

PREFACE

Since the observation in the 19th century that an extract of the suprarenal bodies injected into the circulation caused a rise in blood pressure, the endocrine system has become a major component in our understanding of human physiology. The introduction of radioimmunoassay techniques and the ability to measure minimal amounts of hormones (a term derived from the Greek “to excite”) have shown that acute exercise causes a release of a large number of hormones and that chronic exercise may further lead to long-term alterations in endocrine homeostasis. Actually, almost every organ and system in the body is affected by physical activity and exercise, much of it through the endocrine and neuroendocrine system.

Investigation of the effect of acute or chronic physical activity on the endocrine system is a complex matter since the stimulus called “exercise” has many components, such as mode, intensity, duration, and others. In addition, several other factors, such as age, gender, training status, body temperature, circadian rhythm, metabolic state, menstrual cycle, and various external conditions as well as psychological factors, can modify the effect of physical activity on hormonal secretion. Moreover, the physiological stimulus of exercise often provokes several and parallel cascades of biochemical and endocrine changes. It is therefore often extremely difficult to distinguish between primary and secondary events and between cause and effect. These limitations will be discussed in Chapter 1.

In this volume we have tried to cover the various hormonal pathways that are known to be altered by exercise and how these changes affect different organs and systems of the body. Other subjects are the hormonal regulation of fluid homeostasis, substrate metabolism, and energy balance. A substantial part of the book is devoted to the exercising female in view of certain unique features, e.g. menstrual cycle, use of contraceptives, pregnancy, menopause, and others. Another important issue is the effect of exercise on puberty and growth. Although investigated for many years, it would be premature to draw final conclusions regarding the precise amount of exercise needed to achieve positive effects without compromising growth and puberty. Exercise has also been observed in altered mood. The role of hormones in the development of “exercise euphoria” is discussed in a separate chapter.

The final chapter will not deal with the effect of physical activity on the endocrine system, but rather with its opposite: the effect of hormones on performance. Unfortunately, the manipulation of physiological stimuli by the use of hormones has become common practice on all levels of sport, from fitness rooms to elite world events. The International Olympic Committee is engaged in what seems to be a lost battle against the increasing sophistication of the use of such hormones as anabolic steroids, hGH, HGC, and EPO to enhance performance.

The editors hope that this volume will not only reflect the present state of our knowledge, but also stimulate further study.

Michelle P. Warren, MD
Naama W. Constantini, MD

2

Exercise and Endogenous Opiates

*Tim Meyer, MD, Lothar Schwarz, MD,
and Wilfried Kindermann, MD, PhD*

CONTENTS

INTRODUCTION

INFLUENCES OF ACUTE EXERCISE ON PERIPHERAL

β -ENDORPHIN LEVELS

INFLUENCE OF TRAINING STATUS ON β -ENDORPHIN SECRETION

FACTORS INFLUENCING THE β -ENDORPHIN RESPONSE TO EXERCISE

IMPLICATIONS OF β -ENDORPHIN LEVELS FOR SPORTS ACTIVITY

CONCLUSIONS

REFERENCES

INTRODUCTION

The discovery of endogenous opiates in 1975 (1) generated considerable research concerning the effects of exercise on the release of these peptides, particularly on β -endorphin, which represents the main focus of this chapter. Previous research considered changes in peripheral blood concentrations induced by different modes of physical activity, influences of training status on the secretion of endogenous opiates, and the physiological meaning of the β -endorphin release during exercise. Such phenomena as “runner’s high,” “second wind,” or “exercise dependency” were related to endogenous opiate activity.

This chapter summarizes what is known about the stimulation of opioid release by physical activity. Physiological mechanisms responsible for the secretion are highlighted, as well as the consequences of opioid activity. Implications for future research, training, and competition are discussed.

INFLUENCES OF ACUTE EXERCISE ON PERIPHERAL β -ENDORPHIN LEVELS

Different modes of exercise were tested for their impact on opioid/ β -endorphin release. Routine incremental graded exercise tests are common in the laboratory and were often chosen as provocative tests for pituitary gland synthesis of endogenous opi-

From: *Contemporary Endocrinology: Sports Endocrinology*
Edited by: M. P. Warren and N. W. Constantini © Humana Press Inc., Totowa, NJ

ates. Endurance competitions of long duration represent another mode of testing opioid reactivity. Thus, aerobic trials and anaerobic exercise bouts were performed to test their effect on endogenous opiates. This leads to a crucial point in hormonal research: accurate determination of exercise intensity—a necessary condition for valid results.

Exercise intensity is usually described using spirometric (maximal oxygen uptake = $VO_2\text{max}$) or metabolic (lactate concentration) parameters. For submaximal exercise, percentages of $VO_2\text{max}$ are given. The aerobic range averages intensities up to 60–70% of $VO_2\text{max}$ corresponding to blood lactate concentrations of 3–4 mmol/L. Higher intensities include increasing anaerobic components.

