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Exercise and Endogenous Opiates

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INTRODUCTION (ENDOGENOUS OPIATES)

Endogenous opiate-like substances were first discovered in the mid-1970s, when opioid receptors were identified and located within the brain and hypothalamus (80). This led to the discovery that endogenous opioid-like molecules, enkephalins (41) and endorphins (6, 62), were produced within the CNS. Subsequently another class of opiate-like molecules known as dynorphins was identified as being synthesized within the body (33). Endogenous opiates therefore fall into three major classes of substances: *endorphins*, a peptide of 31 amino acids long; *enkephalins*, smaller peptide molecules of five amino acids in length (denoted either as leu- or met-, based on the terminal carboxyl amino acid of the peptide); and *dynorphins*, located in the posterior lobe of the pituitary gland (54) and gastrointestinal tract (35) with a 13 amino acid length.

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Enkephalins were first noted in areas of the brain and parts of the endocrine system. The original studies noted that both endorphins and enkephalins were important regulators of pain (3, 62). However, more recent studies have identified that enkephalins play an important role not only with pain regulation but with certain behaviors, cardiac function, cellular growth, immunity, and ischemic tolerance. Various tissues (heart, smooth and skeletal muscle, kidney, and intestines) in animals and humans have recently been shown to have proenkephalin expression (14). Recently, inflammatory cells were shown to produce and release these opiates, and endorphins seem to be involved not only in immune function (51, 52, 72), pain modulation (93), and the exercise pressor response (43, 73, 97) but also in metabolic control (43, 50, 66, 101). Therefore, there are numerous challenges to be clarified concerning the role of these endogenous opiates, on these processes as they relate to exercise. This is especially true dealing with the control of cellular functions not only under normal conditions but when acute and chronic exercise stress is imposed.

Beta-endorphins (β E) were first identified within specific regions of the brain and the hypothalamus. The release of β E into the peripheral circulation was first ascribed to the release from the anterior pituitary gland after being activated by several factors within the hypothalamus. These factors activate the anterior pituitary gland to synthesize the parent molecule pro-opiomelanocortin (POMC) which can be cleaved into various active components, one of them being β E. β E is therefore an important neurotransmitter within the brain and a neurohormone outside the central nervous system when released from the anterior pituitary gland into the circulation, to act on receptors on numerous target tissues throughout the body.

The molecule POMC, the precursor polypeptide for several factors that arise from the hypothalamus and the paraventricular nucleus (PVN) in the brain, can be stimulated to shorter active peptides. POMC has a section towards the C terminus known as β -lipotropin (1–89 amino acids) that ultimately is cleaved to β -lipotropin (1–56) and β E (59–89). Both β E and β -lipotropin molecules help to mobilize lipid molecules from adipose tissue. Originally the assays that were developed to measure these molecules did not effectively differentiate between β -lipotropin and β E, which were thus denoted as having both β -lipotropin/ β E activities. β E is also known to act as a neurotransmitter within the brain.

There is limited information related to exercise and brain β E modulation (39, 83, 90). β E immunoactivity in cerebrospinal fluid (CSF) of spontaneously hypertensive rats was shown to be significantly higher (about twofold) in runners (5–6 weeks) than in controls (39). This latter study also reported that CSF β E was elevated up to 48 h after cessation of voluntary wheel running. It was suggested that this β E effect may be at least partially responsible for the beneficial effect of exercise on controlling blood pressure (39). β E immunoactivity taken from CSF in dogs was shown to increase with low-intensity exercise but not with high-intensity exercise (83). In contrast, circulating β E immunoactivity increased in these dogs at both intensities of exercise (83). This indicates that the β E level within the brain is not reflected by the amount of β E within the circulation. Rat brain receptor binding of [3H]diprenorphine, a β E analog, was not significantly elevated 1 h following a swim but was shown to increase in several regions (5 of 6 rat brain 1 areas) 2 h after the exercise (90). It is unclear if this was related to changes in β E concentration or a change in the availability of the receptor. When naloxone (a receptor antagonist for β E)

was injected into the brain ventricles after 5 weeks of exercise training, the increase in the pain threshold that occurred with the exercise was abolished (94). This suggests that the opioids were involved in elevating pain threshold in response to exercise training in these rats. Clearly more work is needed in this area. The specific areas of the brain that might be involved with BE and pain regulation in response to different types of exercise still needs further investigation.

