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CHAPTER 32

Biological mechanisms of acupuncture

David J. Mayer

Department of Anesthesiology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298–0695, USA

Introduction

This chapter will begin by briefly placing modern acupuncture in an historical context. This will lead, in the following section, to a discussion of some technical difficulties and limitations of experimental paradigms for the study of the clinical efficacy of acupuncture. Then, in order to provide a background for understanding the biological underpinnings of the clinical effects of acupuncture, I will undertake a brief review of selected aspects of the literature concerned with evaluation of the clinical efficacy of acupuncture as a treatment modality for various medical ailments.

The discussion of biological mechanisms involved in acupuncture will focus on the analgesic effects of acupuncture, because little is known about the biological foundation of other acupuncture effects. The analysis of acupuncture analgesia will examine data from both man and other animals. The data from man is restricted primarily to evidence indicating a role for endogenous opioids, and these data will be assessed in detail. There is also extensive evidence for a role of endogenous opioids in animal models of acupuncture analgesia. These data will be discussed as well as data indicating a role for additional neural mechanisms.

*Corresponding author. Tel.: 804–828–9471; Fax: 804–828–4023; e-mail: mayer@hsc.vcu.edu

Historical context

Acupuncture, in some form, was probably practiced as much as 4500 years ago (Epler, 1980; Wu, 1996). The first written documentation on the subject, the *Huang Di Nei Jing* or *The Yellow Emperor's Inner Classic*, has been traced to the period of 480–220 BC (Wu, 1996). Even at this early time, it is important to note that acupuncture was a treatment modality that existed within the wider context of traditional Chinese medicine. Traditional Chinese medicine involves unique, complex, and interactive diagnostic and treatment procedures. In particular, the course of treatment is often dependent upon dynamically varying diagnostic criteria. As will be discussed below, this complex context of acupuncture within traditional Chinese medicine makes the design of double blind, placebo-controlled, randomized clinical outcome trials difficult at best.

Although it is not possible here to provide a detailed description of the development of all the key concepts involved in acupuncture treatment, certain terms and concepts should be understood in order to have a feel for modern experimental evaluations of acupuncture. A key concept in traditional Chinese medicine is 'Qi' (pronounced 'chee'). Most simply, Qi refers to life energy which flows through the body. This energy flows through the body in precisely located pathways or channels called 'meridians'. These meridians are connected to various body organs as well as to each other. According to the principles of traditional Chinese

medicine, illness results from an imbalance of energy flow within these meridians. The rationale for acupuncture, then, is that physical intervention at particular points along meridians can restore the proper energy balance within the body and thus restore good health.

Traditionally, acupuncture treatment has been administered not only by manual needling of acupuncture points but by utilizing other methods of stimulation such as electrical stimulation (electroacupuncture), heat (including moxibustion – burning of the herb moxa), pressure (acupressure), and laser generated light. Generally, the experimental literature has utilized either manual needling or electroacupuncture, because the stimulation parameters are easiest to control with these procedures. In the discussion that follows, only papers utilizing one or the other of these procedures are included unless otherwise stated. An important term related to manual needling and electroacupuncture is 'De Qi'. De Qi refers to a sensation of numbness and mild aching and is often used as a sign of proper needle placement.

The modern age of acupuncture in the West, and particularly in the US, began with the visit of President Richard Nixon to China in 1972. A reporter for The New York Times, James Reston, who was covering this politically important event, was taken ill with appendicitis. Surgery was performed on him utilizing acupuncture as part of the anesthetic regimen. This received wide press coverage and popularized acupuncture as a treatment for pain and other ailments in the US. More importantly perhaps, these events led to the scientific assessment of the clinical efficacy of acupuncture as well as to investigations into the biological foundations of these effects in terms of Western medical concepts.

Experimental evaluation of acupuncture as a treatment modality

Probably the most important questions we can ask about acupuncture in a modern Western scientific context are "does it work?" and, if so, "what are the biological mechanisms underlying its efficacy?" These are, of course, related questions, since we would be little interested in the latter question if the answer to the former question were negative. Indeed, because the title of this paper implies that there is a biological basis for acupuncture, it follows that I believe there is evidence for the clinical efficacy of acupuncture. I will briefly review some of the more recent conclusions about clinical efficacy to provide a context in which to review the data concerning the biological basis of acupuncture effects.

Two recent reviews of the clinical literature have greatly influenced the discussion which follows and are highly recommended to the reader seeking a more in depth review of the topic. The first is a series of manuscripts (Eskinazi and Jobst, 1996) generated at a meeting sponsored by the National Institutes of Health (NIH) Office of Alternative Medicine and the US Food and Drug Administration (FDA) entitled 'Workshop on Acupuncture' in 1994. This meeting was probably critical to the eventual FDA reclassification of acupuncture needles from Class III (experimental) medical devices to Class II (non-experimental but regulated) medical devices in 1996. In a separate series of meetings, the NIH Office of Alternative Medicine in conjunction with several other NIH institutes established a Consensus Development Panel to evaluate the clinical efficacy of acupuncture. The committee issued a report in November 1997 (NIH Consensus Development Panel Program and Abstracts, 1997). The summary of the consensus statement found that:

> There is clear evidence that needle acupuncture treatment is effective for postoperative and chemotherapy nausea and vomiting, nausea of pregnancy, and postoperative dental pain.
>
> There are a number of other pain-related conditions for which acupuncture may be effective as an adjunct therapy, an acceptable alternative, or as part of a comprehensive treatment program, but for which there is less convincing scientific data. These conditions include but are not limited to addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia (general muscle pain), low back pain, carpal tunnel syndrome, and asthma.

In the remainder of this section we will examine the evidence which supports some of these conclusions. First, however, it is important to review some of the difficulties often encountered in the conduct of clinical trials of acupuncture.

