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Exercise-Induced Neuroprotection in SMA Model Mice: A Means for Determining New Therapeutic Strategies

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Abstract Due to the prevalence of neuromuscular disorders such as amyotrophic lateral sclerosis and spinal muscular atrophy in modern societies, defining new and efficient strategies for the treatment of these two neurodegenerative diseases has become a vital and still unfulfilled urge. Several lines of experimental evidence have emphasized the benefits of regular exercise training in mouse models for these affections in terms of life span increase and improvement of both motor capacities and motoneuron survival. Identifying molecules that could mimic the neuroprotective effects of exercise represents a promising way to find novel therapies. Some of the effects of exercise are caused by the overproduction of circulating neurotrophic factors, such as IGF-I, whereas others may be due to modifications of the intrinsic properties of the motoneurons within the spinal cord. The causal relationship that links these potential effects of exercise training and the improvement of motor capacity and life span expectancy is consequently discussed.

Keywords Spinal muscular atrophy · Neuromuscular disorders · Physical exercise · Mouse model · Mechanism of neuroprotection

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Exercise and Neuromuscular Disorders

Increased prevalence of neurodegenerative disease in modern societies has, for long, been related to an increasingly ageing population [1]. However, risk factors associated to modern life style, particularly sedentary life style, may also contribute to the increased occurrence of these diseases [2]. Furthermore, several studies are indicative of a neuroprotective effect of physical exercise. For instance, physical activity increases cognitive ability in ageing humans [3], attenuates motor deficits [4], improves neurological impairments in different neurodegenerative processes [5–7], impedes age-related neuronal loss [6] and increases new neurone formation in mice [8].

Whether regular exercise is beneficial or detrimental in the case of locomotion system impairments had, until recently, been a highly controversial question, especially in the time course of amyotrophic lateral sclerosis and spinal muscular atrophy that represent a common cause of death in adult and childhood, respectively, and for which no efficient therapy is presently available.

Amyotrophic lateral sclerosis (ALS) is a chronic neurodegenerative disease characterized by a progressive motor weakness caused by the selective cell death of motoneurons [9]. On the average, mortality is observed within 4 years after the onset of the first clinical symptoms. The available therapy extends survival in human by approximately 3 months [9]. Mutations in superoxide dismutase 1 (SOD1) have been observed for about 20% of familial ALS patients [10]. SOD1 normally converts superoxide ion, a by-product of mitochondrial metabolism, to water and hydrogen peroxide. Despise the fact that SOD1 activity impairment has been ruled out as the causal event of the disease, there is some evidence of a “gain of

toxic function" for the mutant form of SOD1. The clinical and morphological abnormalities are identical in familial and other forms of ALS, suggesting a common degeneration mechanism. Although there is a wide variety of possible causes for ALS, including environmental agents, oxidative stress, disturbance of the glutamatergic neurotransmission, a large amount of literature data tend to correlate neuronal cell death to glutamatergic excitotoxicity [11]. In the case of chronic neurodegenerative disorder such as ALS, it is generally admitted that excitotoxicity occurs as a secondary process triggered by some other primary pathological event.

Spinal muscular atrophy (SMA) is a neurodegenerative disease characterized by the loss of spinal cord motoneurons. Three types of SMA can be described on the basis of a different time of onset, a specific evolution and the extent of the motor function loss. Molecular analysis has shown that both of the most severe SMA types, namely, the early onset form (type 1) and the milder late onset form (type 2), are linked to a genetic defect on the same locus of chromosome 5 where the *SMN* gene is duplicated in an inverted repeat [12]. Deletion or mutation of the telomeric copy of the *SMN* gene (*SMN1*) causes SMA [13]. The expression of SMN protein encoded by the centromeric *SMN* gene (*SMN2*) only partially compensates the lack of *SMN1* function. Indeed, the predominant SMN form encoded by *SMN2* lacks the carboxy-terminus due to an alternative splicing of exon 7 [14], which leads to the expression of an unstable protein [15].

In most cases, ALS and SMA patients had for long been recommended to avoid physical activity for the sake of their muscle strength and to minimize overwork-induced muscle damage. This recommendation mainly originates from epidemiological studies which showed a higher incidence of ALS in patients who had performed an intense physical activity at work or for leisure before the onset of the disease [16]. Yet, other studies do not support these observations [17–19]. Moreover, for the few ALS patients who suffer from respiratory failure, physical exercise was shown to slower the clinical deterioration as measured by the Norris scale and by respiratory function tests [20]. These contradictory data highlight the difficulties classically encountered in any study on a human population. Some of these studies consist in the mere description of a single case, the other studies being performed on a highly different number of patients submitted to the whole exercise program which precludes any valid comparison to the available data.

