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Review article

The beneficial roles of exercise training via autophagy in neurological diseases and possible mechanisms

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ABSTRACT

Autophagy is a conservative catabolism process, participating in delivering the cytosol and cytosolic components to the lysosome. Abnormal autophagy is related to human pathologies, for instance diabetes, neurodegeneration, cardiovascular, macular degeneration, pulmonary, and cancer. Enormous evidences indicate that autophagy may mediate the cellular pathological condition in the process of neurological diseases. Exercise as a form of physiological stress may cause an adaptation, and autophagy is a necessary process for adaptational response to exercise. Autophagy during exercise may improve neurological function, control tissue maintain tissue integrity, and activate different signals pathway for adaptation. In this review, we summarize the possible mechanisms of exercise training via autophagy in neurological diseases.

1. Introduction

Autophagy is a eukaryocyte catabolic process, which mediates cellular energy sources by "cannibalization" of its own cellular constituents, participating in degradation proteins and other futile cytoplasmic factors [1]. This process also keeps the cell healthy and clean by removing dangerous waste of cytoplasm in recycling pattern [1]. Autophagy is also involved in the maintenance of various physiological responses and plays dual roles in the mediation of cell survival/death (e.g., inducing cytoprotection and cell death) [2].Abnormal downregulation or upregulation of autophagy may be an attribute to various pathologic conditions [3]. Autophagy includes microautophagy and macroautophagy and may be a target that inhibits or abolishes responses to diverse therapeutic conditions [4].The fundamental role of autophagy is maintaining cellular homeostasis and protecting cells against injured organelles and misfolded proteins [5]. Jiang et al. demonstrated that the central nervous system cytotoxicity induced by cisplatin suppressed the astrocyte proliferation and autophagic function via down-regulating the expression of autophagy-related molecules, including SQSTM1/P62, LC3-II, ATG7 and ATG5 [6]. Wu et al. demonstrated that apoptosis and autophagy interplayed with each other closely in mediating the cellular pathological condition in the course of neurological diseases [7]. (Fig. 1.)

Physical exercise has been described as a nondrug therapy against multiple diseases such as cardiovascular diseases, neurological diseases, psychiatric diseases and metabolic diseases [8]. Regular physical activity may exert beneficial effect on adults' health and has been regarded as an effective autophagy inducer [9]. Exercise-induced autophagy may be observed in several tissues and organs, consisting of pancreas, liver, adipose tissue, skeletal muscle, cardiac muscle, and cerebral cortex [10]. Smuder et al. suggested that exercise plays a crucial role in protecting skeletal muscle from Doxorubicin-caused activation of autophagy [11]. In addition, Lu et al. showed that treadmill exercise could obviously alleviate streptozotocin-caused neurodegenerated disorder in hippocampal CA1 area of rat and signigicantly maintained hippocampal-dependent cognitive function [12]. Tang et al. showed that treadmill exercise may obviously improve neurological function and facilitate angiogenesis by up-graduating MT1-MMP expression in peri-ischemic brain microvessels [13]. In summary, exercise training may play an important role in neurological diseases by mediating autophagy.

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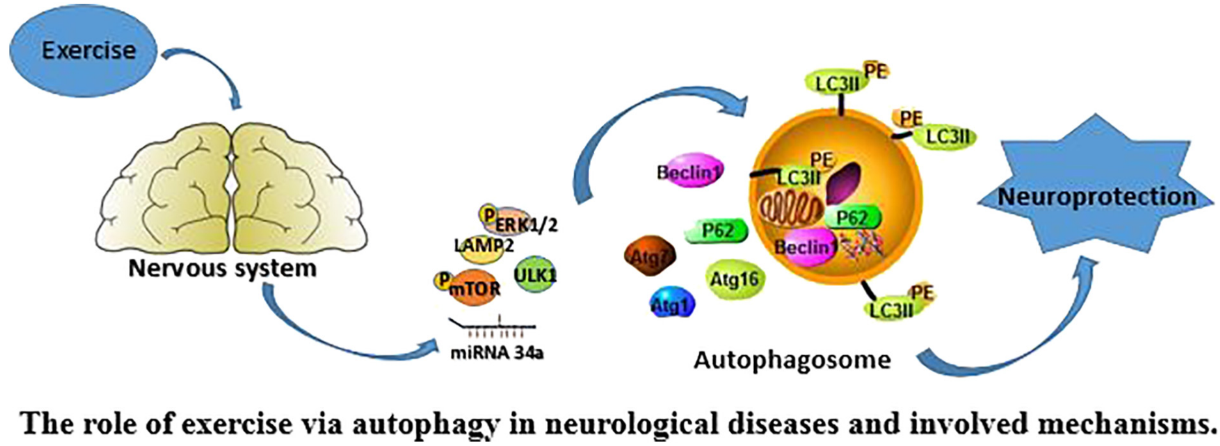

Fig. 1. The role of exercise via autophagy in neurological diseases and involved mechanisms.

