Functional Motor Nerve Regeneration Without Motor-Sensory Specificity Following End-to-Side Neurorrhaphy: An Experimental Study

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Purpose To evaluate the quality of regenerating myelinated axons and motor-sensory specificity in an end-to-side nerve repair model.

Methods We divided 20 rats into 3 groups: (1) end-to-side neurorrhaphy using the ulnar nerve as donor nerve and the musculocutaneous nerve as recipient nerve; (2) normal control; and (3) transected nerve with the stumps buried. At 5 months, we monitored the grooming test, the electrophysiological response, and the histologic changes in nerve and muscle.

Results Grooming recovered successfully, and electrophysiological investigations revealed that the target muscles had been reinnervated in the end-to-side group. The mean wet weight of the reinnervated biceps brachii muscle was 72% of the normal muscle, and the mean muscle fiber cross-sectional area of the reinnervated muscle was similar to the normal muscle. The implanted musculocutaneous nerve contained varying but satisfactory numbers of axons (end-to-side group: 596 ± 348 vs normal group: 1,340 ± 241). Acetylcholinesterase staining revealed a similar percentage of myelinated fibers in the musculocutaneous nerve (39%) and the biceps brachii branch of the musculocutaneous nerve (38%) in the end-to-side group. This was similar to the number of myelinated fibers in the donor ulnar nerve (37%).

Conclusions The present study confirms that limited but functional reinnervation can occur on the basis of collateral sprouting of intact axons from the ulnar nerve. The motor-sensory specificity is not important. *(J Hand Surg 2011;36A:2010–2016. Copyright © 2011 by the American Society for Surgery of the Hand. All rights reserved.)*

Key words Nerve regeneration, end-to-side neurorrhaphy, motor-sensory specificity, experimental, rat.

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END-TO-SIDE NEURORRHAPHY IS a technique in which nerve fibers are transferred from an intact donor nerve to a denervated recipient nerve. Ballance[1] described the technique at the beginning of the 20th century. However, owing to unsatisfactory results, the technique was abandoned until 1992, when Viterbo et al[2] reintroduced this method of nerve repair. Although the value of end-to-side coaptation is debated in the literature, experimental evidence shows that it enhances axonal growth and nerve regeneration inside the recipient stump of motor or sensory nerves.

This phenomenon may result from collateral sprouting induced by neurotrophic factors,[3] which are sub-

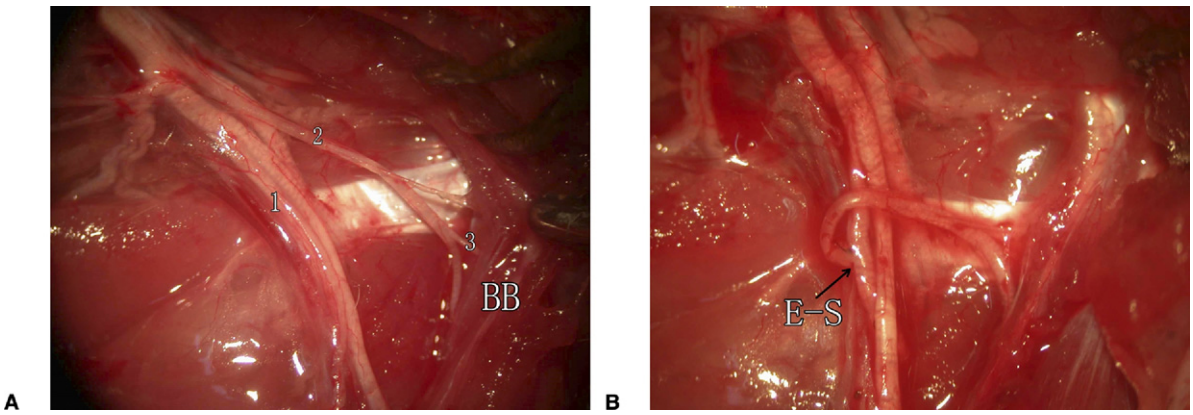

FIGURE 1: A Anatomy of the rat forelimb: 1, ulnar nerve; 2, musculocutaneous nerve; 3, motor branch to the biceps brachii muscle of the musculocutaneous nerve; BB, biceps brachii muscle. **B** End-to-side neurorrhaphy (E–S) of the distal musculocutaneous nerve to the ulnar nerve.

stances exerting an attraction, at a distance, on growing axons. Such factors released from the end-to-side implanted nerve stump cause the uninjured donor-nerve axons to sprout and emerge from its side to pass down the attached distal nerve segment, while the original nerve still continues to its original target organ.

Motor-sensory specificity means preferential motor axonal reinnervation of motor targets and corresponding preferential sensory axonal reinnervation of sensory targets. In a landmark investigation, Brushart[4] demonstrated that the motor axons of the rat femoral nerve exhibited preference for motor pathways after proximal transection. The putative mechanism for this specificity is described in the "pruning hypothesis," which proposes that regenerating neurons project multiple axonal collaterals to sample distal pathways.[5] Motor collaterals projecting to motor pathways are preserved, whereas those projecting to the sensory pathways are pruned, conferring preference to motor regeneration.

We conducted our study using the rat ulnar nerve as the donor nerve and the musculocutaneous nerve as the recipient nerve. Our aims were to evaluate nerve regeneration after end-to-side neurorrhaphy and to study the motor-sensory specificity of the collateral axonal sprouts from the donor nerve.

MATERIALS AND METHODS

Animals and surgery

We carried out the experiments on 20 adult male Sprague-Dawley rats (on average 1 y old, weighing 250 g). The rats were divided into the end-to-side group (n = 8), the normal group (n = 6), and the transected nerve group (n = 6). We anesthetized all rats with intraperitoneally applied ketamine (40 mg/kg) and atropine (0.04 mg/kg) and subsequently exposed the right musculocutaneous and ulnar nerves. For the rats in the end-to-side group, we created a window in the ulnar nerve epineurium by making a 1-mm incision. The musculocutaneous nerve was transected and the distal stump was attached in end-to-side fashion with a 10-0 atraumatic monofilament polyamide (Ethicon, San Angelo, TX) stitch into the perineurial window (Fig. 1). The proximal stump of musculocutaneous nerve was tightly ligated and turned back to prevent spontaneous reinnervation. In the normal group, we exposed the right musculocutaneous and ulnar nerve, then closed the skin. In the nerve transected group, we transected the musculocutaneous nerve, tightly ligated both stumps of musculocutaneous nerve, and turned them back to prevent spontaneous reinnervation. Once recovered, the rats were housed individually in boxes in an approved animal house facility under veterinarian supervision.

We carried out the experiments with the advance approval of our university's committee for animal rights and in full accord with the Helsinki Declaration on Animal Rights.

Grooming test

To determine functional nerve recovery in the rat forelimbs, we performed a grooming test,[6] which consisted of spraying water over the animal's face to elicit grooming movements of the forepaws toward the head. In normal grooming, the animal raised both forelimbs, licked them, and reached up behind the ears. The grooming response was graded from 0 to 5: 0, no response; 1, flexion at elbow, not reaching the snout; 2, flexion reaching the snout; 3, reaching below the eyes; 4, reaching to the eyes; 5, reaching to the ears and