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sensación y percepción del dolor: criterio interdisciplinario neurofisiológico, quirúrgico y farmacológico

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sensation and perception of pain: interdisciplinary neurophysiological, surgical and pharmacological approach

Resumen

En este estudio se consideró que la experiencia del dolor es una modalidad sensorial específica, con su propio "aparato" sensorial constituido por estímulos, receptores, fibras aferentes, vías y centros de integración. Desde el punto de vista psicofisiológico, el dolor parece seguir los principios del proceso sensorial que siguen otras modalidades sensoriales, y según los cuales pueden distinguirse dos etapas consecutivas, sensación y percepción, moduladas por el enfoque de la atención. Sin embargo, ciertas peculiaridades hacen diferente la experiencia del dolor: si se considera la gran importancia de los estímulos dolorosos, que monopolizan de manera continua la atención y producen diversas reacciones emocionales y vegetativas aversivas intensas, puede suponerse la existencia, en los pacientes que sufren dolor crónico, de un estado mental persistente sensibilizado para la percepción del dolor que produce un cuadro clínico caracterizado por depresión, ansiedad y deterioro mental y físico.

Además, se consideró al dolor como un problema médico primario. Esto es, cuando los médicos se ven forzados a combatir el dolor independiente de su causa, como en los pacientes de dolor crónico cuyos orígenes no pueden erradicarse (cáncer in-

Abstract

In this paper, we considered the pain experience as a specific sensory modality, with its own sensorial "apparatus", including stimuli, receptors, afferent fibers, pathways and integrative centers. Psychophysiologically, pain seems to follow the principles of the sensory process of other sensory modalities; where two consecutive stages sensation and perception, modulated by the attention focus, can be distinguished. A number of peculiarities however, make to pain experience different: considering the high relevance of pain stimuli that monopolizes continuously the attention focus and produces a number of intense aversive emotional and vegetative responses; we can visualize in patients with chronic pain a persistent mental state sensitized for pain perception, producing a clinical picture of depression, anxiety and mental and physical deterioration.

In addition, we considered pain as a primary medical problem. That is, when physicians are forced to combat pain irrespectively of its cause, as in patients with chronic pain where causes cannot be erradicated (invasive cancer) or precised (primary and secondary denervation). In these patients, medical and surgical procedures are currently oriented either ot block the pain "apparatus" or to electrically stimulate the somatosensory

vasor) o precisarse (desnervación primaria y secundaria). En estos pacientes los procedimietnos médicos y quirúrgicos se orientan en la actualidad para bloquear el "aparato" del dolor o para estimular de manera eléctrica a los sistemas somatosensorial competitivo y endorfinérgico eferente, con lo que se inhibe la sensación del dolor a nivel de médula espinal. Cabe suponer, sin embargo, que el conocimiento de la percepción del dolor modulada por mecanismos telecefálicos permitirá desarrollar nuevos procedimientos terapéuticos para lograr un control eficiente de este fenómeno, en particular en los pacientes con dolor crónico en los que se conserva de manera constante la sensación del mismo.

competitive and the efferent endorphinergic systems, which inhibit pain sensation at the level of the spinal cord. We believe however, that the knowledge of pain perception modulated by telencephalic mechanisms, will permit the development of new therapeutic procedures for an efficient control of pain, particularly in those chronic pain patients, where pain sensation is constantly maintained.

Historical perspective

Pain has been a traditional preocupation for humanity and medicine; and along its history a great effort has been performed to understand and control. Acute pain is a symptom which plays an important protective role, warning patients that something is wrong; and orienting physicians to stablish the diagnosis. On the contrary, chronic pain is a pathologic condition, with an obscure function or no function at all, that produces a general deterioration in patients.

Prehistoric people had no difficulty in understanding pain associated with injury, but they were mystified by pain caused by disease. Ancient Egyptians and Babylonians believed that pain from disease was caused by spirits of dead and perceived in the heart and blood vessels. Huang-Ti, the "Yellow Emperor" (2600 B.C.) considered that pain and disease resulted from an imbalance between the body fluids "Ying" and "Yang", and that such imbalance could be corrected with acupunture.[75]

From these preliminary considerations, pain has been generally visualized as a medical problem secondary to a recognized cause; and the ideal approach has been to terminate pain by combating its causes. The prolem persists however, when the causes of pain cannot be eliminated, as in patients with invasive cancer; or when the causes of pain cannot be identified, as in patients with partial denervation of the primary and secondary neurons of the pain afferent pathways. The increasing number of such cases by increased mean longevity, and occupational and vehicle accidents on one hand; and the recent neurostimulation techniques introduced for pain control on the other, have motivated that our knowledge of primary pain have increased more during the last twenty years than during the rest of its history.

