Neurophysiological effects of dorsal column stimulation in man and monkey

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In 18 patients with cancer and intractable pain, capacitatively coupled pulses of 0.25 msec duration were delivered transcutaneously at 100 Hz to sets of five in-line electrodes implanted subdurally over the dorsal columns. Averaged somatosensory-evoked potentials were recorded from scalp electrodes before, during, and after application of current. All but one patient experienced relief of pain during stimulation, persisting for as long as several hours afterward. Eleven patients developed hyperactive deep reflexes, pathological reflexes, and decreased perception of joint rotation, pain, and touch below the level of current application. Somatosensory-evoked potential amplitudes were markedly reduced. All neurological findings returned to control values within 1 hour after each of repeated applications of current. Histological examination of spinal cord sections from four cancer patients showed no changes secondary to long-term current application.

Similar currents were applied to the spinal cord of 15 monkeys with chronically implanted bipolar recording or stimulating electrodes over the lower, middle, and upper thoracic cord, in nucleus ventralis posterior lateralis (VPL), and over the sensory motor cortex (SMC). With application of current, the responses in VPL and SMC to peripheral stimulation were abolished. Evoked potential responses were abolished between bipolar stimulating electrodes and bipolar recording electrodes separated by the five in-line electrodes used to supply the 100 Hz current. However, when both stimulating and recording electrodes were either above or below the five in-line electrode set, evoked responses were unaffected. The findings indicate that applied currents blocked neuronal transmission by producing local changes in the cord. The prolonged alteration of cerebral evoked potentials and relief of pain, however, could also be related to involvement of supraspinal neurons.

KEY WORDS • pain • dorsal column stimulation • implanted electrodes • evoked potentials • spinal cord

The application of currents through electrodes placed on the dorsal column of the human spinal cord has been shown to relieve pain. The selection of the dorsal columns for electrode placement has been based upon the gate theory proposed by Melzack and Wall, who suggested that impulses conducted over large afferent fibers activated cells of the substantia gelatinosa which in turn affected small fiber input by
presynaptic inhibition. More recently the theory has been modified to include descending fibers from higher levels in addition to those from dorsal roots. Consequently the relief of pain may not depend solely upon activation of dorsal column fibers; other elements of the spinal cord may be affected by the currents. To investigate this, a series of experiments were carried out in monkeys and the results compared with findings obtained from patients in whom electrodes had been chronically implanted over the dorsal columns.

Materials and Methods

Clinical Studies

Electrode sets connected to subcutaneous receiving units were chronically implanted in 18 patients with cancer and intractable pain. Each set was made up of five platinum iridium discs 2 mm in diameter arranged in line 4 mm apart on center and embedded in dacron-reinforced Silastic (Fig. 1). Electrodes 1, 3, and 5 were connected to the positive terminal and 2 and 4 to the negative. The sets were placed in the subdural space over the dorsal surface of the spinal cord and fixed to the dura with horizontal mattress sutures. The receiving unit was placed in a subcutaneous pocket either in the flank or over the anterolateral aspect of the chest. The frequency of the currents applied by the transmitter could be varied between 5 and 200 Hz, with pulse current amplitudes up to 3 mA and durations of 0.1 to 1.0 msec. Capacitative coupling was used to minimize migration of ions. In most of the patients, frequencies of 70 to 100 Hz were used with pulse widths of 0.25 msec and an estimated pulse current of 0.5 to 1.0 mA. To check the integrity of the system prior to closure, electronic stimuli were applied at low frequency through the electrode set and evoked potentials recorded from scalp electrodes with methods previously described. Application of currents to the implanted unit was begun several days following the operation. Neurological examination and evoked potential recordings secondary to transcutaneous stimulation of peripheral nerves were done before, during and after current application. The amount of current required to produce paresthesias and reduce evoked potential amplitude was measured in one patient, using a Tektronix P6021 probe to record the pulse current into each of the five electrodes.

In four patients with implants, the portion of the spinal cord beneath the electrode set was removed at autopsy. Each of these patients had had current applied to the cord for a total of at least 100 hours. Spinal cords were also obtained from four patients who died of cancer but had no evidence of metastases involving the central nervous system (CNS), and from four patients who died of non-neoplastic disorders. The spinal cords were stained by the Marchi method to demonstrate degenerating myelin.

