

G. Stux · R. Hammerschlag (Eds.)

Clinical Acupuncture

Scientific Basis

With Contributions by

B. M. Berman

S. Birch

C. M. Cassidy

Z. H. Cho

J. Ezzo

R. Hammerschlag

J. S. Han

L. Lao

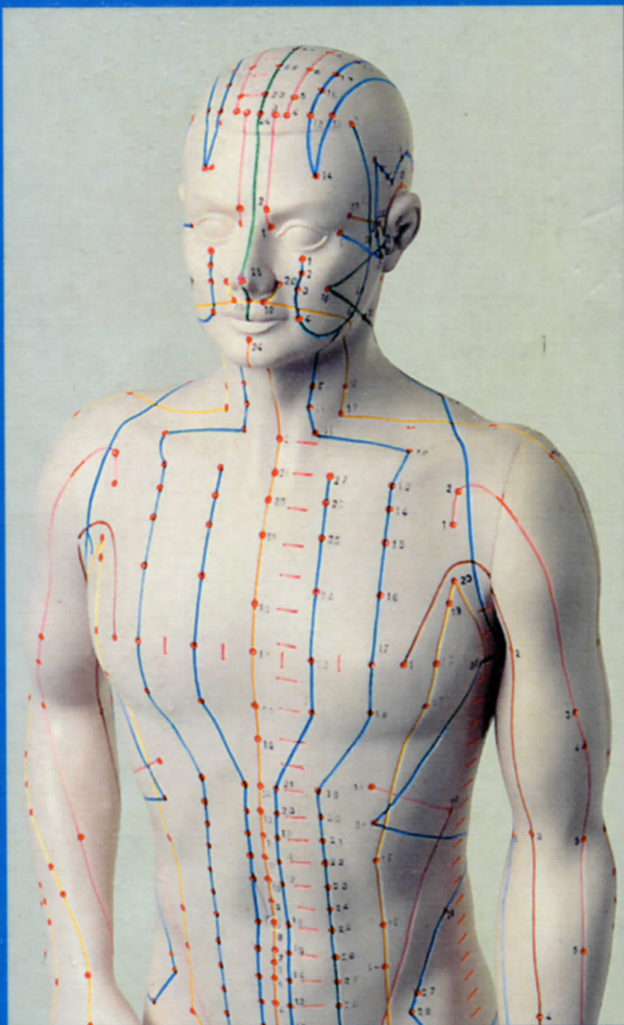
T. Oleson

B. Pomeranz

C. Shang

G. Stux

C. Takeshige



鍼灸

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Clinical Acupuncture *Scientific Basis*

Interest in acupuncture by health care consumers and providers alike has grown dramatically in the past decade. The increased use of acupuncture is attributed to its medical effectiveness, cost effectiveness and credibility provided by clinical trials and physiological research. Acupuncture is rapidly moving out of the arena of “alternative” medicine, in large part again because it is grounded more firmly than other alternative treatments in research.

This book provides an up-to-date understanding of the scientific basis of clinical acupuncture for researchers, health care practitioners, administrators and patients.

From the Contents:

- Review of Neurophysiological Research
- Assessing Clinical Efficacy of Acupuncture
- Proposed Standards of Acupuncture Treatment for Clinical Studies
- Considerations for Designing Future Acupuncture Trials
- Future Directions in Physiological Research

Gabriel Stux
Richard Hammerschlag
(Editors)

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J. Ezzo, R. Hammerschlag, J. S. Han, L. Lao, T. Oleson,
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With 40 Illustrations, some in Color
and 27 Tables

Preface

In 1988, when “Scientific Bases of Acupuncture” was published, its editors noted that 12 years had passed since the acupuncture endorphin hypothesis was first postulated, an event that marked the start of serious basic research on acupuncture. The editors also suggested that more was known about the mechanisms of acupuncture analgesia than many procedures of conventional medicine and, in consequence, it was time to stop referring to acupuncture as an “experimental procedure.”

Now another 12 years have passed. Acupuncture research, both basic and clinical, has greatly expanded. Modern biomedical techniques, including those of molecular biology and medical imaging, have revealed increasingly detailed physiological correlates of acupuncture action. Clinical researchers from Europe, North America, and Asia have devised a variety of protocols to test acupuncture efficacy according to generally accepted standards for randomized controlled trials. A critical review of acupuncture research by the United States Food and Drug Administration resulted in the label “experimental” being legally removed from the packaging of acupuncture needles in 1996, just as the editors of “Scientific Bases of Acupuncture” had proposed. A year later, again in large part a result of increased and improved acupuncture research, a consensus conference on acupuncture convened by the U. S. National Institutes of Health concluded its panel report with the endorsement “... *there is sufficient evidence of acupuncture’s value to expand its use into conventional medicine and to encourage further studies of its physiology and clinical value*” (JAMA 280:1518–24).

