

7.30 pm. On arrival he had hyperpyrexia (41.6°C), hypotension (80/40 mm Hg), and generalised muscle twitching. Sedation was extremely difficult despite large doses of intravenous haloperidol and chlorpromazine, and he was eventually given sodium thiopentone. He remained feverish for some hours. Overnight he passed only small amounts of dark urine and by the next morning his plasma urea and creatinine concentrations had risen to 17.5 mmol/l (105 mg/100 ml) and 500 µmol/l (5.7 mg/100 ml) respectively. Plasma creatine phosphokinase (13 760 IU/l), alanine transaminase (1100 IU/l), aspartate transaminase (1715 IU/l), and urate (1230 µmol/l (20.7 mg/100 ml)) were all raised. He remained hypotensive, and after three cardiac arrests he died at 11.45 am.

The disproportionately high plasma creatinine concentration for such a short period of renal failure and the enzyme results suggested extensive rhabdomyolysis. At necropsy he was noted to have multiple superficial cuts and abrasions and areas of bruising; the tissue beneath these areas showed extensive haemorrhage and bruising. Examination of the kidneys showed extensive casts in the tubules compatible with myoglobin.

Subsequent toxicological analysis revealed an extremely high plasma lysergide concentration before death of 14.4 ng/ml.

### Discussion

Both these patients appeared to develop rhabdomyolysis after being in a straitjacket because they became violent after taking lysergide. There is no evidence that lysergide is directly

nephrotoxic, although, as with fits, the violent movements caused by the lysergide itself might have resulted in rhabdomyolysis. It is more likely, however, that the rhabdomyolysis was caused by muscle injury related to the restraint imposed by the straitjacket. Straitjackets are rigid, and extensive superficial and muscle injuries might be caused when they are used to control violent patients. There are no other reports of straitjackets causing rhabdomyolysis despite their use for decades. Nevertheless, patients who have taken lysergide may become very violent, and possibly the combination of extreme violence and severe restraint precipitated the onset of rhabdomyolysis in these patients. Thus, although it can be difficult to control such patients, even straitjackets cannot be used without risk.

### References

- 1 Bywaters EGL, Beall D. Crush injuries with impairment of renal function. *Br Med J* 1941;ii:427-32.
- 2 Grossman RA, Hamilton RW, Morse BM, Penn AS, Goldberg M. Non-traumatic rhabdomyolysis and acute renal failure. *N Engl J Med* 1974;291:807-11.
- 3 Koffler A, Friedler RM, Massry SG. Acute renal failure due to non-traumatic rhabdomyolysis. *Ann Intern Med* 1976;85:23-8.

(Accepted 29 March 1984)

## Release of $\beta$ endorphin and met-enkephalin during exercise in normal women: response to training

TREVOR A HOWLETT, SUSAN TOMLIN, LEWIS NGAHFOONG, LESLEY H REES, BEVERLY A BULLEN, GARY S SKRINAR, JANET W McARTHUR

### Abstract

Plasma  $\beta$  endorphin and met-enkephalin concentrations were measured in response to treadmill exercises in 15 normal women before, during, and after an intensive programme of exercise training. Significant release of  $\beta$  endorphin occurred in all three test runs, and the pattern and amount of release were not altered by training. Before training dramatic release of met-enkephalin was observed in seven subjects and smaller rises observed in a further four, and this response was almost abolished by training. This represents the first observed "physiological" stimulus to met-enkephalin release.

Endogenous opioid peptides play a part in adaptive changes to exercise training and probably contribute to the menstrual disturbances of women athletes.

### Introduction

Exercise training is becoming increasingly popular in both Great Britain and the United States for the prevention and treatment of disease, over 20 000 people having competed in a recent London marathon alone. For women, however, regular strenuous physical exercise may result in several menstrual disturbances, including delay of the menarche,<sup>1</sup> secondary amenorrhoea,<sup>2</sup> and inadequate luteal phase.<sup>3</sup> These women have been reported to have low circulating gonadotrophin concentrations with abnormal pulsatility and exaggerated responses of gonadotrophin during a luteinising hormone releasing hormone test,<sup>4</sup> suggesting that the amenorrhoea is mediated at the hypothalamic level. Endogenous opioid peptides inhibit pulsatile gonadotrophin release<sup>5</sup> and have been implicated in these exercise induced changes, as infusion of the opiate antagonist naloxone causes a striking increase in amplitude of luteinising hormone and follicle stimulating hormone pulsations in amenorrhoeic runners.<sup>4</sup>

