Chapter 8
Physical Activities and Prevention of Neurodegenerative Diseases

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Abstract Physical activity (PA) boosts mental health and well-being in both healthy and diseased populations. As regards to the latter, its therapeutic effects have been noted in patients diagnosed with various neurodegenerative disorders, and in this chapter we summarize these effects. The neuroprotective effects of PA are conferred via improved neuronal hormones, neurotransmitters, and neurotrophic factor production. These changes are effected through several cellular and molecular mechanisms. PA also leads to enhanced neuroplasticity and neuronal survival, as well as the optimization of physiological and neuroendocrine responses to physical and psychosocial stressors. PA also contributes to the sensitization of the autonomic nervous system, central nervous system, and parasympathetic nervous system. This is done via the promotion of angiogenesis, autophagy, neurogenesis, and synaptic plasticity, amongst other neurological processes. Altogether, PA confers neuroprotective and neuropreventive effects, including improved cognition, memory, sleep, and angiogenesis in the nervous system, and reduced anxiety, insulin resistance, neuro-inflammation, and stress.

Keywords Physical activity (PA) · Neurodegenerative diseases · Neuroprotective and neuropreventive effects · Neuronal hormones · Neurotransmitters · Neurotrophic factors

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8.1 Introduction

Neuroprotection is the process of interfering with the processes responsible for cellular dysfunction and death. This is done to avert neuronal cell death. The notion of neuroprotection has piqued the scientific community's interest in the search for new medicines that can assist maintenance of brain tissue while also improving overall outcomes [1]. In the elderly, the most prominent risk factor for neurological illnesses is aging [2]. Physical activity reduces the risk of Alzheimer's disease (AD) and dementia by 45% and 28%, respectively, according to epidemiological research [3, 4].

Physical activity (PA) has garnered much attention as a potential neurological disease-modifying therapeutic method, based on prior studies [5–7]. PA has appropriately been described as a non-drug therapy for a variety of disorders. These include cardiovascular, metabolic, neurological and psychiatric diseases [8]. For example, a study by Lu et al. investigated the effect of treadmill-mediated physical activity on cognitive function in a rat model of AD caused by streptozotocin. They found a significant inhibition of neuronal apoptosis in the rat hippocampal Cornu ammonis (CA1) [9]. Furthermore, Lu et al. showed that the induction of angiogenesis probably occurred due to the upregulation of MT1-MMP expression caused by the treadmill exercise. This, in turn, conferred neuroprotection to the rat models of AD against cerebral ischemia [10]. Also, there are considerable data from various *in vivo* studies on neurological disorders and physical activity that indicate the therapeutic potential of exercise for improving cognition [11, 12].

Various PA-induced molecules involved in neurological processes have been discovered, due to considerable breakthroughs in molecular methods [13]. The identified neurological molecules include brain-derived neurotrophic factor (BDNF), endothelial nitric oxide synthase), insulin-like growth factor (IGF), nerve growth factor, superoxide dismutase (SOD), and vascular endothelial growth factor (VEGF), whose levels are increased in the brain hippocampus. In contrast, there occurs a decline in the production of free radicals that are detrimental to neurological functions. Together, these are involved in memory [14]. Figure 8.1 illustrates the neuroprotective and neuropreventive effects of PA for various neurodegenerative disorders.

PA has been shown to slow the progression of neurodegeneration and is known to help reduce the risk of dementia and other neurodegenerative disorders such as Parkinson's disease (PD), AD, and others [15]. In a meta-analysis, PA was found to be a safe and efficient additional therapy for improving attention, cognition, and memory, impairment of which is associated with various neurological disorders such as AD, PD, Huntington's disease, multiple sclerosis, schizophrenia, and unipolar depression. PA also improves psychomotor speed, and quality of life, with no complications [16]. Authors of another study reported that PA in midlife maintains functions associated with cognition and minimizes or postpones the risk of dementia in later life [17]. Furthermore, PA and diet modulate the substrates involved in brain neuroplasticity, including antioxidant defense, inflammation, neurogenesis,

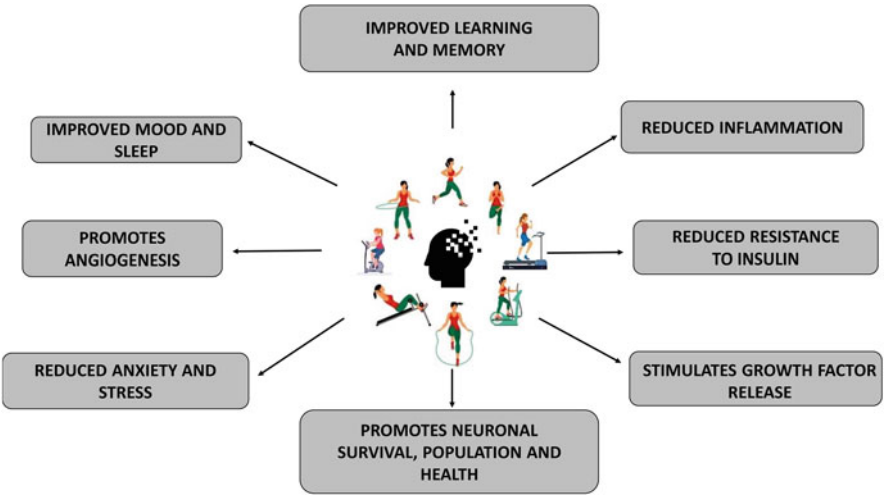

Fig. 8.1 The neuroprotective and neuropreventive effects of PA for various neurodegenerative disorders

