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HYPOTHESES

Endorphins and exercise: physiological mechanisms and clinical implications

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ABSTRACT

THORÉN, P., J. S. FLORAS, P. HOFFMANN, and D. R. SEALS. Endorphins and exercise: physiological mechanisms and clinical implications. *Med. Sci. Sports Exerc.*, Vol. 22, No. 4, pp. 417–428, 1990. In this paper we discuss recent experimental and clinical findings which lead us to propose that prolonged rhythmic exercise can activate central opioid systems by triggering increased discharge from mechanosensitive afferent nerve fibers (Group III or A-delta) arising from contracting skeletal muscle. We review evidence that supports the concept that many of the cardiovascular, analgesic, and behavioral effects of exercise are mediated by this mechanism and that the same or similar mechanisms are responsible for the central and peripheral effects of acupuncture. Based on this hypothesis, and supporting evidence from human and animal studies, we suggest a mechanism and a potential therapeutic role for exercise in the treatment of selected patients with disorders as diverse as hypertension, addiction, depression, and anorexia nervosa.

ACUPUNCTURE, ANOREXIA, BLOOD PRESSURE REGULATION, DEPRESSION, ENDORPHINS, EXERCISE, HYPERTENSION, IMMUNITY, PAIN

The increasing popularity of regular exercise can be attributed, in part, to an increased public awareness of its beneficial effects on physical and emotional well-being. In the last few years, regular exercise has been shown to reduce mortality from cardiovascular and respiratory disorders (106) and to lower the blood pressure of patients with essential hypertension (103,147). Regular exercise also appears to improve the lipid profile of some individuals (143,160), enhance mood (101), and decrease sensitivity to pain (69). Many of these positive effects have been attributed to the exercise-induced stimulation of endogenous opioid production although the mechanisms mediating this activation of central opioid pathways are poorly understood.

Our aims in this paper are 1) to review evidence from our laboratories and others which indicates that stimulation of somatic afferent nerves in exercising muscle can activate central opioid systems, 2) to discuss the potential involvement of opioids in blood pressure regulation and hypertension, and 3) to discuss how acute exercise (and acupuncture) may, through opioid pathways, influence pain perception, immunity, addiction, depression, and anorexia. It is important to note that our discussion of these topics is sometimes purely speculative. However, it is hoped that many of our ideas will form the basis for working hypotheses from which experimental studies can be conducted.

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ENDOGENOUS OPIOID SYSTEMS

Opiates have been used by man for thousands of years. Their analgesic, euphoric, and addictive effects have been the subject of intense clinical research for most of this century. Our understanding of the mechanism of action of opiates in neural tissue has been greatly advanced by the development of binding techniques to identify opioid receptors (111,135,142). Endogenous peptides with opiate activity were initially named enkephalins, but soon several such peptides were described. Thus, a more appropriate term to use is (endogenous) opioids, in contrast to the (exogenous) opiates. The opioids can roughly be subdivided into three groups, endorphins, enkephalins, and dynorphins, stemming from three major precursor molecules. The endorphin family includes several forms of beta-endorphin as well as alpha- and gamma-endorphin. The most important enkephalins are the pentapeptides leucine-enkephalin and methionine-enkephalin. The dynorphin family includes dynorphin A, dynorphin B, and neo-endorphin. Neurons containing each of these peptides have been described (for review, see 58). These endogenous opioids are widely distributed in areas of the central nervous system involved in regulating sympathetic outflow, in autonomic ganglia, and in plexi of the gut (5,31,146). Enkephalins are present in nerve terminals surrounding the nucleus tractus solitarius, the

dorsal vagal nucleus, and the nucleus ambiguous, i.e., areas involved in autonomic circulatory control (78,124).

