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Physical Exercise and Neuroinflammation in Major Depressive Disorder

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Abstract

Major depressive disorder (MDD) is a prevalent psychiatric disorder associated with varied prognosis, chronic course, and duration of illness with reduced quality of life. One factor that significantly contributes to the relevant disease burden of MDD is the heterogeneous treatment response patients experience with current treatment options. A variety of experimental protocols in humans and animals have highlighted that inflammation and neuroinflammation are relevant biological factors that interact with external stimuli and neurophysiological mechanisms, and can trigger MDD. It is well established that exercise is efficacious in treating mild to moderate depression with response rates comparable to mainstream therapies such as antidepressant medication and cognitive behavioral therapy. Several studies have shown that physical exercise is beneficial for a range of chronic diseases. Indeed, physical exercise can promote molecular changes that swerve a chronic pro-inflammatory state to an anti-inflammatory state in both periphery and central nervous system. The changes caused by physical exercise include an increase in PGC1α gene expression, a transcriptional co-activator involved in reducing the synthesis and releasing of pro-inflammatory cytokines, and an increase in anti-inflammatory cytokines. PGC1α changes the metabolism of kynurenine towards, and, in turn, it reduces glutamatergic neurotoxicity. Moreover, some studies have shown that physical exercise promotes alterations in the circuitry of monoaminergic neurotransmission, at least in some aspects, through the effects on the release of proinflammatory cytokines. This review will highlight the effects of physical exercise as therapy and its relation with the biological mechanisms involved in the pathophysiology of MDD, with particular emphasis in the interactions among physical exercise, hypothalamic-pituitary-adrenal (HPA) axis, neuroinflammation, and with the neurotransmitters underlying the main brain circuits involved in the MDD.

Keywords Exercise · Neuroinflammation · Neuroprotection · Major depressive disorder

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Introduction

Major depressive disorder (MDD) is a prevalent psychiatric disorder associated with varied prognosis, chronic course, and duration of illness with reduced quality of life and increased suicide risk [1, 2]. In addition to potential suicidal risk, MDD leads to functional impairment, which causes a burden to patients, their families, and society [1, 3]. Moreover, MDD affects more than 300 million people worldwide, and it is a leading cause of disability among people [3].

The search for biomarkers is impaired by the heterogeneity of MDD [4] and the limitation of its current diagnostic categories such as self-reports, measurement-based scales, with a lack of understanding of the molecular blood testing compared to other diseases [5]. In clinical practice, efforts are made to understand the illness characteristics [6], duration of illness [7], family history of mood disorders [8], depression symptoms and its subtypes [9], comorbid psychiatric disorders [9], and others.

Neuroimaging studies have shown that MDD is associated with cerebral volume alterations and functional changes in brain networks related to emotional processing and cognition [10]. Patients with MDD often have cognitive dysfunction in domains like attention, executive functions, memory, or psychomotor speed [11], which has been classically considered to be secondary to affective symptoms. Nowadays, however, this traditional view is changing since cognitive dysfunction has proved to be a central and lasting feature of MDD [12].

One factor that contributes in a relevant way to the significant burden of MDD is the heterogeneity in the responses to the available treatment options [13]. Initial response rates to treatment with selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) are approximately 50%, with remission rates for SSRI and SNRI treatment ranging from 30 to 35% [14]. Moreover, patients with remitted depression show residual cognitive dysfunction [15], leading to impairment in psychosocial functioning [15, 16]. Considering that one of the main targets in the treatment of MDD is achieving a functional recovery besides symptomatic recovery [8, 15], there is an urgent need to develop novel alternative strategies for the treatment of MDD. Thus, compared with these expensive treatments, physical exercise can play a critical role in improving the brain functions on multiple levels [17].

Exercise as an add-on to conventional antidepressant therapies is a promising treatment strategy for MDD [18]. It is well established that exercise is efficacious in treating mild to moderate depression with response rates comparable to mainstream therapies such as antidepressant medication and cognitive behavioral therapy [19–22]. Among several mechanisms possibly underlying the beneficial effects of physical exercise, recent research points to an interaction between physical exercise, reduction of peripheral inflammation and neuroinflammation, and better performance in limbic cerebral circuits related to reward and MDD [23]. However, there is still a lack of understanding of the neurobiological mechanisms that underlie or mediate the antidepressant effects of exercise. Also, neurobiological effects and hippocampal neurogenesis seem to occur differently according to the type of physical training, that is, if the training is aerobic (AT) or resistance (RT) [24]. Therefore, this review will highlight the effects of physical exercise as therapy and its relation with the biological mechanisms involved in the pathophysiology of MDD, with special emphasis on the interactions between physical exercise, neuroinflammation, and the neurotransmitters underlying the main brain circuits involved in MDD.