The present book is nothing less than a celebration of the coming of age of acupuncture research. Reflecting the broad spectrum of modern-day acupuncture research, its chapters include an assessment of systematic reviews of acupuncture trials, proposed standards of acupuncture treatment in clinical research, qualitative methods to gauge patient satisfaction with Oriental medicine treatment, and physiological models of auricular acupuncture, meridians, and homeostatic responses to acupuncture. Our hope is that the state-of-the-art reviews presented in these pages will encourage consideration of the millennia-old practice of acupuncture as a contemporary, evidence-based treatment option.

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Contributors

Brian M. Berman (bberman@compmed.ummc.umaryland.edu)
Complementary Medicine Program, University of Maryland School
of Medicine, James L. Kernan Hospital Mansion, 2200 Kernan Drive,
Baltimore, MD 21207-6697, USA

Stephen Birch (71524.3461@compuserve.com)
Foundation for the Study of Traditional East Asian Medicine
W.G. Plein 330, 1054 SG Amsterdam, The Netherlands

Claire M. Cassidy (honeeum@aol.com)
Paradigms Found Consulting, 6201 Winnebago Road, Bethesda,
MD 20816, USA

Zang Hee Cho (zcho@uci.edu)
Department of Radiological Sciences, University of California,
Irvine, CA 92697, USA

Jeanette Ezzo (jeanetteezzo@prodigy.net)
Epidemiology Faculty, Project LEAD, 1905 W. Rogers Avenue,
Baltimore, MD 21209, USA

Richard Hammerschlag (rzhammer@compuserve.com)
Oregon College of Oriental Medicine, 10525 S.E. Cherry Blossom
Drive, Portland, OR 97216, USA

Ji-Sheng Han (jshh@public.bta.net.cn)
Neuroscience Research Center, Beijing Medical University, Beijing,
China 100083

I.-K. Hong
Dept. of Information Engineering, Kwangju Institute of Science
and Technology, Kwanju, Korea

Lixing Lao (LLao@compmed.ummc.umaryland.edu)
Complementary Medicine Program, University of Maryland School
of Medicine, James L. Kernan Hospital Mansion, 2200 Kernan Drive,
Baltimore, MD 21207-6697, USA

S.-H. Lee
Dept. of Acupuncture, South Baylo University, Anaheim, CA 92801,
USA

C.-S. Na

Dept. of Meridianology, Oriental Medical College, Dong Shin University, Naju, Korea

Terry Oleson (terryoleson@earthlink.net)

Health Care Alternatives, PMB 2657, 8033 Sunset Boulevard, Los Angeles, CA 90046-2427, USA

Bruce Pomeranz (varadi9180@home.com)

Departments of Zoology and Physiology, University of Toronto, 25 Harbor Street, Toronto, Ontario M5S 1A1, Canada

Charles Shang (cshang@emory.edu)

Department of Medicine, Emory University School of Medicine, 69 Butler Street, S.E., Atlanta, GA 30303, USA

Gabriel Stux (106657.3550@compuserve.com)

Acupuncture Center Düsseldorf, Goltsteinstraße 26, 40211 Düsseldorf, Germany

Chifuyu Takeshige (Makoton@cc.showa-u.ac.jp)

Department of Medicine, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan

E. K. Wang (ekwong@uci.edu)

Dept. of Ophthalmology, University of California, Irvine, CA 92697, USA

Acupuncture Analgesia – Basic Research

B. Pomeranz

1.1

Introduction

In recent years, acupuncture analgesia (AA) in the west has been restricted mainly to the treatment of chronic pain and not used for surgical procedures, except for demonstration purposes. In some Western countries, however, AA is used in combination with nitrous oxide, sufficient N₂O being given to render the patient unconscious but not for analgesia [80], or with fentanyl [89]. How could a needle inserted in the hand possibly relieve a toothache? Because such phenomena do not conform to accepted physiological concepts, scientists were puzzled and skeptical. Many explained it by the well-known placebo effect, which works through suggestion, distraction, or even hypnosis [201, 202]. In 1945, Beecher [9] showed that morphine relieved pain in 70 % of patients, while sugar injections (placebo) reduced pain in 35 % of patients who believed they were receiving morphine. Thus, many medical scientists in the early 1970s assumed that AA worked by this placebo (psychological) effect. However, there were several problems with this idea. How does one explain the use of AA in veterinary medicine over the past 1000 years in China and approximately 100 years in Europe and its growing use on animals in America? Animals are not suggestible and only a very few species are capable of the still reaction (so-called animal hypnosis). Similarly, small children also respond to AA. Moreover, several studies in which patients were given psychological tests for suggestibility did not show a good correlation between AA and suggestibility [101]. Hypnosis has also been ruled out as an explanation, as two studies [6, 58] have shown that hypnosis and AA respond to naloxone differently, AA being blocked and hypnosis being unaffected by this endorphin antagonist.

