Chapter 3

Pathophysiology of Peripheral Nerve Injury

Mary F. Barbe, PhD, and Ann E. Barr, DPT, PhD

"To kill an error is as good a service as, and sometimes even better than, the establishing of a new truth or fact."

—Charles Darwin (1809–1882)

Objectives

On completion of this chapter, the student/practitioner will be able to:

- Relate the structural anatomy of the peripheral nerve to the etiologies of injury.
- Outline the role of cytokines in the inflammatory cascade of peripheral nerve injury.
- Define spinal cord sensitization as it relates to peripheral nerve injury.
- Define the local and systemic impact of peripheral nerve inflammation.
- Define "fibrosis" as it relates to peripheral nerve injury.

Key Terms

- Fibrosis
- Inflammation
- Neuropathy
- Overuse

Introduction

Neuropathies can result from mechanical trauma, such as shear or compressive forces on the nerve, particularly if repeated, and have been linked to the following risk factors: gender (female), advanced age, and reduced fitness.[1–4] Patients with median nerve **neuropathy** report symptoms such as pain in the hands and wrists or fingers that may travel into the forearm, elbow, and shoulder; paresthesias; numbness; and weakness.[5] An objective diagnosis of median nerve dysfunction is typically based on electrophysiological evidence of slowed median nerve conduction localized to the wrist, although the combination of electrodiagnostic findings and symptom characteristics is reported to provide the most accurate diagnosis of carpal tunnel syndrome (CTS).[2]

Peripheral Nerve Damage and Inflammation With Overuse

Risk factors for the development of neuropathies include the performance of jobs characterized by repetitiveness, forcefulness, or awkward postures.[1,3,6,7] A relationship between advancing age and susceptibility to other risk factors for neuropathies has also been reported,[3,5,6,8] albeit one longitudinal study suggested that slowing of conduction in the median nerve occurs naturally with increasing age.[4] CTS has the highest incidence rate of all occupation-related peripheral neuropathies, with 10,780 combined cases reported to the U.S. Occupational Safety and Health Administration in 2009 by private industry and state and local government, resulting in a median of 21 lost workdays per case. The overall CTS incidence rate affects 1 in 10,000

workers. Among female workers, CTS affects 1.5 in 10,000 workers, whereas among men, CTS affects 0.7 in 10,000 workers. The incidence rate for CTS was highest among workers 45 to 64 years old (1.5 in 10,000) compared with rates of 0.3 in 10,000 for workers 20 to 24 years old and 0.7 in 10,000 for workers 25 to 34 years old.[8] In a 3-year prospective study of incidence in newly hired workers in computer-intensive jobs, computer operators older than age 30 showed an increased risk of developing neck, shoulder, arm, and hand symptoms, such as pain, aching, burning, numbness, or tingling.[8] The most common disorder identified by the study relative to this population was somatic pain syndrome. Our laboratory has reported that patients with upper extremity **overuse** injuries have increased frequency of local signs of pain and tenderness, peripheral nerve irritation and weakness, and increased frequency of these symptoms at multiple anatomical sites (mean age = 45 years; age range, 19 to 74 years; 23 of 31 subjects older than 30). These findings correlated with increased serum inflammatory cytokines.[9,10]

Effects of Overuse on Nerves in Human Subjects

Human studies examining tissue biopsy specimens in patients with long-term chronic overuse syndromes found evidence of nerve compression and injury, **inflammation, fibrosis,** and degeneration. Freeland et al.[11] detected increased tenosynovium interleukin (IL)-6, an inflammatory cytokine, and increased serum malondialdehyde, a cell injury biomarker and a reactive oxygen species that initiates arachidonic acid metabolism into products (e.g., prostaglandin E_2), in patients with CTS. As mentioned earlier, increased inflammatory cytokines have also been detected in serum of patients with early onset of moderate to severe symptoms of upper limb overuse injury,[9] presumably as a result of increased cytokines in injured or inflamed tissues. However, despite numerous epidemiological studies demonstrating a positive relationship between exposure to repetitive or forceful motion and the prevalence of overuse injuries,[1] the mechanisms of pathophysiology are incompletely understood. Animal models provide an opportunity to examine such tissue effects at a much earlier time point and under experimental conditions in which exposure can be controlled. In an effort to understand the underlying mechanisms of these disorders, we and numerous other authors have developed animal models of overuse injuries.[2,12–17]

Rat Model of Overuse Injury

Whishaw[18,19] quantified the similarities between rats and humans in targeted reach submovements of the upper extremity. Also, Viikari-Juntura[20,21] stated that laboratory studies of animals examining the effects of repetitive loading on tissue function may be extrapolated to human exposures and responses. We developed a unique rat model of voluntary repetitive reaching in which rats can be trained to perform an upper limb repetitive hand and wrist–intensive task. Reach rate and force levels used in our model, which are shown in Table 3-1, were derived from investigations of industrial workers by Silverstein et al.[22,23] They defined risk levels for repetitiveness to be high when reaching and grasping motions are performed faster than 30 sec/cycle. Force is considered negligible to low if less than 15% of maximum voluntary contraction (MVC) is required and high if it is greater than 50% of MVC. Our rat model of a paced reaching and grasping task may be generalized to humans in terms of both behavioral and tissue responses for some types of physically constrained and paced occupational tasks, as explained further elsewhere.[24,25] An example of such a paced task would be packing, in which a worker repeatedly places small objects presented on a conveyor belt into a package crate.

