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Opioid Modulation of Feeding Behavior Following Repeated Exposure to Forced Swimming Exercise in Male Rats[1]

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DAVIS, J. M., D. R. LAMB, G. K. W. YIM AND P. V. MALVEN. *Opioid modulation of feeding behavior following repeated exposure to forced swimming exercise in male rats.* PHARMACOL BIOCHEM BEHAV **23**(5) 709–714, 1985.—Patterns of normal and stimulated food intake (FI) as well as its possible endogenous opioid (EO) modulation were investigated in male rats given regular swimming exercise (trained; TR) and compared with nonexercised sedentary (SED) controls. Rats in the TR group had lower body weights as well as reduced 24 hr FI due to lower nocturnal FI. TR rats also ate less food in response to injections of 2-deoxy-D-glucose (2-DG) but not insulin (INS) when injections were given during the first 4–5 weeks of training. However, this difference between TR and SED rats in the 2-DG induced feeding was not demonstrable after 10 or more weeks of training. Plasma concentrations of immunoreactive B-endorphin (IR-B-ep) were elevated, as expected, in TR rats (10–12 weeks) during nocturnal sampling whereas the nocturnal increase of IR-B-ep was absent in SED controls. However, these SED rats did increase daytime IR-B-ep in response to 2-DG and acute exercise, albeit somewhat less in magnitude when compared to TR rats. Injection of naltrexone (NTX) decreased feeding in TR rats (10–12 weeks) but not in contemporary SED controls. In summary, exercise training modified feeding behavior, and at 4 weeks of training, TR rats ate less in response to opioid-related feeding stimulus of 2-DG, but responded similarly to insulin (relatively opioid independent) treatment. At later stages of training this difference between TR and SED rats disappeared. Moreover, SED rats had atypical profiles of IR-B-ep and reduced hypophagic responses to NTX suggesting that TR rats might have greater EO modulation of feeding at this stage.

Exercise training Opioids Food consumption 2-Deoxy-D-glucose Insulin

ENDOGENOUS opioids, particularly B-endorphin (B-EP), have been implicated in the mechanism of overeating and obesity in rodents and humans [12, 15, 20]. Furthermore, data from our laboratory indicate that endogenous opioids are associated with food intake following a single bout of strenuous swimming exercise in male rats [7]. Therefore, we hypothesized that adaptive changes in one or more endogenous opioid systems may also be associated with the long-term changes in food intake observed during chronic exercise training.

It is well established that a schedule of daily 20–120 min sessions of running or swimming is associated with reductions in 24 hr food intake in male rats as well as humans [4, 17, 18], and that this reduction may be more related to the intensity of the exercise than to the total energy expenditure [9,11]. However, no attempt has been made to relate these changes in food intake to changes in endogenous opioid function. Information is also lacking regarding a more general adaptation of the endogenous opioid system to chronic swim training. An adaptation of the hypothalamic, pituitary-adrenal system to strenuous swimming stress is strongly suggested by Selye's classic test on stress [21]. Although only one study reported adaptive changes in plasma B-EP levels following exercise training [5], adaptive changes in pituitary and plasma B-EP levels may be implied from changes in plasma glucocorticoid levels [10, 23, 29] because changes in plasma B-EP levels are usually associated with changes in adrenocorticotropin (ACTH) and are regulated by similar controls [1].

The present experiments were designed to determine if repeated exposure to short duration, high-intensity swimming exercise in male rats was associated with changes in plasma B-endorphin (B-ep) or other measures of opioid modulation of food intake. Some studies were completed early in the training period, i.e., between the fourth and fifth weeks (Experiments 1 and 2), whereas other studies occurred in the final 3 weeks of the 12 week training period (Experiments 3, 4, 5 and 6). The experimental strategy was to compare the following variables in trained and sedentary rats: (a) feeding responses to stimuli previously charac-

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terized as "opioid-dependent," i.e., 2-deoxy-D-glucose (2-DG) and spontaneous nocturnal feeding, and relatively "opioid-independent," i.e., exogenous insulin; (b) inhibition of feeding behavior by the opiate receptor blocker, naltrexone; and (c) basal and stimulated concentrations of immunoreactive B-EP (Ir-B-ep) in blood plasma. It was hypothesized that these comparisons would provide insight into exercise-induced adaptive changes in the endogenous opioid regulation of food intake and in the regulation of Ir-B-ep release into the blood.