Until 1973, the evidence for AA was mainly anecdotal, with a huge collection of case histories drawn from one quarter of the world's population. Unfortunately, there were few scientifically controlled experiments to convince the skeptics. In the past 25 years, however, this situation has changed considerably. Scientists have been asking two important questions: does AA really work by a physiological rather than a placebo/psychological effect and, if so, by what mechanism?

The first question had to be approached via controlled experiments to rule out placebo effects, spontaneous remissions, etc. These experiments have been carried out in clinical practice on patients with chronic pain, in the laboratory on humans, studying acute laboratory-induced pain (see Sect. 1.6), and on animals (see Sect. 1.6). From these numerous studies, it can be concluded that AA works much better than placebo.

Hence, AA must have some physiological basis. But what are the possible mechanisms? Only the answer to the second question (how does AA work?) could possibly dispel the deep skepticism toward acupuncture.

1.2

Neural Mechanisms of Acupuncture Analgesia

Twenty years of research in my laboratory coupled with over 100 papers from the western scientific literature led to a compelling hypothesis: AA is initiated by the stimulation of small diameter nerves in muscles which send impulses to the spinal cord. Then, three neural centers (spinal cord, midbrain, and pituitary) are activated to release transmitter chemicals (endorphins and monoamines) which block "pain" messages. Figures 1 and 2 summarize various aspects of the hypothesis of the neural mechanism of AA.

We explain the figures and present some of the evidence for this hypothesis. Fig. 1 shows how pain messages are transmitted from the skin to the cerebral cortex. On the left is skin, with a muscle beneath it in the lower left corner. An acupuncture needle penetrates the muscle. The next rectangle is the spinal cord, and to the right are rectangles depicting various brain structures: midbrain, thalamus, pituitary-hypothalamus, and cerebral cortex. As shown in the legend to Fig. 1, open triangles represent excitatory terminals (acting at the synapse) and closed triangles inhibitory terminals. Large arrows indicate the direction of impulse flow in the axons and small arrows the painful stimulus.