In our model, rats are placed into operant test chambers for rodents with a portal located in one wall, as described previously.[26–29] They are trained to perform a repetitive reaching task in which they reach through the portal to grasp and retrieve a food pellet or to grasp and isometrically pull a force handle that is attached to a force transducer, until a predetermined force threshold is reached and held for at least 50 msec. On successful achievement of reach force and time criteria, the rat releases the handle and retrieves a food pellet reward by mouth from a food trough. Using this apparatus, the short-term effects (3 to 12 weeks) of a voluntary low force task performed at low, moderate, or high reach rates, with force requirements of low or high

Table 3-1 Repetitive Task Group Parameters of the Barbe and Barr Rat Model of Overuse

Group	Target Reach Rate (Reaches/min)	Actual Reach Rate (Reaches/min)	Reach Force (% of Maximum Pull Force)
HRHF	8	12	60 ± 5
MRHF	4	9.4	60 ± 5
HRLF	8	12	15 ± 5
HRNF = MRNF	4	8	<5*
LRNF	2	3.3	<5*

HRHF = high repetition high force; MRHF = moderate repetition high force; HRLF = high repetition low force; HRNF = high repetition negligible force, redefined as MRNF based on the repetition rate; LRNF = low repetition negligible force.
*The negligible force rats retrieved a 45-mg food pellet, which was estimated to be less than 5% maximum pulling force.

(see details in Table 3-1), on sensorimotor behavior, forelimb musculoskeletal and nerve tissues, spinal cord, and brain have been determined.[26–41] With regard to the peripheral nerve, the short-term effects of repetitive or forceful tasks on nerve pathophysiology have been characterized, focusing on injury, inflammation, inflammation-induced catabolic changes, and fibrotic changes that might contribute to peripheral nerve injury and degeneration. Inflammation-induced central nervous system changes that might contribute to sensorimotor behavior changes, such as the development of pain behaviors as a result of spinal cord sensitization or the development of reduced fine motor control as a result of sensory and motor cortex reorganization, have also been investigated in our model.

Nerve Injury, Inflammation, and Fibrosis Induced by Overuse

A peripheral nerve injury mechanism has been identified in our overuse model. We have observed demyelination and focal axonal swelling in the median nerve at the level of the wrist, suggestive of focal nerve injury, in combination with increased extraneural connective tissue and fibroblasts, suggestive of nerve fibrosis (Fig. 3-1A–D).[27,28,35,36] These tissue changes were accompanied by a decrease in nerve conduction velocity (Fig. 3-1E) as well as changes in forepaw sensation and a decrease in grip strength, both significantly correlating with the declines in nerve conduction velocity (Fig. 3-2). This correlation strongly indicates that nerve compression injury is contributing to these behavioral declines. The declines in median nerve conduction were exposure-dependent with reductions ranging from 9% to 23% depending on the level of task intensity and the age of the rat, with greater losses with high repetition high force tasks and in aged rats. Chronic inflammatory responses were also induced by task performance, such as persistently increased macrophages and proinflammatory cytokines in nerves and serum (Fig. 3-1F).[26–28,30,31,40,42–44] Increased fibrotic

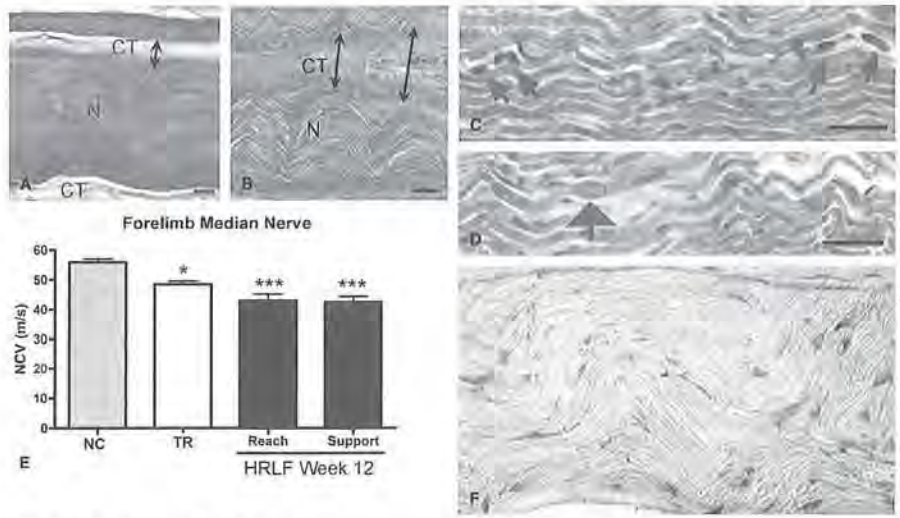


Figure 3-1 Development of pathology in median nerve in a rat model of repetitive reaching and grasping. Rats performed a high repetition low force (HRLF) task for 12 weeks. A, Median nerve of a normal control rat. B, Median nerve from 12-week HRLF rat showing an increase in connective tissue (CT), indicative of nerve fibrosis. C, Median nerve from 12-week HRLF rat showing increased inflammatory cells (arrows) within the median nerve. D, Median nerve from 12-week HRLF rat showing presence of axonal swelling (arrow), indicative of nerve injury. Scale bars = 5 μm. E, Bar graph showing decreased nerve conduction velocity (NCV) in median nerve of 12 week HRLF rats compared with normal control rats (NC) and rats that underwent the initial training only (TR). *$P < 0.05$ compared with NC. ***$P < 0.001$ compared with NC. F, Median nerve of 12-week HRLF rat showing presence of tumor necrosis factor (TNF)-α, a key proinflammatory cytokine. *(Used by permission from Elliott MB, Barr AE, Clark BD, Wade CK, Barbe MF. Performance of a repetitive task by aged rats leads to median neuropathy and spinal cord inflammation with associated sensorimotor declines. Neuroscience. 2010;170:929–941.)*