Depression, Inflammation, and Neuroinflammation

Clinical and translational studies indicate that stress and depression are associated with increased immune system activity, increased leukocyte function, and the release of pro-inflammatory cytokines [25]. Cytokines also interact with pathways associated with MDD, including neurotransmitter metabolism, neuroendocrine functions, and neural plasticity [26]. Patients with depression have high levels of pro-inflammatory mediators such as interleukins (IL) (IL-1, IL-2, and IL-6) and tumor necrosis factor-α (TNF-α) [27]. Studies with animal models have also shown that depressive-like behaviors are associated with increased inflammatory markers peripherally and in brain regions involved with MDD [28, 29]. Even more relevant are some observations that increased pro-inflammatory immune mediators appear to be more related to the vulnerability of individuals to stress [28] and poor response to classical pharmacological treatments [30]. Also, long-term social stressors are more associated with increased chronic inflammatory processes and depression [31].

A significant association of cytokine function with the mechanisms related to mood and the onset of MDD can be attributed to the fact that cytokines can reduce the levels of serotonin and cause changes in other mechanisms of neurotransmission and neuronal signaling in brain regions involved with MDD [32]. It is also essential to consider that cellular-mediated immune activation is involved with a reduction in serotonin levels from tryptophan as well as glucocorticoid resistance in immune cells, culminating in symptoms of depression [33]. Similar to MDD, pro-inflammatory cytokines alter the functional status of the serotonergic pathways originating from *raphe nuclei*, which are directed to the limbic and cortical system [23].

Inflammation and HPA Axis: Functions in the Stress and Depression

Among the critical physiological processes that occur with immune activation, hormonal changes related to stress and depression may be included [34]. The hypothalamic-pituitary-adrenal (HPA) axis is a crucial component involved in the vast physiological network activated by stress [35, 36]. The relationship between the immune system and the HPA axis appears to be more complex. In addition to involving a mutual relationship, other systemic mechanisms are involved, such as the function of the autonomic nervous system and the variation in tissue response to glucocorticoids. The subchronic release of glucocorticoids during a period of stress promotes an immunosuppressive effect, in the sense of restoring immune function to basal levels and, thus, preventing an inflammatory overshoot [37, 38]. However, with prolonged stress, high glucocorticoid levels extrapolate the allostatic load, altering certain aspects of the regulation of immune function. Thus, chronic stress shifts the balance from healthy function to unhealthy function. In these situations, the immune system becomes inefficient to act in pathological situations like infections and cancer, for example [39]. The fact that individuals have increased inflammation and pro-inflammatory markers

after prolonged stress has directed research to evidence that some individuals develop resistance to glucocorticoids and thus, the immune system becomes nonresponsive to the suppressive function of the HPA axis, culminating in chronic inflammation. Chronic psychosocial stress appears to involve relative resistance to glucocorticoids and increased circulating inflammatory markers, even when significant variations in HPA axis activity do not occur [40]. In turn, inflammatory cytokines stimulate the HPA axis, increasing the release of glucocorticoids. Importantly, dysregulation of the immune system and persistent inflammation are inherent characteristics of recurrent MDD. The conditions associated with chronic inflammation inhibit the negative feedback from the HPA axis, increase the permeability of the blood-brain barrier, impairing the function of neurotransmitters, thus culminating in the relapse of depression [41, 42]. Studies have shown that IL-1 stimulates the release of corticotrophin-releasing factor (CRF) through the hypothalamus and ACTH through anterior pituitary [43]. The cytokines TNF-α, IL-1, and IL-6, when released into the systemic circulation, stimulate the HPA axis individually or synergistically between them [44]. It is also important to note that in addition to increasing HPA axis activity in response to chronic stress, some pro-inflammatory cytokines appear to activate transcription factors and, consequently, potentiate HPA activity [45].

An important factor to consider is that two subtypes of MDD characterized according to the degree of inflammation and the level of activation of the HPA axis are present in the population. Although some researches have failed to detect well-established differences between the degree of inflammation and the level of HPA axis activity, other studies have observed functional parameters that make it possible to characterize the two MDD subtypes [46]. The melancholic depression has a positive correlation with the activation of the HPA axis, whereas the atypical depression is related to an increase in the degree of inflammation in co-occurrence with functional aspects inherent in the metabolic disturbances [46].