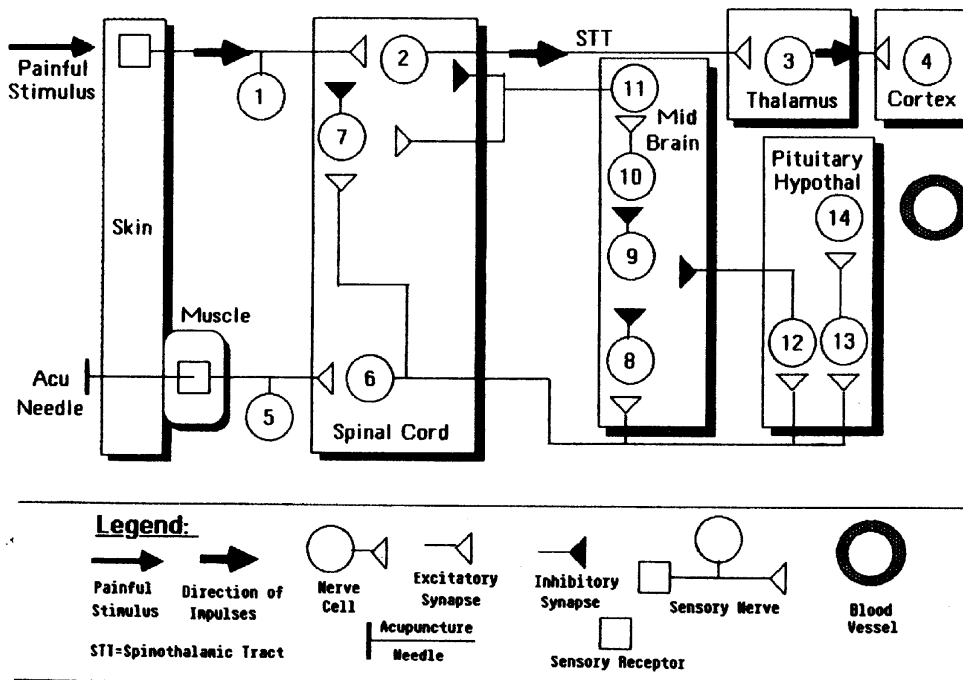


Fig. 1. Pain transmission

To understand the pain transmission as shown in Fig. 1, follow the thick arrows at the top. An injury to the skin activates the sensory receptors of small afferent nerve fibers (labeled 1) of A delta and C axon size. (Nerve fibers are classified by size and according to whether they originate in skin or muscle: large diameter myelinated nerves A beta (skin) or type I (muscle) carry "touch" and proprioception, respectively. Small diameter myelinated A delta (skin) or types II and III (muscle) carry "pain" messages, as do the smallest unmyelinated C (skin) and type IV (muscle). Types II, III, IV, and C also carry nonpainful messages.) Cell 1 synapses onto the spinothalamic tract (STT) cell in the spinal cord (labeled 2). The STT (cell 2) projects its axon to the thalamus to synapse onto cell 3, which sends impulses to the cortex to activate cell 4 (probably in the primary somatosensory cortex). I must point out that this diagram is oversimplified, since there are at least six possible pathways carrying pain messages from the spinal cord to the cortex but, for the sake of clarity, only the STT is shown.

It is best to go to Fig. 2 to see how the other cells operate (cells 5–14). In Fig. 2, the acupuncture needle is shown activating a sensory receptor (square) inside the muscle, and this sends impulses to the spinal cord via the cell labeled 5, which represents type II and III muscle afferent nerves (small diameter myelinated afferents). Type II afferents are thought to signal the numbness of De Qi needling sensations and type III the fullness (heaviness and mild aching) sensation [203]. Any soreness felt is carried by unmyelinated type IV afferents from the muscle, although soreness is not

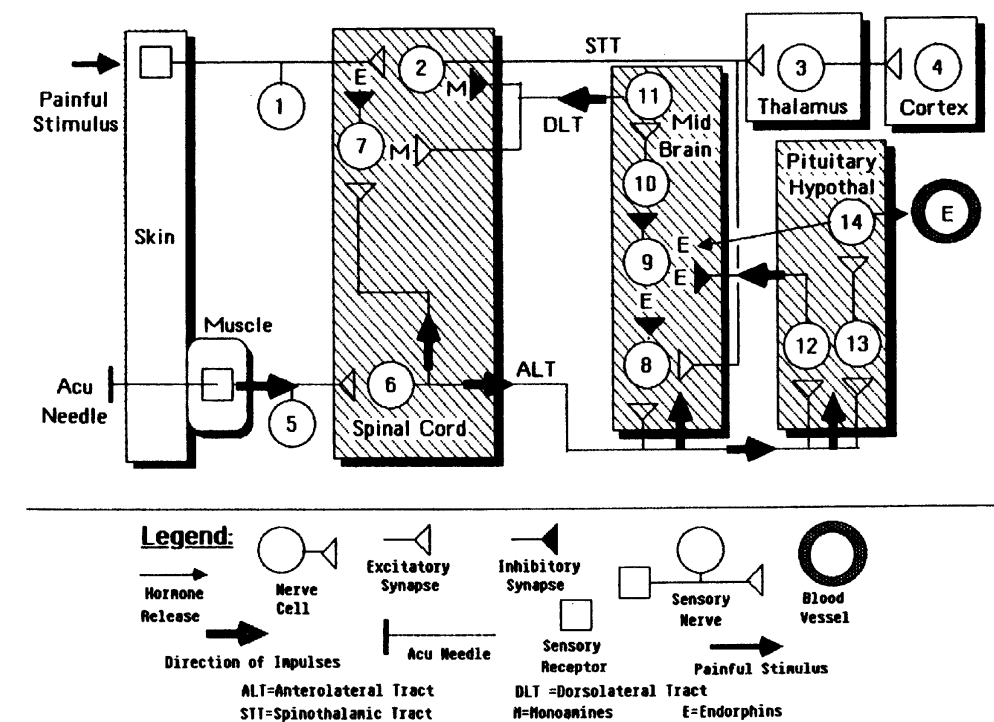


Fig. 2. Acupuncture (low frequency, high intensity)

usually part of the De Qi sensations. In some acupuncture points, e. g., at the fingertips or over major nerve trunks, there are no muscles and here different fibers are involved. If cutaneous nerves are activated, A delta fibers are the relevant ones. Cell number 5 synapses in the spinal cord onto an anterolateral tract (ALT) cell (labeled 6) which projects to three centers, the spinal cord, the midbrain, and the pituitary-hypothalamic complex.