Incremental Graded Exercise

Incremental graded exercise tests were found to elevate β -endorphin levels 1.5- to 7-fold (2–5). This wide range appears to be caused by different protocols and—probably even more important—varying degrees of exhaustion. Published data do not always permit a measurement of the participants' exertion. However, some studies suggest that the amount of β -endorphin release depends on exercise intensity (6–9), whereas others report contradictory findings (10,11). De Meirleir et al. (12) introduced lactate measurements into opioid research to describe the metabolic demand of exercise more adequately. They reported no significant changes in β -endorphin concentrations with lactate values around 3 mmol/L. Above this level, peptide levels were elevated in parallel to lactate.

Corresponding results stem from Donevan and Andrew (7). No increase in β -endorphin was noted after 8 min of cycling exercise at 25 and 50% of $VO_2\text{max}$, but a 1.5-fold increase after a stage with 75% $VO_2\text{max}$ of the same duration and even a 4.4-fold one after 95%. Both of the two higher intensities probably represent anaerobic workloads for the untrained participants. Lactate values were not given.

Nearly the same results are reported for 10 min of cycling exercise in 12 male students whose β -endorphin concentrations did not increase at 40 and 60%, but at 80 and 100% of $VO_2\text{max}$ (13). Adrenocorticotrophic hormone (ACTH), which is derived from the same precursor as β -endorphin, gave similar reactions to 50, 70, and 90% of $VO_2\text{max}$ in 21 subjects at differing endurance training levels (14).

A more precise evaluation of exercise intensity was used by Schwarz and Kindermann (15), who calculated the workload on a bicycle ergometer according to the individual anaerobic threshold (IAT), which describes the beginning of a disproportionate increase in lactate levels during incremental exercise (16). Beyond the IAT β -endorphin concentrations increased approximately parallel to lactate (schematic illustration in Fig. 1). The highest concentrations were reached 5 min after cessation of exercise (three times the resting value), and there was a correlation between lactate and β -endorphin concentrations. This suggests a link between endorphin levels and exercise intensity. Below the IAT, no changes in β -endorphin levels were detected.

Bouts of Anaerobic Exercise

Short bouts of anaerobic exercise (highly intensive with a duration of a few seconds to several minutes, e.g., the Wingate test) induce a two- to fourfold increase of β -endorphin depending on the duration of exercise stress. Protocols of not more than 1 min of anaerobic activity and maximal lactate values between 12 and 15 mmol/L approximately double the β -endorphin concentration (9,15,17), whereas longer exercise durations result in a more pronounced β -endorphin response (18). Again, a positive correlation between lactate

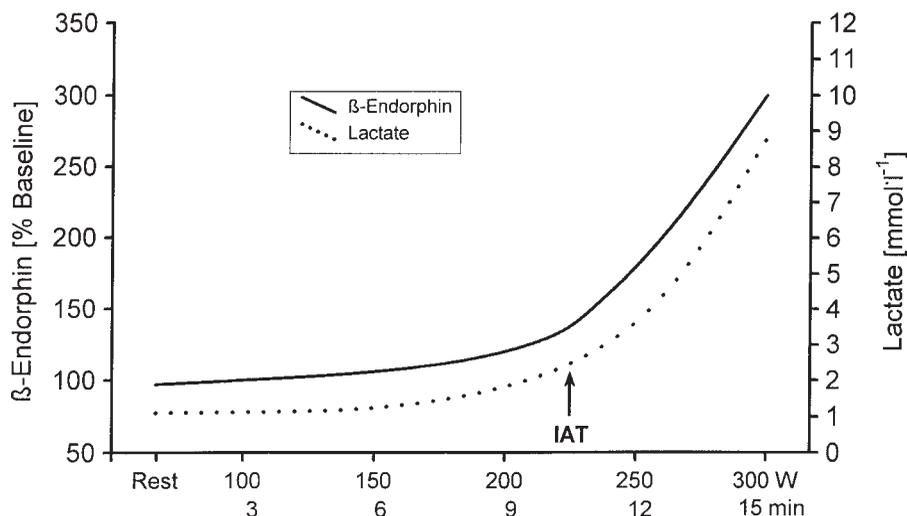


Fig. 1. β -Endorphin lactase during incremental graded exercise (schematic drawing derived from ref. 15). IAT = individual anaerobic threshold.

and β -endorphin could be established (15), and additionally, catecholamine levels were correlated to maximal lactate concentrations.

Aerobic Exercise of Longer Duration

Longer-lasting exercise for more than 10 min is typically performed at lower intensities that do not induce high lactate concentrations, nor do they regularly fulfill other criteria (concentrations of catecholamines and cortisol) responsible for the release of β -endorphin in incremental or anaerobic exercise. Nevertheless, some investigators reported elevated β -endorphin levels after extensive endurance tasks (10,19–24), whereas others found concentrations unchanged (12,25–28). Two methodological shortcomings limit the generalizability of the older studies: high crossreactivity between β -endorphin and β -lipotropin, low number of subjects. However, the determination of exercise intensity remains crucial, and this may vary considerably even in longer-lasting physical activity, which complicates the assessment of results.

