Metabolism
Clinical and Experimental

VOL 45, NO 2 FEBRUARY 1996

Defective Endogenous Opioid Response to Exercise in Type I Diabetic Patients

T. Wanke, M. Auinger, D. Formanek, M. Merkle, H. Lahrmann, E. Ogris, H. Zwick, and K. Irsigler

Plasma β-endorphin (β-E) concentration was determined before, during, and after a standardized incremental exercise test to maximal capacity in eight type I diabetic patients and eight normal control subjects. Diabetic patients were studied under normoglycemic and hyperglycemic conditions in a single-blind random fashion to differentiate between the effects of acute hyperglycemia and of diabetes per se on the β-E response to exercise. The perceived magnitude of leg effort elicited by exercise was evaluated using a category scale. Whereas plasma β-E concentrations increased in control subjects with increasing workload, causing significantly higher β-E levels at the end of exercise than at the beginning ($P < .001$), no such increase could be observed in the diabetic patients under normoglycemic and hyperglycemic conditions. In addition, baseline plasma β-E concentrations were significantly lower in normoglycemic ($P < .01$) and hyperglycemic ($P < .001$) diabetic patients than in control subjects. Even during the recovery period, patients' β-E levels remained significantly lower than those of control subjects. At submaximal levels of power output, the perceived intensity of leg effort was significantly higher in normoglycemic and hyperglycemic diabetic patients than in control subjects. We conclude that in type I diabetic patients, the ability of the endogenous opioid system to respond to exercise-induced stress is impaired under hyperglycemic and even under normoglycemic conditions. Considering the effect of endogenous opioids on stress tolerance, such changes may compromise exercise performance in diabetic patients.

PATIENTS WITH DIABETES mellitus are known to have a reduced tolerance to stress induced by pain. For example, it is known that diabetic patients have a lower pain tolerance than age-matched control subjects, and that elevated glucose levels result in a decrease in pain tolerance in normal subjects.[1] In animal experiments, diabetes was shown to diminish the tolerance to nociceptive thermal stimulation.[2] From the results of this and other animal studies it was concluded that alterations in the neuroendocrine mechanisms modulating peripheral and central β-endorphin (β-E) levels in response to stress are responsible for the reduced stress tolerance in diabetic patients.[2-4]

It is well documented that stressful situations such as exercise until exhaustion increase the concentration of immunoreactive β-E.[5,6] Endogenous opioids may account for the increase in pain threshold and for mood alterations including joy and euphoria that result from a single bout of exercise.[7,8] They are also considered to increase acidosis tolerance.[9]

It has not been investigated until now how the endogenous opioid system in insulin-dependent diabetes mellitus (IDDM) patients responds to stress induced by an incremental exercise test to maximal capacity. We hypothesize that the ability of the endogenous opioid system to respond to exercise in IDDM patients is reduced, which may affect the magnitude of effort sensations elicited by exercise. To test this hypothesis, we analyzed the plasma β-E response to exercise and the perceived magnitude of leg effort during exercise in eight IDDM patients. Since both acute hyperglycemia and diabetes per se are known to affect the endogenous opioid system,[1,4] the patients were studied under normoglycemic and hyperglycemic conditions, and the insulin dosage administered was constant in both conditions. Thus, it was possible to differentiate between the effects of hyperglycemia and of diabetes per se on the endogenous opioid response to exercise. The results were compared with those in healthy subjects.

From the Pulmonary Department and L. Boltzmann Institute for Environmental Research and the Third Metabolic Department and L. Boltzmann Research Institute for Metabolic Diseases and Nutrition, Lainz Hospital, Vienna; and the Department of Nuclear Medicine, SMZ Ost, Vienna, Austria.

Submitted August 27, 1994; accepted June 5, 1995.

Supported by a grant from the "Medizinisch-Wissenschaftlichen Fonds des Bürgermeisters der Bundeshauptstadt Wien."

Address reprint requests to T. Wanke, MD, Lainz Hospital, Pulmonary Department, Wolkersbergenstr. 1, A-1130 Wien, Austria.