β E within the circulation has been implicated in a number of processes including immune function, pain modulation, and assisting in glucose and lipid homeostasis. The major function of these endogenous opiate-like molecules was first identified as modulators of pain and euphoria based on the receptors they activated. As a result of this, the phenomena known as “runner’s high,” “second wind,” and “exercise dependency” were postulated to be related to this endogenous activity.

This chapter will summarize what is currently known about the stimulation of these endogenous opiates in response to exercise or physical activity. The influence of an acute bout of exercise on the β E response will be presented first as these studies were the impetus of the original research. The influence of training on β E will then be presented. The influence of an acute bout of exercise on enkephalins will then be presented. This will be followed by the influence of training on enkephalins. The physiological mechanisms responsible for the activation and the secretion of these substances will be discussed when known and related to functional outcomes when possible.

INFLUENCE OF ACUTE EXERCISE ON β E LEVELS

The initial studies that were conducted to examine the impact of exercise on endogenous β E levels utilized various modes of exercise. The original articles examined various activities such as running at various distances to determine if blood β E level was elevated (10, 12, 13, 100). These studies noted elevated β E after the activities. This led to more controlled studies utilizing incremental graded exercise tests within laboratories to ascertain the β E response (31, 36, 37, 69, 75, 84). These studies suggest that blood β E can increase from 1.5 to 7-fold following these graded exercise tests. The large variation in the β E response was in part attributed to procedural methods for the exercise tests as well as methods to determine β E.

AEROBIC EXERCISE AT VARIOUS WORK INTENSITIES RELATED TO % VO_2 MAX (AEROBIC CAPACITY)

Several studies determined if there was an intensity of exercise effect on the blood β E level. McMurray et al. (68) was one of the first studies to examine the β E response to a specific exercise intensity. Donovan and Andrew (16) noted that β E did not increase after 8 min of cycling at 25% and 50% VO_2 max but increased after 75% VO_2 max after similar duration. They also noted a greater increase in β E at 95% VO_2 max. Goldfarb et al. in that same year examined several intensities of exercise (60, 70, and 80% VO_2 max cycling exercise) to determine if there was a critical intensity needed to induce circulating β E increases (29). β E concentration increased in the two higher exercise intensities but not at 60% VO_2 max. The time course of β E changes at these exercise intensities up to 30 min of exercise was examined with β E increases occurring

sooner with the highest exercise intensity (by 5 min). Research comparing 60% VO_2 max and 80% VO_2 max as well as self-paced running for 30 min noted only an increase after the 60% run (20); however they utilized βE /B-lipotrophin immunoreactivity. A run at 60% VO_2 max for 60 min noted no change in βE (61). Exercise at 80% VO_2 max for 30 min with or without naloxone increased βE with a greater increase with naloxone (1). These studies taken together suggest that circulating βE can increase with an appropriate minimal intensity of exercise ($>60\%$ VO_2 max) but this is not always the case. Later it was reported that gender did not influence the βE response to either 60 or 80% VO_2 max (32, 36, 85).

It was noted that menstrual cycle had minimal effects on the exercise βE response in women (28, 32). The time course information also suggested that higher intensities of exercise would result in βE increases more rapidly (20, 22, 31, 36). However, other factors might have differed which could have contributed to the discrepancy in the literature such as nutritional status of the individuals, time of day, immune function, and training status. Farrell et al. utilized well-trained endurance athletes and noted that βE +/ β -lipotropin levels only increased at 92% VO_2 max whereas lower intensities did not elicit significant increases (20).

Instead of a critical intensity related to one's aerobic capacity, other studies related the increase in circulating βE to the lactate threshold (89). They plotted the change in lactate with increased work intensity and compared the βE response. Incremental increases in exercise intensity elevated circulating βE levels and showed a similar pattern of change as blood lactate. However, it should be noted that these similar changes are only for short-duration incremental exercise. For activities with longer duration, the βE increase does not always coincide with lactate changes (29). In addition, other factors such as diet, training status, and immune function can influence the βE response.