Of special interest has been the beta-endorphin system which contributes to the regulation of blood pressure, pain perception, and the control of body temperature (8,47,65). This system has cell bodies in the median eminence of the hypothalamus and innervates much of the hypothalamus, midbrain, and rostral parts of the medulla oblongata involved in central regulation of autonomic outflow (1,5,14,29,139). A second, independently regulated beta-endorphin containing system is found in the anterior pituitary, where both beta-endorphin and ACTH are synthesized in corticotropic cells, as part of a common precursor molecule, proopiomelanocortin (POMC) (28,89). Since beta-endorphin and ACTH are secreted in equimolar concentrations from the adenohypophysis in response to exercise and other stressful stimuli, most of the beta-endorphin measured in peripheral blood reflects co-release with ACTH rather than hypothalamic-brainstem beta-endorphin activity (53). Stress-specific increases in plasma beta-endorphin and ACTH levels are often not associated with increases in brain endorphin concentrations (116). Indeed, since the blood-brain barrier is relatively impermeable to circulating peptides (9), peripheral concentrations of beta-endorphin would not be expected to modify central beta-endorphin activity. These observations emphasize the need for caution when attempting to assess central beta-endorphin activity from peripheral plasma beta-endorphin concentrations.

Opioid receptors are also present on peripheral sympathetic and cardiovascular structures (66,67), and their effect is inhibitory on peripheral sympathetic transmission (67,72,80,159). However, these effects are seen when the opioid peptides are used in pharmacological doses. Further, their role seems to be of different importance between species, and in pithed rats (where all CNS influences are excluded) opioid agonists do not affect blood pressure (30,39,84).

In general, both centrally and peripherally administered opiates produce bradycardia and hypotension by enhancing parasympathetic and inhibiting sympathetic outflow (65). Administration of synthetic opioids into the cisterna magna of dogs produces a fall in blood pressure (83). However, there also are studies indicating increased blood pressure and sympathetic activity after central administration of opioids (3,38,91,113,144,148). Sympathetic reflex responses to both pressor and depressor stimuli are attenuated by morphine or opioid analogs and potentiated by naloxone, an opioid antagonist with high affinity for mu-receptors (99,112). However, when naloxone is used in high doses, it either may lose its specificity for opioid receptors or may have agonist effects. Further, naloxone can influence pharmacological responses to some non-opiate drugs, including those interacting with dopaminergic and GABAergic systems (126).

The contribution of central opioid systems to cardiovascular regulation in intact conscious animals or humans is not always evident under resting conditions but can be detected once a real or perceived stress disrupts normal homeostatic mechanisms and displaces blood pressure outside its usual range (118). Most investigators have failed to detect any changes in blood pressure or heart rate in normal subjects given naloxone in doses of up to 20 mg i.v. (71,151,157,165). However, the reflex sympathoexcitatory responses to tilt, sodium nitroprusside-induced hypotension, or the cold pressor test can be attenuated by an enkephalin analogue, DAMME, or augmented by naloxone (16,120). Furthermore, nocturnal hypotension, which appears to be mediated by endogenous opioids, can be abolished if subjects receive high parenteral doses of naloxone (0.2 $mg \cdot kg^{-1}$) immediately prior to sleep (118,119). The decrease in blood pressure with sleep, expressed in absolute units, is also greater in patients with essential hypertension than in normal subjects (42). The results of several clinical studies indicate that high doses of naloxone are needed to block the cardiovascular and endocrine effects of endogenous opioid systems; however, these effects are observed only after a delay of a few hours. One explanation for this latter observation is that endogenous opiates mediate their effects through an intermediary neurotransmitter which requires *de novo* synthesis (118).

ACTIVATION OF CENTRAL ENDORPHIN SYSTEMS BY EXERCISE

Our principal hypothesis is that central nervous system (brain and spinal cord) opioids are activated by prolonged exercise. However, the physiological adjustments to exercise are complex, and any involvement of central opioids may be obscured by the central and peripheral actions of other neurotransmitters, hormones, and metabolic by-products of exercise.

What then is the evidence in support of this hypothesis? In humans, many investigators have examined opioid concentrations in the plasma before, during, and after exercise to test this postulate. Most investigators have shown an increase in peripheral blood beta-endorphin concentration following exercise (26,34,46,48,69,86), although some have failed to show a consistent increase (82); for review, see Allen (2). However, as mentioned previously, most of the beta-endorphin measured in plasma reflects hypophyseal co-release with ACTH in response to stressful stimuli rather than activation of specific CNS beta-endorphin pathways.