Several groups have reported the effects of a running-based training in ALS mouse model that express different mutant forms of the SOD1 gene [21–23]. They generally agreed on benefits induced by physical activity, including a 10-day increase in the life span of mutant mice submitted to training in comparison to their sedentary counterpart. Surprisingly, according to Veldink, the analysis of the spinal cord anatomy of trained vs untrained mice has revealed no difference in neuron distribution and survival. Recently, a combination of insulin-like growth factor 1 (IGF-1) delivery and exercise in wheel has been shown to exert remarkable effects on survival and function in ALS mice [24]. These results have shown that exercise increases the life span of ALS mice of 24 days, (which represented two times as much as the maximal increase reported in previous studies) and significantly protected motoneurons from death. These contradictory results concerning the effects of exercise in neuroprotection (i.e., no effect reported by Veldink et al. [22] contrasting with a significant neuroprotection of motoneurons) described by Kaspar's team suggest that different exercise protocols, albeit solely based on running, may have different effects. The molecular mechanism(s) underlying these exercise effects is still unknown.

Exercise in SMA: A Milestone in the Treatment of Neurogenerative Diseases

We have recently evaluated the running-based training efficiency on type 2 SMA-like mice [25]. We submitted a survival motor neuron (SMN)-null mouse carrying a single copy of a human *SMN2* transgene [26] to a running-based training in wheel. Forced wheel running exerts beneficial effects on the life span of type 2 SMA-like mice as well as on the associated clinical symptoms. Survival was extended by 57.3%, which is more than the improvement recorded with the administration of sodium butyrate, which extends survival by 39% only in this model when treatment was initiated immediately after the diagnosis was ascertained [27]. All the aspects of the SMA-like phenotype were improved by exercise, as shown by improved weight curves, and a gain in motor capacities has been observed in open field and during grip assays.

These benefits are associated to a reduction of neuronal death in the lumbar anterior horn of the spinal cord of running-based trained mice in comparison to untrained animals. Most importantly, exercise enhanced motoneuron survival. Indeed, the comparison of the motoneuron populations of trained vs untrained SMA-like mice indicated a dramatic motoneuronal death before, and also after postnatal day 10 on one hand, and a most efficient effect of exercise in limiting motoneuron apoptosis on the other hand. This effect is observed from the very beginning of the training. Indeed, no significant difference could be observed on motoneuronal populations between 10 and 13 days in trained mice.

The exercise-induced neuroprotection is most likely caused by a change in exon 7 splicing pattern of *SMN2* gene leading to an increased amount of exon 7-containing

transcripts in the spinal cord of trained type 2 SMA-like mice, suggesting a proportional increase of intact SMN proteins, which likely maintained a normal SMN function in motoneurons. The dramatic increase of the amount of exon-7-containing SMN transcripts in the spinal cord of trained mice (about 34-fold) in comparison to untrained SMA-like mice, detected by real-time reverse transcriptase polymerase chain reaction in the whole lumbar spinal cord at 13 days of age, should be interpreted keeping in mind the fact that unlike spinal cords from trained animals, a massive neuronal death occurred at this time in spinal cords from untrained mice. Our Southern blot data indicated that exercise interferes on the regulation of the *SMN2* gene splicing rather than on its transcriptional activation. These results suggest that exercise exert direct and specific effects on the post-transcriptional machinery independently from its well-known overall modification of gene expression.

In addition, we have analyzed the phenotype of two muscles from the calf, the slow-twitch *soleus* and the fast-twitch *plantaris*. This analysis have shown an overall conserved fiber area in running-based trained animals, in contrast to an increased muscular atrophy in untrained type 2 SMA-like mice. The exercise-induced maintenance of the muscle phenotype is consistent with the improvement of the motor capacities of trained mice, in contrast to an increased muscular atrophy in untrained type 2 SMA-like mice. The exercise-induced maintenance of the muscle phenotype is consistent with the improvement of the motor capacities of trained mice, as revealed by the behavioral tests. These effects on skeletal muscle fibers might be a beneficial consequence of the exercise-induced protection of motoneurons. The crucial role of nerve activity on muscle growth has been fully illustrated by the dramatic changes induced by motoneuron silencing. Muscle inactivity after spinal cord injury is classically associated with muscle atrophy [28]. Thus, the exercise-induced arrest of the neuron death in the spinal cord that was observed from the beginning of the exercise program was probably followed by an arrest of progressive muscle atrophy. As shown for the motoneuronal population, the exercise program stops the time course of the disease from the very beginning of its installation.

