Pain reduction by electrical brain stimulation in man

Part 1: Acute administration in periaqueductal and periventricular sites

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Acute studies performed in five patients indicate that electrical stimulation of the brain could be a powerful tool for the reduction or control of intractable pain. While chronic or spontaneous pain could be relieved by stimulation of the periaqueductal gray matter, the accompanying side effects render it impossible to stimulate this site regularly. On the other hand, stimulation of medial thalamic sites, particularly medial to the nucleus parafascicularis, yielded good relief of chronic pain at parameters which did not cause many undesirable side effects. The same parameters also produced inhibition of acute pain in two of the five patients.

KEY WORDS • brain stimulation • analgesia • pain • central gray matter • medial thalamus

CONTROL of chronic intractable pain has been a dilemma for the neurosurgeon for many years. Traditional approaches, such as spinothalamic tractotomy, posterior rhizotomy, or lesioning of the brain stem, thalamus, thalamofrontal projection, or cingulum, have the disadvantage of restriction of relief to specific segments of the body, gradual return of pain with time, or, more seriously, permanent neurological complications, such as weakness, urinary retention, or personality changes.

In the last few years, there has been a shift in the treatment of chronic pain from ablative surgery toward stimulation procedures. Peripheral nerve stimulation and dorsal column stimulation have been successfully used in humans under selected conditions. While they have laid the technical groundwork for practical use of stimulation procedures, both techniques have been limited in relieving pain restricted to specific regions of the body. Furthermore, analgesic effectiveness of dorsal column stimulation appears to be short lived, due to the electrode isolation resulting from tissue scarring. In the present paper, we report the study of electrical stimulation of the brain as an alternative approach for pain relief, which has the potential to control a variety of pain types throughout the body. This study was based on a number of practical and theoretical considerations presented below.

Previous Experimentation

The successful employment of brain stimulation as an analgesic tool was first reported by Heath and Mickle, who
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described pain reduction from septal stimulation in a young woman. Later reports\textsuperscript{3,4} confirmed the phenomenon, although Gol\textsuperscript{4} reported success in only two out of six cases. These results were difficult to interpret, since a number of emotional side effects resulted from stimulation of the septal area.

Meanwhile, animal investigation revealed that stimulation of a number of mesencephalic and diencephalic sites could produce analgesia. Reynolds\textsuperscript{15} first described analgesia upon stimulation of the central gray matter of the rat. Further effective sites were found to surround the periaqueductal and periventricular areas in the rat.\textsuperscript{1,2,8,10} Stimulation in the area of the dorsal raphe nucleus in the cat was also successful in producing analgesia.\textsuperscript{6} Such analgesia did not appear to result from the production of seizures, or from any sensory or motor deficit; neither did it appear to be associated with specific emotional changes in the animal.\textsuperscript{6} Indeed, the animals were generally behaviorally intact over several months of chronic stimulation. A further characteristic of analgesia produced by stimulation was that the inhibition of acute pain appeared to outlast the termination of stimulation by several minutes.\textsuperscript{10}

There are strong indications that analgesia produced by electrical stimulation of these sites is an active process, dependent on the integrity of certain nerve pathways for its effectiveness. Depletion of cerebral dopamine and serotonin interferes with stimulation-produced analgesia, and their elevation potentiates it. Norepinephrine, on the other hand, appears to exercise an inhibitory effect on stimulation-produced analgesia, since its selective blockade increases the pain inhibition.\textsuperscript{1,2}

A further indication of the active nature of analgesia produced by stimulation is offered by electrophysiological findings, which have indicated that central gray stimulation leads to inhibition of pain-sensitive lamina V cells in the cat spinal cord.\textsuperscript{6} In addition, electrolytic lesions in the central gray area do not yield analgesia,\textsuperscript{7} suggesting that stimulation-induced analgesia is effective by activating a pain inhibitory mechanism, rather than by merely interrupting pain input. It was this pain inhibitory process that we hoped to take advantage of in the clinical situation.