Experimental design problems associated with clinical trials of acupuncture

As with any treatment regimen, it would be desirable to have demonstrable evidence that acupuncture is both safe and efficacious in its clinical application. The issue of safety has been addressed by the United States FDA, and, with only minor reservations (Lao, 1996), has been considered safe when practiced by appropriate professionals. The issue of efficacy is much more complicated. The most important complications generally surround the issue of "efficacy compared to what." For some (Brown, 1998), even if acupuncture were to be no more efficacious than a placebo manipulation, it would be of value. For the FDA, comparison to a placebo would be less important than comparison to another treatment of known efficacy (Eskinazi and Jobst, 1996). To the scientist looking to evaluate the biological mechanisms involved in acupuncture effects, it might be important to demonstrate not only that acupuncture is more efficacious than a placebo but also, in addition, that acupuncture, at putatively appropriate sites, is more efficacious than treatment at inappropriate sites. One result of these varied goals is that the vast literature on acupuncture (Medline alone lists over 6000 references!) contains clinical trials of varying experimental design that are often difficult to compare and subject to statistical procedures such as meta-analysis. Nevertheless, it is possible to classify the experimental designs into a limited number and to evaluate their strengths and weaknesses (Birch et al., 1996).

Acupuncture compared to no treatment

As mentioned above, this design can demonstrate efficacy but cannot discriminate this efficacy from placebo effects. For the purposes of the discussion of biological mechanisms, results from experiments of this design are of little value.

Acupuncture compared to a treatment of known efficacy

This is a design that is acceptable to the FDA. That is, for the purposes of this regulatory body, it is of critical importance to have evidence (in addition to evidence for safety) that a procedure is at least as effective as some commonly used biomedical treatment. It is assumed that this standard treatment has been shown to be efficacious (i.e. to have a greater effect than placebo), but this is often not the case (Brown, 1998).

For our purpose here, which is to discuss the biological mechanisms underlying clinically demonstrable acupuncture effects, this design, at best, can shed light on what I will refer to as 'the weak hypothesis' of acupuncture. This hypothesis is that acupuncture produces effects that are greater than those resulting from placebo manipulation. Support for the weak hypothesis does not require that theoretically *correct* acupuncture points be shown to have greater effects than theoretically *incorrect* control points. It only requires that acupuncture, at theoretically *correct* acupuncture points, have effects greater than placebo. Again, this design is only of value for our current purposes when the standard treatment has been shown to be efficacious.

Acupuncture needling compared to various placebo or sham manipulations

This design offers an immediate advantage over the previous one in that a placebo or sham manipulation is included. Thus no assumptions are made about the efficacy of a standard treatment compared to a placebo or sham treatment.

There are several variants of this design. Some of these only permit testing of the weak hypothesis, while some allow examination of the strong hypothesis. In its most strongly stated sense, the 'strong hypothesis' is that acupuncture combined with traditional Chinese medical diagnosis is superior to treatment in which some facet of this total treatment modality is controlled by substitution of a putatively ineffective procedure or procedures. Few if any experiments have really examined this most strongly stated paradigm for

understandable reasons. First of all, the subtleties of the diagnostic system would tend to result in disparate treatment regimens in patients. This would make it difficult to achieve a homogeneous treatment group. In addition, with traditional Chinese medicine, the treatment is altered depending upon the progression of treatment. This would almost certainly unblind the experiment and introduce unacceptable heterogeneity of treatment groups. Thus, even the strong hypothesis must be weakened somewhat to conform to Western experimental design requirements. Nevertheless, for our purposes here, I will consider a test of the strong hypothesis any experiment which, in general, examines the possibility of acupuncture at particular sites along classical meridians tends to be a key variable. Some experiments do meet this criterion. It should be pointed out, however, that the Westernizing of experimental designs makes rigorous demands upon theories of acupuncture and traditional Chinese medicine in that factors which are variables in traditional Chinese medicine must be made constants in Western experimental designs. Thus, the absence of evidence supporting the strong or even the weak hypothesis of acupuncture must be interpreted with caution.

In one common variant of placebo controlled double blind experiments, the placebo manipulation is applied at the same point as active needling. The placebo manipulation can be tapping of a blunt needle or application of inactive transcutaneous electrical nerve stimulation (TENS) electrodes. This design has several associated problems. Probably the most important problem is that it is difficult to maintain blind conditions in this type of experiment if the experimenter administering the treatment is skilled in acupuncture, because an inactive procedure will be obvious. This is even more the case if the experimenter uses feedback from the subject such as the perception of De Qi as a guide for needle placement. In a similar common variant of this type of trial, the placebo manipulation is sham needling at the same point as active needling. That is, the needle is inserted but not manually rotated or electrically stimulated. This controls for the type of manipulation (i.e. needle vs. a pill or capsule) and needle insertion itself. Thus it is a reasonable test of the weak hypothesis. It has the disadvantage that mere needle placement produces less intense sensations than active needle manipulation. Thus, it might be argued that active needle manipulation produces a stronger placebo effect than does needle placement alone, and treatment effects could still be attributed to a placebo effect.

Probably the most rigorous experimental design which comes closest to testing the strong hypothesis is to utilize active manipulation (needling or electrical stimulation) at a putatively effective site for the syndrome being treated and the same manipulation at a nearby site which is situated on an active meridian but which is putatively not effective for the syndrome under treatment. The experimenter should be blind as to the syndrome being treated. This design controls for the type of manipulation, needle insertion itself, the particular point being tested, and the subjective sensations produced by the active manipulation. Should the active site be more effective than the inactive site, it is a convincing demonstration of the strong hypothesis. On the other hand, failure to observe an effect is weak evidence against the weak hypothesis, because stimulation at many points can be effective, and the particular points which might be effective are often controversial.

Evidence supporting efficacy of acupuncture

In this section, I will briefly and selectively examine some of the evidence for the clinical efficacy of acupuncture. The best support for the strong hypothesis of acupuncture comes from studies of its effects on nausea and vomiting. These data will be examined first. Second, since most of the data concerning biological mechanisms of acupuncture effects are related to analgesic effects, I will review what I consider to be convincing evidence for the weak hypothesis of acupuncture with regard to postoperative dental analgesia.

