Eur J Appl Physiol (2007) 100:371–382
DOI 10.1007/s00421-007-0469-9

REVIEW ARTICLE

# The effect of physical therapy on beta-endorphin levels

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Accepted: 6 April 2007 / Published online: 5 May 2007


**Abstract** Beta-endorphin ($\beta$E) is an important reliever of pain. Various stressors and certain modalities of physiotherapy are potent inducers of the release of endogenous $\beta$E to the blood stream. Most forms of exercise also increase blood $\beta$E level, especially when exercise intensity involves reaching the anaerobic threshold and is associated with the elevation of serum lactate level. Age, gender, and mental activity during exercise also may influence $\beta$E levels. Publications on the potential stimulating effect of manual therapy and massage on $\beta$E release are controversial. Sauna, mud bath, and thermal water increase $\beta$E levels through conveying heat to the tissues. The majority of the techniques for electrical stimulation have a similar effect, which is exerted both centrally and—to a lesser extent—peripherally. However, the parameters of electrotherapy have not yet been standardised. The efficacy of analgesia and the improvement of general well-being do not necessarily correlate with $\beta$E level. Although in addition to blood, increased brain and cerebrospinal fluid $\beta$E levels are also associated with pain, the majority of studies have concerned blood $\beta$E levels. In general, various modalities of physical therapy might influence endorphin levels in the serum or in the cerebrospinal fluid—this is usually manifested by elevation with potential mitigation of pain. However, a causal relationship between the elevation of blood, cerebrospinal fluid or brain $\beta$E levels and the onset of the analgesic action cannot be demonstrated with certainty.

**Keywords** Beta-endorphin · Physiotherapy · Exercise · Electrotherapy · Hydrotherapy

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## Introduction

Beta-endorphin ($\beta$E), a neuropeptide consisting of 31 amino acids, is a derivative of pro-opiomelanocortin (POMC) (Harbach et al. 2006). Originally isolated from the pituitary gland and the hypothalamus, $\beta$E has been found in a variety of tissues and organs (e.g., inflamed tissues, synovia, eye). The family of endorphins comprises alpha-, beta-, gamma-, and sigma-endorphins; of these, $\beta$E plays an outstanding role in the mechanisms of pain (Holden et al. 2005). The binding affinity of $\beta$E is the highest for MU-1 opiate receptors, whereas it is relatively lower for MU-2 delta and kappa receptors.

POMC is the precursor to ACTH as well as to other bioactive peptide hormone such as the opioid peptide $\beta$E, and alpha-MSH, which plays an active role in skin pigmentation. The POMC precursor is expressed in the corticotroph cell population of the anterior pituitary but is also expressed in melanotrophs, which constitute the majority cell population of the intermediate pituitary. POMC is a 30–32 kDa molecule composed of three main regions:

- an N-terminal alpha-MSH-containing sequence,
- the central ACTH (1–39) sequence (with the alpha-MSH precursor as its N terminus), and
- the C-terminal $\beta$-lipotropin (LPH) sequence, which can be processed into gamma LPH and $\beta$E.

In common with other peptide hormone precursors, such as proenkephalin or the common precursor to arginine vasopressin and neurophysin II the proteolytic cleavage of POMC is regulated in a tissue- and cell-specific manner (Laurent et al. 2004).

Up to a certain threshold level, the production of proprietary "narcotics" in the brain is independent of pain stimuli. Disorders with chronic pain are characterised by elevated endogenous opiate and cannabinoid levels in the brain. This results in the elevation of pain threshold and consequently, higher pain tolerance. Endogenous opiates and cannabinoids suppress pain by acting on spinal and supraspinal targets. The analgesic action of endogenous cannabinoids is mediated by—among others—certain endogenous opiates. Two of the five known endogenous opiates, i.e. enkephalin and dinorphin mitigate pain both at spinal and at supraspinal level; however, their mechanisms of action are different. According to current knowledge, endomorphine and nociceptine act at spinal level only. Endogenous cannabinoids can relieve pain both at spinal and at supraspinal level. $\beta$E acts on supraspinal (diencephalic enkephalin- and dinorphin) neurons. The central cells of the substantia grisea are richly innervated by the descending axons of hypothalamic $\beta$E neurons (Palkovits 2000). In addition to the relief of pain, $\beta$E regulates hunger; it is linked also to the production of sex hormones. Laughing releases endorphin and thereby attenuates pain. Although euphoria following physical exertion (e.g. 'runner's high') was originally attributed to the effect of adrenocortical hormones, it is currently thought to result from endorphin-induced analgesia. Recently, a tentative role for the analgesic effect of endocannabinoids has been hypothesised; however, pertinent evidence is scarce (Dietrich and McDaniel 2004). According to data from the literature, stress is a potent inducer of $\beta$E release. During the stress reaction, corticotropin-releasing hormone (CRH) cleaves POMC to release ACTH (which then mobilises glycocorticoids), and $\beta$E (Przewlocki and Przewlocka 2001). A discussion of opiate effects would be incomplete without a brief reference to opioid antagonists. The most widely known of these is naloxone, which binds to MU-opioid receptors. Clinically, it is used in the management of opioid overdosage; however, it also blocks the analgesic action of endorphin (Meissner et al. 2004). Recently, neutral antagonists have been tested for suppressing opioid effects (Sadee et al. 2005). Exercise and naloxone might influence $\beta$E levels interactively (Angelopoulos 2001).

