

Low CSF Met-Enkephalin Levels in Cluster Headache Are Elevated by Acupuncture

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Accepted for Publication: May 24, 1989

SYNOPSIS

Significantly lower met-enkephalin levels were found in CSF from cluster headache sufferers as compared to age-matched healthy volunteers, whereas it was not possible to demonstrate any clear-cut difference for β -endorphin. CSF opioid levels may rise following manual or electroacupuncture. It was studied whether traditional Chinese (manual) acupuncture affected CSF levels of met-enkephalin or (β -endorphin in these patients, and to what extent this treatment would be beneficial for the headache. A significant rise in lumbar CSF met-enkephalin levels was found, whereas no clear change in β -endorphin levels was obtained. The treatment was, however, of little value in preventing the headache.

(*Headache* 29:494-497, 1989)

INTRODUCTION

Opiate peptides (endorphins) participate at several levels in the central control of pain.^{1,2} Traditional Chinese acupuncture with manual rotation and electroacupuncture with electrical stimulation of needles are reported to elevate CSF levels of endorphins, which is believed to contribute to the analgesic action.¹ Diverging reports exist on the type of endorphin affected by acupuncture. Early reports indicated a rise of non specified endorphins in man and β -endorphin-like substances in lumbar and ventricular CSF in chronic pain and brain tumor patients with electroacupuncture.³⁻⁵ Later reports indicate a rise in leu- and met-enkephalin in CSF and brain parenchyma of rat following manual or electroacupuncture^{6,7} (see also reviews^{1,8,9}). CSF met-enkephalin levels rise in heroin addicts following electroacupuncture.¹⁰ Several of these reports do not indicate the stimulation parameters used at electroacupuncture. It is believed that low frequency stimulation (below 10 Hz) activates the same physiological mechanisms as classical needling acupuncture, whereas at high frequency electroacupuncture a non-opioid gate mechanism may predominate.¹¹

Met-enkephalin-like levels are reported to be low in sufferers from cluster headache as compared to controls.¹² This was confirmed in the present study. Traditional Chinese acupuncture was therefore tried as a treatment for cluster headache in these patients. The effect of this treatment on CSF levels of met-enkephalin and β -endorphin was measured, and the possible beneficial effect on the headache was evaluated.

PATIENTS AND METHODS

The study was performed on 7 male cluster headache patients, who had at least one attack per day at the time of sampling. Three of the patients were secondary chronic, the remaining 4 were periodic sufferers. Their age ranged from 22 to 57 years, with a mean age of 37.2. Two CSF samples were taken from each patient by lumbar puncture, performed by one of the authors (J.E.H.); the first sample was taken 1 week before the start of acupuncture treatment, and the second in conjunction with the third treatment with acupuncture 4 weeks later (30-60 min afterwards), since the full effect on pain is usually obtained after some treatments. By this time the patients were still within the period of attacks. Five healthy male volunteers served as controls, aged 24-55 years, mean 39.1 years. For β -endorphin analysis CSF from two further controls, aged 42 and 45 years, was obtained. The punctures were performed at the same time during the day, 13:00 hours \pm 30 min, to avoid errors due to circadian variations. CSF was sampled directly on ice. The first 10 ml were collected in EDTA vials containing 5000 units Trasylol for β -endorphin analysis. The following 5 ml dropped into vials containing 0.75 ml of 1.6% glycine in 1 M HCl¹³ for met-enkephalin analysis. It was found separately that met-enkephalin levels were usually lower in CSF collected in Trasylol. Vials for CSF met-enkephalin were transferred on ice to a deep freezer (-80°C) within a few minutes. Vials for CSF β -endorphin were centrifuged at 4°C to eliminate possible blood cells. 1 ml was collected for

estimation of albumin, and the remainder frozen at -80°C until analysis. A blood sample was taken at the same time for estimation of albumin. CSF and plasma levels of albumin were determined by electroimmunoassay, and for each of the cluster headache patients the CSF/plasma albumin ratio was calculated and compared to reference values.

Manual acupuncture was performed in a separate department by one of the authors (M.E.) with needles placed according to traditional Chinese medicine; ipsilaterally in the face at points St 2, 5, 6, GB14 and Ex2, ipsilaterally at GB20 and bilaterally in the thumb grip at Li4 (Fig. 1) One treatment of 30 min duration was given once a week. The treatment was interrupted after 5 weeks if no improvement occurred. During treatment the needles were intermittently manipulated (rapid rotation by hand during a few seconds every 10 min).