Acupuncture effects on nausea and vomiting

Although the NIH Consensus Development Panel on Acupuncture concluded "there is clear evidence that needle acupuncture treatment is effective for postoperative and chemotherapy nausea and

vomiting," there is little data available in the abstracts of the conference on which to evaluate the data on which this conclusion is based (NIH Consensus Development Panel Program and Abstracts, 1997). Andrew Parfitt authored the abstract for the Consensus Development Statement. Fortunately, Parfitt also authored a recent review of the topic (Parfitt, 1996) which emanated from the FDA conference mentioned previously. It is assumed that this review includes most, if not all, of the data considered by the NIH Consensus Development Panel. In this section, I will summarize Parfitt's review of the effects of acupuncture on perioperative and chemotherapy-induced nausea and vomiting.

Table 1 summarizes the outcomes of studies of the effect of acupuncture on perioperative nausea and vomiting. First, it can be seen that all except one of the studies reporting a reduction in nausea and/or vomiting emanated from one laboratory. The design of these four trials (Dundee et al., 1986; Ghaly et al., 1987; Dundee et al., 1989) is quite varied, since they represent a progressive refinement of the explicit hypotheses tested. The designs range from a preliminary open trial (Dundee et al., 1986) to a complex, well designed, sham acupuncture controlled trial comparing various forms of acupuncture (manual, electro, pressure) at Pericardium 6 (P6) and standard antiemetic treatment (Dundee et al., 1989). The effects observed were large and highly significant. Importantly, in the sham controlled trials, acupuncture at a nearby putatively inactive site was no more effective than no treatment, thus providing evidence for the strong hypothesis. The results of Dundee's group are supported by one other study (Ho et al., 1990)

Concerning the negative trials of acupuncture on perioperative nausea and vomiting, three (Weightman et al., 1987; Yentis and Bissonnette, 1991; Yentis and Bissonnette, 1992) of the four of these can probably be explained by the fact that acupuncture was administered while the patient was under general anesthetic. Dundee has criticized this design by providing evidence that acupuncture is much less effective when given under anesthesia (Dundee and Ghaly, 1989). The fourth negative study (Lewis et al., 1991) is more difficult to reconcile with positive studies, but the negative results may be due to one or more of the many variables which differed between this study and the positive trials discussed above.

Several conclusions about acupuncture effects on perioperative nausea and vomiting can be made from these studies. It is clear that the number of trials carried out has been relatively small, but several of them are of very high quality. It is disappointing that so many of the positive trials come from one group. This does not negate the impressiveness of the findings, particularly since most of the negative trials can be readily explained. It would be desirable to have further trials run by other groups, but it seems reasonable to conclude at this point that Dundee's group has provided convincing evidence of acupuncture's effectiveness for the treatment of perioperative nausea and vomiting. In addition, they provide some evidence in support of the strong hypothesis of acupuncture in that acupuncture at a specific point (Pericardium 6 or P6) is more effective than a nearby control point.

A small number of trials have examined the effect of Pericardium 6 acupuncture on nausea and vomiting induced by chemotherapeutic agents in patients with various carcinomas. All of these studies have used a design in which acupuncture was used as an adjuvant to antiemetic medication. In the most convincing of these studies, acupuncture at a nearby non-acupuncture point was

TABLE 1

Evidence for efficacy of P6 acupuncture on nausea and emesis (from Parfitt, 1996)

	Perioperative Studies		Chemotherapy Studies	
	Dundee et al.	Other Studies	Dundee et al.	Other Studies
Positive Results	4	1	2	1
Negative Results	0	4	0	0

used as a control in a crossover design (Dundee et al., 1989). P6 acupuncture plus antiemetic medication was found to produce greater antiemetic effects than antiemetic medication alone or antiemetic medication plus sham acupuncture. Because P6 acupuncture was shown to be effective in this trial, subsequent trials, for ethical reasons, could not utilize sham points. Nevertheless, Dundee's group went on to show very large and probably clinically important antiemetic effects of P6 acupuncture in large groups of patients (Dundee et al., 1989). Similarly another group, (Aglietti et al., 1990), has reported impressive results. Thus, as with studies examining perioperative antiemesis, these studies provide some support for the strong hypothesis of acupuncture analgesia.

Acupuncture effects on postoperative pain

A very large number of studies exist which have examined the effect of acupuncture on pain. It is not the purpose of this chapter to provide a comprehensive review of the analgesic efficacy of acupuncture. Rather, the intent is to establish efficacy at least under some circumstances and to evaluate whether there is support for the strong or weak hypotheses of acupuncture.

The NIH Consensus Development Panel on Acupuncture concluded, "there is clear evidence that needle acupuncture treatment is effective for . . . postoperative dental pain." Lao reviewed this evidence in the NIH Consensus Development Panel statement (NIH Consensus Development Panel Program and Abstracts, 1997), and this section summarizes his analysis.

Table 2 summarizes the results of the studies of postoperative pain reviewed by Lao. It can be seen that, in spite of the variability of study designs and types of surgery utilized, acupuncture is consistently effective in reducing postoperative pain. Despite this consistency, however, it is important to note that none of the trials reviewed utilized active stimulation of a putative non-acupuncture point as a control. Thus, at this time, there is strong evidence that acupuncture can reduce at least some forms of pain, but there is, as yet, only evidence to support a weak hypothesis of acupuncture analgesia. Indeed, as will become clear below, there is good reason to believe that acupuncture for pain induces analgesia through more than one mechanism.

Biological mechanisms involved in acupuncture

With the popularization of acupuncture in the West in the early 1970s came an interest in understanding the biological mechanisms underlying acupuncture effects in the context of Western science. Perhaps the first acupuncture effect to be examined scientifically (Mayer, 1975) and certainly the one examined most extensively to date is the effect of acupuncture on pain. This probably resulted from a coincident revival of interest in the early 1970s of mechanisms of pain modulation as well as the fascinating discoveries of the opioid receptor (Hiller et al., 1973; Pert and Snyder, 1973; Terenius, 1973) and endogenous opioids (Hughes, 1975). Because so much effort has been focused on the issue of the scientific basis of acupuncture analgesia, this review will be restricted to that topic. In order to provide the reader with the scientific background for an understanding of this research, I will first provide a review of our current understanding of the neural mechanisms of pain modulation systems. Then I will review studies of the scientific basis of acupuncture analgesia in

TABLE 2

Evidence for efficacy of acupuncture on postoperative pain (from Lao in: NIH Consensus Development Panel Program and abstracts, 1997)

	General Surgery	Dental Surgery	
		RCT	Non-RCT
Positive Results	3	3	3
Negative Results	1	0	0

RCT = randomized controlled trial

man, and finally I will relate these to similar studies in experimental animals.

