Pain reduction by electrical brain stimulation in man

Part 2: Chronic self-administration in the periventricular gray matter

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Electrical stimulation of the periventricular gray matter is an effective means of relieving several types of pain without destruction of neural tissue. The effects are long lasting, often bilateral, and with judicious use do not appear subject to adaptation. However, sustained uninterrupted stimulation for several hours does lead to a reversible decrease in effectiveness. Side effects from stimulation are minimal and cause little or no untoward emotional changes. The results are discussed in terms of activation of an endogenous pain inhibitory mechanism that involves naturally occurring opiate-like factors such as the enkephalins and endorphins.

KEY WORDS • pain • brain stimulation • periventricular gray • enkephalin

Electrical stimulation of the periaqueductal gray matter has been demonstrated to produce dense analgesia with few behavioral side effects in the rat and the cat. Similarly, we have demonstrated the analgesic effect of central gray stimulation in the human; however, it was often accompanied by untoward side effects, such as vertigo and a sensation of smothering and nausea. Very effective pain relief was obtained from stimulation of the periventricular gray matter near the posterior third ventricle without the noxious side effects obtained by periaqueductal gray stimulation. This report summarizes the long-term effects of intermittent stimulation of the periventricular gray for relief of intractable pain in eight patients.

Clinical Material and Methods

Patient Selection

The patients selected met several basic criteria: 1) their pain was of known etiology; 2) all reasonable conventional methods had been tried or were refused by the patients; 3) psychological testing ruled out psychotic or severely disturbed patients; 4) informed consent was obtained from the patients for an experimental operation; 5) all patients agreed to be available for extensive, long-term follow-up studies; and 6) all narcotics and analgesic
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drugs were discontinued before surgery (with the exception of the patient in Case 8).

Surgical Procedure

The surgical procedure was performed in two stages. The first stage was carried out under local anesthesia to allow intraoperative testing of the electrode placement, with the patient kept under minimal sedation with diazepam (10 mg intramuscularly). The patient’s head was placed in a Trent Wells stereotaxic unit* and trephined just behind the coronal suture line on the side contralateral to the more intense pain. After Conray ventriculography, a Medtronics four-contact, Schrifer-type platinum-iridium electrode† was introduced so that its tip lay 2 to 3 mm lateral to the ventricular wall, just anterior to the posterior commissure. Based on previous acute studies, the electrode was aimed at a site medial to the parafascicularis nucleus, in the periventricular gray region (Schaltenbrand-Bailey coordinates Fp = 10, Ht = 0, Lat = 2–5 mm).‡ Stimulation studies were begun 5 mm above target, and final choice of electrode location was determined by the depth of the hypalgesia, lack of noxious side effects, and the duration of pain relief beyond the period of stimulation. The electrodes were connected to a temporary percutaneous lead to allow testing of the effectiveness of the placement for 7 to 14 days. The second stage of surgery was then carried out under general anesthesia. It consisted of connecting the electrode to a Medtronics induction receiver and rectifying unit,§ and implanting the receiver in the subcutaneous tissue over the pectoralis muscle (Fig. 1).

Chronic Stimulation

After recovery from surgery, each patient received a pocket-sized Medtronics stimulator,‖ connected to an inductance antenna, which transmits the pulse current when placed over the subcutaneous receiver.

*Stereotaxic unit manufactured by Trent Wells, Inc., South Gate, California.
†Four-contact, Schrifer-type platinum-iridium electrode manufactured by Medtronics, Inc., 3055 Old Highway 8, Minneapolis, Minnesota.
‡Induction receiver and rectifying unit and pocket-sized stimulator manufactured by Medtronics, Inc., 3055 Old Highway 8, Minneapolis, Minnesota.

Stimulation consisted of a capacitor-coupled square wave typically 0.250 msec in duration. The patient has control over the amplitude (0 to 4 volts) and the frequency (0 to 250 Hz). The maximum amplitude, as well as the pulse duration, can be preset internally by the physician not to exceed a certain level within the above range.

A period of careful work with each patient was aimed at helping him with the use of the stimulator, and finding the ideal combination of amplitude, frequency, and duration of stimulation to produce the longest lasting relief of pain with minimal side effects. After the patient felt comfortable with his treatment, he was discharged and followed closely as an outpatient.

Evaluation of Pain Relief

We felt it was important to devise a certain set of criteria to estimate changes in chronic and acute pain in our patients and to rate the degree of effectiveness of brain stimulation on a long-term basis.
Testing Acute Pain. For acute pain testing, four methods were employed.