0026-0495/96/4502-0001$03.00/0

SUBJECTS AND METHODS

Subjects

The study was performed with eight IDDM patients and eight healthy control subjects. Control subjects were matched with diabetic patients in age, sex (one female per group), height, and weight. They had not participated in any physical training programs and had not smoked more than five cigarettes per day during the past 5 years. IDDM patients met the following selection criteria: insulin dependence from the time of diagnosis, age of onset less than 30 years, regular attendance at our diabetic department, no episode of ketoacidosis or severe hypoglycemia during the previous 6 months, no clinical symptoms or signs of somatic neuropathy, and no other therapy except insulin. Among diabetic patients, the mean duration of diabetes was 15 ± 2.3 years and mean hemoglobin A_{1c} (HbA_{1c}) concentration was 8.7% ± 0.4% (normal, <6%). All patients were C-peptide–negative and received daily insulin by a continuous subcutaneous infusion pump. The mean daily dosage of insulin was 50 ± 3 IU.

No subject had any symptoms of neuromuscular, cardiovascular, or respiratory disease. Chest radiographic and electrocardiographic examinations showed no abnormalities in any participant. Pulmonary function alterations were excluded by spirometry and plethysmography (Jaeger, Würzburg, Germany). Serum urea and creatinine concentrations were within the normal range in all participants. Somatic neuropathy was assessed clinically by evaluating neuropathic symptoms and signs.[10] Motor and sensory nerve conduction studies were performed by conventional techniques using a DISA electromyograph (DISA Electronics, Skovlunde, Denmark) as described previously.[11] Motor and sensory nerve conduction studies bore evidence of somatic neuropathy in one of eight IDDM patients.

Autonomic neuropathy in IDDM patients was assessed on a different day in a quiet room, as described previously.[11] One patient had an abnormal heart rate (HR) response during deep respiration and Valsalva maneuvers, but all patients had normal orthostatic blood pressure responses, indicating no sympathetic damage. To detect retinopathy, an experienced ophthalmologist performed a fundoscopy. Patients with a high risk of retinal hemorrhage were excluded. No patient had proteinuria, but three patients had microalbuminuria in the range of 20 to 200 mg/24 h. All subjects participating in the study provided informed consent. The study was approved by the Human Subject Committee of the hospital.

Materials and Measurements

The subjects performed exercises on an electromagnetically braked cycle ergometer. Minute ventilation (VE), tidal volume, breathing frequency, oxygen uptake ($\dot{V}O_2$), and carbon dioxide output were measured by analyzing the expirate every 30 seconds with a computerized system (EOS Sprint; Jaeger). Daily calibrations of this system were accomplished with a 2 I syringe and precision gas mixtures. The electrocardiogram and HR were continuously recorded on a strip-chart recorder (Siemens, Erlangen, Germany). Blood glucose concentration was measured by the hexokinase method (Glucose Analyzer 2; Beckman, Fullerton, CA); whole-blood lactate concentration was determined enzymatically (LAC; Eastman Kodak, Rochester, NY). For determination of human β-E levels in plasma, a commercial test kit from Nichols Institute Diagnostics (San Juan Capistrano, CA) was used. This test kit uses a solid-phase, two-site immunoradiometric assay for direct measurement of human β-E levels. The determination was performed on EDTA plasma samples. The samples were collected, centrifuged in a cooled centrifuge at 5°C, and stored on ice for assay at a later date. Frozen plasma samples were thawed only one time for determination of β-E. Samples from diabetic patients and control subjects were assayed together. The standard curve of the test kit was generated using prepared human β-E standards. Intraassay variance (precision) was determined from replicate determinations of selected sera and was found to be 6.7% (coefficient of variation). An interassay variance (reproducibility) of 11.2%, 10.4%, 7.5%, 10.2%, 14.1%, and 14.2% was found at concentrations of 172, 231, 251, 895, 942, and 1,040 pg, respectively, thus giving a precision profile of the test. The mean coefficient of variation obtained from the data of two control sera observed over a period of 9 months (n = 24) was 9.7% at a concentration of 218 pg and 17.8% at a concentration of 959 pg.

HbA_{1c} concentration determined on the first day of investigation was measured by high-performance liquid chromatography. During the cycle ergometer testing, a 10-point modified Borg scale was displayed in front of the subjects.[12] Subjects were asked to estimate the intensity of leg effort elicited by exercise by quantifying their estimate as a number from zero (nothing) to 10 (maximum). They were permitted to indicate positions anywhere between these points if they felt that a fractional increment in sensation had occurred.