Pain modulation systems

The last thirty years has seen a revolution in the understanding of the mechanisms by which pain is processed in the central nervous system (CNS). From the discovery of endogenous opioid receptors and characterization of opioid peptides to the delineation of the CNS structures and pathways responsible for the processing and modulation of nociceptive signals, a remarkable composite of information has become available. Because much of the work carried out on the biological basis of acupuncture analgesia has involved the study of the role of endogenous opioids, it is important that the reader be familiar with developments in this field. This section first examines the development of concepts of endogenous opioid and non-opioid pain modulation systems. Then, the role of opioid peptides in the production of environmentally induced analgesia (EIA) other than acupuncture is reviewed.

Neural substrates of morphine- and stimulation-produced analgesia (SPA)

The earliest firm experimental evidence indicating that opiates produce analgesia in part by activating endogenous pain inhibitory systems was obtained by Irwin et al. (1951), who demonstrated that the ability of morphine to inhibit the spinally mediated tail-flick reflex was compromised in rats with spinal cord transections at the thoracic level. The authors postulated that morphine activates supraspinal neural circuitry that descends to the spinal cord and modulates nociceptive signals.

Despite this observation, it wasn't until the 1960s and 1970s and the development of CNS microinjection techniques that the sites of action underlying morphine's analgesic powers became apparent. In 1964, Tsou and Jang reported that microinjection of morphine into the periaqueductal gray matter (PAG) of the rabbit midbrain produces analgesia. Later, Herz and colleagues implicated several periventricular areas in the midbrain and diencephalon as important sites of action in the rat (Herz et al., 1970). Further investigations by Yaksh and his colleagues using both primates (Pert and Yaksh, 1974) and rats (Yaksh et al., 1976; Yeung et al., 1977; Yaksh and Rudy, 1978) confirmed that a continuum of periaqueductal and periventricular sites extending from the caudal PAG rostrally into the hypothalamus are the most sensitive to the application of morphine. In addition, a direct action of morphine on the spinal cord was described through the use of intrathecal injection techniques (Yaksh and Rudy, 1976).

While these exciting investigations into morphine analgesia (MA) were being carried out, two laboratories discovered that electrical stimulation of discrete brain areas produces analgesia in awake rats (Reynolds, 1969; Mayer et al., 1971). It was not long before several important observations were made which suggested that focal brain stimulation and morphine produce analgesia through activation of similar neural circuitry: (a) The most effective sites of action of both morphine and electrical stimulation appeared to be localized in the midbrain periaqueductal gray matter (Mayer and Liebeskind, 1974; Yeung et al., 1977); (b) Subanalgesic doses of morphine synergized with subanalgesic levels of brain stimulation to produce analgesia (Saminin and Valzelli, 1971); (c) Repeated stimulation resulted in tolerance to the analgesic effects of brain stimulation, a phenomenon invariably associated with repeated administration of opiates (Mayer and Hayes, 1975); (d) Rats tolerant to the analgesic effects of brain stimulation were also tolerant to morphine, despite the lack of prior experience with morphine (Mayer and Hayes, 1975); (e) SPA could be partially reversed by the opiate antagonist naloxone in both rats (Akil et al., 1972; Akil et al., 1976) and humans (Hosobuchi et al., 1977).

This last observation was particularly important because it suggested that electrical stimulation results in the release of an endogenous opiate-like factor. Indeed, concurrent with these MA and SPA investigations, the discovery of stereospecific binding sites for opiates in the CNS was reported (Hiller et al., 1973; Pert and Snyder, 1973; Terenius, 1973). The key to the mystery of naloxone antagonism of SPA seemed close at hand: if there are endogenous opioid receptors located in the mammalian brain, then there should also be corresponding endogenous opiate-like ligands.

These too were discovered (Hughes et al., 1975) and shown to produce analgesia in their own right (Belluzzi et al., 1976). Today it is generally accepted that there are at least three different classes of endogenous opiate-like peptides, endorphins, enkephalins, and dynorphins, as well as different classes of opioid receptor, including μ, δ, κ, and ε.

The neural characterization of MA and SPA

The discoveries outlined above were exciting because they indicated a similar anatomical and neurochemical substrate for MA and SPA. Furthermore, the evidence suggested that morphine and electrical stimulation were activating an inhibitory pathway which coursed from the midbrain to the spinal cord whereupon nociceptive reflexes were being suppressed. Not surprisingly, investigations into the details of this inhibitory pathway were quickly undertaken. As a result, a general conception of descending endogenous pain control mechanisms was suggested involving neural circuitry and transmitters which course from the PAG, through the rostral ventral medulla (including the NRM), and finally through the DLF to the dorsal horn of the spinal cord (Mayer and Price, 1976; Basbaum and Fields, 1978). In essence, the hypothesis consists of the following: the transfer of nociceptive information from peripheral fibers to ascending second order neurons in the dorsal horn can be modulated by this descending neural influence, which can be activated in part at the level of the PAG by release of endogenous opiate-like factors, or by morphine or electrical stimulation. This hypothesis is supported by the fact that the PAG contains relatively large quantities of opioid receptors, enkephalin containing cell bodies and terminals, and β-endorphin containing terminals. The hypothesis described above is still widely accepted today, with descending pain control mechanisms continuing to generate widespread research interest.

Environmental stimuli can activate analgesia

The discovery of endogenous opioid peptides and receptors and the subsequent delineation of the circuitry underlying SPA and MA intrigued researchers, but the physiological role and significance of this circuitry under normal circumstances remained obscure. As a result, investigations were undertaken to determine possible ways in which environmental stimuli (both natural and unnatural) could activate this circuitry and produce analgesia.

Hayes et al. (1976; 1978a; 1978b) were the first to systematically investigate the range of environmental stimuli that could elicit analgesia in the rat. They were able to demonstrate that potent analgesia in a number of nociceptive assays (i.e. tail flick, hot plate) could be elicited by such diverse stimuli as brief footshock, centrifugal rotation, or intraperitoneal injection of hypertonic saline. While these manipulations can be considered stressful, these investigators made the important observation that stress alone was not sufficient to produce analgesia: stressful manipulations such as exposure to brief ether anesthesia or horizontal oscillation did not produce analgesia using the same nociceptive tests (Hayes et al., 1978a).

