

REVIEW ARTICLE

Neuromodulation: An Overview

Francisco Velasco*,**

**Unidad de Neurocirugía Estereotáctica y Funcional, Hospital General de México, México, D.F., Mexico*

***Unidad para Investigación Médica en Neurofisiología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social (IMSS), México, D.F., Mexico*

Received for publication October 12, 1999; accepted October 14, 1999 (99/167).

For over two centuries, electricity has been known to induce modification of neural and nerve fiber activity and has been proposed to be used to treat some neurological dysfunctions. The new era of the use of electrical current in the treatment of neurological symptoms began in 1967 with the use of totally implanted devices that deliver a controlled amount of electricity on a precise structure within the nervous systems and was first used to control pain. Extensive research has been carried out ever since to elucidate the mechanism of action of this treatment and extend its indication for the treatment of the other neurological symptoms. So far, there is evidence that the treatment is safe and efficient for long periods of time, as it does not induce permanent damage to the stimulated structure. Most likely, electrical current at the parameters used for therapeutic purpose induces an inhibition of the structure on which it is applied. However, this may be accompanied by either inhibition or excitation of anatomically related structures. For this reason, it seems more convenient to refer to this type of therapy as neuromodulation.

A review of the historical development of this fascinating area is presented, with special attention to the evidence derived from experimental work on the parameters that electrical current must maintain to avoid damage to the underlying tissue. © 2000 IMSS. Published by Elsevier Science Inc.

Key Words: Electrical stimulation of nervous tissue, Neuromodulation, Pain, Involuntary movements, Epilepsy, Spasticity.

Introduction

The experimental effects of electrical and chemical stimulation of the nervous system on various behavioral and/or electrophysiological responses led to their use for therapeutic purposes. To date, both electrical (ES) and chemical (CS) stimulation have been used to treat a number of neurological symptoms such as pain, movement disorders, spasticity, epilepsy, stupor and coma, psychiatric disorders, neurogenic bladder, peripheral vascular insufficiency, and diaphragmatic palsy. They also have been used to design prototypes for visual and audiogenic prostheses to treat visual and hearing loss.

This Special Issue focuses on the treatment of pain, movement disorders, spasticity, and epilepsy, as these are fields in which neurologists and neurosurgeons are mainly involved. Treatment of stupor and coma and psychiatric disorders are confined to a few reports that await confirmation derived from multicenter studies. Visual and auditory prostheses are still in the developmental phase and bladder, diaphragmatic, and vascular insufficiency treatment by ES has been undertaken by other specialties in medicine.

Historical Notes

There is evidence that mineral sources of electric and magnetic energy such as amber and magnetite were used for therapeutic purposes as early as 9,000 BC in the form of necklaces, bracelets, and amulets. For many centuries and throughout several cultures (Greek, Egyptian, Hebraic, Roman, etc.), the practice of electrotherapy was extended

Address reprint requests to: Francisco Velasco, M.D., UIM Neurofisiología, Centro Médico Nacional Siglo XXI, IMSS, P.O. Box 73-032, México, D.F., México. Tel.: (525) 578-4238; FAX: (+525) 761-6933; E-mail: fvelazco@netservice.com.mx

through the use of several sources, such as minerals, metals, and animals like the torpedo fish and the electric eel.

During the Middle Ages, knowledge of electricity was advanced. Electricity was identified as a form of energy and primitive devices to induce electrical current were developed. In 1745, the capacitor, i.e., a device to create and conserve energy, was simultaneously developed by Von Kleist and Musschenbroek (1).

Experiments in neurophysiology utilizing electrical current began in 1786 when Galvani induced muscular contractions in the legs of frogs by applying a pair of scissors along the trajectory of the sciatic nerve during an electric storm (2). With the design of the battery by Volta (1790) (3), experiences in neurophysiology using electrical current multiplied. It is interesting that the earliest experiences were obtained in humans; for example, D. Larrey, a surgeon of Napoleon's army, stimulated the popliteal nerve to induce contractions of the gastrocnemius muscle in the amputated leg of a soldier in 1793.