Animal Studies

The animal experiments were carried out in 15 stumpetaile macaque monkeys (Macaca arctoides). Bipolar electrodes were chronically implanted over the arm and leg areas of the sensory motor cortex (SMC), and in nucleus ventralis posterior lateralis (VPL) of the thalamus. The potentials evoked by transcutaneous stimulation of the peripheral nerves were recorded as a guide for electrode placement. Two platinum iridium disc electrodes 0.025 mm thick, 2 mm in diameter, and 4 mm apart on center were embedded in a strip of dacron-reinforced Silastic 0.25 mm thick. These bipolar electrodes were im-

*The subcutaneous receivers, electrode sets, and transmitters were supplied by the Clinical Technology Corporation, Kansas City, Missouri.
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planted in the subdural space over the dorsal surface of the upper, middle, and lower thoracic cord, and cauda equina. The high-frequency currents were applied through five in-line sets similar to those used in the humans and placed on the dorsal surface of the cord between the bipolar electrodes located over the upper and middle portions of the thoracic cord. The electrode sets were separated by distances of 1 to 5 cm. The wires from the electrodes were led out through the skin, and the monkeys were provided with canvas jackets to prevent manipulation of the wires. Neither cerebrospinal fluid fistulas nor meningitis were observed in any of the monkeys. Spinal cord electrode location was determined radiographically and anatomically, and depth electrode tip locations were determined histologically.

Capacitatively coupled pulses were applied at 100 Hz with pulse durations of 0.25 msec, and variable pulse current amplitudes up to 1.0 mA. Electrode voltage was measured in addition to current. A 100 ohm resistor placed in series between the five electrode set and the upper and lower cord electrodes was used to measure leakage current between the bipolar electrodes and the five in-line electrode set. Initially the experiments were done with the monkeys under barbiturate anesthesia. Subsequent experiments have been done with awake animals in primate restraining chairs. Evoked potentials were recorded secondary to peripheral and depth stimulation before, during, and after application of current. In some animals a delivery of a single rectangular pulse to the sensory motor cortex was followed by discrete movements of the fingers or toes depending upon the electrode location. The stimulus amplitude required to produce this response was measured as a function of current applied to the cord.

Results

Clinical Studies

In the patients, the intensity of the applied currents was gradually increased until relief of pain was reported. Each patient described paresthesias that increased in intensity as the level of applied current was raised. Seventeen of the 18 patients reported marked or complete relief of pain below the level at which the currents were applied. While a detailed discussion of the clinical results will be the subject of another paper, it should be mentioned that in 10 patients the initial good results were maintained until death 6 weeks to 8 months after implant. Seven patients experienced decreasing relief of pain with stimulation 1 to 3 months postoperatively. Two patients found the associated paresthesias as unpleasant as the pain. Relief of pain usually persisted for several hours after each stimulation. In 11 patients, decreased perception of joint rotation, pain and touch, plus increased deep reflexes, some pathological reflexes, and ankle clonus were observed below the level of current application. Somatosensory-evoked potentials were recorded in six of these patients, and the amplitudes were markedly reduced in each during current application. All of these neurological findings and the somatosensory-evoked potential amplitudes returned to control values within 30 to 60 minutes after each of many applications of current. There were no permanent neurological changes. Microscopic examination of the Marchi-stained spinal cords did not demonstrate any evidence of a lesion beneath the electrodes. Scattered degeneration was seen in three of four patients with implants, three of four cancer patients without implants, and four of four patients who died of non-neoplastic disease.

The findings in two patients deserve special mention. One was a 49-year-old man with carcinoma of the pancreas and severe abdominal and epigastric pain. Electrodes were implanted at the level of the seventh thoracic vertebra. When currents were applied, he developed reduced sensory perception below T-8 with corresponding relief of pain. However, he continued to have a small area of pain immediately above the sensory level. The other patient was a 53-year-old man with carcinoma of the kidney and pelvic metastases. Initially he complained of severe lower abdominal pain. The electrodes were implanted at about T-8. When currents were applied he obtained excellent relief of pain with decreased perception of pain, touch, and joint rotation below the level of the umbilicus. Patellar and ankle reflexes became hyperactive, and he developed ankle clonus and extensor toe signs. Cortical potentials evoked by peroneal nerve stimulation were markedly reduced in amplitude. All neurological findings and the evoked potential amplitude
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returned to control level 30 minutes after the currents were stopped after each of many applications. Pain relief persisted for several hours. He continued to obtain good relief from pain until the unit abruptly stopped working about 4 months following operation. Before it could be replaced, he developed pain in the right shoulder and upper portion of the right arm secondary to right apical metastases. A laminectomy of C-6 was done and the electrodes implanted subdurally. A higher cord level was avoided because of concern over possible interference with pulmonary function. With lower levels of applied current the patient noticed paresthesias in the left leg. As the intensity was increased, he noticed paresthesias in the right leg, then in the left side of the body, the left arm including all five fingers, the left shoulder, and eventually the right arm and the right shoulder. Perception of touch, pinprick, and pain was reduced between C-7 and T-12. The abdominal pain was relieved but the pain in the right shoulder and arm was minimally affected. Perception of joint rotation remained normal in the thumbs, was somewhat decreased in the index fingers, and more markedly decreased in the middle, ring, and small fingers. Potentials evoked by digital nerve stimulation and recorded from scalp electrodes were correspondingly affected, remaining normal from the thumb, but markedly reduced in amplitude from the other fingers. The patient subsequently began to develop increasingly severe pain in the left hip. Although he felt paresthesias in this area when the currents were applied, the pain was not relieved. Again, perception of pain and touch was normal below T-12. With a substantial increase in current intensity producing paresthesias described as nearly intolerable, the patient began to notice a substantial, although incomplete, relief of hip pain. Reexamination demonstrated that the lower level of the zone hypalgnesia was now at approximately L-2. The pain returned promptly when the currents were stopped.

