Neuroscience Letters

Mini-review

Acupuncture and endorphins[☆]

Ji-Sheng Han[*]

Neuroscience Research Institute, Peking University and Key Laboratory of Neuroscience (Peking University), Ministry of Education, 38 Xue-Yuan Road, Beijing 100083, PR China

Abstract

Acupuncture and electroacupuncture (EA) as complementary and alternative medicine have been accepted worldwide mainly for the treatment of acute and chronic pain. Studies on the mechanisms of action have revealed that endogenous opioid peptides in the central nervous system play an essential role in mediating the analgesic effect of EA. Further studies have shown that different kinds of neuropeptides are released by EA with different frequencies. For example, EA of 2 Hz accelerates the release of enkephalin, β-endorphin and endomorphin, while that of 100 Hz selectively increases the release of dynorphin. A combination of the two frequencies produces a simultaneous release of all four opioid peptides, resulting in a maximal therapeutic effect. This finding has been verified in clinical studies in patients with various kinds of chronic pain including low back pain and diabetic neuropathic pain.
© 2003 Elsevier Ireland Ltd. All rights reserved.

Keywords: Acupuncture; Electroacupuncture; Opioid peptides; Pain; Analgesia

Scientific studies using modern technology on acupuncture in China began in the late 1950s when acupuncture was found to be able to successfully ameliorate pain produced by surgical procedures. An interesting finding was that manipulation of a needle in the acupoint of the volunteers produced a slow increase of the skin pain threshold, reaching the peak in 30 min, followed by an exponential decay after the removal of the needle [24]. The involvement of some chemical mediators was suggested. This hypothesis was validated by a CSF cross-infusion study in which the cerebroventricular fluid obtained from the donor rabbit subjected to acupuncture stimulation was infused to the third ventricle of a naive recipient rabbit. A transference of the analgesic effect from the donor to the recipient rabbit was observed [25], a phenomenon which may be interpreted as chemical mediation of electroacupuncture (EA) analgesia. Prior to the discovery of endogenous opioids, we focused on various candidate neurotransmitters including monoamines, and found that serotonin (5-HT) was most important among classical neurotransmitters for the mediation of acupuncture analgesia [12].

The discovery of endogenous opioid peptides enhanced the study of the mechanisms of acupuncture-induced analgesia. The opioid receptor antagonist naloxone was used as a pharmacological tool for the study of the mechanisms of EA. Mayer et al. [21] and Pomeranz and Chiu [23] were among the first to show that acupuncture-induced analgesia can be blocked by naloxone both in humans and in mice, suggesting the participation of endogenous opioids. Further studies [2] revealed that naloxone can only block the analgesic effect induced by EA of low frequency (4 Hz), but not that of high frequency (200 Hz), suggesting that low- rather than high-frequency stimulation triggers the release of opioid peptides. This was in direct contrast with the hypothesis summarized by Hokfelt in 1991 [19] that central neuropeptides can be released only by high-frequency but not low-frequency stimulation.

The discovery of enkephalin in 1975 was soon followed by that of β-endorphin in 1976 and dynorphin in 1979. There was a long lapse before the discovery of the fourth endogenous opioid peptide, the endomorphin, in 1997. While the endomorphin was considered as the pure μ opioid receptor agonist [27] and dynorphin the relatively pure κ opioid agonist [3], the enkephalin and β-endorphin were mixed μ and δ opioid receptor agonists. Based on differences in the IC50 of naloxone toward different types of opioid receptors we found that both low- and high-frequency EA analgesia were naloxone reversible; the key factor was the dosage. Thus, the ID50 of naloxone for blockade of the analgesic effect produced by 2, 15 and 100 Hz EA analgesia was found to be 0.5, 1.0 and 20 mg/kg, respectively [14]. This result suggests that the analgesia induced by 2 Hz EA was mediated by the μ receptor and that of 100 Hz EA by κ opioid receptors. This conclusion was verified later by the use of subtype specific opioid receptor antagonists [5]. The direct evidence was obtained

by measuring the neuropeptide release in the central nervous system triggered by EA of different frequencies. Rats were given EA at 2, 15 or 100 Hz, using radiant heat-induced tail flick latency (TFL) as the endpoint of nociception. Perfusion of the subarachnoid space of the spinal cord was performed and the perfusate was collected in 30 min intervals before or during the EA stimulation. Radioimmunoassay was used to measure the contents of met-enkephalin and dynorphin A and B [8]. Results shown in Fig. 1 show that 2 Hz EA produced a 7 fold increase in met-enkephalin but not dynorphin A. In contrast, 100 Hz EA produced a 2 fold increase in the release of dynorphin A but not met-enkephalin. A parallel change was revealed for both dynorphin A and dynorphin B immunoreactivity (data not shown). EA of 15 Hz produced a partial activation of both enkephalins and dynorphins. No increase in endogenous opioid release was observed in non-responder rats that did not show any increase in TFL after EA stimulation [8].