For radioimmunoassay of β -endorphin, we used a β -endorphin antiserum from MILAB, Sweden (K-7762)¹⁴ in a final dilution of 1:12500, giving 35% binding of the tracer (bound/total). The lower limit of sensitivity was 2.9 fmol/ml. The antiserum has a negligible cross-reactivity against β -lipotropin (1.2%), it cross-reacts with α -endorphin (29%) and β -lipotropin 61-87 (43%). The intraassay and inter-assay variations were 7.1 and 7.2% (n=20), respectively. Immunoreactive met-enkephalin was quantitated using a rabbit antiserum (R-26, K.M. Voight, Ulm, F.R.G.), final dilution 1:20000. ^{125}I -Metenkephalin was purified by high pressure liquid chromatography (HPLC). The lower limit of sensitivity was 10 fmol/ml. The intraassay and interassay variations were 8.0 and 5.6% (n=20), respectively. The antiserum does not cross-react with β -endorphin or dynorphin 1-8. It cross-reacts with met-enkephalin-Arg⁶-Phe⁷ (4%) and with leu-enkephalin (0.5%).¹⁵

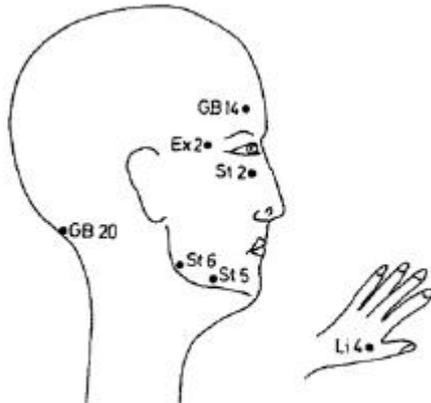


Fig 1.—Position of acupuncture needles in face ipsilateral to the headache side and thumb grip bilaterally.

RESULTS

CSF met-enkephalin-like levels were significantly lower in cluster headache patients as compared to controls. The levels were significantly elevated by acupuncture (Fig. 2). All values were well above the lowest level of detectability, 10 fmol/ml.

Measurements of β -endorphin-like activity in CSF revealed no clear-cut difference between controls and headache sufferers or any change following acupuncture treatment (Fig. 3). However, several values were still below detectability for the high-specificity, fairly high-avidity method used, i.e. <2.9 fmol/ml. Possibly, there is a tendency to lower levels in cluster headache sufferers (see Fig. 3) that is not properly detectable by the present analysis.

The morphological blood-brain barrier was intact in the patients, as indicated by normal CSF/plasma albumin ratios (0.0055 ± 0.0011 and 0.0046 ± 0.0007 before and after acupuncture, respectively; control upper reference levels at the same mean age 0.0074). This excludes the possibility that enhanced CSF peptide levels after acupuncture are due to leakage from the circulation.

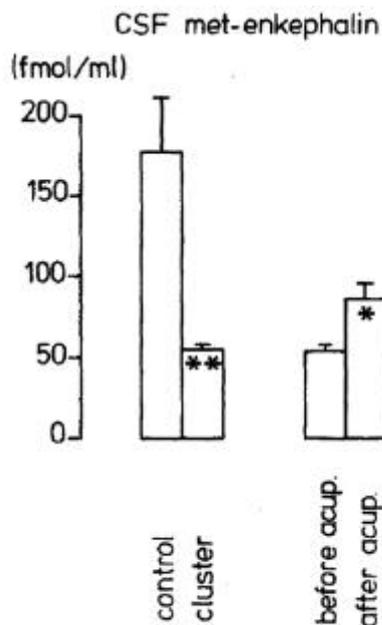


Fig 2.—CSF met-enkephalin levels in controls and cluster headache sufferers before and after acupuncture treatment. Mean \pm SEM. Significance according to Student's t-test for unpaired data: * $0.01 < p < 0.05$, ** $0.001 < p < 0.01$.

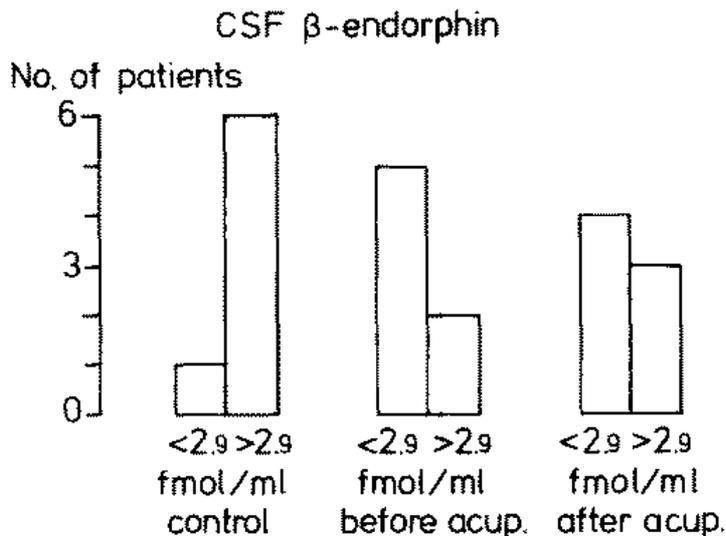


Fig 3.—CSF β -endorphin levels in controls and in cluster headache patients before and after acupuncture treatment. Mean of values above detectability 6.8, 8.1 and 7.8 fmol/ml, respectively, but a higher number of patients than controls had levels below detectability.

