Part III. Consequences of Current Concepts of Pain Mechanisms Related to Pain Management

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Part III of this review describes the impact that acupuncture, our drug culture, and the gate-control theory have had on our progress in elucidating pain mechanisms and in treating pain syndromes. Whether an analgesia is produced by morphine, acupuncture, or electrical stimulation of an appropriate brain region, the analgesia can be blocked by naloxone, a morphine antagonist. This observation, among others, suggests that similar effector mechanisms involving endogenous opiates serve all three types of analgesia. Although the gate-control theory must continually be revised to accord with new information, it has been a major impetus for stimulating fruitful research.

Key Words: Analgesia, Neurophysiology, Pain, Physical therapy.

New knowledge has accumulated faster in the elucidation of pain mechanisms than in any other aspect of neuroscience. At least three factors provided the impetus for this high level of activity. One is the astounding claims made by those who witness the surgical applications of acupuncture in China. The second is the current prevalence and severity of drug addiction in our society. The third is the gate-control theory of pain pronounced by Melzack and Wall in 1965.

ACUPUNCTURE

Acupuncture has been used in China to manage pain for 5,000 years.275 Its use as a substitute for anesthetics in surgery, however, has been of relatively recent origin.275 Acupuncture use is limited to about 5 percent of all surgical cases, in which it appears to work about 95 percent of the time.9 Its success is greater in surgery on the head and neck than on the limbs.9

The inability to provide a reasonable hypothesis to account for acupuncture analgesia was a tremendous embarrassment to Western neuroscientists. Many responded only with great skepticism;276 others sang its praises277, 278; and others began the arduous task of acquiring new knowledge concerning this ancient practice.275, 279-289 Hence, Western medicine is greatly indebted to the Chinese for introducing us to this ancient practice of acupuncture, not because it has become an important tool in modern medicine (its popularity has rapidly waned since its introduction), but because it raised questions whose answers were to be derived by applying the experimental scientific approach.

As a result of cooperation among biochemists, pharmacologists, histologists, electrophysiologists, and other neuroscientists from multiple disciplines working together toward a common goal, “the veil of obscurity is slowly being raised.”290

The explanation for the mechanisms of acupuncture is that an acupuncturist produces analgesia by twirling acupuncture needles in appropriate body regions or sending currents through these needles.251 Presumably the resulting sensory signals activate neurons of an inhibitory center for pain in the ventral central gray matter, with the ultimate release of endogenous opiates. The morphine antagonist, naloxone, blocks acupuncture analgesia, a fact in keeping with this presumption.262, 263 This assumed explanation for the mechanisms of acupuncture awaited the discovery of opiate receptors184-188 and endogenous enkephalins226-260 and β-endorphins261-274 as described in Part II of this review.

Placebos have been as mystifying as acupuncture. It has long been known that placebo administration increases the pain threshold, but only recently has it been shown that this increase in threshold is blockable by naloxone. Hence, it seems likely that placebo effects are also mediated through the inhibitory center...
for pain in the ventral central gray matter, with the ultimate release of endogenous opiates.

**DRUG ADDICTION**

The use of morphine in treating chronic pain leads to tolerance and addiction. That is, a morphine-treated patient soon requires larger injections. He becomes dependent upon morphine and suffers severe physiological consequences when the drug is discontinued or when, for other reasons, he is deprived of morphine. The phenomena of tolerance and addiction, although the heart of the “drug” problem in society today, are poorly understood. From investigations designed to elucidate the mechanisms of drug analgesia, our current knowledge evolved about the structure, distribution, and function of the opiate receptors and the putative neural transmitters with which they interact (see Part II).

An early important result of these investigations was that the injection of morphine into the periaqueductal gray matter produces analgesia. This region of the brain was also shown to possess the highest density of opiate receptors. Was this, then, giving rise to central inhibition of pain?

**STIMULUS-PRODUCED ANALGESIA (SPA)**

About the same time that acupuncture and opiate receptors were being analyzed, it was shown that electrical stimulation of the periventricular and periaqueductal gray matter also gave rise to long-lasting analgesia. Other brain structures were also identified that, when electrically stimulated, produced analgesia. Among these regions were the septal area, the thalamus, the dorsal raphe nuclei of the mesencephalon, the raphe magnus nucleus of the medulla and pons, the lower brain stem, the caudate nucleus, the internal capsule, the central gray matter, the limbic system, and the midbrain. This stimulus-produced analgesia (SPA) is specific for reducing pain; it does not interfere with motor function or gross behavioral responses. The analgesia produced by electrical stimulation of the periaqueductal gray matter has been reported to be sufficient to permit abdominal surgery without anesthetics.

Because SPA promises a revolutionary means for relieving pain, it has attracted the attention of many investigators. As a result, many scattered observations have been reported. Examples of these follow.

The periaqueductal area is not composed of a homogeneous population of neurons. Stimulation of the medial caudal zone of the periaqueductal gray matter produces analgesia, whereas stimulation of the rostral and lateral zones activates nociceptive sensations. Naloxone, a morphine antagonist that blocks opiate receptors, also interferes with the analgesia evoked by electrical stimulation. This observation suggests that both electrical stimulation of the periaqueductal gray matter and acupuncture may involve common effector mechanisms because naloxone blocks the analgesia produced by either. Another recent observation is that SPA has a powerful inhibitory effect on nociceptive neurons in lamina V of the dorsal horn and on neurons of the nucleus gigantocellularis in the medulla but not on the nonnociceptive neurons in the same regions.