More recent studies tested different intensities expressed as percentages of maximal oxygen uptake for their potential to initiate β -endorphin responses. McMurray et al. (8) let subjects cycle for 20 min at 40, 60, and 80% VO_2 max and measured the corresponding levels of lactate and β -endorphin. It was shown that only the highest workload induced lactate concentrations above what is considered the anaerobic threshold. In parallel, β -endorphin levels exclusively rose under this condition.

Another investigation by Goldfarb et al. (29) used a similar design: 60, 70, and 80% of VO_2 max were applied for 30 min on a cycle ergometer. Again only with lactate levels presumably not representing steady-state levels (4.2 and 9.5 mmol/L for the two higher workloads) could β -endorphin increases be detected.

To test if there is a critical exercise duration for a given constant aerobic intensity, Schwarz and Kindermann (24) calculated the IAT for each of 10 nonspecifically trained subjects from an incremental cycle ergometry (16). The IAT represents a physiological breakpoint of exercise intensity beyond which lactate concentrations cannot be held

constant and is situated at 60–80% of VO_2 max, depending on the individual training state. For different modes of exercise (running, cycling), the workload/velocity at the IAT can be maintained for about 1 h. Subjects had to cycle at 100% of the IAT until exhaustion (in this study corresponding to 63% VO_2 max; duration on average 80 min), and they reached lactate steady states between 3 and 3.5 mmol/L. The main observation of the study was an elevation of β -endorphin starting after approx 50–60 min (schematic illustration in Fig. 2).

This may explain the results of Heitkamp et al. (3,4), who found 6.9 and 1.4 times the baseline β -endorphin levels after a marathon in men and women (who had much higher baseline values), respectively. Obviously, other factors than lactate or catecholamine increases alone are involved in initiating a β -endorphin release.

On the other hand, exercising beyond a threshold intensity seems to be necessary for elevating endogenous opioids even in long-lasting endurance exercise. Presumably because threshold was not reached, no changes in β -endorphin concentrations were measured after 2 h of cycling at 50% of the maximal oxygen uptake (26,30).

Resistance Exercise

Resistance training is a relatively new field for β -endorphin research. The determination of exercise intensities is often done as a ratio of the so-called 1 repetition maximum (1 RPM), i.e., the weight that can be lifted/pushed/pulled once by a subject with maximal individual effort. Alternatively, intensities are sometimes defined relative to loads that can be lifted more often (5 RPM for a weight that can be lifted exactly five times).

Depending on the exercise protocol, results of different investigators are inconsistent. Decreases in β -endorphin are reported (31) as well as no change (32) and increases (33,34). A closer look at the applied procedures reveals probable causes for these contradictory findings.

Pierce et al. (32) had trained football players lift $3 \times 4 \times 8 \times 80\%$ of 1 RPM with breaks of 3 min between the sets. The highest recorded heart rates were 157 ± 4 /min, which would suggest an extensive exercise regimen in terms of cardiocirculatory strain for this young group of subjects (20.5 ± 0.4 yr). Putting these facts together, well-trained athletes were stressed in the average range of their strength capacity with relatively long regeneration periods between the loads. The resulting individual cardiovascular load might be evaluated as moderate, and no β -endorphin response occurred.

A more differentiated study design was applied by Kraemer et al. (33), who tested different heavy-resistance protocols for their capability to raise β -endorphin blood concentrations. Only one of the regimens induced significant elevations in hormone levels. This one was characterized by a high number of repetitions and short resting periods in between. Consequently, the highest heart rates and lactate levels were recorded under these conditions.

The somewhat surprising decline in β -endorphin concentration after $3 \times 4 \times 4 \times 80\%$ 1 RPM observed by McGowan et al. (31) cannot be easily commented on, because no information is given about strength-training experience, duration of breaks, and cardiocirculatory strain.

The recent investigations using resistance exercises as stimulus to promote β -endorphin release suggest that—like endurance tasks—the metabolic and cardiocirculatory stress determines the degree of β -endorphin increase. This is in contrast to the traditional way of determining intensity of exercise used by power athletes. At the moment,

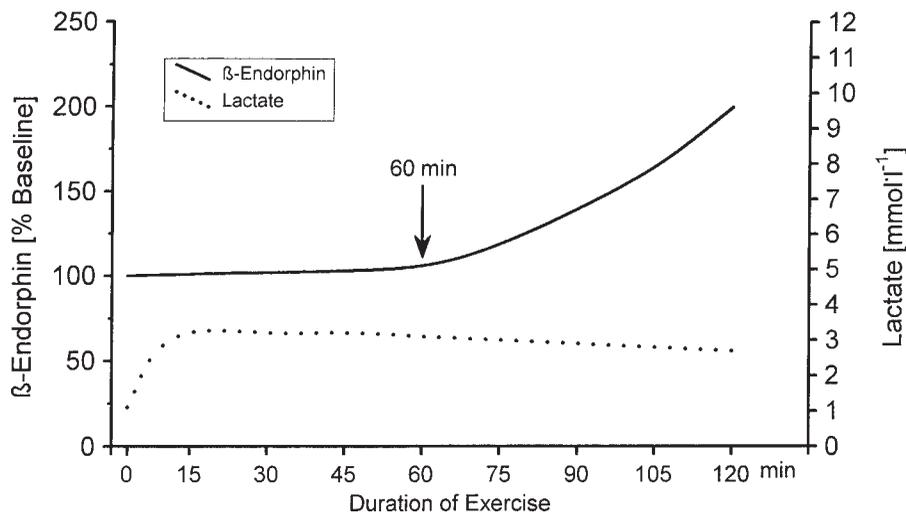


Fig. 2. β -Endorphin and lactate during exercise at the individual anaerobic threshold (schematic drawing derived from ref. 48).

