# ACUPUNCTURE IN HEROIN ADDICTS: CHANGES IN MET-ENKEPHALIN AND β-ENDORPHIN IN BLOOD AND CEREBROSPINAL FLUID

VICKY CLEMENT-JONES LORRAINE MCLOUGHLIN
P. J. LOWRY G. M. BESSER
LESLEY H. REES

*Departments of Endocrinology, Chemical Endocrinology, and Chemical Pathology, St. Bartholomew's Hospital, London EC1A 7BE*

H. L. WEN

*Neurosurgical Unit, Kwong Wah Hospital, Kowloon, Hongkong*

***Summary*** In heroin addicts showing features of heroin withdrawal basal β-endorphin levels were elevated in both blood and cerebrospinal fluid (CSF) and did not change during electroacupuncture, although this therapy suppressed the clinical features of withdrawal. Met-enkephalin levels were not elevated in blood or CSF before treatment. However, successful electroacupuncture was associated with a rise in CSF met-enkephalin levels in all patients studied, although concentrations in blood did not alter.

## Introduction

ALTHOUGH acupuncture is an ancient method of producing analgesia its mechanism of action is uncertain. Many modern Chinese acupuncturists favour low-frequency electrical stimulation through needles rather than classical manual rotation of the needles.[1] Wen reported that auricular electroacupuncture for 15 to 30 min produced subjective improvements in the clinical features of withdrawal in many heroin addicts and that a combination of electroacupuncture and small repeated doses of the opiate antagonist, naloxone, could be used successfully in weaning some of these patients from opiates.[2–4]

Controlled studies in the West have confirmed the reduction in pain perception in man after acupuncture[5,6] and its blockade by naloxone.[7–9] In 1975 two pentapeptides, methionine-enkephalin (met-enkephalin) and leucine-enkephalin (leu-enkephalin), which had potent opiate and analgesic properties in animals and man[10–11] were isolated from brain. Subsequently a family of opioid peptides, α, β, and γ endorphins, each containing the sequence of met-enkephalin, were identified.[12,13] The analgesia produced by these opiate-like neuropeptides is naloxone-reversible, and it seems likely that their release is involved in modulation of pain perception.[14] It seems possible that production of endogenous opiate peptides is increased when acupuncture relieves pain.

Mechanisms of opiate addiction are poorly understood, and Goldstein[15] suggested that chronic abuse with morphine-like narcotics might lead to suppression of endogenous opioid-neuropeptide production and that the features associated with abrupt narcotic withdrawal might be due to deficiency of endogenous endorphins or enkephalins. If acupuncture releases endorphins or enkephalins then this might account for the clinical benefit in alleviating the symptoms of withdrawal in heroin addicts.

These conjectures have led to the present study of the levels of β-endorphin, met-enkephalin, and the related peptide hormones, β-lipotrophin (β-LPH) and corticotrophin, in plasma and cerebrospinal fluid (CSF) of heroin addicts showing features of withdrawal and during their successful treatment with electroacupuncture. We have demonstrated the presence of β-endorphin in human CSF[16] and plasma[17] and of met-enkephalin in plasma (Clement-Jones V, Lowry PJ, Rees LH, Besser GM, unpublished observations).

## Patients

### *Non-addicts*

CSF was collected from 7 patients who were undergoing routine aspiration of lumbar CSF—2 at induction of spinal anæsthesia, 5 before air encephalography under neuroleptanalgesia with diazepam, droperidol, and phenoperidine. Plasma was obtained at 9 AM from 25 healthy volunteers (14 men, 11 women) for met-enkephalin, and from 18 patients (12 men, 6 women) with non-endocrine diseases for lipotrophin assay.

### *Heroin Addicts*

12 male addicts (ages 23 to 51 years) were studied. Three blood samples were taken at 30 min intervals through an indwelling cannula. 6 patients with mild withdrawal symptoms received 30 min electroacupuncture starting after the second venepuncture, with the technique described elsewhere using the auricular points.[2] Lumbar CSF was obtained from all these patients at the second and third venepunctures. Blood was also obtained from a further 6 addicts with severe withdrawal symptoms who were not treated with electroacupuncture. The withdrawal symptoms were documented as described before.[4] All patients gave their informed consent.