Within the spinal cord, cell 6 sends a short segmental branch to cell 7, which is an endorphinergic cell. This cell releases either enkephalin or dynorphin, but not beta-endorphin. (There are three families of endorphins: enkephalin, β -endorphin, and dynorphin, and in Fig. 2 these are all labeled E.) The spinal cord endorphins cause presynaptic inhibition of cell 1, preventing transmission of the painful message from cell 1 to cell 2.

As there are very few axo-axonal synapses between cell 7 and cell 1, it is thought that the endorphin peptides merely diffuse to the receptors located on the terminals of cell 1. There are also postsynaptic endorphin synapses acting directly on cell 2 from cell 7, although these are not shown. Thus, enkephalins and dynorphins block pain transmission at the spinal cord level. The presynaptic inhibition probably works by reducing calcium current inflow during the action potential in the terminals of cell 1, resulting in reduced release of the pain transmitter.

What Fig. 2 does not show are the numerous peptides present in the cell 1 terminals, including cholecystokinin, somatostatin, neurotensin, bombesin, calcitonin gene-related peptide, angiotensin, substance P, and vasoactive intestinal peptide. So far, only cholecystokinin (CCK) has been shown to play a role in AA [72], acting like the opiate antagonist naloxone to block endorphin-mediated AA. Perhaps the ratio of CCK and endorphins is the important variable in producing analgesia.

As shown in Fig. 2, cell 6 also projects to the midbrain, ascending the spinal cord in the ALT. Here, it excites cells 8 and 9 in the periaqueductal gray (PAG), which release enkephalin to disinhibit cell 10, which is thus excited) and in turn activates the raphe nucleus, located in the caudal end of the medulla oblongata (cell 11), causing it to send impulses down the dorsolateral tract (DLT) to release monoamines (serotonin and norepinephrine, labeled M) onto the spinal cord cells [66]. Cell 2 is inhibited by postsynaptic inhibition, while cell 1 is presynaptically inhibited via cell 7. (Cell 7 is excited while cell 2 is inhibited by the monoamines.) Either of the two monoamine mechanisms can suppress the pain transmission. In addition to the raphe magnus, which releases serotonin onto the cord, there is the adjacent reticularis paragigantocellularis (not shown), which may release norepinephrine via the DLT onto the spinal cord. Norepinephrine binds to an alpha receptor in the cord to block pain transmission.

Some believe that serotonin and norepinephrine act synergistically in this regard [64]. There is some evidence that the peptide neurotensin may be the excitatory transmitter between cells 10 and 11 [7]. The precise relationship of these descending monoamine effects to AA is not clear at present, and results suggest that some of the raphe serotonin effect in AA may be mediated by ascending fibers from the raphe to the forebrain (not shown). More work is needed on the role of the monoamine system in AA.

Even less well understood is the action of cell 6 onto cells 12 and 13, the pituitary hypothalamic complex. Cell 12 in the arcuate nucleus may activate the raphe via

β -endorphin, and cell 13 in the hypothalamus may release β -endorphin from the pituitary gland from cell 14 (Fig. 2). While there is some agreement that AA is accompanied by elevated beta-endorphin in the CSF [169] and blood and that pituitary lesions suppress AA [42], there is no agreement on how the β -endorphin from the pituitary reaches the brain to cause analgesia. Too little of it reaches the blood to cross the blood-brain barrier in sufficient quantities. Some evidence suggests that the pituitary-portal venous system can carry hormones in a retrograde direction directly to the brain [13]. Perhaps cell 14 can influence cell 9, as shown by the thin arrows in Fig. 2, without having to cross the blood-brain barrier. If so, the role of circulating endorphins in the blood is unclear. However, there is an important correlate of pituitary β -endorphin release: adrenocorticotrophic hormone (ACTH) and β -endorphin are coreleased into the circulation on an equimolar basis [19, 158]. (They stem from a common precursor).

The ACTH travels to the adrenal cortex, where cortisol is released into the blood [43], which may explain why acupuncture is helpful in blocking the inflammation of arthritis and the bronchospasms of asthma (the doses of cortisol released by acupuncture are small and finely regulated, thus avoiding the side effects of cortisol drug therapy). Because of insufficient data, other centers implicated in the AA-endorphin effects have been left out of our description. These include the nucleus accumbens, amygdala, habenula, and anterior caudate [77, 224]. In Fig. 2, the axon from the STT cell (cell 2) has a collateral fiber dropping down to excite cell 8 in the midbrain to cause analgesia. This is because of a phenomenon discovered in 1979 by Le Bars et al. [95] called DNIC (diffuse noxious inhibitory control), in which one pain inhibits another. Its role in AA has been suggested but never clearly established [14].