neurotropic signaling, and stress response. As a result, these are regarded as crucial therapeutic alternatives for age-related disorders, including dementia [18]. Furthermore, Bass et al. found that PA was positively correlated to the academic performance of schoolchildren [19]. In addition, individuals who exercise aerobically improve their attention, executive function, memory, and processing speed, according to a meta-analysis of randomized controlled studies [20]. Exercise also causes an increased blood flow to the hippocampus and reduced neuro-inflammation [21, 22]. Moreover, numerous biological pathways are affected by PA. In particular, it optimizes the physiological and neuroendocrine responses to physical and psychosocial stressors, acts as an armor against stress in general or stress associated with chronic diseases, promotes a state of anti-inflammation, and enhances the expression of growth factor and neuroplasticity [23]. PA affects brain functioning and causes structural alteration as reported in a neuroanatomical study. Here, there was a significant improvement in the cortical tissue density of the frontal, temporal, and parietal cortices, which are otherwise known to be reduced with age (55 to 79 years). This could be attributed to the cardiovascular fitness levels associated with the PA in the study group [24]. Similar findings were reported in an *in vivo* study, wherein arborization, spine density, and spine morphology were altered among rats that performed voluntary long-term running on the wheel [25]. Interestingly, neuropathology related to AD was attenuated and cognitive functions (hippocampus-mediated) were improved with PA, particularly in the early stages of disease progression. However, specific PA guidelines are yet to be reported [26].

PA, when performed regularly, alleviates the symptoms of AD, as evidenced from animal studies and human clinical trials [23]. PA is also advantageous to PD patients, leading to improved balance, gait, physical functioning, strength, and

quality of life, and reduction in the occurrence of PD [27, 28]. In this chapter, we have summarized the neuroprotective and neuropreventive effects of PA for neurodegenerative diseases to aid researchers and medical professionals interested in this area (Table 8.1).

8.2 Role of PA in Neurodegenerative Disease

A sedentary lifestyle with insufficient exercise may increase the risk of AD, PD, and stroke [133]. Aerobic exercise improves cognitive function in elderly people [134]. This could be attributed to decreased chronic oxidative stress while increasing mitochondrial biogenesis and autophagy upregulation, and the neurotransmitters and trophic factors that are stimulated by PA. These include BDNF, fibroblast growth factor 2, glial-derived neurotrophic factor (GDNF), and IGF-1 [28].

Autophagy, anti-oxidant defense mechanisms, neurogenesis, neural plasticity, and other neurophysiological features and pathways are all affected by PA, along with a reduction in neurodegeneration and neural apoptosis. Neuro-plastic changes in the brain are induced by PA, although there is a lot of variation across people [15]. Regular PA enhances neurological function and promotes autophagy [10, 135]. Also, it stimulates mitochondrial biogenesis and lowers chronic oxidative stress. In the hippocampus, there occurs an enhanced expression of neurotrophic factors (BDNF and GDNF) and neurotransmitters (irisin and dopamine [DA]), while BAX and neuro-inflammatory cytokines are suppressed [136]. PA regulates BDNF, which performs crucial functions that include neuronal stress resistance, synaptic transmission and plasticity, neuronal plasticity, activation of DA and NFκB in the neurons, and neuronal differentiation and maturation [13, 137].

AD is perhaps the most common form of dementia and a major healthcare concern [138]. AD patients are often treated with a combination of pharmacological drugs and counselling to retard disease progression [7, 139]. PA prevents cognitive decline and lowers AD risk [140]. It aids in the stabilization and improvement of cognitive functions as well as the prevention and delay of severe neuropsychological symptoms such as apathy, disorientation, and depression in AD patients [141]. Anti-inflammatory and neurotrophic factors have also been found to be induced by PA [142, 143]. *In vivo* studies have shown that PA can avert damage to white matter (induced by obesity) via suppression of vascular dysfunction and neuro-inflammation. These effects were evident even when there was weight gain in the study animals [144]. Aerobic exercise, in particular, enhances *ABCA1* mRNA expression, which in turn may cause improved cognition via alleviating and avoiding symptoms of AD [145]. The above reports provide strong evidence for the therapeutic utility of PA for age-related neurodegenerative disorders such as AD.

PD is the second most common age-related neurodegenerative disease [146]. PD is characterized by α-synuclein accumulation (cytosolic protein) and dopaminergic degeneration at the cellular level [27]. Many efforts have been undertaken to utilize various ways to address its therapeutic element. However, despite numerous

Table 8.1 Physical activities and prevention of neurodegenerative diseases

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Systematic review	Effect of PA on the PD-associated depression in patients	28749970	[29]
PD	Review	Effect of physical activity on PD	30532351	[30]
PD	Review	Effects of PA on the functional and physical capacities of the PD patients	27567884	[31]
PD	Systematic review	Investigation of effects and molecular mechanisms of PA on PD patients	32215173	[32]
PD	Systematic review	Definition and summary of the concepts and evidences on PA, physiotherapy, and exercise on PD	31970204	[33]
PD	Patient-based epidemiological study	Examination of self-reported activity scores and their associations with clinical attributes (Parkinson progression markers initiative; PPMI) in subjects with early PD	29480222	[34]
PD	Systematic review	Assessment of the efficacy of PA, occupational and physiotherapy therapy on motor and non-motor symptoms in PD	27583249	[35]
PD	Clinical study	Investigation of the relationship between PA-related prodromal attributes and PA	31719136	[36]
PD	Systematic review and meta-analysis	Quantification of association (dose-response) between PA and PD-risk	30646166	[37]
Dementia	Systematic review	Prospective evidence on the risk of developing neurodegenerative disease and PA	18570697	[38]
PD	Review	Role of BDNF in increased PA-induced neurodegenerative processes and neuroregeneration mechanisms	30901514	[39]
PD	Randomized controlled trial	Examination of the relationship between PA and cognition in PD (YOPD)	32353174	[40]
PD	Cohort implementation study	Promotion of PA by telehealth (engage-PD) in PD patients (newly diagnosed) in response to coronavirus pandemic	32734298	[41]

