

Short Notes

Exercise for Neurodegeneration-Related Disorders

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Abstract

Neurodegenerative processes associated with ageing or retarded normal neurodevelopment compromise several domains of health, well-being and the functional capacity of individuals, particularly those of advanced age. Physical exercise has provided a plethora of improvements in functional capacity, neurocognitive ability, neuroaffective status and brain plasticity. Despite all these achievements, further effort requires to be invested in order to challenge one current conviction that there exist no effective treatments, or even a paucity, of intervention, e.g. exercise, available to retard or hinder or reverse the Neurodegeneration processes afflicting the diseased brain.

INTRODUCTION

The regular practice of physical exercise, whether engaged upon for the maintenance of accustomed health condition or acceded to under pressures of an unhealthy or diseased condition, invariably advances well-being and structural and functional integrity through: the advancement of functional and biomarker manifestations during ageing and cellular senescence, the amelioration of cognitive performance deficits by optimal augmentation of cerebral plasticity and the enrichment of individuals' proclivities for advantageous ontogenetic and epigenetic dispositions. The notion of 'organismal robustness', through which 'dormant', or otherwise, genetic predispositions will translate into disease in individuals with decreased organismal robustness [1], offers a growing, as yet underestimated, preventional/interventional aspect of decelerating ageing-related debilities and is bolstered by the concomitant aspect of 'organismal resilience'; regular exercise/activity has been shown to offer consistent benefit for maximizing organismal resilience against a broad range of extrinsic and intrinsic stressors, such as infections, injury/surgery, wound-healing, toxicants, genetic predispositions and frailty [2]. The benefits of exercise for specific neurodegeneration-related disorders are consistently documented: In Parkinson's disease patients exercise programs generally increase quality-of-life and fitness condition [3,4] and motor performance [5,6] but not always in restoring the loss of dopamine (DA) innervation [7]. Nevertheless Shi et al. [8], have demonstrated that physical exercise induced neuroprotective-restorative effects by reducing the degeneration of the nigrostriatal DA system and curtailing the abnormal neuronal spike firing in parkinsonian striatum.

Furthermore, exercise interventions in PD increased both trophic factors and functional capacity, e.g. brain-derived neurotrophic factor (BDNF), and neuroplasticity of DA neurons [9-12]. Under conditions of both normal ageing, Alzheimer's disease (AD) and other types of dementia, physical exercise improves physical health and capacity, quality-of-life, brain plasticity, increasing cognition and reducing the risk of cognitive decline and dementia in later life, as well as greater integrity at different levels of neuronal and brain regional organization [13-16]. The overall purpose of the present treatise is to outline several domains of physical exercise intervention may induce improvements in motor performance and daily activity capacity, neurocognitive functioning and biomarkers of functional and healthy ageing.

Lifestyle and non-invasive, e.g. exercise and dietary considerations, interventions are employed with increasing frequency and efficacy in the facilitation of healthy neurocognitive and biological aging [17-20], particularly since the avoidance of a sedentary existence bears with it essential ingredients for health promotion, necessarily brain health, and prevention of lifestyle-related diseases [21]. Exercise interventions have been shown to be neurorestorative: In MPTP-treated mice showing procedural and working memory impairments and dopamine D2 receptor hypersensitivity, horizontal treadmill running over six weeks ameliorated these deficits [22]. The range of adaptive response to regular physical exercise incorporates several neuroprotection, anti-neurodegenerative and neurorestorative manifestations pertaining to function and biomarker integrity [23-27]; these benefits include also the up-regulation of the enzymatic antioxidant systems and modulation of oxidative damage [28]. For example, among individuals presenting cerebral

palsy, whether as children, adolescents or younger/older adults, the recommendation for activity and reduction of sedentary behavior are a burgeoning necessity [29]. Exercise, through the modulation of intensity-dependent metabolism and/or directly-activated reactive oxygen species-generating enzymes, coordinates the cellular redox state of the ageing/degenerating brain. Reactive oxygen species contribute towards the self-renewing, proliferating and differentiating aspects of neuronal stem cells as well as exercise-mediated neurogenesis and neurorestorative effects [30]. The promotion and maintenance of physical exercise habits among older people demands greater consideration and diligence regarding "activeness" as an 'health-attitude' and present-day lifestyle within a workable social context, this requires initiatives that galvanize a broader range activity habits rather than the limitations of discrete activities [31,32].