Another commonly used experimental strategy has been to determine whether the physiological adjustments to exercise are altered following intravenous administration of naloxone. It has been reported that naloxone results in altered plasma catecholamine, glucose, growth hormone, and cortisol concentrations during or following prolonged, submaximal exercise (35,52,81,100). Further, naloxone has been suggested to block the exercise-induced increase in pain threshold (55,131). Indeed, most of the experimental evidence to date indicates that the circulatory, metabolic, endocrine, and thermoregulatory adjustments to submaximal and maximal exercise are not influenced by pretreatment with naloxone (17,68,93,96,127,140). The failure of naloxone to consistently alter the physiological responses to exercise may be due to the fact that inadequate (low) doses have been used. It can be hypothesized that higher doses of naloxone are required to antagonize the effects of endogenous opioid peptides than of exogenously administered opioid analogues, and higher doses of naloxone are required to antagonize effects mediated by the opioid delta- and kappa-receptors, whereas the mu-receptor is effectively blocked by lower doses (5,25,108,109,114). However, another interpretation of results seen with high doses of naloxone is that they may represent non-opioid effects (126).

Invasive studies in animals have provided the most compelling evidence for the exercise-induced activation of central opioid systems. Prolonged, submaximal exercise (13), but not brief, strenuous exercise (97), increases brain beta-endorphin content and induces an endogenous opioid system (possibly endorphin)-mediated increase in pain threshold (131) in rats. Mice submitted to 3 min of swim-training every 2 h show a clear withdrawal syndrome when given naloxone (24). Recently, Hoffmann et al. (64) have observed a significant increase in beta-endorphin concentration in the cerebrospinal fluid (CSF) of rats trained to run spontaneously compared to the CSF of sedentary controls. CSF beta-endorphin levels remained elevated 24 and 48 h after the end of exercise but were back at control 96 h postexercise. Results of Sforzo et al. (129) also support the hypothesis of involvement of CNS opioids in exercise; they could demonstrate an altered opioid receptor occupancy in discrete brain areas following a 2 h swim in rats. Taken together, the results of these studies provide experimental support for central nervous system opioid involvement in response to prolonged, submaximal exercise.

If central beta-endorphin levels are increased during exercise, what is the stimulus for this augmented release? To address this question, Yao et al. (163,164) simulated the effects of exercise by stimulating the sciatic nerve of conscious rats with a series of low frequency electric pulses. Stimulation activated somatic afferents from leg muscle and evoked powerful rhythmic contractions of the hind limb. Stimulation of the sciatic nerve for 30 min had several effects. First, the pain threshold of these animals was markedly increased long after nerve stimulation ceased. The increase in pain threshold could be blocked by naloxone and thus was dependent on an opioidergic mechanism (163). Second, sciatic nerve stimulation reduced brain norepinephrine synthesis; this effect was also reversed by naloxone (104). The animals also showed sustained behavioral depression after the cessation of nerve stimulation (163).

Further, sciatic nerve stimulation experiments resulted in an interesting and unexpected observation. In rats with increased intestinal secretion induced by choleratoxin, nerve stimulation induced long-lasting decreases in intestinal secretion long after stimulation was stopped. This effect was mediated by efferent nerves to the intestine (20). In these studies, afferent A-delta (or Group III) fibers in the sciatic nerve were also activated if the stimulus intensity was increased. As would be expected, stimulation of these afferents evoked the somatic pressor reflex (163), i.e., the increase in sympathetic outflow, blood pressure, and heart rate that accompanies static, and to a lesser extent rhythmic, exercise (98). At the higher stimulus intensities, Yao et al. (163) also observed a sustained reduction in blood pressure *after* nerve stimulation was stopped. This hypotension was not accompanied by the expected baroreflex-mediated tachycardia and sympathoexcitation; indeed, sympathetic neural outflow was reduced compared to control conditions. Reductions in blood pressure of 20 mm Hg or more, lasting for several hours, were seen in spontaneously hypertensive rats (SHR) but less in normotensive rats and not at all in renal hypertensive rats (59,133,163,164). Both the behavioral and cardiovascular after-effects of nerve stimulation could be blocked, not only by high doses of naloxone (10–15 $mg \cdot kg^{-1}$), but by centrally acting serotonin antagonists. In contrast, dexamethasone, which blocks the release of ACTH and beta-endorphin from the pituitary gland, did not alter the post-stimulation responses. These observations support a role for central nervous system endorphins (opioids), as opposed to peripherally circulating endorphins, in mediating the responses seen after nerve stimulation (163,164).