Other experiments have shown that transection of the dorsolateral quadrant of the spinal cord abolishes SPA on the side of the lesion. This quadrant of the cord contains serotonin-containing fibers descending from the raphe magnus nuclei of the medulla. The full explanation of all of these findings awaits further study. One explanation at this time is that SPA is mediated by serotonergic neurons whose descending fibers terminate in axo-axonic synapses on the small primary afferent terminals in the dorsal horns, as shown by the hypothetical scheme in Figure 12. Electrical stimulation in the periaqueductal gray matter is thought to cause the release of enkephalin from nearby enkephalinerge nerve terminals or interneurons. The enkephalin, in turn, activates serotonergic neurons by interacting with opiate receptors found in abundance on these neurons. Morphine injected into this same brain region is thought to imitate the action of the endogenous enkephalin released by electrical stimulation.

Although the scheme in Figure 12 could explain some aspects of SPA, it fails to account for the very long-lasting analgesia produced by electrical stimulation of the periaqueductal gray matter. Results of a recent study suggest an additional mode of SPA action. This study showed that the long-lasting analgesia produced by stimulation of the periaqueductal gray matter in patients with pain of peripheral origin was accompanied by an increase in the β-endorphin concentration in ventricular cerebrospinal fluid. Naloxone abolished the SPA. The authors proposed that the electrical stimulation of the periaqueductal gray matter might induce antidromic stimulation of the anterior hypothalamic β-endorphin fibers and the subsequent release of β-endorphin into the third ventricle.

Naloxone is thought to block the opiate receptors on serotonergic neurons in the brain as well as those on the terminals of the primary afferent fibers in the dorsal horns because it blocks analgesia whether produced by electrical stimulation of the periaqueductal
gray matter, by injection of morphine into the periaqueductal gray matter, or by acupuncture.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

As physical therapists well know, electrical stimulation in the periphery may also produce analgesia. This technique is called transcutaneous electrical nerve stimulation, or TENS. The reader is directed to the special issue of PHYSICAL THERAPY on TENS, published in December 1978, for details concerning this potentially effective means for managing acute or chronic pain. It is interesting that this clinical technique was a direct result of a contemporary theory about the neural mechanisms of pain. A very brief statement of that theory follows.

GATE-CONTROL THEORY

Until the early 1960s most theories about cutaneous sensation assumed that impulses arriving at the cord over primary afferent fibers would be transmitted pretty much undistorted along ascending relay paths to the primary receiving areas of the cortex. Even though Matthews and co-workers discovered in the early 1930s that sensory input traveling through large-diameter afferent fibers depolarized the central terminals of other dorsal root fibers, this phenomenon ("primary afferent depolarization" or "the dorsal root reflex") was pretty much ignored for 20 years. In the late 1950s the phenomenon was again investigated. This time its importance was recognized and it was incorporated into a theory of the neural mechanisms underlying pain. This theory, published by Melzack and Wall in 1965, was called the "gate-control theory of pain." The theory stated that transmission of sensation is controlled by the balance of activity in small-diameter, slow-conducting fibers and large-diameter, fast-conducting fibers entering the spinal cord. According to the gate-control theory, low-level activity in the small fibers that carry impulses from the nociceptors is normally blocked at the first synapse by activity in large primary fibers and by activity in fibers descending from higher brain regions. The "gate" at the first synapse is opened by intense activity in small fibers, as would occur with intense, painful stimulation during tissue damage. A predominance of activity in large fibers closes the "gate"; a predominance of activity in small fibers opens the "gate." Hence, the "gate" through which pain signals are transmitted to the transmitter (or T) cells is variable.

Impulses descending from higher brain areas were also postulated to participate in the control of the "gate," but these descending pathways were not shown in the diagram of the 1965 paper and, hence, were originally ignored by most readers.

From Parts I and II of this review, it should be obvious to the reader that the gate-control theory has had tremendous impact upon pain research and upon clinical practice. It still sparks debate and controversy and further experimentation, the hallmark of any useful scientific theory. In a 1978 paper defending the theory, P.D. Wall has this to say: "That a gate control exists is no longer open to doubt but its functional role and its detailed mechanism remain open for speculation and for experiment."
of enkephalin in hopes of developing a substance that will resist enzymatic breakdown while having an in vivo potency equivalent to β-endorphin. Thus far, all synthesized enkephalin-like compounds have caused tolerance and addiction—the same disadvantages inherent in long-term use of morphine.

Both our progress in understanding the mechanisms of pain and our application of this knowledge for managing pain are increasing at a remarkable pace. I hope that this pace will continue unabated and that the future will find us with new modalities and pharmacological tools for treating intractable pain syndromes.

Editor's note: A self-assessment quiz, written by the author, is published in this issue.

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(For comprehensive bibliography, obtain Medlars:
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OTHER BRAIN REGIONS GIVING SPA


MECHANISMS OF SPA


GATE-CONTROL THEORY


Editor’s Note: Reprints of the Beverly Bishop articles in this issue will be published. Publication date and prices will be announced in the Journal when available.