In the years that followed these initial observations, many more types of manipulations were discovered to produce potent analgesic effects. It was shown quite early that analgesia could be produced in rats and mice by the stress of a cold water swim (Lal et al., 1978; Bodnar et al., 1978b), vaginal stimulation (Crowley et al., 1976), restraint and forced immobilization (Amir and Amit, 1978), and hypoglycemia brought on either by food deprivation (Bodnar et al., 1978c), or by injection of glucoprivic stressors such as 2-deoxy-D-glucose (2-DG) and insulin (Bodnar et al., 1978a).

Later, the list expanded to include tailshock (Jackson et al., 1979), the stress of burn injury (Osgood et al., 1987), acute environmental heat (Kulkarni, 1980), exposure to a natural predator (Lester and Fanselow, 1985), social conflict (Teskey et al., 1984), and defeat in a fight (Miczek et al., 1982). Even such things as exposure of an unstressed rat to the odors of a stressed rat (Fanselow, 1985), and exposure to ionizing radiation (Teskey and Kavaliers, 1984) were found to produce analgesia.

In addition, more complex psychological phenomena such as classical conditioning (Chance et al., 1977; Hayes et al., 1978a) and learned helplessness (Jackson et al., 1979) were found to be

associated with analgesia. While both paradigms involve stress, they also involve more complex psychological dimensions such as controllability over the stressor, and the association of neutral stimuli with noxious ones. Hayes et al. (1976; 1978a) were the first to use classical conditioning procedures to associate electrical footshock with environmental cues: after exposing rats to grid shock on two consecutive days, on the third day analgesia could be elicited simply by placing the rat on the grid (now a Pavlovian conditioned stimulus or CS). Later, other investigators were able to demonstrate that classically conditioned analgesia (CCA) appeared to meet all of the laws of Pavlovian classical conditioning (Watkins et al., 1982b).

The role of opioid peptides in EIA

One of the most intriguing questions posed by the study of EIA is whether CNS endogenous opioid peptides are critical mediators of analgesia. There is much data concerning this issue, and I will attempt to summarize it here.

Early studies concerned with the role of endogenous opiate-like substances in EIA approached the matter in four ways: (1) studies correlating the onset and time course of analgesia with a rise in endogenous opioid activity in the brain; (2) studies demonstrating reduction of analgesia with opioid antagonists such as naloxone and naltrexone; (3) studies demonstrating cross-tolerance between the analgesic effects of environmental manipulations and that of morphine; (4) studies investigating whether a particular form of EIA utilizes the same anatomical and biochemical substrates as MA and SPA.

Later, the role of opioid peptides in EIA was investigated by examining: (a) the effects of specific blockade of different opioid receptor subtypes; (b) differences in EIA between opioid receptor-rich and opioid receptor-deficient strains of rats and mice, and (c) the effects of inhibitors of opioid degrading enzymes.

Opioid and non-opioid forms of EIA

It soon became apparent to investigators in several laboratories that the degree to which naloxone antagonized different forms of EIA could be traced to variations in parameters related to the environmental manipulation. For example, temporal pattern of the manipulation (i.e. continuous vs. intermittent), duration, number of exposures, intensity, and even body region to which the manipulation was applied, all appear to affect the naloxone-sensitivity of the resulting analgesia. Before long, opioid and non-opioid forms of analgesia produced by footshock, tailshock, swim stress, social conflict, and classical conditioning were described. At this point, the discussion will be restricted to two sets of observations about analgesia induced by footshock (FSIA), because these observations are important to the discussion of acupuncture and animal models of acupuncture.

As mentioned previously, Liebeskind and co-workers (Lewis et al., 1980; Terman et al., 1984) described two forms of FSIA that are naloxone- and naltrexone-sensitive: one produced by 1–2 min of continuous footshock (brief, continuous FSIA which is opioid-mediated, or *opioid B, C-FSIA*), and the other produced by 20 min of intermittent footshock (prolonged, intermittent FSIA which is opioid-mediated, or *opioid P, I-FSIA*). In addition, they described a form of FSIA that is insensitive to opiate antagonists: that produced by 3–5 minutes of continuous footshock (brief, continuous FSIA which is not opioid-mediated, or *non-opioid B,C-FSIA*). In all cases, shock was applied to all four paws.

The second relevant model, developed by Watkins and co-workers (Watkins and Mayer, 1982), showed that 90 s of continuous shock applied to the front paws of a rat produces analgesia in the tail-flick test (termed front paw FSIA) that is sensitive to both systemic (Watkins et al., 1982a) and intrathecal (Watkins and Mayer, 1982) naloxone pretreatment. The same shock delivered to the hind paws, however, produces analgesia (hind paw FSIA) that is not naloxone-sensitive (Watkins and Mayer, 1982).

Another important finding from the literature on environmentally produced analgesia concerns the effect of naloxone on CCA. Hayes et al. (1976; 1978a) and Chance et al. (1977; Chance and Rosecrans, 1979) found that naloxone had no effect on the analgesia produced by their respective conditioning paradigms. The findings of Chance et

al. were in contrast with their demonstration that endogenous enkephalin activity was increased concurrent with CCA (see previous section). However, as the authors correctly pointed out, it remained possible that the changes in opiate-like binding they observed were not causally linked to analgesia. In contrast with these findings, both Fanselow and Bolles (1979) and Gaiardi et al., (1983) reported that naloxone reversed and prevented CCA in their respective paradigms. Interestingly, Watkins and co-workers demonstrated that while front paw and hind paw shock elicit naloxone-sensitive and naloxone-insensitive analgesia respectively (Watkins et al., 1982c), CCA resulting from shock to *either* body region can be prevented by naloxone (Watkins et al., 1982b). The interesting point here is that while endogenous opioids do not appear to mediate hind paw analgesia, they do appear to be involved in the process of learning to associate environmental cues with hind paw shock.