At another angle, it is essential to consider that glucocorticoid resistance and activation of the HPA axis from inflammatory markers seem to lead to a pathophysiological situation in which both HPA axis hyperactivation and increased pro-inflammatory components coexist [40]. Therefore, a third condition seems to be part of the protagonism of the HPA-inflammation pathway and contributes to the recurrence of depression (Fig. 1) [42]. Regarding the theory of resistance to glucocorticoids, it is important to mention researches, which observed increased levels of cortisol and inflammation in TRD patients. In these studies, the authors noted that the same TRD patients showed resistance to glucocorticoids [47, 48].

It should also be mentioned that an increase of glucocorticoids in the prenatal stage can cause alterations in mitochondrial function, with consequent oxidative stress [49]. Also,

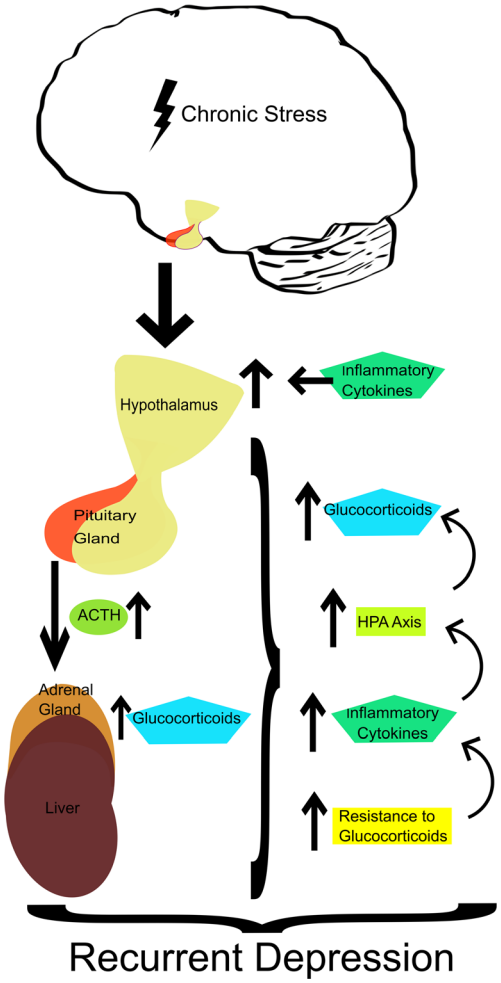

Fig. 1 Resistance to glucocorticoids, inflammation and HPA axis—recurrent depression. The hypothalamic-pituitary-adrenal axis is a key component of the physiological network triggered by chronic stress. Prolonged stress seems to culminate in glucocorticoid resistance in some individuals. Glucocorticoid resistance leads to the coexistence of HPA axis hyperactivity and increased inflammation. This situation underlies the severity and recurrence of depression

rodents subjected to maternal deprivation stress in the first days of life present dysregulation, with a chronic increase in circulating glucocorticoid levels and reduction of the negative feedback process, when submitted to psychosocial stress throughout life. Both animals submitted to maternal deprivation and those receiving exogenous glucocorticoids may exhibit depressive-like behaviors in adult life and impairment in HPA axis regulation [50].

HPA Axis, Microglial Activation, and Inflammation: Functions in the Stress and Depression

Increased release of glucocorticoids during stress induces microglial activation and neuroinflammation [32]. Not disregarding the range of effects exerted by glucocorticoids released from chronic stress, several studies have shown that

the dysregulation of astrocytic function constitutes an important phenomenon inherent to the mechanisms involved in MDD [33]. Chronic microglial and astrocytic activation induces an increase of reactive oxygen and nitrogen species, which may culminate in oxidative and nitrosative stress in the central nervous system [51]. It is also essential to consider that glucocorticoids increase the levels of reactive oxygen species while increasing the toxicity of oxidative stress, which may result in brain damage in regions sensitive to stress in early life [52].

Recent research has pointed out that the function of microglia is one of the critical mechanisms that may be involved with the pathophysiology of MDD [53]. Durable microglial changes may occur from chronic stress and may underlie mood disorders, among other psychiatric disorders and neurodegenerative diseases [54]. Among the several alterations of the activated microglia, which allow the adaptation to act with the most varied pathological conditions, have included the synthesis and release of cytokines and other inflammatory mediators [55]. A postmortem study evidenced the presence of activated microglia in the hippocampus of individuals with mood disorders [56]. Other authors have observed an increase in microglial activation signaling molecules in the PFC, insula, and cingulate cortex in an in vivo study in patients with MDD and a positive correlation with the severity of depression [57]. Among the mediators and mechanisms of microglial activation are cytokines, various inflammatory mediators, such as reactive oxygen species, nitric oxide, neurotransmitters, and hormones released during chronic stress. Microglial proliferation and activation, in turn, increase the release of various cytokines, kynurenine metabolites, and glutamate, while reducing the release of neurotrophic factors, monoaminergic transmission, and hippocampal neurogenesis, which are relevant mechanisms involved in MDD [54]. Increased expression of pro-inflammatory cytokines may increase the activity of the indoleamine 2,3 dioxygenase (IDO) enzyme, responsible for the degradation of tryptophan, a serotonin precursor. In turn, the IDO activates pro-inflammatory genes may potentiate neuroinflammation [58]. It is also essential to consider that stress in early life, a social factor relevantly involved in the onset and severity of depression throughout life [50], seems to modify the genetic scheduling related to inflammatory markers during childhood development, being one of the pathways that goes modifying the neurophysiological and behavioral phenotype, culminating in MDD [59].