This series of experiments illustrates four key points, which we will address in turn: 1) sustained cardiovascular and behavioral changes can be elicited by prolonged sciatic nerve stimulation; 2) these after-effects (e.g., a decrease in blood pressure and sympathetic nerve activity) are in distinct contrast to the direct effects of nerve stimulation; 3) the central opioid and serotonin systems participate in the sustained cardiovascular and behavioral after-effects of nerve stimulation; and 4) the neural and cardiovascular sequelae of nerve stimulation are more evident in SHR, a model

of neurogenic hypertension in the rat, than in normotensive rats.

Recently, Hoffmann and Thorén (60) have shown that circulatory and behavioral responses similar to those observed with sciatic nerve stimulation could be produced by direct electrical stimulation of the gastrocnemius muscle. Muscle stimulation resulted in a long-lasting post-stimulatory drop in blood pressure in SHR (Fig. 1); this could be abolished by naloxone pretreatment. Electrical stimulation of muscle also evoked a 30% increase in pain threshold, which lasted about 3 h after the cessation of the stimulus (63).

What mechanism might account for these sustained, opioid-mediated effects of nerve or muscle stimulation on blood pressure, behavior, pain threshold, and sympathetic neural outflow? As indicated above, these responses appear to be mediated by the activation of A-delta or Group III afferent fibers arising from muscle. Histologically, A-delta or Group III afferents are a prominent group of fine myelinated fibers located in skeletal muscle nerves, originally described as pain-pressure receptors by Paintal (107). More recent investigations indicate that these afferents respond to muscle stretch and contraction with low-frequency discharge (74,75,79). For this reason, Kniffki et al. (79) called the endings of these afferents "ergoreceptors". Group III afferents do not respond to small movements of the limb and therefore are unlikely to be of major importance in motor control.

Contraction of the gastrocnemius muscle to a level greater than or equal to that needed to evoke the pressor reflex stimulates most of Group III afferents (74). One might therefore conclude from these observations that

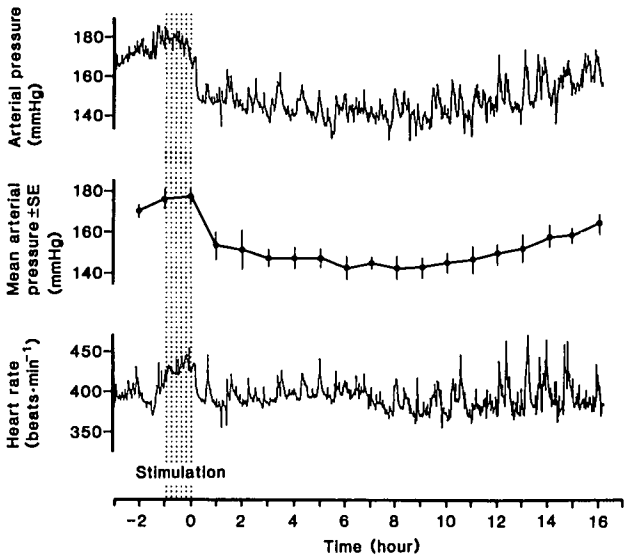

Figure 1—Changes in arterial blood pressure, mean arterial blood pressure, and heart rate induced by stimulation of the gastrocnemius muscle of a spontaneously hypertensive rat. Hypotension persisted for 15 h after 60 min of muscle stimulation. (Reprinted from Hoffmann and Thoren (60), with permission.)