HIGH-INTENSITY BOUTS WITH AN ANAEROBIC COMPONENT

Short bouts of highly intensive exercise (anaerobic exercise), consisting of various types of exercise from a few seconds up to several minutes duration, can induce an increase of βE . A few studies have reported that βE concentration in the circulation can increase about 2–4-fold above resting with these high-intensity anaerobic exercise bouts (22, 69, 84, 89). It was also noted that there was a positive relationship between lactate and the βE response to the exercise (89). These authors also noted a significant increase in blood catecholamines with these exercises that correlated with the maximal lactate concentrations.

Resistance exercise as a stimulus to augment circulating βE concentration in humans has only a limited number of published studies. Conflicting results have been reported and this may be related to differences in subjects, type of exercise intensity, workload volume, and time of measurement. Typically the resistance exercise was related to the person's 1-repetition maximum (1-RM), i.e., the maximum weight that can be lifted or pushed/pulled by a subject with maximal effort. Often the load is referenced as a percentage of this 1-RM. Circulating βE level increased in response to high total workloads (55). These authors noted that the total work, rest to work ratio, and total force needed most likely influenced the βE response. An increase in βE in 28 elite male weight lifters was also reported after a moderate- to high-intensity workload (57). An increase in βE

level was also reported after three sets of work at 85% 1-RM in females but only was significantly elevated (3.7-fold) when the women were in a negative energy balance (102). An increased β E/ β lipotropin level was reported in response to weight lifting in five males (18).

In contrast, low-volume resistance exercise did not result in any change in β E levels (55). Furthermore, blood β E level based on immunoreactivity decreased after exercise compared to at rest in ten male and ten female college-aged students who performed three sets of eight repetitions at 80% 1-RM on four exercises (81). This same group had reported earlier that resistance-trained subjects ($N=6$) showed no change in blood β E level compared to baseline after three sets of eight repetitions at 80% 1-RM (82). Both resistance exercise and treadmill exercise were reported to significantly increase circulating β E/B-lipotropin immunoreactivity (18). Unfortunately the intensity and volume of exercise was not available. McGowan et al. however noted a decrease in β E concentration after exercise at 80% 1-RM in 20 college-aged subjects (both males and females) (67). It appears that resistance exercise of sufficient intensity and volume (workload) can result in a transient β E increase within the circulation in both men and women but this finding is sometimes equivocal.

INFLUENCE OF TRAINING ON BETA-ENDORPHIN LEVELS

The training status of the individual probably should influence the response to exercise for a number of reasons. One reason is related to the relative intensity of the exercise. Well-trained athletes can typically perform at a greater absolute workload and usually would exercise at a higher relative workload compared to an untrained individual. Therefore, when comparing the β E response one should compare the absolute workload and the relative intensity. In addition, other factors might influence the secretion of β E such as the diet or immune function which can be influenced by training. Typically one would expect a downregulation on the secretion of β E to a similar absolute workload. However, there could be an upregulation of the capacity of the hypothalamic–pituitary–adrenal (HPA) axis in trained individuals.

INFLUENCE OF ENDURANCE TRAINING

Resting levels of β E in endurance-trained individuals were reported to be lower (65) or unchanged (30, 36, 37, 40). The studies that reported no changes were mostly cross-sectional studies. In contrast, the studies that reported lower levels used an endurance training program and compared the β E level before and after the training program at rest. In contrast, Heitkamp reported that women who trained three times per week for 30 min per day at their individualized lactate threshold did not have changes to their resting β E (36). Harber and associates compared normal 10 eumenorrheic sedentary, 11 eumenorrheic-trained, and 11 amenorrheic-trained women and reported that β E varied considerably but there was no menstrual cycle effect at rest on β E (34). They also noted that resting β E levels were higher in the trained women compared to the sedentary women. Goldfarb et al. reported a trend for lower β E levels during the luteal phase of the menstrual cycle compared with the follicular phase, but this did not reach significance (32). They also noted no significant difference in resting levels of β E comparing men and women.

Therefore, there is currently no consensus in the literature as to the effect of endurance training on resting β E levels.