Interestingly, we have also shown that in contrast to atrophy, exercise has no effect on muscle hypoplasia, which is detected in the *soleus* and *plantaris* of type 2 SMA-like mice. Constitutive abnormalities of SMA muscle have been reported both in vivo [29] and in vitro [30], suggesting that defects in the *Smn* locus result in a reduction of myoblast number [31]. Thus, SMA muscle hypoplasia is likely to result from myogenesis defects, independently from and in addition to neuronal death. The fact that in our experimental conditions exercise fails to counteract muscle hypoplasia is consistent with previous data recording that exercise is unable to activate muscle cell proliferation [32].

Exercise-Induced Mechanisms of Neuroprotection

Physical exercise participation in maintaining nervous system health and function has consistently emerged as a key factor of plasticity and cell survival. Some of the exercise effects are specifically and directly exerted on nerve cells gene expression, leading to the regulated expression of a wide array of genes [33]. The molecular mechanisms underlying exercise-induced neuronal protection in mouse models of neuromuscular disease still remain to be elucidated. First, exercise might increase survival through a systemic way, such as the activation of neurotrophic signaling pathways. To this respect, endocrine, as well as para/autocrine production of signaling molecules, is likely to enhance general anti-apoptotic pathways leading to a delay in neuronal death. In addition, exercise training might induce a change in the intrinsic properties of the exercise-activated neurons, among which, motoneurons represent a key population in regard of their sensibility to the disease. According to this hypothesis, activated neurons could specifically adapt their physiological properties by the selective modification of gene expression in response to an increased work charge, and thus, become selectively resistant to apoptosis (Fig. 1).

Activation of Neurotrophic Signaling Pathways

Among the possible mechanisms of exercise-induced neuroprotection, the direct involvement insulin-like growth factor 1 (IGF-1) signaling pathway should be preferentially

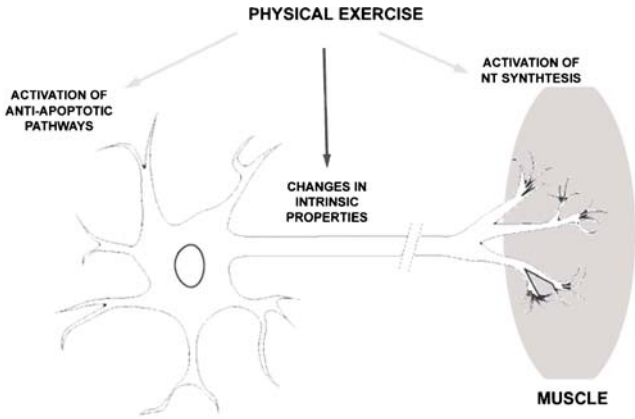

Fig. 1 Pleiotropic effect of exercise training on motoneuron activity and survival. The effect of the exercise-induced increase in neuromuscular activity is threefold: (1) early and direct effect corresponding to a change in electric properties of motoneurons caused by the modified gene expression of glutamatergic and gamma-aminobutyric acid systems (*black arrow*), (2) effects on survival mediated through the synergistic action of antiapoptotic extracellular signaling molecules (e.g., IGF-1 and other growth factors released in the extracellular space, (3) late response on motoneuron survival through muscle adaptation-induced release by the muscle of neurotrophic factors (*gray arrows*)

considered. Indeed, in vivo and in vitro studies have reported a protective effect of IGF-1 on the motoneurons [34, 35]. In addition, denervation at the level of peripheral and central nervous systems in vertebrates is typically followed by a nervous sprouting of neighboring cells [36]. This sprouting can be induced, at the level of the neuromuscular junction, by a high level of IGF-1 and IGF-2 in cellular culture and in adult mouse [37]. Accordingly, works by Torres-Aleman's team have shown that the effects of exercise on the significant diminution of neuron degeneration are mediated by IGF-1, whose blood level increases after exercise [38, 39]. The suppression of circulating IGF-1 abolishes the effects of exercise. IGF-1 seems therefore to have a direct effect on the mechanism that induces neuronal death.