Physical therapy (physiotherapy), an integrating domain of medicine resorts to physical modalities for the work-up, diagnosis, and treatment of disorders and defects. The scope of physiotherapy varies between different countries of the World. In Europe, for example, as well as in other countries rich in mineral waters (e.g. Japan, Israel, and New Zealand), balneotherapy (i.e. healing with medicinal water) is an integral modality of physiotherapy. Nevertheless, remedial gymnastics and exercise therapy are unanimously regarded as the most important modalities of physiotherapy.

Many modalities of physiotherapy (motion exercises, primarily) and other stressing interventions (e.g. hyperthermia) induce $\beta$E release. The elevation of $\beta$E level is associated with a marked analgesic effect (Hargreaves et al. 1990).

Stress induces analgesia by mechanisms within and outside the brain. The sympathetic nervous system is an essential trigger of intrinsic opioid analgesia within peripheral injured tissue. Noradrenaline, injected directly into inflamed hind paws of male Wistar rats, produced dose-dependent antinociception. Alpha(1)-, alpha(2)- and beta(2)-adrenergic receptors were demonstrated on $\beta$E-containing immune cells and noradrenaline-induced adrenergic receptor-specific release of $\beta$E from immune cell suspensions. Thereafter sympathetic neuron-derived noradrenaline stimulates adrenergic receptors on inflammatory cells to release $\beta$E, which induces analgesia via activation of peripheral opioid receptors (Binder et al. 2004).

This review cannot endeavour to discuss the endorphin-releasing effect of alternative therapies (especially of conventional and electro-acupuncture); therefore these will be only shortly mentioned; however, the abundance of reports on this subject should inspire the composition of another, pertinent review article. Although few data are available on the changes of cerebrospinal fluid (CSF) endorphin levels during physiotherapy (mainly electrotherapy), experimental evidence supports that endorphines, released from the anterior pituitary, do not easily pass the blood brain barrier (BBB); therefore, it is usually more adequate to measure endorphine levels in the plasma than the in the CSF. Evidently, the BBB is the primary control filter in the central nervous system, because its surface area is 5,000 times larger than that of the brain-CSF barrier (Witt and Davis 2006). Accordingly, penetration of $\beta$E through this barrier is highly variable, and its non-conjugated forms cannot traverse the BBB at all (King et al. 2001). Often, no correlation can be observed between $\beta$E levels in the CSF and pain intensity measured by a visual analogue scale (Imasato et al. 1997). Although tiredness following physical exercise is influenced by both central and peripheral factors, it is not known in humans, whether the centrally and peripherally released BE correlate with each other or not (Nybo and

Secher 2004). The association of centrally and peripherally released BE is well known in various animal models (Smith et al. 1986). The role of physical exercise induced hypoglycemia, on the central endorphin release has been reported in both humans and in animal models (Inder et al. 1996). Important regulatory role of βE has been shown in central tonic pain (Porro et al. 1999). Interestingly, βE release was recently reported during placebo effect as well (Benedetti 2007). Different mechanisms of central and peripheral βE in the inhibition of intrinsic pain in early and late inflammation were also reported (Machelska et al. 2003). Depolarisation of neurons in the arcuate nucleus of the hypothalamus, was followed by release of βE to the cerebrospinal fluid compartment. Markedly increased levels of endogenous βE were reported in the arcuate nucleus coincident with pain behaviours in response to hind paw injections of formalin (Zangen et al. 1998). Arcuate nucleus is one of the the principal sources of BE in the central nervous system (Bach 1997a, b; Przewlocki and Przewlocka 2001) and therefore these findings may be indicative of a compensatory mechanism in response to prolonged noxious stimuli. Furthermore, activation of the spinal nociceptive pathways by intrathecal capsaicin results in increased βE release in brain lateral ventricular perfusates (Bach and Yaksh 1995). Noxious stimuli have been shown to increase activity in the arcuate nucleus as indicated by increased 2-deoxyglucose (Mao et al. 1993), and blood flow (Morrow et al. 2000) in that region. βE microinjection can reduce pain responses to noxious stimuli (Bach and Yaksh 1995). The analgesic effects of electroacupuncture and arcuate nucleus stimulation can be attenuated by naloxone, further suggesting the involvement of endogenous opioid systems.