(continued)

Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Observational study	Effects of the coronavirus pandemic on PA, psychosocial distress and severity of symptoms in PD patients	32925108	[42]
PD	Review	The impact of PA and inactivity in PD patients	27477046	[43]
Dementia	Clinical study	Impact of PA on subjects diagnosed with the neurodegenerative disease	33467309	[44]
PD	Clinical study	Changes in PA and its correlation with the effects seen in PD patients during coronavirus pandemic	32837960	[45]
PD	Review	Impact of PA on PD	30245949	[46]
PD	Observational study	Using an activity monitor to quantify PA in PD (early)	31420310	[47]
PD	Multi-center clinical study	Intervention of PA in association between cognition in PD and availability of striatal dopamine transporter	30722964	[48]
PD	Prospective and longitudinal clinical study	Self-reported PA levels and PD progression (early)	30554993	[49]
PD	Clinical study	Investigation of the effect of postural stability of the PD-patients on their PA	31688224	[50]
PD	Feasibility study	Technology intervention in assessing PA levels in PD patients (older adults)	1069250	[51]
PD	Clinical study	A gender-based analysis of the factors associated with PA levels in PD patients	31387476	[52]
PD	Cross-sectional study	Investigation of the predictors of PA levels in PD patients	32870459	[53]
PD	Qualitative systematic review	Collective experiences of PD patients and their opinion on PA interventions	30973527	[54]
PD	Clinical study	Identification of potential factors of PA (spontaneous) in PD patients	32369962	[55]
PD	Clinical study	Examination and comparison of self-reported PA, its objective monitoring and PD with respect to its clinical features	31621608	[56]

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Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Clinical study	Promotion of PA in PD patients (older adults) via the *ReadySteady* intervention	32211555	[57]
PD	Clinical study	Correlation of total regular PA, pathologies in brain and PD (older adults)	32348372	[58]
PD	Literature review	Behavioural epidemiologic framework for the scrutiny of PA and PD literature	27777097	[59]
PD	Patient-based study	Mixed-methods approach for unraveling PA in PD patients and veteran	31036158	[60]
PD	Clinical study	Association of mood disorders and cognition with PA (daily) in PD (early-stage, treatment-naive patients)	31571008	[61]
PD	Clinical study	Fall frequency is reduced with increased PA training in PD patients	31648204	[62]
PD	Patient-based study	PD and prolonged impacts of balance-training (HiBalance program) based PA in PD patients (older adults)	31485305	[63]
Dementia and PD	Cross-sectional study	PA's association with dementia risk factors in PD patients	30746564	[64]
PD	Cohort study and meta-analysis	Association of PA with PD risk in the Swedish national march cohort	25410713	[65]
Neurodegenerative diseases	Review	Role of the Chinese nutraceuticals and PA in neurodegenerative tauopathy	33407732	[66]
PD	Observational cross-sectional study	Association of pain in PD patients with PA, mood and sleep	32333551	[67]
PD	Randomized study	Mendelian randomization study (two-sample) for PD and PA	33093192	[68]
PD	Clinical study	Investigation of the role of motor subtypes in PD patients and evaluation of PA by sensor- and patient-based methods	33302434	[69]

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Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Clinical study	Effect of falls on PA in PD patients	26639446	[70]
PD	Clinical study	ICF-based holistic approach for evaluating PA in PD patients	32781376	[71]
PD	Clinical study	Association of PA and PD risk	15728289	[72]
PD	Observational study	Quantification of PA and determinants in PD patients (sedentary lifestyle)	23769178	[73]
PD	Review	Benefits of PA in PD patients	21750523	[74]
PD	In vivo study (C57BL/6 male mice)	Impacts of NAC in neuroinflammation in PD (sub chronic parkinsonism) and utility of PA	30477535	[75]
PD	Clinical study	Determination of the step-rate threshold for PA intensity in PD patients	32255504	[76]
PD	Clinical study	Impact of subthalamic stimulation on motor symptom improvement and PA in PD patients (advanced)	25361545	[77]
PD	Clinical study	Parkinsonism risk and PA in older adults dwelling in community	31046115	[78]
PD	Cross-sectional study	Impact of lower back pain-associated disability in PD patients on PA, functional mobility and QoL	31343700	[79]
PD	Clinical study	Frailty phenotypes in PD female patients and PA	22919489	[80]
PD	Clinical intervention trial	Secondary per protocol analysis of sleep, fatigue, and PA, and PD patients	30258564	[81]
PD	Randomized controlled trial	Objective assessment of PA and its association with physical function, balance and dyskinesia in PD patients	27589536	[82]
PD	Prospective cohort study	Risk of PD and PA	16926235	[83]
PD	Cohort study	Parkinsonism (mild) and PA in PD patients (older adults)	29931236	[84]

