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Modulation of locomotor training in a mouse model with Bcl-2 gene deletion after sciatic nerve crush injury

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Abstract

Introduction and Objective. Peripheral nerve injuries are often a traumatic event that requires long-term rehabilitation-based treatment to regain the best possible mobility. One of the promising approaches to enhance recovery involves the use of locomotor training, which may influence neuroplasticity and functional regeneration. The aim of the study is to investigate the effect of forced treadmill training on locomotor functional recovery following sciatic nerve crush in Bcl-2 deficient mice. It is based on an evaluation of the results of a locomotor analysis of mice with an injured sciatic nerve, taking into account specific gait parameters using the Noldus CatWalk device.

Materials and Method. The animals trained on the treadmill for 30 minutes a day,5 days a week for 4 weeks after a crush injury of the sciatic nerve, at a speed (20 m / min), without rest, at 0 degrees and 30 degrees. The present research indicates that the bcl 2 gene plays an important role in regulating neuronal loss following axon injury. Particular attention is drawn to the fact that the functional recovery of mice lacking this gene is weaker than that of wild-type mice.

Results. The differences observed in the recovery time of function in individual parameters of the treadmill alignment also reflect the dynamic changes taking place in the regenerating nerve. Mice lacking the bcl-2 gene regain their lost functions less clearly.

Conclusions. It is worth emphasizing the necessity to use intensified training. The rapid functional recovery in wild-type mice training at different levels thus demonstrates the importance of the presence of the bcl-2 gene, which clearly plays a decisive role here.

Key words

functional recovery, physical effort, Animal models

INTRODUCTION

In the context of therapy and rehabilitation, it is crucial to understand the mechanisms modulating the expression of genes regulating apoptosis, which can translate into faster functional recovery after injuries. Research into this process utilizes a wide range of tools to assess the impact of individual anti-apoptotic BCL-2 family proteins. This allows us to better understand how the balance between pro- and anti-apoptotic signals affects the fate of cells in various tissues, including nervous tissue. Two distinct apoptotic pathways have been defined: the extrinsic and the mitochondrial apoptosis pathways. Apoptosis is an evolutionarily conserved mechanism and is subject to precise regulation. The inhibition of apoptosis may promote the development of tumours, while abnormal apoptosis is linked to various neurodegenerative diseases. The process of apoptosis is based on the action of proteases called caspases, which, once activated, rapidly dismantle the cells destined for death, ensuring that this process occurs without triggering an immune response. In conditions of proper bodily balance, apoptosis does not induce inflammation because activated caspases simultaneously silence pro-inflammatory pathways. It is increasingly recognized that under specific conditions, such as caspase inhibition, apoptosis and apoptotic mechanisms can be transformed into an inflammatory process [1–4].

Physical training plays a significant role in human life, not only contributing to the improvement of the body's motor functions but also positively influencing the emotional and psychological state, conditioning good physical and mental well-being. Studies show that physical activity lowers levels of neurotoxic, pro-inflammatory and pro-apoptotic factors, while raising factors that inhibit apoptosis, neurotrophic factors, and neurotransmitters. These mechanisms include the regulation of the expression of the apoptotic proteins Bcl-2 and Bax. A better understanding of molecular mechanisms indicates that physical training is not just a simple activity but a series of biochemical reactions. These complex interactions affect our health on many levels. In this way, movement becomes one of the most important tools for prevention and therapy [5, 6].

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DNA recombination technologies enable the development of transgenic animal models for use in studies of many diseases and biological conditions [7]. In this study, a detailed analysis of the process of recovering motor function in transgenic mice was performed, taking into account the intensity of exercise. It is worth noting that the relationship between physical activity and the nervous system is twofold: movement supports the formation of new neurons and promotes brain plasticity, while changes within neurons help improve the body's function during exercise. Understanding these mechanisms becomes key to preventing disorders of physical and mental health [8, 9]. Exercises, therefore, are a useful tool in restoring autonomy and have a beneficial effect on recovery after peripheral nerve injuries [10].

Studies conducted on rodents show that endurance exercises modulate a range of cellular and molecular responses to peripheral nerve damage, thereby stimulating nerve regeneration and recovery after experimental damage within the peripheral nervous system. Treadmill running increases the number of regenerating neurons, affects the rate of axonal growth, the extent of muscle reinnervation after peripheral nerve damage, and the release of neurotrophins and growth factors in the spinal cord, damaged nerve, and reinnervating muscles. By using modern molecular techniques (e.g., mRNA expression analysis, Western blot, caspase activity assays), it is possible to study the effect of specific Bcl-2 proteins on cell survival [11–13].