1. Pinprick testing over most of the body surface. This test was most useful in the operating room and exhibited good correlation with later analgesic effectiveness.

2. A radiant heat test on the arms and legs primarily using the fingers. In this test, a radiant heat lamp was focused on a specific area of the skin by means of a concave reflector placed behind it. The unit (lamp and reflector) was portable and connected to a potentiometer, permitting the alteration of voltage and, thus, radiant heat emitted. Typically, however, the intensity setting remained constant, and the dependent variable was the latency of the withdrawal reflex. Usually, a nonstimulated subject responded at around 3 seconds. A cutoff point was established that terminated the current to the lamp at 6 seconds to prevent any skin damage. The patients were tested on several occasions after their surgery. A baseline response time was established before stimulation, then brain stimulation was initiated at the parameters typically used by the patient, and the radiant heat test was given. The reaction time was compared to baseline, and, if any increase was observed, the patient was tested after the termination of the stimulation and at 2-minute intervals until the reaction time returned to baseline. Typically, the patients exhibited a small but consistent increase in their latency to radiant heat, usually between 15% and 20% over baseline. This effect usually outlasted the termination of stimulation by a few minutes.

3. Ischemic pain. The method of Hilgard was employed to produce ischemic pain on the arm contralateral to the electrode site. The test was carried out in two sessions, 1 week apart. The first session was used to obtain a baseline responsiveness to ischemic pain and determine an end point at which the patient “cannot stand it any longer.” The second session was identical, except it was carried out while brain stimulation was in progress. Most unstimulated patients rated the ischemic pain as unbearable (R = 10) at about 7 minutes. After 10 minutes of electrical stimulation, and while the stimulation continued, the rating of 10 was not obtained until 9.8 minutes had elapsed. Some patients failed to reach a rating of 10 for 15 minutes at which point testing was discontinued. Here again, the analgesic effect of electrical stimulation outlasted the termination of current by up to 30 minutes.

4. Finally, acute exacerbation of the patient’s pain was employed whenever possible to test stimulation effectiveness. This was achieved by either pressure or movement, usually leading to an increase in pain. Typically, patients could sustain a great deal more pressure or movement during and after stimulation.

Subjective Reports of Changes in Chronic Pain. Each patient was interviewed frequently after surgery to discuss the effectiveness of the stimulation. Head and chest x-ray films were taken periodically to ascertain that the electrode had not drifted. Furthermore, the patients were given self-report sheets on which they were asked to rate the amount and duration of relief, the presence and characterization of side effects, emotional changes occurring during the stimulation or since the surgery, and any overall changes in activity or mood. The family of the patient was also interviewed often, and subjective ratings were obtained on the patient’s behavior, activity, sleep, or pain reports.

Rating Scale. To summarize the various impressions of pain from subjective reports, a rating scale was devised focusing on four factors that we felt were important in the evaluation. The ratings yielded a composite score which permitted us to evaluate the success or failure of each particular case. The factors rated and the criteria used are summarized in Table 1.

Case Reports

Case 1

This 31-year-old man was suffering from chronic severe pain in the leg and low back, resulting from lumbar disc disease. He had undergone several procedures for pain relief, including lumbar disc removal with spinal fusion and radiofrequency lumbar facet rhizotomy, without success. He had been unable to continue his work as a house electrician for 2 years due to pain, which prevented him from bending, carrying heavy objects, or maintaining certain body positions necessary.
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### TABLE 1

**Criteria and ratings for evaluating efficiency of stimulation**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
<th>Evaluation</th>
</tr>
</thead>
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<tr>
<td>A: completeness of pain relief during and after stimulation</td>
<td>0</td>
<td>no pain relief</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>minimal relief</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>good relief</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>total relief</td>
</tr>
<tr>
<td>B: duration of analgesia after termination of stimulation</td>
<td>0</td>
<td>analgesia outlasts by less than 1 hr</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>analgesia outlasts for 1-4 hrs</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>analgesia outlasts by 4-12 hrs</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>analgesia outlasts longer than 12 hrs</td>
</tr>
<tr>
<td>C: accompanying side effects</td>
<td>0</td>
<td>intense or negative with any pain relief</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>negative effects only at certain currents</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>innocuous effects, not disturbing to patient</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>no side effects</td>
</tr>
<tr>
<td>D: long term effectiveness</td>
<td>0</td>
<td>analgesic effectiveness disappears in 2 mos</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>over 2 mos, showing decrement</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2 mos to 1 yr, no decrement</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 to 2 yrs, no decrement</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>more than 2 yrs, no decrement</td>
</tr>
</tbody>
</table>

**sum of scores on factors A, B, C, and D**

- 0-4: failure
- 4-6: poor result
- 7-10: good result
- 11-13: excellent result

**natural text**

...tated by his job. Before surgery, he was taking dihydrocodeine (Percodan) and diazepam (Valium) in large amounts.