Protocol

The ergometer tests were performed by IDDM patients under normoglycemic and hyperglycemic conditions on 2 different days separated by 2 weeks. Healthy control subjects were studied on one occasion only. All participants had their usual breakfast at 7:30 AM; IDDM patients received their usual morning insulin dose delivered by the pump subcutaneously. All subjects refrained from alcohol, caffeine, or tobacco consumption during the 12 hours preceding each experimental session. The participants arrived at the laboratory at 9:00 AM. At this time, mean baseline blood glucose concentrations on the 2 days of testing were 6.7 ± 0.3 and 6.6 ± 0.3 $mmol \cdot L^{-1}$, respectively. Subjects had one cannula inserted intravenously in each forearm, through which IDDM patients were connected to a biostator via two lines (Miles, Elkhart, IN). With the help of a feedback program, either insulin through one forearm or glucose through the other was administered by the biostator to the patients to maintain blood glucose at 5.0 to 6.1 or 16.1 to 17.2 $mmol \cdot L^{-1}$, respectively, for 60 minutes. Due to the feedback program to maintain normoglycemia or hyperglycemia over this period, IDDM patients received a mean dosage of 1.2 ± 0.14 or 1.5 ± 0.28 IU insulin, respectively, in addition to the insulin delivered by the pump. With the help of the biostator, the desired blood glucose levels were achieved within 30 minutes. Patients were studied under normoglycemic and hyperglycemic conditions in a single-blind randomized fashion. By examining the IDDM patients under these two conditions with fixed insulin levels, conditions were simulated that often accompany exercise in diabetic patients, in whom hyperglycemia without hyperinsulinemia is common. Furthermore, glucose ingestion is often advocated before exercise in IDDM patients, resulting in an increase of circulating glucose.[13] The healthy subjects were administered 200 mL saline through both cannulas over a period of 90 minutes. Both the patients and the control subjects rested supine on a couch during this period. Thereafter, they sat upright for 15 minutes, and immediately before exercise, the first blood samples were taken in this position from a third catheter placed in another more distal forearm vein to determine blood concentrations of β-E, lactate, and glucose. The subjects were then seated on the cycle ergometer. After 2 minutes of unloaded pedaling, they cycled at 60 rpm at an initial power output of 25W at 2-minute intervals. They were encouraged to continue exercising until exhaustion and were instructed to continue unloaded pedaling during the first 5 minutes after cessation of exercise. Maximal power output (W_{max}, in watts)

was defined as the highest power output maintained for at least 30 seconds. At the end of each workload and at the third minute of the recovery period, blood samples were drawn to determine blood concentrations of β-E and lactate. At the end of exercise, blood samples were also obtained to measure blood glucose concentrations. At the end of each workload, the rate of perceived exertion was also determined using the modified Borg scale.

Data Analysis

The predicted normal values for maximal heart rate (HR_{max}), maximal oxygen uptake ($\dot{V}O_2max$), and W_{max} were those derived from Jones.[14] To compare diabetic patients with control subjects at equivalent workloads, power output was expressed as a fraction of W_{max}. This is because pituitary activation is coupled to relative exercise intensity rather than to absolute workload.[15] Furthermore, when power output is normalized in this way, sex, age, and stature do not contribute to the rating of effort.[12]

Standard linear regression techniques using the least-squares method were used whenever appropriate. Comparisons between groups were made by ANOVA. A two-tailed P value less than .05 was considered statistically significant. Values are expressed as the mean ± SEM.