The present study conducted on mice with damaged sciatic nerves are fully justified, as they allow for determining the optimal minimum time and intensity of exercise, and also enable a better understanding of the mechanisms responsible for functional improvement. Intensive training may particularly support neuronal plasticity, accelerate axonal growth, and increase muscle reinnervation, leading to faster recovery of motor functions.

MATERIALS AND METHOD

Due to the introduced genetic modifications within the group of Bcl-deficient mice, it was necessary to genotype them to confirm the presence of the introduced mutations. The study used mice of the line: 129S1/SvImJ-Bcl2^{tm1Mpin}/J from the (Jackson Laboratory, Bar Harbor, in the (ME), USA. These are animals with disabled expression of the gene encoding the Bcl-2 protein, used in research on processes related to cell apoptosis. Due to the introduced genetic modifications of the examined animals, it was necessary to genotype them to confirm the presence of the introduced mutations. The genotypes of all tested mice were confirmed by PCR tests, performed before the sciatic nerve injury (SNI) and on days 7, 14, 21 and 28 after the procedure. All the mice were genotyped from tail DNA prior to being assigned to proper experimental groups. The animals were housed individually in cages, provided with constant access to food and water. Access to light depended on the daily cycle.

Animals were divided into test groups – operated animals, SNI – group A, B, C, D:

Group A: Bcl-2 deficient mice, trained (no slope).
Group B: Wild-type, trained mice (no slope).
Group C: Bcl-2 deficient mice, trained (30° incline slope).
Group D: Wild-type, trained mice (30° incline slope).

There were 25 males in each group, 100 animals in total (50 mutants and 50 wild-type mice). Additionally, some of the animals underwent moderate training – groups A, B (at 0 degree treadmill angle) and intensified – groups C, D (the incline angle of the treadmill is 30 degrees).

All experimental procedures were approved by the Local Bioethics Commission for Experiments Animals at the Silesian Medical University (SUM) in Katowice (Approval No. 88/2015 of 01/07/2015). All surgeries and euthanasia were performed with general anaesthesia to minimize suffering.

Nerve injury procedure was performed in the operating room of the SUM Experimental Medicine Centre. Under general anaesthesia (thiopental sodium), administered intra-peritoneal at a dose of 420 mg / kg b.w. under aseptic conditions, after shaving and disinfecting the skin with Skinsept (Skinsept Pur, ECOLAB), the skin was incised on the outer surface of the mouse thigh (incision length – 1 cm). Right sciatic nerve was exposed using surgical instruments approximately 5 mm in front of the trifurcation, and crushed using a Yasargil Aneurysm Clip mini temporary with a force of 70.0 gms/0.69 N, duration 60 seconds. The wound was then fitted with 4/0 sutures. Neomycin ointment (5 mg/ g) was applied locally to prevent wound superinfection. After the procedure, the animals were given paracetamol (suspension 120 mg/5 ml) for 3 days in drinking water.

Treadmill training. Exercise was begun on the third day following injury, for 30 minutes a day, and then for 5 days a week for 4 weeks after unilateral sciatic nerve crush injury, at a speed of 20 m / min., without rest at 0 and 30 degrees. Mice were bred in adapted rooms of the SUM Experimental Medicine Centre under standard conditions (12 hour light cycle, standard feed and water *ad libitum*). The experiments were carried out between 09:00 – 14:00.

CatWalk analysis. To evaluate locomotor and gait related parameters before and after the nerve injury, the CatWalk Gait Analysis tool was use. Before starting the evaluation, several test runs were carried out to habituate the animals to the test conditions. The test itself consisted in registering the traces left by the test animal as it moved along the glass plate. Each mouse made at least 2 uninterrupted passes through the area viewed by the camera, which were then subjected to semi-automatic analysis using dedicated software. The computer programme automatically recognized the individual paws of the animal (dividing them into front and back, and right and left), remembering and analyzing the individual fingers of each paw while walking. The gait analysis was performed with the following detection parameters: Camera gain = 28.51, Intensity threshold = 0.32. One of the most difficult, and at the same time most important stage of the study, is the appropriate selection of the analyzed parameters.

