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[Department of Neurology and Physiology, University of California, San Francisco, CA]

Our work centered on the pathway through the medullary region that, when stimulated, evoked analgesia. This article gathered together and reviewed the literature on the subject of pain modulation—to that point scattered among physiology, pharmacology, anatomy, psychology, and clinical journals. [The *SCI*® indicates that this paper has been cited in more than 425 publications.]

Painless Pain

Howard L. Fields
Department of Neurology
School of Medicine
University of California
San Francisco, CA 94143-0114

This review article was published at a very exciting time for pain research. By the mid-1970s, two important advances had laid the groundwork for understanding how, under stressful conditions, significant traumatic injuries can be completely painless in awake neurologically intact patients. The first was the discovery that electrical stimulation of specific brain sites could produce significant and selective analgesia in animals and in human beings with chronic pain.[1,2] The second, which followed closely the first pharmacological characterization of an opioid receptor, was the isolation, purification, and sequencing of endogenous opioid peptides.[3] Although these discoveries were dramatic and indicated a specific brain system for the selective suppression of pain, the specific neural circuitry underlying the analgesia was unknown.

In late 1974, shortly after Allan I. Basbaum's arrival in San Francisco from Pat Wall's laboratory, we began an anatomical study of the outflow of the medullary reticular formation using titrated leucine. Although our initial interest was mostly in the ascending projections from this region, when Allan examined the spinal cord in some of the placement control animals, he found a dense and highly specific descending pathway. We were struck by the selectivity of the terminal fields of this projection for spinal regions involved in pain transmission.[4] Our immediate reaction was that this was the major pathway by which the brain controlled nociceptive input. In fact, the medullary region giving rise to the descending pathway had already been shown to evoke analgesia when electrically stimulated.[5] Two further experiments confirmed that this pathway was a crucial link for pain modulation. First, we electrically stimulated the pathway and showed that it powerfully inhibited spinal pain transmission cells. Second, we showed that lesions of the pathway reduced the analgesic action of morphine. Subsequent work showed that endogenous opioid peptides are intimately associated with this modulatory network. (See reference 6 for a review.)

At the time of these experiments, the field of pain-modulation was very much in its infancy, and the relevant literature was scattered among an array of physiology, pharmacology, anatomy, psychology, and clinical journals. Although there was much that was late-breaking, including our own work, there also was a large body of relevant older literature that had acquired new significance in light of the new work. The review attracted interest both because of the excitement about the new discoveries and the need to know the older work. Since the publication of that review, there has been a mini-explosion in pain modulation research.[7,8]

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8. **Fields H L, Heinricher M M & Mason P.** Neurotransmitters in nociceptive modulatory circuits. *Annu. Rev. Neurosci.* 14:219-45, 1991.

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