The nature of pain, irrespectively of its cause, has been discussed along history in the following terms: emotion vs. sensation, non specific vs. specific sensation; and sensation vs. perception. For example, the Aristotle position (384-322 B.C) that pain is an emotional state (counter-part from pleasure) that is perceived in the heart and the blood vessels,[55] was changed by Herophilus (335-289 B.C) and Descartes (1569-1650 A.D.) for the theory that pain is a form of sensation, where the pain messages are transmitted from the periphery to the brain through "soft" nerves, from cutaneous and visceral tissues in danger to be injured.[14] The conception by Erasmo Darwin[17] and Erb[20] that pain is a phase of unpleasant sensation resulting from the stimulation of any sensory modality, whenever the sensorial motions are stronger than usual; was changed by Schiff,[65] Brown-Sequard,[10] Igo,[37] Collins[16] and others, for the proposition that pain is a specific sensory modality with its own sensorial "apparatus", including stimuli, receptors, afferent fibers, pathways and integration centers.

Recently, the discovery of a functional gate at the dorsal horn of the spinal cord by Melzak and Wall,[55] and the existence of supraspinal influences regulating the afferent conduction of pain by Reynolds[60] and Adams,[1] has oriented our knowledge on the nature of acute and experimental pain as a form of *sensation,* automatically regulated by a spino-reticulospinal loop. However, the fact that in patients with "spontaneous" chronic pain, the narcotic drugs,[64,66] and the supratentorial surgical procedures[70] produce analgesia with no modification of pain threshold (sensation) suggest that, in these cases, pain is a *perceptual problem* which can be modulated by telencephalic rather than spinal mechanisms.

Pain characteristics and evaluation

Pain can be defined as a sensorial experience, evoked by stimuli that threaten the integrity of body tissues and that is subjectively described as something that "hurts".*[54]

Pain is a special sensorial experience where we recognize: high relevance of the painful stimuli, peculiar unpleasant sensation, an intense emotional content and a numerous group of vegetative, involuntary and voluntary reactions.

The sensory process of pain is similar to other sensory modalities including two consecutive stages: sensation and perception. While pain sensation is constant, precise and defined (threshold = 206±21 mcal/seg/cm);[28] pain perception varies according to age, sex, race, experience and personality of each individual. They are two types of pain qualitatively speaking: epicritic and protopathic.

Epicritic pain (such as that produced by the sudden introduction of a needle in the skin) is acute, precise, local, brief, habituable and modulated by the focus of attention. Epicritic pain is transmitted from the periphery to the brain through myelinic fibers and spinothalamic tracts. It responds favorably to medical and surgical analgesic procedures; and it has a well defined protective function.

Protopathic pain (such as that produced by contuse trauma on a nerve or causalgia) is burning, chronic, imprecise and prolonged. This kind of pain is not habituable and monopolizes continuously the attention focus. It responds poorly to analgesic techniques and it has an obscure function or no function at all. In addition, protopatic pain is accompanied by pronounced emotional and vegetative responses, and a persistent state of anxiety, depression and confusion; which are many times difficult to differentiate from the pain experience itself.

According to its temporal course, pain can be acute or chronic. Acute pain is produced by transient nociceptive agents, as is the case of the experimental or laboratory pain, as well as those found in patients with reversible or tractable disorders. Chronic pain is produced by irreversible or intractable disorders. Difference between epicritic vs. protopatic and acute vs. chronic pain is fundamental to understand and control pain. In the present, epicritic acute pain is in general well understood and treated; while the nature of protopatic chronic pain is in general obscure.

