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Exercise Influences in Depressive Disorders: Symptoms, Biomarkers and Telomeres

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Editorial

The exact mechanisms concerning how exercise affects the brain, under conditions of health or disorder, are not fully understood and the literature lacks a sufficiency of well-designed studies concerning the effects of exercise training on depressive disorders. Nevertheless, the observed antidepressant actions of exercise are strong enough to warrant its application as a viable alternative to current medications in the treatment of depressive disorders [1]. The beneficial effects of exercise upon cognitive, executive function and working memory, emotional, self-esteem and depressed mood, motivational, anhedonia and psychomotor retardation, and somatic/physical, sleep disturbances and chronic aches and pains, categories of depression are discussed. The ameliorative effects of physical exercise upon several biomarkers associated with depressive states: hypothalamic-pituitary-adrenal (HPA) axis homeostasis, anti-neurodegenerative effects, monoamine metabolism regulation and neuro-immune functioning have been outlined [2]. The notion that physical exercise may function as "scaffolding" that buttresses available network circuits, anti-inflammatory defences and neuroreparative processes, e.g. brain-derived neurotrophic factor (BDNF), holds a certain appeal. In older adults, it has been observed that exercise was associated with significantly lower levels of depressive symptom severity [3]. An activity program based on "nordic walking", i.e. using staves, was shown to induce a positive effect on depressive symptoms and sleeping disorders in elderly patients, suggesting that Nordic walking based exercise programs should be developed for the elderly who suffer from depression or a sleeping disorder [4-5].

The notion of physical exercise as a "scaffolding" to buttress damage experienced under such conditions as traumatic brain damage and aging provokes the metaphor of transient measures, external to the buildings, that provides for construction, reconstruction and maintenance but not the buildings themselves. Scaffolding provides a normal process that continues across the lifespan involving that application and development of complementary, alternative neural circuits to achieve a particular cognitive goal (252); it is protective of cognition in the aging (or disabled) brain and is reinforced by physical exercise and cognitive engagement (which is harnessed during exercise. Under conditions of traumatic brain injury the notion of scaffolding suggests that exercise buttresses, more or less dependent on extent of injury, the surviving adaptive and neuroreparative processes [6-7]. Studies in transgenic mice and primary human skeletal myocyte studies have shown the critical influence of exercise-responsive transcriptional co-activator PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, which regulates the genes controlling energy metabolism), in coordinating intramuscular lipid-droplet-programming leading to mitochondrial remodeling. PGC-1α regulates also mitochondrial biogenesis and function. In this regard, translational studies that compared individuals who exercised physically with sedentary individuals have identified a dramatically strong association between the expression of intramuscular lipid droplet genes and enhanced insulin action in the exercising individuals [8]. In the context of depressive disorders, the notion of scaffolding suggests that exercise/activity mobilizes available and alternative neural and neuroimmune circuits that may initiate and/or consolidate neuroreparative and anti-inflammatory processes, such as BDNF.

Despite proper understanding of how exercise affects brain integrity and a paucity of well-designed, standardized studies on the exercise intervention on depressive disorders, the consensus of much of the existing remains in favour of the exercise antidepressant actions suggest it to be a major alternative to traditional medication [1], albeit in mild-to-moderate levels of disorder and with patient willingness [9]. The understanding of the mechanisms underlying the effects of exercise on depression constitutes an essential step in the direction of the broad use of exercise as an alternative treatment of depression in the field. In the present review paper, we have based our discussion in a model that highlights the effects of exercise on key depressive symptoms, and on key biomarkers of depression, rather than on depression as a global outcome. In this regard, stress, intense or chronic, and likely both, is a major agent [10] have proposed an hypothesis outlining a mechanism through which physical exercise, as opposed to sedentary living, promotes stress robustness in the face of intense uncontrollable stress. According to this notion, individuals with a sedentary existence respond to an intense acute uncontrollable stressor with excessive 5-HT and NA activity and/or prolonged down-regulation of the CX3CL1-CX3CR1 axis resulting in activation and proliferation of hippocampal microglia with consequent hippocampal-dependent memory deficits and reduced neurogenesis. Contrastingly, physically active individuals respond to the same stressor with constrained 5-HT and NA activity and a rapidly recovering CX3CL1-CX3CR1 axis responses resulting in the quieting of microglia, and protection from negative cognitive and neurobiological effects of stress. The CX3CL1-CX3CR1 expressing microglia fills an important role in limiting neuroinflammatory and neurodegenerative damage in brain cells. The merit of this more detailed approach, focusing on the various and specific effects of exercise on the different facets of symptom-profiles and biomarkers that buttress depressive conditions, concerns the provision for increased understanding of the general process and the perception of existing overall patterns through a more meticulous examination of the far-reaching processes involved.