RESULTS

There were no significant differences in anthropometric data between diabetic and control groups. General characteristics and lung function parameters of the participants are given in Table 1. In all subjects, pulmonary function tests produced values greater than 80% of the predicted values reported by Quanjer.[16]

Exercise Performance

At maximal workload, all subjects reached a respiratory exchange ratio greater than 1.1, indicating exhaustive loading.[17] In all subjects, W_{max} and $\dot{V}O_2max$ were well within the normal expected range reported by Jones.[14] As indicated by the VE_{max}/12s-MVV ratio (maximal exercise ventilation/maximal voluntary ventilation during 12 seconds, in liters per minute), ventilation in both groups did not reach its limiting value. The relationship between HR and $\dot{V}O_2$ was similar in both groups. Mean values for $\dot{V}O_2max$, HR_{max}, VE_{max}, plasma lactate concentration at the end of exercise, and W_{max} are shown in Table 2. Blood glucose concentration at end-exercise was 4.8 ± 0.1 mmol · L^{-1} for control subjects and 6.1 ± 0.1 mmol · L^{-1} and 16.6 ± 0.2 mmol · L^{-1} for normoglycemic and hyperglycemic diabetic patients, respectively.

Table 1. Physical Characteristics and Lung Function Parameters of IDDM Patients and Control Subjects

Characteristic/ Parameter	IDDM Patients (n = 8)	Control Subjects (n = 8)
Age (yr)	33.0 ± 4.1	33.5 ± 3.8
Height (cm)	177.5 ± 5.2	175.8 ± 5.8
Weight (kg)	79.7 ± 7.1	76.3 ± 7.5
BMI (kg/m²)	23.3 ± 0.15	23.1 ± 0.13
FVC (L)	4.65 ± 0.26	4.88 ± 0.34
FVC (% of predicted)	93.5 ± 4.3	97.7 ± 4.1
FEV_1 (L)	3.79 ± 0.26	4.02 ± 0.37
FEV_1/FVC (%)	81.4 ± 0.84	83.1 ± 0.45
TLC (L)	6.74 ± 0.38	6.96 ± 0.58
TLC (% of predicted)	97.3 ± 4.8	104.1 ± 3.9
Raw (kPa/L · s)	0.23 ± 0.04	0.19 ± 0.03

NOTE. Sources of predicted values are given in text. Values are the mean ± SEM.

Abbreviations: FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity; Raw, mean airway resistance.

Table 2. Measurements of Respiratory and Cardiac Function at End-Exercise in IDDM Patients and Control Subjects

Parameter	IDDM Patients (n = 8) Normoglycemic	IDDM Patients (n = 8) Hyperglycemic	Control Subjects (n = 8)
$\dot{V}O_2$			
L/min	2.56 ± 0.20	2.45 ± 0.12	2.65 ± 0.15
% of predicted	94.6 ± 8.3	90.8 ± 6.8	103.0 ± 14.0
Power			
W	192.8 ± 16.1	185.7 ± 14.3	221.6 ± 16.8
% of predicted	90.6 ± 8.1	89.7 ± 5.5	105.3 ± 7.4
HR			
beats/min	168.3 ± 4.7	165.0 ± 7.1	175.1 ± 7.1
% of predicted	89.4 ± 2.4	87.9 ± 2.9	94.8 ± 3.2
VE			
L/min	100.6 ± 7.8	102.3 ± 6.7	112.3 ± 6.4
% of MVV	67.9 ± 3.6	69.3 ± 3.0	79.2 ± 4.2
Lactate (mmol/L)	6.5 ± 0.5	6.2 ± 0.8	7.8 ± 0.8

NOTE. Sources of predicted values are given in text. Values are the mean ± SEM.

Abbreviation: MVV, maximal voluntary ventilation.

Leg Effort During the Incremental Cycle Ergometer Test

Changes in leg effort sensation during exercise are illustrated in Fig 1. At the start of exercise, the two groups had similar Borg ratings for leg effort. However, with increasing workload, the perceived magnitude of effort was significantly greater in normoglycemic and hyperglycemic diabetic patients than in control subjects ($P < .05$). Only at termination of exercise were Borg ratings again similar in both groups. The mean magnitude of leg effort at end-exercise was 7.6 ± 0.5 for control subjects and 7.6 ± 0.6 and 7.5 ± 0.5 for normoglycemic and hyperglycemic patients, respectively (7 = very severe).

