Forum Review Article

Preventive and therapeutic potential of physical exercise

in neurodegenerative diseases

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Abstract

Significance: The prevalence and incidence of age-related neurodegenerative diseases (NDD), tend to increase along with the enhanced average of the world life expectancy. NDD are a major cause of morbidity and disability, affecting the healthcare, social and economic systems with a significant impact.

Critical Issues and Recent Advances: Despite the worldwide burden of NDD and the ongoing research efforts to increase the underlying molecular mechanisms involved in NDD pathophysiologies, pharmacological therapies have been presenting merely narrow benefits. On the other hand, absent of detrimental side effects but growing merits, regular physical exercise has been considered a prone pleiotropic non-pharmacological alternative able to modulate brain structure and function, thereby stimulating a healthier and "fitness" neurological phenotype.

Future Directions: This review summarizes the state-of-the-art of some peripheral and central-related mechanisms that underlie the impact of physical exercise on brain plasticity as well as its relevance for the prevention and/or treatment of NDD. Nevertheless, further studies are needed in order to better clarify the molecular signaling pathways associated with muscle contractions-related myokines release and its plausible positive effects in the brain. Additionally, particular focus of research should address the role of physical exercise on the modulation of mitochondrial metabolism and oxidative stress in the context of NDD.

Introduction

As the average life expectancy increases, age-related neurodegenerative diseases (NDD), such as Alzheimer's Disease (AD) (9), Parkinson's Disease (PD) and others, tend to increase its prevalence and incidence on worldwide population (43). Moreover, being a significant cause of morbidity and disability, NDD have a massive impact on healthcare, social and economic systems (54,170). Despite NDD-increasing trend, pharmacological therapies have been presenting merely narrow benefits (176).

Therefore, the relevance of non-pharmacological therapies in the management of NDD have been rising. Almost absent from side effects, non-pharmacological alternatives, including cognitive stimulation therapy, music therapy, animal-assisted therapy, multi-sensory therapy and physical exercise (PE) have shown promising benefits (33). These therapies aim to preserve or improve cognitive function, the ability to perform activities of daily living and quality of life (204). They also decrease behavioral symptoms in NDD, such as anxiety, depression, apathy, agitation and sleep disturbances (54), as well as to postpone the institutionalization and reduce the burden on caregivers (95).

It has been estimated that approximately 35% of AD cases (105) are attributed to modifiable factors and thus potentially preventable (178). Likewise, a systematic review and meta-analysis including 37 prospective cohort studies showed that postural-instability-gait, hallucinations, orthostatic hypotension, cerebrovascular disease, diabetes mellitus, obesity, cardiac disease, alcohol consumption and smoking increase the risk of PD with cognitive impairment (62).

In accordance, a growing body of evidence reveals beneficial effects of PE on brain health and its important protective impact in the reduction of modifiable risk factor for AD (105,178) and PD (199) contributing to a reduced risk of dementia. Tolppanen and coworkers (182), in a 28-year follow-up study (n = 1511) of subjects diagnosed with dementia/AD found that those engaged in low to moderate levels of leisure-time physical activity in midlife were associated with a higher risk of dementia compared to those categorized in the most active category.

Similar results were found in the 29-year follow-up study, Finnish Twin Cohort (n = 21,791), in which patients submitted to vigorous leisure-time physical activity were more protected against dementia compared to those who were inactive (79). This prophylactic effect of physical activity was confirmed by Blondell (18) and Ojagbemi and coworkers (137) in two meta-analysis comprising 47 and 18 longitudinal studies, respectively and revealing a positive association between higher levels of physical activity, reduced risk of cognitive decline and dementia and helpful effects on activities of daily life and overall quality of life.

Generally, exercise interventions are considered relevant strategies, from midlife to older ages, in dementia prevention. In fact, PE seem to be related to the improvements in several cardiovascular risk factors, such as diabetes, hypertension, obesity, which are recognized as a reversible risk factor for dementia (105). Furthermore, evidence suggest that PE can counteract AD-related pathogenic changes, lower AD biomarkers (23,178), preserve neurogenesis and favor neuroplasticity (80). Yet, some heterogeneity in exercise interventions designs and outcomes, namely in studies with individuals diagnosed with dementia and AD (52,137,178), justify the lack of specific and consensual exercise recommendations (duration, type, intensity) and are limitations to define the effects of exercise on these particular neuro-pathological conditions. Future research addressing this subject is clearly needed.

In contrast, the American College of Sports Medicine (ACSM) published recommendations for exercise prescription of people with PD (1). Those aim to delay disability, balance impairment, falls and contribute to increased quality of life in this population. In line, a 24 studies-based meta-analysis (n=941 participants) concluded that exercise intervention improved balance and gait ability and prevent falls in people with PD (166). In addition, evidences have shown long-term beneficial effects of exercise, such as strength training, aerobic training, tai chi or dance therapy lasting at least 12-weeks in PD patients (108). Notably, the benefits of 4 to 8-weeks of gait or balance training sessions can last up to 3–12 months after cessation (108).

Please insert Fig. 1 here

For several centuries, the axiom claiming "PE leads to a healthy body and mind" has been recurrent. However, only during the last decades have researchers focused on the effects of PE on brain structure and function, with exercise being associated with angiogenesis, neurogenesis and synaptogenesis; therefore considered a potential stimulus to improve learning abilities and memory (186). Although the mechanisms and intermediary mediators that explain exercise-induced brain plasticity remain to be fully elucidated, evidences about the beneficial impact of exercise in people with NDD are overall consistent. The present review aims to provide a state-of-the-art summary of some peripheral and central mechanisms that underlie the impact of PE on brain plasticity, particularly its relevance for the prevention and/or treatment of NDD (Fig. 1). Additionally, it will be highlighted to the role of PE on the modulation of mitochondrial metabolism and oxidative stress in the context of NDD.

Muscle-brain crosstalk: the possible role in neurodegenerative diseases prevention/therapy

While exercising, skeletal muscles communicate with other organs, including the brain. In fact, nowadays it is well established that muscles can operate as an endocrine-type organ perpetrating beneficial whole body health-related effects in distinct organs (70,163). In contrast, lack of contraction-induced myokines release or the production of a distinct set of hormones in the inactive muscle seems to be associated with pathological deleterious consequences (163). It has been proposed that exercise stimulates muscles to produce and release hundreds of myokines and other circulatory factors during contractions (48) and/or during proliferation, differentiation and regeneration of muscle cells (68,69). Thus, in response to PE, myokine signaling along with the release of extracellular vesicles (exosomes) containing peptides, nucleic acids, microRNA (miRNA), mRNA and mitochondrial DNA to the bloodstream (156,157,195,196), seem to mediate inter-organ communication, including the pathways associated to muscle-brain crosstalk.

Although the association between myokines circulating levels and the improvement in cognitive function is not fully understood (90), it has been proposed that exercise affects cognition by inducing neurochemical and structural changes, including neurogenesis and synaptogenesis, particularly in the dentate gyrus of the hippocampus. While human neurogenesis remains controversial (85), it has been extensively demonstrated that PE influences rodents brain and induces neurogenesis throughout its lifespan (103).

