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Examination of Possible Mechanisms by Which Stimulation of the Spinal Cord in Man Relieves Pain[1]

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Abstract. Stimulation of the spinal cord may be very helpful in controlling chronic pain. Traditionally it has been thought that pain control derives from antidromic activation of large-diameter primary afferents in the posterior columns, which inhibits activation of second-order neurons. Evidence against this hypothesis is presented. In addition, it is pointed out that stimulation of the anterolateral quadrant contralateral to the side of pain may require less current for pain control than stimulation with electrodes over the posterior cord. It is suggested that 'frequency-related conduction block' in the spinothalamic tract or in Lissauer's tract may play a role in pain relief. Because of uncertainty about the mechanism it is suggested that the term 'dorsal column stimulation' be replaced by 'spinal axis stimulation'.

The use of spinal cord stimulation to control pain was inspired by the now well-known 'gate control theory' [10]. The electrodes are customarily placed on the posterior aspect of the spinal axis, with the assumption that pain relief arises from activation of the large myelinated primary afferents that course in the posterior columns. Thus, the phrase 'dorsal column stimulation' has been widely adopted to describe this mode of therapy. It is a goal of this presentation to challenge this assumption. It is recommended that the term dorsal column stimulation be replaced by the more neutral phrase spinal axis stimulation because of the possibility that stimulation of other structures in the spinal cord may account for the therapeutic effect.

The first issue to consider is if stimulation of large-diameter primary

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afferents, whether in the peripheral nerve or spinal cord, affects pain perception. *Campbell and Taub* [2] studied the effects of different intensities of electrical stimulation on pain perception in humans. Stimulation failed to affect pain in areas remote to where paresthesias were induced, regardless of parameters used. Low-intensity stimulation at 100 Hz with a 0.5- to 1.0-ms pulse width duration caused an increase in threshold to touch perception while pain perception was unaffected. As the intensity of stimulation increased, there was an initial surge of paresthesias, but adaptation occurred quickly. The electrical stimulus could in this way be raised to higher and higher levels until finally the skin became nearly totally analgesic. The stimulus level that created analgesia, if reinstituted suddenly after a stimulus-free interval of a few minutes, was in itself painful. This suggested that the effect of electrical stimulation on pain was peripheral, i.e., that activity in the primary afferents concerned with pain was blocked. Large-fiber activation was unlikely to be involved, as the loss of touch sensation preceded the effect on pain.

We compared the effects of our intermittent brief stimulus with that of continuous stimulation using the same current. The intermittent stimulus, unlike the continuous stimulus, was in itself painful, suggesting that activity in this instance was present in those fibers concerned with pain perception. To confirm this hypothesis an averaging computer was used to compare the compound action potential obtained under the two situations. The brief intermittent stimulus evoked an A-delta wave in addition to the A-beta wave. With continuous stimulation the A-delta wave disappeared and the A-beta wave had an increased latency and also was smaller in width and height. This result confirmed the supposition that the pain-attenuating effect of peripheral nerve stimulation resulted from blockade of activity of small-diameter afferents concerned with pain perception rather than large-fiber stimulation.

Other work has lent support to this conclusion. *Ignelzi and Nyquist* [7], in a series of experiments in the cat, using the same peripheral nerve stimulator used clinically, have further documented conduction failure in A-delta fibers. *Torebjörk and Hollin* [13] recorded in the awake human from single unit C nociceptive fibers. They were able to induce a conduction block in C fibers using frequencies of stimulation of 10 Hz or greater. The block in C fiber activity correlated with analgesia of the stimulated area. The stimulus itself was not necessarily painful. *Nathan and Rudge* [11] also failed to find an effect of large-fiber stimulation on pain tolerance in humans.

Conduction in all nerve fibers can be blocked with electrical stimulation, provided the frequency of stimulation is high enough. Small-diameter afferents can be blocked at lower frequencies than larger ones. The phenomenon has been referred to as 'frequency-related conduction block' (FRCB) because of this dependence on frequency.

Adelman and Fitzhugh [1] believe that accumulation of potassium in the periaxonal space during rapid stimulation may inactivate sodium conductance channels and thus inhibit propagation of the action potential. The greater surface-to-volume ratio of C fibers might explain why these fibers are more susceptible to FRCB. In situations where diffusion of potassium from the perioaxonal space is impeded, FRCB should occur more readily. *Smith and Hatt* [12] demonstrated that FRCB occurred in that portion of the axon in the crayfish which coursed through connective tissue. *Wall and Gutnick* [14], in an electrophysiological study of neuromas in rats, found that thinly myelinated afferents in the neuroma had spontaneous activity, and that after electrical stimulation this activity disappeared for several minutes. Moreover, the electrical threshold for activation in the neuroma increased. Thus, electrical stimulation might be especially effective in reducing pain in certain pathologic conditions in which the nerve is encased in scar tissue.