Determining the normal course of CatWalk analysis included rejecting those in which the animals displayed additional behavioural activities, such as sniffing or stopping, sudden braking or acceleration. The parameters obtained during the above-mentioned analysis were analyzed in groups, comparing the difference between individual paws or pairs of paws, the ratio of the injured right leg result / left leg result (% ratio) were measured.

Statistical analysis. Performed using Statistica 13,3 by Statsoft. Descriptive statistics were performed. The studied

variables were described numerically by means of: mean, maximum, minimum, standard deviation, standard error, median and modal values, and in tabular and / or graphic form. The Shapiro-Wilk W test and the Lilliefors test were used to test the normality of the distribution of quantitative variables. Two-way and observed frequencies were used to characterize the categorical ordinal variables. The Kruskall-Wallis test was used to test the statistical significance of the differences in quantitative variables between the groups (in the case of no agreement with the normal distribution) or ANOVA (in the case of compliance with the normal distribution). To verify the hypotheses and determine the level of statistical significance of differences in paired data, quantitative variables from dependent measurements (subsequent studies) the RIR Tukey test was used.

RESULTS

All parameters generated by CatWalk were analyzed. Due to the multitude of results obtained, it was decided to present those in which statistical significance was found. For CatWalk parameters graphical presentation statistical analyses results as a relative values ratio right injured leg to left untouched leg results ratio (% ratio).

On days 7 and 14, the greatest differences between the groups were visible [Fig. 1]. The intersection of the curves at days 21 and 28 suggests fundamental differences in neuromuscular plasticity. For the wild-type mice, training was a stimulant, whereas for Bcl-2 mutants, it became a factor influencing the lengthening of the stride cycle, which proves their reduced ability to rapidly adapt to motor activity due to the lack of a protein regulating cell death. The value of the parameter clearly differs from the value in the group of wild mice subjected to intense training (group D) (Fig. 2). The results in this group may have been influenced by the fact that the mice shifted their body weight towards the front paws, and away from the hind legs as they moved faster. This weight shift is possibly a speed increasing strategy.

On days 7 and 14, the greatest statistical differences were observed between the studied groups of animals (Fig. 3). Analysis of the Duty Cycle parameter allows the evaluation of improvement of paw contact with the ground. The wild mice trained in a moderate and intensified manner (Group B and Group D) showed significantly lower values on the days 7 and 14 after injury. A relatively slower improvement of the parameter was shown by the Bcl-deficient mice training on an incline treadmill (Group C). The results were interpreted as a ratio of specific parameters from the left (injured) paw to the right. This comparison allowed for the assessment of gait asymmetry, ignoring variables such as body weight or running speed. A score above 1 indicates that the stride cycle of the injured paw is longer than that of the uninjured paw. The animal moves more cautiously on the injured side, which in the time-course analysis is manifested by a 'stretched' stride. A score below 1 indicates that the stride cycle of the injured paw is shorter than that of the uninjured paw, and may be associated with an analgesic (pain-relieving) gait, in which the mouse attempts to unload the injured paw as quickly as possible (Fig. 3).

Step cycle: defined by the duration of a paw's full contact with the glass (stand), through the forward movement of the paw in the air (swing), until its next contact. *Increase:*

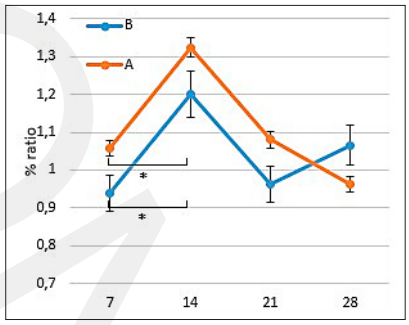

Figure 1. Comparison of changes in the Step Cycle parameter in all study groups with sciatic nerve injury (right leg results/left leg results ratio). (A) Bcl-2 mice, trained (no slope). (B) Wild-type, trained mice (no slope)

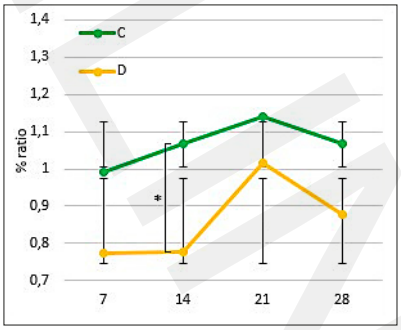

Figure 2. Comparison of changes in the Step Cycle parameter in all study groups with sciatic nerve injury (right leg results/left leg results ratio). (C) Bcl-2 mice, trained (30 degrees incline slope). (D) Wild-type, trained mice (30 degrees incline slope)