Implantation was performed in May, 1973. Since then, he has received excellent pain relief through the use of his stimulator (Table 1, A = 3). Typically, he has employed 0.2 msec pulses, 0.6 to 0.8 volt in amplitude, 10 to 15 Hz in frequency. Following surgery, he used the stimulator for 20 to 30 minutes at bedtime, and pain relief lasted up to 24 hours. At these parameters, during stimulation, the patient senses a slight tingling or cold sensation near his left (contralateral) nostril. With higher current, the paresthesia spreads to the ear, neck, and arm, but paresthesias are not necessary for pain relief (Table 1, C = 2).

His straight leg raising test changes from painful at 20° before stimulation to mildly uncomfortable at 80° during stimulation. Lumbar paraspinal muscle spasm is released and spine motion is increased. Heat lamp testing reveals an increase in radiant heat tolerance of 16% during stimulation contralaterally with little change ipsilaterally, and the effect dissipates with return to baseline levels in 5 minutes. Pinprick sensation is reduced bilaterally over the entire body during stimulation but again returns to normal within 5 minutes after stimulation is discontinued.

Ischemic pain testing contralaterally reveals a 54% increase in pain tolerance during stimulation.

There has been no obvious decrement in the effectiveness of the stimulation over time (Table 1, D = 3). The patient can usually detect any drop in the battery charges (as substantiated by electronic measurement) and reverts to his previous current parameters after replacing the battery. On two occasions he had to either increase the frequency with which he uses the stimulator (up to three times daily) or increase the current parameters. However, these changes do not appear to form a steady trend; rather they seem associated with higher periods of stress, such as a death in the family or the loss of employment, and periods of increased physical activity.

The patient reports an overall feeling of relaxation accompanying the stimulation. However, no electroencephalographic (EEG) changes could be depicted, either during or
<table>
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<th>Case No.</th>
<th>Factors**</th>
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<th>Result</th>
</tr>
</thead>
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<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
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<td>2</td>
<td>1</td>
<td>2</td>
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<tr>
<td>6</td>
<td>3</td>
<td>0</td>
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<td>7</td>
<td>3</td>
<td>2</td>
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</tr>
<tr>
<td>8</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*Factors described in Table 1.
†Patient died from carcinoma within a few months of surgery.
‡Good duration only after use of amitriptyline.

Table 2 Individual scores on each rating factor

He described the pain as “floating away.” If high current levels were used, the patient reported a startle reaction, some dizziness, exhibited some nystagmus, and felt frightened and apprehensive. At the level he typically used, however, the only side effect was a warm sensation down his back, which he perceived as quite pleasant; no other emotional reactions were described (Table 1, C = 2). Pinprick testing revealed bilateral generalized decrease in perception during stimulation that returned to normal rapidly after stimulation was stopped. Ischemic and radiant-heat testing were not done due to the patient’s early death. He died 2 months after surgery as a result of ureteral obstruction and uremia (Table 1, D = 2). During that period, there was no apparent decrement in the effectiveness of brain stimulation. The success rating on this patient was good (Table 2). The brain was obtained at autopsy for histological study.

Case 3

This 24-year-old woman had suffered a right brachial plexus avulsion during a car accident 7 years before implantation of the electrode. Her arm was atrophic and hypersensitive. She had continuous dull pain, which became acutely exacerbated by any sensory stimulation, rendering it “focused” and intense. Since her injury she had been treated with nerve blocks and used the whole spectrum of narcotic analgesics with little success. She was considering either a thalamotomy or amputation of her arm when she came to us. Implantation was carried out in December, 1973. The stimulation makes her arm feel “just like the other.” She can sustain both sensory input and mild noxious input without any pain perception during and after stimulation (Table 1, A = 3). She is now able to use her right arm to help carry or support objects, such as her newborn daughter, without feeling pain. She uses either 0.8 volt at 10 Hz for 30 minutes or 1 volt at 25 Hz for 10 minutes, depending on how much time she has, and obtains excellent relief, lasting 24 hours (Table 1, B = 3). During stimulation she experiences some tingling in her face and a “cold sensation.” However, the overall feeling is one of “well being and relaxation” (Table 1, C = 2). It is not yet clear whether this feeling results from pain relief or is intrinsic to the stimulation.
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It is difficult to conduct acute pain studies on this patient's right arm, since she is suffering from neurological damage that affects her baseline responsiveness. Without stimulation, she typically exhibits normal responsiveness to pinprick on the healthy arm and hyper-responsiveness to pain in her right arm. Brain stimulation produces marked generalized reduction in her sensitivity to pinprick that is more intense contralaterally, especially in the contralateral painful arm. The effect outlasts the stimulation by at least 5 minutes.