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Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Clinical trial	Impacts of a group protocol on PA and changes associated with health locus of control and mood in PD patients with impaired mobility	30624196	[85]
PD	Cross-sectional study	Chair rising ability and its relation to PA and daily activities in PD patients	33292833	[86]
PD	Case control study	Risk of PD and leisure time as well as lifetime occupational PA	27177695	[87]
PD	Patient-based study	PD and falls and their association with PA (daily-living) and motor severity (laboratory-based evaluation) in PD patients	30718220	[88]
PD	Patient-based feasibility study	mHealth-based peer coaching for PA in PD patients	29449201	[89]
PD	Patient-based feasibility study	PA tracking in PD patients via wearables and their accuracy	29729611	[90]
PD	Patient-based study	PA (recreational) and PD risk	17960818	[91]
PD	Cross-sectional study	Attenuation of motor symptoms (nigrostriatal degeneration-independent) in PD patients by PA (non-exercise based)	26330028	[92]
PD	Pilot study	PA relationships with motor symptoms in PD patients as measured by a three-axis accelerometer	32912171	[93]
PD	Large population-based case-control study	PA (recreational and occupational) and PD in Denmark	28319247	[94]
PD and MS	Review	PA-associated behavioral alterations in PD and multiple sclerotic patients	23632452	[95]
PD	Review	PA-induced neuroprotection in PD and role of inflammatory processes and trophic factors	28894046	[96]
	Patient-based study	Neuropsychiatric symptoms of PD and PA	22914597	[97]

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Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Randomised controlled trial	Encouraging PA and fitness in PD patients with sedentary lifestyle	23457213	[98]
DA, PSP, and PD	Pilot study	Fall risk in neurodegenerative patients in relation to PA	30617629	[99]
PD	Narrative review	Amelioration of PD as induced by PA	33532136	[100]
PD	Patient-based study	Association between depression, PA, cognition, and health-related QoL (objectively measured) in PD	29307560	[101]
PD	Multifactorial clinical study	PA, binge eating and nutritional status as determinants of body weight in PD patients	28649617	[102]
PD	Patient-based study	Evaluation of PA (ambulatory) in PD patients	27164042	[103]
PD	Clinical trial	Effects of fatigue on function and PA in PD patients	12682317	[104]
PD	Patient-based study	Evaluation of the factor structure and reliability of PASIPD in PD patients	25184403	[105]
PD	Patient-based study	PA level determinants in PD patients	26982987	[106]
AD, ALS and PD	Mendelian randomization study	Evaluation of PA effects on AD, ALS and PD (neurodegenerative disorders)	33515719	[107]
PD	Case-control study	Wearable devices for PA monitoring in PD patients	28660562	[108]
PD	Review	PA as a rehabilitation tool for PD	25332912	[109]
PD	Pilot study	Evaluation of PA and cognitive association with PD	28596093	[110]
PD	Clinical trial	Cognitive changes (longitudinal) in PD (early) patients and their association with *APOE* genotype and PA	33790041	[111]
PD	Pilot study	PA and its association with BDNF and cognitive function in PD patients	28338380	[112]
PD	Randomized controlled trial	Impact of fatigue on PD patients (idiopathic) and its association with PA	19514069	[113]

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Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Clinical study	Impact of leg muscle fatigue on gait in PD and controls groups based on their PA (high and low)	27264409	[114]
PD	Clinical study	Profiles of PA in PD patients	33581724	[115]
PD	Patient-based study	Social opinion on PD control (early) via PA	19479519	[116]
PD	Clinical trial	Effect of cueing training on PA improvement in PD patients	20179328	[117]
PD	Clinical study	Determination of PA accelerometer cut points for PA evaluation in PD patients (older adults)	26332765	[118]
PD	*In vivo* study (A53T mice models of PD)	Elevated PA and energy expenditure is ameliorated by orexin/hypocretin neuronal inhibition in mouse models of PD	33466831	[119]
PD	Randomized controlled trial	Multifaceted behavioral program (ParkFit study) for the evaluating the efficacy of PA in PD patients	20723221	[120]
PD	Systematic review	A qualitative analysis of the PD patients' experiences and opinions on PA interventions	29135743	[54]
PD	Clinical study	Monitoring (3 months) the association between gait patterns in PD patients and PA (objectively measured)	30416704	[121]
PD	Longitudinal follow-up study	Improved anxiety and apathy with PA in PD (early) patients	33519706	[122]
PD	Patient-based study	Association of PA, daily energy expenditure and loss in weight in PD patients	19117356	[123]
PD	Cohort study	Association of reduced PD risk with PA (heavy and leisurely) and lower BMI	24633681	[124]
PD	Randomized controlled-trial	Assessment of ParkFit program (multifaceted intervention) for promoting PA in PD patients	23972329	[125]
PD	Patient-based study	Investigation of the effects of kinesiophobia and fatigue on PA, functional capacity and QoL in PD patients	33290306	[126]

(continued)

Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Comparative study	Investigation of proxy reports (QoL self-reports and caregiver reports) in PD and PA	16028212	[127]
PD	Randomized controlled-trial	Effects of PA (patterns and levels) and sedentary lifestyle in PD (mild to moderate) patients (elderly)	25655884	[128]
PD	Patient-based study	Non-association of reduced PA with fatigue in PD patients	18591055	[129]
PD	Patient-based study	Investigation of PA (adapted program) on motor and non-motor functions, and QoL in PD patients	25318771	[130]
PD	Patient-based study	Role of PA against neuromuscular deterioration in PD patients	33595917	[131]
PD	Patient-based study	Effect of the coronavirus pandemic on PA, depression, and anxiety in the PD patients	33653991	[132]