Importantly, animal and human studies indicate that the effects of PE on the brain are also mediated by alterations in the systemic environment, including alterations in response to vascular growth factors and increased cerebral blood flow (for refs see 178). Cardiovascular system-related activity induces laminar shear stress on vascular endothelial cells which are related to greater release of insulin growth factor (IGF) and vascular endothelial growth factor (VEGF), promotors of greater blood flow, brain angiogenesis and neurogenesis (24).

The possible therapeutic and preventive role of myokines and other muscle-driven circulating factors produced and secreted during PE against NDD is beginning to emerge. Promising mechanistic data in both animals and humans suggest that targeting the systemic circulatory factors modulated by PE may be also a possible strategy to prevent or delay NDD progression.

Brain-derived neurotrophic factor: the maestro of exercise against neurodegenerative diseases

Brain-derived neurotrophic factor (BDNF) is considered the key molecule for exercise-induced brain plasticity, coordinating the action of other neurotrophic factors, neurotransmitter systems, and hormones (57,143). This neurotrophin has been involved with adult neurogenesis including cell proliferation, differentiation and maturation and is also linked with cell survival and regulation of synaptic plasticity (198). Mechanistic studies support that BDNF mediates exercise-dependent hippocampal neurogenesis and synaptogenesis and is required for

exercise-induced improvements on cognitive function, including memory and learning abilities (187-189).

BDNF can be produced in skeletal muscle in response to mechanic contraction and stimulates lipid oxidation via AMP-activated protein kinase (AMPK) activation (121). However, it is not clear if BDNF can be released from muscles into the bloodstream and directly interact with the brain (121). Instead, it has been proposed that other contraction-induced circulating molecules after being released from skeletal muscle, cross through the blood-brain barrier and are able to promote an increase in brain BDNF expression. Additionally, It has been suggested that PE promotes an increase in central nervous system (CNS) production and release of BDNF (153,164), which can explain the increase in circulating levels of BDNF found after an exercise intervention in young (60) and older adults (41). Interestingly, higher increases in serum BDNF levels were found as a function of age, being the older individuals (over the age of 71) those in which the exercise-induced changes in BDNF perpetrated more benefits on task-switch performance (94).

Zhao and coworkers (202) reported that 6-weeks of high-intensity intermittent swimming altered the expression of 34 miRNAs, including those from the mir-200 family involved in the regulation of postnatal forebrain neurogenesis (12), neurons differentiation and proliferation (140) and miRNAs that target BDNF gene. In fact, the expression of BDNF besides being highly and multi-regulated during transcription and translation, can also be modulated by posttranslational modifications (Fig. 2) and by epigenetic-related mechanisms (for refs see 123), suggesting that an interplay between genetic and environmental stimuli, including exercise, dynamically influence BDNF levels. The synthesis of the mature form of BDNF involves, intra or extracellularly, proteolytic cleavage of the proBDNF precursor. Surprisingly, the pro and mature forms of BDNF bind different receptors and play opposite roles in the brain. ProBDNF preferentially binds p75 neurotrophin receptor (p75 NTR), which facilitates long-term depression (LTD), a marker of reduced synaptic efficacy and cognitive function, and induces apoptosis. In contrast, mature BDNF binds specifically to tyrosine receptor kinase (TrkB) and

promotes cell survival, facilitates long-term potentiation (LTP), a marker of synaptic efficiency, and increases spine complexity (for refs see 123).

This exercise influence on BDNF processing and signaling appears to modulate levels of pro- and mature BDNF in a homeostatic manner (36). Some reports suggest that voluntary exercise did not alter proBDNF levels but increased mature BDNF in mice hippocampus (160). In contrast, in other studies the decline of walking speed in healthy older adults was associated with increased levels of proBDNF in plasma extracellular vesicles, compared to non-decliners (173), suggesting that not only cognitive but also motor functions are associated to BDNF-specific signaling.

Additionally, a common single nucleotide polymorphism in the human BDNF gene, with a valine (Val) to methionine (Met) substitution at codon 66 in the pro-domain of BDNF, was identified. Met variant form (Val/Met heterozygotes and Met homozygotes) potentially affects BDNF activity-dependent neuronal release and distribution (for refs see 123,165). This polymorphism has been associated with structural and functional differences in the brain and as being involved on exercise-induced neuroprotection (for refs see 123,165). Significant levels of PE mitigated poorer working memory performance in Met carriers while had minimal effects on Val homozygotes adult volunteers (40). However, it has been also reported that Met homozygotes mice did not show exercise-induced upregulation of BDNF and increase of newborn neurons (76). Several authors suggested an interaction between BDNF polymorphism and PE on cognitive performance, brain volume and/or cerebral plasticity in elderly healthy volunteers (22,27,28,181) being Val carriers those who exhibited the greatest benefits from exercise. It seems that PE does not sufficiently increase BDNF levels in Met carriers to induce alterations on brain structure and function. Furthermore, the alteration of proBDNF structure in Met carriers impairs the ability of mature BDNF to bind TrkB, whereas the ability of proBDNF to bind p75 NTR remains unaltered, which induces apoptosis (180). Therefore, Brown and coworkers (22) suggested that Met carriers undergoing high levels of PE might experience higher levels of apoptotic signaling in the brain. Accordingly, Lemos and

coworkers (98) reported that only Val homozygote adult healthy men increased BDNF levels after PE, whereas no alterations were found in circulating proBDNF. The authors hypothesized that increased enzymatic machinery responsible for extracellular cleavage of proBDNF might mediate the increased mature BDNF concentrations, which triggers a positive feedback loop in a paracrine manner, inducing benefits to peripheral vasculature. A preliminary study reported that pro and mature BDNF serum concentrations as well as memory were differentially affected by exercise intensity and BDNF genotype in adult males (146). In fact, acute vigorous-intensity PE increased mature BDNF levels, although in a lower magnitude in BDNF Met carriers, but did not significantly affect proBDNF concentrations. Despite an absent impact on mature BDNF levels, acute light-intensity PE improved memory, although over 24h was worse for BDNF Met carriers (146).

Considering all the above mentioned mechanistic implications, multiple lines of evidence implicate BDNF in the process of NDD (165). Alterations in BDNF levels have been reported in AD, PD and Huntington's disease (HD) (for refs see 165). A meta-analysis showed that lower levels of peripheral BDNF are associated to late stage of dementia spectrum (132), suggesting that BDNF could be a critical therapeutic target for preventing cognitive decline. Nevertheless, studies that associate BDNF polymorphism and age-related cognitive impairment are inconsistent. It has been suggested that the BDNF influence on cognitive function may change across lifespan and Met allele may be neuroprotective during later stages of life. Similarly, BDNF polymorphism and the risk for NDD are not consensual. Some evidences showed that older adults carrying the Met allele have an increased risk for development of NDD, but others fail to find this relationship (for refs see 165,194). Interestingly, a meta-analysis also reported sex differences regarding the BDNF isoforms, being the higher susceptibility to AD-associated with women Met carriers (53). Other studies reported that Val homozygotes have an increased risk, in an age-dependent manner, for alterations on brain structures and cognitive functions as well as for the development of NDD (for refs see

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165,194). Small effect sizes, possible ethnicity, gender, and age effects of the BDNF polymorphism may contribute to the conflicting results (165).