In summary, acupuncture stimulates nerve fibers in the muscle which send impulses to the spinal cord and activate three centers (spinal cord, midbrain, and hypothalamus/pituitary) to cause analgesia. The spinal site uses enkephalin and dynorphin to block incoming messages with stimulation at low frequency and other transmitters (perhaps gamma-aminobutyric acid, or GABA) with stimulation at high frequency. The midbrain uses enkephalin to activate the raphe descending system, which inhibits spinal cord pain transmission by a synergistic effect of the monoamines, serotonin, and norepinephrine. The midbrain also has a circuit which bypasses the endorphinergic links at high frequency stimulation. Finally, at the third, or hypothalamus/pituitary center, the pituitary releases β -endorphin into the blood and CSF to cause analgesia at a distance. Also, the hypothalamus sends long axons to the midbrain and activates the descending analgesia system via β -endorphin. This third center is not activated at high frequency stimulation but only at low frequency.

What is the practical significance of this three-level system? When needles are placed close to the site of pain or in the tender (trigger, or Ah Shi) points, they are maximizing the segmental circuits operating at cell 7 within the spinal cord while also bringing in cells 11 and 14 in the other two centers (Fig. 2). When needles are placed in distal points far from the painful region, they activate the midbrain and hypothalamus-pituitary (cells 11 and 14) without the benefit of local segmental effects at cell 7. Moreover, cells 11 and 14 produce analgesia throughout the body, while cell 7 produces analgesia only locally.

Local segmental needling usually gives a more intensive analgesia than distal non-segmental needling because it uses all three centers. Generally, the two kinds of

needling (local and distal) are used together on each patient to enhance one another. Another important practical consequence of this system is the frequency/intensity effect. As shown in Fig. 2, low frequency (2–4 Hz), high intensity needling works through the endorphin system and acts in all three centers, while high frequency (50–200 Hz), low intensity needling only activates cells 7 and 11, bypassing the endorphin system. Numerous studies have shown that the types of analgesia produced by these two approaches are quite different [2]: the low frequency method produces an analgesia of slower onset and, more importantly, of long duration, outlasting the 20-minute stimulation session by 30 minutes to many hours. Also, its effects are cumulative, improving increasingly after several treatments. In contrast, the high frequency, low intensity analgesia is rapid in onset but of very short duration and with no cumulative effects. Many authors have arbitrarily described the low frequency, high intensity type of analgesia as “acupuncture-like” transcutaneous electrical nerve stimulation (TENS) and the high frequency, low intensity type as “conventional” TENS.

Because low frequency, high intensity analgesia produces a cumulative effect, repeated treatment produces more and more benefit for the patient [109, 154, 200] or laboratory animal [151]. This could be due to long-lasting effects of endorphins in the low frequency system. Most conventional TENS (high frequency) devices must be worn continuously by the patients, as the effect is of short duration, and in over 70 % of cases the effectiveness wears off after some months of continuous use because tolerance develops [209]. In contrast, low frequency acupuncture need only be given daily or twice a week because of its long-term cumulative effects [154]. Indeed, too frequent application of low frequency acupuncture produces tolerance. For example, if applied continuously for 6 h, the analgesia weakens and finally disappears [71]. This effect is cross-tolerant with morphine tolerance [71], and the mechanisms involved may be similar to those of addiction to endorphins. Hence, spacing the acupuncture treatments with long enough intervals may prevent tolerance while promoting the cumulative effects.

Perhaps the failure of some Western clinics to achieve success is due to the use of very infrequent treatments (e.g., one per week) and the termination of treatment after only five to ten sessions. In some clinics in Asia, patients are treated daily for a month, then weekly for 6 months, and the results reported anecdotally are excellent. Of course, some patients will never respond to acupuncture for various reasons; non-responders may be genetically deficient in opiate receptors. We have shown that mice genetically lacking endorphin receptors respond poorly to acupuncture [135]. Other failures may be due to deficiency in endorphin molecules; rats lacking endorphin compounds respond poorly to acupuncture [123]. Some nonresponders can be converted to responders by treatment with the safe drug *jd*-phenylalanine, which potentiates endorphins [39, 51, 183]. In clinical practice, a strategy must be developed to allow nonresponders to be recognized while not aborting therapy too soon for potential responders who might show delayed cumulative effects. (One way is to decide after five treatments: if there is no benefit whatsoever, abort; if mild to moderate effects occur, continue and reassess after 10–15 treatments.) Often, the cost of repeated office visits is prohibitive. Hence, our group developed a home acupuncture-like TENS device which gives *De Qi* sensations and can be used by the patient over acupuncture points for 30 min/day for several months [41].

