Title: MYELINATED FIBERS IN PERIPHERAL NERVES SIGNAL THE HYPERALGESIA THAT FOLLOWS NERVE INJURY

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Introduction. Hyperalgesia is an altered state of cutaneous sensibility characterized by a decrease in pain threshold, an increase in pain to suprathreshold stimuli and often spontaneous pain. Cutaneous hyperalgesia is sometimes observed in patients following peripheral nerve injury. We studied the effects of a differential block of A-fiber (ischemic block) or C-fiber (local anesthetic block) function in these patients to determine the type of afferent fibers that signal the hyperalgesia.

Methods. Thirteen patients (7 male, 6 female), 19 - 63 years of age, with peripheral nerve injuries of the forearm or hand resulting in chronic, continuous pain and cutaneous hyperalgesia (10 months to 7 years duration) were studied. Informed consent from the patients and institutional approval for the study was obtained. All patients, except one, had at least one previous surgery. Surgical procedures included excision of neuromas, neurolysis, nerve transfer into muscle, amputations and revisions of amputated stump for relief of their chronic pain. Calibrated monofilament nylon probes (von Frey hairs), a camel's hair brush and light touching were used to test mechanical sensitivity. Heat stimuli were delivered by blunt probes heated to about 46°C or with a non contact laser thermal stimulator. Cold stimuli were delivered with blunt probes cooled to about 0°C. Mechanical and thermal testing was performed on normal and hyperalgesic skin. Subjects rated spontaneous pain and pain evoked by the stimuli before and at intervals after inflation of a blood pressure cuff around the upper arm. Cuff pressure was maintained at 50 to 80 torr above the systolic pressure. It is known that ischemic nerve block results in loss of function in large diameter myelinated fibers first, followed by smaller diameter myelinated fibers, and finally unmyelinated C-fibers. Sensory testing with mechanical and heat stimuli was conducted in the ischemic limb both within and outside the hyperalgesic area. The presence or absence of C-fiber function was determined by testing for perception of warmth and pain to heat stimuli below 47°C. Intact function of A-delta fibers was determined by the ability to perceive cold sensation. In one patient who had pain and hyperalgesia in the hand following traumatic amputation of the index finger, the effect of a local anesthetic block (0.5% lidocaine HCl) of the median and superficial radial nerves at the wrist was also studied. In contrast to the ischemic block, the anesthetic block results in loss of function in C-fibers, before the A-fibers.

Results. Prior to the ischemic nerve block, light stroking of the skin with a camel's hair brush evoked painful sensations in the hyperalgesic areas. Hyperalgesia began to diminish 8 minutes following the inflation (8.2 $\pm$ 1.3, Mean $\pm$ S.E.M.) of the c and completely disappeared by 15-30 minutes (19 $\pm$ 1.4) in all but one subject who could not tolerate the cuff after 25 mins. At the time that hyperalgesia was abolished, subjects could still distinguish warm and cold stimuli though the sense of touch was nearly eliminated. This indicated that C-fiber function and at least some A-delta fiber function was present at the time when hyperalgesia was absent. Hyperalgesia began to recurr 10-25 minutes after release of the cuff. Forty minutes after the local anesthetic block, the sensations of cold, warmth and pain were absent, but touch was present in the normal and hyperalgesic areas indicating that the C-fibers and A-delta fibers were blocked but that at least some A-fibers were still conducting. At this time, hyperalgesia to mechanical stimuli persisted.

Discussion. The pathophysiology of pain and hyperalgesia following peripheral nerve injury is unclear. Our results support the hypothesis that the hyperalgesia is related to activity in A-fibers and not C-fibers. Previous results from reaction time experiments in chronic neuralgia patients by Lindblom and Verillo[1] and differential pressure block experiments in reflex sympathetic dystrophy patients by Wallin et al.,[2] also support this hypothesis. Earlier investigators have suggested that activity in large caliber afferents may block pain-related signals and that pain following nerve injury may reflect loss of large fiber input. Our results suggest that this hypothesis is unlikely as A-fiber blockade (with C-fiber function intact) results in relief of hyperalgesia. The pain-free period following the deflation of the blood-pressure cuff has been used clinically to facilitate physiotherapy in these patients.

References:

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