NOTE: Please see the erratum on p. 7.

This Week's Citation Classic

Mayer D J, Wolfle T L, Akil H, Carder B & Liebeskind J C. Analgesia from electrical stimulation in the brainstem of the rat. *Science* **174**:1351-4, 1971. [Depanment of Psychology, University of California. Los Angeles, CA]

This paper demonstrated that electrical stimulation at several brain stem sites abolished responsiveness to intense pain in rats. These results were interpreted as indicating the existence of a supraspinal endogenous pain suppression system which has an ultimate inhibitory action on pain in the spinal cord. [The *SSCI*® and the *SCI*® indicate that this paper has been cited in more than 490 publications.]

The Opiate of the Rats

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Our involvement in this work was in many ways serendipitous. Tom L. Wolfle, doing his dissertation research in John C. Liebeskind's lab at UCLA, was examining the ability to produce pain by stimulating the periaqueductal gray matter of rats. A series of perplexing observations in his animals led me to conclude that stimulation of the periaqueductal gray matter, contrary to what the available literature stated, could be rewarding.

At this point, an incidental observation was critical for our discovery. When one of these animals pressed the bar to self-stimulate, the train of brain stimulation elicited a stereotyped movement which forced the animal's head into a piece of sharp metal in the corner of the test chamber. I noticed that the animal made no response to this obviously painful stimulation and was immediately reminded of an earlier report by D.V. Reynolds of analgesia from stimulation of this same brain region.[1] Analgesia had been rediscovered. We then devoted considerable effort to verifying the phenomenon in a large number of animals and examining the anatomical specificity of the effect with the collaboration of Brooks Carder and Huda Akil. A mostly phenomenological description of this work was submitted but not accepted for publication in *Science.*

Probably more important than the demonstration of analgesia was our conceptual interpretation of the phenomenon and its relationship to analgesia produced by opiates. At the time, the prevailing theory of opiate analgesia was that these compounds in some way anesthetized central nervous system structures.[2] On careful reading of this literature, however, I concluded that, since depletion of monoaminergic neurotransmitters blocked opiate analgesia, it seemed more likely that opiates produced analgesia by activating rather than inactivating brain structures. Based on this interpretation, we proposed that brain stimulation and opiates produced analgesia by activating an endogenous system for pain inhibition. In addition, since brain stimulation and opiates produced an inhibition of spinally mediated nociceptive reflexes, we proposed the existence of pain inhibitory circuitry in the brain that could inhibit pain transmission early in its course into the nervous system. Liebeskind suggested and prepared a revised version of our earlier manuscript that now included this theoretical explanation, and it was accepted for publication in *Science.*

This work has probably been highly cited for several reasons. It followed only a few years after R. Melzack and P.D. Wall published the Gate Control Theory of Pain.[3] Our paper was important in that it provided the first direct support for one of the major contentions of the theory. Another area of related research, the pharmacology of opiate receptors[4] and endogenous opioids.[5] was almost simultaneously receiving renewed attention. Our work provided another line of support for the concept of an endogenous opiate analgesic system. Finally, our work had direct clinical relevance and applicability to the difficult problem of relief of intractable pain in man.

1. **Reynolds D V.** Surgery in the rat during electrical analgesia induced by focal brain stimulatton. *Science* 164:444-5. 1969. (Cited 515 times.)
2. **Lim R K S.** A revised concept of the mechanism of analgesia and pain. (Knighlon R S & Dumke P R. eds.) *Pain.* Boston, MA: Little Brown, 1986.
3. **Melzack R & Wall P D.** Pain mechanisms: a new theory. *Science* **150**:971-9. 1965. (Cited 1.600 times.) [See also: **Melzack R & Wall P D.** Citation Classic. *Current Contents/Life Sciences* **25**(23): 22. 7 June 1982. Reprinted in: *Contemporary classics in the life sciences. Volume I: cell biology.* Philadelphia: ISI Press. 1986. p. 309.1
4. **Pert C B & Snyder S H.** Opiate receptor: demonstration in nervous tissue. *Science* **179**:1011-3. 1973. (Cited 1.420 times.) [See also: **Pert C B.** Citation Classic. *Current Contents/Clinical Medicine* **17**(40): 16-7, 2 October 1989. *Current Contents/Life Sciences* **32**(40): 16-7. 2 October 1989. and *Current Contents/Social & Behavioral Sciences* **21**(40): 16-7. 2 October 1989.]
5. **Hughes J.** Search for the endogenous ligand of the opiate receptor. *Neurosci. Res. Prog. Bull.* **13**:55-8. 1975.

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