Evaluation of pain experience confronts the problem that there are no operational definitions for pain: the objective responses to pain are nonspecific, i.e. they can be produced by stimuli of other sensory modalities. On the other hand, specific responses to pain are subjective and depend on the individual psychological characteristics. For example, quantitative responses to experimental pain in animals (flexor reflex, vegetative changes and withdrawal, rage and escape responses) can be elicited by a number of nonpainful stimuli. However, the fixed temporal relationship between response and painful stimuli make it reasonable to think (although not always) that responses are related to the pain experience. In addition, the majority of studies on experimental pain in animals are concerned with acute pain responses produced by intensive mechanical, electrical chemical and thermic stimuli delivered to healthy animals. These results however, can be different to those obtained from experimental models of chronic pain. Therefore, chronic pain models in animals are very promising in the research of pain, as the presence of spontaneous rhythmic neuronal activities recorded from the trigeminal sensory nucleus in cats and monkeys with chronic, paroxysmal pain behavior produced by a partial surgical deafferentation[6] or topical application of alumina cream.[49]

In man, methods for pain evaluation have reached high degrees of sophistication. For example, the development of precise stimulation techniques for pain production such as the radiant heather,[28] the pressure

*We must recognize that at present, there does not yet exist a universal definition of pain. Existent definitions are expressed according to the individuals who study pain. For example, the patient refers pain as something that hurts him, but also according to the medical instructions, on its quality (constrictive, burning, pricking, ardent, colicky, etc.), intensity and location as well as its temporal course and also factors precipitating, increasing and decreasing pain.

For a neuroscientist, pain is a sensory modality with its own sensory "apparatus" and modulatory systems. For a social scientist, pain is the expression of suffering which produces complex behavior forms and depends on psychosocial and cultural factors.

algometer,[42] the injection of substances extracted from cutaneous canthoridine vesicles,[82] electric stimulation,[14,82] and laser energy,[13] some of which are applied to cutaneous and depth somatic and visceral territories and to the dental pulp.[2] In addition, a number of somatic (flexor reflex activities), vegetative (galvanic skin reflex) and cerebral (EEG desynchronization) involuntary and voluntary (analogic and digital scales for pain appreciation) responses have been measured when patients are instructed to report pain their threshold, appreciable minimal difference (Fechner-Weber's type), maximal tolerance and tolerance range to pain.[83]

These methods have shown to be reliable in the evaluation of *pain sensation*. In fact, pain threshold (minimal appreciable intensity for specific pain sensation) is similar in different individuals independently of their age, sex, race, experience and personality.[29,66] Pain threshold is not modiffied either by analgesics and narcotics,[63] nor by other forms of analgesia including those produced by brain electrical stimulation.[70] Pain threshold (evaluated by the flexor reflex response) is similar in patients with complete spinal transection, when is determined from cutaneous territories located above and below the spinal transection.[66] In the same normal individual, there is a significant correlation between pain sensation and intensity of stimuli applied to different receptive territories (cutaneous, depth and visceral).[84] The constancy of the pain sensation is better observed when the conditions of the stimulated tissue are similar and when subjects are instructed to maintain their focus of attention on the evaluated stimulus and to differentiate pain sensation from other sensations which can obscure its appreciation.

The problem exists however, when we try to determine the level of *pain perception* both in noninstructed normal subjects (or non cooperative) as in patients with "spontaneous" chronic pain. In these cases, pain threshold varies according to the conditions of attention and suggestion.[23,47] The somatic, vegetative and cerebral involuntary reactions show no correlation with the degree of pain perception, but rather with the level of general alertness.[83,84] Tolerance range may be useful to differentiate sensitive vs. insensitive subjects, but other voluntary responses may be distorted or falsified.[83]

Functional anatomy

Peripheral and central pain mechanisms

At present, there is enough evidence to consider pain as a specific sensory modality, with its own sensorial "apparatus". The main experimental and clinical bases which support this statement are: 1) Pain receptors are free terminal endings normally stimulated by algogenic substances (chemoreceptors).[37] 2) Stimulation of pain receptors generate nerve impulses conducted through C and delta fibers correlating to pain sensation.[6] 3) Pain sensation and other somatic sensation can be dissociated by some clinical disorders: patients with a Brown Séquard syndrome produced by spinal hemisection show contralateral analgesia and ipsilateral anesthesia. Patients with a Dejerine-Roussy syndrome produced by unilateral lesions of the ventro postero lateral thalamic nucleus show contralateral hyperalgesia and anesthesia; and patients with tabes dorsalis produced by lesions of spinal posterior columns show bilateral byperalgesis and analgesia.

