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Free Article

Late recovery following spinal cord injury

Case report and review of the literature

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The authors of this prospective, single-case study evaluated the potential for functional recovery from chronic spinal cord injury (SCI). The patient was motor complete with minimal and transient sensory perception in the left hemibody. His condition was classified as C-2 American Spinal Injury Association (ASIA) Grade A and he had experienced no substantial recovery in the first 5 years after traumatic SCI. Clinical experience and evidence from the scientific literature suggest that further recovery would not take place. When the study began in 1999, the patient was tetraplegic and unable to breathe without assisted ventilation; his condition classification persisted as C-2 ASIA Grade A. Magnetic resonance imaging revealed severe injury at the C-2 level that had left a central fluid-filled cyst surrounded by a narrow donutlike rim of white matter. Five years after the injury a program known as "activity-based recovery" was instituted. The hypothesis was that patterned neural activity might stimulate the central nervous system to become more functional, as it does during development. Over a 3-year period (5-8 years after injury), the patient's condition improved from ASIA Grade A to ASIA Grade C, an improvement of two ASIA grades. Motor scores improved from 0/100 to 20/100, and sensory scores rose from 5-7/112 to 58-77/112. Using electromyography, the authors documented voluntary control over important muscle groups, including the right hemidiaphragm (C3-5), extensor carpi radialis (C-6), and vastus medialis (L2-4). Reversal of osteoporosis and an increase in muscle mass was associated with this recovery. Moreover, spasticity decreased, the incidence of medical complications fell dramatically, and the incidence of infections and use of antibiotic medications was reduced by over 90%. These improvements occurred despite the fact that less than 25 mm2 of tissue (approximately 25%) of the outer cord (presumably white matter) had survived at the injury level.

The primary novelty of this report is the demonstration that substantial recovery of function (two ASIA grades) is possible in a patient with severe C-2 ASIA Grade A injury, long after the initial SCI. Less severely injured (lower injury level, clinically incomplete lesions) individuals might achieve even more meaningful recovery. The role of patterned neural activity in regeneration and recovery of function after SCI therefore appears a fruitful area for future investigation

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Title: Reorganization of descending motor tracts in the rat spinal cord.

Subject(s): CENTRAL nervous system; SPINAL cord

Source: European Journal of Neuroscience, Nov2002, Vol. 16 Issue 9, p1761, 11p

Author(s): Raineteau, Olivier; Fouad, Karim; Bareyre, Florence M.; Schwab, Martin E.

Abstract: Following lesion of the central nervous system (CNS), reinnervation of denervated areas may occur via two distinct processes: regeneration of the lesioned fibres or/and sprouting from adjacent intact fibres into the deafferented zone. Both regeneration and axonal sprouting are very limited in the fully mature CNS of higher vertebrates, but can be enhanced by neutralizing the neurite outgrowth inhibitory protein Nogo-A. This study takes advantage of the distinct spinal projection pattern of two descending tracts, the corticospinal tract (CST) and the rubrospinal tract (RST), to investigate if re-innervation of denervated targets can occur by sprouting of anatomically separate, undamaged tracts in the adult rat spinal cord. The CST was transected bilaterally at its entry into the pyramidal decussation. Anatomical studies of the RST in IN-1 antibody-treated rats showed a reorganization of the RST projection pattern after neutralization of the myelin associated neurite growth inhibitor Nogo-A. The terminal arborizations of the rubrospinal fibres, which are normally restricted to the intermediate layers of the spinal cord, invaded the ventral horn but not the dorsal horn of the cervical spinal cord. Moreover, new close appositions were observed, in the ventral horn, onto motoneurons normally receiving CST projections. Red nucleus microstimulation experiments confirmed the reorganization of the RST system. These observations indicate that mature descending motor tracts are capable of significant intraspinal reorganization following lesion and suggests the expression of cues guiding and/or stabilizing newly formed sprouts in the adult, denervated spinal cord.[ABSTRACT FROM AUTHOR]

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Plasticity of motor systems after incomplete spinal cord injury.

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Although spontaneous regeneration of lesioned fibres is limited in the adult central nervous system, many people that suffer from incomplete spinal cord injuries show significant functional recovery. This recovery process can go on for several years after the injury and probably depends on the reorganization of circuits that have been spared by the lesion. Synaptic plasticity in pre-existing pathways and the formation of new circuits through collateral sprouting of lesioned and unlesioned fibres are important components of this recovery process. These reorganization processes might occur in cortical and subcortical motor centres, in the spinal cord below the lesion, and in the spared fibre tracts that connect these centres. Functional and anatomical evidence exists that spontaneous plasticity can be potentiated by activity, as well as by specific experimental manipulations. These studies prepare the way to a better understanding of rehabilitation treatments and to the development of new approaches to treat spinal cord injury.

Publication Types:
- Review
- Review, Tutorial

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Abstract View

CYTOGENESIS AND IMPROVED FUNCTIONAL RECOVERY AFTER ENRICHED ENVIRONMENT IN THE SPINAL CORD INJURED RAT.

G.C.Koopmans[1]; R.Minnaard[2]; R.Deumens[1]; H.P.-J.Steinbusch[1]; H.W.M.Steinbusch[1]; E.A.J.Joosten[1]

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Spinal cord injured rats housed in an enriched environment (EE) show better locomotor recovery than standard housed (SH) animals. The increased physical activity of rats housed in an EE may promote spinal learning and strengthen the neural circuitry, i.e. Central Pattern Generator (CPG), responsible for locomotion. In the present study it was hypothesized that increased physical activity after spinal cord contusion injury (SCCI) stimulates the formation and integration of newly formed cells in the neural circuitry of the CPG.

Thirty two adult male Wistar rats, received a SCCI by making use of a weight-drop technique (12.5 mm at T11) or were sham operated. The first three weeks after the surgery the animals were housed individually in standard cages, after which 3 injections of Bromodeoxyuridine (BrdU) (100 mg/kg) were administered over a 12 h period with an inter-injection interval of 6h. After the last injection the animals were randomly divided into four groups: group 1 SCCI-EE (n=12), group 2 SCCI-SH (n=12), group 3 sham-EE (n=4) and group 4 sham-SH (n=4) respectively. The animals stayed in these housing conditions for 2 months.

Functional recovery was measured by the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale, BBB subscale, the Gridwalk and the Catwalk. In situ mechanical properties of isometric contractions of the intact ankle dorsal flexor complex was assessed with an experimental device.

The present study shows that exposure to the enriched environment improves gross and fine locomotor recovery. Immunocytochemical staining resulted in clearly recognizable BrdU-labelled cells. We observed abundant BrdU-positive cells throughout the rat lumbar spinal cord. The maximal torque generated by the dorsal flexor complex was lower in SCI-animals than in the sham operated animals.