In 1870, Fritsch and Hitzig (4) produced seizures by applying electrical current in a dog's brain, thus initiating the study of the central nervous system (CNS) with electricity. Electrical currents were extensively used to study spinal reflexes and motor and sensory responses from the nervous system at the beginning of the 20th Century. Of particular interest is the book by Ferrier in 1886 that describes the topography of different areas in the cerebral cortex of animals, using ES to elicit various motor and sensory responses (5).

In 1932, Hess (6) described antagonistic responses that could be obtained through stimulation of the same locus in the thalamus of the cat by varying the frequency of alternating currents (AC). While low frequency stimulation induced sleep, high frequency currents induced arousal. In this manner, Hess demonstrated for the first time that nervous tissue response could be modulated according to the parameters of the ES applied.

In 1942, Dempsey and Morrison (7) described a widespread synchronization of the cortical electroencephalogram (EEG) by stimulation of circumscribed loci in the brain stem and the thalamus, demonstrating the regulatory activity of subcortical structures upon the cerebral cortex. In 1949, Hunter and Jasper (8) were able to correlate low frequency stimulation of the thalamus to behavioral and EEG patterns of sleep and petit mal epilepsy, while high frequency stimulation of the same area induced arousal and EEG desynchronization.

With the publication of the book entitled *Functional Anatomy of the Human Brain*, in 1954 (9), Penfield and Jasper provided invaluable information on the topography of a number of clinical and EEG responses induced by ES. The observations were made during surgical procedures performed under local anesthesia to treat epilepsy. Zanchetti et al. in 1952 (10) demonstrated an increase in the convulsive threshold of pentylene tetrazol seizures by simultaneous electrical stimulation of the vagal nerve.

Cooke and Snider (11) in 1955 and Dow et al. (12) in 1962 prevented seizures originating in the cerebral cortex by stimulation of the cerebellar cortex in animal models of epilepsy.

In 1965, Melzak and Wall (13) proposed the gate control theory of pain. They considered a competitive input of small-diameter fibers associated with noxious information and large-diameter fibers associated with proprioceptive and other forms of sensory information at the entrance of the dorsal roots to the spinal cord. Accordingly, pain perception would depend upon the balance between large- and small-fiber input. Melzak and Wall also suggested that activation of the dorsal column of the spinal cord would induce antidromic potentials of large-diameter fibers that could inhibit the input of small-diameter fibers and decrease pain perception. In 1969, Reynolds (14) electrically stimulated the periventricular gray substance in the thalamus and mesencephalon and reduced painful perception in rats. He interpreted this result as the activation of opioid receptors located in those areas.

In 1972, Consieller et al. (15) demonstrated that morphine delivered to the spinal cord of cats inhibited the activity of nociceptive neurons located in the dorsal horn. Duggan et al. (16) in 1977 suppressed the transmission of nociceptive input by delivering morphine in the substantia gelatinosa of the spinal cord.

In regard to the treatment of involuntary movements, the history has been different. Observations made during stereotactic procedures to treat tremor and rigidity provided information that some symptoms may be decreased by ES used transoperatively to assess the proximity of eloquent areas to the stereotactic target before performing the lesions (17,18). More recently, the experiments by De Long et al. in 1985 (19) provided evidence of the inhibitory influence of the subthalamic nucleus on the activity of the ventrolateral thalamic nucleus (VL), both directly and through the internal globus pallidus, which led to the use of subthalamic nucleus stimulation to treat Parkinson's disease and other involuntary movements.

These are only some of the major experimental observations that supported the use of neuromodulation in the treatment of difficult-to-control pain, seizures, involuntary movements, altered states of consciousness, and spasticity.

Clinically, the use of neural tissue ES to treat neurological symptoms goes back to the past century in Europe and perhaps even more in the Oriental cultures. An interesting photograph was obtained from the photograph archives of the old School of Medicine in Paris; it was taken in 1852. The picture shows Dr. Duchenne applying an electrode along the trajectory of the facial nerve to treat a patient suffering from facial nerve palsy (20) by means of ES.