## Methods

Plasma and CSF were assayed for immunoreactive corticotrophin,[18] β-lipotrophin (N-terminal β-LPH),[19] β-endorphin (C-terminal β-LPH),[16] and met-enkephalin. The met-enkephalin assay (Clement-Jones V, Lowry PJ, Rees LH, Besser GM, unpublished observations) involves extraction of 3–5 ml of plasma or CSF with octadecasilyl (ODS)-silica high-performance liquid chromatography and oxidation of the extract to methionine-sulphoxide enkephalin. The radioimmunoassay of met-enkephalin sulphoxide, rather than the parent peptide, results in a uniquely specific assay showing no cross-reactivity with leu-enkephalin, β-endorphin, or β-lipotrophin. We have previously shown there is no in-vitro generation of artefactual met-enkephalin from related peptides in CSF and plasma. The coefficients of variation were: CSF intra-assay 8%, interassay 10%; plasma intra-assay 9%, interassay 12%. The identity of met-enkephalin in plasma and CSF was confirmed by chromatography. Plasma-cortisol was measured by a modification of the method described by Mattingly.[20]

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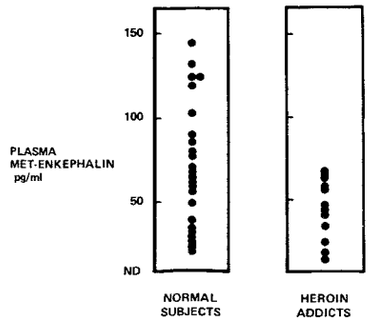


**ig. 1—Plasma immunoreactive met-enkephalin levels in normal subjects and heroin addicts.**

## Results

### Non-addicted Patients

CSF met-enkephalin levels in the 7 patients ranged rom 5 to 29 (mean 13·3) pg/ml. Plasma-met-enkephalin n the 25 healthy subjects ranged from 14 to 140 (mean 59·3) pg/ml (fig. 1).

### Heroin Addicts and Electroacupuncture

β-*Endorphin* in plasma in the addicts showing vithdrawal ranged from 10 to 288 pmol/l in the 22 blood-samples available taken before or unassociated vith acupuncture (fig. 2). 19 (86%) were above the ange previously described in normal subjects (up to 20 mol/l).[16]

*N-Terminal plasma-β-lipotrophin* levels were above ormal (>20 pmol/l) in 15 of the 22 samples (68%) (fig. 2). The C-terminal β-lipotrophin (β-endorphin) mmunoreactivity was elevated above the N-terminal mmunoreactivity (β-lipotrophin) in 16 of the 22 samples 73%). (fig. 2). The mean values for both N-terminal nd C-terminal (endorphin) LPH levels in plasma were igher in the group experiencing severe withdrawal ymptoms. In CSF β-endorphin was above normal in 5 f 6 patients before acupuncture and was higher than he N-terminal β-lipotrophin immunoreactivity in each atient (fig. 2). β-lipotrophin and β-endorphin levels in

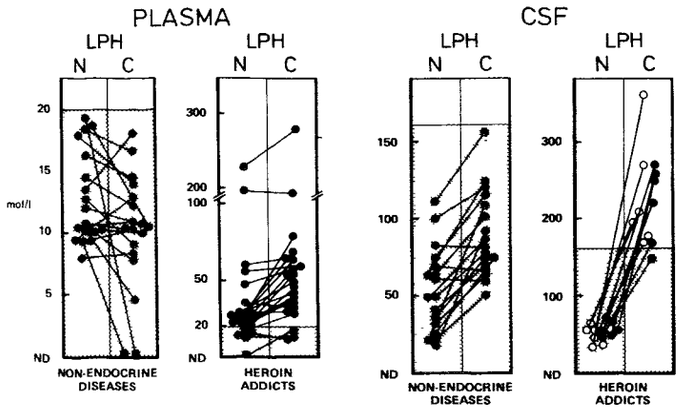


**Fig. 2—Plasma and CSF N-terminal and C-terminal (endorphin) β-lipotrophin levels in patients with non-endocrine disease and heroin addicts.**

Dotted areas represent the ranges observed in normal subjects (plasma) and patients with non-endocrine disease (CSF). Closed circles represent values before electroacupuncture and open circles after electroacupuncture: individual values did not change after electroacupuncture. ND=not detectable. CSF data for patients with non-endocrine-diseases from Jeffcoate et al.[16]