Physical Exercise and Health

The regular physical exercise culminates in a variety of health benefits, such as improvement in cardiovascular and respiratory functions, reduced risk factors for coronary heart disease, and reduced morbidity and mortality. Besides, systematized and regular physical activity provides more independent lifestyle in older people, increased sense of well-being, reduced risk of falls, preservation, or reduction of functional limitations in adults and older, effective therapy for many diseases, and reduction of anxiety and MDD [60, 61]. The literature points out that physical activity can positively affect endothelial function and therefore can be considered a relevant factor in the prevention and management of cardiovascular diseases [62].

In a study of women with type II diabetes mellitus, the authors observed that the combination of aerobic and resistance exercises was more effective in insulin resistance therapy [63]. In a study of older adults diagnosed with diabetes in comorbidity with depressive symptoms and cognitive impairment, it was verified a correlation of diabetes and comorbidities with less routine physical exercises [64].

In patients with Alzheimer's disease, moderate aerobic exercise improved cardiorespiratory fitness, associated with functional capacity and memory performance benefits [65]. A cohort study showed that large amounts of aerobic exercise resulted in cardiorespiratory fitness and it was associated with the highest survival, and the benefits were more significant in older people and hypertensive individuals [66]. Another study found that midlife cardiorespiratory fitness resulted in reduced risk for depression and death from cardiovascular disease after later-life depression [67].

Exercise as Therapy for MDD

Studies have observed that physical exercise can bring benefits as adjunctive and individual therapy in the treatment of MDD [68–71] or be a strategy for the prevention of MDD [72], acting on several biological mechanisms and culminating in positive effects on synaptic plasticity and neurogenesis [17, 73]. In a study of patients with mild to moderately severe depression, the authors observed that physical exercise induced therapeutic response comparable to treatment with a classic antidepressant drug [21]. Studies analyzing moderate aerobic exercise for 8 weeks showed cognitive improvements and reduction of depression rates in MDD patients [74]. Recent research found that depression was positively related to physical inactivity in individuals with fibromyalgia [75]. Also, MDD patients are less engaged in physical activities [76], exhibiting less cardiorespiratory fitness, increased risk of metabolic diseases, and premature mortality [77]. There are evidence and discussion in the scientific literature about different therapeutic effects, comparing AT and RT [24]. However, although more studies have demonstrated the beneficial effects of AT [69], recent studies have noted that RT also provides antidepressant effects [78]. Despite the evidence that AT and RT can influence different biological mechanisms, both seem to exert positive effects on

some biological mechanism involved in mood disorder and cognitive processes [24].

At another angle, it is essential to note that a large amount of acute exercise translates into a stressful event, and the intensity of acute exercise directs the magnitude of stress [79]. Another relevant factor to consider is that the reactivity of healthy populations is quite variable concerning the same relative intensity of acute exercise, suggesting differences between the individuals. However, it appears that improvement in physical fitness generally reduces psychophysiological reactivity to psychosocial stressors, culminating in a physical and mental benefit [80, 81]. Even after a long period of inactivity, an aerobic fitness protocol seems to bring benefits, conferring better function of the HPA axis and the sympathetic nervous system, reducing activity in both physical and psychosocial stress situations [38].

Exercise, Neurotransmitters, and Signaling Pathways

The exact neurobiological phenomena involved in the therapeutic response to physical exercises have not yet been elucidated. However, some neurotransmitters, growth, and transcription factors, and intracellular signaling pathways are the targets of evidence in some studies [75]. Physical exercise prevented cognitive and motor impairments associated with monoaminergic depletion from the administration of reserpine in rats [82]. Recent studies have shown that physical exercise promotes increased serum levels of brain-derived neurotrophic factor (BDNF) in MDD patients [72]. BDNF levels were associated with reduced hypersomnia in MDD patients undergoing an AT-protocol for 12 weeks [83]. Researchers have shown that serum BDNF levels increased significantly after acute exercise in women with MDD. However, acute levels of BDNF have not been correlated with improvements in mood, suggesting that the therapeutic function of BDNF from exercise may be related to its release during chronic exercise [84]. Protocols with voluntary running wheel exercises restored the long-term potentiation (LTP) in strains of stress-sensitive rats and submitted to a schedule of chronic social isolation. Exercise also reversed the hippocampal reduction of glial glutamate transporter (GLT-1) and GluA2 AMPA-receptor subunit from social isolation. The results of these studies suggest that physical exercise exerted a protective role on the damaging effects of social isolation on hippocampal LTP [85].