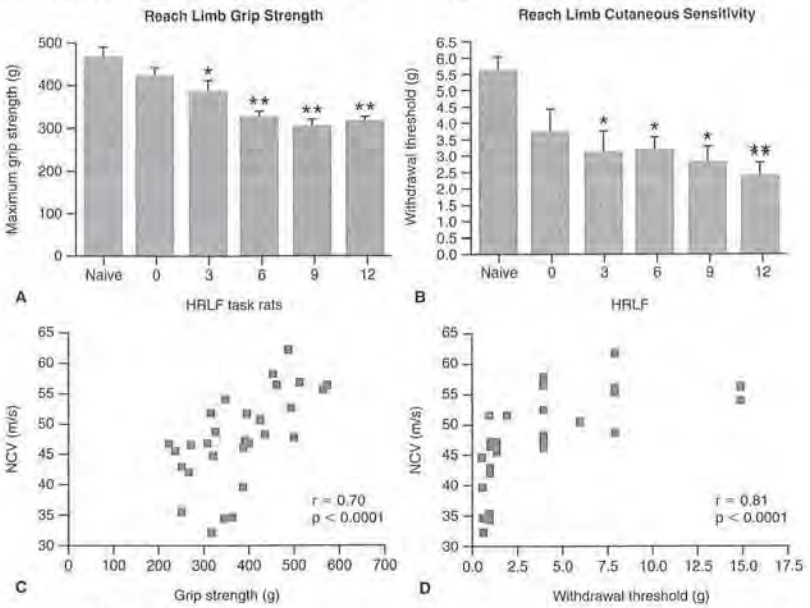


Figure 3-2 Development of grip strength declines and cutaneous hypersensitivity in the reach forelimbs of rats performing a high repetition low force (HRLF) task for 12 weeks. A, Grip strength declines from naive levels with continued task performance. B, Cutaneous hypersensitivity develops, shown as a reduction in Von Frey hair size (threshold) needed to induce a forelimb withdrawal response with continued task performance. C, Scatterplot showing positive correlation between median nerve conduction velocity (NCV) and grip strength by Spearman's *r* test. D, Scatterplot showing positive correlation between median nerve conduction velocity (NCV) and withdrawal threshold by Spearman's *r* test. $^{*}P < 0.05$ compared with NC. $^{**}P < 0.01$ compared with NC. *(Used by permission from Elliott MB, Barr AE, Clark BD, Wade CK, Barbe MF. Performance of a repetitive task by aged rats leads to median neuropathy and spinal cord inflammation with associated sensorimotor declines. Neuroscience. 2010;170:929–941.)*

tissue changes were observed in the synovial sheaths of adjacent flexor digitorum tendons,[38] which likely also contributed to compression of the median nerve.

Spinal Cord Neuroplastic Changes Induced by Peripheral Nerve Inflammation

Several studies have found phenotypic changes in dorsal root ganglion neurons in which the expression of proteins, receptors, neurotransmitters, and neurotrophic factors was altered.[45,46] For example, substance P increases in spinal cord dorsal horns following chronic constriction injury from partial nerve ligation, peripheral nerve injury, or inflammation.[46,47] This increase may be due to inflammation-induced increases in afferent synaptic input to the spinal cord through an increased rate of discharge, increased peptide production by the dorsal root ganglion, or afferent fiber phenotype alterations that favor substance P expression.[48,49] Schaible et al.[50] described this type of afferent influx of excitatory transmitters into the spinal cord dorsal horn after injury as the presynaptic component of central sensitization. An increase in neurokinin 1, a key receptor for substance P, occurs in the postsynaptic spinal cord neurons and most likely occurs as a response to the increased release of substance P from nociceptive afferent terminals.[49]

It was not a surprise to see increased substance P and neurokinin 1 in dorsal horns in cervical spinal cord regions with performance of low and moderate repetitive tasks with or without high force (Fig. 3-3).[34–37] This neurochemical response was associated temporally with a peripheral tissue macrophage or inflammatory cytokine response. This association supports the hypothesis that task-induced peripheral tissue injury

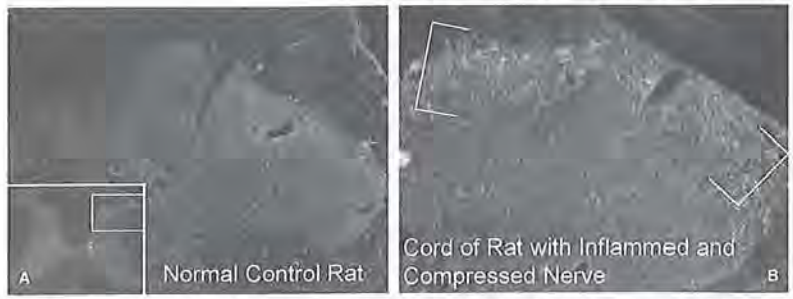


Figure 3-3 Increased substance P, a nociceptor-related neurotransmitter, in the upper laminae of the dorsal horn of cervical spinal cord segments in a rat model of repetitive reaching and grasping. Rats performed a high repetition low force (HRLF) task for 12 weeks. A, The dorsal horn of the untrained side (i.e., the support limb side), showing only a small amount of substance P immunoreactivity (dark staining; HRP-DAB reaction product) in the bracketed area. B, The dorsal horn of the trained side (i.e., the reach limb side), showing an increase of substance P immunoreactivity in the bracketed area.

and inflammation drives a spinal cord neurochemical response from nociceptive afferent terminals. Such increases in substance P and neurokinin 1 are temporally associated with mechanical hypersensitivity[47,51] and behavioral changes (see Fig. 3-2). These studies combined provide evidence that spinal cord sensitization associated with injury and inflammatory conditions may contribute to chronic pain conditions in patients with overuse injury.