Further studies have shown that β-endorphin [18] and endomorphin [17] share similar characteristics of a stimulation-induced release profile as enkephalin, i.e. preferable to 2 Hz stimulation, leaving dynorphin as the only opioid peptide responsive to high-frequency stimulation [15,16]. While there was a general consensus that μ and δ opioid receptor agonists possess an analgesic effect, controversy remains on whether dynorphin is analgesic [15, 22] or hyperalgesic [1,20]. Chavkin et al. reported that dynorphin showed a very potent opioid effect on guinea pig ileum assay, but was not analgesic when injected into the brain [3]. Han [15] and Piersey [22] were the first to show that dynorphin is analgesic when injected intrathecally into the subarachnoid space of the spinal cord of rats or mice. They also warned that dynorphin has a paralytic effect at higher doses. Care should be taken to differentiate the naloxone-resistant, non-opioid paralytic effect from the naloxone-reversible analgesic effect. Therefore, it is critical to see whether analgesia can be produced by accelerating the production and release of the endogenous dynorphin [13,

16]. Cheng et al. [6] reported that dynorphin synthesis is under the control of a "down stream regulatory element with antagonistic modulation" (DREAM), a transcriptional repressor acting constitutively to suppress prodynorphine gene expression. Knocking out DREAM increases dynorphin expression, resulting in a profound reduction in pain behavior in animal models of acute, inflammatory and neuropathic pain [7]. This gives strong support to the hypothesis that endogenously released dynorphin is indeed analgesic rather than hyperalgesic or paralytic (Fig. 2).

From Fig. 2 it is obvious that a sharp demarcation seems to exist between the 2 Hz side and the 100 Hz side. In a chart with a log scale, 15 Hz is in the middle point between 2 and 100 Hz, which can partially activate both sides. In order to maximize the analgesic effect, EA with alternating 2 and 100 Hz (dense and disperse, DD) mode of action is used. Thus, the two electrodes of stimulation can be applied on two acupoints transcutaneously or percutaneously and connected to a pulse generator which emits square waves of 2 Hz for 3 s and then automatically shifts to 100 Hz for 3 s. The analgesic effect induced by this DD mode of stimulation was found to be significantly more effective than the pure low- or pure high-frequency stimulation [4]. This concept of simulation pattern is now accepted by clinicians and is widely used in most EA devices.

A question arises that if the brain can perceive alternative 2 and 100 Hz (2/100) electrical stimulation for the differential release of enkephalin and dynorphin, respectively, could we use 2 Hz stimulation on one hand and 100 Hz on the other hand (2 + 100) simultaneously and continuously, so that enkephalin and dynorphin can be released simultaneously in a full extent? This was tested in a rat experiment. Two possibilities existed. One is that the brain can differentiate the two frequencies clearly and separately, so that both enkephalin and dynorphin are released simultaneously. The other is that signals from the two sites of stimulation are merged in the reticular formation so that they are perceived as 102 Hz, which is almost indistinguishable from 100 Hz. As a result, only dynorphin will be released. Since it has been proved that 2 Hz
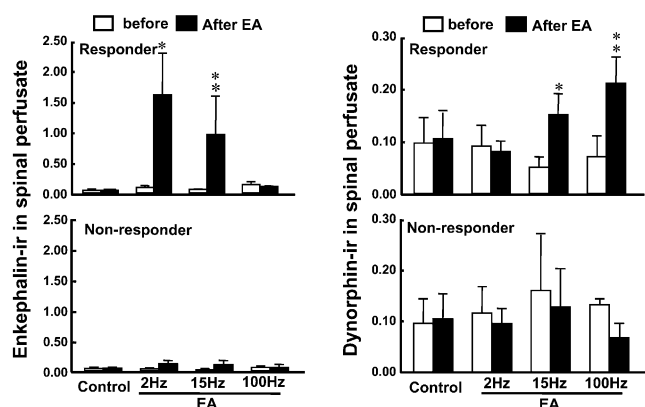

Fig. 1. The effect of EA of different frequencies on the content of ir-enkephalin and ir-dynorphin in the spinal perfusate of responder and non-responder rats [8].
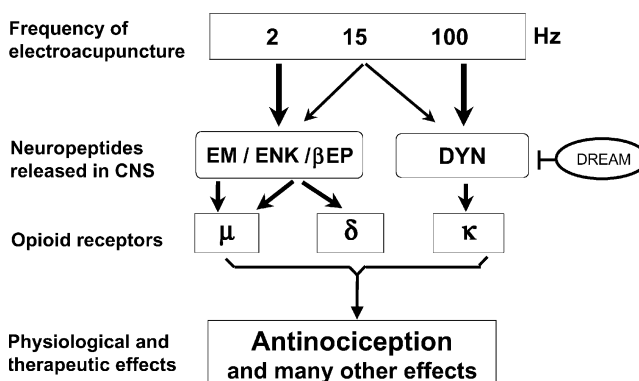

