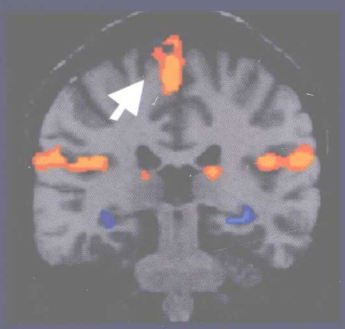
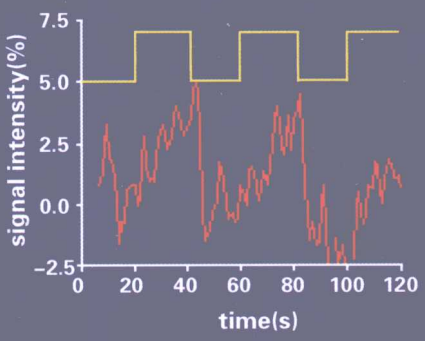
THE NEUROCHEMICAL BASIS OF PAIN RELIEF BY ACUPUNCTURE

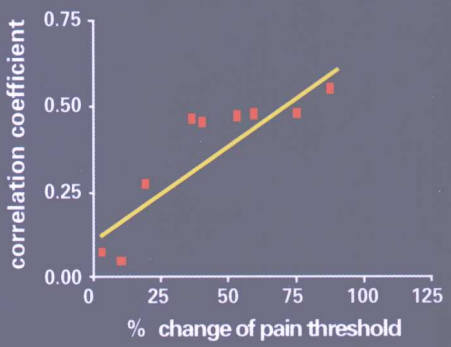
针刺镇痛的神经化学基础

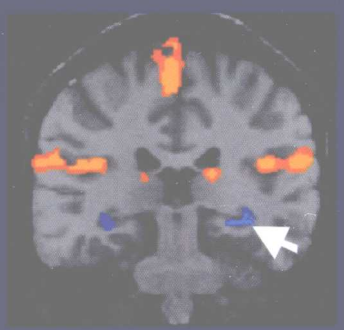
Volume 3 (1997–2006)

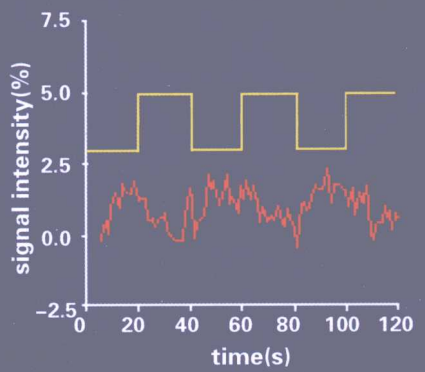
Ji-Sheng Han

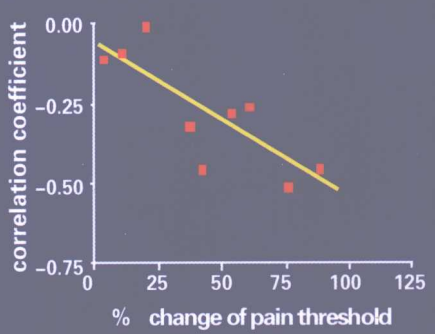












北京大学医学出版社
Peking University Medical Press

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图书在版编目（CIP）数据

针刺镇痛的神经化学基础=The Neurochemical Basis of Pain Relief by Acpuncture. Volume 3 (1997-2006).
第3卷：英文/韩济生编著. —北京：北京大学医学出版社，2007.12
ISBN 978-7-81116-349-0

Ⅰ. 针… Ⅱ. 韩… Ⅲ. 针刺麻醉—神经化学—文集—英文 Ⅳ. R246.2-53

中国版本图书馆CIP数据核字（2007）第154936号

The Neurochemical Basis of Pain Relief by Acupuncture
针刺镇痛的神经化学基础 Volume 3 (1997-2006)

编　　著：韩济生
出版发行：北京大学医学出版社（电话：010-82802230）
地　　址：（100083）北京市海淀区学院路38号 北京大学医学部院内
网　　址：http://www.pumpress.com.cn
E-mail：booksale@bjmu.edu.cn
印　　刷：北京佳信达艺术印刷有限公司
经　　销：新华书店
责任编辑：药　蓉　　**责任校对**：金彤文　　**责任印制**：张京生
开　　本：880mm×1230mm　1/16　**印张**：43　　**字数**：1130千字
版　　次：2008年1月第1版　2008年1月第1次印刷　　**印数**：1-2500册
书　　号：ISBN 978-7-81116-349-0
定　　价：128.00元