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G.C. Koopmans, R. Minnaard, R. Deumens, H.P.-J. Steinbusch, H.W.M. Steinbusch, E.A.J. Joosten. CYTOGENESIS AND IMPROVED FUNCTIONAL RECOVERY AFTER ENRICHED ENVIRONMENT IN THE SPINAL CORD INJURED RAT. Program No. 498.9. *2003 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience, 2003. Online.

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Abstract View

EXERCISE COMPENSATES FOR DECREASES IN BDNF AND SYNAPTIC PLASTICITY IN THE INJURED SPINAL CORD.

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In addition to protecting neurons against various insult types, BDNF promotes neuronal excitability and synaptic facilitation, required for neuronal function. We have shown that exercise increases levels of BDNF in the spinal cord, and here we investigate the role of exercise in promoting synaptic plasticity in the injured spinal cord. The spinal cord (SC) of adult male rats was hemisected at a mid-thoracic level (T7-T9). One week after surgery, the rats were exposed to voluntary running wheels for 0, 3, 7, or 28 days. Taqman RT-PCR measured changes in gene expression levels, and protein levels were determined using ELISA or Western blots in the lumbar SC region. BDNF and synapsin I mRNA were reduced to about 80% of intact controls in the lesioned side SC at all time points examined. BDNF protein levels measured at 28 days were reduced to about 50% of controls. Exercise compensated for the reductions in BDNF with a progressive effect up to 28 days. Exercise increased levels of synapsin I, a downstream effector for the action of BDNF on synaptic plasticity, only after 28 days. CREB, a transcription factor important for neuroplasticity and learning and memory under regulation of BDNF, measured at 28 days showed an injury-related decrease and exercise compensated for this decrease. These results are consistent with the concept that BDNF modulation induced by exercise can play a role in facilitating recovery of locomotion following spinal cord injury. These actions of exercise can be achieved by activating synaptic pathways under the regulatory role of BDNF. (Supported by NIH awards NS38978, NS39522, and UCLA Brain Injury Research Center).

Support Contributed By: NIH awards NS38978, NS39522, and UCLA Brain Injury Research Center

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Eur J Neurosci. 2001 Mar;13(6):1078-84.

Differential regulation by exercise of BDNF and NT-3 in rat spinal cord and skeletal muscle.

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We have investigated the impact of neuromuscular activity on the expression of neurotrophins in the lumbar spinal cord region and innervating skeletal muscle of adult rats. Rats were exercised on a treadmill for 1 day or 5 consecutive days and euthanized at 0, 2 or 6 h after the last bout of exercise. By Day 1, there was no clear evidence of an increase in brain-derived neurotrophic factor (BDNF) mRNA in the spinal cord or the soleus muscle. By Day 5, there was a significant increase in BDNF mRNA in the spinal cord at 2 h post-training, and the soleus muscle showed a robust increase between 0 and 6 h post-training. Immunoassays showed significant increases in BDNF protein in the soleus muscle by training Day 5. Immunohistochemical analyses showed elevated BDNF levels in motoneuron cell bodies and axons in the ventral horn. Neurotrophin-3 (NT-3) mRNA was measured to determine whether selected neurotrophins respond with a selective pattern of induction to neuromuscular activity. In the spinal cord, there was a progressive post-training decrease in NT-3 mRNA following a single bout of training, while there was a significant increase in NT-3 mRNA at 2 h post-training by Day 5. The soleus muscle showed a progressive increase in NT-3 mRNA by Days 1 and 5 following training. These results show that neuromuscular activity has specific effects on the BDNF and NT-3 systems, and that repetitive exercise affects the magnitude and stability of these responses.

PMID: 11285004 [PubMed - indexed for MEDLINE]

Neuroreport. 2002 Dec 20;13(18):2527-30.

Related Articles, Links

Exercise increases mRNA levels for adhesion molecules N-CAM and L1 correlating with BDNF response.

Macias M, Fehr S, Dwornik A, Sulejczak D, Wiater M, Czarkowska-Bauch J, Skup M, Schachner M.

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In situ hybridization was used to evaluate whether long-term moderate locomotor exercise, which up-regulates BDNF and TrkB levels in the spinal gray matter of the adult rat, similarly influences the expression of the cell adhesion molecules N-CAM and L1. Exercise doubled the level of N-CAM mRNA hybridization signal in the lumbar spinal gray. The increase in L1 mRNA was less consistent. N-CAM mRNA levels slightly increased in the white matter. BDNF mRNA levels also increased in cells of the ventral horn and the white matter due to the exercise. These results suggest that exercise-induced rearrangements of the spinal network involve N-CAM, L1 and BDNF, crucial in different aspects of synaptic plasticity and synapse formation.

PMID: 12499861 [PubMed - indexed for MEDLINE]

Acta Neurobiol Exp (Wars). 2000;60(3):371.

Related Articles, Links

Locomotion induces changes in Trk B receptors in small diameter cells of the spinal cord.

Skup M, Czarkowska-Bauch J, Dwornik A, Macias M, Sulejczak D, Wiater M.

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INTRODUCTION AND METHODS: Locomotor training leads to improvement of stepping ability in animals after spinal cord transection (1). Recent data point to neurotrophins as possible factors involved in this improvement. Motoneurones synthesising BDNF, NT-4 and NT-3 are a potent source of neurotrophins for the spinal network (2, 3). Physical exercise increases BDNF neurotrophin gene expression in the rat hippocampus (4). If exercise enhances BDNF expression also in the spinal cord, upregulation of its receptor Trk B may occur. To verify this hypothesis we tested whether exercise influences TrkB receptor system in the spinal cord. Six adult, male Wistar rats walked on the treadmill five days a week, 1,000 m daily with the speed of 20 to 25 cm/s. After 4 weeks of training animals were anaesthetised with pentobarbital sodium (80 mg/kg b.w.) and perfused with 0.01 M PBS followed by 2% paraformaldehyde and 0.2% parabenzoquinone in 0.1 M PB. Three non-trained animals were used as controls. Cryostat 40 microns sections were processed free-floating with TrkB polyclonal antibody (1:1,000, Santa Cruz) and ABC Vectastain detection system. Sections were examined under Nikon light microscope and analysed with Image-Pro Plus 4 software. RESULTS AND DISCUSSION: TrkB immunoreactivity (IR) was detected in number of spinal cells at the lumbar level in non-trained animals (Fig. 1A). The strongest IR appeared in the perikarya and processes of small diameter cells rarely scattered in the grey and white matter. The average area of these cells was 50 micron 2 (+/- 10). Exercise increased by over 50% the number of TrkB immunostained small cells (Fig. 1B). An enhancement of perikaryonal immunostaining of these cells was also observed (Fig. 1B, inset). Testing the identity of Trk B IR small diameter cells did not prove their astroglial (GFAP IR) and gabaergic (GAD IR) phenotype in the grey matter. Some of TrkB IR cells in the white matter were astrocytes. Our data point to physical exercise as a potent method to make spinal cells more receptive to neurotrophic stimuli.