engagement of several large muscle groups during activity such as jogging would result in substantial central nervous system input from these Group III afferents and, if our hypothesis is correct, activation of central opioids. In order to extrapolate from these experiments to the potential activation of central opioids by physical activity in humans, the assumption that sciatic nerve or gastrocnemius muscle stimulation can be used as a model for rhythmic exercise requires further support. However, there is evidence that electrical stimulation of muscle afferents and exercise can induce similar responses. Shyu et al. (131) showed that prolonged exercise in rats can induce opioid mediated increases in pain threshold very similar to those seen with muscle and sciatic nerve stimulation. The authors encouraged SHR to develop spontaneous running behavior by permitting access to training wheels (132). Blood pressure could be measured continuously via an indwelling arterial catheter. After 6–7 wk, the rats ran from 5 to 7 km every night. The blood pressure responses were similar to those observed during the nerve stimulation experiments. After they stopped running, the SHR exhibited a transient decrease in blood pressure (and in some cases, a normalization of blood pressure) lasting for up to 2 h (Fig. 2). When compared with sedentary controls, the SHR that ran nightly also demonstrated a slower rate of development of hypertension (61) and clear behavioral changes with less objective evidence of nervousness and aggression (62). Consistent with the previous experiments, post-exercise hypotension in SHR could be blocked by high doses of naloxone.

When combined with the findings previously outlined, these studies in conscious SHR support our assumption that prolonged exercise can induce physiologic and behavioral effects that are dependent on the activation of central opioid systems. Furthermore, from these results we would also postulate that these effects are mediated via continuous activation of thin myelinated Group III or A-delta fibers arising from the contracting skeletal muscles.

What then is the functional significance of ergoreceptor activation in exercise? We speculate that ergoreceptor activation during exercise may exert seemingly paradoxical influences on the autonomic nervous system. During brief, strenuous muscle contractions, ergoreceptor afferent drive may exert a non-opioid dependent, excitatory influence on autonomic controllers causing withdrawal of cardiac vagal tone and tissue-specific increases in sympathetic neural outflow. These autonomic adjustments would serve to increase heart rate, cardiac output, regional vascular resistance, arterial blood pressure, and, therefore, exercising muscle perfusion pressure and O_2 delivery. This postulate is consistent with recent findings of a tight coupling between brief, electrically induced muscle contractions and bursts of renal sympathetic nerve activity in anesthe-

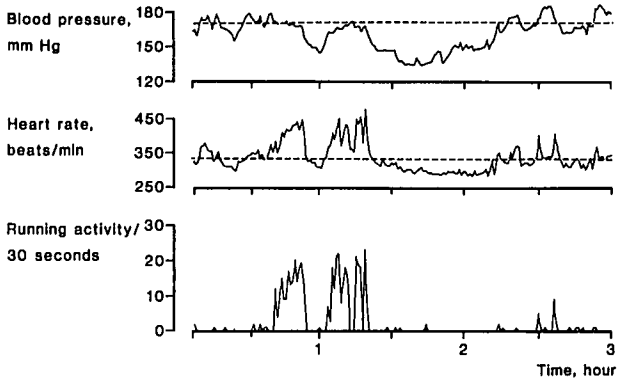

Figure 2—Arterial pressure, heart rate, and running activity in a spontaneously hypertensive rat during three nighttime hours. The *dashed lines* represent mean arterial pressure and mean heart rate, respectively, during the entire nighttime period. Note the decreased blood pressure following running. Hypotension could be abolished if animals were pretreated with naloxone (see text). (Adapted from Shyu and Thoren (134).)

tized cats (150). Such intermittent muscle contractions activate Group III, but not unmyelinated Group IV, muscle afferents (75). Thus, one consequence of ergoreceptor activation may be to work in concert with central volitional influences (i.e., central command) to evoke circulatory and metabolic adjustments that ready the organism for the demands of vigorous exercise. The findings that brain endorphin levels are not increased (97) and that naloxone does not influence the exercise pressor reflex (152) support the view that the endogenous opioid system is not involved in mediating the circulatory adjustments to brief, strenuous muscle activation, although a study by Williams (158) shows that intracisternal injection of naloxone prior to clonidine antagonized the anti-pressor effects of clonidine during muscle contractions.