本书由
北京大学医学部科学出版基金
资助出版

PREFACE

The neurochemical basis of pain relief by acupuncture is a book series reflecting the achievement of the research work going on in the Neuroscience Research Institute, Peking University since 1965. The volume one was published in 1987, collecting the papers published in the period of 1973–1987. This was followed by the second edition recruiting papers published in the period of 1987–1997, in which the research field had been broadened to include acupuncture treatment of drug addiction as well as a small part for the opioid modulation of cardiovascular activities. The current volume (volume 3) collected papers published in the recent 10 years (1997–2006). The scope of research was further broadened to the study of acupuncture treatment of Parkinson's disease and obesity. However, since the mainstream of research was still in the field of studying the mechanisms of pain and pain control, the title of the book was kept unchanged, at least in the current volume. Also remained is the tradition that all the contents are in English, for the convenience of those who use English as their mother language, or are using English as the language for absorbing scientific nutrients.

The publication of this book marked the progress of acupuncture research in this laboratory one decade after the historical landmark of the NIH Consensus Conference on Acupuncture held in Bethesda, MD in Nov 3–5, 1997. Several trends can be seen from the content: (a) a shift of effort from acute pain to chronic pain in the study of acupuncture analgesia; (b) a shift of effort from physical dependence to psychic dependence in the study of drug abuse; (c) a shift of effort from CCK to OFQ and nocistatin in the study of antiopioid peptides; (d) a consistent and in depth study on the functional balance between opioids and antiopioids in the CNS, a virtual example of Yin-Yang balance; (e) the use of the state-of-the-art technology, including functional MRI, ERP, multi-channel intracranial electrodes recording, etc. for the study of the flow of information in the brain network; (f) more sophisticated study on the neurochemical pathways mediating frequency-dependent activation of the endogenous neuropeptides; (g) more evidence of clinical efficacy of the Han's Acupoint Nerve Stimulator (HANS) for pain treatment and for the prevention of relapse to drug abuse.

It should be stressed that all these efforts trying to elucidate the mechanisms of action of acupuncture have been connected with the final goal of making acupuncture as a more widely used medical technique for the good of mankind all over the world. In this context, two pictures were presented to acknowledge two exciting moments separated by one decade. Fig. 1 demonstrates the moment when the editor was giving a talk at the Consensus Conference on Acupuncture in 1997 in Bethesda, MD, USA. Indeed, it was after this conference that acupuncture was formally recognized by the western medical community as well as by the insurance system of the developed countries. Fig. 2 marked another exciting moment on Oct 14, 2007 when a press was held in Beijing on the occasion of the opening of the annual conference of the Chinese Association for the Study of Pain (CASP), when officers from the Ministry of Health of the PRC an-

nounced the inauguration of Department of Pain Management in major hospitals in China. In his congratulation letter to CASP, Dr. TS Jensen, the president of the International Association for the Study of Pain (IASP) wrote: "In this respect China may be a leading example for other countries to follow to advance pain treatment throughout the world."

In compiling this book, there are so many familial faces appeared in my memory, most of them are my colleagues and students. Ten years are a short period of time, compared with the 3000 years of history for acupuncture. But we are proud of having the opportunity to provide our contribution, albeit small, during this critical period of time for the development of this brilliant medical achievement of the mankind.

The financial support provided by the National Natural Science Foundation of China (NNSFC), the Ministry of Science and Technology and the Ministry of Public Health of China, the National Institute of Drug Abuse (NIDA), and the National Center for Complementary and Alternative Medicine (NCCAM), NIH, USA as well as the support from the Wu Jie Ping Medical Foundation of China, are highly appreciated.

The publication of this book would be impossible without the enthusiastic help provided by the Peking University Medical Press.

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of Pain (CASP)
Oct 30, 2007

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1

OVERVIEW

1.1 Acupuncture activates endogenous systems of analgesia

Ji-Sheng Han, M.D.

Introduction

Although acupuncture has been used in China for more than 2,000 years, the study of its mechanisms of action is a recent issue. To rule out the immediate concern that hypnotic-type suggestibility may play a key role in the therapeutic effect of acupuncture. Animal experimentation is indispensable. In the long history of evolution, the brain has developed complex systems for modulating (diminishing or augmenting) pain perception. Notably, the opioid (morphine-like) system and nonopioid analgesic system (e.g., the monoamine neurotransmitters) suppress pain perception, whereas the antiopioid system (e.g., cholecystokinin [CCK]) works against opioid analgesia. By activating the endogenous systems of analgesia, acupuncture is able to lessen the pain to a degree that is clinically significant and applicable.