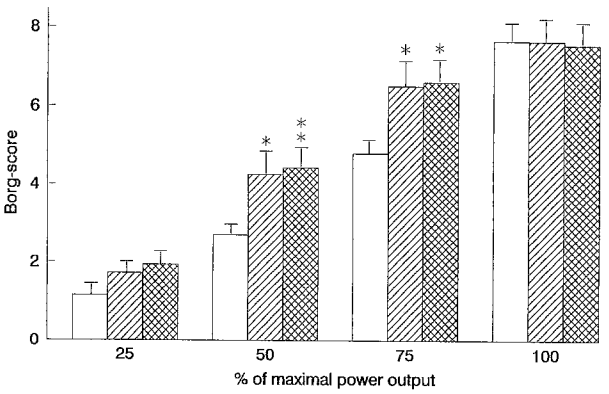

Fig 1. Perceived magnitude of leg effort plotted against power output, expressed as a percentage of W_{max} in normoglycemic (▨) and hyperglycemic (▩) IDDM patients and in control subjects (□). Borg ratings are shown at 25%, 50%, 75%, and 100% of W_{max}. Values are the mean ± SEM. *$P < .05$ v control subjects; **$P < .01$ v control subjects.

Baseline Plasma β-E Concentration and the Plasma β-E Response to Increasing Workloads and Increasing Plasma Lactate Levels

Baseline plasma β-E levels were significantly lower in normoglycemic patients than in control subjects ($P < .01$); hyperglycemia further reduced baseline. β-E levels in diabetic patients ($P < .001$ *v* control subjects; Fig 2). At comparable levels of power output, plasma β-E levels were always significantly lower in diabetic patients than in control subjects (Fig 2). For the control group, the mean β-E concentration was significantly higher at the end of exercise than at the beginning ($P < .001$; Fig 2). In contrast to healthy control subjects, exercise did not increase plasma β-E concentrations in diabetic patients. A significant increase in β-E levels in diabetic patients occurred only during the recovery period; however, even then their plasma β-E levels remained significantly lower than those in the control group. Three minutes after termination of exercise, mean plasma β-E concentration was 38.8 ± 3.8 and 29.5 ± 2.2 pg · mL^{-1} in normoglycemic and hyperglycemic patients, respectively; in control subjects, it was 81.1 ± 8.1 pg · mL^{-1}. In control subjects, a positive linear relationship was found between plasma β-E and lactate levels: β-E = (3.73 · lactate) + 27.5 ($P < .001$, $r = .75$). No such relationship could be demonstrated in the diabetic patients, in whom increased plasma lactate levels led to increased plasma β-E concentrations only in the recovery period, not during exercise.

DISCUSSION

Our study yielded the following results: (1) basal plasma β-E concentrations were significantly lower in normoglycemic and hyperglycemic IDDM patients than in healthy control subjects; (2) in IDDM patients, the ability of the endogenous opioid system to respond to exercise-induced stress was reduced under normoglycemic and hyperglycemic conditions; and (3) at comparable submaximal levels of power output, the perceived intensity of leg effort was significantly higher in normoglycemic and hyperglycemic IDDM patients than in control subjects.

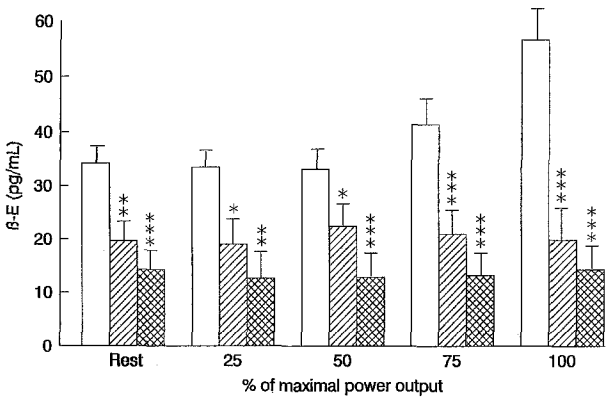

Fig 2. Plasma β-E concentrations in normoglycemic (▨) and hyperglycemic (▩) IDDM patients and in control subjects (□) during exercise. Plasma β-E concentrations are presented at rest and at 25%, 50%, 75%, and 100% of W_{max}. Values are the mean ± SEM. *$P < .05$ *v* control subjects; **$P < .01$ *v* control subjects; ***$P < .001$ *v* control subjects.