Abbreviations: *AD* Alzheimer's disease, *ALS* amyotrophic lateral sclerosis, *APOE* apolipoprotein E, *DA* degenerative ataxia, *ICF* International Classification of Functioning, Disability and Health (ICF), *MS* multiple sclerosis, *NAC* N-acetyl-L-cysteine, *PD* Parkinson's disease, *PSP* progressive supranuclear palsy, *PASIPD* Physical Activity Scale for Individuals With Physical Disabilities, *QoL* quality of life; mHealth, mobile health.

advancements in treatment that have slowed the disease's development and reduced locomotor impairment, clinical management remains a problem [147]. Only high-intensity PA has been shown to be beneficial in alleviating the motor symptoms in PD patients [148]. Furthermore, mood, fatigue, aerobic fitness, motor function, and quality of life have been improved in PD patients [149]. In PD patients, 8 weeks of multi-component PA have improved functional status and gait speed [150]. Another study showed an increase in the concentrations of BDNF, DJ-1, and Hsp70, while aggregation of α-synuclein decreased, in the brains of mice who performed voluntary activity on a running wheel, in contrast to a control group. This provides compelling evidence that the PA can reduce the progression of PD by preventing aberrant protein aggregation in the brain [151]. According to a recent simulation study, PA such as horseback riding improves balance and cognitive impairment in PD-affected elderly [152]. Numerous studies have shown that PA can improve brain function while also reducing the risk of neurodegeneration [153]. PA is also known to improve neuroplasticity through synaptic structural alterations and functional changes in different brain regions. Multiple systems concerning the regulation of

neuroinflammation and glial activation are also modulated [153]. Furthermore, using food additives (for example, carvacrol) in combination with PA has led to a reduction in both rotational behavior and aversive memory deficit when observed in rat models of PD. This study also demonstrated a decline in the levels of lipid peroxidation together with an increase in the hippocampus concentration of total thiol in rat models of PD [154]. These observations strengthen the notion that a combined PA-carvacrol therapy may be a promising therapeutic approach for PA patients suffering from impaired neurobehavioral characteristics [154]. PA is also known to benefit benefits PD patients' health by improving the patient's ability to adjust to impediments encountered during gait [155].

In a pilot study, coordination and manipulation therapy led to improved cardiac function and balance, and reduced mobility disorder, in PD patients over the control group [156]. In another study, the changes in lifestyle concerning PA and including natural anti-oxidants in the diet alleviates dopaminergic neuronal deterioration. However, this requires strategizing PA and dietary incorporation of oxygen radical scavengers as well as iron-binding agents [157]. PAs such as running on a treadmill improve stability in posture and gait activity, and promote α-synuclein and dopaminergic homeostasis *in vivo* However, in the same study PA did not significantly induce cerebral alkaline phosphatase [158].

8.3 Neurological Diseases and the Underlying Mechanisms of PA Intervention

8.3.1 PA-Mediated Regulation of the Neuroendocrine System

If the activity is of sufficient intensity and/or duration, PA serves as a stressor for the human body and acts as a neuroendocrine system activator. Chronic exercise training causes neuroendocrine system modifications, such as a reduction in the hormone stress response to submaximal activity [159]. Many substantial alterations in hormone concentrations (β-endorphin, cortisol, vasopressin, adreno-corticotropic hormone) are induced by PA as compared to resting levels. The higher the PA duration and intensity, the larger is the neuroendocrine response [160]. PA triggers various physiological responses, including stimulation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, which causes optimal metabolic substrate selection and use. The stimulation of the hypothalamus-pituitary-adrenal axis by PA relies upon myriad attributes, including activity type, when it is performed, dietary intake, and characteristics of the individual [161].

8.3.2 PA and Regulation of Neurotransmitters

The central serotonergic, dopaminergic, and noradrenergic systems are all affected by PA [162]. PA gives rise to peripheral physiological adaptations to compensate for the activity-stimulated disruption in homeostasis in the resting state. Alterations in neurotransmitters and monoamine synthesis and metabolism take place during PA, as documented in various studies that used homogenized tissues to evaluate the levels of the neurotransmitters [162]. The use of voltammetry and microdialysis has revealed that PA influences the release of most of the neurotransmitters *in vivo* [162]. DA, noradrenaline, and serotonin or hydroxytryptamine (5-HT) are altered by PA, causing an increase in their release, and also affecting their extracellular levels along with γ-aminobutyric acid (GABA), and glutamate (GLU) [163]. Brain DA upregulation has been reported to be associated with PA-induced elevated serum calcium levels. Consequently, calcium/calmodulin-dependent DA production is influenced via tyrosine hydroxylase enzyme activation [164]. Furthermore, PA improves DA-receptor binding affinity [165, 166]. Also, in response to unpredictable stress, PA causes neural adaptation [167]. The galanin expression in the locus coeruleus is responsible for the PA-mediated anti-stress protective mechanism [168]. The expressed galanin, in turn, causes hyperpolarization of noradrenergic neurons, leading to neuronal firing inhibition by the locus coeruleus. This ultimately suppresses norepinephrine (NE) release [169]. It is well-documented that memory consolidation and retrieval are also aided by NE [170]. In comparison to sedentary controls, elevated levels of NE in the pons and medulla of the spinal cord were observed in chronic treadmill running and wheel running-based activities [171]. PA also elevates the endogenous NE activity levels, indicating an association between PA-mediated improved cognition and NE [163]. PA affects the HT system, however it depends on the region of the brain and is influenced by the intensity and duration of the activity. For example, moderate treadmill activity (4 weeks) caused a decline in the hippocampus levels of 5-HT while its metabolism remained unaffected [172]. In contrast, a high-intensity treadmill activity (1 week) led to a significant elevation of hippocampus levels of 5-HT [173].