With the advent of percutaneously placed epidural stimulating electrodes, the location of the electrode tips for low back and leg pain was shifted down from the midthoracic level and higher to the lower thoracic and lumbar region. With electrodes at these low levels it is plausible that the effective stimulus is being applied not to the dorsal columns, but rather the cauda equina (in the case of electrodes placed in the lumbar region), or Lissauer's tract. The nociceptive afferents of the fifth lumbar root enter the cord at T_{12}, then probably course up Lissauer's tract one to three (possibly more) segments [3] before entering the dorsal horn. Users of spinal axis stimulation generally note that best results are achieved when electrodes are placed within two or three segments of the entry zone of the involved roots. The reason for this may be that the effective stimulation is really being applied to Lissauer's tract, moreover, that FRCB develops in those primary afferents in Lissauer's tract that are concerned with pain sensation.

There is no doubt, however, that stimulation of the spinal cord at much higher levels may provide good pain relief. Once again, this is not proof that stimulation of the dorsal columns causes pain relief. One way to gain insight into this matter is to consider the following: on all the dif-

ferent locations around the spinal cord where electrodes may be placed, where is the location that requires the least current to provide pain relief? *Hoppenstein* [6] provided us a possible answer. A percutaneous technique was used to place electrodes in the subarachnoid space at C_{1-2}. He found that pain relief was obtained with 30 times less current with anterior placement of electrodes as compared to that required when electrodes were placed posteriorly. Moreover, the pain relief was contralateral. The suggestion, therefore, is that the pain relief had something to do with the stimulation of the spinothalamic tract. Since activation of nociceptive neurons in the spinothalamic tract should produce pain, we are led to the conclusion that a blockade must occur, i.e., FRCB must occur in the spinal cord pain pathway, in a manner similar to how peripheral nerve stimulation can block pain. *Long and Erickson* [personal commun.] and *Larson* et al. [8, 9] have also found anterior cord stimulation to be effective in achieving pain relief. There are, of course, technical problems with placement of electrodes anteriorly: it is hard to implant the electrodes in this location, and stimulation of anterior roots may be a problem.

Though in practice there is no proof that stimulation of the dorsal column affects pain perception, there is neurophysiologic evidence that activity in spinothalamic neurons may be depressed by stimulation with electrodes placed over the dorsal columns of anesthetized monkeys [4]. A similar depression of activity in spinothalamic neurons was also noted with stimulation of a nerve which supplied areas other than the receptive field of the neurons from which the recording was obtained. There is simply no convincing evidence in the awake human, however, that such stimulation affects pain perception. Evaluation of neurophysiologic data on sensory systems depends on sound psychophysical data. The neurophysiologic experiments on the spinal cord to date fail to explain why analgesia may be obtained more readily with stimulation of the anterolateral quadrant.

There is much talk of endorphins, enkephalins, and endogenous pain control pathways. The disappointing aspect of all of this is that injection of the narcotic antagonist naloxone has little, if any, effect on pain. In an attempt to determine whether peripheral nerve and spinal cord stimulation induced pain relief by activating endogenous opiate-related pain pathways, we [5] performed a double-blind crossover study in which patients achieving pain relief via electrical stimulation were given placebo and naloxone in a dose as high as 1.6 mg. The study is not yet complete, but in preliminary results no effect of naloxone has been observed. We

believe it is unlikely, therefore, that pain relief occurs via activation of opiate-related endogenous pain control pathways.

Conclusion

Work with peripheral nerve stimulation suggests that large-fiber stimulation confers no pain relief, that instead analgesia is brought about by blockade of fibers concerned with pain. It is, therefore, unlikely that stimulation of the large-fiber primary afferents in the dorsal column should induce pain relief. It is possible to induce pain relief by stimulating the contralateral ventral column using a current far less (namely 1/30) than that used for so-called dorsal column stimulation. It is suggested, therefore, that pain relief results from blockade of conduction of pain pathways in the spinothalamic tract, and that this is what is achieved when we stimulate the spinal cord with electrodes placed over the posterior aspect of the cord.

Certainly there are other possibilities. The term 'dorsal column stimulation' should, for now, cease being used. A more neutral term, such as 'spinal axis stimulation', or perhaps 'spinal cord stimulation' is more appropriate. By so doing we will maintain fertile grounds for future research in this field, and thereby hopefully realize more fully the potential therapeutic benefits.

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