Diverse methodology is another common problem, as some authors measure βE levels, others specify immunoreactive βE activity, but the beta-lipoprotein/βE ratio is used as well. In additon it is much easier to have serial blood samples than CSF samples. It is important to note that corticotropin is co-released with βE (therefore co-vary with cortisol) and may have some indirect effect on βE levels. In this review we will focus on βE level changes during physiotherapy.

## Exercise

### Exercise and βE levels

It is well known that the endogenous opioid system is affected during running and other forms of physical exercise. As supported by the majority of literature data, physical activity enhances βE-release and mitigates pain simultaneously (Goldfarb 2005; Komi 2002). Normally, under nonstress conditions the circulating level of βE is extremely low ($1–100 \times 10^{-12}$ M) (Maisel et al. 1990).

Submaximal exercise (30-min treadmill test) increases βE levels two to fivefolds; however, the magnitude of this increase shows high inter-individual variation (Farrell et al. 1982). Estorch et al. (1998) investigated changes in plasma levels of βE and ACTH before and after a 4 h pedestrian race. After the race βE level increased 2.8 times with respect to basal values and ACTH level increased 3.5 times. In addition there was a positive correlation between ACTH and βE, suggesting the role of stress in increasing βE production.

In another study, βE levels were measured before and after a 30-min treadmill exercise in nine pairs of male monozygotic twin athletes. The exercise-related stress condition induced a significant increase in βE levels (Di Luigi et al. 2003). βE levels of ultra-marathon runners were also significantly increased (Fournier et al. 1997).

Comparison studies conducted on exercise-trained and non-trained individuals failed to demonstrate any difference between resting βE levels. The advantage of exercise-trained individuals became evident only at 110% maximal oxygen consumption ($VO_2$ max); this finding was attributed to exercise-induced adaptation (Farrell et al. 1987). In healthy, exercise-trained volunteers, strenuous workout on a bicycle ergometer increased βE levels threefold and showed positive correlation with exercise capacity (Schwarz and Kindermann 1989). ACTH level and βE levels increase concurrently—anaerobosis is thought to play an important role in this phenomenon (de Meirleir et al. 1986). In a study conducted on marathon runners, ten subjects were tested after completing the 42.195-km distance, and additional five were tested following submaximal exercise testing (50% $VO_2$ max) on a bicycle ergometer. Although βE level increased in both subsets of marathon runners, the duration of exercise—rather then its magnitude—had a greater influence on βE release (Petraglia et al. 1990). During the treadmill testing of exercise-trained individuals, no change of βE, β-lipotropin, or ACTH levels occurred at 50–80% $VO_2$ max. βE level started to increase at 92% and its increase peaked at 98% $VO_2$ max—along with the elevation of serum lactate level. Therefore, the anaerobic component has a great impact, whereas exercise with a negligible only aerobic component does not increase βE level (Rahkila et al. 1988). A study conducted on Nordic cross-country skiers revealed the simultaneous elevation of βE, cortisol, and lactate levels, with no change in met-enkephalin concentration. The increase of βE level was greater in skiers traveling 150 km once a week, than in those covering a mere 20-km distance per week (Mougin et al. 1987). Brief exercise of submaximal intensity is associated with a non-linear elevation of βE level (Kraemer et al. 1989a). The plasma concentrations of βE increase in response to prolonged exercise if the intensity is >50% of $VO_2$ max and during maximal exercise if this is performed for a minimum

of 3 min. At low workloads no rise in βE level is found despite extremely long exposure time (Kraemer et al. 1989b).