ES of peripheral nerves by acupuncture or transcutaneous electrical nerve stimulation (TENS) was used in the Western world to treat pain or to induce a state of analgesia several years before the initiation of chronic ES. The begin-

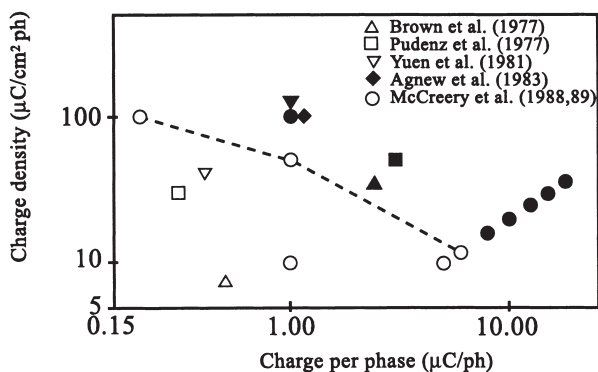


Figure 1. Combinations of charge density and charge per phase used in several studies of stimulation-induced neural injury. The occurrence of neural injury is indicated by filled symbols, absence of damage by open symbols. The broken line connects loci from the author's most recent study, described in the text, using electrodes of various sizes. Loci in the upper left portion of the graph represent small electrodes, while those in the lower right portion represent large (8-mm diameter) disc electrodes. (From Agnew et al., 1989. In: Agnew WF, McCreery DB, editors, *Neural prosthesis*. Minneapolis, MN: Prentice Hall Biophysics and Bioengineering Series, by permission of the publisher).

ning of the modern era of ES started with the introduction of totally implanted devices to stimulate nervous tissue in an attempt to interfere with mechanisms related to the pathophysiology of symptoms (21).

Shealy et al. in 1967 (22) initiated the use of ES in the dorsal column to treat pain. Initially, the electrodes were placed subdurally and later, epidurally. The authors took advantage of the technology developed for the cardiac pacemakers that had been in use by that time for over a decade (23). The new indication in the treatment of neurological disorders promoted the rapid development of totally implanted devices, described subsequently in this special issue on instrumentation.

In 1973, Mazars (24) and Hosobuchi (25) stimulated various sites of the thalamus, the internal capsule, and periventricular gray to induce analgesia, perhaps by enhancing or interfering with opioid receptors and other anatomic-physiological mechanisms of pain perception. Also in 1973, based on the experiments by Cooke and Dow previously described, Cooper et al. (26) stimulated the cerebellar cortex to treat refractory epileptic seizures and described the additional effects on muscular tone of patients suffering from spastic paraplegia.

In 1974, Steude (27) described the analgesic effects of ES of the trigeminal nerve and Gasserian ganglion in cases of facial anesthesia dolorosa. Andy, in 1980 (28), described the effect of ES of centromedian nucleus of the thalamus on painful dyskinesia and in 1982, Bovie and Meyerson (29) attributed the analgesic effect of periventricular gray stimulation to the interference of neuronal activity in the parafascicular nucleus.

In 1985, Heath et al. (30) reported the beneficial effect of cerebellar stimulation on behavioral disorders. In 1987,

Benabid et al. (31) used the thalamic target to treat tremor in the nucleus ventralis intermedius (Vim) of the thalamus to control tremor and rigidity in cases of Parkinson's disease by ES. In the same year, Uthman et al. (32) initiated their experience in seizure control by ES of the vagal nerve and F. Velasco et al. (33) described the anticonvulsive effect of centromedian thalamic nucleus stimulation. In 1988, Sussman et al. (34) presented a short communication on the treatment of seizures by ES of the ventralis anterior nucleus of the thalamus (VA).

In 1991, Tsubokawa et al. (35) described the analgesia induced by ES of the motor—but not of the sensory—cortex of patients suffering from deafferentation pain. In 1995, Limousin et al. (36) reported the control of symptoms of Parkinson's disease by ES of the subthalamic nucleus.