METHOD

General Methodology

Male Sprague-Dawley rats (200–225 g) were purchased from Harlan Sprague-Dawley, Inc. (Indianapolis, IN) and were housed as previously described [7]. During the first week the animals were handled and weighed daily. Increases in body weight were used as an index of animal's general health. Prior to the experimental period the rats were divided into two groups (n=36 each) of equal body weight and designated as either trained (TR) or sedentary (SED). Rats in the SED group remained in their individual cages except when removed for specific experiments and/or periodic weighing. The training program for TR rats consisted of swimming for up to 1 hr during the light phase (between 1500 and 1800 hr) 5 days per week for a period of 12 weeks. The swimming protocol has been previously described [7]. Body weights were determined weekly. During the first 4 weeks of training, the duration of swimming exercise was progressively increased from 10 to 60 min per day. The 60 min duration was maintained for the final 8 weeks of training.

Food intake was measured as described previously [7,8]. In all experiments involving drug treatments, saline was injected for at least 3 days prior to the experimental day to familiarize the rats with the injection procedure. At least 5 days elapsed between consecutive experiments. All data were analyzed with Student's t-test or analysis of variance (ANOVA) as appropriate. When significant F-ratios were found with ANOVA, differences among individual means were analyzed with Newman-Keuls test for multiple comparisons. The hypothesis of equal means was rejected at $p<0.05$.

Experiment 1 (4th Week of Training)

Diurnal patterns of food intake were measured in the TR and SED groups from 2000 to 0800 hr (dark period) and from 0800 to 2000 hr (light period) on two consecutive 24 hour cycles 4 weeks after initiation of training. Diurnal food intake was measured on days when the TR group swam (Experiment 1A) and about 8 days later on a nonswimming day beginning 24 hr after the preceding swim session (Experiment 1B).

Experiment 2 (5th Week of Training)

Two days following Experiment 1A, both the TR and SED groups were divided into three subgroups and assigned to receive an injection of either saline, 2-DG, or INS. Injection of either saline (0.9% NaCl), 2-DG (400 mg/kg), or INS (10 U/kg) was given at 1200 hr, approximately 20 hr following the preceding swim in TR rats. Post-injection food intake was measured from 1200 to 1400 hr and from 1400 to 1800 hr.

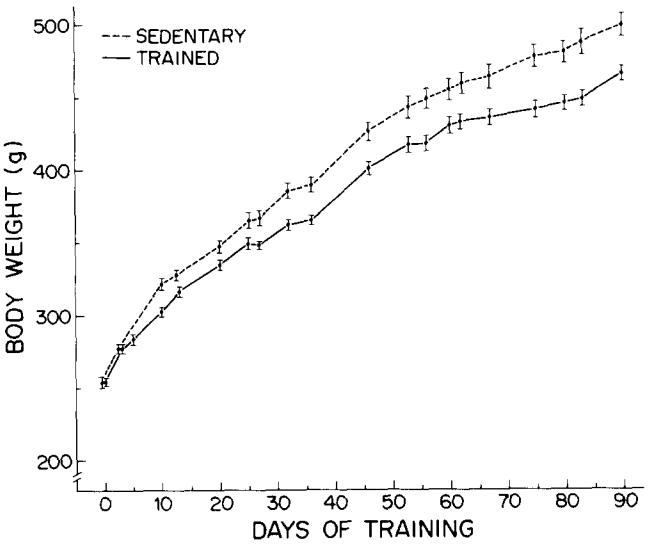

FIG. 1. Body weights for trained and sedentary rats. Each point represents the mean (±SE) of 30–36 rats. Statistically significant ($p<0.05$) differences were found from day 10 through day 90.