2. The mechanisms for exercise via autophagy in neurological diseases

2.1. Exercise and neurological diseases

Exercise may keep weight down, strengthen muscles, and prevent cancer, diabetes, and Alzheimer's disease [14]. The beneficial effects of physical activity might partly contribute to reduce sympathetic nervous system activity and physical inactivity, which may reduce incidence of cardiovascular diseases related to sympathetic nervous system activity [15]. Mattson showed that lifelong intermittent physiological challenges consisting of intellectual endeavors, energy restriction and exercise, could protect brain from Idiopathic late-onset dementia (ILOD) and promote neuroplasticity and brain cellular stress resistance [16]. Marques et al. demonstrated that physical exercise may promote cerebellum and cerebral cortex mitochondrial function, reducing apoptosis-associated markers and oxidative stress [17].

A sedentary lifestyle without adequate exercise training may augment the risk of stroke, Parkinson's and Alzheimer's diseases [18]. Forced treadmill exercise could promote the exploratory and locomotor activity, and lead to obviously down-regulation of hyperphosphorylated and full-length tau in the hippocampus and spinal cord [19]. Alberts et al. showed that forced-exercise and anti-parkinsonian medication provided analogous degree of symptoms improvement in PD patients and both interventions led to similar patterns of fMRI activation [20]. Raichlen et al. suggested that the timing of exercise was crucial for cognitive function, and the combination of cognitive training and exercise could contribute to a better effect than single inervention for certain cognitive domains [21]. Zhao et al. suggested that exercise preconditioning exerted neuroprotective effect after traumatic brain injury (TBI) via alleviating neuronal loss, lesion size and microglial activation, activating the brain-derived neurotrophic factors before trauma, promoting the injury-dependent up-regulation in heat shock protein 70 levels, and suppressing crucial apoptotic pathways [22].

Physical exercise may exert beneficial effect by adjusting lysosomal degradation and mitochondrial quality control, thereby alleviating age-associated cognitive decline [23]. Gusdon et al. demonstrated that physical exercise may promote cerebral mitochondrial function via exerting influence on mitochondrial dynamics and electron transport chain function in aged mice [24]. Ding et al. showed that exercise may promote angiogenesis in brain of aging rats via up-regulating expression of angiogenic factors [25]. Seventy-two days strength- or endurance-oriented exercise training may attenuate insulin-caused pyruvate dehydrogenase dephosphorylation , inhibiting lactate response in a sedentary aging population [26]. Ana et al. provided the evidence of exercise-induced neurogenesis via an imaging of dentate gyrus cerebral blood volume and suggested that exercise could distinctively act on the dentate gyrus, influencing memory and cognitive aging [27]. Bherer et al. showed that both cognitive training and exercise interventions could effectively improve cognitive decline in the aged at-risk individuals [28].

2.2. Autophagy and neurological diseases

Autophagy is a cellular self-digestion pathway and emerged as particularly crucial for CNS proteostasis, and autophagy dysregulation is the most typical feature of neurodegeneration diseases in Huntington's disease (HD), Alzheimer's disease (AD) and Parkinson's disease (PD) [29]. Neurodegenerative disorders are related to impaired mitophagy and dysfunctional mitochondrial contributing to amassing of protein aggregates which ultimately result in neurodegeneration [30]. Abd et al. suggested that excessively expressed mGluR5 down-regulated autophagy and resulted in inhibition of neurotoxic aggregates clearance in multiple neurodegenerative diseases [31]. Dysregulation of neuronal autophagy contributed to synaptic destabilization and axonal degeneration and involved in neurodegeneration process, consisting of Parkinson's disease, Alzheimer's disease, Huntington's disease and ALS [32]. Autophagy may eliminate defective mitochondria, abnormal accumulated proteins, and excessively elevated reactive oxygen species that cause DNA injury and cell death, while inadequate or defective autophagy could aggravate neuronal death in many types of neurodegenerative disorders [7]. Neuropathic pain is induced by lesions of the central neurons and peripheral fibers in the somatosensory nervous system. Yin et al. demonstrated that autophagy is associated with the induction and development of neuropathic pain [33].