Most books might have ended the discussion of AA right here. However, because acupuncture is relatively new to Western medicine and so controversial, more data

are needed to convince students that the acupuncture mechanisms outlined in Figs. 1 and 2 are well-established. Those who are in a hurry can skim or skip the next few pages but should nonetheless scrutinize the reference list (this omits the huge literature from China which, if included, would double the number of citations). It should be apparent that we know more about AA than about many chemical drugs in routine use. For example, we know very little about the mechanisms of most anesthetic gases but still use them regularly. The reader is also referred to the reviews [3, 66, 68, 76, 86, 100, 117, 139, 142, 143, 150, 168, 173, 215, 223, 226].

1.3

Evidence for Endorphins and Acupuncture Analgesia

Perhaps the most exciting experiments which opened up the field of AA to scientific research were those in which endorphin antagonists (e.g., naloxone and naltrexone) were used. That naloxone could antagonize AA was reported initially by two groups [113, 147]. Studying acute laboratory-induced tooth pain in human volunteers, Mayer et al. [113] produced AA by manual twirling of needles in LI.4 (first dorsal interosseous muscle of the hand). In a double-blind design, they gave one group of subjects IV naloxone while another group received IV saline. The saline group achieved AA with a time course typical for clinical reports (30 min to onset of analgesia and effects lasting for over 1 h). The naloxone group showed no AA. As no controls received naloxone alone, one might argue that naloxone hyperalgesia simply subtracted from the analgesia of AA. However, this is probably not the case, since numerous studies on acute laboratory-induced pain have shown that naloxone alone rarely produces hyperalgesia [57]. This suggests that endorphins do not have a basal tone during acute pain. Mayer et al. [113] studied a control group receiving placebo injections. The placebo subjects were told to expect a strong analgesic effect and none was observed, as predicted from Beecher's work on acute pain, where only 3 % of subjects reported placebo analgesia [9].

The other early naloxone study was by Pomeranz and Chiu [147] in awake mice; they used the mouse squeak latency paradigm and gave electroacupuncture (EA) at LI.4. Numerous control groups were used in this latter experiment in an attempt to determine some of the possible artifacts. Each group received one of the following treatments: EA alone, EA plus saline, EA plus IV naloxone, sham EA in a nonacupuncture point, naloxone alone, saline alone, and no treatment at all (just handling, restraint, and repeated pain testing). The results were unequivocal: naloxone completely blocked AA, sham EA produced no effect, and naloxone alone produced very little hyperalgesia (not enough to explain reduction of AA by subtraction). Moreover, the results in mice and in humans indicated firstly that AA was not a psychological effect and secondly that AA truly was blocked by naloxone. In a later study, Cheng and Pomeranz [36, 37] produced a dose-response curve for naloxone and found that increasing doses produced increasing blockade. In a third study in anesthetized cats [146] recording from layer-5 cells in the spinal cord (cell 2 in Fig. 1), the same researchers completely prevented the EA effects with IV naloxone.

Since these early papers, there have been numerous studies in which systemically administered endorphin antagonists have been used to test the endorphin-AA hypothesis. Although most researchers reported naloxone antagonism [25, 28, 32,

34–39, 46, 53, 62, 78, 93, 97, 98, 133, 135, 146, 147, 151, 160, 164, 165, 170, 171, 174, 175, 187, 193, 208, 210, 224, 225], some found no effects of naloxone [1, 30, 31, 137, 185, 200, 211]. Three of these seven failures were obtained with high frequency, low intensity stimulation, which is probably not endorphinergic [1, 200, 211]. In one of the failures [31] low intensity stimulation was used which did not lead to De Qi sensations. In spite of this, four of seven subjects in that study showed naloxone antagonism.

While the reasons for the other three negative papers [30, 137, 185] are not entirely clear, a possible explanation has emerged. Antagonists work best when given before the treatment [144, 206] and fail to reverse analgesia that has already been initiated. Thus, naloxone can prevent AA but often cannot reverse it. (In the three failed experiments, researchers tried to reverse AA, giving the endorphin antagonist after, not before the acupuncture treatments.) Taken together, the overwhelming weight of evidence shows that naloxone antagonizes AA and that the few negative results may be due to poor timing of the naloxone administration. In biology, negative results are often less valid than positive ones.