The findings for β E during exercise are in slightly better agreement. One early study reported a higher β E concentration after 4 months of aerobic training six times per week (10). They reported that the β E level was higher cycling at 85% max heart rate (HR) than before training. This occurred after 2 months of training with no further changes through the rest of the training. It should be noted however that to elicit a similar 85% max HR, the subjects worked at a greater absolute workload.

Most of the other studies have reported no detectable differences in trained and untrained state regardless if it was a cross-sectional design (30) or longitudinal design (7, 19, 36, 37, 40). Goldfarb et al. compared untrained ($N=6$) and trained ($N=6$) cyclists who cycled for 30 min at 60, 70, and 80% VO_2 max with subjects randomly assigned in a counterbalanced order (30). There was no difference in the β E concentration for the trained and untrained at similar relative workloads despite higher absolute workloads for the trained. Both untrained and trained groups responded with higher β E concentrations for the 70 and 80% workloads compared to rest and the 60% VO_2 max. Heitkamp et al. reported that after training the β E response was comparable but was obtained at higher absolute workloads for the trained subjects (36). They also reported that after training the recovery β E was lower suggesting faster removal of the β E. Howlett et al. also reported that there was no difference in β E concentration after endurance training at maximal workloads but met-enkephalin concentration was reduced after 4 months of training (40). Bullen et al. reported greater peak β E/ β -lipotrophin after exercise after 8 weeks of cycling training in seven women (7). Engfred noted there were similar β E increases after 5 weeks of cycling training at 70% VO_2 max to cycling to exhaustion (20). A 12% increase in VO_2 max occurred after 5 weeks of training so that the workload to elicit the cycling after training was at a higher absolute workload. In conclusion, it appears that the blood β E concentration will be similar to before training if the workload is at the same relative intensity of aerobic capacity. This would require a higher absolute workload for the trained individual.

INFLUENCE OF RESISTANCE TRAINING ON CIRCULATING β E

Unfortunately there are few studies that have examined the influence of resistance training and circulating β E. There are no published studies found which indicate that β E concentration would change at rest or at any specific workload or a percentage (%) of one's maximal capacity with resistance training. Fry and coworkers reported similar β E concentration after both 4 and 9 weeks of resistance training to baseline levels (25). It is important to note that most of the resistance research typically utilized resistance trained subjects. As noted above, higher total work volume with resistance exercise resulted in greater increases in circulating β E (56).

β E AND IMMUNE SYSTEM

β E within the circulation has been implicated in a number of processes including modulation of immune function, pain modulation, blood pressure regulation, and assisting in glucose homeostasis. β E receptors have been identified in many locations within

the body including nerves, adipose tissue, pancreas, and skeletal muscle. However, the exact role(s) β E may have on these tissues is still being elucidated.

The influence of β E on immune function has been investigated *in vitro* but has not been adequately investigated *in vivo*. β E (both rat and human) was shown to stimulate T lymphocyte proliferation (38). The data suggests that β E mode of action was not through a mu opioid receptor. It was shown that synthetic β E could bind to non-opioid receptors on T lymphocytes and this binding was not blocked by naloxone or met-enkephalin (74).

β E was shown *in vitro* to stimulate rat spleen lymphocytes in a dose-dependent manner by enhancing the proliferative response to several mitogens (27). This binding was not blocked by naloxone. β E enhanced the proliferative response of splenocytes on T-cells from adult male F344 rats (98). In addition, naloxone was not effective in blocking the β E effect. β E stimulated the proliferative effect on human T lymphocytes using the mitogen concanavalin A (76). This β E-stimulated mitogen response demonstrated a bell-shaped curve indicating that too high a dose would actually inhibit the response. It was noted that this response may change with time, dose, or mitogen used (70). These authors also noted that the inhibition of the immune response to cortisol may be partially reversed by β E. Therefore, the activation of β E may inhibit suppression of the immune response by acting on cortisol actions *in vivo*.