8.3.3 PA and Neural Insulin Signaling

Insulin signaling in the brain is necessary for the survival of neurons and restoration of critical brain functions. Also, it causes aversion and reversal of BDNF transport abnormalities [174]. Abnormalities in the pathways associated with neural insulin signaling are associated with learning, memory impairment and neurodegenerative disorders, while its deregulation is related to cardiovascular diseases, diabetes, hypertension, and obesity [175]. The pyramidal cell axons of the hippocampal-CAl and other brain regions associated with cognition, memory, and learning have overexpressed insulin receptors [176].

The concentration of IRs is comparatively higher in the cerebral cortex, hippocampus, and hypothalamus regions of the brain [177, 178]. BDNF, insulin, IGF-1, IGF-2, and VEGF are actively involved in intracellular hippocampal neuronal signal transmission under normal physiological conditions. This maintains hippocampal neuronal integrity and functionality [179]. The risk of AD development becomes higher when these are suppressed [179]. A decline in aversive memory, elevation in inflammatory markers (interleukin-1(IL1-β), tissue necrosis factor-alpha (TNFα), and NF-kβ), and decline in anti-inflammatory markers (IL-4) have been observed in the rat models with aging. In the same study, histone H4 acetylation levels were found to have decreased. However, PA caused a reversal in the observed levels [180]. Improved hippocampal neuronal insulin signaling and anti-inflammatory effects have been shown to be exerted by PA, along with the elicitation of insulin-sensitizing effects in the peripheral nervous system (PNS) [179, 181]. Researchers have therefore speculated that PA confers neuroprotection and induces similar effects in the central nervous system (CNS) [182]. Many more investigational pieces of evidence suggest that PA assists in neuroprotection by acting on both CNS and PNS. Insulin-independent glucose uptake in the peripheral tissues is promoted by PA through activation of protein kinase. This is achieved by mammalian targets of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) - mediated activation. By contrast, in the CNS, cognition, synaptic plasticity, angiogenesis, and neurogenesis are improved by PA [183–186]. Furthermore, neurotransmitter synthesis and degradation are also regulated by PA [187, 188].

8.3.4 BDNF-Signaling and PA

BDNF is a hippocampal neurotrophin and critical regulator of neuronal and synaptic plasticity, and neuronal stress resistance. It is involved in learning and memory-related processes, and may be a key player in depression [189, 190]. It is well known for stimulating the differentiation and maturation of developing neurons [191]. However, positive regulation of the synaptic transmission and plasticity is undertaken in the mature neurons [192]. As a result, BDNF helps with memory and learning [193]. Brain size in humans and PA endurance are positively correlated, which is suggestive of cognition and locomotion co-evolution [194]. Furthermore, brain BDNF expression is elevated by endurance-based PA, and brain growth (of the hippocampus, in particular) is enhanced by improved PA capacity [195]. PA such as running on the treadmill has been found to ameliorate peri-neuronal net disorganization (specifically on the axotomized motoneurons) and synaptic stripping in peripheral nerve injury. Although this is credited to PA-mediated BDNF increases, the underlying molecular mechanisms remain unclear [196]. The hippocampal- and amygdala-associated neuronal functions are enhanced with PA. AD onset could also be delayed with PA as studied in double transgenic mouse models of (aged 1.5–-4 months) AD. In this study, 10 weeks of treadmill training elevated the memory associated with the hippocampus while the amygdala-associated memory was

restored. Also, the dendritic arbor of amygdala basolateral neurons was restored while those of CA1 and CA3 neurons increased *in vivo*. The amygdala and hippocampal phosphorylated- protein kinase B, phosphorylated-protein kinase C, and p-TrkB (phosphorylated-tropomyosin receptor kinase B) levels (all signaling molecules of BDNF/TrkB) increased due to PA while the soluble amyloid-β levels declined *in vivo* [197]. Treadmill and running wheel exercises *in vivo* (in mouse models aged approximately 4 weeks) significantly elevated the mRNA and protein levels of BDNF and synaptic load in the dentate gyrus. Also, the exercises caused alterations in astrocyte morphology and the orientation of their projections. These could be due to astrocytic TrkB receptor level elevation [198]. The DA content in the neurons and their release are pivotal for neuronal survival as well as learning and memory. All these were modulated by BDNF [199].