The opioid peptide  $\beta$  endorphin and its immediate precursor lipotrophin are both derived from pro-opiomelanocortin<sup>6</sup>—the precursor of adrenocorticotrophic hormone—and are released from the anterior pituitary in response to "stress," including exercise.<sup>7-12</sup> A previous study suggested that the response of  $\beta$  endorphin and  $\beta$  lipotrophin is facilitated by exercise training,<sup>9</sup> and this has been suggested as the biochemical basis of the

Department of Chemical Endocrinology, St Bartholomew's Hospital, London EC1A 7BE

TREVOR A HOWLETT, MA, MRCP, MRC training fellow

SUSAN TOMLIN, technician

LEWIS NGAHFOONG, technician

LESLEY H REES, MD, FRCP, professor of chemical endocrinology

Sargent College of Allied Health Professions, Boston University, Boston, Massachusetts

BEVERLY A BULLEN, ScD, professor of nutrition

GARY S SKRINAR, PhD, assistant professor of exercise physiology

Department of Obstetrics and Gynaecology, Harvard Medical School, Boston, Massachusetts

JANET W McARTHUR, MD, professor

Correspondence to: Professor Lesley H Rees.

"runner's high."<sup>13</sup> The pentapeptide met-enkephalin is costored with catecholamines in the adrenal medulla<sup>14</sup> and might also be expected to be released during stress. †

We now report release of both met-enkephalin and  $\beta$  endorphin in response to exercise in normal women and changes in this response during an exercise training programme.

## Subjects and methods

Eighteen normal young women (age 20-23 years) from an American college who had not previously engaged in regular aerobic exercise volunteered for an intensive eight week training programme in the controlled environment of a university sponsored camp. None were taking any drugs, including hormones. The subjects ran for five days a week, the distance increasing steadily from 4 miles (6.4 km) a day initially to 10 miles (16 km) a day during the second four weeks. In addition, the subjects were expected to spend at least three hours a day in moderately strenuous activities such as cycling or tennis.

**Exercise testing**—Exercise testing on a treadmill was performed during the afternoon in the early follicular phase (four to eight days after onset of the last menstrual period) at the beginning (T1), middle (T2), and end (T3) of the training programme. Each test lasted one hour and consisted of three successive 20 minute runs at approximately 60%, 70%, and 80% of the maximum aerobic capacity which had been measured on the treadmill 48 hours before each test run. A regression equation<sup>15</sup> was used to predict running speeds corresponding to these exercise intensities. Absolute exercise intensity therefore increased during the training programme so that relative intensity remained constant. A forearm cannula was inserted under local anaesthesia at time zero and basal samples withdrawn at 45 and 60 minutes. Treadmill exercise was conducted between 60 and 120 minutes and blood samples drawn during exercise at 80, 100, and 120 minutes and again at 150 minutes after 30 minutes' rest. In addition, on a control day before training samples were taken at the same time intervals without exercise. Samples were centrifuged immediately at 4°C and rapidly frozen before being coded and shipped to London for assay by a technician who was unaware of the timing of the samples.

**Radioimmunoassays**—Samples were collected and radioimmunoassay performed for met-enkephalin-like immunoreactivity and  $\beta$ -endorphin-like immunoreactivity as described.<sup>16,17</sup> The  $\beta$  endorphin assay shows equimolar cross reactivity with  $\beta$  endorphin and its immediate precursor  $\beta$  lipotrophin. All samples from a particular subject were measured in the same assay.

**Statistics**—Wilcoxon's rank sum test for paired data was used to compare peak responses.

## Results

Three subjects were unable to complete the training programme, leaving 15 who performed all three test runs. Owing to failure of the assay, however, two sets of results for each peptide were incomplete and are therefore excluded from analysis; the remaining 13 sets of data were complete and available for analysis. Of the 15 subjects who completed the programme, only three exhibited no change in menstrual function, and the compliance of these subjects in training was rated as only moderate. The other 12 showed various menstrual disturbances, including inadequate luteal phase, polymenorrhoea, and oligomenorrhoea. Once training was stopped menstrual cyclicity returned to normal in all.

