons (56).

PGC-1α, a member of the transcription coactivators family, suggested as a crucial regulator of a cell aerobic metabolism that controls mitochondrial cell enrichment (3, 59, 60), is expressed in very low levels in resting states and robustly increased in response to loads of energy request and ROS accumulation (59) that's is produced by mitochondria under increased catabolic conditions (61). Strongly stimulating PGC-1α expression, AE forces mitochondria to continually adapt their shapes and quantity to cover the energetic challenge, modulating cell expression/activity of mitochondrial metabolic enzymes and compounds to increase antioxidant defense against ROS (60). All these changes are physiologically translated into different individuals' degrees of adaptation like capability to produce energy, tolerance to exercise-intensity and/or duration, and recovery optimization to steady states.

PGC-1α integrates different signaling pathways through a multitude of posttranslational modifications, selective activation of alternative promoters and expression of transcript variants that ultimately regulate the tissue phenotype (61). In muscles, PGC-1α elevation promotes a high endurance phenotype. By mitochondrial biogenesis, PGC-1α promotes the remodeling of muscle tissue to a fiber-type composition that is metabolically more oxidative and less glycolytic, participating in the regulation of carbohydrate and lipid metabolism (3). Whereas in brain, PGC-1α overexpression acts as an endogenous protective mechanism to compensate neuronal redox states (62). PGC-1α-related transcriptional dysregulation in the brain has been linked to several neurodegenerative disorders (63).

Both acute and chronic exercise activate PGC-1α in muscle and brain (64). PGC-1α interacts with a range of transcription factors to induce gene expression. In neurons, PGC-1α binds to the orphan nuclear receptor estrogen-related receptor alpha (ERRα) to ultimately induce *bdnf* activity (56). Also, PGC-1α interaction with the nuclear transcription factor ERRα is necessary for the regulation of *fndc5* expression in both muscle and neurons (65), where FNDC5 positively regulates the expression of *bdnf* (56). Regarding that the exercise selectively induces expression of ERRα gene (*errα*) in brain after PGC-1α stimulation, the increase in *bdnf* expression in parallel, with PGC-1α, ERRα and FNDC5 establish ERRα/PGC-1α → FNDC5 → BDNF pathway mechanism by which aerobic exercise should affect brain BDNF levels supporting and increasing neuroplasticity (56, 58, 66).

FINAL CONSIDERATIONS

Crossing our results with scientific literature it becomes clear that at a metabolic level, aerobic exercise, more precisely, the aerobic energy expense is the key factor for the exercise impact on BDNF gene expression. The higher demands of aerobic energy (higher exercise intensity and/or longer intervention) evoke more adaptive changes of aerobic metabolism together with more consistent BDNF outcomes (higher acute increase and/or changes in basal level). BDNF production increase strongly depends on a dose and pattern of exercise as well as on the metabolic adjustment of organism reliable to fitness condition. At a molecular level, it is possible to suggest PGC-1α as a common molecule that mediates the adaptive responses of oxidative metabolism. Therefore, we believe that the role of exercise on exercise-related improvements of neuroplasticity and cognition must occur through an integrated machinery that embraces aerobic energy expense and BDNF production.

Conflict of interests: None declared.

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