8.3.5 Production and Secretion of Irisin and PA

PA induces the muscle protein FNDC5 (fibronectin type III domain containing 5), which in turn is cleaved and secreted as a myokine called irisin [200, 201]. Irisin is known to promote thermogenesis while improving glucose homeostasis and related obesity. There occurred an enhanced BDNF expression due to a forced neuronal FNDC5 expression [200]. Additionally, elevated blood irisin-induced BDNF and hippocampal neuroprotective gene expression were observed upon adenovirus-mediated peripheral FNDC5 delivery to the liver. It has been suggested that the brain's BDNF expression, endurance-based PA, and metabolic mediators are all linked [200]. It has been further suggested that irisin may serve as a link between motivation and reward mechanisms, and PA. These are, in turn, associated with DA that is activated via BDNF [199]. The neuronal injury induced by ischemia has also been ameliorated by irisin. This was achieved via Akt and ERK1/2 signaling pathway activation. Therefore, it appears that irisin aids the PA-induced neuroprotection against cerebral ischemia. There could be a possible irisin-mediated association between cardio-cerebrovascular disorders and metabolism [202]. Further, irisin has been shown to ameliorate neuronal injury induced by deprivation of oxygen and glucose. This is achieved via inhibition of the ROS-NLRP-3 (reactive oxygen species-Nod-like receptor pyrin-3) signaling pathway (involved in inflammation), which indicates therapeutic effects of irisin in the case of ischemic stroke [203]. Other therapeutic PA effects include neuropathic pain reduction as observed in rat models (male) of chronic constriction injury. In this study, it was observed that the pain threshold increased upon acute administration of irisin while the neuronal number was still reduced [204]. *In vitro* studies reported that a 12-hour irisin pretreatment conferred neuroprotection against amyloid-β toxicity. Here, IL-6 and IL-1β release was also attenuated along with the reduction in COX-2 expression, and AKT phosphorylation in cultured astrocytes. There occurred a reduction in the activation of NFκB in amyloid-β exposed astrocytes due to abrogation of IκBα phosphorylation and loss. These convincing findings suggest irisin as a potential

therapeutic candidate for AD and memory dysfunction associated with diabetes mellitus [205].

8.3.6 PA-Mediated Neuronal Responses: Anti-Inflammatory and Oxidative Responses

To maintain homeostasis, the hypothalamic-pituitary-adrenal axis and the autonomic nervous system are activated in response to PA. Consequently, the plasma levels of catecholamine and cortisol increase. There occurs a stimulation of prolactin and growth hormone secretion. This, in turn, stimulates the TH_2 (T-helper cells) response profile and might impact the immune response generated [206]. Attempts have been made to discover novel biomarkers for characterizing PA-induced responses and unraveling the molecular mechanisms underlying neurodegenerative disorders. This would also be beneficial in assessing the effects of PA in these conditions. Kurgan et al. performed proteomic analysis (liquid chromatography-tandem mass spectroscopy) post-2D-gel electrophoresis on the samples obtained from six patients. A significant alteration was observed in the serum levels of 20 proteoforms post high-intensity PA at durations of 5 and 60 min, respectively. These proteoforms included apolipoproteins, protease inhibitors (serpins), and immune system proteins with known anti-inflammatory and antioxidant effects. These are also documented to have important roles in neuro- and cardio-protection, and lipid clearance [207].

Numerous studies have been performed to determine the synergistic and neuroprotective effects of anti-oxidants and PA on neurons in neurological disorders, such as PD. A combination neuroprotection strategy that involved NAC (N-Acetyl-L-cysteine, an anti-oxidant) and PA revealed its neuroprotective effects on mouse models of PD. Later, it was found that only NAC was responsible for conferring this neuroprotection *in vivo* [75]. PA is also known to induce the production of heat shock proteins (iHSP70, intracellular and eHSP70, extracellular). The iHSP70 activation is essential for anti-inflammatory mechanisms, cellular protection, and promotion of tissue repair while eHSP70 participates in immune system activation. In general, the internalization of eHSP70 (chaperones) by the motor neurons occurs as a stress response to attain cellular protection against oxidative damage and protein denaturation. Furthermore, neurodegenerative disorders (Amyotrophic lateral sclerosis, AD, PD, and Huntington's disease) are often characterized by lower expression levels of iHSP70. Therefore, it is important to elucidate their functional attributes and the neuroprotective effects of PA [208]. In response to PA, the anti-oxidant enzyme SOD is also released [28]. Together, these delay the onset of neurodegenerative disorders such as PD by retarding neural apoptosis, promoting neuroplasticity, and delaying neurodegenerative processes [133].

8.3.7 *Effects of PA on Survival and Apoptosis of Neurons*

PA is known to effectuate brain cell activity, survival, and apoptosis. PA, when performed voluntarily under favorable conditions, has caused cognition improvement, brain microvasculature, and neurogenesis promotion in hypobaric hypoxia exposed rat models. These effects were observed to be mediated via VEGF signaling [209]. PA, in the early stages of life, has been observed to induce prolonged neuronal (cortical) and hippocampal morphological changes in rat models. These *in vivo* effects were noticeable in a subsequent sedentary period. This study's authors speculated that neuronal growth promotion and neurotrophic factor expression are enhanced by PA, which replenishes the neuronal reservoir for later use in life. Also, there occurred PA-induced elevation in the neuronal (cortical) and hippocampal cellular population along with dendritic arborization [210]. Additionally, survival protein expression increased. These included hippocampal BDNF and cortical mTOR [210]. Reportedly, BDNF promotes PA-induced neuroprotective effects against type-II diabetes and dementia [211]. PA training type determined alterations in brain cell survival and inflammatory protein levels and their expression in rat models (aged rats). In particular, PA such as aerobics enhanced brain (cortex) Akt, p38, p70S6k, and ERK protein expression levels [212]. PA such as running improved spatial learning and memory in APP/PS1 transgenic mouse models (middle-aged) of AD. This was attributed to the neurogenesis and neuroprotection conferred by the PA in the dentate gyrus of these mouse models [213].