Although the vast majority of literature data are in support of the role of physical exercise in increasing βE levels, controversial evidence has also been published. In a study conducted on eight healthy volunteers exercising for 1 h, no elevation of βE level could be ascertained after 20 or 60 min (Elias et al. 1986). The same authors observed βE elevation in exercise-trained subjects; however, βE level returned to normal 60 min after concluding physical activity (Elias et al. 1989). In another study, no increase in βE level could be detected after exercise (bicycle ergometer and treadmill) testing at 60% $VO_2$ max (Langenfeld et al. 1987). This finding is in agreement with the observation that endorphin-secretion is stimulated only by relatively strenuous physical activity (Rahkila et al. 1988). Remedial gymnastics can relieve pain only temporarily or for prolonged periods (Zainuddin et al. 2006). Interestingly, exercising at sea level or under hypobaric conditions (at more than 4,000-m height) results in comparable elevation of endorphin level (Kraemer et al. 1991). In marathon runners, elevated post-exercise βE levels had no influence on ventilatory chemosensititvity activity (Mahler et al. 1989).

### The effect of physical and/or mental exercise

A study evaluated the influence of simultaneous physical and mental exercise on βE levels. Exercise alone or in combination with meditation was associated with comparable increases in βE levels. Therefore, mental exertion alone had no influence on βE levels; these were increased by motion exercise only (Øktedalen et al. 2001).

The effect of listening to music during physical exertion was also explored. Two groups of subjects performed an identical set of exercises, but only one group listened to music in the meanwhile. Anaerobic exercise increased βE levels in both groups—regardless of listening/not listening to music (Doiron et al. 1999). Interestingly, listening to music during exercise relieved stress and anxiety in patients with coronary heart disease; however, this was accompanied by the reduction of βE levels (Vollert et al. 2003).

### The effect of exercise in various diseases

Exercise testing according to the Bruce protocol increased βE levels comparably in patients with symptomatic/non-symptomatic heart disease. Changes in βE levels were not associated with the presence or absence of pain during exercise-induced myocardial ischemia (Heller et al. 1987). Elevation of βE level was observed in patients with coronary heart disease during "silent myocardial ischemia" induced by exertion (Hikita et al. 1998).

Although an intensive exercise program for patients with rheumatoid arthritis increased βE level on the short term (after 3 and 6 weeks), this was not accompanied by the elevation of cortisol level. The 1-year follow-up program involved exercises of moderate intensity; this, however, was not associated with further increases in βE and lactate levels (Ekdahl et al. 1990).

In atopic eczema—an essentially stress-oriented disease—intensive exercise uniformly increased βE levels, both in the patient group ($n = 14$) and in matched controls (Rupprecht et al. 1997).

### βE and serum lactate level

Exercise involving anaerobic components increases βE and lactate levels more profoundly (Schwarz and Kindermann 1990). Acidosis is the most potent stimulator of βE release (Taylor et al. 1994).

### Exercise and gender

The potential influence of gender and menstrual cycle on βE level was evaluated in 12 subjects (males and females) undergoing exercise testing at 60 and 80% $VO_2$ max for 25 min. At 80% $VO_2$ max, the magnitude of βE elevation was similar in males and females, regardless of menstrual cycle (Goldfarb et al. 1998). Treadmill exercise for 30 min at 80% of maximum heart rate failed to induce any significant elevation of βE level, which, however, was higher in males, than in females (Kraemer et al. 1989c). As demonstrated in pregnant women, aquatic exercises increase βE level less noticeably, than pregnancy itself. The elevation of βE level was most pronounced during the 15th week of gestation (McMurray et al. 1990).

The effect of exercise tolerance testing was compared in women taking oral contraceptives (OC) and in OC non-user controls. At rest, βE level was higher in the latter subset and its increase was greater during exercise at 60% $VO_2$ max. At 90% $VO_2$ max; however, βE elevation was significant in both groups. Lower resting βE levels in OC users were attributed to the suppression of physiological ovarian cycles (Rahkila and Laatikainen 1992).

Women in labour were subjected to moderate exercise on a bicycle ergometer for 20 min. Exercise mitigated pain and increased βE level without any deleterious influence on the foetus (Hartmann et al. 2005).

### Physical activity and age

Among non-trained individuals, the extent of βE elevation was comparable in the young and in the elderly. That is, age had no influence on the effect of exercise on βE levels (Hatfield et al. 1987; Struder et al. 1999). A negative correlation

exists between βE level of the CSF and advancing age (Nagamitsu et al. 1998). Experience with exercise—i.e. the number of years spent exercising regularly—has no influence on serum lactate or βE levels (unlike testosterone) (Kraemer et al. 1989a). During endurance tests, hormonal response of the elderly is different from that seen in younger individuals (Kraemer et al. 1999).