The monoamines, serotonin, noradrenaline, and dopamine appear to be the three primary neurotransmitters known to be modulated by physical exercise [86]. Researchers have shown that sufficient levels of serotonin are required for the activation of hippocampal neurogenesis after voluntary exercise in mice. The authors argue that neurogenesis mediated at least in part by serotonin may be an essential mechanism in the suggested therapeutic effect of physical activity on depression [87]. Researchers also noted that the bioavailability of serotonin and noradrenaline in the synaptic cleft seems to be a crucial requirement for the effect of physical exercise on the wheel running in reducing depressive-like behaviors in mice [88]. From another perspective, researchers have found that sensitized serotonergic activity in the dorsal striatum appears to be an uncontrollable stress-driven mechanism, to be involved in some underlying behavioral impairments in depression and can be reduced by exercise through the wheel running [11]. As reviewed by Nicastro and Greenwood, physical exercise acts on several structural and functional molecular mechanisms involving the serotonergic neurotransmission system and interfering with the adverse changes from stress [89].

Studies have shown that the wheel running reduces the increase in firing rate of the noradrenergic neurons of the *locus coeruleus* (LC) after chronic stress. The reduced function of noradrenaline is suggested to be a relevant factor in the circuit between LC and dorsal raphe nucleus (DRN), contributing to attenuate the hyperactivation of serotoninergic neurons from stress [90]. The reduction in the rate of noradrenergic triggers after wheel running is suggested to be related to an anxiolytic effect from physical exercise and appears to be stress dependent and auto-inhibitory signaling mediated by specific receptors of peptide galanin, which is co-released from noradrenergic neurons of the LC [91]. From another angle, physical exercise increases the release of noradrenaline in the hippocampus [92]. The release and function of noradrenaline in the hippocampus appears to be at least partially involved in the expression and function of BDNF on neurogenesis and the cognitive functions elicited by physical exercise [89].

Considering the role of physical exercise on dopaminergic neurotransmission, some researchers verified that prolonged well-running potentiated dopaminergic activity in the dorsal striatum of rats submitted to uncontrollable acute stress [11]. A hyperdopaminergic brain state appears to emerge from physical exercise, involving a variety of mechanisms and possibly triggering a range of structural and functional changes that confer the benefits of physical exercise on rewarding and mood behaviors [93].

Markers associated with neurotransmission and neuroplasticity, such as synapsin 1 and synaptophysin increased in the rat hippocampus, after RT and AT, in parallel to an improvement in hippocampal-dependent spatial learning [94]. However, AT preferentially increased the levels of BDNF and calcium/calmodulin-dependent kinase II (CaMKII), whereas RT preferentially increased the phosphorylated-insulin-like growth factor 1 (p-IGF-1) and Akt (Protein Kinase B) in the hippocampus of the animals. These findings indicate that both types of physical activity may exert beneficial effects on hippocampal function, although they have differential preferences for molecular mechanisms [94]. On the other hand, it is important to note that different RT protocols may translate into differences in

hippocampal neuronal plasticity [95]. According to Nokia et al. [96], increased hippocampal neurogenesis appears to occur after AT, but not after RT. However, in the experimental protocol conducted by Novaes Gomes et al. [97], RT, besides increasing adult hippocampal neurogenesis, also increased the expression of the anti-apoptotic protein Bcl-2. Thus, more studies considering different protocols already investigated are essential, in the sense of observing neuronal mechanisms that emerge from the different protocols, as well as the phenotypic behavioral expression.

Depression, Exercise, and Inflammation

Although the biological mechanisms underlying the therapeutic effects of physical exercise are still enigmatic for science, many studies indicate that pro-inflammatory processes are reduced [98]. Several studies point out that chronically increased concentration of systemic cytokines such as IL-1β, TNF-α, IL-6, IL-8, and IL-10 are related to various chronic diseases and MDD [99–101]. Some researchers argue that transient fluctuations occurring in cytokine levels in both muscles and circulation during and after exercise are probably relevant factors inherent in the benefits of physical exercise for health [98]. A reduction in baseline IL-1β blood levels from moderate intensity exercise was predictive of reduced insomnia in MDD patients [83]. Another study with college students found that moderate-intensity exercise was more incisive in reducing symptoms of stress and depression, while at the same time reducing blood levels of TNF-α [102].