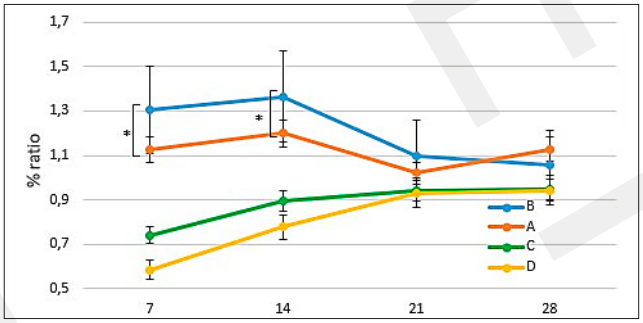

Figure 3. Comparison of changes in the Duty Cycle parameter in all study groups (right leg results/left leg results ratio)

longer step cycle time suggests slower gait. *Decline:* shorter cycle time indicates faster movement.

Duty cycle: expresses stance duration as a percentage of the duration of the step cycle, calculated as follows: *Duty cycle:* stand/stand + swing *100 %. *Increase:* higher percentage of time in ground contact suggests a more stable gait. *Decline:* lower percentage of contact time may indicate faster, more dynamic movement, but also potentially greater risk of losing balance.

Swing: Time that the hind paw is not in contact with the glass floor. Swing [s]. *Increase:* more time in the air indicates more dynamic movement or more uncertain stepping. *Decline:* less time in the air may suggest a more confident and stable gait.

Most interesting statistical differences in the above-mentioned parameter on the days 7, 14 and 21–28 after injury (Fig. 4). Significant statistical differences (marked

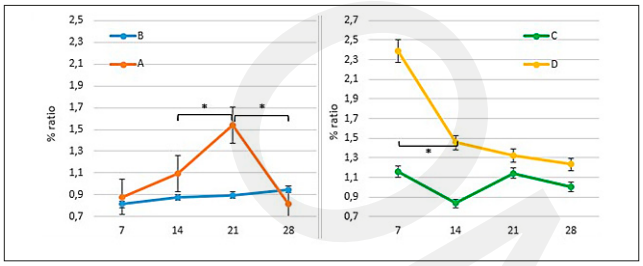

Figure 4. Swing comparison in all groups of mice (right leg results/left leg results ratio)

with asterisks on the graph) emphasize that both the presence of the Bcl-2 gene and the type of training have a measurable and significant impact on the recovery process after sciatic nerve injury. Wild-type mice (group B) demonstrate a stable, low % ratio, indicating optimal gait function compared to group A. In group A, the improvement is temporary but less effective. The greatest improvement is seen in group D. Intensive training combined with the presence of Bcl-2 protein results in the fastest and most pronounced return to previously lost function. Values quickly approach normal. In group C, despite intensive training, the lack of Bcl-2 limits full functional recovery.

It is worth emphasizing that physical exercise, including locomotor training, positively affects the nervous system by stimulating the expression of neurotrophic factors such as BDNF. Intensive training (groups C and D) is likely more intense, leading to a stronger neurotrophic response.

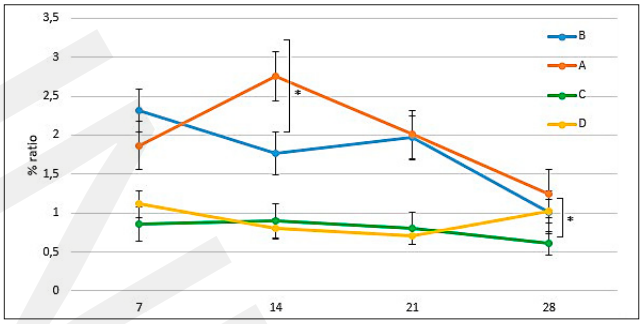

Figure 5. Comparison of changes in the Print Area parameter (right leg results/left leg results ratio). The average of the hind paw print areas in groups

Print Area: measures the amount of skin in physical contact with the floor. The average of the hind paw print areas.