β E was noted to enhance human natural killer cell function *in vitro* in a dose-dependent manner but was inhibited by naloxone (53). This suggests that the mode of action on natural killer cells appears to be different than the enhancement of T lymphocyte function. The β E levels effect on natural killer cell activity (NKCA) and amount was examined after exercise (26). Naltrexone treatment given 60 min before a run at 65% VO_2 max which elevated blood β E levels at 90 and 120 min did not alter the exercise response in NKCA or counts. These authors suggested that β E may work independent of the mu receptor action to assist NKCA (49). Chronic exercise (wheel running for 5 weeks) in spontaneously hypertensive rats enhanced NKCA. The β E levels in CSF increased after the running and enhanced lymphoma cell clearance from the lungs. The delta-receptor antagonist naltrindole significantly but not completely inhibited the enhanced NKCA after 5 weeks of exercise. Neither α nor β receptor antagonists influenced the NKCA. These authors suggested that the endurance training mediated central receptor-mediated adaptations. However, if β E levels in the periphery were given subcutaneously, this did not alter NKCA *in vivo* (49). In contrast, NKCA after central injection of a delta opioid receptor agonist was enhanced (2). In addition, a single injection of a mu agonist into the intracerebral ventricle reduced NKCA. Furthermore, a single morphine injection into the periaqueductal area suppressed NKCA (103). This suggests that central mediated β E levels may act to modulate NKCA via both delta and mu receptors. Clearly more research with human models is needed but this may be difficult as most of these actions appear to be centrally mediated.

Additional modes of action of β E on the immune response include mononuclear cell chemotaxis (78, 99), immunoglobulin migration (88, 99), and lymphokine production (99). Macrophages showed migration to β E levels injected into the cerebral ventricles in rats (99). Human neutrophils demonstrated enhanced migration to β receptors when β E was infused and this response was blocked by prior incubation with naloxone. Analogs of opioids appear to have different responses when injected into the cerebral ventricles (88). Some may stimulate macrophages and others may influence neutrophils.

The chemotaxis response appears to be dose dependent (78). High doses of β E levels (10^{-3} M) inhibited the chemotaxis response whereas low concentrations stimulated upregulation of neutrophils. Since physiological β E concentration is below the high-dose level utilized even when elevated by exercise or other stressors, it is likely that β E at these low levels provide a stimulatory effect on this aspect of the immune system.

It has been suggested that the opioid peptides such as β E and the enkephalins have a similar structural component of interleukin-2 (48). Interleukin-2 and other interleukins are involved in the inflammatory response and are targets of β E levels and cortisol. It is highly likely that both β E levels and cortisol influence the immune response by interacting with interleukins (104). The inhibitory response may act at a number of levels including the attenuation of the production of both interleukin-1 and interleukin-6 in a dose-dependent manner.

It appears that β E levels may act on a number of immune factors both centrally and in the periphery and may act through both opioid and non-opioid receptors. Additionally, β E action may work through direct inhibition of cortisol.

Both β E and cortisol influence immune function with β E generally enhancing immune function and cortisol acting as an immunosuppressant. The interplay of β E and cortisol in regulating immune function in response to both acute and chronic exercise requires more research to clarify their contributions. Adaptation effects to training also need further study. In addition, nutritional factors (i.e., carbohydrate level) have not been adequately examined in relation to both β E and cortisol influence on the immune response and with exercise. A recent study reported β E increased to a similar level after cycling to exhaustion at 90% VO_2 max after cycling for 60 min at 65% VO_2 max independent of a high or a low glycemic diet or placebo prior to the exercise (44).

ENDOGENOUS OPIOIDS AND PAIN PERCEPTION

There are numerous citations that have implicated endogenous opioids and pain perception. A good number of these have suggested that endogenous opioids are involved in the processes of myocardial ischemia and or angina (46, 95). It was reported that endorphins could modulate adenosine-provoked angina pectoris-like pain in a dose-dependent manner in seven healthy subjects (95). In contrast, met-enkephalin had no apparent effect on the pain. There may be a gender difference as angina pectoris pain induced by adenosine was attenuated by β E in males (both healthy and with coronary artery disease) but β E infusion did not modulate the pain nor did naloxone in females (87). Increased plasma concentrations of β E were shown to alter peripheral pain threshold but did not alter angina threshold in patients with stable angina pectoris (46). Therefore, peripheral pain may be influenced by β E, and the β E level may in part manifest some alteration in pain threshold. However, it is more likely that peripheral nerves which contain β E and/or immunocytes which release β E are involved with altering pain perception and reduction of damage (72).