PLASMA CORTICOTROPHIN, CORTISOL, AND N- AND C-TERMINAL β-LIPOTROPHIN LEVELS IN 6 ADDICTS UNDERGOING ELECTROACUPUNCTURE

| Patient no. | Time from electro-acupuncture (min) | Corticotrophin (pg/ml) | Cortisol (nmol/l) | LPH (pmol/l) | |
|---|---|---|---|---|---|
| | | | | N | C |
| 1* | −30 | 36 | 500 | 17 | 10 |
| | 0 | 30 | 520 | 21 | 37 |
| | +30 | <20 | 480 | 12 | 18 |
| 2 | −30 | 31 | 440 | 14 | 29 |
| | 0 | 24 | 270 | 12 | 31 |
| | +30 | <16 | 250 | 16 | 18 |
| 3 | −30 | 28 | 410 | < 4 | 18 |
| | 0 | <18 | 380 | 14 | 13 |
| | +30 | <20 | 360 | < 6 | 17 |
| 4 | −30 | 28 | 410 | 32 | 30 |
| | 0 | 46 | 720 | 22 | 45 |
| | +30 | 37 | 520 | 9 | 46 |
| 5 | −30 | 29 | 235 | 10 | .. |
| | 0 | 46 | 460 | 24 | .. |
| | +30 | 39 | 355 | 15 | .. |
| 6* | −30 | 44 | 380 | 14 | 42 |
| | 0 | 64 | 385 | 28 | 80 |
| | +30 | 62 | 620 | 22 | 42 |

*No clinical response to acupuncture.

plasma (see table) and in CSF (fig. 2) did not change with electroacupuncture.

*Plasma - corticotrophin.* — Plasma - immunoreactive-corticotrophin levels in the 6 patients with mild withdrawal symptoms were within the normal range (<10–80 pg/ml) (see table). Levels fell in 4 of the patients undergoing electroacupuncture. In 1 patient corticotrophin levels were undetectable both before and after acupuncture. Corticotrophin levels in patient 6 (see table), who failed to respond to treatment, did not change. In the 6 patients experiencing severe withdrawal symptoms, corticotrophin levels were for technical reasons available in only 3 (18 samples), but these were all elevated (range 88–428 pg/ml).

*Plasma-cortisol.*—Basal plasma-fluorogenic-cortisol levels in addicts undergoing electroacupuncture were within the normal range (mean 396 nmol/l) and fell during treatment in all except patient 6, who showed no clinical response (see table). Plasma-cortisol levels in 6 addicts who had severe withdrawal symptoms but who did not undergo electroacupuncture were higher (mean 609 nmol/l, range 410–980 nmol/l).

*Met-enkephalin.*—The basal met-enkephalin levels in the plasmas of the heroin addicts lay within the normal range except in 2 subjects with severe withdrawal symptoms who had lower levels (<14 pg/ml). However, the

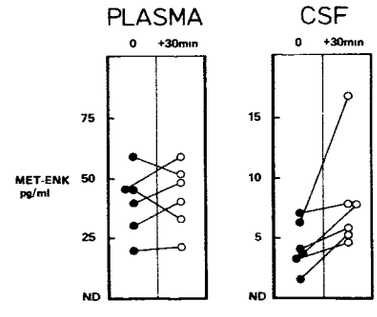


**Fig. 3—Plasma and CSF immunoreactive met-enkephalin levels in heroin addicts before (●) and after (○) 30 min electroacupuncture.**

mean met-enkephalin level (40·4 pg/ml) in the addicts was lower than the mean level in the normal subjects (69·3; p <0·02) (fig. 1). Similarly the mean basal CSF met-enkephalin level (4·5 pg/ml) in the addicts was lower than the mean level in the 7 patients tested (13·3 pg/ml; p <0·05). In each of the 6 patients treated with electroacupuncture CSF met-enkephalin rose after the procedure, although plasma levels did not change (fig. 2). In association with the rise in CSF met-enkephalin relief of the withdrawal symptoms occurred in 4 patients; one of those who failed to show a clinical response had the highest pretreatment level and the smallest rise in response to acupuncture.