Schematically, the physiopathology of pain can be described as follows (figure 1A):

Nociceptive stimuli harm cutaneous and other tissues producing algogenic chemical substances: histamine, ATP, bradikinine, prostaglandines and others.[74-81] These substances stimulate free endings[37] of myelinic delta (diameter = 1-5.0 μm) and amyelinic C fibers (diameter = 0.5-1.0 μm) of paraspinal neurons, generating and transmitting pain impulses to the spinal cord.[16]

Epicritic pain impulses are transmitted by delta fibers, penetrating the spinal cord; and terminating in neurons located at the substantia gelatinosa (rexed layers 2 + 3) and at the posterior horn (layers 4 + 5). From here these impulses are conducted through a paucisynaptic, spinothalamic pathway, crossing at the corresponding spinal level and ascending through the anterolateral spinal colum to the ventrobasal posterior thalamic nucleus (Vcpci and Li Por) and connecting with projection neurons to the opercular cortex (CS3b) (figure 1A, continuous lines).

Protopatihic pain impulses are transmitted by C fibers, penetrating the spinal cord and terminating in

neurons also located in layers 2 + 3 and 4 + 5. From here, these impulses are conducted through polysynaptic spinoreticular pathways, crossing at various spinal levels and ascending through spinal "fasciculus propius" and the bulbar, pontine and mesencephalic reticular formation to centromedian and intralaminar thalamic nuclei, and connecting with projection neurons to the cingulate gyrus and other regions of the limbic system (figure 1A, discontinuous lines).

Pain impulses are transmitted from epicritic to protopathic systems by collaterals at the level of the mesencephalon and thalamus. Here, pain impulses activate the ascending reticular system for wakefulness and general alertness. In addition, these impulses are integrated here and perceived to produce pain experience with its peculiar unpleasant character. That is, here pain sensation is transformed into pain perception and in this process also participates the functional activities of the limbic structures in their association with the frontal, parietal and temporal cortices.

Para algesic mechanisms

Epicritic and protopathic pain impulses activate other peripheral, spinal and diencephalic neuronal systems in their trajectory from the receptor to the cerebral cortex, producing a number of para algesic reactions (figure 1A, circles). For example, at the peripheral level, axonic reflexes from delta and C fibers complete the triple cutaneus reaction of Lewis (erithema, edema and secondary vasodilatation).[46] In the spinal cord, pain impulses activate motoneurons through polysynaptic flexor reflexes, which in turn produce an intensive prolonged contraction of the corresponding muscles, increasing pain by secondary ischemia. In addition, pain impulses produce irradiated or referred pain by activation of the intersegmental sensory systems.

In the diencephalon, pain impulses activate hypothalamic neurons producing a number of vegetative reactions associated to pain as tachycardia, vasoconstriction, hypertension, mydriasis and perspiration. Decrease of the cutaneous electric conductance by perspiration associated to pain and other relevant stimuli is known as the "psychogalvanic reflex".

Competitive mechanisms

Melzak and Wall[55] described a gate model in the spinal cord, which explains the analgesic effect of non painful somatosensory impulses from muscle, tendinous and cutaneous receptors, transmitted by large myelinic nerve fibers which inhibit pain impulses. Accordingly, painful and non painful somatosensory impulses compete with each other for activating or inhibiting the spinal neurons located at the layers 2 + 3 and 4 + 5 of the spinal posterior horn, following the principle of reciprocal innervation.

Other gate somatosensory systems have been proposed at the thalamic[2] and cortical levels[27] on the grounds that electrical stimulation of nonpainful systems produce analgesia and their lesions produce hyperalgesia. Whether these thalamocortical effects on pain modulation occur at the thalamocortical or spinal levels is an open question (figure 1A, double lined and dotted lines).