Several studies have reported that exercise can modulate pain perception and this has been attributed to endogenous opioids. Both acute and chronic exercise were reported to significantly enhance mu opioid receptor (MOR) expression in the hippocampal formation (15). However, acute and chronic exercise had no significant effect on MOR expression in trained rats. Immunohistochemical techniques showed a higher number of

MOR-positive cells after acute exercise compared to a control group. These authors noted that both acute and chronic exercise modulate MOR expression in the hippocampus region of rats. Higher pain thresholds for pain were reported in individuals who exercised for both finger and dental pulp stimulations (17). Plasma β E levels increased after exercise to exhaustion as did cortisol and catecholamines but pain threshold level changes did not correlate with plasma β E. Furthermore, naloxone failed to affect pain thresholds, despite the fact that with naloxone and exercise, β E levels increased to a greater extent. These authors suggested that the pain-related changes with exercise were not directly related to plasma β E. Janal et al. reported that after a 6.3 mile run at 85% VO_2 max, hypoanalgesic effects to thermal, ischemic, and cold-pressor pain occurred, together with enhanced mood (45). In this study, naloxone infusion partially inhibited some of the pain and mood effects with the exercise. This suggests that that exercise can modulate pain and it appears it is related to β E but may not be directly related to the plasma β E concentration.

Perception of pain in trained ($N=17$) men after a run (12 min for maximal distance) with either placebo or with naloxone was examined (79). After the exercise β E levels increased in a similar manner for both trials, but pain level was greater with the naloxone treatment. These authors concluded that the perception of pain associated with exhaustive exercise may be related to endogenous opiates but this had no effect on performance. Low-intensity exercise was noted to reverse muscle pain in rats and this was blocked by naloxone (3). Microinjections of opiates into the periaqueductal gray matter in the brain of rats attenuated pain symptoms (91). It was noted that systemic and supraspinal opiates could suppress pain in rats (62). These studies suggest that pain can be altered by opiates and that exercise can modify pain; however the alteration in pain does not appear to be related to circulating β E.

Neuropathy-induced mechanical hypersensitivity occurred in wild-type mice subjected to a chronic constriction injury of the sciatic nerve (60). It was reported that T lymphocytes infiltrating the injury site (11% of total immune cells) released β E. Corticotropin-releasing factor (CRF) was applied at the injured nerve site and fully reversed the hypersensitivity. These authors noted that the T lymphocytes which contain β E are crucial for not only immune function but also altered pain with peripheral nerves.

It is now clear that β E are located in parts of the immune system, and can act both centrally and peripherally to help modulate pain. It is unclear how these different areas in the body respond to both acute and chronic exercise, but it appears that β E are involved. Part of the modulation of pain perception is clearly related to MOR within the brain, and more research is needed to understand the effects of both acute and chronic exercise on these receptors. In addition, circulating β E may increase, but this may not always be related to pain modification, and naloxone may not always block this effect. Therefore, the peripheral mediated β E effect on pain thresholds may not be related to the MOR in the periphery.

β E AND GLUCOREGULATION

The opioid system has been implicated in the control of blood glucose concentration during rest (23, 86) and exercise (24, 43, 44). β E and opiate receptors have been isolated from sites that are involved in glucoregulation (103). Additionally, it has been

reported that β E appears to play a role in metabolic regulation during exercise or muscle contraction (50). A bolus injection of β E followed by intravenous infusion of β E in rats raised β E levels 6–7-fold and resulted in higher plasma glucose levels at 60 and 90 min of exercise compared to saline infusion (24). Lower insulin and higher glucagon levels were evident compared to saline infused rats at these times. Additionally β E exerts an effect on insulin and glucagon at rest (23, 77) in humans and animals. β E infusion without a bolus infusion of β E compared to saline infusion enhanced glucose homeostasis and exacerbated the glucagon rise in rats that were exercised (43). This study reported that β E infusion independent of a β E bolus during exercise can attenuate the blood glucose decline and increase the glucagon response to exercise. Additionally, β E infusion alone did not alter insulin, catecholamines, corticosterone, or FFA's response during exercise. It appears that β E infusion alone at a level to increase β E at 2.5-fold greater than normal levels does not inhibit insulin whereas, if the β E level increased to greater than 2.5-fold (infusion and/or increase by exercise), inhibition of insulin occurs to help maintain blood glucose.