speculations about a threshold analogous to the anaerobic threshold for endurance exercise seem to be premature.

Summary

β -endorphin increases are induced by anaerobic exercise, and incremental exercise which reaches anaerobic stages. Lactate and—probably—catecholamine concentrations are the main factors being correlated with these responses. Consequently, exceeding the intensity of the individual anaerobic threshold raises β -endorphin levels. Duration of aerobic exercise seems to be an independent factor that stimulates β -endorphin release after about 1 h if a threshold intensity—possibly around 55–60% VO_2max —is reached. For resistance exercises, an evaluation of the metabolic and cardiocirculatory strain is preferable to the classic view of counting repetitions for predicting the β -endorphin response. The involved mechanisms may be the same as in endurance exercise.

INFLUENCE OF TRAINING STATUS ON β -ENDORPHIN SECRETION

Apparently, the training status should influence β -endorphin responses to exercise, because it interferes with the determination of intensity. Well-trained endurance athletes can usually perform work at higher relative workloads than untrained persons. Therefore, at least an individualized intensity determination or, alternatively, a highly homogeneous group of subjects seems warranted for research purposes. On the other hand, chronic training stress may alter the hormonal response of the anterior pituitary gland. Theoretically, the capacity to produce β -endorphin may increase, and a chronic suppression of the hypothalamic-pituitary-adrenal (HPA) axis is possible.

Influence of Endurance Training

Resting levels of β -endorphin in endurance-trained individuals were reported to be lowered (35,36) or unchanged (37,40). Both studies showing no change were done cross-sectionally and, therefore, susceptible for selection biases, whereas the other two

investigations applied an endurance training program. Another cross-sectional investigation (14) discovered higher basal values for ACTH and cortisol in trained runners, possibly indicating a parallel behavior of β -endorphin, but trials were executed at an unusual evening time.

The findings under exercise conditions are in slightly better agreement. Only one study showed higher β -endorphin concentrations after 4 mo of mixed aerobic training 6 times a week (20): Cycling at 85% of the individual maximal heart rate induced larger hormonal increases than before the training period. This was evident after 2 mo, and no further significant changes occurred until the end of the training program.

Other investigators did not detect any differences between the trained and untrained state no matter if designed cross-sectionally (38,39) or longitudinally/interventionally (37,40). Boineau et al. (37) performed their trials, including 10 min of exercise at 70% VO_2 max and an incremental test to exhaustion with a considerable number of 39 subjects. Neither influences of training status (which was not exactly specified) nor of gender on the β -endorphin response were observed. The investigation of Berk et al. (38) showed higher hormone values after exercise, but a closer look at the data reveals that this conclusion has to be confined to female subjects of which the number is not given. With a total of six untrained participants, one can assume that single outliers have a large influence on the results, which were not tested statistically. Putting this together, no really substantial differences between trained and untrained subjects were documented.

The same is true for the study from Goldfarb et al. (39), who compared six cyclists and six untrained individuals cycling for 20 minutes at 60, 70, and 80% of VO_2 max. No significant β -endorphin differences were obtained, despite higher lactate concentrations in the untrained group at the two higher workloads. The authors interpret these findings in opposition to the lactate threshold hypothesis, which states a connection between β -endorphin response and excess of the threshold intensity. This might be misleading, since it is well known that trained athletes very often have lower stress-induced lactate levels compared to untrained persons, even if matched for individualized intensity. Therefore, identical absolute lactate levels do not necessarily indicate the same stress for these groups.

The only interventional investigation available as a detailed publication analyzed data from 13 women before and after a strenuous training program for 2 mo (40). Exercise testing was done in the same manner as in the aforementioned study. The authors reported no differences in β -endorphin release with growing endurance capacity, but met-enkephalin concentrations were reduced in the trained state.

Influence of Resistance Training

Very little is known about effects of resistance training on the release of β -endorphin. The recent studies investigating the influence of resistance training on concentrations of endogenous opioids were mostly conducted with athletes who did resistance training for a few years on a recreational basis or as an adjunct to their routine exercise practice (32,33), but no data from elite power athletes are available. From a theoretical point of view, with growing strength identical external (and presumably even relative) workloads are mastered with reduced exertion and cardiocirculatory stress; this would mean lower β -endorphin levels during resistance exercises. To our knowledge, there is no evidence for changed peptide blood levels under resting conditions in resistance-trained individuals, and no comparison between resistance-trained and untrained persons has been conducted yet.