Significant statistical differences at day 14 (p=0.027) and day 28 (p=0.035 RIR Tukey test) after injury (Fig. 5). Particularly noteworthy is the group of Bcl-deficient mice with moderate training (Group A). This group clearly differs from the others with the value of the parameter, possibly due to the transfer of body weight to the injured paw. This phenomenon, in turn, may indicate the occurrence of superficial sensory disturbances and the balance to the limb with the damaged sciatic nerve, which was confirmed by the von Frey filament examination of sensation (data not included).

Print Length: describes the length (horizontal direction) of the complete paw print. *Increase:* longer prints, which may indicate a stronger stride or greater propulsive force. *Decline:* shorter prints, which may suggest weakness or less muscle involvement in movement.

Changes in the above-mentioned parameter starts from day 7 until day 14 after injury in Group B (p=0.021) and between

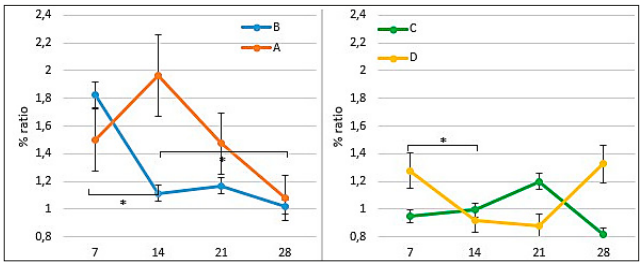

Figure 6. Comparison of changes in the Print Length [cm] parameter

days 14 and 28 in Group A (p=0.112 Kruskall-Wallis test) (Fig. 6). Relatively best results were observed in upslope Group (C, D) on day 14 after nerve injury. The results for the Print Length parameter indicated less foot contact with the ground in mice during moderate training. Similar results were obtained in terms of the paw leg length. On day 7, the highest values of the above-mentioned parameter were achieved by mice running at an angle of 30 degrees. Of these two groups, Bcl-deficient mice regain their normal gait function much faster (on day 21 from injury C) (Fig.7). Statistical significance was obtained on days 7 and 28 after injury. The greatest changes in the study groups occur on days 7 and 14 after injury. Better values are obtained by mice running at an angle of 30 degrees (Group C and Group D). Statistical significance was found on days 7, 14, 21 after injury (Fig. 8).

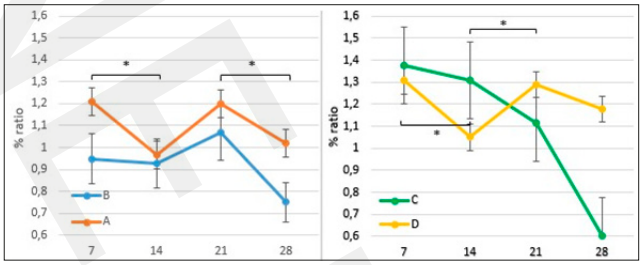

Figure 7. The Stand Index parameter describes the speed at which the paw is released from the ground

Stand index: is the speed of raising the paw from the time point of maximum contact. *Height:* longer time of contact of the paw with the ground, which may suggest greater stability or support force. *Decline:* shorter time of contact, indicates a faster reaction or difficulty in maintaining balance.

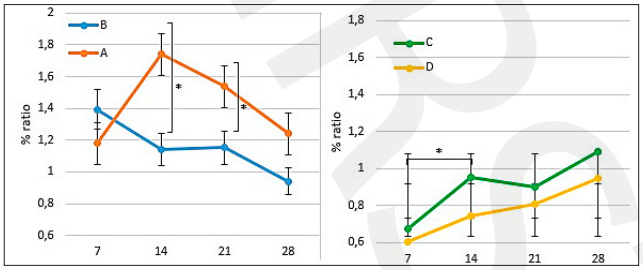

Figure 8. Comparison of the Swing speed [s] parameter in mice subjected to intensified exercise

Swing speed: indicates the speed of a swing, computed from stride length and swing duration, and expressed in pixels/seconds. *Increase:* higher speed of paw movement in the air may indicate faster movement of the animal. *Decline:* lower speed of paw movement may indicate slower and more cautious stepping.

DISCUSSION

When peripheral nerve fibres are disrupted, degeneration occurs in the distal area of the axon and may extend proximally. This process, known as Wallerian degeneration, exhibits distinct morphological features influenced by variables such as fibre type, temperature, distance from the injury, and age of the organism. Additionally, secondary degeneration may arise from mechanisms including neurotoxicity, vascular disturbances, glial scarring, apoptosis, and demyelination. These phenomena highlight the need to develop effective strategies for regeneration and rehabilitation aimed at restoring motor function as early as possible. One such approach is locomotor training.