Experiment 3 (10th–12th Week of Training)

Food intakes for SED and TR groups following the injection of 2-DG and insulin were again compared. Each group was divided into three subgroups (n=11) and injected with either saline, 2-DG, or INS as described for Experiment 2. The injections were given at 1200 hr, and food intake was measured from 1200 to 1400 hr, 1400 to 1600 hr, and 1600 to 1800 hr. As in Experiment 2, drugs were injected 20 hr following the preceding swim in TR rats.

Experiment 4 (10th–12th Week of Training)

Naltrexone was tested at four dosages for its ability to antagonize nocturnal feeding in the TR and SED rats. Testing was done on a day when TR rats swam as usual. The TR and SED group were divided into five subgroups and assigned to one of four naltrexone dosage groups or to a control saline group. Naltrexone was prepared in 0.06, 0.25, 1.0, and 4.0 mg/kg dosages and injected subcutaneously about 15 min prior to onset of darkness in the animal room. Separate persons injected the TR and SED animals progressing from the lowest to the highest dosages. Five minutes following injection of the last rat, a premeasured portion of food was placed on each cage floor, and food intake was measured from 2000 to 0800 hr.

Experiments 5 and 6 (10th–12th Week of Training)

SED and TR rats that had not swam for 24 hr were rapidly decapitated for estimation of basal concentrations of plasma Ir-B-ep during the light period (1100–1130 hr) or during the dark period (2045–2145 hr). Other rats from the TR and SED groups were decapitated between 2045 and 2145 hr, but these rats had swam for about 60 min between 1700 and 1800 hr on the day of decapitation. It should be noted that in contrast to TR rats, SED rats were not accustomed to swimming exercise.

Other subgroups of TR and SED rats were decapitated

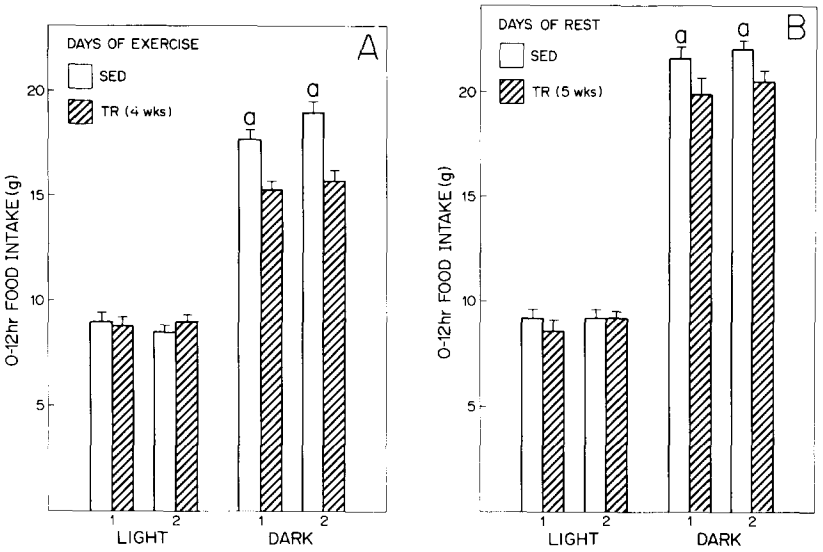

FIG. 2. Food intakes (g/12 hr; ±SE) in trained (TR) and sedentary (SED) rats measured separately for the illuminated period (LIGHT) and for darkness (DARK) on two consecutive days (denoted 1 and 2). Panel A represents days when TR rats swam and Panel B represents two consecutive days when TR rats did not swim. a=$p<0.05$ vs. TR rats.

during the light period but immediately after completion of a 60 min swim (with 2% of body weight attached) or 60 min after an injection of 2-DG (400 mg/kg) at about 1200 hr. Control rats for both treatments remained in their cages for 60 min prior to decapitation.

RESULTS AND DISCUSSION

Mean body weight of the TR group was reduced by 6% ($p<0.05$) compared to the SED group by the second week of the training period and remained 4–8% lower than that of the SED group for the remainder of the study (Fig. 1). These data confirmed previous work that demonstrated a training-induced reduction in the growth of male rodents [2, 6, 9, 11, 16, 19, 22, 25, 26].