The role of BDNF polymorphism in exercise-induced protection against NDD remains to be elucidated. In a longitudinal study, Kim and coworkers (88) suggested that Met allele may confer vulnerability for dementia in elders engaged in less PE. On the other hand, beneficial contribution of 16-week multimodal PE training was reported on cognitive function of elderly individuals with mild cognitive impairment independently of the BDNF genotype. However, only BDNF Met carriers exhibited exercise-induced elevation of peripheral BDNF levels (130).

Please insert Fig. 2 here

Cathepsin B mediates BDNF expression

Cathepsin B is a lysosomal cysteine protease, involved in the degradation of peptides and proteins. In the context of the NND, alterations in cathepsin B concentration, activity and localization in aging neurons have been associated with age-related neuropathologies. Cathepsin B seems to be involved in the formation and clearance of amyloid-β (Aβ) peptides (AβPP β-secretase activity and Aβ degradative activity) (72,127), being plasma cathepsin B levels higher in persons with AD compared to healthy-controls (174). Similarly, cathepsin B seems to be associated with the degradation of α-synuclein, one of the pathological hallmarks in PD (122), whereas others studies report that cathepsin B is involved in triggering intracellular aggregate formation by α-synuclein fibrils (184). Cathepsin B might also be involved in the motor neuron degeneration in amyotrophic lateral sclerosis (ALS), being diffusely distributed within degenerative neurons (86). Likewise, cathepsin B was found in neurites and dendrites as well as in pathological plaque structures of Parkinsonism-dementia of Guam and senile dementia patients (77).

However, despite the above evidences of a "pro" neuro-pathological impact of cathepsin B, the real role of cathepsin B in NDD remains controversial. In fact, some consistent studies also suggest that cathepsin B plays a neuroprotective role in AD progression, being candidate as protective target for AD intervention. Cathepsin B has been considered central in neuroprotective lysosomal activation, neuronal survival (49), and anti-amyloidogenic activity (127). Mueller-Steiner and coworkers (127) reported an increased hippocampal and cortical amyloid depositions in the absence of cathepsin B and a reduction of pre-existing amyloid deposits and thioflavin S-positive plaques following overexpression of cathepsin B in a cathepsin B-deficient mouse model of AD overexpressing human amyloid-protein precursors. Likewise, treatment with cysteine cathepsin inhibitor, cystatin C, induced insoluble α-synuclein accumulation in primary cultured neurons from mice (175). Moreover, adenoviral overexpression of cathepsin B reduced hippocampal amyloid depositions and ameliorates learning and memory in the Morris water maze task in an Aβ precursor protein-presenilin 1 (APP/PS1) double transgenic mouse model of AD (39). Accordingly, enhanced cathepsin B activity in the brain was associated with reduced Aβ levels in mice overexpressing human amyloid precursor protein (192). Overall, despite controversial findings, data also suggest that enhancing the activity or levels of cathepsin B could provide a promising strategy for maintaining lysosomal function and for preventing and/or treating NDD (29).

As referred before, in response to PE, skeletal muscle cells are able to produce and secret several myokines in an endocrine-like way. Accordingly, it has been suggested that exercise-related muscle contractions also increase the production and the circulating levels of cathepsin B (125,191), which is able to cross the blood-brain barrier and mediates BDNF expression in the hippocampus; therefore promoting brain plasticity and improving cognition and memory function (Fig. 3). Fourteen and thirty days of voluntary running increased cathepsin B levels in plasma and gastrocnemius of mice and in plasma of Rhesus monkeys (125). Moreover, four months of PE increased circulatory levels of cathepsin B, which were positively correlated with an increase in aerobic and cognitive (hippocampus-dependent task) performance in young-

adults (125). Other reports suggest that long-term PE decreased peripheral resting levels of cathepsin B in male young and middle-aged rugby players, suggesting higher efficiency of cathepsin B signaling in trained individuals (32). In contrast, Gourgouvelis and coworkers (59) failed to find alterations in plasma cathepsin B levels in young men following 8-weeks of moderate PE, regardless of mild improvements in cardiorespiratory fitness. Similarly, 6-weeks of high-intensity interval training did not induce changes in serum levels of total and precursor (pro) cathepsin B (133). The association found between cardiorespiratory-fitness gains and larger decreases in total and pro cathepsin B might reflect higher demand of active cathepsin B in response to exercise, i.e, increased cleavage of cathepsin B precursor (pro cathepsin B) into the active cathepsin B (133). Importantly, genetic knockout approaches showed that cathepsin B is a mediator of exercise-induced cognitive function, adult neurogenesis and antidepressant effects (125). Interestingly, these mice also exhibit impairments in spatial memory retention and reduced inhibitory neurotransmission in the hippocampal dentate gyrus, suggesting a critical role of cathepsin B as a myokine that mediates exercise-induced neuroprotection. Overall, the definitive role of exercise increased cathepsin B levels in the specific context of NDD remain to be fully elucidated.

Please insert Fig. 3 here

FNDC5/Irisin induces BDNF expression

As illustrated in Fig. 3, muscular contraction stimulates the synthesis of fibronectin type III domain-containing protein 5 (FNDC5), a transmembrane precursor protein expressed in muscle under the control of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) (20). FNDC5 is cleaved and secreted into the bloodstream as the myokine irisin, associated with the browning effect of adipose tissue and also with the expression of hippocampus BDNF (198).

In fact, as irisin can cross the blood-brain barrier (155), the increased systemic irisin levels seem to regulate exercise-induced hippocampal BDNF expression, and therefore is a potential mediator of neuroprotection (197,198). Notably, PE elevates plasma irisin levels in an aged-independent way, i.e., both in young (14) and older adults (124). Similarly, a 12-week resistance training elevates circulating irisin levels in older adults and 19 months old mice (87). Moreover, animal studies suggest that a single bout of PE increases serum and skeletal muscle irisin levels (21,141) and 6-weeks of voluntary exercise increased irisin levels in the brain (185). Nevertheless, some concerns about the accurate irisin detection have arisen, particularly in humans (201). Moreover, some studies failed to show an increase of FNDC5/irisin expression after exercise. It has been pointed out that different regimens and modes of exercise, the time point of sampling and studied population, could explain the different results (201). A meta-analysis reported that chronic PE leads to unchanged or significantly decreased circulating irisin levels in randomized controlled trials (148). Kuster and coworkers (93) reported that irisin serum levels remained unchanged in old adults at risk of dementia after 10-weeks of exercise. It seems that in contrast to data obtained following chronic PE, baseline irisin levels transiently rise after acute high-intense exercise, but soon after return to basal levels, with the higher increases of basal levels seen in untrained or sedentary individuals to whom exercise constitutes a particular energetic challenge (74,75).