Efferent modulation of pain afferences

Reynolds[60] and Adams[1] have shown that electrical stimulation of the periaqueductal gray substance produces powerful analgesic effects in rats and man, respectively. These analgesic effects are produced by the activation of an endorphinergic system located in the medial portions of the diencephalon and brain stem (periventricular reticular formation, periaqueductal gray substance and the raphe magnum), which inhibits pain at the spinal gelatinous substance through serotonergic reticulospinal fibers descending within the postero lateral columns.[18]

Supraspinal control of the somatosensory afferent conduction at the spinal cord was initially proposed by Hagabarth and Kerr[30] and Hernández Peón[32] (figure 1A, squares and discontinuous lines).

Surgical analgesia

Surgical relief of pain is indicated in those patients with chronic pain refractory to medical analgesic treatment and to other analgesic thechniques (acupunc-

ture, hypnosis, suggestion, etc.). Surgical procedures for the treatment of pain comprise those that harm the sensorial pain "apparatus", used in patients with invasive carcinomas; and those that electrically stimulate the competitive (gate) and or the supraspinal efferent systems modulating pain conduction, used in patients with chronic pain by denervation of primary (trigeminal pain anesthesia) and secondary neurons (postcordotomy dysesthesias).

Figure 1B summarizes the type of surgical operations employing harmful procedures to block the epicritic and protopathic systems: the selective C and delta fibers rhyzotomy used in trigeminal neuralgia; the lateral cordotomy (section of the spinothalamic tract),[69] the lesion of Vcpci and Li Por thalamic nuclei[27] and ablation of the opercular cortex[24] interfering with the epicritic system; and the myelotomy (section of the spinal "fasciculus propious" and cross fibers of the spinothalamic tract,[72] the lesion of the medial portion of the mesencephalic reticular formation[8] and parafascicular, centro median and intralaminar thalamic nuclei,[61,63,72,73] and the ablation of the supracallosal portion of the gyrus cingulum,[5,36] which interfere with the protopathic system.

Other harmful procedures have been oriented to control paralgesic vegetative and emotional reactions: lesion of the posterior hypothalamus.[22,63] and the amygdaloid complex;[38,51] and interference with pain subjective analysis and interpretation: lesion of the pulvinar parietal,[23,44,55] and dorsomedianfrontal connections.[7,22,52]

Anterior lobe hypophysectomy empirically utilized for pain control in patients with mammary and prostatic carcinomas, possibly works by altering the normal content of endorphins and serotonin[56] (see below).

Figure 1C summarizes the type of surgical operations employing electrical stimulation procedures to activate the competitive and supraspinal efferent systems: transcutaneous,[67] posterior spinal roots,[47] VPL thalamic nucleus[27] and primary somatosensory cortex[27] stimulations activate the competitive system; and periventricular reticular formation and periaqueductal gray matter[1,35,58,59] and posterolateral spinal column[26,47] stimulation activates the supraspinal efferent system (figure 1C). Whether the analgesic effect of neurostimulation is due to an independent or combined activation of these systems in an open question.

Medical analgesia

Aspirin type analgesic compounds control pain by a peripheral effect, inhibiting the synthesis of prostaglandins. This analgesic effect is independent of hypothermia and the antiinflammatory properties of aspirin.[3,11]

Opioid narcotics, as morphine and meperidine, produce analgesia by simulating the action of endorphins in the supraspinal efferent system modulating pain, and their analgesic power depends directly on their affinity for the endorphinergic receptors.[24] Morphinic and neurostimulation analgesia is produced by a common mechanism, documented as follows:

1. Opioid receptors and endorphins are normally located on the same brain loci where electrical stimulation produces analgesia (periventricular reticular formation, periaqueductal gray substance and raphe magnum).[4,34]

2. Electrical stimulation induced analgesic effects are reproduced by topical microinjections of opioid compounds in the same cerebral loci.[25]

3. Naloxone (opioid antagonist) blocks the analgesic effects produced by both morphine and neurostimulation.[1,3]

4. Periaqueductal lesions block both opioid and neurostimulation analgesia.[18]

Besides surgical and medical analgesia, there are other procedures which improve pain. These procedures are useful only in some patients highly suggestionable; that is, patients showing a peculiar capacity to deviate their focus of attention from pain to other stimuli or thoughts. (about 15 per cent). Acupuncture, hypnosis, suggestion, placebos and active muscular relaxation techniques are useful in improving acute and chronic pain in these patients. Our knowledge of the analgesic effect of these traditional techniques has been however, more empirical than scientific and the are currently being investigated in the Western World.