Experiment 1

Both TR and SED rats had diurnal variation ($p<0.0001$) in 12 hr FI on days of exercise (Fig. 2A) and of rest (Fig. 2B). FI also differed ($p<0.01$) between TR and SED rats on both days. The interaction of treatment (TR or SED) and diurnal period was also significant ($p<0.0001$ in Experiment 1A; $p<0.05$ in Experiment 1B). Post hoc comparisons among individual means (Newman-Keuls) confirmed this interaction by showing that differences between TR and SED groups only occurred during darkness when FI was large. Although training-induced reductions in nocturnal food intake occurred on both days of rest and on swim days, the percentage reduction was greater on days of swimming (8% vs. 16%, respectively; Fig. 2A, 2B). Therefore, the nocturnal hypophagia associated with swim training appears to be at least partly an adaptation rather than simply an acute response to a single bout of swimming.

Involvement of endogenous opioids in exercise-induced depressions in nocturnal feeding is uncertain. However, nocturnal feeding can be reduced by opiate receptor antagonists [13,14], and elevated feeding during darkness is accompanied by a doubling of plasma Ir-B-ep [8]. These results are

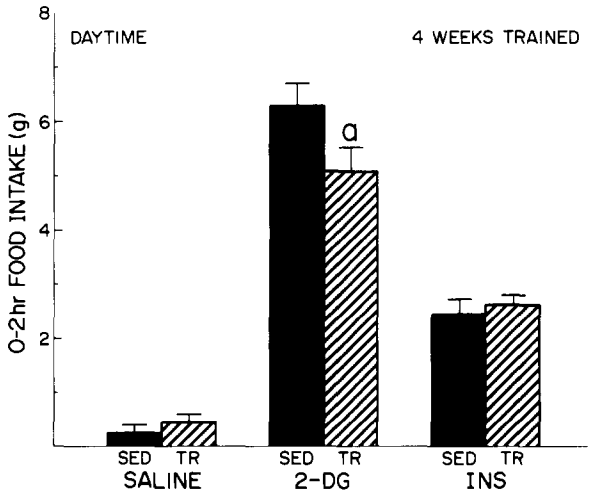

FIG. 3. Stimulation of food intake (g/2 hr) during the light period 4 weeks following initiation of training. Saline (0.9% NaCl), 2-DG (400 mg/kg), and insulin (INS: 10 U/kg) were injected at 1200 hr, approximately 20 hr following the last swim in the trained rats (TR). Each bar represents the mean (±SE) food intake for 11 rats. a=$p<0.05$ vs. sedentary control rats (SED).

at least consistent with hypothesis that rats trained for 4 weeks have a nocturnal deficiency of endogenous opioids associated with the nocturnal hypophagia.

Experiments 2 and 3

Daytime FI stimulated by injections of 2-DG and INS were compared between TR and SED rats at 4 weeks (Fig. 3) and 10 weeks (data not shown) of training or sedentary existence. 2-DG induced feeding was attenuated ($p<0.05$) in TR

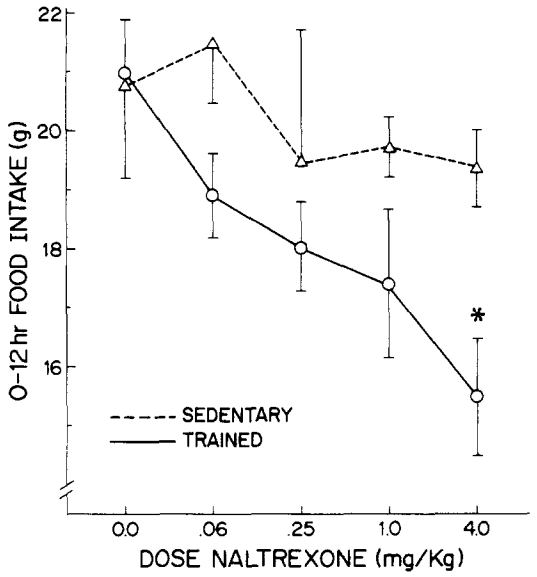

FIG. 4. Dose-dependent reduction of food intake (g/12 hr) during animal room dark period by naltrexone in rats trained by swimming for 12 weeks, but not in sedentary controls. Each point represents mean (±SE) for 6 rats. *=$p<0.05$ vs. 0.0 dose of naltrexone.