The patient has become much more cheerful and active since her surgery. On one occasion, she broke the connection to her receiver while horseback riding for the first time in 7 years. She was hospitalized, and the wire was repaired. Since her surgery, she has been employing exactly the same current parameters, with no loss of effectiveness. Radiant heat testing and ischemic pain testing were not done due to neurological damage to the right arm. Overall, her results are excellent (Table 2).

Case 4

This 45-year-old man had suffered from chronic back and right hip pain since 1946, when he was in the Army. He underwent several operations, including lumbar laminectomies with disc removal, rhizotomy, and lumbar facet rhizotomy. He had markedly restricted level of activity and was unable to work for several years. He refused a lumbar spine fusion and was considered for the brain-stimulation procedure.

The electrode was implanted in January, 1974. At first, we considered his case a failure: 15 Hz stimulation, just above threshold for paresthesias of the face, produced good temporary pain control but, within 30 minutes of discontinuing stimulation, the pain would return to its previous level. Pinprick testing revealed generalized increased confusion of sharp and dull with single pinpricks but repeated pricks were always interpreted correctly during stimulation. Radiant heat testing showed a 14% increase in tolerance to pain after 6 minutes of stimulation. Ischemic pain threshold was increased by 27% during stimulation. Continuous stimulation revealed that the patient tended to develop "tolerance" and the stimulation became ineffective. Institution of stimulation at frequent intervals, such as a 10-minute period every 30 minutes, produced approximately 50% relief of pain.

The patient was then placed on a combination of amitriptyline (Elavil) 150 mg before sleep, and fluphenazine hydrochloride (Prolixin) 1 mg three times daily. While this regimen alone pre- or postoperatively was not sufficient for relieving this patient's pain, it appeared to synergize with the brain stimulation, increasing the duration of its effectiveness. In the early weeks of medication, the patient exhibited a steady decrement in the use of the stimulator, with the pain relief lasting progressively longer. He has been stable for the last 22 months using the stimulator at 0.8 volts, 15 Hz, once to three times daily for 15 minutes (Table 1, B = 2, D = 3). He received total pain relief that outlasts the stimulation by several hours. While he had described some paresthesias, numbness in his legs, and a "bubbling sensation" initially, he now only described slight "tightening" sensation in the back (Table 1, A = 3, C = 2).

He is now working full-time as a construction electrician and uses the stimulator every 8 hours, with complete control of pain. We now consider the outcome of this case good (Table 2).

Case 5

This 62-year-old man had a Pancoast tumor of the lung, resulting in bilateral neck, shoulder, arm, and chest pain. He was using meperidine (Demerol), 100 mg every 3 hours, with interspersed phenothiazines for about 80% pain relief. He was operated on in June, 1974, with implantation of the right periventricular gray region. Stimulation produced good pain relief with heat paresthesia in the left side of the face, and spread of heat into the left arm when the current was increased (Table 1, A = 2, C = 2).

Postoperatively, he could be maintained on amitriptyline (Elavil), 100 mg daily, with stimulation at 2- to 4-hour intervals (Table 1, B = 1). Pinprick testing revealed bilateral reduction in sensation in both extremities with no obvious dermatomal pattern. Little or no change in sensation was observed in the region of the trunk, although the chronic chest pain was blocked by stimulation. Radiant and ischemic pain tests were not carried out. The disease progressed rapidly, and the patient died in August, 1974 (Table 1,
Case 6

This 40-year-old man suffered a severe back injury, and underwent several operations, including a laminectomy and a facet rhizotomy. When he came to us, he was taking dihydrocodeineone (Percodan) six times daily, and diazepam (Valium) four times daily. This regimen allowed him only markedly restricted activity. His pain consisted of bilateral back and leg pain, more severe on the right side, and associated with paresthesias of coldness, tingling, and sensory loss from previous surgery.