### PLASMA $\beta$ ENDORPHIN

Plasma  $\beta$ -endorphin-like immunoreactivity showed significant increases above basal, reaching peak values in all exercise tests at 120 minutes—that is, at the end of the exercise period. The magnitude of the response was very variable and no clear change in amount or pattern of release was seen during training. In the first treadmill run before training all subjects showed a definite rise in plasma  $\beta$  endorphin concentrations above basal values but peak concentrations varied from 40 to 1706 ng/l (normal <10-80 ng/l). There was a tendency for those subjects with higher basal values to have the highest rises of  $\beta$ -endorphin-like immunoreactivity during exercise. In the later two treadmill runs only two subjects showed a progressive increase in release of  $\beta$  endorphin with training, most showed no consistent change, and two showed diminishing release. Despite this variability

among individual subjects the peak  $\beta$  endorphin responses to exercise (fig 1) were significantly different from control for each of the three test runs at the 1% (T1, T3) or 5% (T2) level, but there was no difference between runs. There was no change in mean basal  $\beta$  endorphin concentration in response to training.

### PLASMA MET-ENKEPHALIN

Plasma met-enkephalin responses to exercise were dramatic but more heterogeneous than were the changes in  $\beta$  endorphin (fig 2).

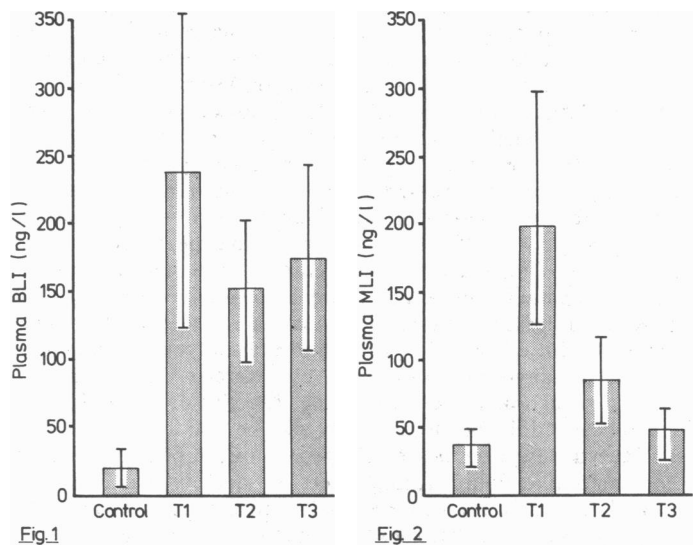


FIG 1—Peak plasma  $\beta$ -endorphin-like immunoreactivity (BLI) during three treadmill runs compared with control day. Values are means. Bars are SEM.

FIG 2—Peak plasma met-enkephalin-like immunoreactivity (MLI) during three treadmill runs compared with control day. Values are means. Bars are SEM.

On the control day plasma met-enkephalin concentrations varied between <10 and 208 ng/l (mean 64.2 (SD 46.6) ng/l). In the first treadmill run before training seven subjects exhibited a rise in plasma met-enkephalin-like immunoreactivity to well outside this resting range, one subject reaching a peak of 1063 ng/l—over five times the upper limit of normal. Four other subjects had definite rises of met-enkephalin values within the resting range, and two subjects had no clear response. The time course of the response was different from that of  $\beta$  endorphin, peak values occurring half way through the exercise period at 80 or 100 minutes and falling back towards basal by 120 minutes. Despite the large variation in response, the peak responses for the group as a whole were significantly different from the control day at the 1% level.

Met-enkephalin release clearly diminished during training. In the second treadmill run one subject achieved a peak met-enkephalin concentration of 526 ng/l, but in only two other subjects did values exceed the resting range. Four subjects had no clear response to exercise, and the remaining subjects had smaller rises within the normal range. During the third exercise test at the end of training six subjects had no response at all to exercise and the maximum value in the remainder was only 228 ng/l. Times of maximum response in both T2 and T3 runs occurred later, at 100 and 120 minutes, and responses were not statistically different from control. No changes in mean basal concentrations of met-enkephalin occurred in response to training.

In view of the heterogeneity of the met-enkephalin response, correlations were sought between the magnitude of the rise in met-enkephalin and a number of variables, including degree of fitness before training, compliance with training programme, and subjective reaction to exercise testing; no relation was apparent. Severity of menstrual disturbance observed was also unrelated to the peak values of either met-enkephalin or  $\beta$  endorphin, although subjects who were considered most compliant with the training programme tended to have the worst menstrual derangements.

## Discussion

This study showed definite release of both  $\beta$  endorphin and met-enkephalin in response to treadmill exercise. The  $\beta$  endorphin response agreed with other studies<sup>7-12</sup> and presumably represented release from the anterior pituitary, in parallel with adrenocorticotrophic hormone, in response to the stress of exercise. We were unable, however, to confirm the reported<sup>9</sup> facilitation of  $\beta$  endorphin release with exercise training.