Nonetheless, decreased serum levels of BDNF and irisin were suggested as potential blood-based biomarkers of cognitive decline (93). FNDC5/Irisin levels were reduced in the hippocampus and cerebrospinal fluid of AD patients and transgenic AD mice (106). Moreover, Lourenço and coworkers (106) showed that FNDC5/Irisin is an important mediator of the beneficial effects of exercise in AD models, as the blockade of either peripheral or brain FNDC5/irisin attenuated the neuroprotective impact of PE on synaptic plasticity and memory, while peripheral overexpression of FNDC5/irisin rescued memory impairment in AD mice.

Whether FNDC5/Irisin are critical to exercise-induced neuroprotection against NDD remains to be fully resolved. We anticipate that studies on the role of FNDC5/Irisin as a regulator of

neuronal development and survival as well as on the related signaling pathways activated by exercise against aging-related neuropathologies will emerge.

Interleukin 6 (IL6) and neuroinflammation

Interleukin 6 (IL6), classically associated with chronic inflammation, obesity and type-2 diabetes, is involved in both pro- and anti-inflammatory processes (162). Regarding its neurological impact, IL6 can cross the blood-brain barrier (119) and act on neural cells, including neurons, astrocytes and microglia. In the CNS, IL6 is synthesized mainly by microglial cells and astrocytes, but also by neurons. IL6 levels have been suggested to be elevated in the nigrostriatal region and in the cerebrospinal fluid, but not in the serum of patients with PD (71). However, others report increased levels of IL6 in PD patients and also that the individuals with higher serum IL6 levels have lower performance in functional mobility, gait speed and balance tests, which may be associated with functional disability in PD (161). While the modulation of IL6 levels is controversial in PD patients, increased circulating levels of IL6 have been found in AD patients (42). In this context, the contribution of inflammation to the pathological progression of AD seem to be associated with Aβ formation; even though it is not possible to ascertain if Aβ is a cause or a consequence of the neuroinflammatory state (11). Pathologically-increased IL6 has been associated with impaired neuroplasticity and cognitive functions. In fact, through activation of inflammatory pathways in the brain, cytokines, including IL6 influence the phosphorylation of the BDNF receptor (TrkB), thereby interfering with BDNF signaling (for refs see 82). In fact, a significant reduction in BDNF was observed in the hippocampus and cerebral cortex following the administration of pro-inflammatory cytokines or substances that are inducers of cytokines production (for refs see 82). However, IL6 murine forebrain knockout showed compromised neural progenitor proliferation, survival, and phenotypic maturation in the hippocampal dentate gyrus, subventricular zone (172).

PE seems to be a potential mechanism to direct and tune the inflammatory response in animal models of AD (84). Tau-transgenic mice, overexpressing human Tau23, submitted to 3-months

of PE decreased neuroinflammatory response characterized by activated astroglia and microglia in an exercise intensity-dependent manner. In parallel, PE attenuated the increased expression of IL-6 and other inflammatory markers in Tg mice brains (97). Similarly, voluntary exercise in the triple transgenic AD mouse model regulated metabolic abnormalities and decreased phenotype-associated apoptosis and expression of inflammatory markers, including IL6 in the hypothalamus, suggesting that exercise may prevent the progression of dementia (37).

During exercise, IL6 is also produced and released by myocytes to the bloodstream (Fig. 4A) (128). This muscle-derived IL6 has been associated with improved insulin sensitivity and fat oxidation, suggesting that, in this particular case, it has a metabolic rather than an inflammatory role (for refs see 143). PE has been suggested to acutely increase IL6 levels that return to baseline after exercise cessation. Increased plasma IL6 in AD patients was also reported following 16-weeks of moderate-to-high intensity exercise (81); however, other studies showed that chronic aerobic or resistance regimens did not change (183) or even decreased (129) circulatory IL6 levels in adults with mild cognitive impairment.

In the context of the neuroprotective benefits perpetrated by PE, the possible mechanistic pathway involving IL6 and BDNF signaling has not been studied yet (Fig. 4B). However, in response to acute and severe muscle-damaging exercise, serum BDNF levels decreased, whereas IL-6 levels increased and have been associated with peripheral fatigue in young healthy men (190). Moreover, a recent meta-analysis (171) showed that regular PE seems to be able of decrease IL6 and tumor necrosis factor-α (TNF-α) levels, despite positive effects on BDNF expression. In fact, a complex signaling pathway involving the modulation of IL-6, BDNF and adenosine receptors levels, which result in the neuroprotection of axotomized retinal ganglion cells, has been proposed (144). In a cell culture-based study, 45 min of IL6 treatment, but not 4, 24 or 48h, increased BDNF levels being transient levels of extracellular BDNF important for the IL6 induced rat retinal ganglion cells survival (145). Moreover, expression of BDNF gene exons I, II, and IV was reduced in the rats' hippocampus after acute treatment with

E.coli (30), suggesting that inflammation may affect specific isoforms of the BDNF gene. Nevertheless, further studies are needed to study the mechanisms underlying the modulation of BDNF by neuroinflammatory conditions as well as signaling pathways by which PE may positively influence this process.

Please insert Fig. 4 here

Kynurenine metabolism shift

Increased levels of kynurenine (KYN), a catabolite of the amino acid tryptophan, are associated with the action of proinflammatory cytokines, including IL6 in the KYN pathway, namely through stimulation of an important pathway in macrophages featuring indoleamine 2,3 dioxygenase (IDO) (for refs see 10). In fact, besides being a precursor of serotonin, tryptophan can also be degraded to KYN. Additionally, KYN may be catabolized to kynurenic acid (KINA) mainly in astrocytes or to 3-hydroxykynurenine (3HK) and ultimately to quinolinic acid (QUINA) in brain microglia (for refs see 91). KYN, in contrast to KYNA, is able to cross the blood-brain barrier and be metabolized to QUINA or KYNA in the CNS (Fig. 4C). As metabolites of this KYN pathway, 3HK generates free-radical species able to enhance brain oxidative stress conditions; QUINA is associated with neuronal excitotoxicity (agonist of N-methyl-D-aspartate receptors (NMDAR)); whereas KYNA, depending on its concentration, have a neuroprotective effect against excitotoxicity and apoptotic signaling (NMDAR antagonist) (for refs see 91). In this sense, the catabolism of KYN into KYNA in the peripheral tissues may also decrease the amount of KYN passing to the brain; therefore, reducing the potential central formation of neurotoxic compounds mediated by the KYN pathway of tryptophan metabolism.

Considering its impact in the CNS, dysregulation of the KYN pathway and altered levels in KYN metabolites have been detected in NDD, including AD, PD and HD (for refs see 177). In fact, cognitive performance was negatively associated with QUINA and positively associated

with KYNA concentrations in plasma (61). Accordingly, higher QUINA levels were associated with poorer performance in attentional and executive functions of older adults at risk of dementia (93). Moreover, increased activation of the KYN pathway and a shift toward the formation of neurotoxic metabolites, namely higher levels of 3HK and QUINA were found in the hippocampus (19) as well as in plasma (61) of AD patients (Fig.4C).