Animal Models for Acupuncture-Induced Analgesia

Animals. Although monkeys and cats are closer to humans, rabbits and rats are the most frequently used animals in most studies published so far. Comparative anatomy is used to determine the site for the insertion of a needle corresponding to the point for acupuncture ("acupoint") of humans.

Pain modalities. Pain can be classified as acute (caused by wound, surgical trauma, etc.) or chronic (caused by inflammation, nerve injury, etc.). In animal experiments, what is measured is not subjective feeling; rather, it is the objective reactions to "painful" (noxious) stimuli, manifested as escape behavior or vocalization. Nociceptive responses can be induced by heat and mechanical, chemical, electrical, and other stimuli that mimic acute pain. Chronic pain can be induced by nonbacterial inflammation or nerve injury (partial ligation or complete severance). A lowering of the pain threshold or an exaggerated pain behavior (hypersensitization) indi cates the existence of chronic "pain". Compared with acute pain models, chronic pain models are obviously closer and more relevant to most clinical situations.

Method of acupuncture. Manual twisting of the needle, the classical means of acupuncture, has often been replaced by electroacupuncture (EA), whereby electrical pulses are administered via stainless steel needles inserted through the skin into the deep tissues. The intensity (1 to 3 mA), pulse-width (0.2 to 1.0 ms), and frequency (1 to 100 Hz) can thus be precisely determined. A further modification is to use skin electrodes applied on the acupoints to replace the needles, which is called "acupoint nerve stimulation" (ANS), or "acupuncture without a needle", which is technically close to "transcutaneous electrical nerve stimulation" (TENS), although the principle and rationale of the two therapeutic methods are essentially different.

Acupuncture Activation of Endogenous Opioid Systems

Twenty years after the publication of the first biochemical evidence for the existence of opioid receptors by Pert and Snyder in 1973, the delta opioid receptor was cloned independently in 1992 by Evans and colleagues in the United States and Kieffer and colleagues in France, followed by the cloning of mu and kappa opioid receptors in 1993. On the other hand, five different kinds of opioid peptides have been characterized in the recent two decades (1975 to 1997). The possible relation of opioid peptides and opioid receptors with acupuncture-induced analgesia (AA) is listed in the following table (Table 1).

The involvement of opioid peptides and opioid receptors in AA has been studied from different approaches, for example, (1) blockade of the effect of AA by opioid receptor antagonists, including the universal opioid antagonist naloxone (Pomeranz, Chiu, 1976; Mayer, Price, Rafii, 1977) and selective mu, delta, or kappa receptor antagonists (Chen, Han, 1992; Han, Wang, 1992); (2) blockade of AA by microinjection of an antibody against enkephalin, β-endorphin, or dynorphin into the central nervous system (CNS) (Han, Xie, Zou, et al., 1982); (3) measurement of the release of opioid peptides in brain and spinal cord during and following EA stimulation (Han, Chen, Sun, et al., 1991), and the like.

An important finding was that the ability of EA to accelerate the release of endogenous opioids in CNS depends, among other things, on the frequency being used. The 2-Hz EA increased the release of β-endorphin in the brain and enkephalin in the whole CNS, whereas 100-Hz EA increased the release of dynorphin in the spinal cord. This finding, originally discovered in rats (Fei, Xie, Han, 1987) has been verified in humans (Han, Chen, Sun, et al., 1991). In a recent study, the neural pathways for 2-Hz and 100-Hz EA stimulation have been worked out

Table 1

Opioid peptide	Aminoacid residues	Year discovered	Opioid receptor matching	Optimal frequency	Site of action	
					Brain	Cord
Enkephalin	5	1975	delta>mu	2-Hz	++	++
β-Endorphin	31	1976	delta=mu	2-Hz	+++	+
Dynorphin	17	1979	kappa	100-Hz	+	+++
Orphanin FQ	17	1995	ORL1	100-Hz	(-)	+(antiopioid)
Endomorphin	4	1997	mu	?	++	+++

(Guo, Fang, Wang, 1996a, 1996b). Thus, by turning the dial of the stimulator, one could differentially control the release of three kinds of opioid peptides. To accelerate the release of all three kinds of opioid peptides, one could use the "dense-and-disperse" wave, that is, 2-Hz for 3 seconds followed by 100-Hz for 3 seconds, shifting back and forth automatically (Chen, Guo, Chang, Han, 1994). This wave form results in the simultaneous release of all three kinds of opioid peptides. The synergistic interaction between the opioid peptides (Huang, Ren, Lu, Han, 1987) can produce a most potent analgesic effect.