Last year, Fisher provided experimental evidence of seizure control by VA nucleus stimulation and reported the success of the method in clinical cases. Velasco et al. (37) provided evidence that stimulation of the epileptic foci may induce decrease of seizure activity and seizure control. Today, the same group presents evidence that stimulation of subthalamic fibers, termed prelemniscal radiation, induces improvement of Parkinson's disease symptoms.

Throughout this issue, we have had the opportunity of bringing together most of the outstanding experts in neuromodulation who either have described some of the procedures to treat neurological symptoms or who have the greatest experience in the use of a particular procedure. For their assistance and participation, we would like to express our gratitude.

Before going into the material of this issue, I would like to refer to an experimental work of utmost importance, i.e., evidence provided concerning the ranges at which ES of neural tissue may be considered safe.

Several experimental models have been used to study the effect of ES on the neurons themselves. One of the simplest models and perhaps the model that has provided the most evidence on this matter is the use of implanted electrodes in the motor cortex of the cat to perform controlled microstimulation while orthodromically induced potentials were being recorded from the cerebral peduncle (38). The amount of current delivery measured as charge per phase, i.e., the amount delivered in each phase (positive/negative) of a biphasic stimulus, measured in nano Coulombs (nC) or micro Coulombs (μ C), the charge density that is the charge per phase multiplied by the electrode's surface expressed in C/cm^2 , the frequency of stimulation in Hertz, and the duration of stimulation in hours and the fragmentation of the metal used to build up the electrodes were varied in those experiments. The local effects on neurons by histology or electron microscopy subsequent to different forms of stimulation and related their observations to other experimental studies that dealt with lesions caused by chronic stimulation, providing valuable information concerning the ranges of safety of ES have been analyzed (39–42).

Table 1. Effect of electrical stimulation

	Current intensity	Charge density	Charge per phase	Frequency of stimulation
Neuronal excitation	5–15 μ A	50–150 μ C/cm ²	1.0–5.0 μ C/ph	10–40 Hz
Neuronal inhibition	40–80 μ A	400–800 μ C/cm ²	0.5–1.0 μ C/ph	40–60 Hz
Neuronal lesion	800–1,200 μ A	>800 μ C/cm ²	>2.0 μ C/ph	>40 Hz

Progressive lesion: it depends on the metals used to build up electrodes and current densities inducing fragmentation of the electrode.

In Table 1, we presented the effects of subacute (minutes) ES on evoked potentials and neuronal changes. Neuronal excitation (increase in pyramidal tract-evoked potentials) was obtained within a narrow, small intensity and current charge. A neuronal inhibition was obtained within a range 3–5 times greater than that necessary to induce excitation. Neuronal lesion not exceeding 750 μ m around the electrode was induced by currents over 10 times those necessary to produce inhibition. However, stronger current charges caused a progressively enlarging lesion dependent on fragmentation of the electrode's metal (43). Lesions induced were principally neuronal shrinkage secondary to disruption of their membrane, but local vascular changes mainly in the form of hypoxia and hypoglycemia were also induced, as well as increments in [K⁺] in the interstitial space (38).

The safety of the procedure more clearly related inversely to charge density and charge per phase and was in agreement with other experiments of ES in different areas of the brain and the cerebellum and different animal species (Figure 1). Chronic (hour) stimulation tends to induce progressive inhibition of the stimulated tissue when other stimulation parameters are unchanged.

From these studies, we may conclude that with the intensity currents and paradigms of stimulation used for clinical work, we are most likely to be inducing inhibition of the stimulated tissue. Therefore, the term neuromodulation seems more appropriate than that of ES.

The objectives of this Special Issue would be to review the instrumentation used in clinical work and the indications and contraindications of each procedure, and to provide an outline of the surgical techniques used for implantation and the manner by which the results may be evaluated. Because all devices are used chronically, adequate monitoring of the functioning of the device and the effectiveness of neuromodulation throughout the treatment period is imperative for all procedures. Finally, because most procedures are designed as alternatives to traditional lesion procedures used in neurosurgery, and in view of the expensive cost of instrumentation, the evaluation of cost benefits of each particular procedure should be considered.