Type of exercise

As regards the type of exertion, resistance exercise does not increase βE level (Pierce et al. 1993). The relationship between the level of training and serum βE concentration was studied in 12 exercise-trained and in 11 non-trained individuals. Moderate-only exercise did not induce any increase, whereas more intense exercise increased βE levels in both groups. Alpha-endorphin levels were higher in the exercise non-trained group (Viru and Tendzegolskis 1995). Dietary supplements (e.g. gamma-oryzanol supplementation) administered during resistance exercise did not influence βE level (Fry et al. 1997). By contrast, the changes of βE level during resistance exercise may be dependent on exercise protocol (performance level, effort, and resting period between exercises) (Kraemer et al. 1993).

Synovial fluid

Information on the changes of synovial βE level during exercise is relatively meagre. In dogs, regular physical activity increases βE levels (vs. controls) in cartilage and the synovial membrane. βE has been located around the chondrocytes (Karahan et al. 2002).

## Manual therapy

Several authors have demonstrated the positive effect of spinal manipulation on back pain. Manipulation influences the neurochemical mechanisms of analgesia. A randomised study was conducted on three groups of male patients:

- Group I underwent spinal manipulation,
- Group II was sham-treated, and
- Group III served as control.

According to the trial protocol, spinal manipulation was preceded by a 20-min resting period and followed by 40 min of testing. In Group I, manipulation was performed in the cervical segment. Fictitious manipulation was done in Group II and no treatment was undertaken in Group III. As stated in the trial report, plasma βE level increased significantly as early as from the fifth minute of manipulation, whereas it declined steadily in the placebo and control groups (Vernon et al. 1986).

Another study investigating the plasma levels of immunoreactive ACTH, βE, and cortisol during manual therapy yielded conflicting results. Forty male patients (20 symptomatic and 20 symptom-free) were enrolled into four identical groups. Spinal manipulation was performed in two of these, whereas sham-treatment was undertaken in the remaining two groups. Blood sampling was done at baseline and after treatment. No differences could be ascertained in ACTH and βE levels of the treatment group and of the sham-treated group. Cortisol levels, however, decreased in all four groups. According to the authors, these findings rule out the existence of any analgesic effect related to the humoral βE response to spinal manipulation. It was concluded that manual therapy does not activate the hypothalamic–pituitary–adrenal axis (Christian et al. 1988).

## Massage

Massage was found to reduce cortisol level, as well as to increase dopamine and serotonin concentration in the saliva and in the urine (Field et al. 2005). The effect of massaging the dorsal region for 30 min on βE and β-lipoprotein levels was studied in 21 healthy adults. No significant differences were found between controls ($n = 11$) and treated patients ($n = 10$) as regards βE or β-lipotropin levels (Day et al. 1987).

Massaging of the connective tissue was shown to increase plasma βE level. In this study, plasma βE level of 12 subjects was measured at baseline as well as 5, 30, and 90 min after massaging the connective tissue for 30 min. Moderate elevation of βE levels suggested a relationship between βE release and the mitigation of back pain and heat sensation, as well as the positive subjective effect of massaging (Kaada and Torsteinbo 1989).

## Balneo- and hydrotherapy

In a study of 12 healthy individuals, serum vasopressin levels were found elevated (compared to baseline) 1 h after taking a sauna bath. βE levels were unchanged, just as serum osmolarity, plasma renin, norepinephrine, epinephrine, cortisol, aldosterone, and met-enkephalin levels (Bussien et al. 1986). By contrast, a study conducted on six young and healthy individuals found that having a sauna bath increases serum βE and ACTH, but has no influence on met-enkephalin level (Vescovi et al. 1990). (Heat probably triggers a specific neuroendocrine reaction.) Another study by (Vescovi et al. 1992) enrolled eight cocain addicts (following a 14-day abstinence period) and eight healthy males. Subjects had taken a sauna bath of 90°C temperature and 10% humidity for 30 min, and then, had a rest for further 30 min in a room of 21°C temperature. Cardiovascular indices (blood pressure, heart rate, and

body temperature) and endocrine parameters (serum βE, ACTH cortisol and prolactin levels) were measured at baseline, immediately after sauna, and at the end of the subsequent resting period. At baseline, PRL level was elevated in cocaine-dependent subjects, but no other differences could be ascertained. Immediately after the sauna, elevation of all hormonal parameters studied was seen in healthy controls only. At the end of the 30-min resting period, however, only serum cortisol level remained elevated.

As demonstrated in a subsequent study on eight heroin addicts (enrolled after 14 days of abstinence) and eight healthy controls, baseline βE levels were lower in the group of heroin addicts. Taking a sauna increased serum βE and ACTH levels significantly in healthy controls only. The increase of systolic blood pressure was less pronounced in heroin-dependent subjects (Vescovi 1989).