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J Neurosci. 2001 May 15;21(10):3457-75.

Neurotrophic factors and receptors in the immature and adult spinal cord after mechanical injury or kainic acid.

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Delivery of neurotrophic factors to the injured spinal cord has been shown to stimulate neuronal survival and regeneration. This indicates that a lack of sufficient trophic support is one factor contributing to the absence of spontaneous regeneration in the mammalian spinal cord. Regulation of the expression of neurotrophic factors and receptors after spinal cord injury has not been studied in detail. We investigated levels of mRNA-encoding neurotrophins, glial cell line-derived neurotrophic factor (GDNF) family members and related receptors, ciliary neurotrophic factor (CNTF), and c-fos in normal and injured spinal cord. Injuries in adult rats included weight-drop, transection, and excitotoxic kainic acid delivery; in newborn rats, partial transection was performed. The regulation of expression patterns in the adult spinal cord was compared with that in the PNS and the neonate spinal cord. After mechanical injury of the adult rat spinal cord, upregulations of NGF and GDNF mRNA occurred in meningeal cells adjacent to the lesion. BDNF and p75 mRNA increased in neurons, GDNF mRNA increased in astrocytes close to the lesion, and GFRalpha-1 and truncated TrkB mRNA increased in astrocytes of degenerating white matter. The relatively limited upregulation of neurotrophic factors in the spinal cord contrasted with the response of affected nerve roots, in which marked increases of NGF and GDNF mRNA levels were observed in Schwann cells. The difference between the ability of the PNS and CNS to provide trophic support correlates with their different abilities to regenerate. Kainic acid delivery led to only weak upregulations of BDNF and CNTF mRNA. Compared with several brain regions, the overall response of the spinal cord tissue to kainic acid was weak. The relative sparseness of upregulations of endogenous neurotrophic factors after injury strengthens the hypothesis that lack of regeneration in the spinal cord is attributable at least partly to lack of trophic support.

PMID: 11331375 [PubMed - indexed for MEDLINE]

Muscle Nerve. 2004 Jan;29(1):73-81.

Exercise-induced gene expression in soleus muscle is dependent on time after spinal cord injury in rats.

Dupont-Versteegden EE, Houle JD, Dennis RA, Zhang J, Knox M, Wagoner G, Peterson CA.

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Cycling exercise attenuates atrophy in hindlimb muscles and causes changes in spinal cord properties after spinal cord injury in rats. We hypothesized that exercising soleus muscle expresses genes that are potentially beneficial to the injured spinal cord. Rats underwent spinal cord injury at T10 and were exercised on a motor-driven bicycle. Soleus muscle and lumbar spinal cord tissue were used for messenger RNA (mRNA) analysis. Gene expression of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) was elevated 11- and 14-fold, respectively, in soleus muscle after one bout of exercise performed 5 days after spinal cord transection. Also, c-fos and heat shock protein-27 (HSP27) mRNA abundance were increased 11- and 7-fold, respectively. When exercise was started 2 days after the injury, the changes in gene expression were not observed. By contrast, at 2 but not at 5 days after transection, expression of the HSP27 gene was elevated sixfold in the lumbar spinal cord, independent of exercise. Electromyographic activity in soleus muscles was also decreased at 2 days, indicating that the spinal cord was less permissive to exercise at this early time. Long-term exercise for 4 weeks attenuated muscle atrophy equally well in rats started at 2 days or 5 days after injury. We conclude that BDNF and GDNF released from exercising muscle may be involved in exercise-induced plasticity of the spinal cord. Furthermore, the data suggest that the lumbar spinal cord undergoes time-dependent changes that temporarily impede the ability of the muscle to respond to exercise.

PMID: 14694501 [PubMed - indexed for MEDLINE]

J Neuropathol Exp Neurol. 2002 Feb;61(2):142-53.

Related Articles, Links

Effects of brain-derived neurotrophic factor (BDNF) on compression-induced spinal cord injury: BDNF attenuates down-regulation of superoxide dismutase expression and promotes up-regulation of myelin basic protein expression.

Ikeda O, Murakami M, Ino H, Yamazaki M, Koda M, Nakayama C, Moriya H.

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Neurotrophins enhance the survival of cells in the nervous system under both physiological and pathological conditions, such as those caused by disease or trauma. We recently demonstrated that expression of brain-derived neurotrophic factor (BDNF) was up-regulated in neurons and glia after compression-induced spinal cord injury (SCI). We show here the effects of BDNF on the oligodendrocyte survival and functional recovery after SCI. The effects of intrathecally administered BDNF on both Cu/Zn superoxide dismutase (CuZnSOD) and myelin basic protein (MBP) expression were examined using rats that had received compression-induced spinal cord injury. CuZnSOD expression in the spinal cord was down-regulated within 24 h of compression-induced injury and then recovered. Continuous infusion of BDNF inhibited the acute down-regulation of CuZnSOD expression. In situ hybridization showed that CuZnSOD was expressed in both neurons and glia. Although MBP expression was greatly reduced after injury, BDNF administration promoted the recovery of MBP expression nearly to a control level after 2 wk. Furthermore, BDNF administration also prompted behavioral recovery. These results suggest BDNF's usefulness in human clinical applications. The attenuation of CuZnSOD down-regulation may be related to a protective effect of BDNF and the promotion of MBP up-regulation may be related to a long-lasting restorative effect.

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Acta Neuropathol (Berl). 2001 Sep;102(3):239-45.

Acute up-regulation of brain-derived neurotrophic factor expression resulting from experimentally induced injury in the rat spinal cord.

Ikeda O, Murakami M, Ino H, Yamazaki M, Nemoto T, Koda M, Nakayama C, Moriya H.

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Brain-derived neurotrophic factor (BDNF), a member of the nerve growth factor family of trophic factors, has multiple functions including a role in the promotion of neuronal survival and nerve fiber elongation in both the central and the peripheral nervous systems. We assessed the expression of endogenous BDNF following an experimentally induced compression injury to the spinal cord. Expression of BDNF mRNA was increased following the spinal cord injury; reaching maximum levels 24 h after the injury. Expression of BDNF mRNA returned to the levels observed in sham-operated control animals within 3 days of the injury. Using the in situ hybridization technique, we observed a wide distribution of BDNF expression among the different cell types in the spinal cord, including motor and sensory neurons, and in glia cells, including astrocytes. We also observed expression of BDNF in putative macrophages and/or microglia; however, this effect was not observed until day 7 following spinal cord injury. These results suggest that BDNF is synthesized in both neurons and astrocytes during the acute response to injury to the spinal cord, functioning in a mainly neuroprotective role. This is followed by a later phase of expression in which BDNF is produced by macrophages and/or microglia, apparently functioning in a restorative capacity.