Autophagy damage is the characteristic of neurodegenerative disorders including dementia with Lewy bodies (DLB) and Parkinson's disease (PD) [34]. Suppression of autophagy could induce protein aggregation which caused neural death, and activated autophagy was beneficial for cellular models in simulation of Huntington's and Parkinson's diseases [35]. Autophagy modulators, including forkhead box O 1 (FOXO1), tuberous sclerosis complex 2 and sestrin 3 (SESN3), take part in formation of Lewy bodies, and the expression levels of these molecules may be up-regulated along with senescence related to PD or normal aging [34]. Obergasteiger et al. suggested that autophagy was a downstream target of Parkinson's disease [36].The exhaustion of autophagic and mitochondrial bioenergetics store may lead to the aggravation of PD in leucine rich repeat kinase 2(LRRK2) G2019S mutation carriers via elevated non-manifesting LRRK2 G2019S mitochondrial performance in mitochondrial-challenging conditions and up-regulated autophagy [37]. The effect of Ganoderma lucidum extract for both autophagic response to oxidative damage and mitochondrial function may improve PD pathology and symptoms, which might be related to the activation of PINK1/Parkin and AMPK/mTOR signaling and finally directly or indirectly resulting in the mitophagy [38].

Macroautophagy/autophagy dysfunction with the amassment of autophagosomes is a neuropathological characteristic in early stage of Alzheimer's disease, directly interferring amyloid beta (Aβ) metabolism [39]. Gao et al. showed that endolysosomal and autophagic dysfunction may lead to neurodegenerative diseases via disturbing the degradation of probably neurotoxic molecules for example tau and amyloid-β [40]. Autophagic vacuoles (AVs) and autophagosomes were excessively accumulated in the brain tissue of AD patients, possibly resulting from incomplete fusion and digestion of autophagosome-lysosome, and potentially combining with induction of autophagic initiation [41]. Mutant APP (mAPP) and amyloid beta (Aβ) may contribute to autophagy/mitophagy, mitochondrial and synaptic abnormalities in hippocampal neurons, resulting in neuronal dysfunction [42]. Autophagic dysfunction leads to failure of clearing proteinopathies, resulting in the additional aggregation of pathological deficits, which in turn further damage autophagic flux in in early stage of AD [43]. The regulation of autophagy was associated with the neuroprotective effect of mesenchymal stem cells conditioned medium (ucMSCs-CM) against Aβ25–35-induced cell death and promotion of Aβ phagocytosis [44].

The age-related failure in activity of chaperone-regulated autophagy (CMA) may lead to the dysfunction of CMA - regulated homeostasis, indicating that the decline of CMA might be a crucial harmful factor in promoting the pathological development in many kinds of age-associated diseases [45]. The decline of chaperone-regulated autophagy activity with age involves accumulation of aggregated/oxidized/impaired proteins, leading to tissue dysfunction and probably neurodegeneration [45]. Age-associated decrease of autophagy interrupts neuronal homeostasis and then promotes the progress of neurodegenerative disorders because of the accumulation of toxic protein polymeride in neuronal cell [46]. In addition, Gao et al. showed that inhibiting autophagy was involved in of motor dysfunction improvement, brain edema mitigation, spatial learning and memory deficits alleviation after traumatic brain injury (TBI) via IL-33/ST2 signaling pathway [47]. Song et al. showed for the first time that insufficient BNIP3-regulated mitophagy and damaged autophagy degradation participated in mechanisms underlying chronic hypoxia-induced neuronal cell injury [48].

2.3. The induction of autophagy by exercise in various conditions

Exercise as a physiological therapy may potently activate autophagy during a short time [49]. Exercise-induced autophagy may maintain tissue integrity, inhibit inflammation reactions, control tissue injury or activate direct signals pathway for adaptation [50]. Halling et al. suggested that autophagy capacity changes induced by exercise consists of both elevated autophagy flux and activated transcription of crucial autophagy genes, possibly leading to enhancement of autophagy activity [51]. Vainshtein et al. suggested that exercise could obviously upregulate various mitochondrial gene transcripts and autophagy-associated genes, as well as lead to promotion of mitophagy in mitochondria and enhancement of autophagy and mitophagy flux [52]. Marques et al. demonstrated that the beneficial effects related to exercise in autophagy signaling, mitochondrial biogenesis and dynamics led to a more robust phenotype via enhancing mitochondrial plasticity [17]. Acute suppression of autophagy in females resulted in the occurrence of mitochondria dysfunction during physical activity, including higher oxidative damage, decreased physical performance and increased depolarized fibers during muscle contraction [53].