## Discussion

Heroin addicts showing signs of withdrawal have been shown to have elevated β-endorphin-like immunoreactivity in both blood and CSF. We have not previously encountered higher levels of C-terminal β-lipotrophin (β-endorphin) than N-terminal β-lipotrophin in plasma. In normal subjects the C/N ratio approximates to unity, and under conditions of stress, including pain, and in patients with raised β-lipotrophin levels due to corticotrophin-related endocrine disease higher N than C levels have been found. This is due to increased secretion of γ-lipotrophin, which does not contain the C-terminal aminoacid sequence of β-endorphin.[16,21] It seems, therefore, that increased blood and CSF β-endorphin is a feature of the heroin-withdrawal state, and this might represent the body's attempts to compensate for heroin withdrawal. These observations are of particular interest in the light of the suggestion that during withdrawal endorphin may be suppressed.[15] This does not appear to be so: it seems possible, rather, that the opiate-receptor mechanisms change during heroin abuse so that normal amounts of β-endorphin are unable to activate them adequately on withdrawal of the narcotic. Further studies are required to establish the precise reasons for the elevated blood and CSF β-endorphin levels which did not change during electroacupuncture. Chromatography is required to confirm that this immunoreactive material is β-endorphin in the heroin addicts.

As might be expected, plasma corticotrophin and cortisol levels were higher in the addicts with severe withdrawal symptoms. However, corticotrophin and cortisol levels in the addicts with mild withdrawal symptoms undergoing electroacupuncture were normal and fell in most cases with relief of symptoms.

Indirect evidence supports the involvement of endorphins or enkephalins in acupuncture in animals and man. Thus, naloxone counteracts the diminished pain perception after acupuncture in normal subjects and in mice.[7,8,22] The delay before the onset of electroacupuncture analgesia and prolonged analgesia afterwards suggests the involvement of humoral factors such as the endorphins. In neurophysiological studies electroacupuncture reduced the firing responses of single neurons in the spinal cord of the cat to noxious stimuli, with time delay and prolonged recovery.[23] Further evidence for the involvement of a humoral factor is the report that transfer of CSF from animals which had undergone acupuncture produced analgesia in recipient rabbits.[24] However, central mechanisms are likely to be involved as well, since the analgesia is blocked if the acupuncture needle point or peripheral nerve innervating it is anæsthetised.[25] Further support for a role of endogenous opiates in the mechanism of acupuncture is the demonstration of poor electroacupuncture analgesia in mice deficient in opiate receptors.[26] Sjölund, using chromatography and a radioreceptor assay which binds a variety of opiate agonists, reported an increase in material with opioid activity in human lumbar CSF after electroacupuncture through surface electrodes for lumbar pain.[27] This material did not have the chromatographic characteristics of met-enkephalin and was of larger molecular size. This is in striking contrast to our data, which have shown rises in met-enkephalin but not in β-endorphin after acupuncture in the addicts. Akil and others[28] reported an increase in ventricular enkephalin-like material after electrical stimulation of the periaqueductal grey matter using a radioreceptor assay and a radioimmunoassay which shows some cross-reaction with both leu-enkephalin and β-endorphin. Akil and others also showed with an unextracted assay,[29] which also detects β-LPH, increases in ventricular β-endorphin after similar stimulation.

Levels of plasma-met-enkephalin in the addicts undergoing withdrawal were within our normal range although at the lower end. Basal CSF-met-enkephalin levels in the addicts were lower than in the 7 other subjects tested; but further CSF samples, particularly from normal subjects, need to be assayed before definite conclusions can be drawn whether the addicts may be deficient in CSF met-enkephalin. However, our findings of raised met-enkephalin levels in CSF after electroacupuncture in addicts are the first definite in-vivo evidence of release of met-enkephalin as measured by a specific assay system and suggest that met-enkephalin release may indeed be involved in the physiological basis of effective electroacupuncture.

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Requests for reprints should be addressed to G.M.B., Department of Endocrinology, St. Bartholomew's Hospital, London EC1A 7BE.