Neuroreport. 1996 Sep 2;7(13):2221-5.

Related Articles, Links

Treatment with genetically engineered fibroblasts producing NGF or BDNF can accelerate recovery from traumatic spinal cord injury in the adult rat.

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We tested the hypothesis that NGF or BDNF can protect damaged neural structures following spinal cord injury. Spinal contusions were produced in adult rats by a weight drop method. Thereafter, unmodified Rat 1 fibroblasts or fibroblasts engineered to secrete NGF or BDNF were injected into the injury site. Weekly assessments of recovery were made for 6 weeks using a locomotor rating scale. All rats were immediately paraplegic, then began to recover. At 1 week after injury, the ratings of locomotor performance in rats implanted with NGF- or BDNF-secreting fibroblasts were significantly increased over those of rats implanted with unmodified fibroblasts. This trend toward enhanced recovery persisted during the duration of the experiment, although the difference became smaller. Histological examination after 6 weeks showed a larger cross-sectional area of spinal cord at the maximal injury site in the animals treated with NGF or BDNF. These results demonstrate a significant biological effect of treatment with neurotrophins in traumatic spinal cord injury.

PMID: 8930993 [PubMed - indexed for MEDLINE]

J Neurotrauma. 2003 Jun;20(6):603-12.

GDNF and BDNF alter the expression of neuronal NOS, c-Jun, and p75 and prevent motoneuron death following spinal root avulsion in adult rats.

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In the present study, we examined the effects of glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), and insulin growth factor (IGF-1) on adult motoneuron survival following spinal root avulsion. The expression of neuronal nitric oxide synthase (nNOS), c-Jun, and the low-affinity neurotrophin receptor (P75) following treatment with these neurotrophic factors was also examined. In control animals, approximately 80% of spinal motoneurons were nNOS positive at 3 weeks following the lesion, whereas in GDNF or BDNF treated animals no nNOS positive motoneurons were found at the same time point. Following injury and treatment with GDNF and BDNF increased numbers of motoneurons were c-Jun and P75 positive. By 6 weeks following the lesion, only approximately 28% of motoneurons persisted in control animals whereas about 90% of motoneurons survived injury following treatment with either GDNF or BDNF. In contrast, CNTF and IGF-1 were ineffective in either inhibiting nNOS expression or preventing motoneuron death. Our results provide in vivo evidence that the survival of injured adult mammalian motoneurons can be promoted by specific neurotrophic factors, and that this effect is associated with inhibition of nNOS expression and up-regulation of c-Jun and P75 expression.

PMID: 12906744 [PubMed - indexed for MEDLINE]

Exp Neurol. 1997 Dec;148(2):475-94.

Related Articles, Links

FULL-TEXT ARTICLE

Neurotrophic factors increase axonal growth after spinal cord injury and transplantation in the adult rat.

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The capacity of CNS neurons for axonal regrowth after injury decreases as the age of the animal at time of injury increases. After spinal cord lesions at birth, there is extensive regenerative growth into and beyond a transplant of fetal spinal cord tissue placed at the injury site. After injury in the adult, however, although host corticospinal and brainstem-spinal axons project into the transplant, their distribution is restricted to within 200 micron of the host/transplant border. The aim of this study was to determine if the administration of neurotrophic factors could increase the capacity of mature CNS neurons for regrowth after injury. Spinal cord hemisection lesions were made at cervical or thoracic levels in adult rats. Transplants of E14 fetal spinal cord tissue were placed into the lesion site. The following neurotrophic factors were administered at the site of injury and transplantation: brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), ciliary-derived neurotrophic factor (CNTF), or vehicle alone. After 1-2 months survival, neuroanatomical tracing and immunocytochemical methods were used to examine the growth of host axons within the transplants. The neurotrophin administration led to increases in the extent of serotonergic, noradrenergic, and corticospinal axonal ingrowth within the transplants. The influence of the administration of the neurotrophins on the growth of injured CNS axons was not a generalized effect of growth factors per se, since the administration of CNTF had no effect on the growth of any of the descending CNS axons tested. These results indicate that in addition to influencing the survival of developing CNS and PNS neurons, neurotrophic factors are able to exert a neurotropic influence on injured mature CNS neurons by increasing their axonal growth within a transplant.

PMID: 9417827 [PubMed - indexed for MEDLINE]

J Neurotrauma. 2000 Dec;17(12):1219-31.

Related Articles, Links

Effect of brain-derived neurotrophic factor, nerve growth factor, and neurotrophin-3 on functional recovery and regeneration after spinal cord injury in adult rats.

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This study examined whether continuous intramedullary infusion of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), or neurotrophin-3 (NT-3) had either an early neuroprotective effect or a delayed effect on regeneration after spinal cord injury (SCI) in adult rats. BDNF, NGF, NT-3 or vehicle was infused at a rate of 625 ng/h into the SCI site at T3 through an implanted cannula attached to an osmotic pump. This infusion was maintained for 14 days after a 35-g clip compression injury. At 4 weeks after injury, the axonal tracer fluorogold (FG) was introduced into the spinal cord caudal to the lesion and the animals sacrificed 3 days later following behavioral assessment. The inclined plane score was significantly higher in BDNF-treated animals (45 +/- 3 degrees) compared to control animals (36 -/+ 1 degrees) at 1 week after injury ($p < 0.05$), although the scores were not significantly different at later times. BDNF-treated animals also showed more FG-labeled cells in the red nucleus and sensorimotor cortex (1,638 +/- 350 and 124 +/- 83, respectively) compared to controls (1,228 +/- 217 and 36 +/- 15, respectively) and a lower percent cavitation at the injury site (21.4 +/- 10.4%) compared to control animals (32.3 +/- 11.7%). Invasion & proliferation of Schwann cells and formation of peripheral myelin were more prominent at the injury site in the BDNF-treated animals than in the other groups. These results indicate that continuous intramedullary infusion of BDNF provides neuroprotection and enhances some regenerative activity after SCI.

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Exp Neurol. 2002 Aug;176(2):289-307.

Long-term locomotor training up-regulates TrkB(FL) receptor-like proteins, brain-derived neurotrophic factor, and neurotrophin 4 with different topographies of expression in oligodendroglia and neurons in the spinal cord.