There is no doubt that the use of neuromodulation is rapidly expanding and that in addition to the benefit neuromodulation provides to our patients, these procedures also offer a unique opportunity to acquire knowledge concerning the physiology of the human brain. Consequently, information

concerning the possible mechanisms of action of these procedures will also be welcome.

References

1. Schechter DC. Early observations on natural and artificial electrical phenomena. Electrical response in animal and early therapeutic applications. In: Schechter DC, editor. Electrical cardiac stimulation. Medtronic;1983. p. 14.
2. Sirol M. Galvani et le galvanisme: l'électricité animale. Thesis. Toulouse, France: Faculté Mixte de Médecine et de Pharmacie de Toulouse;1939. p. 120.
3. Volta A. On the electricity excited by the mere contact of conducting substances of different kinds. Phil Tr 1800;90:403. Milan, Italy: Le Opere, U. Hoepli;1918.
4. Fritsch G, Hitzig E. Ueber die elektrische erregbarkeit des grosshirns. Arch Anat Physiol 1870;37:300.
5. Ferrier D. The function of the brain. London: Smith Elder;1886. p. 267.
6. Hess WR. Beiträge zur physiologie des hirnstammes. I. Die methodik der lokalisierten reiseung und ausschaltung subkortikaler hirn abschnitte. Leipzig, Germany: Thieme;1932. p. 362.
7. Dempsey EW, Morrison RS. The mechanisms of thalamocortical augmentation and repetition. Am J Physiol 1942;138:297.
8. Hunter J, Jasper HH. Effects of thalamic stimulation in unanesthetized animals. Electroencephalogr Clin Neurophysiol 1945;1:305.
9. Penfield W, Jasper HH. Epilepsy and the functional anatomy of the human brain. Boston, MA, USA: Little, Brown Co.;1954. p. 326.
10. Zanchetti A, Wang SC, Moruzzi G. The effect of vagal afferent stimulation on the EEG pattern of the cat. Electroencephalogr Clin Neurophysiol 1952;4:357.
11. Cooke RM, Snider RS. Some cerebellar influences on electrically induced cerebral seizures. Epilepsia 1955;4:19.
12. Dow RS, Fernández-Guardiola A, Manni E. The influence of the cerebellum on experimental epilepsy. Electroencephalogr Clin Neurophysiol 1962;14:383.
13. Melzack R, Wall P. Pain mechanisms: a new theory. Science 1965;150:971.
14. Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science 1969;164:444.
15. Consieller C, Menetrey D, Le Bars D, Besson JK. Effet de la morphine sur les activités des interneurons de la couche V de Rexed de la corne dorsale chez le chat spinal. J Physiol 1972;65:220.
16. Duggan AW, Hall JG, Headley PM. Suppression of transmission of nociceptive impulses by morphine selective effects of morphine administered in the region of the substantia gelatinosa. Br J Pharmacol 1977;61:65.
17. Hassler R. The influence of stimulations and coagulations in the human thalamus on the tremor at rest and its physiopathological mechanism. Vol. 2. London: Excerpta Medica Foundation;1955. p. 637.
18. Mazars G, Merienne L, Cioloca G. Control of dyskinesias due to sensory deafferentation by means of thalamic stimulation. Acta Neurochir Suppl (Wien) 1980;30:239.
19. De Long MR, Coucher MD, Georgopoulos AP. Primate globus palli-