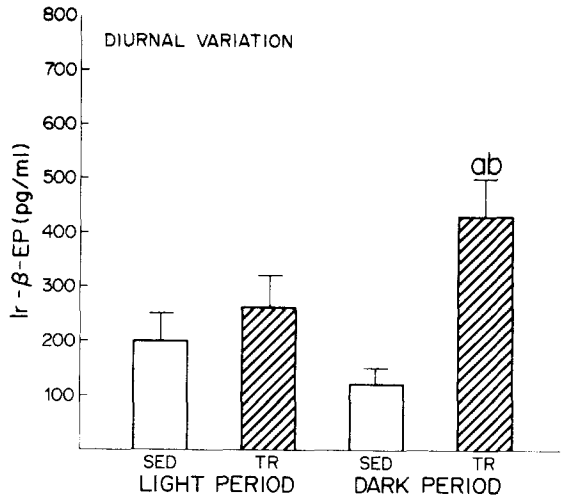

FIG. 5. Diurnal variation in basal concentrations of plasma immunoreactive B-endorphin (Ir-B-ep) in trained (TR) and sedentary (SED) rats after 12 weeks of training. Two subgroups (n=6 each) of the TR and SED groups were decapitated between 2045 and 2145 hr (DARK PERIOD) or between 1100 and 1130 hr (LIGHT PERIOD), and trunk blood was collected for Ir-B-EP analysis. Bars represent mean (±SE) plasma Ir-B-ep concentrations (pg/ml). a=$p<0.05$ vs. TR-LIGHT PERIOD, b=$p<0.001$ vs. SED-DARK PERIOD.

as compared to SED rats at 4 weeks but not at 10 weeks. INS induced feeding was not affected by training. Because these feedings stimuli were injected at least 20 hr after the previous swim, these 2-DG results at 4 weeks of training may reflect a chronic deficiency of unidentified EO hypothesized to be activated by 2-DG [27].

Experiment 4

Whereas 12 hr nocturnal FI had been reduced in TR rats at 4 weeks of training (Fig. 2), there were no differences in this parameter at 11 weeks (compare 0.0 doses in Fig. 4). However, the ability of NTX to inhibit nocturnal FI appeared to differ between groups (Fig. 4). In a 2-way ANOVA, the main effects of NTX dose ($p<0.01$) were significant, but their interaction was nonsignificant. Post hoc comparison of individual means revealed that the 4 mg/kg dose of NTX decreased ($p<0.05$) 12 hr nocturnal FI only in TR rats. This apparently greater involvement of EO in the feeding behavior of TR rats is inconsistent with the hypothesized deficiency of opioids during training. The reasons for the inability of naltrexone to reduce food intake during the dark period in the SED group are not apparent. Lowy, Maickel and Yim [13] showed previously that the shorter acting opiate antagonist, naloxone, significantly depressed 3 hr food intake during darkness in non-trained rats.

Experiments 5 and 6

Figure 5 summarizes the diurnal variation in basal concentrations of plasma Ir-B-ep for TR and SED rats. Concentrations representing the dark period were from a combination of rats that did not exercise on the day of decapitation and those that swam for 60 min between 1700 and 1800 hr. This combination of data was possible because plasma Ir-B-ep was not affected by the exercise ending about 3 hr earlier. The means for rested and exercised SED rats were