Based on the above clinical and animal findings, it was felt that electrical stimulation of periaqueductal and periventricular sites in the human may provide a nondestructive technique for pain relief. It carried the potential for relieving arm, neck, and head pain, as well as midline and visceral pain, without the potential for permanent neurological sequelae. Preliminary investigation was necessary to ascertain the effectiveness of the analgesia and the extent of the accompanying side effects in man. Therefore, this investigation was carried out as an acute study, during which time patients undergoing thalamotomy were stimulated prior to lesioning, and a measurement of pain reduction was obtained.

**Clinical Material and Methods**

Five patients were studied. They were all scheduled for production of thalamic lesions, aimed at relieving chronic pain,\textsuperscript{18} or, in one case, intention tremor. They all agreed to undergo additional stimulation studies before the lesioning procedures.

**Surgical Procedures**

The surgical procedure was performed under local anesthesia (lidocaine). The patient’s head was placed in the stereotaxic unit, and, after trephination, a Conray ventriculogram was performed in order to visualize by x-ray the anterior and posterior commissure and allow coordination with the Schaltenbrand and Bailey Atlas.\textsuperscript{18} A 5 $\times$ 1.1 mm monopolar stainless steel electrode* was stereotaxically placed in various brain sites, primarily in periaqueductal and periventricular locations. It was introduced anteriorly and oriented in such a fashion as to traverse the medial thalamus in its descent to the mesencephalon. The target point was the ventral aspect of the periventricular gray area. Usually, stimulation studies were begun 20 mm above target and carried out at 5 mm intervals approaching and at the target site. At the end of the stimulation study, the electrode was withdrawn and stereotaxically aimed at the lesion site, usually more laterally, but through the same trephine opening. All placements were verified by x-ray film.

*Stainless steel electrode manufactured by Radionics, Inc., 76 Cambridge Street, Burlington, Massachusetts.
Brain Stimulation and Assessment of Pain Responsiveness

A Radionics stimulator† was employed to deliver short (1 msec) capacitor-coupled square pulses, 25 to 75 Hz in frequency, for periods varying from a few seconds to several minutes, depending upon the patient's response. The current was terminated immediately if the patient reported any noxious side effects. The voltage was gradually increased by half-volt steps, until the patient described a clear response, or a maximum of 5 volts was reached. A baseline description of the patient's pain was obtained, and he was asked to describe any unusual sensations or changes in pain that he experienced upon stimulation. Further, he was questioned about his chronic pain, and painful areas were specifically tested by pressure or movement to determine changes in sensitivity. Before and during stimulation, the patient's responsiveness to pinprick was tested over the whole body. At the end of each stimulation trial, the duration of post-stimulation reduction in pain and sensitivity to pinprick was measured. The above procedures were carried out at each of the stimulation sites between medial thalamus and central gray matter. Before proceeding to the next site, it was ascertained that the sensory changes from the previous stimulation trial had subsided.

Special attention was paid to the occurrence of sensory, motor, or autonomic side effects of the stimulation. The vital signs were monitored during and immediately after stimulation. Testing sessions were tape-recorded and transcribed later.

Case Reports

Case 1

This 65-year-old man suffered from severe phantom limb pain, with burning paresthesias perceived in the amputated right foot and leg. He had undergone the amputation procedure following diabetic gangrene, and his phantom pain occurred at the site which had been painful prior to surgery. The target stimulation point was the anterior periaqueductal gray matter at the level of the pons. The stimulation point during the descent to target included medial posterior thalamic nuclei, a tegmental site at the superior collicular level, and central gray matter.

The patient reported good-to-excellent relief of chronic pain from the stimulation. With stimulation at the level of the nucleus medial basalis posterior, he reported a sensation like a "vapor" arising from his chest toward the face, but also reported good reduction of spontaneous pain. With the electrode at the tegmental and periaqueductal sites, he complained of slight dizziness and shortness of breath; nystagmus was clear-cut at target, probably due to associated stimulation of the medial longitudinal fasciculus. However, stimulation at the level of the nucleus parafascicularis produced excellent chronic pain relief without untoward side effects, and with a general sensation of well-being and relaxation. The blockade of pain outlasted 1 minute of stimulation by about 10 minutes. Pinprick testing did not reveal any apparent reduction of acute pain at the level of stimulation used which did not exceed 2 volts.