It should be pointed out that IGF-1 is one of the most promising therapeutic molecules in ALS. IGF1 blood level is significantly lowered in ALS patient in comparison to normal controls [40]. This modification is associated to an increase of the expression of IGF receptors at the level of the spinal cord in ALS patients [38]. These assumptions are strengthened by two recent studies by Kaspar's team [24, 41] that reported an important increase of the duration of ALS mouse life span after IGF-1 overexpression through a direct effect on the motoneurons and by a distinct effect at a molecular event lying between the delivery of IGF-1 and exercise, which would result in a synergistic effect on survival. A drug treatment in combination to appropriate exercise might, to this date, constitute the most promising therapeutic strategy for ALS.

The potential therapeutic action of the IGF-1 pathway in SMA models has not been yet directly investigated.

The specific effects of the exercise-induced activation of the IGF-1 pathway in neuron remains to be further evaluated. The binding of the IGF-1R to its specific ligands IGF-1 or IGF-2 leads to the activation of different signaling pathways, including the phosphatidylinositol 3-kinase (PI3-kinase)-Akt and Ras-mitogen-activated protein kinase kinase (MEK)-mitogen-activated protein (MAP) kinase pathways [42]. Among these signaling proteins, MAPKs, PI3-kinase, and Akt have all been shown to be essential for IGF1-mediated neuron survival.

A central role of the PI(3)K/AKT pathway in neuroprotection was first suggested by the observation that PI(3)K inhibitors block the survival effect of IGF-1 in neurons [43]. PI(3)K enzymes are normally present in cytosol and can be activated directly through the direct recruitment to intermediate signaling proteins, notably insulin receptor substrate IRS-1, or indirectly through activated Ras. Active PI(3)K enzymes catalyze the formation of the lipid 3′-phosphorylated phosphoinositides, which regulate the localization and activity of a key component in cell survival, the Ser/Thr kinase Akt [42]. Active Akt targets several key proteins which keep neuronal cells alive, including apoptosis regulators, such as member of the Bcl-2 family, and transcription factors protein, such as Forkhead, cAMP-response-element-binding protein (CREB) and NF-kB, all of which are involved in regulating cell survival. Active Akt supports the survival of neurons in the absence of trophic factors, whereas a dominant-negative mutant of Akt inhibits neuronal survival even in the presence of survival factors [44]. These results establish an essential role for Akt in neuronal survival.

Igf-1 also stimulates docking of the adaptor protein Shc to activated IGF-1 receptors. This triggers the activation of the small GTP-binding protein Ras and the downstream MAP kinase cascade, which includes the subsequent sequential phosphorylation and activation of the kinases Raf, MAP kinase/ERK kinase (MEK), and extracellular signal-regulated protein kinase (ERK). The effect of the MAP kinase pathway on survival is at least partly mediated by the activation of the pp90 ribosomal S6 kinase (RSK) family members. Like Akt, RSK phosphorylates Bad and both kinases might act synergistically in inhibiting Bad's pro-apoptotic activity. The effect of RSKs on neuronal survival is not limited to the phosphorylation of Bad; RSKs are also potent activators of the CREB transcription factor. Because CREB is known to activate transcription of *bcl-2*, it can stimulate cell survival directly. Thus, although there is a divergence in the survival pathways downstream of the IGF-1R, both the PI(3)K-Akt and MAP kinase pathways converge on the same set of proteins, Bad and CREB, to inhibit neurone apoptosis.

Other mechanisms could explain the observed effects of the training and could act synergically to IGF-1. Thus, physical exercise is clearly associated to the overproduction of members of the growth factor family of fibroblast growth factors and of neurotrophic factors by the muscle [45], and by the brain [46, 47]. This suggests a role of the physical activity in mechanisms of resistance to the neuronal degeneration. Among the previously described neurotrophins, brain-derived neurotrophic factor (BDNF) and the neurotrophin-4 (NT4) represent potential candidate as messenger mediating the effects of exercise. A central involvement in the exercise-induced brain plasticity induced by exercise has been suspected for BNDF. Its own expression [46] and the expression of receptors and interacting molecules were upregulated after exercise [48]. Similarly, NT4 is overexpressed by the muscle after exercise and induces the sprouting of the motoneurons [49].

Changes of the Intrinsic Properties of Exercise-Activated Motoneurons

A paradox lies between the selective degeneration of motoneuron recorded in ALS and SMA and the apparently ubiquitous genetic underlying these neurodegenerative dis-

eases. Several hypotheses can be proposed to solve this controversy. However, in the specific case of SMA, it has been speculated that large amounts of SMN protein may be required for specific pre-mRNA splicing in motoneurons and that a loss of functional SMN protein would result in a defect restricted to some RNA molecules in these specific cells, leading to their selective death. Thus, what are these molecules and how can the other neurons compensate for the loss of SMN function remain two fundamental questions to progress in our comprehension of the SMA physiopathology.