For example, a Norwegian medical delegation visiting the Popular Republic of China in 1973[2] verified that in fact, acupuncture has certain analgesic effects

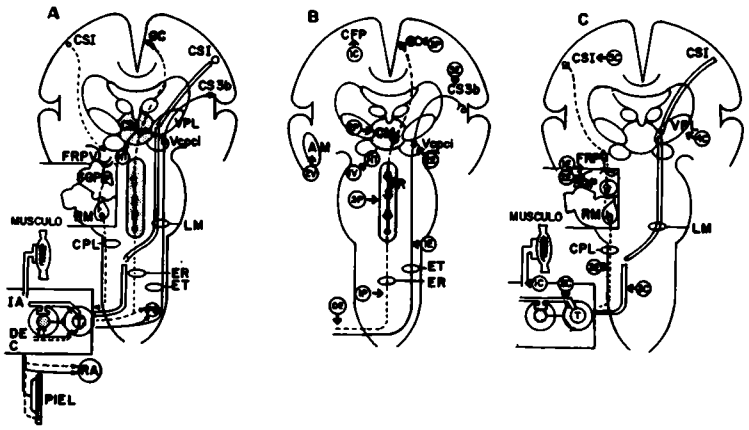

Figure 1A. Epicritic and protopatic pain systems. Paralgesic mechanisms. Modulator, competitive and efferent systems.

Epicritic pain system (continuous lines). Epicritic impulses originate from the nerve free endings of the skin to be transmitted through myelinic delta fibers (DE). After a synaptic relay at the 2 + 3 and 4 + 5 Rexed layer neurons, ascending to the association somatosensory cortex (CS3b) through spinothalamic pathways: spinothalamic tract (ST) and ventro-baso-posterior-thalamic nuclei (Vcpci).

Protopatic pain system (discontinuous lines). Protopatic impulses originate from the nerve free endings of the skin and are transmitted through amyelinic fibers C. After a synaptic relay at the 2 + 3 and 4 + 5 Rexed layer neurons, ascending to the gyrus cingulum (GC) through spinoreticular pathways: fasciculus propius (SR), reticular formation and parafascicular, centro median and intralaminar thalamic nuclei (CM).

Paralgesic reactions (circles). Triple cutaneouss responses produced by delta and C fiber axonic reflexes (RA), muscle contraction and referred pain produced by polysinaptic multisegment spinal reflexes (PS); and vegetative reactions produced by thalamohypothalamic activation (HT).

Competitive somatosensory system (duble lines). Nonpainful stimuli originate from muscles, joints and skin receptors and are transmitted through gross myelinic libers (IA). After a synaptic relay at the 2 + 3 and 4 + 5 Rexed layer neurons ascending to the primary somatosensory cortex (CSI) through the lemniscal pathways: medial lemniscus (ML) and ventro postero lateral thalamic nucleus (VPL).

Nonpainful and painful stimuli compete at the gelatinous substance (2+3) and posterior horn (4+5) of the spinal cord (Gate theory) and perhaps at the VPL-CM thalamic and CSI-CS3b cortical levels.

Efferent system (squares). The periventricular reticular formation (PVRF), periaqueductal gray matter (PAG) and raphe magnum (RM) brain stem structures, control the afferent transmission of pain impulses at the spinal gate, through descending fibers running by the posterolateral column.

Figure 1B. Surgery of pain (lesion procedures).

Selective rhyzotomy of delta and C fibers (OE) block peripheral pain impulses.

Blockage of the epicritic system. Cordotomy or section of the spinothalamic tract (1E), lesion of the ventro basal posterior thalamic nuclei (2E) and ablation of the opercular cortex (3E).

Blockage of the protopathic system: myelotomy or section of the spinoreticular tract (1P), lesion of the mesencephalic reticular formation (3P), parafascicular, centromedian and intralaminar thalamic nuclei (2P) and ablation of the gyrus cingulum (3P).

Blockage of the vegetative and emotional reactions: lesion of the posterior hypothalamus (IV) and amygdaloid complex (2V).

Blockage of the pain integration systems: lesion of pulvinoparietal and dorsomedian-frontal thalamo cortical connections (1C).