He was operated on in July, 1974, with a left periventricular electrode placement. Stimulation produced relief of bilateral pain, but was more marked on the right, and required longer duration of stimulation for relief on the left side (Table 1, A = 3). Side effects occurred if stimulation was increased and consisted of a "fogging of vision" with no detectable strabismus or nystagmus (Table 1, C = 2). Acute pain testing revealed no loss of sensitivity to pinprick or reduction of radiant heat pain. Ischemic pain testing was not accomplished. The relief of pain does not outlast stimulation by more than 10 to 15 minutes. Thus, continuous stimulation is required during severe pain episodes, which are intermittent and related to levels of activity (Table 1, B = 0). The patient is now attending rehabilitation classes, and can use stimulation during class and examinations without interference with mental function (Table 1, D = 3). We consider the results in this patient to be poor (Table 2).

Case 7

This 51-year-old man underwent cervical disc surgery 8 years ago, that involved damage to the spinal cord. As a result of that he suffered neurogenic pain on the right side of his body. Attempts at pain control included reoperation for disc removal, cervical rhizotomy, and high cervical cordotomy. At the time of surgery, his pain involved an aching, burning, paresthetic, and dysesthetic sensation in the right arm and both legs. He also had associated right hemiparesis.

An operation was carried out in July, 1974, with insertion of an electrode into the left periventricular gray. Stimulation at 25 Hz produced the sensation of heat in the right side of his face, but later this was replaced by a sensation of tingling in the area of his pain, some blurring of vision, and dryness of the mouth (Table 1, C = 2). Acute pinprick, radiant heat, and ischemic testing could not be carried out contralaterally due to sensory loss resulting from the spinal cord damage. Ipsilateral radiant heat testing revealed only a 5% increase in pain threshold. Pain relief required only a 30- to 45-minute period of stimulation, three times per day; his sensations would then return to normal except for some muscle tightness from his hemiparesis (Table 1, B = 2, A = 3). No change in stimulus parameters has been required in the intervening 18 months (Table 1, D = 3), and the result is considered good (Table 2).

Case 8

This 54-year-old man's initial pain was secondary to lumbar disc rupture. He developed arachnoiditis and, subsequently, had spinal cord stimulation, cordotomy, and bilateral basilar intralaminar thalamotomy, and was eventually free of pain for 1 year. However, he developed an acute right hemiparesis coupled with a thalamic syndrome involving pain and dysesthesias. He became addicted to morphine, taking 15 mg every 2 to 4 hours, and refused to withdraw at the time of surgery. A left periventricular electrode was inserted in January, 1975, with good subjective loss of paresthesias and objective loss of dysesthesias. No effect on the patient's addiction to morphine could be demonstrated; he suffered physiological withdrawal symptoms approximately 48 hours after discontinuing his narcotics, despite the almost continuous use of his brain stimulator. The main side effect reported from stimulation was the sensation of heat in the contralateral face, spreading to the arm and then the leg with increased stimulus intensity. However, the patient insisted on continuing his narcotic medication and was erratic in response to stimulation. He continued to report some relief of dysesthesias, but was inconsistent in his reports on relief of chronic pain. Therefore, it was thought unwise to internalize his system, and the electrode was removed after 3 weeks of chronic percutaneous stimulation. This patient was considered a failure (Table 2).
Histology

Both patients who were operated on for control of pain from carcinoma died shortly after surgery, approximately 2 months after electrode insertion. Figure 2 shows the electrode tip in the periventricular gray area in Case 2. The electrode array was designed such that stimulation was between the tip and 5 mm proximal to the tip. No gliosis or tissue damage was noted after 2 months of stimulation at the rate of 20 minutes every 4 to 6 hours. Figure 3 is the camera lucida drawing of the tip placement in Case 5, showing its location at the lateral aspect of the periventricular gray. Again, stimulation was carried out across 6 mm of tissue without significant gliosis or tissue destruction.

Discussion

The results reported in this paper support the notion that brain stimulation in the periventricular area could effectively replace lesioning as a neurosurgical tool for pain reduction. At this point, we would consider our results quite encouraging (six good, one fair, one poor). We are currently following up these patients with interviews, questionnaires and acute and chronic pain tests. With the longest follow-up time exceeding 42 months, there are no apparent changes in the effectiveness of the stimulation. For example, there is little long-term habituation to the stimulation with repeated daily use. However, acute habituation does result from sustained use of the stimulator over several hours.
Thus, the intensity, frequency, and rate of stimulation are critical and should be carefully titrated for each patient, in order to insure long-term effectiveness. A further series of 15 patients have since been operated on and studied during the last 2 years. The results are consistent with the above data, with a success rate of approximately 75% to 80%.