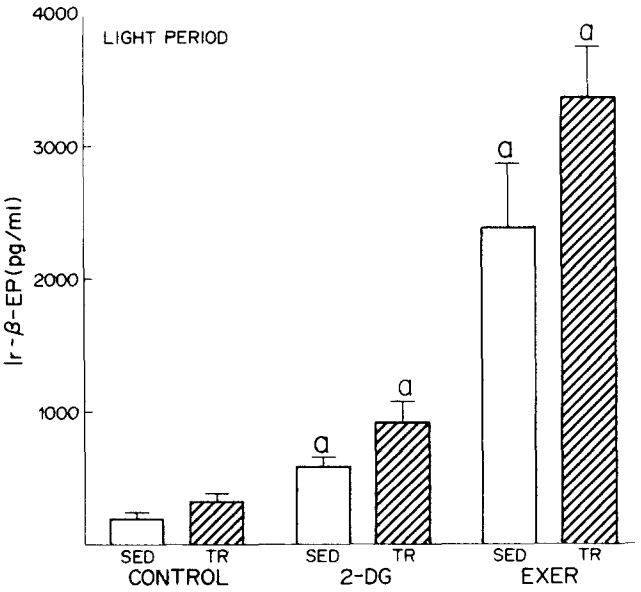

FIG. 6. Induced increases of plasma immunoreactive B-endorphin (Ir-B-ep) during the light period and following 2-deoxy-D-glucose (2-DG) and swimming (EXER) in trained (TR) and sedentary (SED) rats. Two subgroups (n=6 each) of the TR and SED groups were either injected with 2-DG (400 mg/kg) or forced to swim 60 min. Control (CON) rats remained in their cages. Bars represent mean (±SE) for blood samples 60 min after 2-DG injection or initiation of swimming. a=$p<0.05$ vs. appropriate control group.

120±40 and 120±50 pg/ml, respectively. The means for rested and exercised TR rats were 410±120 and 510±60 pg/ml, respectively.

TABLE 1

BODY WEIGHT, DIURNAL VARIATION OF PLASMA β-EP-ir, AND INHIBITION OF NOCTURNAL FEEDING BEHAVIOR BY OPIATE ANTAGONISTS IN THREE GROUPS DIFFERING IN AGE, BODY WEIGHT, AND/OR ACTIVITY SCHEDULE

Group	Approximate Body Weight (g)	Plasma Ir-β-ep (pg/ml)* Light period	Plasma Ir-β-ep (pg/ml)* Dark period	Inhibition of Nocturnal Feeding by Opiate Antagonists
Young Untrained	200–350	160 ± 60†	480 ± 50†	YES‡
Older Untrained	500	200 ± 50§	120 ± 30§	NO¶
Older Trained	460	260 ± 60§	430 ± 70§	YES¶

*Means ± SE.
†Reference [8].
‡References [3] and [13].
§Fig. 6.
¶Fig. 5.

Plasma Ir-B-ep concentrations were similar in TR and SED rats during the light period but markedly different during the dark period (Fig. 5), when the differences in food intake also occurred (Fig. 2). Furthermore, only TR rats showed significant ($p<0.05$) light:dark variation in plasma Ir-B-ep. The lack of diurnal variation in Ir-B-ep of SED rats relate to the failure of naltrexone to antagonize nocturnal feeding in SED rats (Fig. 4) since both results are consistent with reduced opioid modulation of feeding behavior in the SED animals

Injections of 2-DG or acute swimming exercise during the light period both increased ($p<0.001$) plasma Ir-B-ep (Fig. 6). The poststimulus concentrations of Ir-B-ep did not differ significantly between TR and SED rats, although there was a tendency for higher concentrations ($p<0.10$) in TR rats. However, when the poststimulus concentration of Ir-B-ep was expressed as a multiple of the control concentration, the increase following 2-DG was 3-fold for both groups, and the increase following exercise was 13-fold for both groups.

The precise relationship of the present estimates of plasma Ir-B-ep to exercise-induced changes in feeding behavior is unclear. Only a portion of the Ir-B-ep estimate is likely to be biologically active B-EP because B-lipotropin crossreacts in the radioimmunoassay [8]. Moreover, plasma levels of B-EP may be too low to physiologically modulate feeding behavior, and B-EP activity within the central nervous system may be ultimately responsible for the physiological and/or behavioral effects [11]. Alternatively, other opioid peptides in blood, cerebrospinal fluid, or brain tissue may mediate the exercise-induced changes in feeding behavior. However, there is evidence to indicate that changes in plasma Ir-B-ep may be an index of endogenous opioid activity associated with feeding [8].

OVERALL DISCUSSION

The experiments reported here cannot distinguish between the specific effects of the muscle contractions associated with swim training and the nonspecific effects of the "emotional" stress inherent in the swim. Accordingly, we recognize that our conclusions about exercise must also include the nonspecific stress of the exercise training. To our knowledge there are no published reports which have separated the effects of the "metabolic stress" of intense physical exercise from other non-specific stress effects. This is an intriguing area and one which deserves careful systematic research but was beyond the scope of the current investigation.