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Neurotrophins are potent regulators of neuronal survival, maintenance, and synaptic strength. In particular, brain-derived neurotrophic factor (BDNF), acting through full-length TrkB receptor (TrkB(FL)), is implicated in the stimulation of neurotransmission. Physical activity has been reported to increase BDNF expression in the brain and spinal cord. In this study we have evaluated the hypothesis that activation of a spinal neuronal network, due to exercise, affects the entire spinal neurotrophin system acting via TrkB receptors by modulation of BDNF, neurotrophin 4 (NT-4), and their TrkB receptor proteins. We investigated the effect of treadmill walking (4 weeks, 1 km daily) on distribution patterns and response intensity of these proteins in the lumbar spinal cord of adult rats. Training enhanced immunoreactivity (IR) of both neurotrophins. BDNF IR increased in cell processes of spinal gray matter, mainly in dendrites. NT-4 IR was augmented in the white matter fibers, which were, in part, of astrocytic identity. Training strongly increased both staining intensity and number of TrkB(FL)-like IR small cells of the spinal gray matter. The majority of these small cells were oligodendrocytes, representing both their precursor and their mature forms. In contrast, training did not exert an effect on expression of the truncated form of TrkB receptor in the spinal cord. These results show that both neuronal and nonneuronal cells may be actively recruited to BDNF/NT-4/TrkB(FL) neurotrophin signaling which can be up-regulated by training. Oligodendrocytes of the spinal gray matter were particularly responsive to exercise, pointing to their involvement in activity-driven cross talk between neurons and glia.

PMID: 12359171 [PubMed - indexed for MEDLINE]

J Neurosci Res. 2003 Oct 15;74(2):221-6.

Neurotrophic factors expressed in both cortex and spinal cord induce axonal plasticity after spinal cord injury.

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We reported recently that overexpression of neurotrophin-3 (NT-3) by motoneurons in the spinal cord of rats will induce sprouting of corticospinal tract (CST) axons (Zhou et al. [2003] J. Neurosci. 23:1424-1431). We now report that overexpression of brain-derived neurotrophic factor (BDNF) or glial cell-derived neurotrophic factor (GDNF) in the rat sensorimotor cortex near the CST neuronal cell bodies together with overexpression of NT-3 in the lumbar spinal cord significantly increases axonal sprouting compared to that induced by NT-3 alone. Two weeks after unilaterally lesioning the CST at the level of the pyramids, we injected rats with saline or adenoviral vectors (Adv) carrying genes coding for BDNF (Adv.BDNF), GDNF (Adv.GDNF) or enhanced green fluorescent protein (Adv.EGFP) at six sites in the sensorimotor cortex, while delivering Adv.NT3 to motoneurons in each of these four groups on the lesioned side of the spinal cord by retrograde transport from the sciatic nerve. Four days later, biotinylated dextran amine (BDA) was injected into the sensorimotor cortex on the unlesioned side to mark CST axons in the spinal cord. Morphometric analysis of axonal sprouting 3 weeks after BDA injection showed that the number of CST axons crossing the midline in rats treated with Adv.BDNF or Adv.GDNF were 46% and 52% greater, respectively, than in rats treated with Adv.EGFP or PBS ($P < 0.05$). These data demonstrate that sustained local expression of neurotrophic factors in the sensorimotor cortex and spinal cord will promote increased axonal sprouting after spinal cord injury, providing a basis for continued development of neurotrophic factor therapy for central nervous system damage.

PMID: 14515351 [PubMed - indexed for MEDLINE]

Gene Expr. 2005;12(2):107-21. Related Articles, Links

Exercise-induced gene expression changes in the rat spinal cord.

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There is growing evidence that exercise benefits recovery of neuromuscular function from spinal cord injury (SCI). However, the effect of exercise on gene expression in the spinal cord is poorly understood. We used oligonucleotide microarrays to compare thoracic and lumbar regions of spinal cord of either exercising (voluntary wheel running for 21 days) or sedentary rats. The expression data were filtered using statistical tests for significance, and K-means clustering was then used to segregate lists of significantly changed genes into sets based upon expression patterns across all experimental groups. Levels of brain-derived neurotrophic factor (BDNF) protein were also measured after voluntary exercise, across different regions of the spinal cord. BDNF mRNA increased with voluntary exercise, as has been previously shown for other forms of exercise, contributed to by increases in both exon I and exon III. The exercise-induced gene expression changes identified by microarray analysis are consistent with increases in pathways promoting neuronal health, signaling, remodeling, cellular transport, and development of oligodendrocytes. Taken together these data suggest cellular pathways through which exercise may promote recovery in the SCI population.

PMID: 15892452 [PubMed - indexed for MEDLINE]

Brain Res. 2003 Oct 10;987(1):93-9.

Voluntary exercise increases neurotrophin-3 and its receptor TrkC in the spinal cord.

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We have evaluated changes in the expression of neurotrophin-3 (NT-3) and its tyrosine kinase C (TrkC) receptor in the neuromuscular system as a result of voluntary physical activity. We assessed changes in the mRNAs and proteins for NT-3 and TrkC in the lumbar spinal cord and associated soleus muscle following 3 and 7 days of voluntary wheel running. We used quantitative Taqman RT-PCR to measure mRNA and ELISA to assess protein levels. NT-3 mRNA and protein levels increased in the spinal cord to reach statistical significance after 7 days of exercise compared to sedentary control rats. Immunohistochemical analyses localized the elevated NT-3 to the substantia gelatinosa (SG) and nucleus of the dorsal horn. TrkC mRNA levels were significantly elevated in the spinal cord after 3 and 7 days of running. In the soleus muscle, NT-3 mRNA levels and its receptor TrkC were elevated after 3 days, while NT-3 protein levels remained unaffected. The results demonstrate that voluntary exercise has a differential effect on NT-3 as well as its receptor TrkC in the neural and muscular components of the neuromuscular system, and emphasize the role of voluntary activity on the spinal cord and muscle.

PMID: 14499950 [PubMed - indexed for MEDLINE]

☐ 1: Proc Natl Acad Sci U S A. 1995 Oct 10;92(21):9771-5.

Related Articles, Links

Rescue of adult mouse motoneurons from injury-induced cell death by glial cell line-derived neurotrophic factor.

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Glial cell line-derived neurotrophic factor (GDNF) has been shown to rescue developing motoneurons in vivo and in vitro from both naturally occurring and axotomy-induced cell death. To test whether GDNF has trophic effects on adult motoneurons, we used a mouse model of injury-induced adult motoneuron degeneration. Injuring adult motoneuron axons at the exit point of the nerve from the spinal cord (avulsion) resulted in a 70% loss of motoneurons by 3 weeks following surgery and a complete loss by 6 weeks. Half of the loss was prevented by GDNF treatment. GDNF also induced an increase (hypertrophy) in the size of surviving motoneurons. These data provide strong evidence that the survival of injured adult mammalian motoneurons can be promoted by a known neurotrophic factor, suggesting the potential use of GDNF in therapeutic approaches to adult-onset motoneuron diseases such as amyotrophic lateral sclerosis.

