ACUPUNCTURE NEUROPHYSIOLOGY

Bruce Pomeranz
Department of Physiology, University of Toronto, Canada

There are probably two reasons why the Chinese discovered acupuncture and the Europeans did not. First, ancient Chinese science was mainly empirical with a distaste for theories. Second, Chinese science had a very different paradigm than the Western world; it emphasized holistic patterns, relationships, cycles and processes. In contrast, the Western paradigm emphasized linear causality and reductionist explanations. For example, if the Chinese empirically observed that an injury in one site healed a disease in another body region, they used this relationship to heal future patients. No linear causal explanations were needed since all relationships were considered possible. Acupuncture was introduced into Europe in the 17th century but has not been widely accepted in the West because of this clash of paradigms. How could a needle inserted into the hand possibly cure a toothache? Because acupuncture analgesia (AA) did not fit the existing physiological paradigms, modern Western scientists dismissed it as a placebo effect (working through suggestion or distraction or even hypnosis). In 1955, Beecher had shown that sugar injections (placebo) reduced pain in 30% of patients who believed they were receiving morphine. There were several problems, however, with the placebo explanation for acupuncture. How does one account for its use in veterinary medicine? Are animals suggestible? In addition, how can placebo explain acupuncture effects in infants far too young to be suggestible? Goldstein and Hilgard and also Mayer and co-workers have shown conclusively that hypnotic analgesia and AA function through quite different mechanisms.

Up to 1976, the evidence for AA was mainly anecdotal. There were few scientifically controlled experiments Since then, however, the situation has changed dramatically. Scientists have begun to ask two separate questions: (1)Does AA really work (that is, by a physical rather than a placebo effect)? (2)If it does work, what is the mechanism of AA?

The first question was answered in the affirmative when it was shown in animals and again in humans that acupuncture caused AA while sham acupuncture (needles outside the acupoint regions) had no analgesic effect. These experiments were done on acute laboratory pain where the placebo effect does not cause as much analgesia as it does for chronic clinical pain. Several controlled clinical trials on chronic pain patients, comparing real acupuncture to sham acupuncture, have also shown that acupuncture works better than placebo. However, as indicated by a recent review of the clinical research, many of the clinical studies on chronic pain were inadequate, using too few patients in view of the statistical problems involved. Hence, while it is a fact that AA is not a placebo effect in acute laboratory pain, more research is needed to be certain that this is also true for chronic clinical pain. Perhaps more importantly, when acupuncture was compared to conventional treatment of chronic pain, it was found to be just as effective (with fewer side effects).

It is the answer to the second question (How does AA work?) which does most to dispel the deep scepticism toward acupuncture. Twenty years of research into the neurophysiological mechanisms of AA with over 500 published papers has led to the following explanation: It is evident that needling stimulates peripheral nerves (e.g., in the muscles) which send messages to the brain to release endorphins (morphine-like peptides in the brain); these neurochemicals then cause analgesia by blocking the transmission of painful messages. Three possible sites of endorphin AA effects are shown in Fig. 1. In one site, the pituitary gland is shown releasing endorphins into the bloodstream; this hormone travels to other parts of the brain and spinal cord to block transmission of painful messages. At another site, AA is achieved, by exciting periaqueductal grey neurons in the midbrain which release endorphins that act as local transmitters to excite raphe cells (by disinhibition); the excited raphe neurons in turn send neural messages to the spinal cord to inhibit firing of the spinothalamic tract neurons, perhaps by the release of the monoamines. A third site of action involves the spinal cord endorphin system; here local spinal cord neurons release endorphins to block release of neurotransmitters from the afferent fibers carrying painful messages into the cord.

What is the evidence for the AA-endorphin mechanisms outlined in Fig. 1? In 1977, we showed that during AA spinothalamic tract neurons no longer respond to

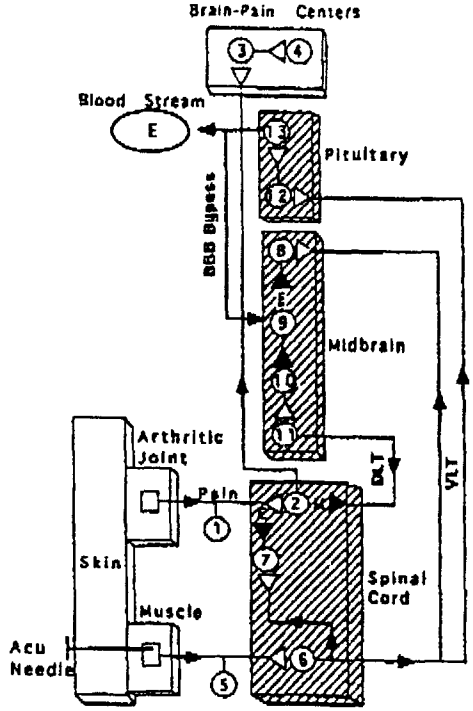

Fig. 1. Acupuncture analgesia is produced from three sites (see cross hatched areas): the spinal cord, the midbrain, and the pituitary. In this figure, open triangles depiet excitatory synapses, closed triangles inhibitory synapses, A painful message is shown traveling from an arthritic joint, along a pain fiber (cell 1) into the spinal cord to activate cell 2. This in turn sends a message to the brain pain centers (cells 3 and 4) where pain is detected. To produce analgesia, the acupuncture needle activates a high threshold muscle sensory nerve (cell 5), which sends messages to cell 6 in the spinal cord which in turn goes to the three sites (the cross hatched areas); to the spinal cord (cell 7), to the midbrain (cell 8), and to the pituitary (cell 12). Cell 7 in the spinal cord releases endorphins (E) to cause pre-synaptic inhibition of cell 1, thus blocking incoming pain messages. Cell 8 in the periaqueductal gray of the midbrain inhibis cell 9 by releasing endorphins (E), which in turn inhibits cell 10, resulting in excitation of cell 11 (in the raphe nucleus); cell 11 sends messages back down to the spinal cord where monoamines (M) inhibit cell 2. In the pituitary gland, cell 12 causes cell 13 to release endorphins (E) into the bloodstream or directly into the cerebrospinal fluid which bypasses the blood brain barrier (BBB); these circulating endorphins block pain via neurons in the brain such as cell 9. (N.B.: This diagram is a simplification and omits several additional sites in the brain which have been implicated in endorphin mediated acupuncture analgesia).