Physical exercise forestalls both cellular senescence and immunosenescence with active elderly individuals at lower risk for deterioration through a multitude of malignancies including cancer forms, e.g. prostate and colon, osteoporosis, depression and dementia [33], in many cases extending life-expectancy by several years and patients' quality-of-life [34,35], and metabolic processes [36,37]. Activity programs induce major effects on the neuroimmune system functioning and alter dramatically cytokine production, particularly IL-6, IL-1, TNF- α , IL-18 and IFN gamma, which are involved actively in the modulation of synaptic plasticity and neurogenesis [38]. These cytokines may contribute also to reactive oxygen species production through which alterations affect the availability of lipids, proteins, and DNA and regulate directly brain function and integrity [30]. Zimmer et al. [39], have described the influence of physical activity upon objective and subjective cancer-related cognitive impairments in 19 studies involving both humans and laboratory rodents. They observed patient/rodent improvements in both types of studies and posited the general conclusion that the activity-exercise programs reduced inflammation and provided partial benefits for cancer-related cognitive performances. Among chronic diabetic patients, prevention programs are imperative for minimizing the risk of onset of neurodegenerative diseases since a single bout of exercise was found to be efficacious in obese, glucose-intolerant laboratory rodents [40]. Cerebrovascular complications, caused by inflammatory, oxidative, and metabolic changes expressed in diabetes type II patients may induce blood-brain-barrier breakdown may allow peripherally-located pro-inflammatory molecules, e.g. ceramides, to infiltrate thereby activating stress pathways with subsequent promotion of several neuropathological features of dementia including brain insulin resistance, mitochondrial dysfunction, and accumulation of neurotoxic beta-amyloid oligomers, with consequential and subsequent synaptic loss, neuronal dysfunction, and cell death [41]. Physical exercise augmented antioxidative capacity, reduced oxidative stress, and induced anti-inflammatory effects buttressing endothelial function with accompanying elevations of brain capillarization and angiogenesis. Exercise also counteracted dyslipidemia and reduced the increased levels of ceramide and enhanced beta-amyloid clearance through up-regulation of beta-amyloid transporters, elevated basal testosterone, reduced in diabetes II, and promoted neurogenesis.

The influences of physical exercise parameters, such as whether endurance, i.e. aerobic, or resistance, intensity, duration, frequency, type of muscular contraction, extent of exertion and solicited energetic metabolism upon neuroprotective expressions over a range of neurodegenerative disorders has been explored to a limited extent. Applying mouse models of spinal muscular atrophy, high intensity swimming and low intensity running activities have provided behavioural, biochemical and cellular markers of ameliorative manifestations [42,43]. Spinal muscular atrophy presents a collection of autosomal recessive neurodegenerative diseases that differ with regard to clinical outcome, characterized by the specific loss of spinal motor neurons, caused by insufficient level of expression of the protein survival of motor neuron. Chali et al. [44], have shown that both types of exercise, swimming and running, enhanced markedly motor neuron integrity and survival, independent of disorder expression, thereby promulgating the maintenance of neuromuscular junctions and skeletal muscle phenotypes, with particular regard to the soleus, plantaris and tibialis of the exercised mice. Critically, both types of exercises improved dramatically the properties of neuromuscular excitability. Additionally, all of the exercise-activity engender benefits were both quantitatively and qualitatively associated with the specific characteristics of each type of exercise, which implies that the correspondent neuroprotective effects were strongly dependent on the specific activation of certain motor neuron subpopulations. Normal aging, accompanied by energy process dysregulation, directs microglia towards a pro-inflammatory phenotype with subsequent release of IL-1 β and IL-6 [45-47], whereas exercise exerts an anti-inflammatory effect [48-51]. Littlefield et al. [50], observed that voluntary running wheel exercise bolstered the induction of a neuroprotective microglia phenotype against pro-inflammatory reductions in hippocampal neurogenesis in aged rat brains.