Further, PA such as treadmill exercise retarded Aβ-42 deposition via β-secretase (BACE-1) and C-99 inhibition and checked memory impairment (PS2 mutation-induced) in the cortex and the hippocampal region of PS2 mutant mouse models (aged). Also, there occurred a downregulation of protein disulfide (PDI) and glucose-related protein/binding immunoglobulin protein (GRP78/Bip) expression and abrogation of activating transcription factor-alpha (ATF6α), eukaryotic initiation factor-2α (eIF2α), Jun N-terminal kinases-p38- mitogen-activated protein kinases (JNK-p38 MAPK), protein kinase R-like endoplasmic reticulum kinase (PERK), and spliced X-box binding protein 1 (sXBP1). PA also led to Bcl-2 upregulation, CHOP, caspase-3, and caspase-12 activation, and BAX downregulation in PS2 mutant mouse models (aged) [214]. PA with varied intensities was observed to produce distinct effects on the nervous system. For instance, moderate intensity PA (treadmill) conferred neuroprotection in rat models of ischemia over a high-intensity workout, which causes downregulation of the neurotrophic factors influencing cell cycle-related protein expression levels [215]. PA that involved voluntary running stimulated progenitor cell proliferation in the dentate gyrus, and neurogenesis [216]. Reportedly, PA confers protection to the injury-susceptible retinal ganglion cells. This could be due to neuronal functional restoration and survival via thwarting of synaptic elimination (complement-mediated), and abrogation of retinal BDNF loss by the PA [217]. Finally, PA was observed to positively affect BDNF resting serum levels and cognition in adolescent mouse

models (male) that were exposed to aerobics-based PA (moderate to high intensity) [218].

8.3.8 PA and Its Effects on Neural Autophagy

Under conditions of stress, such as restricted food supplies, evolution favored species with greater cognitive and physical abilities. This is suggestive of the fact that brain function can be improved by PA and dietary restrictions. Autophagy, DNA-repair proteins, mitochondrial biogenesis, neurotrophic factors, and protein chaperones are all involved in the neuronal signaling pathways for stress-response under energy limitations. The risk of neurodegenerative disorders, such as AD, PD, depression, and stroke might increase due to dietary malpractices, suppressed cellular adaptive stress responses, and lack of PA [133]. Furthermore, brain functions have been shown to improve *in vivo* with PA and dietary regulations, which checked the neurodegenerative processes. PA along with dietary regulations stimulate the signaling pathways for cellular adaptive stress responses, which, in turn, promote proteostasis, DNA repair, mitochondrial biogenesis, and neurotrophic signaling [219]. Aerobics-based PA and food deprivation have been observed to activate the neuronal signaling pathways involving PGC-1α, NFκB, CREB, and Ca^{2+}. These, in turn, induce mitochondrial biogenesis and cellular stress responses [220].

Autophagy is the cell's natural, conserved breakdown process, which removes unwanted or malfunctioning components via a lysosome-dependent, controlled mechanism. It enables the breakdown and recycling of cellular components in a controlled manner. Autophagic dysfunction leads to an increased sensitivity to stress conditions such as oxidative damage or starvation, loss of stem cells, neurodegeneration, and a rapid deterioration in neuromuscular function *in vivo* [221]. Autophagy plays a pivotal role in the production of β-amyloid and therefore its dysfunction can cause AD progression. Under genetically hyper-activated autophagic conditions, there occurs a significant decline in the accumulation of β-amyloid in knock-in mouse models of AD ($Becn1^{F121A}$). A restoration in the cognitive decline and survival was also observed in this study. This could be due to the mutated Becn 1 ($Becn1^{F121A}$), which led to a significant decline in the BECN 1 and BCL2 (inhibitor) interaction. Consequently, there occurred a constitutive autophagy activation. The amyloid-β-oligomers were found to be segregated inside the brain autophagosomes *in vivo*. Finally, PA was observed to be a physiological inducer of autophagy, which confers neuroprotective effects similar to those of Becn1. These included the removal of amyloid-β and improved memory *in vivo* [222].

8.4 Conclusion

Physical activities have been shown to improve people's overall health and well-being when they participate in them regularly. Regular exercisers reap the benefits in every part of the body in some way. When it comes to the effects on neuronal cells and brain function, numerous studies show that the PA has neuroprotective effects. The neuroprotective effects of physical activity are elicited by signaling processes that have yet to be fully understood. However, hormones such as irisin, neurotransmitters such as DA, and neurotrophins such as BDNF are known to directly participate in these signaling mechanisms. Furthermore, PA improves balance, cognition, and gait in PD patients, and retards disease progression by preventing brain aggregation of the protein. Furthermore, disease progression is retarded and the onset of neuropsychological symptoms is delayed in AD patients, along with improved cognition and memory. PA affects different neurophysiological aspects in afflicted patients. These include anti-inflammatory and anti-oxidant responses, autophagy, cell survival, apoptotic pathways, and hippocampal insulin signaling. PA is also known to upregulate BDNF expression that contributes to its neuroprotective effects. These neuroprotective mechanisms also involve Akt are DA, GABA, and irisin. In conclusion, PA is an excellent therapy for patients diagnosed with various neurological disorders when used in combination with other well-established treatment regimens.

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