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# MITRAL-ANNULUS CALCIFICATION AND CEREBRAL OR RETINAL ISCHÆMIA

D. P. DE BONO C. P. WARLOW

*Departments of Cardiovascular Medicine and Clinical Neurology, University of Oxford, Radcliffe Infirmary, Oxford*

***Summary*** Radiological and echocardiographic evidence of extensive mitral-annulus calcification was present in 8 patients (aged 64 to 78) from a series of 151 consecutive patients presenting with symptoms of retinal or cerebral ischæmia but in none of 188 controls matched for age and sex. The mitral-annulus calcification syndrome appears to be significantly associated with cerebral emboli, particularly in the elderly. Echocardiography is a valuable noninvasive means of making the diagnosis and distinguishing the condition from others with similar physical signs.

## Introduction

RESURGENT interest in the heart as a potential source of cerebral emboli has emphasised the role of hæmodynamically benign valve lesions, in particular mitral-leaflet prolapse,[1] in providing sites for the formation of thrombus. We describe here the association of another cardiac lesion—mitral-annulus calcification—with cerebral or retinal ischæmia, presumably due to arterial embolism, in 8 patients from a prospective study of cardiac abnormalities in patients with cerebral or retinal ischæmic episodes. Mitral-annulus calcification is a common necropsy finding in the elderly,[2] and there have been several reports of its clinical,[3,4] radiographic,[5] and echocardiographic[6] features. Some of these accounts discuss the possibility of cerebral or systemic emboli, but since their material was obtained either by retrospective survey of necropsy examinations or from referrals to specialist diagnostic services the incidence and natural history of this complication are not well documented. Mitral-annulus calcification may also mimic other cardiac conditions which demand different therapeutic approaches.

## Patients and Methods

151 consecutive patients were studied as part of a prospective investigation into the causes of cerebral and retinal vascular disease. All had been referred to a neurology department and were studied whether or not there was prior suspicion of a cardiac defect. The neurological diagnoses included carotid-territory transient ischæmic attacks (TIA) 20, amaurosis fugax 40, retinal-artery occlusion 15, basilar TIA 23, other TIA not definitely ascribable to carotid or basilar territories 28, and cerebral infarction (confirmed by computerised tomography) 25. There were 95 men and 56 women, of whom 35 men and 24 women were over 60 years old. Controls matched for age and sex were selected from hospital outpatients and ambulant inpatients presenting with diagnoses not related to cardiac or cerebrovascular disease. The control group included 102 men and 86 women, of whom 34 men and 23 women were over 60. 146 control patients had primarily neurological diagnoses, including intracranial neoplasm, epilepsy or transient loss of consciousness, cervical spondylosis, and lumbar radiculopathy. 42 controls had non-neurological diagnoses, including lymphoma, peptic ulceration, hepatic cirrhosis, and venous thrombosis. In addition to a clinical examination, 12-lead electrocardiography (ECG), and routine chest radiography, all patients and controls had an M-mode echocardiogram (S.K.I. Ekoline with Honeywell recorder) and a 24 h ambulatory ECG recording (Oxford Medical Instruments system).

## Case-reports

*Case 1* was a woman aged 70 who in February, 1978, had a ½ h episode of dizziness followed later the same day by sudden and persistent blindness in the left eye. The next day she had severe rotational vertigo and nausea for 2 h. She had had similar vertiginous symptoms for 2 days in July, 1977. Apart from this her previous history was uneventful. On examination, the left eye perceived hand movements only, and there was a left afferent pupil defect. Visual acuity was 6/9 on the right, with a field defect in the lower nasal quadrant. The left fundus showed the characteristic features of central-retinal-artery occlusion, and there was a white embolus in the superior retinal artery at the edge of the optic disc. The right fundus showed a retinal infarct in the superior temporal region, with white emboli in three branch arteries. Blood-pressure was 185/80 mm Hg, and there was no evidence of cardiac failure. On auscultation there was a harsh systolic murmur, loudest at the cardiac apex but radiating to the neck and axilla. Peripheral pulses were natural. ECG showed sinus rhythm with right bundle-branch block; no other arrhythmias were detected during 24 h monitoring. Chest radiography showed cardiac enlargement; calcification in the mitral-valve ring was not apparent on the original postero-anterior film but was subsequently demonstrated by fluoroscopy. Blood-count was normal, and blood-cultures were sterile. The erythrocyte-sedimentation rate (ESR) was 20 mm/h (Westergren). Echocardiography (see figure) showed a mass of echoes in the region of the posterior mitral-valve leaflet and adjacent annulus—the

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