Telomeres, regions of repetitive nucleotide sequences (TTAGGG)-DNA, protein-nucleotide complexes, at each end of a chromatid maintained and lengthened by telomerase, shorten with cell division leading eventually to cellular senescence and mortality [11].

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TTAGGG repeats are lost from telomeres as the cells proliferate, the so-called 'end-replication problem', linked to DNA damage response and apoptosis [12]. They may be viewed as biological clocks since short, or 'shortened', telomeres are linked not only with age-related diseases, disease-specific and all-cause mortality [13-15], despite the lack of any relationship between telomere length and subjective age that was observed also [16], but also psychiatric conditions such as schizophrenia [17-19]. Notwithstanding the lack of result [16], there is a consensus that telomere length shortens with each cell division and with increasing chronological age and short telomeres have been associated with a range of age-related diseases. In depressive/anxious patients also telomere length is generally reduced [20-21]. From a genetic perspective, [22] observed that that higher adherence to a Mediterranean diet was associated with longer lengths of leucocyte telomeres among Caucasians, but not among African Americans and Hispanics [23-24]. Furthermore, a diet high in vegetables but low in cereal, meat, and dairy might be associated with longer leucocyte length among healthy elderly adults. Despite certain negative findings [25], there exists plausible evidence that physical exercise preserves telomere length under varying conditions [26-28]. Nevertheless, the same authors [29] concluded that longer telomere length was associated with slower decline in grip strength in Chinese older persons. In a study of 20 young (22-27 years) and old (66-77 years) men that were either endurance-trained athletes or medium-level activity, Osthus obtained longer telomere length among the older endurance trained athletes than medium-level trained older men. This difference was not obtained for the young athletes/medium-level trained. They suggested that VO2max was associated positively with telomere length and concluded that the exercise regime provided a protective effect on muscle telomere length in older adults.

In older adults, the impact of psychosocial stress on telomere length may be different due to the lifetime exposure to competing causes of telomere length-shortening [30-32]. Nevertheless, [33] concurrently assessed telomere length and telomerase activity in individuals presenting clinically significant, chronic major depressive disorder and matched controls but failed to provide strong evidence of an association of major depressive disorder with shorter LTL, while telomerase activity was lower in men with major depressive disorder. Despite that result, [34], from a comprehensive meta-analysis, described the significant relationship between depression and shorter telomere length as consistent with the notion positing that psychological distress, such as experienced in depression, results in physiological changes leading to shortened telomere length. Resilience, defined as relative resistance to the adverse effects of risk experiences [6], has been developed to encompass the notion of multisystem resiliency, consisting of emotional regulation, social connections and healthy behaviors in major depression-telomere length associations [35-36]. In a study of patients presenting major depression, they found that the highest levels of multisystem resiliency were associated with the longest telomere lengths. In a sample of older, postmenopausal women, [37] showed that shorter telomere length was linked to high levels of stress and non-healthy behaviors. Moderate levels of physical activity/exercise also have proven beneficial for greater telomere length and telomerase activity [38-42].

A sedentary lifestyle opens the gate for depressiveness and associated conditions to enter: it was observed that persistent-severe levels of depression were increased significantly under conditions of low levels of high density lipoprotein (HDL), hypertriglyceridemia, and metabolic syndrome in men, and hypertriglyceridemia, metabolic syndrome in women, with smoking, alcohol consumption and lack of exercise conspicuous in both genders [43].

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