Fig. 2. Schematic diagram showing the opioid mechanisms of EA-induced analgesia.
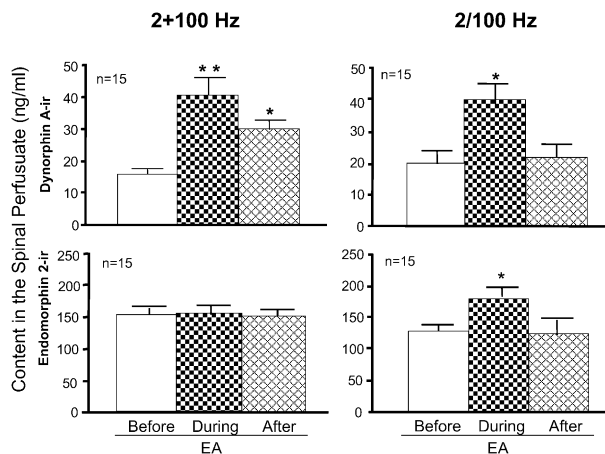
Fig. 3. A combination of electrical stimulation of different frequencies may produce different profiles of neuropeptide release. "2/100 Hz" stands for an alternative mode of stimulation where 2 Hz is alternating with 100 Hz, each lasting for 3 s. "2 + 100 Hz" is a mode of stimulation where 2 Hz stimulation is applied on the left hindleg and 100 Hz on the right hindleg. Perfusate from the spinal subarachnoid space was used for radioimmuno-assay of met-enkephalin and dynorphin A [26].

EA can activate enkephalin, β-endorphin and endomorphin simultaneously, we used endomorphin as a representative marker in the present study. Some of the results are depicted in Fig. 3. As was predicted, 2/100 Hz stimulation increased the release of both dynorphin and endomorphin, whereas 2 + 100 Hz stimulation increased the release of only dynorphin, but not endomorphin. In other words, 2 + 100 stimulation does not seem to carry the pure 2 Hz information [26]. It is thus obvious that a proper combination of different frequencies may produce a maximal release of a cocktail of neuropeptides for better therapeutic effects.

The findings obtained from experimental animals need to be confirmed in humans in clinical practice. White and his colleagues at the University of Texas Southwestern Medical Center of the United States have performed a series of studies to assess whether electrical stimulation of the alternative mode would produce a significantly stronger analgesic effect than that produced by stimulation of fixed frequency. Taking the reduction of the post-operative requirement of opiate dosage as an index for analgesia, they have revealed that the alternative mode stimulation reduced the morphine requirement by 53%, whereas a constant low (2 Hz) or constant high (100 Hz) frequency produced only a 32% or 35% decrease, respectively [10]. Similar results were obtained in clinical studies on low back pain [9] and diabetic neuropathic pain [11].

In conclusion, study on the mechanisms of acupuncture effects has led to a major finding in neuroscience that neuropeptides in CNS can be mobilized by electrical stimulation of different frequencies applied at peripheral sites. Details of the interface between electrical coding and chemical coding and the potential clinical application of these findings deserve further investigation.

References

[1] R.M. Caudle, A.J. Mannes, Dynorphin: friend or foe?, Pain 87 (2000) 235–239.

[2] R. Chang, B. Pomeranz, Electroacupuncture analgesia could be mediated by at least two pain-relieving mechanisms: endorphin and non-endorphin systems, Life Sci. 25 (1979) 1957–1962.

[3] C. Chavkin, L.F. James, A. Goldstein, Dynorphin is a specific endogenous legend of the κ-opioid receptor, Science 215 (1982) 413–415.

[4] X.H. Chen, S.F. Guo, C.G. Chang, J.S. Han, Optimal conditions for eliciting maximal electroacupuncture analgesia with dense and disperse mode stimulation, Am. J. Acupunct. 22 (1994) 47–53.

[5] X.H. Chen, J.S. Han, All three types of opioid receptors in the spinal cord are important for 2/15 Hz electroacupuncture analgesia, Eur. J. Pharmacol. 211 (1992) 203–210.

[6] H.Y.M. Cheng, G.M. Pitcher, S.R. Laviolette, I.Q. Whishaw, K.I. Tong, L.K. Kocheritz, T. Wada, N.A. Joza, M. Crackower, J. Goncalves, I. Sarosi, J.R. Woodgette, A.J. Oliveira-dos-Santos, M. Ikura, D. van der Kooy, M.W. Salter, J.M. Penninger, DREAM is a critical transcriptional repressor for pain modulation, Cell 108 (2002) 31–43.