The findings obtained demonstrate that locomotor activity has a significant impact on movement-related parameters within the first 2 weeks following sciatic nerve injury in both wild-type and bcl-2 knockout mice. Wild-type mice recovered motor and physical function more efficiently, regardless of the training regimen applied. In contrast, bcl-2-deficient mice responded more favourably to intensified exercise, with clear improvements compared to moderate training. These effects were particularly evident when analyzing functional discrepancies between the injured and uninjured hind limbs. Similar outcomes have been documented in previous studies; for example, incline treadmill training has proven more effective than flat-surface walking, enhancing running velocity. Supporting data is also emerging from sports science research, suggesting that implementing moderate treadmill exercise immediately after sciatic nerve transection may enhance axonal repair, reestablish reflexes, and improve adaptive motor responses [14].

Depending on the training modality, mice adopted various movement strategies, such as stiffening the ankle joint through co-activation of antagonistic muscles, or compensating at proximal joints [15]. Post-injury, the affected foot tended to rest flat on the treadmill, while adjustments in hip and knee joint mobility aim to preserve limb alignment, consistent with uninjured animals. This adapted gait is retained after reinnervation and reinforced by enhanced antagonist muscle coordination [16].

The most substantial improvements in the studied parameters occurred during the first 2 weeks of rehabilitation, echoing observations by Sabatier et al., who noted improved motor axon regeneration without heightened risk of degenerative processes [17]. The significance of this period is underscored by theories attributing post-axotomy neuronal death to increased oxidative stress. Other hypotheses emphasize the regulatory role of the Bcl-2 protein in apoptosis, influencing interleukin-1β conversion and modulating survival-related proteins [18]. Contemporary studies reinforce the key role of the bcl-2 gene in maintaining neuronal viability following axonal damage. Mice lacking this gene exhibit notably weaker recovery outcomes than their wild-type counterparts. Differences in the timing and extent of functional recovery—measured through treadmill-based assessments—reflect complex, ongoing neurobiological processes, including neurotrophin expression, neuronal survival, axonal outgrowth, and remyelination. The data highlight the particular importance of applying intensified locomotor training in bcl-2-deficient mice to achieve more favourable outcomes. In wild-type mice, rapid progress under varied treadmill conditions illustrates the critical contribution of Bcl-2 to effective recovery.

Although peripheral nerves are inherently capable of regeneration, the process is typically inefficient. Neurotrophic factors, especially brain-derived neurotrophic factor (BDNF), are emerging as essential modulators of axonal regrowth. Intensified treadmill training appears to enhance regenerative responses in neuropraxic injuries, and may serve as a compensatory mechanism in animals lacking Bcl-2 [19, 20].

Training intensity may also modulate glial cell behaviour. Microglia and macrophages contribute to tissue repair at the lesion site, and their proliferation, influenced by neuronal signals and astrocytic interactions, can be altered by physical activity [21, 22]. In some studies, forced treadmill running reduced microglial activity, suggesting a possible stress-mediated mechanism [23]. Voluntary or low-intensity exercise may induce lower stress levels and thus preserve glial responsiveness. Conversely, stress-triggered norepinephrine release—associated with anti-inflammatory effects—may also play a beneficial role. These mechanisms could explain why wild-type mice benefitted similarly from both moderate and intense training, while reduced microglial reactivity was observed only under milder conditions [24, 25].

Recovery after sciatic nerve damage is influenced by multiple factors, including the onset and type of training. Current evidence suggests that moderate, daily treadmill activity is a highly effective rehabilitation strategy. Endurance-based protocols initiated early after injury may shorten the recovery period, while also minimizing stress-related complications.

CONCLUSIONS

1) Locomotor training significantly influences the rate of functional recovery of damaged neural connections.
2) Moderate, daily endurance training appears to be the best form of rehabilitation after nerve injury.
3) In wild-type mice, both moderate and intense training led to rapid and effective functional improvement. This may indicate that the presence of Bcl-2 protein promotes recovery regardless of the intensity of physical exercise.
4) The early post-injury period is crucial for axonal regeneration.

The first 2 weeks after injury may be the time of intensive improvement in neurobiological processes.

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