The interpretation of changes in β-E levels due to exercise has to be made cautiously. First, the physiological significance of such changes has not been definitely established. Results of animal studies suggest a stimulating effect of β-E on glycogenolysis, gluconeogenesis, and glucose-stimulated insulin secretion.[18,19] There are indications that exercise-induced changes of pain perception are connected with increased levels of β-E in the peripheral blood, and that opioids modulate the perceived effort elicited by exercise.[7,20-22] Considering the correlation between exercise-induced increases in plasma β-E and lactate levels, some investigators suggest that acidosis tolerance might be influenced by opioids.[6,9] These findings indicate that endogenous opioids may well be involved in the body's broad defense against exercise-induced stress. They probably contribute to the integrated hormonal and metabolic response to exercise.[5,23,24]

Second, peripheral β-E levels probably do not reflect central nervous system levels.[25] The pituitary appears to be the main source of circulating β-E in the blood, whereas the brain appears to be the primary source of cerebrospinal fluid (CSF) β-E.[26] A dissociation between these two pools of endogenous opioids could be present. However, Rapaport et al[27] found significant entry of synthetic opioid peptide analogs into the extracellular space of rat brain after intravenous administration. In another animal experiment, it was clearly demonstrated that reflux of β-E from blood into CSF contributed to its increased level in CSF during endotoxin stress.[28] In humans, intravenous infusion of β-E was shown to markedly increase CSF β-E levels.[29] This close correlation is further supported by animal experiments in which stress-induced analgesia was associated with increases in central and peripheral opioid levels.[30,31] In addition, lactic acid accumulation was shown to stimulate both central and peripheral endogenous opioid pathways.[32,33]

Our hyperglycemic patients had no increase in plasma β-E during exercise, and their perceived magnitude of effort sensation at comparable submaximal levels of power output was higher than that in our control subjects. The results of our study may correlate with previously published reports in which acute glucose loading was shown to decrease the antinociceptive potency of morphine and thus the ability to tolerate pain.[1,34] In addition, our study showed that the endogenous opioid system of our normoglycemic diabetic patients had an altered response to exercise, and their perceived magnitude of effort sensation elicited by exercise was also significantly higher than that of the control subjects. Basal plasma β-E levels of our hyperglycemic and normoglycemic patients were also significantly lower than those in control subjects. Although there was a trend in our diabetic patients toward lower β-E levels basally and during exercise under hyperglycemic conditions, the results of our study indicate that irrespective of glucose loading, diabetes per se has a decisive impact on endogenous opioid activity. It has been shown earlier in animal studies that diabetes reduces central and peripheral

levels of β-E and thus the ability of the neuroendocrine system to regulate β-E levels in the pituitary and hypothalamus in response to stress.[2,3,35] In humans, diabetes has been shown to reduce plasma β-E levels and pain tolerance.[1,36,37] Until now, there have been only speculations about the mechanism that causes these alterations in the endogenous opioid system in diabetes. This may be attributed to changes in the neurotransmitter activity, since diabetes is accompanied by significant alterations in neurotransmitter levels and turnover.[38] Another explanation may be that pituitary function per se is altered in diabetes, thus leading to a diminished release of β-E from the pituitary.[2,3] It has also been suggested that the central synthesis of β-E from proopiomelanocortin may be changed in diabetes.[36] Since diabetic patients have a diminished cerebrovascular reserve,[39] cerebral blood flow alterations may contribute to the impaired and delayed response of the endogenous opioid system to stress.

Physical conditioning is known to facilitate exercise-induced secretion of β-E in humans.[23] One can argue therefore that a physical deconditioning of the diabetic patients might have influenced our results. For several reasons, this appears unlikely. Like our diabetic patients, none of our healthy subjects participated in any physical training program. Body mass index was similar in both groups. Furthermore, mean values for FVC and $\dot{V}O_2max$ were not significantly different statistically in the patient group and in the control group. FVC and $\dot{V}O_2max$ are known to be physiologic markers of physical activity.[14,40] Therefore, our results cannot be explained by a decreased physical activity of our diabetic patients.