Orphanin FQ was a newly cloned (1995) opioid peptide that seemed to play an antagonistic role against opioid analgesia (Tian, Xu, Fang, et al., 1997a; Tian, Xu, Zhang, et al., 1977b). A novel opioid peptide, endomorphin, reported by Zadina and colleagues in 1997, is a small peptide with high selectivity for the mu receptor. Its possible role in AA has yet to be determined.

The Role of Monoamines: Serotonin, Dopamine, and Noradrenaline

Most of the serotonin (5-HT) existing in the CNS stems from neurons aggregated along the midline of the brain. Blocking the biosynthesis of 5-HT by pCPA, destruction of the 5-HT neurons by 5,6-DHT, or blockade of 5-HT receptors by cinnanserine led to a marked reduction of AA, suggesting the importance of 5-HT in the mediation of AA, both in the brain and the spinal cord (Han, Chou, Lu, et al., 1979). The receptors involved were 5-HT_{1A} and 5-HT_{1C2} (Xu, Qiu, Han, 1994). In contrast to 5-HT, catecholamines (dopamine [DA] and noradrenaline [NA]) play different roles in different parts of the CNS; that is, they antagonize AA in the brain and potentiate AA in the spinal cord (Xie, Tang, Han, 1981).

Antiopioid Peptides: Cholecystokinin and Orphanin FQ

One of the basic principles of Chinese traditional medicine (TCM) is that everything can be divided into two, and overactivation of one part inevitably leads to a corresponding change on the counterpart of the system. A delicate balance between the two parts is symbolized as Yin and Yang. In the study of AA, it was found that prolonged acupuncture or EA stimulation for several hours produces a gradual decrease of the analgesic effect, which was titled "acupuncture tolerance". It simulates the development of morphine tolerance after its repeated injection (Han, Lin, Tang, 1981). Detailed studies revealed that prolonged EA stimulation accelerated the production and release of the peptide CCK that works against opioid effect (Zhou, Sun, Han, 1993). The cellular and molecular mechanisms of the antiopioid effect of CCK have been elucidated (Han, 1995). In the rat experiment, acupuncture tolerance can be prevented or reversed by intracerebroventricular (icv) injection of CCK antiserum that prevents CCK from binding to its receptor (Han, Ding, Fan, 1986). The results suggest that (1) the use of EA for a single treatment should not exceed 1 hour and that (2) CCK antagonist may be useful in preventing the development of acupuncture tolerance.

Another interesting phenomenon is the individual variation in the effect of AA. About two-thirds of the animals are high responders (increase of pain threshold more than 60 percent), and one-third are low responders (pain threshold changes less than 60 percent). The mechanisms of being a low responder are at least twofold: (1) a low level of opioid peptides is released in the CNS (Fei, Xie, Han, 1987) and (2) a high level of CCK is released in response to EA stimulation (Liu SX, et al., unpublished). Recent studies have revealed that a low-responder rat can be changed into a high responder if the CCK gene expression is suppressed by the antisense technology (Tang, Dong, Wang, et al., 1997). The CCK-B antagonist L-365260, a product of Merck Sharp Dohme, now available only for experimental use, could be taken as an adjunct for acupuncture treatment once it is clinically available, so that even a low responder can benefit from acupuncture treatment.

It is interesting to note that the newly cloned peptide orphanin FQ (OFQ) may perhaps be categorized into the antiopioid family because icv injection of OFQ dose dependently attenuated both morphine analgesia (Tian, Xu, Wang, et al., 1997a) and AA (Tian, Xu, Zhang, et al., 1997b) and icv injection of antisense RNA complementary to OFQ receptor, which reduces the

number of OFQ receptors, produced a marked potentiation of EA analgesia (Tian, Xu, Zhang, et al., 1997b).

Conclusions

Acupuncture is a kind of medical technique whereby a moderate degree of peripheral stimulation can cause a maximal activation of the endogenous systems of analgesia that form the physiological and neurochemical mechanisms of AA. Because this is a kind of physiological modulation, the effect of acupuncture can only reduce rather than abolish pain. Although properly managed acupuncture produces little aversive side effects, it should not be used too often to avoid the development of tolerance. The efficacy of AA may be further improved by modulating the delicate balance between opposing neurochemical factors.

Future Research

Study on chronic pain. Most of the knowledge about AA in animal experiments today was obtained in acute pain models. It was only recently that the effect of acupuncture on chronic pain was observed. Preliminary results have shown that the optimal parameters of EA (intensity, frequency, spacing of multiple treatments, etc.) for the treatment of chronic pain are different from those for acute pain, which requires further investigation.