Summary

It is difficult to come to definitive conclusions about the influences of training on the β -endorphin response to exercise, because study results are rare and inconsistent. Endurance training seems to have a lowering effect on hormone resting levels, but changes in the reaction to exercise stress have not been documented clearly yet. One problem might be intensity determination again, because with growing endurance capacity, even relative workloads (as percentages of VO_2 max or of the maximal heart rate) do not indicate the same degree of stress for an individual compared to the untrained state. Consequently, better ways of intensity determination have to be introduced to attain reliable results. The calculation of the individual anaerobic threshold represents a well-validated method feasible for all ergometric testing if lactate measurements are utilized.

No assumptions can be made for effects of the resistance training status, because very few studies have been conducted in this area. On the other hand, individualized intensity determination adequate for hormonal research may be even more difficult than in endurance training.

FACTORS INFLUENCING THE β -ENDORPHIN RESPONSE TO EXERCISE

ACTH and Cortisol

ACTH and β -endorphin are derived from the same precursor molecule in the anterior pituitary gland, and the secretion of both is stimulated by corticotropin-releasing factor (CRF) (41–43). Consequently, the diurnal rhythms of β -endorphin and cortisol are similar as the secretion of cortisol is induced by increasing ACTH levels (44).

Correlations between cortisol and β -endorphin were also reported after a long-distance nordic ski race (45), but other investigators could not replicate these statistical results with incremental graded bicycle exercise and exhaustive work at the individual anaerobic threshold (15,24). The reason for these discrepant findings may be found in the different biological half-lives of β -endorphin and ACTH (approx 20 and 3 min, respectively). There is a time delay between the ACTH release and the cortisol secretion by the adrenal medulla. Thus, without a causal relationship, there might be an “incidental” correlation between β -endorphin and cortisol.

Catecholamines

As pointed out earlier in this chapter, the individual anaerobic threshold (16) probably represents a physiological breakpoint for β -endorphin release. It marks the beginning of the lactate increase in incremental graded exercise, but catecholamine secretion is stimulated overproportionally beyond this intensity, too (46). Consequently, a relationship between both hormones may be assumed, but research is resulting in inconclusive results (46–48). A correlation between endogenous opiates and catecholamines could only be established in short-term anaerobic exercise with considerable lactic acidosis (15), but not in incremental graded exercise and endurance exercise of longer duration until exhaustion (15,24).

Attenuation of adrenergic activity in the central nervous system may be mediated by β -endorphin (49). On the other hand, in animal experiments, an infusion of the adrenoceptor agonist isoprenaline led to elevations in β -endorphin concentrations (50).

Table 1
Exercise-Related Effects of β -Endorphin and Mechanisms Presumably Being Responsible

<i>Proposed effects</i>	<i>Possible mechanisms</i>	<i>References</i>
Euphoria, "runner's high," "second wind"	Stimulation of opiate receptors in the central nervous system	(13,22)
Pain inhibition, increase in acidosis tolerance	Stimulation of central and/or peripheral opiate receptors	(12,44)
Overtraining	Exhaustion of hypophyseal secretion capacity	(7)
Exercise addiction (detraining symptoms)	Downregulation of opiate receptors	(21)
Inhibiting cardiocirculatory effects	Inhibition of catecholamine release	(37,46a,52)
Influence on glucose homeostasis	Inhibition of insulin, stimulation of glucagon	(17,19,38,53)
Influence on fat metabolism	Direct lipolytic effects	(10,25)
Reproductive dysfunction	Feedback inhibition of sex hormones	(6,50)
Immunological effects	Inhibition of natural killer (NK) cell activity	(20)
Anorexia nervosa	Initiation of a self-rewarding system of exercise and starving	(35)

This suggests a physiological inhibition system in which β -endorphin limits the effects of catecholamines and responds to increasing levels of epinephrine and norepinephrine.

Lactate, Acid-Base Status

There is another mechanism that could be involved in inducing β -endorphin release: changes in the acid-base status, which accompany physical activity with a considerable anaerobic component. Recently, it was shown that buffering the lactate acidosis resulting from running on a treadmill at 85% VO_{2max} leads to reduced levels of β -endorphin (51). In seven subjects, the best correlations with β -endorphin concentrations were observed for base excess and pH. These results correspond well with the findings of Schwarz and Kindermann (15) demonstrating a lactate-dependent threshold for raised β -endorphin values. Since lactate is the main agent responsible for declining pH values during high-intensity exercise, it seems tenable that its effect on the anterior pituitary gland is mediated via acidosis.

IMPLICATIONS OF B-ENDORPHIN LEVELS FOR SPORTS ACTIVITY

There are a few exercise-related phenomena that were connected to levels of endogenous opiates (Table 1). The most obvious one is pain perception, because the main pharmacologic effect of opiates lies in the modulation of pain. There are indications that exercise-induced release of β -endorphin attenuates pain (53,54). At least for strenuous workouts, a point for athletes can be assumed in decreasing the perception of pain. A connection between peripheral blood and brain pools of the peptides that cannot cross

the intact blood–brain barrier was considered a necessary condition for this effect. However, peripheral pain receptors are influenced by circulating β -endorphin, too (52,55).