Neuroprotective effects have been disclosed repeatedly among ageing individual as most generally obtained in laboratory studies. Due to the induction of neuroprotective mechanisms, e.g. neurotrophic factors and angiogenesis, exercise exerts a neuroprotective effect upon the progression of manifest dementia [52,53]. In aged rats (27 month-old), swimming exercise combined with diselenide-supplemented diet rendered marked neuroprotective effects as displayed by reduction of apoptosis and glial cell activation [54]. Within the context of traumatic brain injuries, such as stroke, Otsuka et al. [55] have demonstrated that preconditioning exercise schedules enhanced the levels of expression of midkine, brain-derived neurotrophic factor, glial fibrillary acidic protein, modulating cell communication and regulating the blood-brain barrier, and platelet endothelial cell adhesion molecule, involved in leucocyte transmigration and angiogenesis, in the Exercised group compared with the expression levels in the Non-exercised group following brain ischemia. In contrast, the expression levels of activated caspase 3 and NT were reduced in the area surrounding the necrotic lesion thereby reducing neuronal apoptosis and oxidative stress. Physical exercise antagonized abnormal activations of the RhoA/Rho kinase pathway, involved in neuroinflammatory and pro-oxidative responses, axonal retraction, and apoptosis; the pathway is linked to aging-related

neurodegenerative mechanisms, thereby providing a marked extent of neuroprotection in aged rats [56]. In this context, the issue of whether or not an extended exercise regime offers long-lasting resistance, i.e. neuroprotective alterations, to beta-amyloid-induced network dysfunction in hippocampal cell population activity poses a relevant question. Isla et al. [57], observed that hippocampal cell populations' activity that was recorded in slices obtained from voluntarily-exercised mice that were provided with free access to a running wheel over a period of 21 days displayed greater power and faster frequency composition than those hippocampal slices obtained from sedentary animals. Hippocampal networks from exercising mice that were rendered insensitive to beta-amyloid-induced inhibition of spontaneous population activity prompting the conclusion that voluntary exercise produced a long-lasting neuroprotective influence upon the hippocampal tissue. Trivino-Paredes et al. [58], have provided a comprehensive description of the interactive influences of gonadal hormones, stress hormones and metabolic hormones upon hippocampal structural plasticity with regard to the mediatory role of physical exercise parameters, frequency, duration and intensity and training regimes.

One hallmark of the pathophysiological progression of Alzheimer's disease and dementia conditions is observed in the severe hippocampal atrophy brought about by inexorable neuronal loss. Long-term physical exercise diminished hippocampal CA1 neuron loss linked with the complete abolishment of spatial memory deficits [59]. These influences of exercise upon the integrity of hippocampal and other brain regions involved in higher levels of functioning underline the multidomain importance of exercise interventions for prevention of cognitive decline and somatic concomitants of deterioration [60]. It is increasingly evident that globally structured exercise programs/schedules ought to be designed to alleviate different aspects of psychophysiological function in elderly populations with the chosen activity regimes varying with 'training-volume' in relation to age, gender, exercise background [61]. According to the notions of Laitman and John [62] age-related cognitive decline is driven by CNS structural and functional deterioration, neurovascular decline and pro-inflammatory (microglia) reactivity; in this context, physical exercise, through reduction of systemic inflammation, promotion of angiogenesis and neurogenesis, provides both neuroprotective and neurorestorative manifestations. Lancioni et al. [63], observed that patients' improved commitment and indications of positive personal affected strongly their applicability and potential benefits of the program in daily contexts. Similarly, exercise interventions effectively minimized the decline in activities of daily living in patients diagnosed with dementia [64].

Future considerations need to appraise more systematically the relationships between functional decline and the neurorestorative properties of different types of exercise interventions. Critically, efforts must be made to challenge one current conviction that there exist no effective treatments, or even a paucity, of intervention, e.g. exercise, available to retard or hinder or reverse the neurodegeneration processes afflicting the diseased brain.

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