[7] M. Costigan, C.J. Woolf, No DREAM, no pain. Closing the spinal gate, Cell 108 (2002) 297–300.

[8] H. Fei, G.X. Xie, J.S. Han, Low and high frequency electroacupuncture stimulation release met-enkephalin and dynorphin A in rat spinal cord, Sci. Bull. China 32 (1987) 1496–1501.

[9] E.A. Ghoname, W.F. Craig, P.F. White, H.E. Ahmed, M.A. Hamza, B.N. Henderson, N.M. Gajraj, P.J. Huber, R.J. Gatchel, Percutaneous electrical nerve stimulation for low back pain: a randomized crossover study, J. Am. Med. Assoc. 281 (1999) 818–823.

[10] M.A. Hamza, P.F. White, H.E. Ahmed, E.A. Ghoname, Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile, Anesthesiology 91 (1999) 1232–1238.

[11] M.A. Hamza, P.F. White, W.F. Craig, E.S. Ghoname, H.E. Ahmed, T.J. Proctor, C.E. Noe, A.S. Vakharia, N. Gajraj, Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain, Diabet. Care 23 (2000) 365–370.

[12] J.S. Han, P.H. Chou, C.H. Lu, T.H. Yang, L.H. Lu, M.F. Ren, The role of central 5-HT in acupuncture analgesia, Sci. Sin. 22 (1979) 91–104.

[13] J.S. Han, X.H. Chen, S.L. Sun, X.J. Xu, Y. Yuan, S.C. Yang, J.X. Han, L. Terenius, Effect of low- and high-frequency TENS on met-enkephalin-Arg-Phe and dynorphin A immunoreactivity in human lumbar CSF, Pain 47 (1991) 295–298.

[14] J.S. Han, X.Z. Ding, S.G. Fan, The frequency as the cardinal determinant for electroacupuncture analgesia to be reversed by opioid antagonists, Acta Physiol. Sin. 38 (1986) 475–482.

[15] J.S. Han, C.W. Xie, Dynorphin: potent analgesic effect in spinal cord of the rat, Life Sci. 31 (1982) 1781–1784.

[16] J.S. Han, G.X. Xie, Dynorphin: important mediator for electroacupuncture analgesia in the spinal cord of the rabbit, Pain 18 (1984) 367–376.

[17] Z. Han, Y.H. Jiang, Y. Wan, Y. Wang, J.K. Chang, J.S. Han, Endomorphin-1 mediates 2 Hz but not 100 Hz electroacupuncture analgesia in the rat, Neurosci. Lett. 274 (1999) 75–78.

[18] C.M. He, J.S. Han, Attenuation of low rather than high frequency electroacupuncture analgesia following microinjection of β-endor-

phin antiserum into the periaqueductal gray in rats, Acupunct. Sci. Int. J. 1 (1990) 19–27.

[19] T. Hokfelt, Neuropeptides in perspective: the last ten years, Neuron 7 (1991) 867–879.

[20] T.M. Laughlin, A.A. Larson, G.L. Wilcox, Mechanisms of induction of persistent nociception by dynorphin, J. Pharmacol. Exp. Ther. 299 (2001) 6–11.

[21] D.J. Mayer, D.D. Price, A. Rafii, Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone, Brain Res. 121 (1977) 368–372.

[22] M.F. Piercey, K. Varner, L.A. Schroeder, Analgesic activity of intraspinally administered dynorphin and ethylketocyclazocine, Eur. J. Pharmacol. 80 (1982) 283–284.

[23] B. Pomeranz, D. Chiu, Naloxone blocks acupuncture analgesia and causes hyperalgesia: endorphin is implicated, Life Sci. 19 (1976) 1757–1762.

[24] Research Group of Acupuncture Anesthesia, Peking Medical College, Effect of acupuncture on the pain threshold of human skin, Natl. Med. J. China 3 (1973) 151–157.

[25] Research Group of Acupuncture Anesthesia, Peking Medical College, The role of some neurotransmitters of brain in acupuncture analgesia, Sci. Sin. 17 (1974) 112–130.

[26] Y. Wang, Y. Zhang, W. Wang, Y. Cao, J.S. Han, New evidence for synergistic analgesia produced by endomorphin and dynorphin, Chin. J. Pain Med. 8 (2002) 118–119.

[27] J.E. Zadina, L. Hackler, L.J. Ge, A.J. Kastin, A potent and selective endogenous agonist for the μ-opiate receptor, Nature 386 (1997) 499–501.