Numerous studies show spinal cord inflammatory responses after unilateral peripheral nerve injury as well. For example, peripheral nerve crush or ligation leads to an increase in activated microglia and increased production of proinflammatory cytokines in neurons and glial cells in spinal cord segments innervating that nerve.[51–55] We observed increased interleukin (IL)-1β and tumor necrosis factor (TNF)-α immunoexpression in neurons within the dorsal horn superficial lamina in aged rats that had performed a moderate demand task (HRLF) for 12 weeks compared with normal control rats (Fig. 3-4A).[36]

Cortical Brain Neuroplastic Changes Induced by Repetitive Strain Injury

The possibility that both peripheral inflammatory and central cortical neuroplastic change mechanisms coexist with altered motor performance has been studied only more recently.[32] We examined primary somatosensory cortical (S1) and primary motor cortical (M1) changes in rats performing a reaching and grasping task with moderate repetition and negligible force demands for 2 hours per day, 3 days per week for 8 weeks. We found repetitive task-induced degradation of S1 neuronal properties, such as increased cortical receptive fields that represented several forepaw subdivisions (i.e., several digits or palmar pads rather than a single digit or pad), increased receptive fields that represented both glabrous and hairy surfaces, and increased cortical responsiveness to light tactile stimulation. In addition, the receptive fields located on the glabrous forepaw were significantly larger in rats performing repetitive tasks than in control rats. Also, the forepaw representation in the S1 cortical map was patchy and disrupted in rats performing repetitive tasks relative to control rats. In the aforementioned study, the enlargement of S1 receptive fields and the emergence of large receptive fields that encompassed the whole forepaw (digits and palmar pads) or dorsal hand and wrist or forearm correlated statistically with a reduction in successful reaches, an increase in the inefficient raking food retrieval pattern, and an increase in reach time. These findings support our hypothesis that ambiguous interpretation of tactile cues results in reduced motor performance, particularly with fine motor skills. These data confirm and extend data found in primates in which repetitive, rewarded hand grasp led to a dedifferentiation of the finger maps in the S1 cortex, characterized by enlarged, overlapping receptive fields; the emergence of multidigit and hairy-glabrous receptive fields; and abnormal somatosensory maps in the thalamus.[56–58]

In the motor (M1) cortex, performance of a moderate repetitive task in our model drastically increased the size of the M1 forepaw maps, especially the movement representation of the digits, digits-arm, and elbow-wrist specifically involved in the behavioral task.[32] The

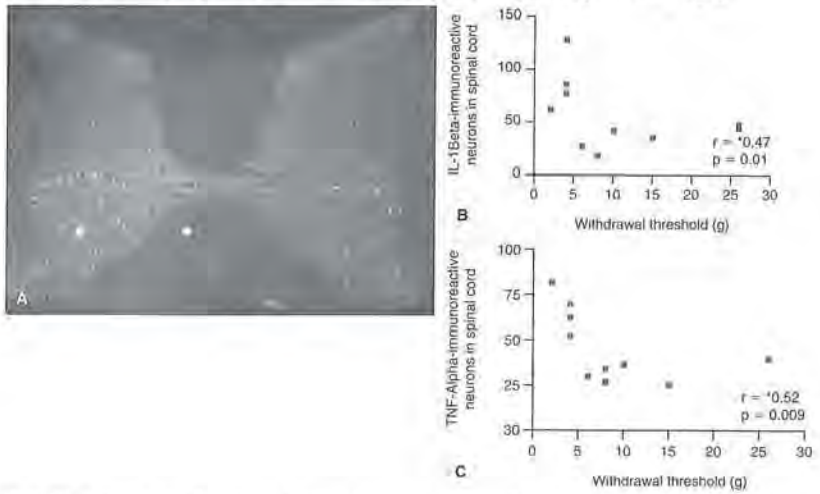


Figure 3-4 Increased proinflammatory cytokines in neurons scattered throughout the cervical spinal cord segments in a rat model of repetitive reaching and grasping. Rats performed a high repetition low force (HRLF) task for 12 weeks. A, Low-power micrograph showing increased tumor necrosis factor (TNF)-α (white staining), a key proinflammatory cytokine, in neurons throughout the spinal cord gray matter. B, Scatterplot showing negative correlation between interleukin (IL)-1β immunoreactivity in neurons and withdrawal threshold by Pearson's *r* test. C, Scatterplot showing negative correlation between TNF-α immunoreactivity n neurons and withdrawal threshold by Pearson's *r* test. *(From data generated for Elliott MB, Barr AE, Clark BD, Wade CK, Barbe MF. Performance of a repetitive task by aged rats leads to median neuropathy and spinal cord inflammation with associated sensorimotor declines. Neuroscience. 2010;170:929–941.)*

movement representation area of the elbow-wrist multijoint responses tripled, and the arm-digits multijoint areal extent was 17 times larger than in untrained rats. The cortical increase in the multijoint movement representation for elbow-wrist, arm, and arm-digits correlated strongly with the increased prevalence of a degraded reaching and grasping strategy. Unexpectedly, but interesting to consider here as well, task-induced peripheral increases in inflammatory cytokines in muscles and nerves of rats performing repetitive tasks had a strong negative correlation with not only grip strength but also with the amount of current required to evoke movements of the wrist, elbow-wrist, and arm-digits multijoints in the primary motor cortex. The higher the inflammation in flexor muscles and nerves specifically involved in the task, the lower the threshold required to elicit arm-digits movements, which was decreased in trained rats relative to controls. This latter finding suggests that the peripheral inflammatory responses are altering the cortical maps negatively and altering, in this indirect manner, the ability to perform fine motor tasks.

Links Between Pain Behaviors and Peripheral or Central Neural Changes

Peripheral Nerve Sensitization

Heightened pain sensitivity is a known consequence of increased inflammatory mediators, particularly TNF-α. Proinflammatory cytokines activate and sensitize peripheral terminals of nociceptors both directly (e.g., within the nerve) and indirectly (e.g., in surrounding tissues), leading to hypersensitivity.[59,60] We reported a correlation between increased inflammatory cytokines in the median nerve and forepaw mechanical hypersensitivity.[36] Alternatively, a task-induced systemic cytokine response may also be associated with the widespread mechanical hypersensitivity found in our rat model. We previously observed a significant correlation between reduced grip strength and task-induced increases in serum inflammatory cytokines[30,36] as well as a significant correlation between cutaneous

hypersensitivity and task-induced increases in spinal cord inflammatory cytokines (Fig. 3-4B and C).[36] These findings combined suggest that inflammation-driven peripheral sensitization contributes to sensorimotor changes with performance of repetitive tasks.