INFLUENCE OF ACUTE EXERCISE ON ENKEPHALINS

There is some evidence that exercise can increase enkephalin concentration and or opioid receptor numbers within the brain (11, 15). These alterations in the brain have been linked to changes in mood state (45), the exercise blood pressure control (4, 42, 47, 73), cardiac ischemia and angina (95), pain (94, 95), and immune function (8). However, it should be understood that some of the actions of these opioid molecules may manifest themselves in other compartments such as vascular control. Research is unfolding as to the actions of these enkephalins and enkephalin-like molecules. For example, proenkephalin peptide F which is primarily released from the adrenal gland and co-released with epinephrine has immune-modulating functions (8, 51, 96).

Met-enkephalin levels were reported to be unchanged after a Nordic ski race determined in both highly trained ($n=11$, active for 150 km/week with greater than 3 years' experience) or recreationally trained ($n=6$, active for 20 km/week with no competitive experience) skiers (71). The distance covered was 75.7 km and subjects were allowed to have water and food ad libitum. Met-enkephalin concentration in plasma was determined at rest prior to a graded treadmill exercise to exhaustion and after a run of 87.2 km in these same individuals (5 min post). The basal level of enkephalin was 171.7 ± 7.16 fmol/mL and increased after the treadmill exercise to 265.8 ± 9.88 fmol/mL and further increased after the run to 378.3 ± 15.16 fmol/mL. These authors suggested the increase in met-enkephalin in plasma may be related to intensity and duration of exercise (93). These same authors tested unfit ($n=24$) and fit ($n=23$) subjects utilizing a progressive intensity treadmill run to exhaustion with 4 min stages of at least five stages. Met-enkephalin concentration in plasma was lower for the unfit compared to the fit (126.3 ± 5.3 fmol/mL vs. 156.7 ± 6.9 fmol/mL). Both groups demonstrated increased plasma met-enkephalin after the treadmill exercise with the fit group showing a greater response (unfit = 180.4 ± 5.3 fmol/mL vs. fit = 278 ± 6.58 fmol/mL) (92). In contrast, Boone et al. reported that met-enkephalin was no different in trained and untrained subjects following 4 min of exercise at 70% VO_2 max and 2 min at 120%

VO₂ max (5). These authors noted that cryptic met-enkephalin (activated) was elevated similarly in both groups after the 70% VO₂ max and returned to baseline levels at the higher workload.

The response to exercise in met-enkephalin concentration in the plasma from trained and untrained subjects was reported to be similar (47). Subjects were rested for at least 15 min prior to a resting blood sample and then performed a graded treadmill protocol to maximum, and then another blood sample was obtained. There was no difference in the met-enkephalin concentration in plasma, red cells, cytoplasm, or ghosts comparing the pre- to postexercise in either the trained or untrained. However, the degradation rate was slower in the trained group to the untrained group independent of time (pre- and postexercise). The authors suggested this may facilitate opioid responses and could provide added tolerance for the trained subjects.

One of the early works in this area examined leu-enkephalin activity in plasma both before and after a competitive run (21). Experience runners (9 males and 5 females) gave a resting blood sample and after (2.5–8 min) the 10 mile road race. The resting value of leu-enkephalin was 22.2 ± 13.7 pmol/mL and increased ($p > 0.05$) to 26.05 ± 21.5 pmol/mL which was modest at best. The change in leu-enkephalin was inconsistent and variable and did not relate to time of completion as some runners showed increases, others decreased with most showing very little change.

In conclusion, the influence of exercise in met-enkephalin is variable and appears to depend on the type of assay used. There is inconsistency in the results, as some studies suggest enhanced levels and others no change. This may be related to fitness level, but again, there are not enough studies to suggest that aerobic capacity or fitness level consistently influence the met-enkephalin level. There appears to be a lack of research with leu-enkephalin, with one study suggesting modest changes after a 10 mile run but with large variations in the individual response of study participants.