2.4. The role of exercise via autophagy in neurological diseases and involved mechanisms

Kim et al. showed that exercise training may promote autophagy response [54]. Treadmill exercise may induce autophagy in the cerebral cortex and autophagy was crucial in regulating exercise-induced metabolic benefits in adult mice [55]. Exercise preconditioning and p38 suppression may provide neuroprotective effects following cerebral ischemic stroke via inhibiting autophagy [56]. Physical exercise improved neurological function possibly by suppression of apoptosis, promotion of neurogenesis and alleviation of autophagosome accumulation in the peri-infarct area following transient MCAO in rats [57]. Zhang et al. demonstrated that treadmill training preconditioning might exert neuroprotection by decreasing the brain infarction after ischemic stroke by inhibiting autophagy, via up-regulating the phosphorylated ERK1/2 level and reversing degradation of p62 [56]. In addition, Early exercise preconditioning may inhibit exhaustive exercise injuries via induction of mitophagy by recruiting the autophagosome protein LC3 to translocate Bnip3 to the mitochondria, which is probably activated by H_2O_2 and impacted by Beclin1-dependent autophagy [58]. Moderate physical exercise might improve mitophagy and autophagy, contributing to prevention of early neurodegeneration in substantia nigra [59]. Exercise training could alleviate the reduction of autophagic activity in peripheral blood mononuclear cells (PBMCs) from elderly subjects via down-regulating p62 protein expression, upregulating the LC3II/I ratio, and altering the levels of autophagy regulatory proteins, consisting of Atg12, Atg16,beclin-1, and phosphorylated ULK-1 [60]. Dagon et al. demonstrated that exercise may induces autophagy via AMPK-dependent activation of ULK1/Atg1 [61]. Mejías et al. suggested that 8 weeks-resistance exercise might activate autophagy, inhibit apoptosis and block activation of NLRP3 inflammasome in PBMCs from the elderly [62]. Kou et al. showed that swimming exercise could improve abnormal mitochondrial dynamics and inhibit autophagy function by reducing miR-34a levels, thereby delaying the aging process [63].

Ogura et al. showed for the first time that exercise causes a biphasic change in autophagy with an initial reduced LC3II following exercise and a subsequent up-regulated 1 h thereafter, which might be associated with regulation of mTOR [64]. Kang et al. showed that aerobic exercise such as treadmill exercise may improve abnormal autophagy via decreasing the expression level of mTOR that regulated the autophagy activity in Alzheimer's disease [65].Treadmill training might upregulate autophagy-lysosomal activity, which obviously decreases Aβ deposition in APP/PS1 transgenic mice [66]. Late running training obviously influenced on structural plasticity via promoting the dendritic complexity, and further increased Aβ clearance through the blood-brain barrier, decreased beta-amyloid (Aβ) plaque burden, and alleviated autophagy dysfunction, oxidative injury, inflammation response, microgliosis, leading to improvement of memory performance and mitigation of agitation [67].

Endurance exercise in PD patients may promote recovery of damaged dopaminergic neuronal function via multiple synergic neuroprotective pathways, consisting of elevated antioxidative capacity, promoted neurogenesis, and concordant autophagy [57]. Yong et al. showed that treadmill exercise improved motor function and alleviated the pharmacologically induced dopaminergic neuronal cell death in the substantia nigra (SN) pars compacta of PD rats. Morevoer, the autophagy induced by exercise was not due to the disruption of fusion processes between lysosomes and auto- phagosomes, which was proved by the promoting of LAMP2 expression and down-regulation of p62 expression [68]. Koo et al. suggested that treadmill training may decrease alpha-synuclein levels via enhancing autophagic flux and promoting mitochondrial function, improving motor deficits in chronic chronic 1-methyl-1,2,3,6-tetrahydropyridine with probenecid (MPTP/P)-caused mouse model with PD [69]. Fucà et al. suggested that motor training may increase BDNF expression and alleviate the pathologic autophagic flux so as to slower neurodegeneration in tambaleante (tbl) mice [70].

In conclusion, although physical exercise is considered to be influential for pathology and physiopathology in nervous system, mechanisms of physical exercise for nervous system remain thus unclear. Autophagy pathways is essential for neural health and exert an important role in neurological diseases and developmental processes. Physical exercise plays a crucial role in neuroprotective effect via regulation of autophagy in nervous system via regulating autophagy-related factors, transcription of crucial autophagy genes, autophagy flux and accumulation of autophagosome. Therefore, physical exercise is promising to facilitate neuronal functional recovery by regulating autophagy in multiple neurological diseases. Moreover, physical exercise may combine with pharmacological therapy or other physical treatment to cure patients with neurological diseases. In the future, we need to further investigate the effect of physical exercise on autophagy in order to achieve the suitable intervention targets which could be valuable for making optimal treatment strategy for neurological diseases.

Conflict of interest

The authors declare no conflicts of interest.

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