Figure 1C. Surgery of pain (electrical stimulation).

Stimulation of the competitive system: transcutaneuous (1C) and posterior roots (2C), posterior columns (3C) spinal and thalamic VPL (3C) and cortical CSI (4C) electrical stimulation.

Stimulation of the efferent system: PVRF (1E), PAG (2E) and PLC (3E) electrical stimulation.

on acute pain during surgery. However, this analgesic effect appears to be limited according to the scientific western criteria:[39]

Acupuncture is always used in combination with high doses of analgesic and hypontic drugs and supplemented by local procaine-like analgesics; also it is limited to the 30 per cent of suitable candidates selected on the bases of their tolerance to pain according to Western criteria. The use of acupuncture in the large general hospitals of the P.R.C. has been decreased from 60 to 15 per cent in a period of six years (1967-1973) after its opening to the Western world.

In relation to its mechanisms of action, there is no experimental evidence whatsoever, which indicates that acupuncture functions by a vital energy (ch'i) distributed along a net of 12 channels or meridians. On the contrary, acupuncture points really correspond to the main nervous branches, which activate the competitive somatosensory systems by combined acupuncture and electrical stimulation. In addition, acupuncture liberates an edorphineserotonin-like substance into the cerebrospinal fluid[71] and its analgesic effect is blocked by naloxone in patients suffering chronic pain, suggesting an effect on the supraspinal efferent system modulating pain.

Sensation vs. perception of pain

Sensation and perception are two normal stages of the sensory process in different sensory modalities. During the sensation environment stimuli are detected, while during perception they are analyzed: to see as opposed to watch, to hear instead of listening and to feel rather than to palpate such are the differences between sensation and perception as equivalents in the visual, auditory and somatosensorial modalities. Selective attention is a functional filter located between sensation and perception which blocks irrelevant stimuli and facilitates relevant stimuli for producing sensory, mnesic and motor responses.

Pain experience follows these stages and filtering of the sensory process. Some distinctive pecularities of the pain experience have to be recognized: nociceptive stimuli are always relevant due to the quality, intensity and information content of painful stimuli. Epicritic stimuli are modulated by the attention process, which is able to block them when are applied monotonously (habituation) or when other more relevant intercurrent stimuli are presented (distraction). Protopatic stimuli however, monopolize continuously the attention focus and produce a conscious perception of pain and blockage of the other non painful stimuli As a consequence, an inefficient behavior and constant perceptual, mnesic and motor response to pain is produced. Other distinctive quality of pain experiences is its capacity in producing aversive emotional and vegetative reactions. The presence of a persistent mental state oriented and sensibilized to pain perception produces in the individual a picture of depresion and anxiety conducted to a physical and mental general deterioration.

In the analyses of pain experience integration, it sems fundamental to stablish precisely the anatomical region where painful stimuli are filtered or discriminated. This will permit in the future to develop medical and surgical procedures for better control of the sensation and perception of pain.

In the case of tactile and proprioceptive somatosensory stimuli, it has been postulated that functional filter of stimuli operates at 2 different levels of the CNS: at the spinal level, by means of a spino-reticulo-spinal loop in animals[31] and at the diencephalic level by means of a cortico-reticulo-thalamo-cortical loop in man.[76]

In animals, there is also evidence of an automatic pain control in a spino-reticulo-spinal circuit formed by spino-reticular and spino-thalamo-reticular afferent pathways and by an efferent descending system which includes midline brain stem structures controlling the pain input at the substantia gelatinosa through descending fibers running at the postero lateral spinal columns.

In man, there is evidence that this circuit operates when patients are expose to painful stimuli.[19] In fact, pain is blocked by lesions of spino-thalamic and spino-reticular pathways by anterolateral cordotomy[69] and myelotomy,[33] and by neurostimulation of the periaqueductal gray substance, periventricular reticular formation[1] and the spinal posterior columns.[47] In addition, pain in produced by stimulation of the anterolateral columns[69] or by morbid lesions at the posterolateral spinal columns in patients with tabes dorsalis. We think that the spinal control of pain is concerned to the pain sensation, which represents the

obligatory or automatic aspect of pain. Pain sensation seems to be constant in different individuals and in different cutaneous, depth and visceral regions of same individual, and can be documented by the constancy of the pain threshold and the amplitude of early components of the brain evoked potentials produced by nociceptive stimuli (see below).