Furthermore, BDNF may modulate KYN metabolism during stress. Using BDNF knockout models, KYN was preferentially metabolized to the neurotoxic intermediate 3HK following repeated unpredictable mild stress (38). In accordance, Kuster and coworkers (93) reported stress-related increases of 3HK and reductions of BDNF levels in old adults at risk of dementia, suggesting that this metabolic interplay might contribute to the increased risk of cognitive deficits and dementia in stressed individuals. On the other hand, 10-weeks of PE and cognitive training had opposite effects increasing BDNF and reducing 3HK levels, respectively. Based on all the above-mentioned assumptions, multiple mechanisms seem to be associated to the beneficial neurological phenotype perpetrated by exercise-induced BDNF expression; however, whether or not the KYN pathway is definitively one of them remains to be clarified.

Although some reports failed to find unequivocal modulatory effects of PE on KYN metabolites in human serum (67), Agudelo and coworkers (2) reported alterations in KYN metabolism mediated by overexpression of PGC1α after 4-weeks of voluntary exercise in mice, particularly an increased expression of KYN aminotransferases (KATs) in skeletal muscle, which convert KYN into KYNA. This reduces KYN levels from circulation and prevents its accumulation and the neurotoxic potential of its derivatives in the brain. On the other hand, KYNA does not cross blood-brain barrier, but increases adipose tissue energy expenditure (Fig. 4C) and promotes an anti-inflammatory phenotype of the resident immune cells (3). Furthermore, PGC1α induces the expression of glycolysis and malate-aspartate shuttle genes in skeletal muscle, thus increasing the energy efficiency of glucose oxidation. This process seems to be dependent on KYN catabolism, allowing the trained skeletal muscle to use KYN to support aspartate biosynthesis and mitochondrial function as part of the adaptations to PE (4).

The impact of exercise on CNS functioning is well established and, at least in part, seems to be mediated by circulating levels of several muscle-driven myokines. There are also evidences suggesting that other mediators that escort PE, including adipokines and hepatokines, can modulation the CNS (96,143). However, despite accumulated suggestions, mechanistic details regarding the direct or indirect impact of PE on BDNF modulation, and consequently on the pathogenesis or progression of NDD remains to be clarified.

BDNF and mitochondrial-related mechanisms

As PE enhances neuroplasticity, neurogenesis, synaptic plasticity and synaptogenesis, it is expected that also increases the energy supply to maintain renewed brain architecture. Energy for neurons action potential firing, ion channel flux and transmitter recycling and for maintaining the membrane potential is dependent on mitochondrial metabolism (for refs see 109). Moreover, mitochondrial transport through dendrites/axons and back to neurons cell body are also energy dependent. Therefore, brain mitochondria are crucial not only for neurotransmission, but also for short-and long-term exercise-induced neuronal and cognitive adaptations. In fact, tightly coupled to increased energy requirements, strategies to optimize brain oxygen use, including angiogenesis (135) and mitochondrial function (115) have been associated with chronic PE engagement.

On the other hand, dysfunction in mitochondrial-related metabolic processes seems to contribute to the pathogenesis and development of AD, PD, HD and ALS (126). Besides the compromised energy production, increased oxidative stress as well as disturbances on calcium handling, mitochondrial dynamics, mitochondrial quality control, mitophagy, mitochondrial permeability transition pore opening (mPTP) and apoptotic signaling have been implicated in the pathogenesis of NDD (109). In fact, despite being considered as "complex diseases" associated with deficits and impairments in multiple cellular processes, a recent "medical hypothesis" concerning NDD suggest that oxidative damage to critical mitochondrial electron tunneling proteins lead to a pathological reactive oxygen species (ROS)

overproduction that predispose mitochondrial network to further dysfunction (15). Consequently, the accumulation of mitochondrial damage over time can lead to progressive neuronal structural and/or functional impairment and, ultimately, lead to the apoptotic or necrotic neurons death that characterize NDD.

PE is a "powerful" early mitochondrial-driven non-pharmacological intervention that can be applied throughout life with positive effects on mitochondrial physiology of different tissues. Generally, data suggest that exercise positively influences mitochondrial bioenergetics and network regulation in skeletal and cardiac muscles (13,107,116,117) and non-contractile tissues, including the liver, adipose tissue and the brain (16,58,115,159). Considering its pleiotropic feature, the systemic effect of exercise is unique as it can target not only the mitochondrial dysfunction characteristic of NDD, but also metabolic and cardiovascular disturbances that represent a major risk to NDD development.

In the recent years, data suggested that exercise mediated BDNF expression can promote adaptations of brain mitochondrial network (113,115). Actually, BDNF receptor trkB can positively modulate mitochondrial biogenesis, through PGC1α mediated mechanisms, and the expression of proteins involved in mitochondrial resistance and survival, including antiapoptotic and quality control factors, antioxidant enzymes and/or the up-regulation of DNA repair mechanisms (5,31,200). In response to exercise stimulus, PGC1α is known to co-activate several transcription factors aimed to up-regulate nuclear- and mitochondrial-encoded genes, including mitochondrial transcription factor A (TFAM); therefore inducing mitochondrial biogenesis and improving mitochondrial bioenergetics (78). Recently, among other mechanistical hypotheses, Sestrins, a highly conserved family of stress-inducible proteins (193), have been considered has mediators, at least in part, of some exercise-related benefits, including mitochondrial biogenesis. In fact, although only few studies have measured the impact of chronic exercise on Sestrin levels, available data seem to suggest that physical exercise improves this protein content through AMPK signaling pathway, and subsequently upregulates PGC1α and mitochondrial biogenesis (89).

BDNF increased respiratory coupling in synaptosomes through stimulation of NADH dehydrogenase activity of the mitochondrial complex I (111), and produced, in mouse brain mitochondria co-incubated with synaptosomes containing signal transduction pathways, a concentration-dependent increase in the respiratory control index, a measure of respiratory coupling efficiency, ATP synthesis, and organelle integrity (110). Also, the exercise-mediated production of the ketone body β-hydroxybutyrate modulates neuronal bioenergetics by increasing mitochondrial respiration, which drives changes in the expression of BDNF in cultured cerebral cortical neurons. Notably, the resulting increase in BDNF expression seems to be mediated by mechanisms involving, at least, the generation of ROS (112).

Please insert Fig. 5 here

Does exercise antagonize age-related neurodegenerative diseases through redox-mediated mechanisms?