Recent studies have observed that physical exercise in the young phase of life reduced depressive-like behaviors, improved hippocampal mitochondrial function and oxidative balance, and reduced glucocorticoid levels in the circulation of animals exposed to synthetic glucocorticoids in the prenatal stage [50]. These data suggest that physical exercise is in some way involved in mechanisms of regulation of the HPA axis, implying in the reorganization of the physiological activities inherent to the restoration of the oxidative balance and the reduction of inflammatory processes. Chronic physical exercise, mainly moderate aerobic exercise has an antioxidant function, and it seems that this action performed by physical exercise is inherent to its benefit against cardiovascular diseases, among other diseases and disorders [103].

It is noteworthy that levels of some pro-inflammatory cytokines appear to be higher in patients with treatment-resistant depression (TRD) and that an increase of the circulating basal TNF-α levels was positively correlated with the antidepressant effect from a 12-week aerobic exercise protocol. Besides, the reduction of depressive symptoms in TRD patients was positively correlated with the reduction of IL-1β levels following the chronic exercise protocol [104]. These pieces of evidence suggest that TRD is linked to severe chronic inflammatory conditions and in comorbidity with chronic diseases, whose pathophysiological mechanisms suffer interference from physical exercise, culminating in an improvement in general health conditions. Indeed, researchers point out that increased inflammation is one of the critical elements of TRD and represents a common link between depression and poor overall health in these patients [105].

The benefits of physical exercise can be attributed to the anti-inflammatory effects, at least partially, from the reduction of visceral adiposity. These considerations are based on the fact that adipose tissue is a significant contributor to circulating levels of IL-6 and TNF-α [106].

Concerning IL-6, studies on the functions of physical exercise have been observing that the active muscle rapidly increases the release of this cytokine. From these findings, the authors have been suggesting that IL-6 is also a myokine and exerts beneficial effects on metabolic functions and against low-grade inflammation involved in various chronic diseases [107]. Although IL-6 is considered a pro-inflammatory cytokine, research also points out that IL-6 induces an increase in anti-inflammatory cytokines such as IL-10 and reduces the release of other pro-inflammatory cytokines, such as TNF-α [31, 108].

Exercise, PGC1α, and Inflammation: Function in the Depression

Some studies indicate that endurance training increases the release of transcriptional factors, which among other functions, increases PGC1α gene expression, one of the genes regulated by physical exercises, and that regulates the transcriptional co-activator of peroxisome-proliferator-activated receptor- γ (PPAR-γ) coactivator 1α, a potent activator of mitochondrial biogenesis and oxidative metabolism. Increased expression of the PGC1α gene can increase mitochondrial density and myofibrillar proteins of muscle fibers, where oxidative metabolism predominates [98, 109, 110]. PGC1α is also a highly conserved co-activator of transcription factors and is heavily involved in the preservation and protection against neuronal loss [111]. A noteworthy factor observed in various experimental protocols is that PGC1α gene expression appears to correlate positively with the reduction of inflammatory proteins, such as IL-6 and TNF-α [112]. Another critical factor that should synergistically be acting is the fact that PGC1α interferes in mechanisms that reduce oxidative stress [113, 114], considering that reactive oxygen species are known to induce the increase of inflammatory cytokines [115, 116]. An equally or more prominent phenomenon comes from research, which has observed that PGC1α promotes the conversion of peripheral kynurenine to kynurenic acid, a compound of the pathway, which, unlike kynurenine, does not cross the blood-brain barrier, thus preventing neuroinflammatory effects from the metabolism of kynurenine in the brain. The authors verified that PGC1α

prevented depressive-like behavior induced by chronic stress in mice by preventing the action of kynurenine in brain regions such as the hippocampus [117]. The pathway of tryptophan metabolism, spanning the formation of kynurenine and quinolinic acid, is a toxic pathway and is involved in a range of neurodegenerative diseases and psychiatric disorders, including MDD [101, 118]. The balance between the toxic metabolic pathway and the kynurenine pathway, which is shown to be neuroprotective seems to be a phenomenon to be considered in research that looks at mechanisms for therapeutic intervention in MDD. New protocols of research with animals and human patients have been highlighting the involvement of this pathway in neuroinflammation and other mechanisms underlying the depressive disorder [119–123]. The toxicity associated with the kynurenine pathway is primarily understood as the balance between the excitotoxicity exerted by quinolinic acid, an N-methyl-D-aspartate (NMDA) glutamatergic receptor agonist, and the neuroprotection exerted by kynurenic acid, a 27-nicotinic cholinergic and NMDA receptor antagonist [123]. Notwithstanding other forms of intervention on tryptophan metabolism, research observing the effects of endurance training deserves further study [122, 124].