There is limited information on exercise training programs with enkephalins. Chen et al. examined the acute and chronic exercise training effects on leu-enkephalin in the caudate-putamen of rat brains and compared the levels to sedentary control rats (11). The trained rats exercised on a motorized treadmill for 5 weeks with a progressive increase in time and speed and ran 5–7 days per week ultimately running for 25 min/day at 35 m/min. This latter group was then either exercised or rested and then sacrificed. The staining of leu-enkephalin was primarily in the PVN and the caudate-putamen region (CPR). The acute exercise increased staining in the CPR region and remained elevated in this region for up to 180 min postexercise but gradually decreased over time after exercise (11). These results suggest that there is a central mediated enkephalin response influencing the brain and that acute exercise increased enkephalin in this brain region. Unfortunately this study did not have a sedentary acute exercise group, to determine if the endurance training had any influence.

There is also some information that has dealt with the influence of exercise on the proenkephalin peptide F that is typically released from the adrenal gland (medulla) and is often co-released with epinephrine (64). The influence of intensity of exercise and training was examined in college-aged students (59). The trained subjects were middle-distance runners ($n=10$) and the untrained individuals ($n=10$) were not in any formal activity for two years. The subjects had their VO₂ max determined on a cycle ergometer and then returned to do several 8 min stages which elicited 28, 53, and 84% VO₂ max

and then went to VO_2 max. Blood was obtained at the end of each workload and during recovery. Peptide F levels at rest were twice as high in the trained group compared to the untrained but were very low (<0.1 pmol/mL). Neither group demonstrated any significant change in peptide F at the 28% workload with both groups having similar levels. At 54% workload the trained group showed a significant increase and at higher work intensities the peptide F level stayed fairly constant (0.4 pmol/mL). In contrast, the untrained group did not demonstrate as rapid an increase and only reached a similar level of peptide F at 100% VO_2 max. However, the peptide F levels continued to increase at 5 min into the recovery and then started to decline. It is interesting to note that the epinephrine level for both groups showed a similar response. This suggests that the alterations in peptide F level may be related to other factors than its release.

The effect of fitness and intensity of exercise was examined in women to see if peptide F levels might be altered differently in women (96). Women who were endurance trained (>3 times per week, 30–45 min per session) were compared to inactive women. They were exercised on a cycle ergometer at 60% (15 min) and 80% VO_2 max (15 min) during the early phase of the follicular phase of the menstrual cycle. Blood was collected at rest and 10 min into each intensity and 5 min into recovery. The authors reported that only the fit women demonstrated a significant increase in peptide F at the 80% intensity workload. However, this increase was very modest from 0.046 to 0.056 pmol/mL. In contrast, the untrained women showed a greater epinephrine level compared to the fit women. This again suggests dissociation in the amount of epinephrine and peptide F within the circulation.

The influence of menstrual cycle on peptide F to maximal exercise was reported in ($N=8$) eumenorrheic women (58). There appears to be a slight but nonsignificant (0.06) effect of menstrual cycle on plasma peptide F level at rest. In addition, there was no exercise main effect on plasma peptide F levels. These results suggest there may be fluctuations in peptide F levels over time as well as over the course of the menstrual cycle. This suggests that the minor changes in the previous study with much lower peptide F levels may be an anomaly. Clearly, more research studies are needed as there is inconsistency in the results with exercise on peptide F levels. Furthermore, many of the variables that might influence baseline peptide F levels should be considered.

The roles of peptide F are not well defined at this time. It is clear that it is co-released from the adrenal medulla, but its actions and implications with exercise have not been elucidated. Peptide F appears to have an important role in the immune system. Therefore, peptide F and its possible exercise-modulated effect on immune function should be further investigated.

SUMMARY

In conclusion, exercise of sufficient intensity and duration may influence the endogenous opioids, but what is measured in the circulation does not necessarily reflect what happens within the brain. Numerous factors such as sex, menstrual cycle, diet, plasma volume, carbohydrate level, and inflammation can influence the endogenous opioids. Furthermore, immune function and neural control can clearly alter endogenous opioid activity. Finally, a greater understanding of the influence within the brain needs to be established.

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