PMID: 7568215 [PubMed - indexed for MEDLINE]

Exp Neurol. 2003 Oct;183(2):508-15.

Gene transfer of glial cell line-derived neurotrophic factor promotes functional recovery following spinal cord contusion.

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Neuronal cell death and the failure of axonal regeneration cause a permanent functional deficit following spinal cord injury (SCI). Administration of recombinant glial cell line-derived neurotrophic factor (GDNF) has previously been reported to rescue neurons following severe SCI, resulting in improved hindlimb locomotion in rats. In this study, thus, GDNF gene therapy using an adenoviral vector (rAd-GDNF) was examined in rats following SCI induced by dropping the NYU weight-drop impactor from a height of 25 mm onto spinal segment T9-T10. To evaluate the efficacy of intraspinal injection of recombinant adenovirus into the injured spinal cord, we observed green fluorescent protein (GFP) gene transfer in the contused spinal cord. GFP was effectively expressed in the injured spinal cord, and the most prominently transduced cells were astrocytes. The expression of GDNF was detected only in rats receiving rAd-GDNF, not the controls, and remained detectable around the injured site for at least 8 days. Open-field locomotion analysis revealed that rats receiving rAd-GDNF exhibited improved locomotor function and hindlimb weight support compared to the control groups. Immunohistochemical examination for the neuronal marker, calcitonin gene-related peptide (CGRP), showed an increase in CGRP+ neuronal fibers in the injured spinal cord in rats receiving rAd-GDNF treatment. Collectively, the results suggest that adenoviral gene transfer of GDNF can preserve neuronal fibers and promote hindlimb locomotor recovery from spinal cord contusion. This research should provide information for developing a clinical strategy for GDNF gene therapy.

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Trends Neurosci. 2002 Sep;25(9):462-7.

Do human bipeds use quadrupedal coordination?

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Tackling the question of whether control of human gait is based on that of a quadrupedal locomotion system is of basic and practical relevance. During evolution, the increased influence of a direct cortical-motoneuronal system in parallel with more specialized hand function might have replaced phylogenetically older systems that organized locomotor movements. However, recent research indicates that interlimb coordination during human locomotion is organized in a similar way to that in the cat. Hence, it is hypothesized that during locomotion, corticospinal excitation of upper limb motoneurons is mediated indirectly, via propriospinal neurons in the cervical spinal cord. This allows a task-dependent neuronal linkage of cervical and thoraco-lumbar propriospinal circuits controlling leg and arm movements during human locomotor activities. The persistence of such movement control has consequences for rehabilitation and the applicability of animal research to human patients with spinal cord injury.

Publication Types:
- Review
- Review, Tutorial

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A mechanized gait trainer for restoration of gait

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Abstract--The newly developed gait trainer allows wheelchair-bound subjects the repetitive practice of a gait-like movement without overstressing therapists. The device simulates the phases of gait, supports the subjects according to their abilities, and controls the center of mass (CoM) in the vertical and horizontal directions. The patterns of sagittal lower limb joint kinematics and of muscle activation for a normal subject were similar when using the mechanized trainer and when walking on a treadmill. A non-ambulatory hemiparetic subject required little help from one therapist on the gait trainer, while two therapists were required to support treadmill walking. Gait movements on the trainer were highly symmetrical, impact free, and less spastic. The vertical displacement of the CoM was bi-phasic instead of mono-phasic during each gait cycle on the new device. Two cases of non-ambulatory patients, who regained their walking ability after 4 weeks of daily training on the gait trainer, are reported.

Key words: *center of mass (CoM), gait rehabilitation, gait trainer.*

Abstract View

ALTERNATE LEG MOVEMENTS CONTRIBUTE TO AMPLIFY LOCOMOTOR-LIKE MUSCLE ACTIVITY IN SPINAL CORD INJURED PATIENTS.

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Locomotor-like electromyographic (EMG) activity can be induced even in the paralyzed lower limb muscles of patients with spinal cord injury (SCI) by imposing stepping movements to their both legs. Although the significant role of the afferent input related to hip joint movement and body load has been emphasized considerably in the previous studies, the contribution of "alternate" leg movement pattern has not been fully investigated. The present study was designed to investigate to what extent the alternate leg movement influenced the locomotor-like EMG activity. The knee-locked leg swing movement was imposed on 6 complete SCI patients using a gait training device. The following four different experimental conditions were adopted; (i) unilateral movement, (ii) bilateral synchronous (in-phase) movement, (iii) bilateral alternate (anti-phase) movement, and (iv) bilateral alternate movement with the body weight partially (50%) unloaded. In all experimental conditions, the passive leg movement induced the EMG activity in the soleus and gastrocnemius muscles in all SCI patients and in the biceps femoris muscle in 5 of 6 patients. The EMG level quantified by the mean amplitude of EMG activity was significantly larger for alternate leg movement than for unilateral and bilateral synchronous movements, although the hip and ankle joint movements were identical in all experimental conditions. For example, the bilateral alternate leg movement increased soleus EMG level by approximately 200% as compared to unilateral and bilateral synchronous leg movement conditions. Furthermore, unloading the body weight tended to make the EMG activity level greater. These results suggest that the alternate leg movements and its interaction with load information play a substantial role to amplify the induced the locomotor-like muscle activity in the lower limb.

Support Contributed By: the Japanese Ministry of Health, Labour and Welfare

Abstract View

NEURAL REORGANIZATION OF THE FUNCTIONALLY ISOLATED HUMAN SPINAL CORD OCCURS AFTER STAND TRAINING.

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The functionally isolated human spinal cord has been shown to respond to the level of limb load during stepping. In spinal cord injured subjects who had undergone repetitive step training lower limb EMG activity was higher at higher limb load levels indicating that load is an important sensory cue in generating locomotor patterns. In this study our aim was to assess whether repetitive limb loading over several weeks can induce reorganization of the functionally isolated human spinal cord. We assessed whether specific afferent cues related to the regimen of specific repetitive limb load patterns would alter the efferent response to the same kinematic and kinetic cues. Six functionally complete spinal cord injured subjects were randomly assigned to a training intervention consisting of 80 sessions of either bilateral or unilateral limb loading. We recorded bilateral hip, knee and ankle angles, individual limb loads and bilateral electromyography (EMG) from sixteen lower limb muscles during manually assisted bilateral and unilateral standing and stepping using body weight support on a treadmill. Data were measured before and after each training intervention. Standing and stepping EMG patterns were modulated by the pattern of repetitive limb loading. When the same kinematics and kinetics were presented both the timing and amplitude of the lower limb EMG were altered. Further, efferent responses following training were similar among subjects who received the same training intervention during standing and stepping paradigms. These results indicate that relearning a specific motor task may be highly dependent on the specific repetitive afferent stimuli provided when supraspinal input is limited.