As the reader can see from the studies on naloxone-sensitivity and cross-tolerance outlined above, some forms of EIA appear to depend on a critical opioid synapse for their mediation while other forms do not have such a dependence. As a result of this distinction, the terms 'opioid' or 'opiate' analgesia, and 'non-opioid' and 'non-opiate' analgesia were born (Chance, 1980; Lewis et al., 1980; Bodnar et al., 1980; Watkins and Mayer, 1982). This distinction appears to have clear clinical relevance since the non-opioid analgesias tend to be quite powerful and not as prone to tolerance as the opioid forms. Indeed for the sake of simplicity I will refer to naloxone-sensitive forms of EIA as 'opioid' and naloxone-insensitive forms as 'non-opioid' for the remainder of this chapter.

The reader should be aware, however, that there are some problems inherent in this terminology. For instance, naloxone antagonism is a necessary criterion for implicating endogenous opioids in EIA. It is not, however, a sufficient criterion (Hayes et al., 1977) since the actions of naloxone may not be specific to opioid receptors: for instance, naloxone may act as a GABA antagonist (Sawynok et al., 1979).

It should be clear to the reader that endogenous pain control mechanisms are very complex. It should also be clear that it is impossible to synthesize the results presented above into a comprehensive and coherent view of environmental modulation of pain. The main reason for this is the lack of consistency across laboratories in terms of the parameters used to elicit analgesia. From the myriad of conflicting and seemingly irreconcilable results, however, two points are indisputable: (1) opioid peptides play a role in at least some forms of EIA; (2) there is more than one set of neural and hormonal circuitry by which nociceptive signals can be modulated and suppressed.

Evidence for a role of endogenous opioids in acupuncture analgesia in man

There now exists an extensive literature that provides evidence that at least some forms of acupuncture stimulation, as well as some forms of a closely related treatment procedure known as transcutaneous electrical nerve stimulation (TENS), activate endogenous opioid mechanisms in humans. The belief that an acute painful stimulus can be used to alleviate ongoing pain has been held since antiquity and is known as counterirritation. This concept has a great deal in common with acupuncture and TENS. All use the application of somatic stimuli, either noxious or innocuous, to obtain relief from pain. Importantly, pain relief often persists beyond the period of treatment. The site of treatment in relation to the painful area is highly variable, ranging from the painful dermatome itself to a theoretically unpredictable constellation of points in classical Chinese acupuncture. Last, the duration of treatment varies from less than a minute to hours. All of these factors have also been shown to be important determinants of the analgesic effects produced by various forms of somatosensory stimulation in animals as discussed previously. Thus, the highly variable effects observed in the clinic would be predicted from animal research. Results of studies in humans, like those of animal studies, suggest the involvement of both opioid and non-opioid systems.

Perhaps the first clear demonstration of the involvement of endogenous opioid mechanisms in acupuncture analgesia came from Mayer et al.

(1977). Pain thresholds to electrical stimulation of the tooth were significantly increased by bilateral, high intensity, low frequency acupuncture stimulation of points between the thumb and index finger on the Large Intestine (LI) meridian. Subjects were randomly assigned to two groups who received either intravenous saline or 0.8 mg naloxone on a double blind basis. The group receiving naloxone showed a complete reversal of acupuncture analgesia, whereas the saline group showed no decrease in analgesia. The initial results indicated an involvement of an opioid system in at least one form of somatosensory-evoked, environmental analgesia whose parameters of stimulation were generally similar to classical forms of Chinese acupuncture.

The effect of naloxone on this type of pain reduction, though challenged by one group of investigators (Chapman et al., 1980; Chapman et al., 1983), has since been replicated several times and in different ways by others, using diverse experimental approaches that range from visual analog scaling of supra threshold clinical pain to measurement of the nociceptive component of the eye blink reflex (Willer et al., 1982). Table 3 summarizes the studies that have examined the effect of naloxone on acupuncture analgesia, as well as those studies that have measured acupuncture-induced changes in plasma or cerebrospinal fluid (CSF), β-endorphin, or enkephalin levels. It is important to note that acupuncture is not a uniformly defined procedure. The only criterion for including a study in this table was that the authors call the procedure acupuncture. Many of the procedures discussed below under TENS are similar or identical to those defined as acupuncture here. Sixteen studies have measured the effect of naloxone on clinical or experimental analgesia produced by acupuncture. Of these, 11 reported that naloxone reduced the analgesia while five found no effect. In two of the studies failing to find a naloxone effect, the negative interpretations of the results have been called into question (Mayer and Price, 1981). A third negative study examined long-term effects of acupuncture on migraine headache (Lenhard and Waite, 1983) and thus does not fit into the general paradigm of the other studies addressed here. The fourth negative study (Kenyon et al., 1983) employed a dose of naloxone (0.4 mg) that is on the low end of the range of effective doses. Thus, it seems clear that naloxone, at least in the majority of studies (11 of 16), antagonized acupuncture analgesia, and at least some of the negative results may have been related to methodological problems.

The effects of acupuncture on CSF and plasma endorphin or enkephalin levels present a somewhat less consistent picture, but this is not surprising considering the complexities of these types of data. Considering that one could question the entire concept of plasma endorphin levels, since they are indicative of CNS levels in only very indirect ways, a somewhat consistent picture emerges. As can be seen in Table 3, six studies have reported increases in endorphin or enkephalin levels while eight have reported no effects. Interestingly, four of the six studies showing increases measured these levels in CSF. Such results should be interpreted with extreme caution, since the meaning of increases in plasma endorphin levels is entirely unclear and even CSF endorphin levels are likely to be ambiguous, since the site of endorphin release probably varies with the particular type of acupuncture stimulation. Nevertheless, an overview of the data supports an involvement of endogenous opioids in at least some forms of acupuncture analgesia.