Age-induced tissue loss and organ dysfunction were earlier proposed on the base of the so-called "free radical theory" (64) and the later designated "mitochondrial theory" referring to mitochondria as "biological clocks" (65). In accordance with both hypotheses, aging occurs due to the accumulation of oxidative damage in major cellular molecules and components (lipids, DNA and proteins), which results in structural and functional cellular/mitochondrial impairments (64,65). Although oxidative stress and cellular senescence are considered key mechanisms involved in the etiology of several organ pathological conditions (for refs see 101), brain seems to be particularly vulnerable to ROS deleterious effect due to its low antioxidant capacity, high oxygen consumption rates and oxidable substrates content (154). Moreover, certain regions of the brain have elevated levels of transition metals, such as iron, that can act as powerful catalysts for ROS formation (147). These distinctive features dispose nervous tissue to an extreme susceptibility to oxidative stress and consequently to deleterious impact on brain function (Fig.5). In accordance, brain redox disturbances have been, directly and

indirectly, associated with the pathogenesis and progression of many neurodegenerative disorders, such as ALS, PD, AD and HD (for refs see 134). Brain's susceptibility to increased oxidative stress negatively affect brain BDNF levels (147), compromising, as referred above, the crucial role of this neurotrophin as modulator of the learning and memory abilities (44,152) as well as its function regarding neuronal activity, plasticity and survival (92,120). Due to the critical harmful impact of oxidative stress in NDD, antioxidant molecules have been searched as potential therapeutic tools (179). However, since, *per se*, no convincing or definitive clues exist regarding their neuroprotective efficacy (104), other non-pharmacological preventive and therapeutic approaches have been considered (179). Among these, a significant set of narrative (102,138) and meta-analysis (8) highlight the positive neurological impact of PE across the lifespan. Accordingly, studies have shown that sedentary lifestyle is associated with lower cognitive performance (45), being dementia patients more physically inactive than their healthy counterparts (66). Considering the potential mechanistic interaction between the etiology of NDD, exercise-related redox positive modulation and neurological adaptations, Navarro et al. (131) reported that PE prevented the age-related increase in brain protein carbonyl content and the decrease in cytochrome c oxidase activity. These adaptations clearly mitigated the impairment of behavioral performances, the development of further cellular oxidative stress, and the decrease of mitochondrial function. Moreover, 9-weeks of swimming training improved cognitive functions in parallel with attenuation of oxidatively damaged proteins in both young and middle-aged rats (149). Surprisingly, data suggest that the beneficial redox modulation afforded by PE in female mouse brain cortex (47) and hippocampus (46) is apparently biphasic. The first 2-months of training were still associated with an increase in oxidative stress markers, suggesting that the hippocampus and brain cortex undergo significant redox adaptations. However, the later 4-months were linked to an increase in antioxidant enzymatic activities, unaltered brain thiobarbituric acid reactive substances (TBARS) levels and a decrease in the prooxidant molecule methylglyoxal and pro-apoptotic signaling. In addition, a redox beneficial phenotype adaptation induced by regular PE seems to be related to specific areas of the brain. Data from Marques-Aleixo and coworkers (115)

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revealed that 12-weeks of treadmill running induced lower carbonyl groups, malondialdehyde (MDA) and increased Bcl2 levels in rats' cerebellum mitochondria (but not in the brain cortex), despite higher PGC1-α and TFAM levels, augmented resistance to calcium-induced mPTP opening, and lower Bax and mitofusin 1(Mfn1) contents in the brain cortex.

Detailed mechanisms regarding the PE-related redox-based contribution to more robust brain phenotypes in active/physically trained subjects are comprehensively discussed in recent reviews (147,150).

As previously mentioned, mitochondria, the subcellular network responsible for ATP production, also play an essential role in several other cellular processes, such as calcium signaling, lipid synthesis and trafficking, metabolite transport, apoptotic signaling, quality control regulation and ROS production in the cell (73). Under physiological conditions, such as those associated with resting or moderate PE, mitochondrial-related ROS are produced as normal byproducts of the oxidative phosphorylation (OXPHOS) process; an efficient antioxidant system mitigates its potentially harmful effects avoiding substantial deleterious consequences. In these circumstances, ROS are involved in distinct intracellular pathways acting as second messengers; therefore, subtle rise above the steady-state ROS concentration has been considered to have a fundamental physiological role, including as signaling mediators of the antioxidant defense network (56,167). Generically, a plethora of studies performed both in humans and in animal models report that chronic moderate PE are associated with the development of a more robust antioxidant profile in different tissues, including brain.

In contrast, when mitochondrial function is compromised and a considerably higher electron leakage from the electron transport chain occurs, an imbalance in the redox steady state may occur either by an increased ROS production or by a decreased antioxidant defense capability. In fact, a supra-physiological production of mitochondrial ROS linked to a defective scavenging system has been consistently associated with aging and age-associated deleterious conditions, such as NDD (7,169). Being aging the main risk factor for late-onset NDD and

those to mitochondrial bioenergetic deficits, decreased ROS scavenging ability and increase in ROS production (99,113), age-related chronic oxidative stress seems to be a critical factor, for example, for hyperphosphorylation of tau (a key feature involved in the development of nerve cells degeneration) in AD neurons, thereby linking mitochondrial oxidative stress with AD onset and progression (17). Moreover, disrupted Ca^{2+} homeostasis leads to the overaccumulation of Ca^{2+} in mitochondria, which further negatively affects mitochondrial redox homeostasis and ultimately stimulates the opening of the mPTP. This event jeopardizes transmembrane potential, induces the collapse of mitochondrial bioenergetics and results in the activation of the mitochondrial-driven apoptotic signaling. In fact, despite the mechanistic basis of mPTP opening associated with neurodegenerative diseases is still unclear, studies using mPTP inhibition highlight its potential role in the treatment of various neurodegenerative diseases (83).

As mentioned, the proposed efficacy of chronical forms of PE at antagonizing the harmful consequences of aging and the associated NDD seems to be related, at least partially, to the powerful effects in the boosting of antioxidant systems and the downregulation of the enhanced ROS generation characterizing these physiopathological conditions. PE seems to mitigate the levels of oxidative stress, and improve the deleterious consequences on mitochondrial biogenesis and OXPHOS activity commonly occurring in the different NDD (17,113,118). Despite mitochondrial-redox changes are accepted as crucial beneficial features of an exercise-related protective phenotype that are able to mitigate the development and symptoms of NDD (Fig. 5), further studies are needed to explore the underlying mechanisms. Nevertheless, the mechanisms related to exercise-induced improvements in mitochondrial and tissue antioxidant capacity do not seem to be exclusive of the brain. As demonstrated in several other tissues, ROS generated during acute bouts of PE seem to be important regulatory or signaling pathways mediators of the adaptive responses (149,151,152). In fact, ROS-mediated regulation can modulate not only antioxidant expression (25), but also uncoupling proteins (UCPs) (6) and heat shock proteins (HSPs) (26) that are known to be

associated with a favorable phenotype against pathological conditions of enhanced oxidative stress. This joint upregulation mediated by feedback mechanisms prevent the extent of oxidative stress and apoptosis, ultimately leading to neuroprotection.

It is important to underline that exercise could display different kinds of stressful stimuli and respective adaptations, depending on the frequency (acute vs. chronic), intensity and duration of practice. Regarding frequency, regular exercise is classically associated with several health benefits, as the exposure to a set of stress bouts increases cellular resistance against ROS and upregulates the expression and/or activity of several proteins involved in the antioxidant machinery (50,51). On the other hand, the effect of an acute single exercise bout in different organs has been earlier shown to induce ROS overproduction, especially when performed at high-intensity levels, being antioxidant alterations controversial (50,51). The gap between neurochemical changes and behavioral improvements following acute exercise was recently highlighted by Basso and Suzuki (2017), namely due to the lack of studies that correlate mitochondrial signaling pathways and cognitive function in rodents.