The release of met-enkephalin, though more variable, is of great interest, since this was the first known "physiological" stimulus to met-enkephalin release. During the first treadmill run several subjects achieved peak plasma concentrations of met-enkephalin previously found only in chronic renal failure<sup>18</sup> or in dogs during septic shock,<sup>19</sup> and this contrasts with the absence of release which we have observed in response to other forms of stress<sup>18</sup> and the small but significant release observed after chlorpropamide and ethanol.<sup>20</sup> The source of this release of met-enkephalin remains unknown, although possibilities include secretion from the adrenal medulla, sympathetic nerve endings, or gut; decreased rate of degradation; or release of immunoreactive met-enkephalin from precursors in plasma.<sup>18</sup>

The function of these endogenous opioid peptides in plasma is also unknown. Since opioid receptors in the median eminence of the hypothalamus, outside the blood-brain barrier, inhibit pulsatile release of luteinising hormone releasing hormone<sup>21</sup> probably the release of opioids into plasma contributes to the menstrual disturbances caused by exercise. Other factors, however, such as the release during exercise of prolactin<sup>22</sup> and the pineal indole melatonin<sup>23</sup> may also be important.

Nevertheless, the release of large amounts of both  $\beta$  endorphin and met-enkephalin during exercise—and in particular the virtual abolition of met-enkephalin during our training programme—suggests that these endogenous opioids play a part in the body's adaptation to exercise training.

These studies were supported by the Medical Research Council, the joint research board of St Bartholomew's Hospital, and the National Institutes of Health (NIH grant No HD 18569/01).

## References

- Warren MP. The effects of exercise on pubertal progression and reproductive function in girls. *J Clin Endocrinol Metab* 1980;**51**:1150-7.
- Feicht CB, Johnson TS, Martin BJ, Sparkes KE, Wagner WW. Secondary amenorrhoea in athletes. *Lancet* 1978;iii:1145-6.
- Shangold M, Freeman R, Thysen B, Gatz M. The relationship between long distance running, plasma progesterone and luteal phase length. *Fertil Steril* 1979;**31**:130-3.
- McArthur JW, Bullen BA, Bettins IZ, Pagane M, Badger TM, Klubanski A. Hypothalamic amenorrhoea in runners of normal body distribution. *Endocr Res Commun* 1980;**7**:13-25.
- Moult PA, Grossman A, Evans JM, Rees LH, Besser GM. The effects of naloxone on pulsatile gonadotrophin release in normal subjects. *Clin Endocrinol (Oxf)* 1981;**14**:321-4.
- Nakanishi S, Inoue A, Kita T, et al. Nucleotide sequence of cloned cDNA for bovine corticotrophin- $\beta$ -lipotropin precursor. *Nature* 1979;**278**:423-7.
- Fraiooli F, Moretti C, Paolucci D, Alicicco E, Crescenzi F, Fortunio G. Physical exercise stimulates marked concomitant increase of  $\beta$ -endorphin and adrenocorticotrophin (ACTH) in peripheral blood in man. *Experientia* 1980;**36**:987-9.
- Colt EWD, Wardlaw SL, Frantz AG. The effect of running on plasma  $\beta$ -endorphin. *Life Sci* 1981;**28**:1637-40.
- Carr DB, Bullen BA, Skrinar GS, et al. Physical conditioning facilitates the exercise-induced secretion of  $\beta$ -endorphin and  $\beta$ -lipotropin in women. *N Engl J Med* 1981;**305**:560-3.
- Bortz WM, Angwin P, Mefford IN, Boarder MR, Noyce N, Barchas JD. Catecholamines, dopamine and endorphin levels during extreme exercise. *N Engl J Med* 1981;**305**:466-7.
- Gambert SR, Garthwaite TL, Pontzer CH, et al. Running elevates plasma  $\beta$ -endorphin immunoreactivity and ACTH in untrained human subjects. *Proc Soc Exp Biol Med* 1981;**168**:1-4.
- Farrell PA, Gates WK, Maksud MG, Morgan WP. Increases in plasma  $\beta$ -endorphin/ $\beta$ -lipotropin immunoreactivity after treadmill running in humans. *J Appl Physiol* 1982;**52**:1245-9.
- Appenzeller A. What makes us run? *N Engl J Med* 1981;**305**:578-89.
- Viveros OH, Diliberto EJ, Hazum E, Chang K-J. Opiate-like materials in the adrenal medulla: evidence for storage and secretion with catecholamines. *Mol Pharmacol* 1979;**16**:1101-8.
- Daniels J, Krahenbuhl G, Foster C, Gilbert J, Daniels S. Aerobic responses of female distance runners to submaximal and maximal exercise. *Ann NY Acad Sci* 1977;**301**:726-33.
- Clement-Jones V, Lowry PJ, Rees LH, Besser GM. Development of a specific extracted radioimmunoassay for methionine enkephalin in human plasma and cerebrospinal fluid. *J Endocrinol* 1980;**86**:231-43.
- Jeffcoate WJ, Rees LH, McLoughlin L, et al.  $\beta$ -Endorphin in human cerebrospinal fluid. *Lancet* 1978;ii:119-21.
- Smith R, Grossman A, Gaillard R, et al. Studies on circulating met-enkephalin and  $\beta$ -endorphin. Normal subjects and patients with renal and adrenal disease. *Clin Endocrinol (Oxf)* 1981;**15**:291-300.
- Evans SF, Medbak S, Hinds CJ, Tomlin SJ, Varley JG, Rees LH. Plasma levels and biochemical characterisation of circulating met-enkephalin in canine endotoxin shock. *Life Sci* 1984;**34**:1481-6.
- Medbak S, Wass JAH, Clement-Jones V, et al. Chlorpropamide alcohol flush and circulating met-enkephalin—a positive link. *Br Med J* 1981;**283**:937-9.
- Grossman A, Moult PJA, Gaillard RC, et al. The opioid control of LH and FSH release: effects of a met-enkephalin analogue and naloxone. *Clin Endocrinol (Oxf)* 1981;**14**:41-7.
- Moretti C, Fabbri A, Gnessi L, et al. Naloxone inhibits exercise induced release of PRL and GH in athletes. *Clin Endocrinol (Oxf)* 1983;**18**:135-8.
- Carr DB, Reppert SM, Bullen BA, et al. Plasma melatonin increases during exercise in women. *J Clin Endocrinol Metab* 1981;**53**:224-5.