Besides the spinal modulation of pain sensation however, there is evidence in man suggesting that there are some other brain mechanisms modulating pain perception: the large variability of perception of acute and chronic pain stimuli, depending on individuals sex, race, experience, anxiety, emotion and culture; and the constancy of pain sensation during analgesa induced by the majority of medical and surgical procedures,[28,4764,66,79] document the importance of brain mechanisms modulating the pain perception.

The sensory process (sensation, perception and attention) has been recently analyzed by means of the cerebral evoked potentials. Early or short latency evoked potentials (P40-P5, P20) result from the activation of the specific visual, auditory and somatosensory pathways and centers and are related to the stage of sensation; while late or long latency evoked potentials (P200) result from the activation of a non-specific polysensory system related to the stage of perception.[77,80] That is, while amplitude of early potentials remains constant, that of the late potentials varies according the selective attention of the individual to the applied stimuli.

In the case of pain sensory process, early (N65) and late (P200) evoked potentials have been recorded from vertex to painful stimuli.[12,15,64] It can be noticed that early pain evoked potentials are different, while late pain evoked potentials are similar to those of other sensory modalities, suggesting that pain perception (but not sensation) is processed by the same non-specific sensory system of other sensory modalities. In addition, it has been shown that amplitude of early and late pain evoked potentials varies according to the stimulus intensity. However, only amplitude of late pain evoked potentials (not that of early) correlates to the subjective appreciation of pain (perception).[15]

In a recent work,[79] we studied the effect of fentanyl (opioid agonist) and naloxone (opioid antagonist) on the early and late evoked potentials to somatic and auditory stimuli, in patients underwent minor surgical procedures. These opioid compounds were used to induce and regulate an state of analgesia. In these experiments, we observed that fentanyl reduced while naloxone increased amplitude of late, with no changes in that of the early potentials (figure 2).

On the assumption that amplitude of early potentials reveals the permeability ot the specific afferent systems associated to sensation; while that of the late potentials reveals the excitability of the non-specific systems associated to perception, these data suggest that opioid agonists and antagonists affects perception (not sensation) of pain and other sensory modalities. Whether the effect is due on the perceptual stage independently to their analgesic properties is an open question.

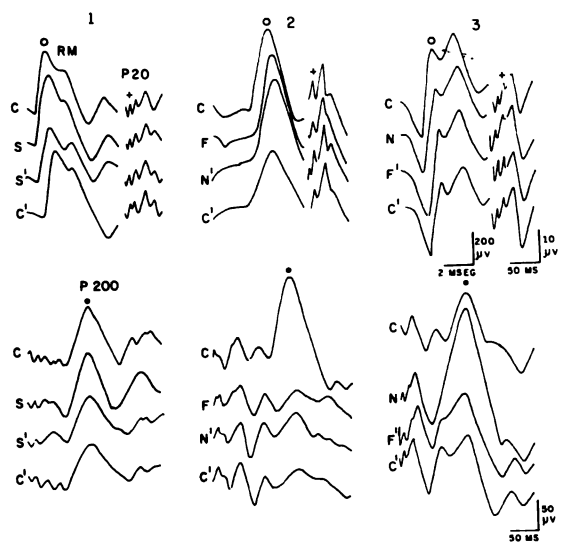

Figure 2. Effects of Fentanyl and Naloxone on cerebral evoked potentials. Changes in amplitude of the muscular response (RMo) and early P20 (+) and late p. 200 (.) evoked potentials to median nerve single shock stimulation from 3 different patients under 3 different paradigms (1, 2 and 3) with 4 consecutive conditions each:

Paradigm 1: initial base line (C), first injection of saline solution (S) second injection of saline solution (S1) and final base line (C').

Paradigm 2: C, first injection of Fentanyl (F), second injection of Naloxone (N1) and C'.

Paradigm 3: C, first injection of Naloxone (N), second injection of Fentanyl (F1) and C1.

Notice that P200 late potential decreases with Fentanyl and increases with Naloxone and that these effects are not totally reverted after the second injection. In addition, that no amplitude changes in muscular response and early P20 potential are found with these compounds. Modified from Velasco et al (79).

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