Other proposed—mostly psychological—mechanisms depend on a central action of endogenous opiates, and this research field represents the domain of animal studies and naloxone (opioid antagonist) trials. The most popular hypothesis claims that the so-called runner's high stems from the action of endogenous opiates. Withdrawal symptoms in endurance athletes ("detraining syndrome") are explained by a reduced stimulation of β -endorphin release. Even a resulting exercise dependency is discussed (53,56). Additionally, in the overtraining syndrome, a reduction in β -endorphin levels was observed (57). There is a striking temporal coincidence between the often narratively reported "second wind" in endurance events and the onset of a β -endorphin elevation in aerobic exercise of long duration, i.e., after approx 1 h (24). Altogether, the action of endogenous opiates can be described as a rewarding system that makes the athlete continue physical activity. On the other hand, physiological arousal may be limited to more easily tolerable amounts by attenuating pain and catecholamine action. These assumptions have to be considered speculative, since most of their contents are from indirect deductions via animal trials or psychological reactions to naloxone applications. For obvious reasons, research on humans is difficult, but in the near future, new imaging techniques could be a valuable tool in identifying central nervous system effects of endogenous opiates during exercise.

CONCLUSIONS

The release of β -endorphin during exercise is dependent on intensity and duration of the physical activity. If a threshold intensity is exceeded, rising levels of endogenous opiates can be expected. There seems to be a link to the overproportional increase of lactate and concomitant acidosis. With lower intensities of approx 55–60% of the maximal oxygen uptake, a duration of about 1 h has to be reached before β -endorphin increases. Consequently, common recreational exercise might be too extensive or short-lasting to induce hormone release from the anterior pituitary gland.

In contrast, elite athletes may experience higher levels of endogenous opiates more often—at least in competition. A physiological purpose under these conditions could be the modulation of pain to withstand further exhaustion and the improvement of mood, which may be connected to phenomena like the "second wind" or "runner's high." Sudden cessation of regular training is supposed to induce a depressed mood, which is considered to be part of the "detraining syndrome" by various authors. Some of them even claim the existence of "exercise dependence" partly based on the missing action of endogenous opiates.

At the moment, there is no indication for the introduction of β -endorphin research results into training and competition practice. It is hardly to be expected that the momentary knowledge about this group of hormones can lead to a more precise control of exercise. A more interesting research field seems to be the interrelationship between β -endorphin and other hormones to elucidate the mechanisms into which endogenous opiates are involved in athletes. The actual methods of investigation probably represent too crude tools to discover the basis of psychological exercise effects. An introduction of refined techniques seems necessary.