Support Contributed By: HA2-0201-2B, 030-495-84

Abstract View

NEURAL ADAPTATION WITH LOCOMOTOR TRAINING IN THE FUNCTIONALLY ISOLATED HUMAN SPINAL CORD.

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We test a locomotor model from animal literature with three components that interact to generate the motor pattern from the human spinal cord during stepping the: 1) intrinsic functional organization of interneurons; 2) central state of excitability (CSE); and 3) ensemble of afferent information that is provided. We studied the lower limb motor patterns from 18 clinically complete spinal cord injured (SCI) subjects during clonus, and during manually assisted standing and stepping using body weight support on a treadmill before and after repetitive step training. Electromyographic (EMG) activity during stepping at different treadmill speeds the same day and before and after repetitive training showed a similar change in motor output. At the slower speed and pre-training there was clonic EMG activity and co-contraction of flexors and extensors of the same limb. At the higher treadmill speed and post-training clonic EMG activity was reduced and flexors and extensors of the same leg alternated. Pre-training patterns induced by manually assisted stepping using BWST were highly variable among SCI subjects some subjects there was minimal or no EMG activity. We suggest the varied EMG patterns before training comprise of different levels of adaptation that occur after SCI injury. All SCI subjects generated EMG activity that was modulated differently at the same load, speed and kinematics after training. Flexor activity was prominent and maintaining extension during stance was a challenge in SCI subjects chronically unloaded before training. This was reduced after training as evidenced by the lower limb EMG activity. These results suggest that the functionally isolated human spinal cord can adapt to the specificity of repetitively provided sensory cues. We also suggest that the interneurons that generate locomotor activity in humans also contribute to other movements including clonus.

Support Contributed By: NIH/NINDS R01 36854 and P01 16333

Citation:
S.J. Harkema, J. Beres-Jones, C.K. Ferreira. NEURAL ADAPTATION WITH LOCOMOTOR TRAINING IN THE FUNCTIONALLY ISOLATED HUMAN SPINAL CORD. Program No. 493.10. *2003 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience, 2003. Online.

Close

Abstract View

MOTOR RECOVERY AFTER CERVICAL SPINAL CORD INJURY: A POSSIBLE ROLE FOR POST-INJURY ACTIVITY.

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Altered post-injury activity has been shown to affect anatomical plasticity and sensorimotor recovery after either cortical or thoracic spinal cord injuries. No study to date, however, has investigated the effects of altering post-injury activity after cervical spinal cord injury in an adult animal model. Cervical spinal cord injuries disrupt ascending and descending supraspinal and segmental pathways, as well as segmental neurons and permanently impair forelimb sensorimotor function. We investigated the effects of increasing post-injury activity (enriched environment) on forelimb motor recovery after cervical spinal cord injury. Following C4-5 over-hemisections, animals were housed in either standard or enriched environments for 10 weeks. Forelimb movements were evaluated during multiple activities including skilled reaching, grooming, exploration, and locomotion at 4, 6 and 8 weeks. Preliminary results indicate that increased post-injury activity improved recovery of locomotion but not automatic or skilled forelimb movements. Specifically, using the "CatWalk" automated quantitative gait analysis system we observed that both the forelimb base of support and swing phase of gait were closer to normal in lesioned animals housed in enriched environments than those housed in standard environments. These observations suggest that increased post-injury activity can improve postural alignment and proximal forelimb motor control during a rhythmic alternating movement after cervical spinal cord injury.

Support Contributed By: NIH NS 27054 and T32 HD 07459.

Citation:
J.V. Lynskey, M. McAtee, H.N. Dai, E. Iarikov, F.P.T. Hamers, B.S. Bregman. MOTOR RECOVERY AFTER CERVICAL SPINAL CORD INJURY: A POSSIBLE ROLE FOR POST-INJURY ACTIVITY. Program No. 498.10. *2003 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience, 2003. Online.

Am J Physiol Cell Physiol 275: C1124-C1133, 1998;
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Early changes in muscle fiber size and gene expression in response to spinal cord transection and exercise

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Muscles of spinal cord-transected rats exhibit severe atrophy and a shift toward a faster phenotype. Exercise can partially prevent these changes. The goal of this study was to investigate early events involved in regulating the muscle response to spinal transection and passive hindlimb exercise. Adult female Sprague-Dawley rats were anesthetized, and a complete spinal cord transection lesion (T_{10}) was created in all rats except controls. Rats were killed 5 or 10 days after transection or they were exercised daily on motor-driven bicycles starting at 5 days after transection and were killed 0.5, 1, or 5 days after the first bout of exercise. Structural and biochemical features of soleus and extensor digitorum longus (EDL) muscles were studied. Atrophy was decreased in all fiber types of soleus and in type 2a and type 2x fibers of EDL after 5 days of exercise. However, exercise did not appear to affect fiber type that was altered within 5 days of spinal cord transection: fibers expressing myosin heavy chain 2x increased in soleus and EDL, and extensive coexpression of myosin heavy chain in soleus was apparent. Activation of satellite cells was observed in both muscles of transected rats regardless of exercise status, evidenced by increased accumulation of MyoD and myogenin. Increased expression was transient, except for MyoD, which remained elevated in soleus. MyoD and myogenin were detected both in myofiber and in satellite cell nuclei in both muscles, but in soleus, MyoD was preferentially expressed in satellite cell nuclei, and in EDL, MyoD was more readily detectable in myofiber nuclei, suggesting that MyoD and myogenin have different functions in different muscles. Exercise did not affect the level or localization of MyoD and myogenin expression. Similarly, Id-1 expression was transiently increased in soleus and EDL upon spinal cord transection, and no effect of exercise was observed. These results indicate that passive exercise can ameliorate muscle atrophy after spinal cord transection and that satellite cell activation may play a role in muscle plasticity in response to spinal cord transection and exercise. Finally, the mechanisms underlying maintenance of muscle mass are likely distinct from those controlling myosin heavy chain expression.

: Muscle Nerve. 2004 Feb;29(2):234-42.

Passive exercise and fetal spinal cord transplant both help to restore motoneuronal properties after spinal cord transection in rats.