Case 2

This 63-year-old woman suffered from intractable right brachial plexus pain resulting from carcinoma of the breast. The stimulation target was the anterior periaqueductal gray matter, but the actual route of the electrode was too posterior; therefore, the patient received stimulation in the posterior medial thalamus and medial pulvinar, and in the posterior aspect of the periaqueductal gray area, close to the superior colliculi. The patient reported good-to-very good pain relief at all sites, outlasting 2 minutes of stimulation by up to 30 minutes. However, clear eye movement occurred with the electrode at the deeper sites, undoubtedly due to stimulation of the vicinity of the superior colliculus. All sites were similar with regard to pain relief and eye movements. However, stimulation of the posterior medial thalamus produced the best pain relief, with least side effects. No loss of pinprick sensation was obtained using up to 3.5 volts at 50 and 75 Hz.

Case 3

This 60-year-old man had carcinoma of the left ureter and kidney, causing bilateral abdominal pain, particularly severe in the left

†Radionics stimulator (RFG-3AV) manufactured by Radionics, Inc., 76 Cambridge Street, Burlington, Massachusetts.
flank. His stimulation sites involved the nucleus centromedianis, medialis caudalis, posterior medial pulvinar, tegmentum, and posterior periaqueductal gray area at the level of the superior colliculi. In general, the patient reported a small degree of pain relief and did not lose pinprick sensation. The best result was obtained at the level of the nuclei medialis caudalis and parafascicularis. At this level, when higher current amplitudes were employed, he also reported a "funny feeling" which he could not describe.

The side effects of stimulation were of interest. Nucleus centromedianis stimulation produced mild dizziness; medialis caudalis stimulation produced nausea and a "funny feeling" with some pain relief; medial pulvinar stimulation produced paresthesia in the contralateral arm, dizziness, and a tightness of the chest with little pain relief; tegmental and periaqueductal gray matter (posterior) stimulation produced dizziness, nystagmus, conjugate deviation of the eyes, and tingling paresthesia contralaterally. Stimulation was carried out at 75 Hz and did not exceed 2 volts.

Case 4

This 66-year-old man suffered from thalamic syndrome and intention tremor following a stroke. The patient complained of intense pain during passive and active movement of the right arm and leg and, upon testing, showed some loss of proprioception in the right hand and some increase in acute pain threshold. The target in this case was a medial site next to the third ventricle and rostral to the previous periaqueductal target point. Stimulation studies were carried out at the level of the nucleus dorsalis intermedialis of the thalamus, medial fascicular posterior, nucleus centromagnocellularis, and nucleus parafascicularis. The patient reported some tingling sensation and some shortness of breath associated with a slight increase in blood pressure at the more rostral site. However, very good pain relief was obtained with 75 Hz and 4 to 5 volts, which brought about very few undesirable side effects. At the level of the parafascicularis, excellent analgesia was obtained with 3 volts at 75 Hz but he had mild complaints of shortness of breath. Chronic pain was abolished, and complete bilateral analgesia to pinprick was observed. This reduction involved areas of the chest and face, as well as the limbs and lasted about 3 to 5 minutes following stimulation.

Case 5

This 70-year-old man had a progressive bilateral familial intention tremor, more marked on the right side. The patient did not suffer from chronic pain, but agreed to acute pain studies. In this case, the two sites tested were medial pulvinar and the ventral medial nucleus of the thalamus. Stimulation of both areas produced good-to-very good hypalgesia and resulted in no side effects, except for some increase in resting and intention tremor.

Medial pulvinar stimulation with 75 Hz, 1 to 5 volts, produced reduction in pinprick appreciation bilaterally over the entire body that outlasted stimulation by 1 minute and increased his tremor. Ventral medial nucleus stimulation with 75 Hz, 1 to 5 volts, produced an increase in contralateral tremor, and reduced pinprick sensation at 75 Hz, 4 volts. At the latter site, the hypalgesia was limited to the contralateral side of the entire body and outlasted stimulation by 8 minutes.