- dus and subthalamic nucleus functional organization. *J Neurophysiol* 1985;53:530.
20. Poulet J, Sournia JC, Martiny M. Histoire de la médecine de la pharmacie, de l'art dentaire et de l'art vétérinaire. Paris, France: Soc. Française d'Éditions Professionnelles, Médicales et Scientifiques;1990. p. 363.
 21. Mullet K. State of art in neurostimulation. *PACE* 1987;10:162.
 22. Shealy C, Mortimer J, Hagtors N. Dorsal column electroanalgesia *J Neurosurg* 1970;32:560.
 23. Chardack WM, Gage AA, Greatbatch W. A transistorized self-contained implantable pacemaker for the long-term corrections of complete heart block. *Surgery* 1960;48:643.
 24. Mazars GL, Merienne L, Cioloca C. Stimulation thalamiques intermittentes antalgiques. *Rev Neurol (Paris)* 1973;128:136.
 25. Hosobuchi Y, Adams JE, Fields HL. Chronic thalamic and internal capsular stimulation for the control of facial anesthesia dolorosa and dysesthesia of thalamic syndrome. *Adv Neurol* 1973;4:783.
 26. Cooper IS, Rickland M, Amin I, Cullinan T. A long term follow up study of cerebellar stimulation for the control of epilepsy. In: Cooper I, editor. *Cerebellar stimulation in man*. New York: Raven Press;1978. p. 19.
 27. Steude U. Percutaneous electro-stimulation of the trigeminal nerve in patients with atypical trigeminal neuralgia. *Acta Neurochir (Wein)* 1978;21:66.
 28. Andy JO. Parafascicular centromedian nuclei stimulation for intractable pain and dyskinesia (painful dyskinesia). *Appl Neurophysiol* 1980;43:133.
 29. Boivie J, Meyerson BA. Correlative anatomical and clinical study of pain suppression by deep brain stimulation. *Pain* 1982;13:113.
 30. Heath RG, Walker CF, Dempsey CW, Franklin PE. Neurolith stimulation of the cerebellar vermis as treatment for intractable behavioral disorders and epilepsy. In: Lazorthes Y, Upton BM, editors. *Neurostimulation. An overview*. New York: Futura Publishing;1985. p. 231.
 31. Benabid AL, Pollack P, Louveau A. Combined (thalamotomy and stimulation) stereotactic surgery of the Vim thalamic nucleus for bilateral Parkinson's disease. *Appl Neurophysiol* 1987;50:344.
 32. Uthman BM, Wilder BJ, Hammond EJ, Reid SA, Traver WB. Safety and efficacy of vagus nerve stimulation in the treatment of complex partial seizures in man. *Epilepsia* 1990;31:603.
 33. Velasco F, Velasco M, Ogarrio C, Fanghänel G. Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures. A preliminary report. *Epilepsia* 1987;28:421.
 34. Sussman NM, Goldman HW, Jackel RA. Anterior thalamic stimulation in medically intractable epilepsy. Part II. Preliminary clinical results. *Epilepsia* 1988;29:677.
 35. Tsubokawa T, Katayama Y, Yamamoto T. Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl (Wien)* 1991;52:137.
 36. Limousin O, Pollak P, Benazzouz A, Hoffman D, Le Bas JF, Brousselle E, Perret JE, Benabid AL. Effect of Parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 1995;345:91.
 37. Velasco M, Velasco F, Velasco AL, Boleatga B, Jiménez F, Brito F, Márquez I. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. *Epilepsia* 2000. In press.
 38. Agnew WF, Yuen TG, McCreery DB. Morphological changes following prolonged electrical stimulation of the cat's cortex at defined charge densities. *Exp Neurol* 1983;79:397.
 39. Brown WJ, Babb TL, Soper HV, Lieb JP, Ottino CA, Crandall P. Tissue reactions to long term electrical stimulation of the cerebellum in monkeys. *J Neurosurg* 1977;47:366.
 40. McCreery DB, Agnew WF, Yuen TG, Bullara LA. Comparison of neural damage induced by electrical stimulation with faradic and capacitor electrodes. *Ann Biomed Eng* 1988;16:463.
 41. Pudenz RH, Bullara LA, Jacques P, Hambrecht FT. Electrical stimulation of the brain. III. The neural damage model. *Surg Neurol* 1975;4:389.
 42. Yuen TG, Agnew WF, Bullara LA, Jacques P, McCreery DB. Histological evaluation of neural damage from electrical stimulation: considerations for the selection of parameters for clinical application. *Neurosurgery* 1981;9:292.
 43. Agnew WF, McCreery DB, Yuen TG, Bullara LA. Effects of prolonged electrical stimulation of the central nervous system. In: Agnew WF, McCreery DB, editors. *Neural prosthesis*. Minneapolis, MN, USA: Prentice Hall Biophysics and Bioengineering Series;1989. p. 226.