Eight healthy males were subjected to sauna baths in three sessions. First, a dry heat bath of 80°C temperature was applied; this was increased to 100°C during the next session. On the third occasion, bath temperature was 80°C and cabin air was dry initially, but subsequently, humidity was increased progressively. The increase in body temperature, heart rate, and serum norepinephrine level was the greatest during Session 3 and the smallest during Session 1. Significant elevation of βE level was seen during Session 2 only. ACTH levels increased during Sessions 2 and 3, whereas the elevation of growth hormone and testosterone levels was observed during Sessions 2 and 3, respectively. Cortisol level decreased significantly during Sessions 1 and 2. PG-$E_2$ and thromboxane $B_2$ levels did not change significantly during any of the Sessions (Kukkonen-Harjula et al. 1989). According to a review article, sauna bathing may increase βE level—presumably to an extent proportional to the magnitude of euphoria. Norepinephrine, antidiuretic hormone, growth hormone, and prolactine levels increase along with the activity of the rennin–angiotensin–aldosterone axis. The changes of ACTH and cortisol are inconsistent (Kukkonen-Harjula and Kauppinen 1988). Elevation of prolactin and norepinephrine level was ascertained in 11 healthy women after their taking a Finnish sauna bath. The changes of βE, epinephrine, corticotropin, and cortisol levels were variable and not statistically significant, compared to untreated controls (Laatikainen et al. 1988). In a study conducted in 12 psoriatic patients with skin manifestations, participants were subjected to balneo-phototherapy on 35 occasions. At baseline, the extent and severity of the skin disease were determined and blood was drawn for βE measurement. As evidenced by the latter, serum βE level did not change despite the clinical improvement of skin lesions (Hollo et al. 2004). The authors concluded that βE level does not necessarily predict the changes of skin lesions, because βE has a range of neuroimmunological effects and skin lesions are not directly influenced by βE. A 30-min bath of 38°C temperature had no influence on βE levels in 17 patients (Digiesi et al. 1987). A study into the mode of action of radon-thermal water investigated the effect of exposure to heat and radiation separately. The elevation of βE, alpha-ANP, ACTH, insulin, glucose-6-PDH levels was greater and the reduction of serum vasopressin concentration was smaller after radon-exposure (Yamaoka et al. 2004).

Kubota et al. (1994) reported the case of a 21-year-old patient with atopic dermatitis, who has been taking 47°C, 3-min bath four times a day for a month, in the hope of a beneficial effect on his skin lesions. The patient was unable to abandon this bathing habit on his own; this could be accomplished only by 1-month isolation in the hospital. The authors attribute the patient's "addiction" to the transient elevation of serum βE levels in response to thermic stress.

The mechanism of euphoria caused by bathing in 47°C thermal water from Kusatsu (Japan) was studied by determining serum βE and met-enkephalin levels before and 2 min after the bath. βE level increased from its baseline value of 16.2–49.5 pg/ml; met-enkephalin level remained unchanged. Therefore, the onset of euophoria is potentially explained by the elevation of βE level (Kubota et al. 1992).

### Mud therapy

Seventeen osteoarthritic patients underwent a 12-day course of daily mud baths. Blood samples for the determination of serum βE, ACTH, and cortisol levels were obtained at baseline, after the first and the twelfth bath, as well as 1 month later. βE level decreased significantly by the end of mud therapy, whereas ACTH levels remained stable persistently. Although serum cortisol level decreased significantly after the first and the twelfth session, no change could be ascertained on the long term (Pizzoferrato et al. 2000).

Treatment with mud from thermal springs at the Aegean Sea resulted in transient but significant elevation of βE and ACTH levels in six healthy individuals. Elevated βE level is thought to play a role in the development of tolerance to the substantial heat exposure associated with mud bathing. Repetitive elevation of βE levels may contribute also to the mitigation of joint and muscle pain. The elevation of ACTH level reflects a pituitary response to heat-induced stress (Giusti et al. 1990).

Although different neuropeptides respond differently to thermal stimuli (thermoregulation), heat stroke and fatigue ensuing in scorching heat undoubtedly result in the elevation or βE level (Kraemer et al. 2003).

## Phototherapy

Sunbathing is known to induce a kind of pleasure and accordingly, whole-body exposure to ultraviolet radiation

has been postulated to influence βE synthesis favourably. Twenty-six healthy volunteers were exposed to 15 J/cm² UVA irradiation on a single occasion, but this had no effect on βE level. Repeated irradiation of 35 subjects with UVA and UVB did not influence ATCH level either (Wintzen et al. 2001). Gambichler et al. (2002) published similar observations regarding immunoreactive βE and met-enkephalin.