A few weeks after the first naloxone results were announced in the research news section of *Science* [110], a letter to the editor in the same journal justifiably criticized the use of naloxone as the sole proof of the AA-endorphin hypothesis [75]. This criticism is based mainly on the argument that naloxone might possess unknown side effects unrelated to opiate receptor blocking. Small doses which were effective in preventing AA in man ($5 \cdot 10^{-8}$ M) and in mice and cats (10^{-6} M) would tend to implicate receptor effects, but the effectiveness of small doses of naloxone is clearly not enough evidence to prove specificity [162]. However, since that letter was written, 17 different lines of experimentation have emerged which have independently provided support for the AA-endorphin hypothesis:

1. Many different opiate antagonists block AA [33–37].
2. Naloxone has a stereospecific effect [36, 37].
3. Microinjection of naloxone or antibodies to endorphins blocks AA only if given into analgesic sites in the central nervous system [15, 45, 67, 72, 73, 133, 144, 151, 216, 221, 224].
4. Mice genetically deficient in opiate receptors show poor AA [135, 159].
5. Rats deficient in endorphin show poor AA [123, 175].
6. Endorphin levels rise in blood and CSF during AA and fall in specific brain regions during AA [5, 45, 52, 74, 77, 83, 90, 108, 111, 125, 136, 169, 195, 225].
7. AA is enhanced by protecting endorphins from enzyme degradation [39, 45, 51, 54, 63, 82, 91, 123, 175, 225].
8. AA can be transmitted to a second animal by CSF transfer or by cross-circulation and this effect is blocked by naloxone [98, 105, 157].
9. Reduction of pituitary endorphins suppresses AA [42, 111, 152, 177, 179, 180, 181].
10. 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 enkephalin synthesis. This could explain the enduring effects of EA and the potentiation of repeated daily treatments [60, 220].
11. There is cross-tolerance between AA and morphine analgesia, implicating endorphins in AA [33, 34, 71].

12. AA is more effective against emotional aspects of pain. This is typical of endorphins [218].
13. Lesions of the arcuate nucleus of the hypothalamus (the site of β -endorphins) abolishes AA; this is cell 12 in Fig. 2 [177, 178, 204].
14. Lesions of the periaqueductal gray (site of endorphins) abolishes AA [205].
15. The level of c-Fos gene protein (which measures increased neural activity) is elevated in endorphin-related areas of the brain during AA [59, 96, 132].
16. Evidence suggests that, in addition to monoamines mediating 100 Hz EA effects, dynorphin (one of the three endorphins) may also be involved. Thus, at 100 Hz there is an elevation of dynorphin levels in the dorsal horn of rat spinal cord [217] and there is an elevation of dynorphin A in lumbar punctures in humans receiving 100 Hz EA [69, 70]. Moreover, rats given EA at 100 Hz show AA, which is blocked by the dynorphin kappa antagonist (norbinaltorphimine), while the EA at 2 Hz is blocked by mu and delta antagonists, suggesting involvement of enkephalins and β -endorphin at these lower frequencies [34, 35].
17. Electroacupuncture in rats elevated precursors of the three endorphins, preproenkephalin, prodynorphin, and preproendorphin mRNA. Moreover, antisense nucleotides for c-fos or c-jun successfully blocked the EA-induced prodynorphin mRNA [60].

In summary, 17 different lines of research strongly support the AA-endorphin hypothesis. Despite so much convergent evidence for this hypothesis, skepticism persists:

1. Some cite the few failures of naloxone to reverse AA [31]. It has already been suggested above that naloxone reversal experiments are prone to difficulty because naloxone prevents but does not reverse AA. Moreover, the number of successful naloxone antagonisms of AA far exceeds the number of failures (28 successes versus 7 failures). In general, negative results in biomedical research are less reliable than positive results.
2. Some state that naloxone antagonism is necessary but not sufficient evidence [75]. That is why we have presented 17 different lines of evidence (only one line of evidence depends on naloxone).
3. Some attack the animal studies of AA as being unrelated to AA in humans [31]. Firstly, there have been numerous experiments in humans with the same AA-endorphin outcome as in lower animals. Secondly, the similarity of results across many species proves the generality of the phenomenon. Thirdly, there is no proper objective measure of pain in man. Fourthly, if skeptics are correct, then the entire animal “pain” literature should be discarded, a literature which provided our initial insights into endorphins, brain stimulation analgesia, TENS, and other results that have been highly applicable to human pain.
4. Some are concerned that AA in animals may be merely stress-induced analgesia (which also releases endorphins) and hence has nothing to do with acupuncture in humans [31]. At a conference on stress-induced analgesia at the New York Academy of Sciences, we gave a lecture entitled “Relation of stress-induced analgesia to acupuncture analgesia.” Some of the points made in that paper [140] were:
 - A. Sham EA on nearby nonacupuncture points in animals induces no AA, thus controlling for stress [27, 43, 55, 56, 102, 147, 176, 186].