Animal Studies

In the monkeys, application of currents to the spinal cord was followed by a marked reduction in amplitude of potentials recorded from electrodes in VPL and over SMC secondary to stimulation of dorsal columns and peripheral nerves (Fig. 2). When the stimulating electrodes on the spinal cord were separated by the five electrode set from the recording electrodes, the spinal-cord-evoked responses were abolished during current application and for variable periods thereafter (Fig. 3). When the stimulating and recording electrodes were both either above or below the five electrode set, however,
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Fig. 3. Recordings of cord-to-cord-evoked potentials before, during, and after current application to five in-line electrodes on the dorsal surface of the cord. The stimulating and recording electrodes are separated by the five in-line current electrodes. Barbiturate anesthesia. Analysis time is 62 msec, stimulus at arrow. Response obliterated with 500 μA peak pulse current applied to five electrode set. Recovery at approximately 10 minutes after 100 Hz current is off.

evoked responses were unaffected by the applied currents (Fig. 4). The five in-line electrode sets were also used for application of high frequency current and simultaneous low frequency stimulation. Electrodes 1 and 5 were connected to the positive pole, and Electrode 3 to the negative pole of a constant current generator.* This generator supplied currents at 100 Hz and 0.25 msec duration to Electrodes 1, 3, and 5 while a similar generator delivered 0.1 msec rectangular pulses at 4 Hz to Electrodes 2 and 4. As the amplitude of the high frequency currents was increased, evoked potentials recorded from the spinal cord and cerebral electrodes diminished (Fig. 5). Currents spreading from the five-electrode set to the upper or lower bipolar sets had amplitudes less than 0.001 of the current supplied to the five electrode array.

Pulse currents of 0.5 mA, which reduced scalp-evoked potentials, were measured in one patient. For an electrode area of 0.03 cm², a 100 Hz pulse frequency, and an 0.25 msec pulse duration, the average electrode current is \( I_{ave} = 0.0125 \, mA \) and the average current density at the electrode surface is \( J_{ave} = 0.42 \, mA/cm² \). In their patients Shealy, et al.,* measured average currents of 0.5 mA; since their electrodes had an area of 0.25 cm², the average current density at the electrode surface was 2.0 mA/cm².

In monkeys, pulse currents of 0.1 to 0.5 mA routinely suppressed evoked spinal cord potentials. The average power density calculated from the input current and voltage drop across each electrode of the five in-line array was less than 10% of the 8 mW/cm² suggested as a power density well below the threshold for neuronal damage.* The five in-line electrode system implanted on the spinal cord was connected in the following ways to determine which configuration could most efficiently block SMC responses secondary to peripheral nerve stimulation: 1) a monopolar array relative to a distal electrode; 2) one electrode negative and one positive; 3) Electrodes 1 and 5 connected together relative to Electrode 3, and 4) Electrodes 2 and 4 connected together relative to Electrode 3. While spinal-cord-evoked potentials could be blocked by application of current with each of these electrode combinations, the power density was greater in each instance as compared with the power density of the normally connected five in-line array. With monopolar systems, the power density and the amount of current required to block spinal cord transmission was significantly less when the electrode on the spinal cord was negative than when it was positive.

In awake animals, application of single rectangular pulses through electrodes over arm and leg cortical areas produced discrete movements of the fingers and toes, respectively. The pulse current threshold amplitude was 4 to 10 mA, depending on the precision of electrode placement. When the 100 Hz currents were applied to the thoracic cord at


Fig. 4. Recordings of the potentials evoked from the cauda equina to the lower thoracic spinal cord. Stimulating and recording bipolar electrodes are both below the five in-line current electrodes. The responses are unaffected by the applied currents. Noise on the lower trace is due to applied currents. Analysis time is 62 msec, stimulus at arrow.
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Fig. 5. Potentials recorded from bipolar electrodes on the dorsal aspect of the spinal cord (upper thoracic) above the five electrode set evoked by stimulation through Electrodes 2 and 4 of the five in-line array before, during, and after application of current at 100 Hz through Electrodes 1, 3 and 5. Barbiturate anesthesia. Analysis time is 31 msec, stimulus at arrow. Response is reduced with 500 µA pulse current applied to Electrodes 1, 3 and 5. Recovery approximately 20 minutes after 100 Hz current is off.

sufficient intensity to affect somatosensory-evoked potentials, the threshold for the toe movement was reduced 50% while that for finger movement was unaffected.