Spinal Cord Central Sensitization

The phenomenon of central sensitization is characterized by adaptations in neurons and glial cells, such as changes in neuronal structure, protein production, function, and survival within the central nervous system, which contribute to abnormal pain behaviors.[61] For example, it has been proposed that spinal cytokines released in the dorsal horn nerve terminal region ipsilateral to the affected peripheral nerve spread to nearby spinal nerve terminals and affect uninvolved peripheral nerves and central sensory processing.[62] These changes may elicit remote and contralateral sensitization effects. We have observed forepaw hypersensitivity bilaterally in our model.[25,36] However, we also showed that the nonreach limb is used as a support limb in our model.[38] The bilateral hypersensitivity responses in our study are not a type of "mirror allodynia" sometimes seen after unilateral nerve ligation, in which there is a contralateral spread of symptoms via spinal cord mechanisms,[52,62,63] but rather are due to bilateral use of the forelimbs in performing the task and then bilateral changes in the median nerves.

We have also reported the presence of hind paw mechanical hypersensitivity in our model[25,36] in limbs not involved with performing an upper extremity repetitive task. We observed hind paw mechanical hypersensitivity in aged rats performing a HRLF task for 12 weeks[36] and an early increase in hind paw sensitivity at 3 weeks in young rats performing a high repetition high force (HRHF) task (before the development of hyposensation in these latter rats). These findings are suggestive of an extraterritorial spread of symptoms via central sensitization mechanisms that may contribute to pain behaviors with overuse injuries. Studies showing mirror allodynia (mechanical hypersensitivity) or extraterritorial hyperalgesia in cases of unilateral nerve injury provide evidence of nerve injury–induced mechanisms of central sensitization.[62] We suggest that the hypersensitivity in the uninvolved hind paws in our model may be due to increased proinflammatory cytokines in cervical spinal cord affecting cells or processing in distal spinal cord segments (see Fig. 3-4).

Does Sensitization Result From Both Peripheral and Central Changes?

Signs of injury and inflammation occurring in the median nerve in addition to the spinal cord inflammatory response prevent us from separating peripheral versus central mechanisms contributing to observed cutaneous sensation changes in forepaws. Proinflammatory cytokines have been shown to sensitize peripheral terminals of nociceptors both directly and indirectly, leading to hypersensitivity.[59,60] We reported the presence of inflammatory cytokines in peripheral nerves, in musculoskeletal tissues, and widely circulating in serum in our model (see Fig. 3-1F).[25,26,30,33,38,40,44] We also reported statistical correlation between these cytokine increases, hypersensitivity, and declines in grip strength in several studies, suggesting a link between increased peripheral cytokines and pain-related behaviors with overuse injuries.

Nerve compression can be initially irritating to nerves, resulting in cutaneous hypersensitivity. Our findings of mechanical hypersensitivity in the presence of decreased nerve conduction velocity and histological findings of increased extraneuronal connective tissue and axonal swelling in the median nerve are suggestive of nerve compression with long-term repetitive task performance, particularly HRHF tasks. Hand and arm pain in the distribution of the median nerve is a common symptom in patients with electrophysiologically diagnosed CTS, particularly in patients who engage in full-time intensive manual work.[64]

With regard to central sensitivity, we can only point to numerous other studies showing spinal cord inflammatory responses after unilateral peripheral nerve injury (e.g., increased spinal cord cytokines produced by neurons and glia, increases that are temporally associated with mechanical hypersensitivity).[52,53,65–69] The contribution of central sensitization to repetition-induced hypersensitivity is also suggested by studies from our laboratory showing increased substance P and neurokinin-1 receptors in spinal cord dorsal horns.[34–37] These increases in substance P correlated statistically with declines in forelimb grip strength[34] and coincided with degraded forelimb movement patterns.[37] We have also observed increased substance P in forelimb tendons with HRHF task performance—changes that correlate strongly with declines in grip strength[38] and bring us back to a potential peripheral sensitization mechanism. We hypothesize that both mechanisms are at work in our model as well as in cases of overuse injury in which chronic pain is present.