The results obtained during the early phases of training (Figs. 2 and 3) were consistent with the hypothesis that an endogenous opioid deficiency is at least partially responsible for alterations in feeding behavior observed following 4 weeks of swim training. Food consumption was attenuated in the TR rats (relative to SED controls) during feeding stimulated by darkness and 2-DG administration (opioid-dependent stimuli), but it was unchanged during the light period and following insulin injection (relatively opioid-independent feeding stimuli). Although these data were consisten with our hypothesis, they were are not conclusive. It is conceivable, for example, that the observed hypophagia during darkness and the attenuation of feeding in responses to 2-DG were associated with a prolonged effect of an acute swim and did not represent a chronic adaptation to training. Our opioid hypothesis would have been more strongly confirmed if decrements in plasma Ir-B-ep had accompanied the reduced feeding in darkness and following 2-DG injection and if opiate receptor blockade had lesser effects on nocturnal feeding in trained rats compared to controls. However, these experiments were not performed because greater effects were expected after more prolonged training.

A series of unexpected results were obtained after 10 weeks of swim training. Spontaneous nocturnal food intake was similar in TR and SED rats (0.0 dose of NTX in Fig. 4). Feeding responses to 2-DG were similar at 10 weeks in TR and SED rats (Fig. 4), whereas they had differed at 4 weeks (Fig. 3). In addition, the largest dose of NTX depressed nocturnal food intake in TR but not SED rats (Fig. 4). Plasma Ir-B-ep was also unexpectedly depressed in SED rats during the dark period (Fig. 5). Therefore, the results obtained after 10 weeks of training were inconsistent with the hypothesized

training-induced reduction in opioid-mediated feeding. On the contrary, it might now be hypothesized that the SED rats had a reduced degree of opioid modulation of feeding except for their normal feeding response to 2-DG.

It is interesting to note that the SED rats seem to be abnormal, when compared to younger untrained rats, with respect to endogenous opioid involvement in feeding behavior. The SED rats showed no increase in plasma Ir-B-ep during darkness, and their nocturnal food intake was unaffected by opiate receptor blockade. It has been shown previously in younger rats (approximately 200–350 g) that nocturnal feeding is accompanied by significant elevations in plasms Ir-B-ep [8], and is effectively antagonized by opiate receptor blocking agents [3, 13, 14]. The precise mechanisms responsible for these observations cannot be elucidated from the experiments reported here. In an effort to clarify the apparent relationships among exercise training, body weight (and/or age), plasma Ir-B-ep, and inhibition of nocturnal feeding by opioid antagonists, a retrospective comparison of data from various studies in this laboratory is presented in Table 1. The similarity between young untrained rats and older trained rats in diurnal profiles of plasma Ir-B-ep and in inhibition of nocturnal feeding suggest that exercise training may delay the onset of specific age-related processes that involve: (1) attenuated Ir-B-ep release in response to darkness, and (2) loss of endogenous opioid involvement in certain types of feeding behavior. On the other hand, the differences in age between rats that weigh 200–350 g and those weighing 460–500 g is relatively small, and it is possible that phenomena other than "aging" might better explain the apparent differences among groups shown in Table 1. For example, opioid modulation of feeding might be adversely affected in rats who are allowed to remain sedentary for 10–12 weeks.

In conclusion, the data presented in this paper as well as the preceeding paper [7] are consistent with the hypothesis of an endogenous opioid involvement in the brief period of hyperphagia immediately after strenuous swimming in male rats, but they do not provide sufficient evidence to demonstrate an involvement of endogenous opioids in the more prolonged hypophagia following an acute bout of swimming [7]. The present data suggest some reduction in the modulation of feeding by endogenous opiates following 4–5 weeks of swim training. However, after 10–12 weeks of training, TR rats appeared to have more, not less, opioid modulation of feeding and diurnal secretion of Ir-B-ep compared to SED controls which had lived a sedentary existance for the entire period of training.

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