As it stands, this approach appears to offer several advantages. Brain stimulation appears effective in controlling pain throughout the body, including ipsilateral pain, midline, visceral, and upper extremity pain. In contrast to other stimulation procedures, such as dorsal column stimulation\(^\text{14}\) or internal capsule stimulation\(^\text{1,7}\), this technique is not dependent upon paresthesias for effectiveness. Aside from the electrode track, there appears to be no irreversible damage to the brain resulting from this procedure.

As was the case with acute stimulation\(^\text{12}\), excellent pain reduction with few or no sensory side effects was obtained by low-frequency low-amplitude current in the periventricular region. Here again, increase in the above parameters often resulted in noxious side effects. However, with the optimal stimulation conditions, the experienced patient can distinguish accurately the presence or absence of very low currents, in the absence of any stimulus effects other than the decrease in pain intensity.
Pain reduction by chronic brain stimulation

There are indications that focal stimulation of the brain produces different effects on chronic pain as compared to acute pain. In general, it appears that chronic pain is more easily blocked by electrical stimulation, requiring lower stimulation intensities, and exhibiting longer duration of inhibition after the termination of stimulation. It remains unclear whether this discrepancy can be attributed to a difference in the intensity of the two types of pain, a difference in the levels of neural integration, or a difference in the specific anatomical and biochemical pathways that carry or modulate the two types of noxious stimuli. It should be noted that most patients report some temperature sensations at current parameters which also produce good blockade of chronic pain. This temperature effect might serve as a good indicator of analgesic sites in the operating room, if there are difficulties in measuring changes in pain responsiveness.

That the focal stimulation produces differential effects on various sensory and emotional phenomena is further supported by the long-term results of this technique. As mentioned above, there is evidence of short-term tolerance resulting from continuous stimulation for several hours. However, the analgesic potency is restored if stimulation is discontinued for 1 or 2 days. On the other hand, long-term adaptation is avoided by the intermittent use of the stimulator. It is noteworthy that some of the side-effects seem selectively to disappear during long-term use. This appears true for both sensory side-effects, such as tingling, or noxious side effects appearing at higher current levels, such as startle. Consequently, after as little as a few weeks of use, the patient can withstand higher current parameters with less repercussions. This phenomenon cannot be attributed to nonspecific tissue damage, since the histological material showed no damage or electrode insulation after 2 months of stimulation. Further, the very selectivity of the habituation points to active adaptive mechanisms, rather than a nonspecific decrease in sensitivity.

The interactions with monoamine-altering drugs is yet another indication of the complex nature of the pain blockade by focal stimulation. Four of our patients received amitriptyline (Elavil) in order to potentiate the effectiveness of stimulation in pain control. As a tricyclic antidepressant, this drug presumably blocks the reuptake of all three monoamines, leading to a potentiation of the effects of the neurotransmitters. This potentiation of pain relief occurs before the antidepressant effect of amitriptyline, and has been observed in patients unaffected by this drug before stimulation. This finding is consonant with animal work demonstrating that monoamines play an important role in the modulation of stimulation-produced analgesia.

While the mechanisms underlying pain inhibition by electrical stimulation remain obscure, several lines of evidence point to the possible involvement of the opiate-like peptides endogenous to the brain. These peptides (enkephalins and endorphins) have been described recently by several investigators. They are naturally occurring substances that cause morphine-like analgesia, tolerance and dependence when microinjected in rat brain.

It has been suggested that electrical stimulation blocks pain by activating the endogenous opiate system and releasing the endogenous opioid peptides. Consistent with this hypothesis, we have recently shown in five electrode-implanted patients that the inhibition of acute and chronic pain can be prevented by injection of 1 mg of the opiate antagonist, naloxone. Further, neurochemical studies in six patients indicate a release of enkephalins into the ventricular fluid upon analgetic stimulation. It appears that the localized and intermittent nature of focal electrical stimulation in the periventricular gray matter, activates the powerful pain inhibitory mechanisms harnessed by opiates, while avoiding some of the side effects, including extreme tolerance with chronic use.

Acknowledgment

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