Exercise, Inflammation, Neurotransmission, and Depression

An expressive range of research has shown that there is an interaction between a reduction of peripheral inflammation and neuroinflammation, better performance of neurotransmission and brain plasticity, associated with a reduction of depression after physical exercise [24]. Persistent low-grade inflammation interferes with the regulation and consequent function of neurotransmitters related to emotions, as well as induces hormonal changes similar to the variations that occur after stress [32].

Studies with animal models observed that the association of a complex diet, aiming the reduction of inflammation and oxidative stress, together with physical exercises, reduced the anhedonic behavior and induced an increase in mRNA levels for BDNF and hippocampal neurogenesis in mice submitted to chronic stress [125].

Voluntary wheel running reversed the increase in circulating corticosterone levels and the reduction of the hippocampal glucocorticoid receptor (GR) and BDNF mRNA, in parallel with a reduction in anhedonic behaviors and spatial cognitive performance impairment of rats undergoing chronic stress [126]. Running wheel increases cognitive performance in parallel to neuronal and astrocytic plasticity in brain regions involved with depression and cognition, such as the hippocampus and PFC [127].

By registering the serotonergic neurotransmission, extensive connection with several mechanisms associates physical activity with immune and inflammatory mechanisms in the restoration or improvement of serotonergic neurotransmission and, consequently, of the therapeutic function in MDD. Increased GABAergic inhibitory tonus caused by IL-1β in the dorsal *raphe nucleus* inhibits the firing of the serotonergic pathway to the limbic system [128]. Chronic increase of pro-inflammatory cytokines induces variations in serotonin transporter activity, modulating serotonin levels at neuronal termination [129]. The downregulation of IDO activity by varying the metabolism of kynurenine to the production of neuroprotective metabolites, such as kynurenic acid, in detriment of neurotoxic metabolic synthesis, such as quinolinic acid, is one of the important functions in the metabolism of tryptophan and serotonergic neurotransmission [130]. In addition to the deviation of metabolic activity, a reduction in the activity of IDO reduces the degradation of tryptophan, the precursor of the neurotransmitter serotonin [131]. Regarding this condition, it is essential to emphasize that physical activity increases the amount of free tryptophan peripherally, allowing an increase in the flow of tryptophan to the central nervous system [23].

About noradrenergic neurotransmission, researchers have shown that exercise reduces the levels of proinflammatory cytokines, improves the oxidative balance profile while reversing the imbalance between inhibitory and excitatory neurotransmission on noradrenergic hyperactivity in hypertensive animals from high salt intake [132]. The balance of noradrenergic neurotransmission is important, considering that the basal levels of noradrenaline seem to inhibit the release of proinflammatory cytokines from the microglia [133, 134].

In a model of immune challenge through lipopolysaccharide (LPS), chronic treadmill exerted a protective effect on the dopaminergic neuronal loss in the substantia nigra, induced by inflammation and microglial activation. The protective effect of exercise occurred through the activation of the BDNF-TrkB signaling pathway and not due to the modulation of inflammation and microglial activation [135]. Dopaminergic injury in the *nucleus accumbens* (NAc) induced by inflammation also appears to be a protective target by physical exercise [23]. It is important to note that the NAc is a critical region of the mesolimbic reward pathway [136]. Thus, the protective effect of physical exercise on the NAc or another region of the pathway may play an essential role in the treatment of MDD.

With the registration to the glutamatergic neurotransmission, the deregulation of the kynurenine balance, producing an increase in the release of quinolinic acid from an increase of inflammatory cytokines, is a neurotoxic pathway, given the increased activation of glutamatergic NMDA receptors [124]. The activation and apoptosis of astrocytes also occur from the increase of activation of NMDA receptors, which may predispose to harmful positive feedback, due to the loss of astrocytes and reduction in glutamatergic reuptake, in addition to damage in other mechanisms of astrocytic protection. In addition to astrocytic damage, immune-glutamatergic-

astrocytic dysregulation is involved in reduced expression of various trophic factors, culminating in neuronal loss and depression [137].

Final Considerations and Future Directions

Studies to date indicate that physical exercise may be a therapeutic strategy individual or adjunctive to other therapeutic forms used in MDD [69, 70].

Biological mechanisms triggered by physical exercise are diverse, involving interference in neural circuits in the limbic system and invoking changes in neurotransmission systems that are in some way related to depressive disorders. The pathways through which physical exercise can interact with limbic neuronal circuits are still poorly understood. However, remote and recent studies highlight that an interaction network involving HPA axis, oxidative balance, immune system, and inflammation seems to be the main actor involved in the communication of physical exercise with the nervous system and the consequent benefits of physical exercise as an antidepressant therapy, especially in individuals who present depression in comorbidity with inflammation or diseases with chronic inflammation, such as type 2 diabetes mellitus [23].