Recently, it has been demonstrated that type I diabetic patients with and without autonomic neuropathy have a reduced exercise tolerance.[41,42] Macroscopic and microscopic coronary artery disease, left-ventricular contractile dysfunction, peripheral arterial disease restricting the increase in skeletal muscle blood flow during exercise, decreased pyruvate dehydrogenase activity, and reduced muscle glycogen stores were, among others, mentioned as possible causes for the impaired exercise performance of IDDM patients.[41,42] We suggest that the inability of diabetic patients to react to exercise-induced stress by appropriately adjusting plasma β-E levels may account for their reduced tolerance. This hypothesis is supported by the observation that in healthy subjects, pretreatment with the opioid antagonist naloxone increased the perceived effort sensation elicited by exercise, and that patients with coronary artery disease had a better exercise tolerance when their baseline plasma β-E levels were higher.[22,43] Our study therefore contributes to a new understanding of exercise tolerance in IDDM patients.

ACKNOWLEDGMENT

We are indebted to the Central Laboratory of the Lainz Hospital, Vienna, for determination of blood lactate levels.

REFERENCES

1. Morley GK, Mooradian AD, Levine AS, et al: Mechanism of pain in diabetic peripheral neuropathy. Am J Med 77:79-82, 1984

2. Forman LJ, Estilow S, Lewis M, et al: Streptozocin diabetes alters immunoreactive β-endorphin levels and pain perception after 8 wk in female rats. Diabetes 35:1309-1313, 1986

3. Forman LJ, Estilow S, Mead J, et al: Eight weeks of streptozotocin-induced diabetes influences the effects of cold stress on immunoreactive beta-endorphin levels in female rats. Horm Metab Res 10:555-558, 1988

4. Ramabadran K, Bansinath M, Turndorf H, et al: The hyperalgesic effect of naloxone is attenuated in streptozotocin-diabetic mice. Psychopharmacology 97:169-174, 1989

5. Allen M: Activity-generated endorphins: A review of their role in sports science. Can J Appl Sport Sci 8:115-133, 1983

6. Schwarz L, Kindermann W: Changes in β-endorphin levels in response to aerobic and anaerobic exercise. Sports Med 13:25-36, 1992

7. Paulev PE, Thorboll JE, Nielsen U, et al: Opioid involvement in the perception of pain due to endurance exercise in trained man. Jpn J Physiol 39:67-74, 1989

8. Appenzeller O: What makes us run? N Engl J Med 305:578-579, 1981

9. 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 23:30-38, 1983

10. Dyck PJ: Detection, characterization and staging of polyneuropathy: Assessed in diabetics. Muscle Nerve 11:21-32, 1988

11. Wanke T, Abrahamian H, Lahrmann H, et al: No effect of naloxone on ventilatory response to progressive hypercapnia in IDDM-patients. Diabetes 42:282-287, 1993

12. Killian KJ, Summers E, Campbell EJM: Dyspnea and leg effort during incremental cycle ergometry. Am Rev Respir Dis 145:1339-1345, 1992

13. Ruegemer JJ, Squires RW, Marsh HM, et al: Differences between prebreakfast and late afternoon glycemic responses to exercise in IDDM-patients. Diabetes Care 13:104-110, 1990

14. Jones NL: The interpretation of stage 1 exercise test results, in Jones NL (ed): Clinical Exercise Testing. Philadelphia, PA, Saunders, 1988, pp 158-185

15. Luger A, Deuster PA, Kyle SB, et al: Acute hypothalamic-pituitary-adrenal responses to the stress of treadmill exercise. N Engl J Med 316:1309-1315, 1987

16. Quanjer PhD: Standardized lung function testing. Bull Eur Physiopathol Respir 19:1-95, 1983

17. Jones NL: Normal standards, in Jones NL (ed): Clinical Exercise Testing. Saunders, Philadelphia, PA, Saunders, 1988, pp 306-311

18. Allan EM, Green IC, Titheradge MA: The stimulation of glycogenolysis and gluconeogenesis in isolated hepatocytes by opioid peptides. Biochem J 216:507-510, 1983

19. Farrell PA, Sonne B, Mikines K, et al: Stimulatory role for endogenous opioid peptides on postexercise insulin secretion in rats. J Appl Physiol 65:744-749, 1988

20. Jonal MN, Colt EWD, Clarke WC, et al: Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: Effects of naloxone. Pain 19:13-25, 1984

21. Surbey GD, Andrew GM, Cervenko FW, et al: The effect of naloxone on the performance of intense exercise. Med Sci Sport Exerc 15:150, 1983 (abstr)