## Cryotherapy

In a study, whole-body cryotherapy (−110 to −160°C) was associated with the elevation of βE and ACTH levels on days 7 and 14 of treatment; however, participants received kinesitherapy concomitantly (Zagrobelny et al. 1992).

## Electrotherapy

Beta-endorphin levels are higher in cerebrospinal fluid (CSF) obtained from cerebral ventricles, than in samples taken by lumbar puncture. The periventricular grey matter and ventral posterolateral thalamic nuclei of patients suffering from intractable pain were stimulated with electrodes. Electrostimulation involved both regions in six and only the thalamic nuclei in three patients. The elevation of βE level in cerebral, but not in spinal liquor samples was observed after stimulation of the thalamic nuclei only. The elevation of βE level was proportional to the extent of analgesia reported by the patients (Young et al. 1993).

Similar changes were seen in 16 patients with phantom pain responsive to stimulation of the periaqueductal grey matter. The mode of action of the latter is thought to involve the release and binding of βE to opiate receptors in the anterior hypothalamus and consequent activation of descending serotonergic pathways known to attenuate pain (Hosobuchi 1980). In six patients with tumour pain, stimulation and coagulation of the posteromedial hypothalamus increased low (200 pg/ml) baseline βE levels in the CSF. In three patients, βE level remained consistently elevated for about 6–24 h after coagulation (Tari et al. 1983).

### Transcranial electrostimulation (TES)

Elevation of βE level in the cerebrospinal fluid and the plasma was detected 30 min after *trans*-cranial electric stimulation with biphasic and rectangular output current, composed of high-frequency pulse trains (peak-to-peak intensity 250–300 mA, frequency 167 kHz), modulated by low frequency (77 Hz) (Kuzin et al. 1984).

In a placebo-controlled study of 20 patients with lumbar pain, TES mitigated pain substantially in both the treatment and in the placebo group. However, elevation of serum βE level was observed in the treatment group only (Gabis et al. 2003).

According to an open study conducted on 39 patients with arthritic pain, 77 Hz TES improved clinical parameters and increased serum βE concentration at the level of a statistical tendency (Komarova et al. 1998). Treatment with the LISS cranial stimulator (delivering currents of 15,000 Hz carrier and 500 Hz modulating frequency) mitigated pain and sleep abnormalities, reduces spasticity, and improves depression. These changes were accompanied by the elevation of plasma βE, GABA, and dehydroepiandrosterone levels, as well as the reduction of serum cortisol concentration (Liss and Liss 1996). Other investigators, however, failed to detect any change of βE levels—although treatment undoubtedly alleviated anxiety and depression—in alcoholic patients (Krupitsky et al. 1991). Another study compared the effects of pharmacotherapy ($n = 114$), TES ($n = 61$) and placebo ($n = 14$) on vasolability caused by vegetative dystonia. Both pharmacotherapy and TES proved significantly superior to placebo. TES accomplished the normalisation of plasma βE levels in all 22 patients in whom this parameter was monitored (Akimov et al. 1991).

### Spinal cord stimulation (SCS)

The effects of electrostimulation of the dorsal column on the levels of endogenous opioids and biogen amines in cerebral and lumbar liquor samples were studied in 17 patients with chronic pain. At baseline, βE level was below normal. Dorsal column stimulation failed to increase norepinephrine, epinephrine, dopamine, βE, β-lipotropin and ACTH levels of the CSF. Treatment alleviated pain substantially in 16 patients; βE and β-lipotropin levels increased by 50% in six of these—this suggests the role of the endogenous opioid system (Tonelli et al. 1988). In 12 patients with severe lower limb ischaemia, long-term SCS accomplished substantial improvement of microcirculation and healing of trophic ulcers within a year. Patients were symptom-free 10 days after the discontinuation of treatment; this is probably related to persistently high βE (and met-enkephalin) levels (Fontana et al. 2004).

### Transcutaneous muscle electrostimulation

The effect of the electrostimulation of skeletal muscle on plasma βE level was studied in nine patients with spinal injury ($C_5$-$Th_{12}$ lesion). Subjects with an injury older than 5 years had higher plasma βE levels. Nevertheless, exercising the muscles by electrostimulation increased plasma βE concentration in all patients and in proportion to the intensity of the exercise. The elevation of βE level was

associated with an improvement of depression—this suggests a relationship between βE level and mood (Twist et al. 1992).