Discussion

In the patients, relief of pain and disturbed sensory perception did not occur at a dermatomal level higher than that at which the electrodes were placed on the cord. If these effects were secondary to the influence of large fibers upon smaller ones, it could be anticipated that the pain would be relieved at least several segments above the level of implant. The patient with the C-7 implant experienced paresthesias in the distribution of C-5 and C-6, indicating that the descending branches of large fibers entering the cord at these levels were affected by the applied currents. Although the reduction in the cortical- and thalamic-evoked potentials could be attributed to the high frequency of the stimulation, this would not apply to the responses recorded from dorsal columns in the monkey. The fibers in these tracts are capable of following a high rate of stimulation, and it was only when current intensity was increased substantially beyond threshold that block of transmission was observed. Furthermore, in the patient with the cervical implant, although paresthesias were felt in the shoulder and all five fingers, neither perception of joint rotation in the thumb nor the amplitude of evoked potentials secondary to stimulation of its digital nerve were affected. Involvement of descending pathways is indicated by the development of increased deep reflexes and clonus in the humans and of alteration of threshold for cortically-induced movement in the monkey. This, too, appears related to local effects beneath the electrodes, since in the monkey responses secondary to stimulation and recording either both above or both below the level of current application were unaffected. Although the currents affected neuronal function, clinically this appeared reversible, and the histological examination did not indicate neuronal damage secondary to long-term application of current. Scattered degeneration was seen in the spinal cord of patients with and without implants, and in the former group was never localized beneath the electrodes. The degeneration seen could have been artifact or perhaps was secondary to the disease causing death.

Our observations suggest that the relief of pain may be secondary to interference with neuronal transmission in that segment of the cord directly beneath the electrode set. In at least some patients, interference with transmission over the spinothalamic pathways appears necessary for relief of pain. For example, in the patient with the cervical implant, hip pain was relieved when the intensity of applied current was sufficient to move the lower edge of the zone of hypalgesia from T-12 to L-2, suggesting an increased current density in the more lateral portions of the spinothalamic tract. To accomplish this, the current density in the dorsal columns was necessarily increased to an even greater degree, producing paresthesias of unacceptable intensity. Consequently, the motor effects secondary to the spread of current to the lateral columns, the paresthesias, the
changes in perception of joint rotation, and the effects on evoked potentials may not be necessary concomitants of pain relief. These transient but still undesirable side effects are probably related to the increased current density produced in the posterior portion of the cord when currents applied through dorsal column electrodes must be increased sufficiently to achieve an effective current density in the more lateral portion of the spinothalamic tract. Therefore, application of current through electrodes placed anteriorly may, in some instances, produce the best results. Preliminary observations in one patient in whom we have implanted a five electrode set on the anterior surface of the cord have supported this hypothesis. After application of current through the anterior electrode, a sensory level developed, pain was reduced, but paresthesias were not experienced.

The block in neuronal transmission that we found in the monkeys and in some of our patients is at variance with the observations of others who did not find changes in sensory perception in their patients when currents were applied to the dorsal columns. This apparent conflict may be related to the different electrode configurations employed. We have made Teledeltos paper plots of current distribution which indicate that with the five in-line electrode set, a substantially greater amount of the applied current is confined to the spinal cord as compared to the other electrode arrays which have been used. Consequently, for equal amounts of current applied, the current density within the spinal cord will be significantly greater with the five in-line electrode array than with the other configurations. Furthermore, not all of our patients who experienced relief of pain with application of current were observed to have changes in sensory perception. Rather, only those with severe pain requiring relatively high levels of applied current developed hypalgesia, which, as the current was increased, became analgesia. It is possible that, with a smaller current density, transmission in the spinothalamic tract is sufficiently compromised to relieve certain types of pain without producing a clinically demonstrable sensory deficit. The paresthesias associated with dorsal column stimulation may also have a masking effect.

While interference with neuronal transmission across the level of current application accounts for the relief of pain during the time currents were applied and shortly thereafter, it may not account for the more extended relief of pain experienced by many of the patients. Melzack and associates³,⁴ have reported prolonged effects upon activity in visual, somatic, and motor neurons after brief stimulation of a paw. These changes in neural activity could be abolished by division of the anterior quadrants of the cord, and could be reproduced by reticular stimulation, suggesting that the effects were mediated over extralemniscal pathways.³ A similar mechanism may be responsible for the prolonged relief of pain following cessation of applied current.

References


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