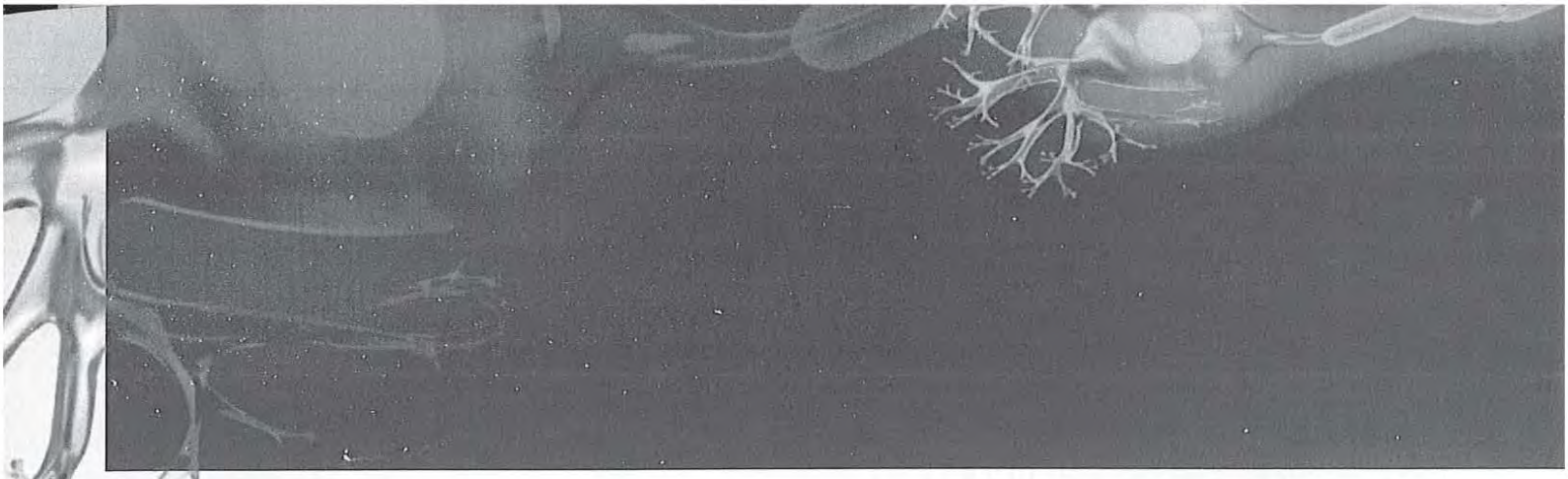
Our data from a rat model of overuse injury show that peripheral nerve injury, peripheral inflammatory responses, spinal cord sensitization, and central neuroplastic mechanisms coexist. Each of these factors appears to contribute to motor behavior declines and the development of pain-related behaviors. What was previously unknown was whether peripheral inflammation was primarily responsible for the movement performance deficits that emerge in these rats over time or whether cortical degradation was responsible for the movement defects.[56] It is clear from our studies

that *both* sensorimotor cortical reorganization and peripheral inflammation and injury mechanisms contribute to declines in movement performance and changes in movement patterns in the progression of the overuse injury.

References

1. Bernard B. *Musculoskeletal Disorders and Workplace Factors.* NIOSH Report 97-141. Cincinatti: National Institute for Occupational Safety and Health; 1997.
2. Rempel DM, Diao E. Entrapment neuropathies: pathophysiology and pathogenesis. *J Electromyogr Kinesiol.* 2004;14:71–75.
3. Zambelis T, Tsivgoulis G, Karandreas N. Carpal tunnel syndrome: associations between risk factors and laterality. *Eur Neurol.* 2010;63:43–47.
4. Nathan PA, Keniston RC, Myers LD, Meadows KD, Lockwood RS. Natural history of median nerve sensory conduction in industry: relationship to symptoms and carpal tunnel syndrome in 558 hands over 11 years. *Muscle Nerve.* 1998;21:711–721.
5. Gerr F, Marcus M, Monteilh C. Aerobic exercise, median nerve conduction, and the reporting of study results. *J Occup Environ Med.* 2002;44:303.
6. Bureau of Labor Statistics. *Nonfatal Occupational Injuries and Illnesses Requiring Days Away From Work.* Washington, D.C.: U.S. Department of Labor; 2010.
7. Szabo RM. Carpal tunnel syndrome as a repetitive motion disorder. *Clin Orthop Relat Res.* 1998;(351):78–89.
8. Gerr F, Marcus M, Ensor C, et al. A prospective study of computer users: I. study design and incidence of musculoskeletal symptoms and disorders. *Am J Ind Med.* 2002;41:221–235.
9. Carp SJ, Barbe MF, Winter KA, Amin M, Barr AE. Inflammatory biomarkers increase with severity of upper-extremity overuse disorders. *Clin Sci (Lond).* 2007;112:305–314.
10. Carp SJ, Barr AE, Barbe MF. Serum biomarkers as signals for risk and severity of work-related musculoskeletal injury. *Biomark Med.* 2008;2:67–79.
11. Freeland AE, Tucci MA, Barbieri RA, Angel MF, Nick TG. Biochemical evaluation of serum and flexor tenosynovium in carpal tunnel syndrome. *Microsurgery.* 2002;22:378–385.
12. Topp KS, Byl NN. Movement dysfunction following repetitive hand opening and closing: anatomical analysis in Owl monkeys. *Mov Disord.* 1999;14:295–306.
13. Hollander MS, et al. Effects of age and glutathione levels on oxidative stress in rats after chronic exposure to stretch-shortening contractions. *Eur J Appl Physiol.* 2010;108:589–597.
14. Baker BA, Hollander MS, Mercer RR, Kashon ML, Cutlip RG. Adaptive stretch-shortening contractions: diminished regenerative capacity with aging. *Appl Physiol Nutr Metab.* 2008;33:1181–1191.
15. Stauber WT, Willems ME. Prevention of histopathologic changes from 30 repeated stretches of active rat skeletal muscles by long inter-stretch rest times. *Eur J Appl Physiol.* 2002;88:94–99.
16. Willems ME, Miller GR, Stauber FD, Stauber WT. Effects of repeated lengthening contractions on skeletal muscle adaptations in female rats. *J Physiol Sci.* 2010;60:143–150.