REFERENCES

1. Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 1975;258:577–580.
2. Gerra G, Volpi R, Delsignore R, Caccavari R, Gaggiotti MT, Montani G, et al. ACTH and beta-endorphin responses to physical exercise in adolescent women tested for anxiety and frustration. *Psychiatry Res* 1992;41:179–186.
3. Heitkamp HC, Huber W, Scheib K. β -Endorphin and adrenocorticotrophin after incremental exercise and marathon running—female responses. *Eur J Appl Physiol* 1996;72:417–424.
4. Heitkamp H-C, Schmid K, Scheib K. β -endorphin and adrenocorticotrophic hormone production during marathon and incremental exercise. *Eur J Appl Physiol* 1993;66:269–274.
5. Oleshansky MA, Zoltick JM, Herman RH, Mougey EH, Meyerhoff JL. The influence of fitness on neuroendocrine responses to exhaustive treadmill exercise. *Eur J Appl Physiol* 1990;59:405–410.
6. Colt EW, Wardlaw SL, Frantz AG. The effect of running on plasma beta-endorphin. *Life Sci* 1981;28:1637–1640.
7. Donevan RH, Andrew GM. Plasma beta-endorphin immunoreactivity during graded cycle ergometry. *Med Sci Sports Exerc* 1987;19:229–233.
8. McMurray RG, Forsythe WA, Mar MH, Hardy CJ. Exercise intensity-related responses of beta-endorphin and catecholamines. *Med Sci Sports Exerc* 1987;19:570–574.
9. Rakkila P, Hakala E, Salminen K, Laatikainen T. Response of plasma endorphins to running exercises in male and female endurance athletes. *Med Sci Sports Exerc* 1987;19:451–455.
10. 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;52:1245–1249.
11. Goldfarb AH, Hatfield BD, Sforzo GA, Flynn MG. Serum beta-endorphin levels during a graded exercise test to exhaustion. *Med Sci Sports Exerc* 1987;19:78–82.
12. de Meirleir K, Naaktgeboren N, Van Steirteghem A, Gorus F, Olbrecht J, Block P. Beta-endorphin and ACTH levels in peripheral blood during and after aerobic and anaerobic exercise. *Eur J Appl Physiol* 1986;55:5–8.
13. de Vries W, Bernards A, de Rooij M, Thijssen J, van Rijn H, Koppeschaar H. Different responses of stress-related hormones to dynamic exercise. *Med Sci Sports Exerc* 1996;28:S 76.
14. Luger A, Deuster PA, Kyle SB, Gallucci WT, Montgomery LC, Gold PW, et al. Acute hypothalamic-pituitary-adrenal responses to the stress of treadmill exercise. Physiologic adaptations to physical training. *N Engl J Med* 1987;316:1309–1315.
15. Schwarz L, Kindermann W. Beta-endorphin, adrenocorticotrophic hormone, cortisol and catecholamines during aerobic and anaerobic exercise. *Eur J Appl Physiol* 1990;61:165–171.
16. Stegmann H, Kindermann W, Schnabel A. Lactate kinetics and individual anaerobic threshold. *Int J Sports Med* 1981;2:160–165.
17. Brooks S, Burrin J, Cheetham ME, Hall GM, Yeo T, Williams C. The responses of the catecholamines and beta-endorphin to brief maximal exercise in man. *Eur J Appl Physiol* 1988;57:230–234.
18. Krüger A, Wildmann J. Anstieg des β -Endorphinspiegels bei Wiederholungsbelastungen. *D Z Sportmed* 1986;245–250.
19. Bortz WM, Angwin P, Mefford IN, Boarder MR, Noyce N, Barchas JD. Catecholamines, dopamine, and endorphin levels during extreme exercise [letter]. *N Engl J Med* 1981;305:466–467.
20. Carr DB, Bullen BA, Skrinar GS, Arnold MA, Rosenblatt M, Beitins IZ, et al. Physical conditioning facilitates the exercise-induced secretion of beta-endorphin and beta-lipotropin in women. *N Engl J Med* 1981;305:560–563.
21. de Wet EH, Barnard HC, Luus HG, Oosthuizen JM, Bornman MS. Beta-endorfin—en leusienkefalienkonsentrasies in marathonatlete. *S Afr Med J* 1992;81:335.
22. Dearman J, Francis KT. Plasma levels of catecholamines, cortisol, and beta-endorphins in male athletes after running 26.2, 6, and 2 miles. *J Sports Med Phys Fitness* 1983;23:30–38.
23. Gambert SR, Garthwaite TL, Pontzer CH, Cook EE, Tristani FE, Duthie EH, et al. Running elevates plasma beta-endorphin immunoreactivity and ACTH in untrained human subjects. *Proc Soc Exp Biol Med* 1981;168:1–4.
24. Schwarz L, Kindermann W. Beta-endorphin, catecholamines, and cortisol during exhaustive endurance exercise. *Int J Sports Med* 1989;10:324–328.