Two of the 7 patients improved slightly during the treatment with acupuncture. Both suffered from chronic cluster headache, and the improvement started around the third treatment. In one of these patients the attack frequency was reduced by about 1/3, and in the other the intensity of pain during attacks was reduced by at most 25%.

DISCUSSION

Met-enkephalin is a transmitter substance in interneurons in the dorsal horn of the spinal cord. They are located in close connection to the central end of the C-fibres and block transmission at the level of these terminals or the closely located second-order neuron or relay neurons in between these two neurons.¹⁶ Enkephalinergic nerves from raphe nuclei (magnus in particular) run parallel to descending serotonergic fibres to suppress nociceptive input in the dorsal horn, probably by direct inhibition of second-order neurons.^{1,16} Further, enkephalinergic neurons with terminals in the periaqueductal gray and rostral ventral medulla participate in pain control via complex pathways.¹⁷ β -Endorphin neurons in CNS are predominantly located in the arcuate nucleus and medial basal hypothalamus.¹⁸ The axons terminate in the lateral septal nucleus, nucleus accumbens and periaqueductal gray. Also the caudate nucleus and limbic nuclei are rich in opioids and opiate receptors.¹⁹ These are the central sources for enkephalin and β -endorphin in CSF. There is evidence for involvement of one or several of these neurons in the beneficial effect of acupuncture on pain.¹

The low CSF met-enkephalin-like levels found in cluster headache sufferers in this and other¹ studies indicate diminished release into CSF due to lowered neuronal activity at one or several of the terminal locations for these neurons, or an accelerated degradation (enhanced activity of enkephalinase, aminopeptidase, dipeptidylaminopeptidase, and/or angiotensin-converting enzyme),²⁰ or both. However, the CSF enkephalinase activity during attacks is not enhanced,²¹ and captopril, an enkephalinase and angiotensin-converting enzyme inhibitor, is without beneficial effect in sufferers.²² This leaves a lowered neuronal activity as the most likely explanation for the low CSF levels. Such lowered activity may be due to a primary process in enkephalinergic neurons, but may also be secondary as a result of autoinhibition (a chronic overstimulation of CNS opiate receptors by some agonist, endogenous or exogenous, tends to lower release from enkephalinergic neurons).

Today several varieties of acupuncture are utilized to obtain analgesia in various pain conditions. Needles are utilized in classical Chinese manual acupuncture and electroacupuncture at low and high frequency, in contrast to pressure acupuncture and low frequency transcutaneous electrical nerve stimulation. Combinations of these are also used. The stimulation points chosen for the treatment of the same disease may vary as well as the technique. This may be one explanation for the divergent findings on changes in CSF of the various endorphins following acupuncture. We chose to study the effect of classical Chinese acupuncture on CSF met-enkephalin and β -endorphin levels. There was some earlier indication that such treatment elevates CSF enkephalin levels.⁷ The patients chosen suffered from cluster headache, a disease with intense pain during attacks, and with low CSF met-enkephalin-like levels as measured between attacks.¹² This opened the possibility to test whether this type of acupuncture could elevate low CSF enkephalin levels, and possibly be beneficial to sufferers from this disease by lowering pain perception.

Manual acupuncture in cluster headache sufferers caused a significant rise in CSF met-enkephalin levels, but no clear-cut change in β -endorphin levels. The elevated CSF levels caused by acupuncture will most likely depend on activation of central enkephalinergic neurons, involving links to central serotonergic and noradrenergic pain modulating pathways.^{1,9} The rise occurred from a lower basal met-enkephalin level than in the non-headache control group, but may nevertheless indicate that this opiate peptide, and not, for example, β -endorphin, is mainly linked to the pain modulation obtained by this type of acupuncture. It is probable, but not studied here, that this treatment would enhance CSF met-enkephalin levels also in healthy subjects. It must be considered that our time delay before sampling after acupuncture, the slow CSF flow at the spinal level to the location for sampling (lumbar), and the rapid degradation of enkephalins outside neurons, may be factors which affect the values obtained, and therefore these may not truly reflect maximum changes in central opioid levels.

It might have been expected that the elevation of CSF met-enkephalin levels by acupuncture would have been parallel to a reduction of pain in cluster headache sufferers. However, only 2 of 7 patients given this treatment improved slightly, and only 1 of these 2 patients found it worth-while to continue this treatment beyond the period of 5 weeks. A better outcome in cluster headache patients was reported in another study using needle electroacupuncture or transcutaneous electrical nerve stimulation.²³ In migraine, in which low CSF enkephalin-like levels during attacks¹² and low CSF β -endorphin levels during and between attacks have been found,^{24,25} manual as well as electroacupuncture has been found to be of some value in the treatment.²⁶

The study was supported by grants from the Swedish Medical Research Council (no. 14X-732/ 5680) and Greta and Johan Kock's Foundation, Sweden.

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