painful inputs and that this effect was blocked by naloxone (an endorphin receptor blocker). It has also been shown in mice and humans that naloxone blocked AA using behavioral measurements. However, the naloxone experiments were criticized on the grounds that naloxone, a drug, might have unknown side effects and hence

the results might be unrelated to endorphin mechanisms. To counter this argument 15 converging lines of research strongly support the AA-endorphin hypothesis:
Four different opiate antagonists block AA.

1. Naloxone has a stereospecific effect. Microinjection of naloxone (or antibod-
2. ies to endorphins) blocks AA only if given into analgesic sites in the central nervous system.
3. Mice genetically deficient in opiate receptors show poor AA.
4. Rats deficient in endorphin show poor AA.
5. Endorphin levels rise in blood and CSF during AA and fall in specific brain regions during AA.
6. AA is enhanced by protecting endorphins from enzyme degradation.
7. AA can be transmitted to a second animal by CSF transfer or by cross-circulation, and this effect is blocked by naloxone.
8. Reduction of pituitary endorphins suppresses AA.
9. There was a rise in messenger RNA for proenkephalin in brain and pituitary: this lasted 24 − 48 h after 30 min of EA, indicating a prolonged increased rate of synthesis of enkephalin. This could explain the enduring effects of EA and the potentiation of repeated daily treatments.
10. There is cross-tolerance between AA and morphine analgesia, implicating endorphins in AA.
11. AA is more effective against emotional aspects of pain; this is typical of endorphins.
12. Lesions of the arcuate nucleus of hypothalamus (the site of β-endorphins) abolishes AA.
13. Lesions of the periaqueductal grey (site of endorphins) abolishes AA.
14. The level of c-fos gene protein (which measures increased neural activity) is elevated in endorphin-related areas of the brain during AA.

There is considerable evidence for the three pathways shown in Fig. 1. First, to prove the involvement of the peripheral nerves several experiments were done: electrical recordings from the nerves showed that AA activated sensory afferents; blockade of these nerves with xylocaine abolished AA in animals and humans. To test the involvement of the pituitary, several experiments were carried out: both surgical removal of the pituitary and suppression of pituitary endorphins by chemi-

cal manipulations suppressed AA in animals. Experiments to test the involvement of the midbrain were done because it had been shown that morphine pain relief was largely mediated by this system. A variety of results confirmed the midbrain-AA-endorphin effects: direct lesions of the raphe, cutting the output fibers in the dorsolateral tract of the spinal cord, blockade of serotonin receptors, blockade of serotonin synthesis, and direct microinjection of naloxone into the midbrain all reduced AA. Enhancement of serotonin synthesis increased AA; moreover, the measurement of serotonin showed that it was released during AA. Another monoamine, noradrenaline, has also been implicated.

Finally, the evidence for the third endorphin system (in the spinal cord) mediating AA effects is also very convincing. Naloxone applied directly onto the cord via a chronically implanted intrathecal cannula blocks AA. Endorphin antibodies applied here also do the same. It is interesting to note that only antienkephalin and antidynorphin antibodies are effective in blocking AA, which is consistent with the finding that only Met-enkephalin and dynorphin (and no beta-endorphin) are present in the spinal cord.

In conclusion there is considerable evidence that circuits shown in Fig. 1 mediate AA. This, in combination with the AA endorphin results (outlined above), confirms the existence of the AA-endorphin mechanisms.

Partly as a result of this research, more and more physicians outside China are using acupuncture to treat chronic pain. It is estimated that approximately 5000 MDs in Germany, 30,000 in France, and 60,000 in Japan use acupuncture along with drugs, nerve blocks, and other approaches to treat patients with chronic pain. The numbers are much lower in Great Britain and North America, but they have been on the increase since the discovery of the endorphin-AA mechanisms. There are over one million practitioners outside China who use acupuncture, and the numbers are growing rapidly.

Further reading

1. Hans JS, Terenius L. (1982): Neurochemical basis of acupuncture analgesia. *Annu Rev. Pharmacol Toxicol* 22:193-220.
2. He L. (1987): Involvement of endogenous opioid preptides in acupuncture analgesia. *Pain* 31:99-121.

3. Macdonald AJR (1989): Acupuncture analgesia and therapy. In: *Textbook of Pain*, Wall PD, Melzack R., eds. Edinburgh: Churchill Livingstone.
4. Pomeranz B., Stux G. (1989): *Scientific Bases of Acupuncture*. Berlin; Springer.
5. Stux G., Pomeranz B. (1995): Basics of Acupuncture. 3rd ed. Berlin; Springer.
6. Zou K. (1987): Neurochemical mechanisms of acupuncture analgesia. *Pain Headache* 9:266-282.

Key words: Endorphin; Pain, chemical; Pain, neurophysiological mechanism; Placebo effect, transcutaneous electrical nerve stimulation (TENS).