25. Elias AN, Fairshter R, Pandian MR, Domurat E, Kayaleh R. Beta-endorphin/beta-lipotropin release and gonadotropin secretion after acute exercise in physically conditioned males. *Eur J Appl Physiol* 1989;58:522–527.
26. Kelso TB, Herbert WG, Gwazdauskas FC, Goss FL, Hess JL. Exercise-thermoregulatory stress and increased plasma beta-endorphin/beta-lipotropin in humans. *J Appl Physiol* 1984;57:444–449.
27. Kraemer RR, Blair S, Kraemer GR, Castracane VD. Effects of treadmill running on plasma beta-endorphin, corticotropin, and cortisol levels in male and female 10K runners. *Eur J Appl Physiol* 1989;58:845–851.
28. Langenfeld ME, Hart LS, Kao PC. Plasma beta-endorphin responses to one-hour bicycling and running at 60% $\text{VO}_{2\text{max}}$. *Med Sci Sports Exerc* 1987;19:83–86.
29. Goldfarb AH, Hatfield BD, Armstrong D, Potts J. Plasma beta-endorphin concentration: response to intensity and duration of exercise. *Med Sci Sports Exerc* 1990;22:241–244.
30. Viru A, Tenzegolskis Z. Plasma endorphin species during dynamic exercise in humans. *Clin Physiol* 1995;15:73–79.
31. McGowan RW, Pierce EF, Eastman N, Tripathi HL, Dewey T, Olson K. Beta-endorphins and mood states during resistance exercise. *Percept Mot Skills* 1993;76:376–378.
32. Pierce EF, Eastman NW, Tripathi HT, Olson KG, Dewey WL. Plasma β -endorphin immunoreactivity: Response to resistance exercise. *J Sports Sci* 1993;11:499–502.
33. Kraemer WJ, Dziados JE, Marchitelli LJ, Gordon SE, Harman EA, Mello R, et al. Effects of different heavy-resistance exercise protocols on plasma β -endorphin concentrations. *J Appl Physiol* 1993;74:450–459.
34. Walberg Rankin J, Franke WD, Gwazdauskas FC. Response of beta-endorphin and estradiol to resistance exercise in females during energy balance and energy restriction. *Int J Sports Med* 1992;13:542–547.
35. Belikow J, Starich GH, Lardinois CK. The effect of aerobic conditioning on plasma β -lipotropin and β -endorphin levels in humans. *Abstract Med Sci Sports Exerc* 1988;20:S 40.
36. Lobstein DD, Rasmussen CL. Decreases in resting plasma beta-endorphin and depression scores after endurance training. *J Sports Med Phys Fitness* 1991;31:543–551.
37. Boineau RE, Cureton KJ, Hitri A, DeMello JJ, Singh MM. Effects of state of training and gender on plasma beta-endorphin responses to exercise. *Abstract Med Sci Sports Exerc* 1985;17:209.
38. Berk LS, Tan SA, Anderson CL, Reiss G. β -endorphin response to exercise in athletes and non-athletes. *Abstract Med Sci Sports Exerc* 1981;13:134.
39. Goldfarb AH, Hatfield BD, Potts J, Armstrong D. Beta-endorphin time course response to intensity of exercise: effect of training status. *Int J Sports Med* 1991;12:264–268.
40. Howlett TA, Tomlin S, Nghafoong L, Rees LH, Bullen BA, Skrinar GS, et al. Release of beta endorphin and met-enkephalin during exercise in normal women: response to training. *Br Med J Clin Res Ed* 1984;288:1950–1952.
41. Mains RE, Eipper BA, Ling N. Common precursor to corticotropins and endorphins. *Proc Natl Acad Sci USA* 1977;74:3014–3018.
42. Vale W, Rivier C, Yang L, Minick S, Guillemin R. Effects of purified hypothalamic corticotropin-releasing factor and other substances on the secretion of adrenocorticotropin and beta-endorphin-like immunoactivities in vitro. *Endocrinology* 1978;103:1910–1915.
43. Young EA, Akil H. Corticotropin-releasing factor stimulation of adrenocorticotropin and beta-endorphin release: effects of acute and chronic stress. *Endocrinology* 1985;117:23–30.
44. Dent RR, Guilleminault C, Albert LH, Posner BI, Cox BM, Goldstein A. Diurnal rhythm of plasma immunoreactive beta-endorphin and its relationship to sleep stages and plasma rhythms of cortisol and prolactin. *J Clin Endocrinol Metab* 1981;52:942–947.
45. Mougin C, Baulay A, Henriët MT, Haton D, Jacquier MC, Turnill D, et al. Assessment of plasma opioid peptides, beta-endorphin and met-enkephalin, at the end of an international nordic ski race. *Eur J Appl Physiol* 1987;56:281–286.
46. Urhausen A, Weiler B, Coen B, Kindermann W. Plasma catecholamines during endurance exercise of different intensities as related to the individual anaerobic threshold. *Eur J Appl Physiol* 1994;69:16–20.
47. Sutton JR, Brown GM, Keane P, Walker WHC, Jones NL. The role of endorphins in the hormonal control and psychological responses to exercise. *Int J Sports Med* 1982;2:19–24.
48. Thompson DA, Penicaud L, Welle SL, Jacobs LS. Pharmacological evidence for opioid and adrenergic mechanisms controlling growth hormone, prolactin, pancreatic polypeptide, and catecholamine levels in humans. *Metabolism* 1985;34:383–390.

49. Gold MS, Redmond DEJ, Kleber HD. Clonidine blocks acute opiate-withdrawal symptoms. *Lancet* 1978;2:599–602.
50. Berkenbosch F, Vermes I, Binnekade R, Tilders FJ. Beta-adrenergic stimulation induces an increase of the plasma levels of immunoreactive alpha-MSH, beta-endorphin, ACTH and of corticosterone. *Life Sci* 1981;29:2249–2256.
51. Taylor DV, Boyajian JG, James N, Woods D, Chicz-Demet A, Wilson AF, et al. Acidosis stimulates β -endorphin release during exercise. *J Appl Physiol* 1994;77:1913–1918.
52. Fraioli F, Moretti C, Paolucci D, Alicicco E, Crescenzi F, Fortunio G. Physical exercise stimulates marked concomitant release of beta-endorphin and adrenocorticotrophic hormone (ACTH) in peripheral blood in man. *Experientia* 1980;36:987–989.
53. Arentz T, de Meirleir K, Hollmann W. Die Rolle der endogenen opioiden Peptide während Fahrradergometerarbeit. *D Z Sportmed* 1986;37:210–219.
54. Kemppainen P, Pertovaara A, Huopaniemi T, Johansson G, Karonen SL. Modification of dental pain and cutaneous thermal sensitivity by physical exercise in man. *Brain Res* 1985;360:33–40.
55. Allen M. Activity-generated endorphins: a review of their role in sports science. *Can J Appl Sport Sci* 1983;8:115–133.
56. Janal MN, Colt EW, Clark WC, Glusman M. Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. *Pain* 1984;19:13–25.
57. Urhausen A. Das Übertrainingssyndrom—Ein multifaktorieller Ansatz im Rahmen einer prospektiven Längsschnittstudie bei ausdauertrainierten Sportlern. Postdoctoral Thesis, Institute of Sports and Performance Medicine, Saarbrücken, Germany, 1993.