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Spinal cord transection influences the properties of motoneurons and muscles below the lesion, but the effects of interventions that conserve muscle mass of the paralyzed limbs on these motoneuronal changes are unknown. We examined the electrophysiological properties of rat lumbar motoneurons following spinal cord transection, and the effects of two interventions shown previously to significantly attenuate the associated hindlimb muscle atrophy. Adult rats receiving a complete thoracic spinal cord transection (T-10) were divided into three groups receiving: (1) no further treatment; (2) passive cycling exercise for 5 days/week; or (3) acute transplantation of fetal spinal cord tissue. Intracellular recording of motoneurons was carried out 4-5 weeks following transection. Transection led to a significant change in the rhythmic firing patterns of motoneurons in response to injected currents, as well as a decrease in the resting membrane potential and spike trigger level. Transplants of fetal tissue and cycling exercise each attenuated these changes, the latter having a stronger effect on maintenance of motoneuron properties, coinciding with the reported maintenance of structural and biochemical features of hindlimb muscles. The mechanisms by which these distinct treatments affect motoneuron properties remain to be uncovered, but these changes in motoneuron excitability are consistent with influences on ion conductances at or near the initial segment. The results may support a therapeutic role for passive limb manipulation and transplant of stem cells in slowing the deleterious responses of motoneurons to spinal cord injury, such that they remain more viable for subsequent alternative strategies.

PMID: 14755488 [PubMed - indexed for MEDLINE]

Abstract View

VOLUNTARY WHEEL RUNNING IMPROVES RECOVERY FROM A CONTUSION INDUCED SPINAL CORD INJURY.

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Recently, locomotor training has been shown to improve overground locomotion in patients with spinal cord injury (SCI). This has triggered renewed interest in the role of exercise in rehabilitation after SCI. However, animal models of the role of exercise in the recovery of function following SCI are lacking. Here, we show that in mice, exercise in the form of voluntary wheel running improves recovery from SCI. C57Bl/10 female mice received a T9 moderate contusion injury after 3 weeks of voluntary wheel running or 3 weeks of standard single housing conditions. Following a 7-day recovery period, running mice were returned to their running wheels. Weekly open-field behavior measured locomotor recovery using a BBB scale adapted for mice. By 14 days post-SCI, running mice had significantly higher BBB scores than sedentary mice. Using a repeated measures ANOVA across the 8 weeks of testing, locomotor recovery of running mice was significantly improved compared to sedentary animals ($p<.05$). Therefore, exercise can be beneficial to recovery from SCI.

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Supported treadmill ambulation training after spinal cord injury: a pilot study.

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OBJECTIVES: To conduct a pilot study of weight-supported ambulation training after incomplete spinal cord injury (SCI), and to assess its safety. DESIGN: Quasiexperimental, repeated measures, single group. SETTING: Veterans Affairs medical center. PATIENTS: Three subjects with incomplete, chronic, thoracic SCIs; 2 classified as D on the American Spinal Injury Association (ASIA) impairment scale and 1 as ASIA impairment scale C. INTERVENTION: Subjects participated in 12 weeks of training assisted by 2 physical therapists. The training consisted of walking on a treadmill while supported by a harness and a pneumatic suspension device. Support started at 40% of body weight and a treadmill speed of.16kmph, and progressed by reducing support and increasing treadmill speed and continuous treadmill walking time up to 20 minutes. Training was conducted for 1 hour per day, 5 days per week for 3 months. Treadmill walking occurred for 20 minutes during the sessions. MAIN OUTCOME MEASURES: Gait function (speed, endurance, walking status, use of assistive device and orthotics); oxygen costs of walking; brain motor control assessment; self-report indices; ASIA classification; muscle function test; and safety. RESULTS: All 3 subjects increased gait speed (.118m/s initially to.318m/s after training 12wk), and gait endurance (20.3m/5min initially to 63.5m/5min). The oxygen costs decreased from 1.96 to 1.33mL x kg(-1) x m(-1) after 12 weeks of training. CONCLUSIONS: This pilot study suggests that supported treadmill ambulation training can improve gait for individuals with incomplete SCIs by using objective gait measures. The self-report indices used have promise as patient-centered outcome measures of this new form of gait training. A larger, controlled study of this technique is warranted.

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Exercise restores levels of neurotrophins and synaptic plasticity following spinal cord injury.

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We have conducted studies to determine the potential of exercise to benefit the injured spinal cord using neurotrophins. Adult rats were randomly assigned to one of three groups: (1) intact control (Con); (2) sedentary, hemisected at a mid-thoracic level (Sed-Hx), or (3) exercised, hemisected (Ex-Hx). One week after surgery, the Ex-Hx rats were exposed to voluntary running wheels for 3, 7, or 28 days. BDNF mRNA levels on the lesioned side of the spinal cord lumbar region of Sed-Hx rats were approximately 80% of Con values at all time points and BDNF protein levels were approximately 40% of Con at 28 days. Exercise compensated for the reductions in BDNF after hemisection, such that BDNF mRNA levels in the Ex-Hx rats were similar to Con after 3 days and higher than Con after 7 (17%) and 28 (27%) days of exercise. After 28 days of exercise, BDNF protein levels were 33% higher in Ex-Hx than Con rats and were highly correlated (r=0.86) to running distance. The levels of the downstream effectors for the action of BDNF on synaptic plasticity synapsin I and CREB were lower in Sed-Hx than Con rats at all time points. Synapsin I mRNA and protein levels were higher in Ex-Hx rats than Sed-Hx rats and similar to Con rats at 28 days. CREB mRNA values were higher in Ex-Hx than Sed-Hx rats at all time points. Hemisection had no significant effects on the levels of NT-3 mRNA or protein; however, voluntary exercise resulted in an increase in NT-3 mRNA levels after 28 days (145%). These results are consistent with the concept that synaptic pathways under the regulatory role of BDNF induced by exercise can play a role in facilitating recovery of locomotion following spinal cord injury.

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Related Articles, Links

Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus.

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Exercise is an important facet of behavior that enhances brain health and function. Increased expression of the plasticity molecule brain-derived neurotrophic factor (BDNF) as a response to exercise may be a central factor in exercise-derived benefits to brain function. In rodents, daily wheel-running exercise increases BDNF gene and protein levels in the hippocampus. However, in humans, exercise patterns are generally less rigorous, and rarely follow a daily consistency. The benefit to the brain of intermittent exercise is unknown, and the duration that exercise benefits endure after exercise has ended is unexplored. In this study, BDNF protein expression was used as an index of the hippocampal response to exercise. Both daily exercise and alternating days of exercise increased BDNF protein, and levels progressively increased with longer running duration, even after 3 months of daily exercise. Exercise on alternating days was as effective as daily exercise, even though exercise took place only on half as many days as in the daily regimen. In addition, BDNF protein remained elevated for several days after exercise ceased. Further, after prior exercise experience, a brief second exercise re-exposure insufficient to cause a BDNF change in naive animals, rapidly reinduced BDNF protein to levels normally requiring several weeks of exercise for induction. The protein reinduction occurred with an intervening "rest" period as long as 2 weeks. The rapid reinduction of BDNF by an exercise stimulation protocol that is normally subthreshold in naive animals suggests that exercise primes a molecular memory for BDNF induction. These findings are clinically important because they provide guidelines for optimizing the design of exercise and rehabilitation programs, in order to promote hippocampal function.

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