17. Sommerich CM, Lavender SA, Buford JA, J Banks J, Korkmaz SV, Pease WS. Towards development of a nonhuman primate model of carpal tunnel syndrome: performance of a voluntary, repetitive pinching task induces median mononeuropathy in *Macaca fascicularis. J Orthop Res.* 2007;25:713–724.
18. Sacrey LA, Alaverdashvili M, Whishaw IQ. Similar hand shaping in reaching-for-food (skilled reaching) in rats and humans provides evidence of homology in release, collection, and manipulation movements. *Behav Brain Res.* 2009; 204:153–161.
19. Whishaw IQ, Pellis SM, Gorny BP. Skilled reaching in rats and humans: evidence for parallel development or homology. *Behav Brain Res.* 1992;47:59–70.
20. Viikari-Juntura ER. The scientific basis for making guidelines and standards to prevent work-related musculoskeletal disorders. *Ergonomics.* 1997;40:1097–1117.
21. Viikari-Juntura E, Silverstein B. Role of physical load factors in carpal tunnel syndrome. *Scand J Work Environ Health.* 1999;25:163–185.
22. Silverstein BA, Fine LJ, Armstrong TJ. Hand wrist cumulative trauma disorders in industry. *Br J Ind Med.* 1986;43:779–784.
23. Silverstein BA, Fine LJ, Armstrong TJ. Occupational factors and carpal tunnel syndrome. *Am J Ind Med.* 1987;11:343–358.
24. Barr AE, Barbe MF. Pathophysiological tissue changes associated with repetitive movement: a review of the evidence. *Phys Ther.* 2002;82:173–187.
25. Barr AE, Barbe MF, Clark BD. Systemic inflammatory mediators contribute to widespread effects in work-related musculoskeletal disorders. *Exerc Sport Sci Rev.* 2004;32:135–142.
26. Barbe MF, Barr AE, Gorzelany I, Amin M, Gaughan JP, Safadi FF. Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. *J Orthop Res.* 2003;21:167–176.
27. Clark BD, Al-Shatti TA, Barr AE, Amin M, Barbe MF. Performance of a high-repetition, high-force task induces carpal tunnel syndrome in rats. *J Orthop Sports Phys Ther.* 2004;34:244–253.
28. Clark BD, Barr AE, Safadi FF, et al. Median nerve trauma in a rat model of work-related musculoskeletal disorder. *J Neurotrauma.* 2003;20:681–695.
29. Rani S, Barbe MF, Barr AE, Litivn J. Role of TNF alpha and PLF in bone remodeling in a rat model of repetitive reaching and grasping. *J Cell Physiol.* 2010;225:152–167.
30. Barbe MF, Elliott MB, Abdelmagid SM, et al. Serum and tissue cytokines and chemokines increase with repetitive upper extremity tasks. *J Orthop Res.* 2008;26:1320–1326.
31. Barr AE, Safadi FF, Gorzelany I, Amin M, Popoff SN, Barbe MF. Repetitive, negligible force reaching in rats induces pathological overloading of upper extremity bones. *J Bone Miner Res.* 2003;18:2023–2032.
32. Coq JO, Barr AE, Strata F, et al. Peripheral and central changes combine to induce motor behavioral deficits in a moderate repetition task. *Exp Neurol.* 2009;220:234–245.
33. Driban JB, Barr AE, Amin M, Sitler MR, Barbe MF. Joint inflammation and early degeneration induced by high-force reaching are attenuated by ibuprofen in an animal model of work-related musculoskeletal disorder. *J Biomed Biotechnol.* 2011;2011:691412.
34. Elliott MB, Barr AE, Barbe MF. Spinal substance P and neurokinin-1 increase with high repetition reaching. *Neurosci Lett.* 2009;454:33–37.
35. Elliott MB, Barr AE, Clark BD, Amin M, Amin S, Barbe MF. High force reaching task induces widespread inflammation, increased spinal cord neurochemicals and neuropathic pain. *Neuroscience.* 2009;158:922–931.
36. Elliott MB, Barr AE, Clark BD, Wade CK, Barbe MF. Performance of a repetitive task by aged rats leads to median neuropathy and spinal cord inflammation with associated sensorimotor declines. *Neuroscience.* 2010;170:929–941.