Evidence for a role of endogenous opioids in TENS analgesia in man

For reasons that will become clear below, the literature on opioid involvement in TENS for relief of pain is relevant to the discussion of acupuncture analgesia. The literature concerning the involvement of endogenous opioids in TENS analgesia is even more complex than that associated with acupuncture analgesia. This is likely to result from a greater variability in the intensity, frequency, duration, location, and other parameters of TENS. Despite this diversity in experimental paradigm, some general consistencies are apparent in the literature. While only four of 13 studies of TENS analgesia have reported naloxone antagonism, all four studies used low-frequency TENS (Table 4). Conversely, none of seven studies using high-frequency TENS found a naloxone antagonism (see

TABLE 3

Involvement of opioids in acupuncture analgesia in man

Effects of Naloxone		Plasma β-Endorphin		CSF β-Endorphin		Enkephalin	
He and Dong, 1983	<	Szczudlik, Kwasuki, 1984	=	Clement-Jones et al., 1980	>	Khiser et al., 1973 (Plasma)	>
Lenhard and Waite, 1983	=	Umimo et al., 1984	=	Sjolund et al., 1977	>	He and Dong, 1983 (CSF)	>
Kenyon et al., 1983	=	Szczudlik and Lypka, 1983	=			Clement-Jones et al., 1980	=
Chapman et al., 1980	=	Khiser et al., 1973	=				
Chapman et al., 1983	=	Szczudlik and Lypka, 1983	=				
Willer et al., 1982	<	Masala et al., 1983	>				
Tsunoda et al., 1980	<	Moret et al., 1991	=				
Boureau et al., 1979	<	Lundeberg et al., 1989	=				
Sjolund and Eriksson, 1979	<	Pintov et al., 1997	>				
Chapman, 1978	<						
Mayer et al., 1977	<						
Ernst and Lee, 1987	<						
Eriksson et al., 1991	<						
Moret et al., 1991	=						
Kitade et al., 1988	<						
Yoon et al., 1986	<						

<, decrease in analgesia, β-endorphin, or enkephalin level; =, no change; >, increase in analgesia, β-endorphin, or enkephalin

Table 4 for references). The effects of TENS on endorphin levels have been less well studied. As seen in Table 4, three of the six reported studies found an increase in endorphin levels while the remainder found no effects. Such results should be interpreted in light of the caveats discussed above.

Overall, generally consistent patterns of physiological effects appear to result from various types of somatosensory stimulation therapies for pain. Low-intensity high-frequency electrical stimulation tends to produce a relatively fast onset of reduction in pain that does not long outlast the stimulation period and is not likely related to release of endogenous opioids (Mannheimer and Carlsson, 1979; Watkins and Mayer, 1982). High-intensity low-frequency mechanical (classical acupuncture) or electrical (electroacupuncture or TENS) stimulation tends to reduce pain after a delayed onset, yet outlasts the stimulation period (Mannheimer and Carlsson, 1979). It is this type of somatosensory stimulation that is likely to activate endogenous opioid analgesic mechanisms. The general patterns of somatosensory stimulation and their associated analgesic mechanisms are consistent with reports in the animal literature (Watkins and Mayer, 1982; Han et al., 1984) that suggest that certain types

TABLE 4

Involvement of opioids in TENS analgesia in man

Effects of Naloxone				Effects on β-endorphin			
High-frequency		Low-frequency		High-frequency		Low-frequency	
Lundberg et al., 1985	=	Lundberg et al., 1985	<	O'Brien et al., 1984 (plasma)	=	O'Brien et al.,1984 (plasma)	=
O'Brien et al.,1984	=	O'Brien et al.,1984	=	Hughes et al., 1984 (plasma)	>	Hughes et al., 1984 (plasma)	>
Freeman et al., 1983	=			Facchinetti et al., 1984	>		
Casale et al., 1983	=	Casale et al., 1983	<	Johansson et al., 1980 (CSF)	=		
Willer et al.,1982	=	Willer et al.,1982	<				
Pertovaara, Kemppainen, 1981	=	Pertovaara, Kemppainen, 1982	=				
Sjolund, Eriksson, 1979	=	Sjolund, Eriksson, 1979	<				

<, decrease in analgesia, β-endorphin, or enkephalin level; =, no change; >, increase in analgesia, β-endorphin, or enkephalin

of sensory stimulation either activate opioid or non-opioid systems depending on parameters of stimulation. Moreover, the body areas that are affected by the opioid analgesic mechanism often include those that are remote from the site of TENS or acupuncture stimulation (Mannheimer and Carlsson, 1979; Watkins and Mayer, 1982). A spatially diffuse analgesia would be consistent with a neurohumoral release of β-endorphin from the posterior pituitary, as indicated by Pomeranz et al., (1977). Taken together, the observations of naloxone reversibility, increased CSF levels of β-endorphin (or enkephalin), and a spatially diffuse area of analgesia provide convincing evidence that endogenous opioids can function to modulate pain transmission in man.

Acupuncture and transcutaneous nerve stimulation appear to be forms of counterirritation that activate both opioid and non-opioid systems. The variable clinical outcomes observed following these treatments probably result from differential recruitment of segmental, extra segmental, opioid, and non-opioid pain inhibitory systems, all of which are now known to be activated by these types of stimulation in animals.

The question of actual or potential clinical utility of the various general analgesic mechanisms is another issue altogether. For example, one could question the utility of an endogenous opioid mechanism that has a delayed onset, a highly variable and usually modest efficacy, and perhaps many of the same problems associated with exogenous opioid administration, including tolerance and dependence. Nevertheless, the characterization of physiological mechanisms that underlie various forms of somatosensory stimulation for pain reduction remains of great theoretical and practical importance.

Studies of the biological mechanisms of acupuncture analgesia (AA) in animals

As we have seen from the studies of acupuncture analgesia in man described above, the types of experimentation that can be carried out in humans are often limited by practical and ethical considerations. Thus, although there is evidence for opioid involvement in AA in man, the lines of evidence available are limited. Beginning in the mid-1970s, several groups began to utilize animal models of AA, and a great deal of data has been generated about AA. In this section, I will focus on four issues that I consider of greatest importance about AA in animals. First, I will discuss the issue of animal models of AA. Then, I will discuss the data available about the issue of meridian theory. Next, I will review the considerable evidence indicating a role for endogenous opioids in at least some animal models of AA in animals. Finally, I will briefly discuss the role of a few other biological mechanisms involved in AA, and relate them to other types of environmental analgesias discussed above.