(Accepted 27 April 1984)

ONE HUNDRED YEARS AGO What all medical men will at once recognise as a singularly vivid and truthful representation of a distinct variety of insanity, is afforded by Miss Lingard's rendering of the character of Pauline in the new play of "Called Back" at the Prince's Theatre. This representation, it is at once obvious, has not been excogitated from the inner consciousness of the actress, nor drawn from poetical pictures or conventional notions of mental derangement. It is a delicately idealised but still veritable reproduction of the clinical features of that form of madness which most commonly results from sudden and terrible mental shock in young women of fine and sensitive nervous organisation. If an infinite capacity of taking trouble be the essential constituent of genius, Miss Lingard has certainly vindicated her claim to some share of that divine gift; for, while studying the part of Pauline, she has visited a number of asylums, public and private, in London and its neighbourhood, and has carefully observed for herself the facial expression, attitude, and gestures of the patients who were pointed out to her as being in morbid mental states analogous to that which she desired to depict. Having gathered up the physiognomical traits which were suitable for reproduction on the stage, and woven them into a typical representation, she obtained introductions to one or two of the leading alienists of the day, and submitted to their judgment her conception of the mental trouble which she desired to body forth. The result of this painstaking research, and guidance by

skilled criticism, is that she has succeeded in producing a portraiture of madness in one of its most interesting and least repulsive phases, which is equally artistic and faithful to nature. Pauline's madness is not, as stage-madness often is, an impossibility or bundle of inconsistencies provocative of laughter or disgust, but genuine melancholia attonita, such as may be seen any day in the wards of our lunatic hospitals. It is melancholia attonita of the first degree, shorn of its coarser manifestations, and lifted into the region of poetry, by the grace, beauty, and pathos that are mingled with it. In her pained and bewildered look, her passive mood, her rhythmic movements, her statuesque attitudes, her echo-answers, Miss Lingard presents to us an accurate delineation of the symptoms of that semi-cataleptic stupor, which sometimes falls all at once like a curtain over the mind that has been shaken by a swift and appalling emotion, and that rises again with equal celerity when the thrill of the cataclysm has subsided, and when some stirring chord of memory or feeling has been touched. Pauline's condition, from the moment when she drops unconscious at the sight of her brother's murder, admits of accurate diagnosis and prognosis, and her recovery is just what might have been predicted. Miss Lingard is to be congratulated on having produced a most able and impressive study of madness. (*British Medical Journal* 1884; i: 1100.)