37. Elliott MB, Barr AE, Kietrys DM, Al-Shatti T, Amin M, Barbe MF. Peripheral neuritis and increased spinal cord neurochemicals are induced in a model of repetitive motion injury with low force and repetition exposure. *Brain Res.* 2008;1218:103–113.
38. Fedorczyk JM, Barr AE, Rani S, et al. Exposure-dependent increases in IL-1beta, substance P, CTGF, and tendinosis in flexor digitorum tendons with upper extremity repetitive strain injury. *J Orthop Res.* 2010;28:298–307.
39. Rani S, Barbe MF, Barr AE, Litvin J. Induction of periostin-like factor and periostin in forearm muscle, tendon, and nerve in an animal model of work-related musculoskeletal disorder. *J Histochem Cytochem.* 2009;57:1061–1073.
40. Xin DL, Harris MY, Wade CK, Amin M, Barr AE, Barbe MF. Aging enhances serum cytokine response but not task-induced grip strength declines in a rat model of work-related musculoskeletal disorders. *BMC Musculoskelet Disord.* 2011;12:63.
41. Rani S, Barbe MF, Barr AE, Litvin J. Periostin-like-factor and Periostin in an animal model of work-related musculoskeletal disorder. *Bone.* 2009;44:502–512.
42. Elliott MB, Barr AE, Clark BD, Amin M, Amin S, Barbe MF. High force reaching task induces widespread inflammation, increased spinal cord neurochemicals and neuropathic pain. *Neuroscience.* 2009;158:922–931.
43. Fedorczyk JM, Barr AE, Rani S, et al. Exposure-dependent increases in IL-1beta, substance P, CTGF, and tendinosis in flexor digitorum tendons with upper extremity repetitive strain injury. *J Orthop Res.* 2010;28:298–307.
44. Al-Shatti T, Barr AE, Safadi FF, Amin M, Barbe MF. Increase in inflammatory cytokines in median nerves in a rat model of repetitive motion injury. *J Neuroimmunol.* 2005;167:13–22.
45. Hammond DL, Ackerman L, Holdsworth R, Elzey B. Effects of spinal nerve ligation on immunohistochemically identified neurons in the L4 and L5 dorsal root ganglia of the rat. *J Comp Neurol.* 2004;475:575–589.
46. Chao T, Pham K, Steward O, Gupta R. Chronic nerve compression injury induces a phenotypic switch of neurons within the dorsal root ganglia. *J Comp Neurol.* 2008;506: 180–193.
47. Rothman SM, Winkelstein BA. Chemical and mechanical nerve root insults induce differential behavioral sensitivity and glial activation that are enhanced in combination. *Brain Res.* 2007;1181:30–43.
48. Neumann S, Doubell TP, Leslie T, Woolf CJ. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. *Nature.* 1996;384: 360–364.
49. Pitcher GM, Henry JL. Nociceptive response to innocuous mechanical stimulation is mediated via myelinated afferents and NK-1 receptor activation in a rat model of neuropathic pain. *Exp Neurol.* 2004;186:173–197.
50. Schaible HG, Ebersberger A, Von Banchet GS. Mechanisms of pain in arthritis. *Ann N Y Acad Sci.* 2002;966:343–354.
51. Winkelstein BA, Rutkowski MD, Sweitzer SM, Pahl JL, DeLeo JA. Nerve injury proximal or distal to the DRG induces similar spinal glial activation and selective cytokine expression but differential behavioral responses to pharmacologic treatment. *J Comp Neurol.* 2001;439:127–139.
52. DeLeo JA, Colburn RW, Rickman AJ. Cytokine and growth factor immunohistochemical spinal profiles in two animal models of mononeuropathy. *Brain Res.* 1997;759:50–57.
53. Hunt JL, Winkelstein BA, Rutkowski MD, Weinstein JN, DeLeo JA. Repeated injury to the lumbar nerve roots produces enhanced mechanical allodynia and persistent spinal neuroinflammation. *Spine (Phila Pa 1976).* 2001;26:2073–2079.
54. Rutkowski MD, Winkelstein BA, Hickey WF, Pahl JL, DeLeo JA. Lumbar nerve root injury induces central nervous system neuroimmune activation and neuroinflammation in the rat: relationship to painful radiculopathy. *Spine (Phila Pa 1976).* 2002;27:1604–1613.
55. Winkelstein BA, Rutkowski MD, Weinstein JN, DeLeo JA. Quantification of neural tissue injury in a rat radiculopathy model: comparison of local deformation, behavioral outcomes, and spinal cytokine mRNA for two surgeons. *J Neurosci Methods.* 2001;111:49–57.
56. Byl NN, Melnick M. The neural consequences of repetition: clinical implications of a learning hypothesis. *J Hand Ther.* 1997;10:160–174.
57. Byl NN, Merzenich MM, Cheung S, Bedenbaugh P, Nagarajan SS, Jenkins WM. A primate model for studying focal dystonia and repetitive strain injury: effects on the primary somatosensory cortex. *Phys Ther.* 1997;77:269–284.
58. Byl NN, Merzenich MM, Jenkins WM. A primate genesis model of focal dystonia and repetitive strain injury: I. learning-induced dedifferentiation of the representation of the hand in the primary somatosensory cortex in adult monkeys. *Neurology.* 1996;47:508–520.
59. Moalem G, Tracey DJ. Immune and inflammatory mechanisms in neuropathic pain. *Brain Res Rev.* 2006;51:240–264.
60. Schafers M, Sorkin L. Effect of cytokines on neuronal excitability. *Neurosci Lett.* 2008;437:188–193.
61. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science.* 2000; 288:1765–1769.
62. Chacur M, Milligan ED, Gazda LS, et al. A new model of sciatic inflammatory neuritis (SIN): induction of unilateral and bilateral mechanical allodynia following acute unilateral peri-sciatic immune activation in rats. *Pain.* 2001;94:231–244.
63. Kelly S, Dunham JP, Donaldson LF. Sensory nerves have altered function contralateral to a monoarthritis and may contribute to the symmetrical spread of inflammation. *Eur J Neurosci.* 2007;26:935–942.
64. Bonfiglioli R, Mattioli S, Violante FS. Relationship between symptoms and instrumental findings in the diagnosis of upper limb work-related musculoskeletal disorders. *Med Lav.* 2007;98:118–126.
65. Hatashita S, Sekiguchi M, Kobayashi H, Konno S, Kikuchi S. Contralateral neuropathic pain and neuropathology in dorsal root ganglion and spinal cord following hemilateral nerve injury in rats. *Spine (Phila Pa 1976).* 2008;33:1344–1351.
66. Hubbard RD, Winkelstein BA. Transient cervical nerve root compression in the rat induces bilateral forepaw allodynia and spinal glial activation: mechanical factors in painful neck injuries. *Spine (Phila Pa 1976).* 2005;30:1924–1932.
67. Schafers M, Svensson CI, Sommer C, Sorkin LS. Tumor necrosis factor-alpha induces mechanical allodynia after spinal nerve ligation by activation of p38 MAPK in primary sensory neurons. *J Neurosci.* 2003;23:2517–2521.
68. Ohtori S, Takahashi K, Moriya H, Myers RR. TNF-alpha and TNF-alpha receptor type 1 upregulation in glia and neurons after peripheral nerve injury: studies in murine DRG and spinal cord. *Spine (Phila Pa 1976).* 2004;29:1082–1088.
69. Shubayev VI, Myers RR. Anterograde TNF alpha transport from rat dorsal root ganglion to spinal cord and injured sciatic nerve. *Neurosci Lett.* 2002;320:99–101.



Peripheral Nerve Injury

An Anatomical and Physiological Approach for Physical Therapy Intervention

Stephen J. Carp, PT, PhD, GCS
Doctor of Physical Therapy Program
Temple University
College of Public Health

F.A. Davis Company • Philadelphia

F. A. Davis Company
1915 Arch Street
Philadelphia, PA 19103
www.fadavis.com

Printed in the United States of America

Last digit indicates print number: 10 9 8 7 6 5 4 3 2 1

Senior Acquisitions Editor: Melissa Duffield
Developmental Editor: Andrea Edwards
Director of Content Development: George Lang
Design and Illustration Manager: Carolyn O'Brien

Library of Congress Control Number: 2015935849