Animal models of acupuncture analgesia

As is the case with all animal models of diseases and treatment modalities, an animal model of AA should be simple, reproducible, intuitively similar to the symptoms in man, and predictive of outcomes in man. Although some of these goals are met in animal models of AA, others are not. For example, although acupuncture is generally used to treat pain of extended duration in man, animal models of AA have utilized almost exclusively acute painful stimuli. Because we now know that chronic pain produces long lasting alterations of the nervous system (Mao et al., 1995), these models may not be the most appropriate.

In general, animal models of AA have utilized electrical stimulation of acupuncture points, because this allows precise description and manipulation of the stimulation parameters. While this is an advantage, it is considerably different from the manual stimulation used in man. In addition, it is not always clear that the intensities of stimulation used in animal studies are comparable to those used in man (Bossut and Mayer, 1991).

Probably the most commonly employed model of AA was developed in the laboratory of Ji-Sheng Han in Beijing (Han et al., 1979). This model utilizes electrical stimulation of varying frequencies to several acupuncture points in the rat or rabbit. The painful stimulus is usually the application of heat to the tail, and the response measured is the latency of tail withdrawal from the heat

source. Even this simple model has generated controversial results when seemingly minor variations are utilized which is not surprising when viewed in the light of the data described above concerning other environmentally induced analgesias. This issue is of some considerable importance with regard to the involvement of endogenous opioids in AA and will be discussed further in the following section.

Scientific evidence about the role of classical meridians in AA

A question that concerned acupuncture researchers beginning in the mid-1970s has been the relationship of classical meridians utilized for acupuncture to Western knowledge of anatomy and physiology. A definitive answer to this question has resulted from experiments in animals and man. Chiang et al., (1973) first addressed this issue by showing that injection of a local anesthetic into deep structures but not subcutaneously under acupuncture points blocked the sensation of De Qi and analgesia in man. This experiment demonstrated the importance of the De Qi sensation. More importantly, it demonstrated that acupuncture must activate the nervous system, probably deep muscle afferents, in order to produce analgesia. Several experiments in animals supported this observation and demonstrated that the critical primary afferents are group II and III fibers from deep structures (Toda and Ichioka, 1978; Pomeranz and Paley, 1979; Lu, 1983). Finally direct nerve recording experiments in man demonstrated that De Qi results from activation of type II and III primary afferent fibers (Wang et al., 1985). Thus, it is activation of the nervous system, not changes in energy flow along meridians, that is critical for the analgesic effects of acupuncture.

Evidence for a role of endogenous opioids in acupuncture analgesia in animals

A considerable body of evidence now exists to support the concept that at least some forms of AA invoke the activation of endogenous opioid systems. This literature is complicated by the fact that, as was the case with EIA discussed above, changes in the stimulation parameters or experimental situation can affect the involvement of endogenous opioids. For example, AA resulting from low frequency (2 Hz) stimulation is antagonized by naloxone, but similar stimulation at high frequency (100 Hz) is not antagonized (Han et al., 1986b). To complicate matters even further, even low frequency AA can only be antagonized if the animals have had repeated exposures to acupuncture stimulation (Bossut and Mayer, 1991). This latter finding suggests that at least some component of the experimental model of AA may resemble the classically conditioned analgesia describe in the section above on EIA. Nevertheless, with these caveats in mind, I will now summarize the lines of evidence indicating a role for endogenous opioids in at least some forms of AA.

Numerous experiments have now demonstrated that opioid antagonists can prevent AA. This has been shown in various species including the mouse (Pomeranz and Chiu, 1976), rat (Han et al., 1986b), and rabbit (Zhou et al., 1981). Several different antagonists in, addition to naloxone, have been shown to be effective, and the effect has been shown to be stereospecific (Cheng and Pomeranz, 1980). Although it is critical to demonstrate opioid antagonist prevention of AA, it has been argued that this is not sufficient evidence to implicate endogenous opioids, because opioid antagonists may have other effects (Hayes et al., 1977). Although this criticism has been blunted somewhat by the large number of antagonists now known to prevent AA, there are several other lines of evidence which implicate endogenous opioids in AA.

Another common criterion invoked to implicate endogenous opioids in various forms of analgesia is the development of tolerance to the analgesic manipulation. This is based on the rationale that if the manipulation produces analgesia by release of endogenous opioids, tolerance should develop to the endogenous opioids as it does to administration of exogenous opioids. Indeed, tolerance to AA has been demonstrated (Han et al., 1986a). The related phenomenon of cross-tolerance with other opioid analgesias has also been shown to occur (Han et al., 1981; Han and Xie, 1984). It should be pointed out that this observation is at odds with the usual

(Han et al., 1979) reduces AA. Also, AA is reduced by administration of the serotonin receptor antagonist cinnanserin (Han et al., 1979; Cheng and Pomeranz, 1981). Increasing serotonin levels by giving its precursor 5-HTP increases AA (Cheng and Pomeranz, 1981). There is considerably less data available concerning the role of catecholamines in AA, but in general these transmitters are considered to be antagonistic to AA (Cheng and Pomeranz, 1981).

Following the reports that CCK antagonizes opioid forms of EIA and morphine analgesia and is involved in the development of tolerance to these analgesic effects (Watkins et al., 1984; Watkins and Mayer, 1986), Ji-Shen Han's laboratory did a series of experiments showing a parallel involvement of CCK in AA. They showed that Intracerebroventricular or intrathecal administration of CCK antagonized AA and that CCK antiserum reversed the development of tolerance to AA (Han et al., 1985; Han et al., 1986a). In addition, they have shown that animals that are low responders to AA can be converted into high responders by administration of an antisense oligonucleotide to CCK mRNA (Tang et al., 1997).

All of the above should make it clear that acupuncture analgesia is probably a subset of analgesias under the general rubric of counter irritation analgesia. Taken together, these findings indicate a wealth of knowledge as well as a wealth of complexity involved in the neural mechanisms of counterirritation and acupuncture analgesia. Perhaps the most important point to be made is that a single neural mechanism underlying these phenomena is unlikely. Rather, it appears that the particular parameters of stimulation such as frequency, intensity, and duration determine which of several neural systems are activated. Varying parameters of stimulation are likely to activate several of these systems to varying degrees. This fact makes careful control of stimulation parameters essential for the study, comparison, and clinical use of these modalities.

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