In contrast to the acute severe single exercise bouts, the ability of the regular exercise to induce more resistant phenotypes against harmful stress conditions, such as age-related NDD have been widely accepted (118). Among distinct neuronal sources of ROS production, mitochondria have been considered as one of the most relevant (7), being also important potential target substructures for exercise-induced adaptation in the context of aging and NDD. As referred, studies have shown that chronic PE in the form of endurance training and also voluntary physical activity, offer neuroprotection through the modulation of pathways involved in redox regulation, mitochondrial bioenergetics, biogenesis, dynamics, quality control and apoptotic signaling (150). This PE cross-tolerance effect has been demonstrated in studies performed in AD and PD models (17,139). Several studies argue that regular PE programs implemented in AD animal models promote the improvement of brain antioxidant capacity, being some controversial results attributed to different used protocol variables, such as exercise intensity, volume, duration, animal age and sex (see 17 for refs). However, regarding the potential impact of intensity on brain redox balance, Ogonovszky and coworkers (136)

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demonstrated that even severe training programs or overtraining neither increased DNA damage in the brain nor altered the activity of 8-oxoguanine DNA glycosylase (OGG1), a key enzyme involved in 8-oxo-7,8-dihydroguanine repair.

In addition, recent data from our group (16) showed that long-term PE act both as a preventive and therapeutic tool against AD-induced cognitive and behavioral impairments in rodents. Data reveal that chronically exercised animals had positive alterations in *in vitro* mitochondrial oxygen consumption endpoints that might underline the observed neurobehavioral improvements. In fact, the exercise-reverted mitochondrial structural damage was associated with a beneficial impact on mitochondrial biogenesis, dynamics and mitophagy-related mechanisms that, at least in part, could explain exercise-induced neuro-molecular protection. Surprisingly, an early study from Gusdon and coworkers (63), report that PE training improved mitochondrial function in aged mice through the amelioration of mitochondrial respiratory chain function and quality control mechanisms, although without alterations in mitochondrial biogenesis or oxidative stress biomarkers.

Most studies focused on aerobic-endurance and/or long duration PE models for the prevention or treatment of NDD and revealed different behavioral, biochemical, and molecular effects. However, recent research has suggested that resistance (strength) exercise training can also importantly contribute to the prevention of NDD as well for maintaining, developing, and recovering brain activities through specific neurochemical adaptations. Pinho and coworkers (147) suggested an interplay between muscle and brain that contribute to cognition-redox regulation. The cellular mechanisms driven the regulation of brain oxi-reductive alterations by resistance exercise are so far not completely clear. Nevertheless, the proposed adaptive changes may be related to brain redox regulation involving different proteins and pathways, such as the mammalian target of rapamycin (mTOR) and cAMP-response element-binding protein (CREB) (100,158), both responsible for enhanced translation initiation from protein kinase B (Akt) phosphorylation, leading to both muscle and brain BDNF expression and activation. Increased BDNF levels lead to the activation of nuclear factor erythroid-2-related factor 2 (Nrf2), ultimately regulating the expression of several antioxidant molecules,

maintaining mitochondrial function, redox and protein homeostasis (147). Although not yet abundant, some studies reported brain alterations in some molecules with antioxidant potential after resistance training, namely increases in copper zinc superoxide dismutase (SOD-Cu/Zn) activity in hypothalamus of rats with type-2 diabetes (142) and in the reduced glutathione content and glutathione peroxidase activity in animals with experimental autoimmune encephalomyelitis, an established model of multiple sclerosis (168).

In addition to the role of each organelle *per se*, many cellular metabolic pathways heavily rely on the tuned coordination of distinct sub-cellular compartments of the cell with each other (34). Recently, it has been suggested that physical contact sites between mitochondria and lysosomes provide an evident platform for cross-organelle signaling. However, the endosomes also form contact sites with mitochondria, which are dependent on Rab5 and are induced upon conditions of enhanced mitochondrial oxidative stress (73). In fact, under these conditions, the endosomal system appears to rapidly respond to damaged mitochondria through a rescue pathway, resulting in the recruitment of Alsin, a protein that has been implicated in early onset of ALS, and Rab5 recruitment to mitochondria, with consequent inhibition of cytochrome c release, decrease in mitochondrial oxygen consumption and hence, increased overall cell viability. Regarding the role of mitochondrial-endosomal contact sites in NDD (34,73), recent data suggest that under oxidative stress and activation by Alsin, the small GTPase Rab5 translocates from early endosomes to mitochondria. This way, it seems that early endosomes cooperate with mitochondria, via Rab5, as a cytoprotective mechanism against oxidative stress in ALS and, eventually, in other NDD (73) and motor behavior abnormalities. Accordingly, a study conducted by Devon and coworkers (35) showed that Alsin-null mice revealed a marked decrease of Rab5-dependent endosome fusion activity as well as a significant disturbance in endosomal transport of IGF1 and BDNF receptors that may underlie the motor behavioral abnormalities observed in the context of ALS. Considering the mechanistic benefits of PE in mitigating the development and progression of NDD, it is tempting to speculate that the referred mitochondrial-lysosome cross-talk might possibly be considered a further interesting mechanism to explore. In fact, whether or not PE interferes with early endosomes-

mitochondrial functioning, for instance in the recruitment of Rab5 to mitochondria mediated by Alsin with consequent downregulation of apoptotic signaling via mitochondrial-dependent ROS modulation is so far unknown. Future studies using other differentiated approaches will provide deeper insights into the role of PE on mitochondria–lysosome and endosomal crosstalk on NDD pathogenesis and progression.

Also determinant to preserve tissue and cellular viability, adaptation, plasticity and survival under physiological, but particularly under stress conditions such as those characterizing NDD, are the mechanisms associated with cellular quality control. As mentioned, these involve the interplay of cellular substructures, including mitochondrial, lysosomes and endoplasmic reticulum networks, and signaling pathways related to apoptotic cell death, mitochondrial dynamics through biogenesis, fusion and fission, and auto(mito)phagy (Fig. 6). The interaction between mitochondrial dynamics and autophagy is also recognized as critical for mitochondrial homeostasis and redox balance. In fact, decreased mitochondrial potential or mutations in PTEN-induced kinase 1 (PINK1) may result in the accumulation of PINK1 in the outer mitochondrial membrane, allowing Parkin to bind to depolarized mitochondria inducing mitophagy (203). PINK1 mutations have been associated with PD by altering mitochondrial physiology, namely by inducing mitochondrial cristae fragmentation and also leading to increased oxidative stress (55). In accordance, recent studies from our group have shown in rodents that both endurance treadmill training and voluntary activity were able to mitigate the alterations in mitochondrial function, oxidative stress and damage, and in signaling protein markers associated with apoptosis, mitochondrial biogenesis, fusion, fission and auto(mito)phagy (Fig. 6) induced by doxorubicin in brain cortex and cerebellum (114). Importantly, this cross-tolerance effect of exercise seen on both mitochondrial function, molecular markers of oxidative stress and damage as well as on signaling proteins associated with mitochondrial plasticity and quality control was also evident in the plethora of behavioral performance endpoints tested.

In summary, a considerable amount of research suggests a close link between cellular and mitochondrial redox alterations and the more resistant phenotypes of exercised subjects

against the deleterious effects related to NDD. This boosting effect, observed both at preventing and in treating neuropathological conditions, is particularly evident when preferentially aerobic-based metabolic stimulus is provided, such as those characterizing endurance training or voluntary physical activity. Further studies are needed in order to clarify both the efficacy and the related mechanisms associated with the plausible positive effects (by preventing and treating) of a more contractile-based stimulus characterizing resistance (strength) training against the harmfulness of NDD.