The identification of genes whose expression is modified by exercise in motoneurons should represent a powerful tool in answering both of the previous questions. It is now well established that exercise regulates the expression of a broad array of genes directly in neurons [48]. These genes range from ubiquitous signal transduction pathways and transcription factors to neuron-specific functions, such as synaptic trafficking, and electric properties, such as the component of the glutamatergic and the gamma-aminobutyric acid systems.

The expected consequences of these changes in gene expression likely rely in the structure, morphology, and functions of the motoneurons. In response to an increased activity, exercised motoneurons display evidence for dendrite restructuring, increased protein synthesis, increased axon transport, enhanced neuromuscular transmission dynamics, and changes in electrophysiological properties [50]. The latter may involve alterations in ion conductances, which, in turn, would include changes in the gene expression of the ion channel subunits which underlie these conductances. These functional adaptations to training are reversible [50], leading to the concept of a probable exercise-induced activation of silent pathways in resting neurons. This activation is likely to save motoneurons from death in SMA-like mice. Thus, identifying this pathway should imply consequences in the therapeutic strategy (Fig. 2).

An important aspect of these exercise-induced effects in neurons is the cell-specific aspect of the changes. This aspect is particularly obvious in the results of the electrophysiological study reported by Beaumont and Gardiner [51]. Thus, the effects of exercise were shown to be restricted to a subpopulation of motoneurons presumably recruited relatively more frequently during the proposed activity. The running-based training similar to the one we have described for SMA-like mice [25] is likely to recruit preferentially spinal motoneurons, which may adapt to an increased electric activity by modifying their electric properties leading to their increased survival.

Conclusion

Exercise program in SMA-like mice may lead to the activation of anti-apoptotic pathway in motoneurons. This effect should proceed through the liberation of signaling molecules such as IGF-1 and/or neurotrophin, among which, BDNF and NT4 are powerful candidates.

Exercise program in SMA-like mice may restore a close to normal expression of disease-altered neuronal genes and/or modify the expression of unaltered genes which counteract the disease progression. The latter may include the activation of alternative molecular pathways used in SMA healthy neurons to compensate the lack of SMN function.

All of these mechanisms potentially act in synergy, which suggests two successive and complementary neuron responses to exercise. Changes in gene expression directly in exercised-motoneurons should be very early, as no intermediate mechanism is required. The immediate effect of exercise on neuron has not been directly addressed, but we have provided several lines of evidence for a very fast response of neuron to increased activity. In type 2 SMA-like mice, physical exercise stopped the neuron death from the very beginning of training, as highlighted by similar motoneuronal populations at 10 and 13 days in trained mice; by contrast, untrained mice displayed dramatic motoneuron loss during the same period [25].

To this first and fast response of motoneuron, the activation of anti-apoptotic pathway would constitute a complementary phase of neuroprotection, which might require more time for maximal efficiency as a cascade of molecular event, i.e., the intracellular pathway activating the synthesis of the signal molecule by a target cell, of physiological event, i.e., the transport of the signal molecule to motoneurons, of the neuroprotective event, i.e., the activation of anti-apoptotic pathway.

The analysis of the differential effects of acute (3 days) or chronic (28 days) exercises in the gene expression in the normal rat hippocampus identified genes that displayed

Fig. 2 Morphology of the SMA 2-like mouse models. From *right to left*: untrained type 2 SMA-like mouse, trained type 2 SMA-like mouse, untrained wild-type mouse

differential time expression patterns preferentially activated in acute or in chronic exercise [48]. Very interestingly, the early activated genes are principally implied in the electric properties of neurons, and more accurately, the neurotransmitter system such as the *N*-methyl-D-Aspartate receptor gene subunits, the excitatory amino-acid carrier 1, and the glutamic acid decarboxylase. Among the slow-activated genes, signals transduction-related molecules, such as MAP-kinases, Protein kinase C-delta, and CREB are to be found.

Physical exercise proves to activate efficient pathway of neuroprotection in two major neuromuscular disorders, ALS and SMA. Thus, the exhaustive and precise characterization of a correlation between exercise and specific gene expression in neuromuscular system of mutant mice that are models of these disorders should allow for proposing candidate molecules that would improve the motor capacity on one hand and lead to propose alternative re-education protocols of the motor system for human patients on the other.

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