A combination of acupuncture with drugs. By combining acupuncture with certain analgesic or anesthetic drugs, it is possible to achieve a state of complete analgesia, with the amount of drug reduced to as little as 50 percent of normal dosage, thereby reducing the unwanted side effects of the analgesics or anesthetics (Han, 1996).

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Acknowledgment: This work is supported by NIDA grant DA 03983 and a grant from the National Natural Science Foundation of China.

1.2 Acupuncture anesthesia (AA) versus acupuncture-assisted anesthesia (AAA)

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It has been four decades since the first use of acupuncture for anesthetic purpose ("acupuncture anesthesia", AA) in surgical operations in the late 1950s. It was certainly unique in the whole history of acupuncture medicine to have thousands of hospitals involved in such a large scale clinical practice in millions of operations. After 4 decades of clinical operations it is the right time to look back the whole process and see what we could learn from the past and what we should do in the future.

1. Acupuncture-induced analgesia is the key for AA. Acupuncture has a wide range of physiological and therapeutic effects on human body. To fulfill the requirement of anesthesia for surgical operations the analgesic effect produced by acupuncture is obviously of first place importance as compared to the other therapeutic effects such as the stabilizing effect of cardiovascular functions, the enhancement of immunological functions, etc..

2. Acupuncture-induced analgesia is not strong enough to completely block the sharp acute pain produced by surgical procedures. This is reasonable, since (1) pain induced by traumatic stimulation is a bio-warning mechanism which is of ultimate importance for the survival of an organism in order to react with fight or flight; (2) this bio-warning system may subject to mild modifications (weakening or sensitization) but is certainly resistant to any attempt for its total abolishment unless under anesthetic intervention. In fact a loss of pain sensation is considered as a disease; (3) the efficacy of acupuncture can not be strengthened by the unlimited increase of stimulation intensity since this would by itself result in the production of server pain which is not acceptable for the patient; (4) acupuncture-induced analgesia can be augmented by the use of some non-analgesic substances in an attempt to slow down the degradation of endogenous opioids peptides, to prolong the synaptic activity of 5-HT, to block the receptors of dopamine and CCK, etc., yet it is still difficult, if not impossible, to produce a complete analgesia against surgical procedures.

3. Acupuncture or related techniques can reduce the surgically induced pain by half. It has been a difficult task to provide a quantitative estimate of the degree of acupuncture-induced analgesia. In the 1960s, people used to estimate the success of AA by a 4 score system with score 1 as "essentially no pain", which is obviously an arbitrary subjective scaling rather than an objective quantitative estimate. Another approach was to use anesthetics (epidural, inhalation, intravenous, etc.) to ensure a complete analgesia and to assess the reduction of the amount of anesthetics consumed in the AA group as compared to the control group without acupuncture or related treatment. Wang BG and his colleagues (1994) in the Beijing Tiantan Hospital used the Han's Acupoint Nerve Stimulator (HANS) in combination with the inhalation anesthetic enfluran for cranial operations and found a profound reduction of 45% to 48% of enfluran consumption as compared to the control group without HANS treatment. Qu GL and his colleagues (1996) of the Shanghai First People's Hospital combined electroacupuncture (EA) with epidural anesthesia for kindney transplantation resulting in a reduction of epidural anesthetics by 48%. Qin BG of the Chengdu TCM college and colleagues (1996) in a multicenter study combined EA with epidural anesthesia showed a reduction of the dose of lidocaine by 40%–46% as compared to the group using lidocaine alone without EA. In a recent study Wang BG in collabration with Paul White (1996) in the South West University of Texas, USA used HANS in combination with patient-controlled analgesia (PCA) for control of the post-operative pain recorded a 54% reduction of hydromorphone for satisfactory analgesia. It is interesting to mention that in the rat experiment, the analgesic effect produced by EA of 100 Hz for 30 min was roughly equivalent to 4 mg/kg of morphine (the full dose of morphine in the rat is 8–10 mg/kg for strong analgesic effect). Taking all the data together one can estimate that the analgesic effect induced by EA of HANS is equivalent to half of the full dose of narcotic analgesics. In other words, it is not feasible to use acupuncture or EA only without the supplement of anesthetics in order to achieve a satisfactory anesthesia/analgesia.

4. The benefit of using acupuncture in combination with anesthetics. What then is the rational of using acupuncture if its efficacy is only equivalent to half of