Please insert Fig. 6 here

Acknowledgments

List of abbreviations

ACSM - American College of Sports Medicine

AD – Alzheimer's disease

AMPK - AMP-activated protein kinase

Akt - protein kinase B

ALS - Amyotrophic lateral sclerosis

APP/PS1 - Aβ precursor protein-presenilin 1

Aβ – Amyloid-β

BDNF - Brain-derived neurotrophic factor

CREB - cAMP-response element-binding protein

FNDC5 – Fibronectin type III domain – containing protein 5

HD - Huntington's disease

HSPs – Heat shock proteins

IDO – Indoleamine 2,3dioxygenase

IGF – Insulin growth factor

IL-6 – Interleukin 6

KATs – Kynurenine aminotransferases

KYN - Kynurenine

KINA - Kynurenic acid

LTD - Long-term depression

LTP - Long-term potentiation

MDA - Malondialdehyde

Met – Methionine

Mfn1 – Mitofusin 1

mPTP - mitochondrial permeability transition pore

MiRNA – MicroRNA

mTOR – mammalian target of rapamycin

NDD - Neurodegenerative diseases

Nrf2 - Nuclear factor erythroid-2-related factor 2

NMDAR - N-methyl-D-aspartate receptor

OGG1 – 8-oxoguanineDNA glycosylase

PD – Parkinson's disease

PGC1α - Peroxisome proliferator-activated receptor-γ coactivator 1α

PINK1 - PTEN-induced kinase 1

Pro-CTSB - Cathepsin B precursor

p75 NTR - p75 neurotrophin receptor

OXPHOS - Oxidative phosphorylation

QUINA - Quinolinic acid

ROS – Reactive oxygen species

SOD-Cu/ZN - copper zinc superoxide dismutase

TBARS - Thiobarbituric acid reactive substances

TFAM - Mitochondrial transcription factor A

TNF-α - Tumor necrosis factor-α

TrkB - Tyrosine receptor kinase B

UCPs - Uncoupling proteins

Val - Valine

VEGF - Vascular endothelial growth factor

3HK - 3-hydroxykynurenine

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Figure legends:

Figure 1. The preventive and therapeutic effect of exercise on neurodegenerative diseases. Exercise reduces peripheral risk factors for cognitive decline and mediates metabolic, structural and functional alterations on brain cells that can delay the cognitive decline induced by neurodegenerative diseases. *To see this illustration in color, the reader is referred to the online version of this article at www.liebertpub.com/ars.*

Figure 2. Exercise modulates BDNF pathway. BDNF gene expression can be controlled by several different mechanisms. Those include, genetic differences (as Val66Met and other polymorphisms), physical exercise and neurodegenerative diseases. Although not consensual, a reduction in BDNF levels gene expression are reported in neurodegenerative conditions. In contrast, exercise is a non-pharmacological intervention able to increase neuronal BDNF gene expression. Moreover, exercise is also able to influence BDNF processing and thus the levels of pro and mBDNF. ProBDNF and mBDNF exert opposite effects by binding to different receptors. Binding of mBDNF to TrkB receptor in either paracrine or autocrine signaling elicits neuronal survival, growth, LTP and gene modulation and *de novo* expression of BDNF. Alternatively, binding of proBDNF to p75NTR affects neuronal function and leads to LTD and apoptotic cell death. LTD Long-term depression; LTP long-term potentiation; mBDNF mature brain-derived neurotrophic factor; proBDNF brain-derived neurotrophic factor precursor; TrkB tyrosine kinase receptors; p75 NTR p75 neurotrophin receptor. *To see this illustration in color, the reader is referred to the online version of this article at www.liebertpub.com/ars.*

Figure 3. Exercise-dependent factors that stimulates BDNF gene expression. Among other myokines, physical exercise activates cellular pathways that increased biosynthesis and release into the blood of cathepsin B and irisin from the muscles. These muscle-derived factors cross the blood brain barrier and signal on receptors located on glial or neuronal cells, thereby

triggering the expression BDNF, and other growth factors, promotors of brain plasticity. *To see this illustration in color, the reader is referred to the online version of this article at www.liebertpub.com/ars.*

Figure 4. The role of exercise-induced IL6 and KYNA levels against neurodegenerative diseases. **A**, Exercise induces skeletal muscle transient release of IL6 and promotes the biosynthesis of KATs, which converts liver-derived KYN to KYNA. **B**, In neurodegenerative diseases, increased IL6 has been associated with impaired neuroplasticity and cognitive functions, at least in part, by inflammatory pathways in the brain that influence the phosphorylation of the BDNF receptor and interfere with BDNF signaling. However, exercise acutely elevates IL6 levels that can cross the blood brain barrier and are associated with a neuroprotector phenotype. **C**, In neurodegenerative diseases toxic compounds from KYN pathway are associated with increased oxidative stress, inflammation and impaired cognitive functions. Instead, exercise increased peripheral KYNA levels are associated with adipose tissue energy expenditure and anti-inflammatory phenotype and do not cross blood brain barrier, preventing KYN neurotoxic accumulation into the brain. BDNF, Brain derived neurotrophic factor; IL6, Interleukin 6; KATs, kynurenine aminotransferases; KYN, kynurenine; KYNA, kynurenic acid; QUINA, quinolinic acid; 3HK, 3-hydroxykynurenine. *To see this illustration in color, the reader is referred to the online version of this article at www.liebertpub.com/ars.*

Figure 5. Oxidative stress modulation by exercise and neurodegenerative diseases**.** Scheme summarizing the described alterations associated with increased oxidative stress in neurodegenerative diseases (red) and the adaptations induced by chronic physical exercise that can counteract neurodegenerative conditions (green). TCA, tricarboxylic acid cycle; mPTP, mitochondrial permeability transition pore. *To see this illustration in color, the reader is referred to the online version of this article at www.liebertpub.com/ars.*

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Figure 6. Mitochondrial impairment in neurodegenerative disease and exercise-induced brain mitochondrial improvement. Neurodegenerative diseases are associated with the impairment of mitochondrial bioenergetics, increased oxidative stress and apoptotic signaling, which may be associated with the deterioration of cognitive function. Additionally, these processes may be associated with possible mitochondrial network fragmentation and activation of auto(mito)phagy signaling. The biological mechanisms underlying exercise-induced neuroprotection involves the improvement of mitochondrial function. In fact, exercise seems to increase resistance to oxidative stress and decrease apoptotic signaling and increase mitochondrial biogenesis. It is possible that exercise modulate some of the metabolic sensors that may contribute to increase the quality control and the plasticity of the cerebral mitochondrial network. Thus, exercise can promote selective fusion of mitochondria and the segregation of damaged mitochondria signaled for mitophagy. This dynamic modulation could have potentially important implications for the brain cells and cognitive functions. *To see this illustration in color, the reader is referred to the online version of this article at www.liebertpub.com/ars.*

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