In addition to investigating the interaction of inflammatory cytokines, coupled with functional mechanisms inherent to neuronal signaling in regions and limbic brain circuits, it is essential to consider other biological markers that emerge from physical exercise, such as PGC1α, which underlies a range of biological changes that target the benefits of antidepressant therapy (Fig. 2). Among the biological mechanisms already evidenced from PGC1α is the balance of the kynurenine pathway. For example, PGC1α together with PPARα/δ increases kynurenine aminotransferase (KAT) enzyme expression thereby swerving the synthesis of quinolinic acid to kynurenic acid and thereby protecting the brain from the neurotoxic actions promoted by quinolinic acid [118]. Increased PGC1α gene expression in skeletal muscle promotes stress resilience in mice [117]. Moreover, PGC1α is related to the reduction of oxidative stress and inflammatory cytokines, these being biological mechanisms already highlighted because they are involved in neurotoxicity and MDD.

Therefore, protocols of physical exercises in humans with MDD, as well as experimental protocols of chronic stress and physical exercises in laboratory animals, to investigate the interrelationship between mediators that emerge from physical exercise, inflammation, and interaction with circuits cerebral, neurotransmitter systems, and neuronal and glial signaling

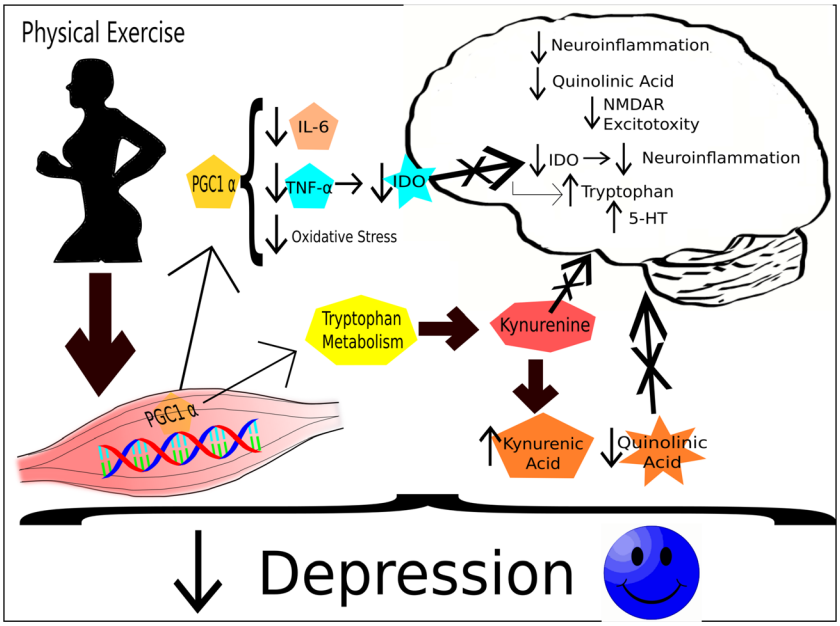

Fig. 2 Transcriptional and anti-inflammatory mechanisms of physical exercise in the antidepressant function. Physical exercise increases the expression of the transcriptional co-activator of peroxisome-proliferator-activated receptor- γ (PPAR-γ) coactivator 1α, (PGC1α). In addition to the effects on muscle energy metabolism, PGC1α is potentially involved in the protection of neuronal loss. Increased PGC1α expression is related to a reduction of oxidative stress and pro-inflammatory cytokines, such as IL-6 and TNF-α. PGC1α, together with PPARα/δ, promotes the synthesis of kynurenic acid by increasing the expression of kynurenine aminotransferase (KAT) enzyme. In this way, PGC1α reduces the production of quinolinic acid, an NMDA receptor agonist, and therefore reduces glutamatergic excitotoxicity. Kynurenic acid does not cross the blood-brain barrier. Thus, by diverting the metabolism of tryptophan and kynurenine, PGC1α reduces the deleterious effects of kynurenine in the brain. The reduction of proinflammatory cytokines also reduces the activity of the indoleamine 2,3 dioxygenase (IDO) enzyme and, therefore, the degradation of tryptophan, increasing its availability and consequently, the availability of the serotonin neurotransmitter. Since IDO activates pro-inflammatory genes, its reduction also culminates in reduced neuroinflammation

pathways, are incredibly relevant. These protocols can add light to therapeutic strategies and target study markers.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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