Discussion

The present study indicated that, as predicted by animal investigation, stimulation of the mesencephalic gray regions was indeed effective in producing reduction of chronic pain and hypalgesia to pinprick. Unfortunately, it produced numerous undesirable side effects, including nystagmus, nausea, vertigo, and a feeling of a "rising vapor." It was difficult to dissociate these side effects from the relief of pain through the manipulation of current parameters. Therefore, we felt that the central gray area would not serve as a good site for chronic electrode implants. The major conclusion from the present study concerns the importance of the medial thalamic sites as analgesic areas. In four out of five patients, the electrode traversed the periventricular gray area along the medial aspect of the nucleus parafascicularis (Fig. 1). At that site, and at the optimal parameters, three of five patients reported good-to-excellent reduction of chronic pain with minimal side effects; they expressed a feeling of relaxation and well-being, with no overwhelming emotional overtones. Two patients had hypalgesia to pinprick testing during stimulation and one
FIG. 1. Sites of stimulation in the five patients projected on the Schaltenbrand and Bailey Atlas. AQ = aqueduct of Sylvius; COI = inferior colliculi; COS = superior colliculi; HPTH = hypothalamus; RU = red nucleus; TH = thalamus.

patient felt little effect on his chronic pain or pinprick sensation. The patients effectively stimulated with reduction of acute or chronic pain were often affected bilaterally, and the pain reduction outlasted the termination of stimulation by an appreciable amount of time.

The effectiveness of the medial thalamus and central gray matter in producing pain control in the human may appear paradoxical in view of the findings by others that both sites produce noxious side effects in man. As indicated at the beginning of this paper, we selected the sites on the basis of animal work and were careful in examining both the pain reduction and noxious side effects of central gray stimulation. We found that pain reduction from medial thalamic stimulation could be obtained with minimal emotional concomitants. We feel that the explanation of this discrepancy lies in the choice of current parameters. In the present study, pain reduction and hypalgesia were reported at relatively low amplitude and low frequency of stimulation. This result could not be attributed to suggestion or placebo, since it was not obtained from other sites; further, double-blind trials with no effective stimulation never led to reports of pain loss in these patients. It is entirely conceivable that, at the low current parameters, the pain-free subject may report no effect, thus causing the experimenter to increase stimulation levels. In each of the present cases, raising frequency or increasing the stimulation above a certain level led to reports of poorly described noxious effects, such as discomfort, oppressiveness, or anxiety. Therefore, it appears reasonable to postulate that pain transmission and analgesia are modulated by different cell populations in the periventricular area, having different stimulation thresholds, but lying in close anatomical proximity.

A few observations were made in this stage and later confirmed in patients with chronically implanted stimulators. Most striking was the fact that the pain loss could outlast 1 minute of stimulation by an ap-
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preciable period, up to 1 hour. This stimulation-induced pain blockade did not follow a clear dermatomal pattern. While being primarily localized on the side contralateral to the stimulation, the analgesic effect often exhibited a bilateral peripheral field, especially in the more medial aspects of the body. Finally, there appear to be some differences in the control of acute and chronic pain, in terms of duration of stimulation needed for their blockade and the length of the post-stimulation effect. This chronic-acute distinction was not explored systematically in this study, but was more thoroughly examined in subsequent chronic work. In contrast to peripheral nerve stimulation techniques or spinal cord stimulation, the present procedure is not dependent for its effectiveness on production of paresthesias. While some sensory changes, such as tingling or numbness were reported by the patient, these sensations did not appear to be a requirement for the analgesic effectiveness of stimulation.

This series of acute studies indicates that stimulation of an area between the nucleus parafascicularis and third ventricle at the level of the posterior commissure could produce effective control of pain with minimum side effects, and long duration following stimulation. Therefore, this region was chosen as the target point for subsequent permanent implants in an attempt to allow patients chronic self-administration of current for pain control.

References


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