22. Grossmann A, Bouloux P, Price P, et al: The role of opioid peptides in the hormonal responses to acute exercise in man. Clin Sci 67:483-491, 1984

23. Carr D, Bullen B, Skrinar G, et al: Physical conditioning

facilitates the exercise-induced secretion of beta-endorphin and beta-lipotropin in women. N Engl J Med 305:560-563, 1981

24. Moretti C, Fabbri A, Gnessi L, et al: Naloxone inhibits exercise-induced release of PRL and GH in athletes. Clin Endocrinol (Oxf) 18:135-138, 1983

25. Rossier J, French ED, Rivier C, et al: Foot shock induced stress increases β-endorphin levels in blood but not in the brain. Nature 270:618-620, 1977

26. Santiago TV, Edelman NH: Opioids and breathing. J Appl Physiol 59:1675-1685, 1985

27. Rapaport SI, Klee KD, Pettigren KD, et al: Entry of opioid peptides into the central nervous system. Science 207:84-86, 1979

28. Carr DB, Jones KJ, Bergland RM, et al: Causal links between plasma and CSF endorphin levels in stress: Vector-ARMA analysis. Peptides 6:5-10, 1985 (suppl 1)

29. Gerner RH, Sharp B, Catlin DH: Peripherally administered β-endorphin increases cerebrospinal fluid endorphin immunoreactivity. J Clin Endocrinol Metab 55:358-360, 1982

30. Madden J, Akil H, Patrick RL, et al: Stress induced parallel changes in central opioid levels and pain responsiveness in the rat. Nature 265:358-360, 1977

31. Osgood PF, Murphy JL, Carr DB, et al: Increases in plasma beta-endorphin and tail flick latency in the rat following burn injury. Life Sci 40:547-554, 1987

32. Petrozzino JJ, Scardella AT, Santiago TV, et al: Dichloracetate blocks endogenous opioid effects during inspiratory flow-resistive loading. J Appl Physiol 72:590-596, 1992

33. Goldfarb AH, Hatfield BD, Armstrong D, et al: Plasma beta-endorphin concentration: Response to intensity and duration of exercise. Med Sci Sports Exerc 22:241-244, 1990

34. Simon GS, Dewey WL: Narcotics and diabetes. I. The effects of streptozotocin-induced diabetes on the antinociceptive potency of morphine. J Pharmacol Exp Ther 218:318-323, 1981

35. Timmers K, Vogles NR, Zalenski C, et al: Altered β-endorphin, met- and leu-enkephalins, and enkephalin-containing peptides in pancreas and pituitary of genetically obese diabetic (db/db) mice during development of diabetic syndrome. Diabetes 35:1143-1151, 1986

36. Solerte SB, Fioravanti M, Petraglia F, et al: Plasma β-endorphin, free fatty acids and blood lipid changes in type 2 (non–insulin dependent) diabetic patients. J Endocrinol Invest 11:37-428, 1988

37. Solerte SB, Fioravanti M, Petraglia F, et al: Circulating opioids and plasma renin activity in insulin-dependent diabetics with renal haemodynamic alterations. Nephron 46:194-198, 1987

38. McCall AL: The impact of diabetes on the CNS. Diabetes 41:557-570, 1992

39. Dandona P, James IM, Newburg PA, et al: Cerebral blood flow in diabetes mellitus: Evidence of abnormal cerebrovascular reactivity. Br Med J 2:325-326, 1978

40. Weiss ST: Pulmonary function as a phenotype physiologic marker of cardiovasular morbidity and mortality. Chest 99:265-266, 1991

41. Ramires PR, Forjaz CLM, Silva MER, et al: Exercise tolerance is lower in type 1 diabetics compared with normal young men. Metabolism 42:191-195, 1993

42. Kremser CB, Levitt NS, Borow KM, et al: Oxygen uptake kinetics during exercise in diabetic neuropathy. J Appl Physiol 65:2665-2671, 1988

43. Falcone C, Specchia G, Rondanelli R, et al: Correlation between beta-endorphin plasma levels and anginal symptoms in patients with coronary artery disease. J Am Coll Cardiol 11:719-723, 1988