### Transcutaneous electrical nerve stimulation (TENS)

In healthy individuals, TENS increases βE level in the cerebrospinal fluid in proportion to the duration of stimulation (Salar et al. 1981). On the other hand, in a placebo-controlled study of 31 healthy volunteers, neither low-, nor high-frequency TENS was found to influence plasma βE levels compared to placebo (Hughes et al. 1984). A study evaluated the effects of 85 vs. 0.5-Hz, 80-μs, rectangular-waveform TENS on plasma βE level. Both plasma βE level and pain threshold increased 30 min after treatment—this indicates the potential role of the endogenous opioid system in eliciting post-stimulatory analgesia (Facchinetti et al. 1984). Pain relief during catheterisation of the right side of the heart was supplemented with spinal cord stimulation in 14 patients. βE release from the myocardium was probably involved in the mechanism of analgesia (Eliasson et al. 1998). The effects of TENS, naloxone 50 mg, and placebo were explored during the catheterisation of 11 patients. As naloxone failed to suspend the analgesic action of TENS, the authors assume that the latter is related not to βE, but short-acting opioid-receptor agonists (such as met-enkephalin, dinorphin) or non-opioid mechanisms (Mannheimer et al. 1989). The effect of TENS (40–80 Hz) on plasma βE levels was studied in ten healthy volunteers free of pain and in a group of 38 patients with postoperative pain. Within the latter subset, 28 patients received active therapy, whereas the remaining ten underwent placebo treatment. Blood samples were obtained at baseline and 1 h post stimulation. Baseline βE levels were comparable in all three groups; however, ACTH, cortisol, and prolactin levels were higher in patients experiencing pain. TENS increased βE and reduced prolactin levels; ACTH and cortisol levels did not change (Rodriguez et al. 1992). In another study, 42 patients were stratified into groups treated with either 80 or 2-Hz TENS, or into the group of untreated controls. Pain threshold and plasma βE level were measured at baseline, as well as during and 17 h after treatment. No difference in βE levels could be ascertained between groups and in different time points. Naloxone did not alter the pain threshold of these patients, and this suggests that the endogenous opioid system has no role in the mode of action of TENS (O'Brien et al. 1984).

The parameters (e.g. frequency, intensity) of TENS applied during labour have been shown to influence the changes of plasma βE level (Sokolova et al. 1990). Contradictory data are available about the effect of TENS on low back pain (Khadilkar et al. 2005).

In mice, βE alleviates muscle fatigue in healthy animals. Muscle contractions elicited by electrostimulation of the phrenic nerve released βE in dystrophic mice. The authors suggested that βE-release improves muscle function during exercise (Khan et al. 2005).

### Chinese acupuncture

Although acupuncture is a physiotherapeutic modality of alternative, rather than conventional medicine and the results of meta-analyses are contradictory (Sood et al. 2005), its βE-elevating effect is abundantly documented in the literature (Cabyoglu et al. 2006). Acupuncture elevates βE levels both centrally and on the periphery (Zhang et al. 2005). Electroacupuncture with 2-Hz stimulation releases enkephalin, βE and endomorphin, whereas stimulation at 100 Hz liberates dinorphin (Han 2004).

## Conclusion

Beta-endorphins are essential factors of the mechanism of pain. Within the whole family of endogenous opiates, this endorphin derivative has the ultimate role in accomplishing analgesia.

In addition to the appropriate subjective and semi-objective scales, the measurement of βE level is suitable for monitoring the analgesic efficacy of physiotherapy.

According to data from the literature, exercise (physical activity) increases endorphin level in the plasma in a vast majority of cases. It can be concluded that dynamic exercise increases βE level, whereas resistance exercise has only a smaller effect on βE level. Anaerobic—but not aerobic—exercise increases βE level through the elevation of serum lactate concentration. Although relevant data are meagre, it seems that age and gender also exert a lesser influence on plasma βE level.

Data on the effects of manual therapy and massage are inconsistent. Contradictory data are available about the effect of manual therapy and massage on the plasma level. Phototherapy does not increase βE level. The potential influence of hydro- and balneotherapy on βE mobilisation is related to their thermal effect, primarily, similar to other heat stimuli.

Various modalities of electric stimulation act predominantly by central mechanisms. Chinese acupuncture can accomplish a convincing elevation of βE level. Nevertheless, the majority of published studies describe the βE-enhancing effect of peripheral stimulation. The role of TENS therapy in regulating βE levels is still questionable. The relief of pain and the improvement of general well being accomplished by conventional physiotherapy are not necessarily related to biochemical changes occurring in the blood. In addition to the diversity of methodologies, this may emphasise the influence of other factors (e.g. cannabinoids).

Although it might be accompanied by an elevation of $\beta$E level, pain relief is not necessarily a consequence of the latter.

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