On the other hand, continued stimulation of ergoreceptors, e.g., during prolonged, submaximal exercise, may lead to the activation of the endogenous opioid system, specifically to the augmented release and action of opioids centrally. Increased central opioid concentrations have been shown to exert a sympathoinhibitory influence in animals at rest (115). During exercise, this inhibitory influence is likely to be masked by the excitatory autonomic effects of central command, central and peripheral thermoreceptor stimulation, and/or chemosensitive afferent feedback from the contracting muscles (117). This may explain why plasma catecholamine levels increase, rather than decrease, during prolonged, submaximal work (45). However, with the cessation of exercise and its attendant excitatory inputs, the psychophysiological effects of prolonged central opioid activation may become manifest, thus explaining the circulatory depression and behavioral changes observed during recovery. The physiologic importance of this mechanism may be to reduce the organism's energy needs (decreased catabolic state) while energy stores are being replenished (increased anabolic state) to prepare for the next period of high metabolic demand. This idea is consistent with the known energy substrate-mobilizing effects of sympathetic neural activation and adrenal catecholamine release during exercise (45). This is further supported by a recent study by Farrell et al. (37), where they showed that exercise-induced opioid activation stimulates glucose stimulated insulin secretion. This is of importance in post-exercise restoration of energy stores. The central opioid-mediated increase in pain threshold presumably would reduce the physical discomfort associated with prolonged, fatiguing exercise.

BLOOD PRESSURE REGULATION AND THE MANAGEMENT OF ESSENTIAL HYPERTENSION BY EXERCISE

We will now discuss evidence that activation of the endogenous opioid system by exercise may be involved in blood pressure regulation, since this is one of the best studied areas. Many groups have investigated the involvement of endogenous opioids in blood pressure control directly (3,38,54,85,113,123). However, the results of these experiments are inconsistent and vary according to injection site, dose, opioid type, and species of laboratory animal used.

Exercise appears to have three distinctly different effects on blood pressure. An acute bout of exercise will increase both arterial blood pressure and heart rate. The second effect, more evident in patients with hypertension than in normotensive subjects (10), is a decrease in blood pressure in the immediate post-exercise period, when compared with pre-exercise levels, which often lasts for several hours. Indeed, blood pressure tends to fall, even before the subject stops exercising (10,43). The third effect is a chronic reduction in blood pressure at rest often observed after weeks or months of regular endurance (aerobic) exercise (70,103). Unlike the second effect, this sustained lowering of blood pressure can be seen in the absence of preceding exercise. We believe that this chronic effect of regularly performed exercise is of great interest and of both physiological and clinical importance.

The hypotensive effects of both acute and regular exercise on blood pressure suggest a mechanism by which some forms of hypertension may be managed without drugs (27,32,43,49,50,70,103,128,147,153, 155). In general (cf. 128), most investigators have shown clinically important, albeit modest (around 10 mm Hg), effects of regular exercise on the blood pressure of patients with essential hypertension. Whether exercise can lower blood pressure in experimental (Dahl salt sensitive) hypertension remains controversial (125,130,145).

Both a single prolonged bout and repeated brief bouts of submaximal, rhythmic exercise induce marked post-exercise decreases in blood pressure, often lasting for several hours. This phenomenon, mainly seen in hypertensive patients, was originally described by Gordon (49) and again by Fitzgerald (41) in a "personal" paper and has been confirmed by other investigators (10,43,70,73,155).

Although the mechanisms have not been elucidated, the observation that this post-exercise hypotension is not accompanied by the anticipated baroreflex tachycardia (10,155) suggests that reflex circulatory control has been altered by exercise. This concept is supported by studies demonstrating that the ability to vasoconstrict during orthostasis is impaired after exhaustive isotonic exercise of even brief duration (12). These findings in humans with hypertension parallel those previously described in studies of spontaneously running SHR (Fig. 2) (134). For this reason, we considered whether similar mechanisms were responsible for post-exercise hypotension in SHR and in humans with essential hypertension. Knowing that the sustained after-effects of sciatic nerve stimulation included a decrease in sympathetic outflow as well as a fall in blood pressure (163), we hypothesized that a single bout of exercise, sufficient to reduce the blood pressure of patients with hypertension, would also lower sympathetic nerve activity (SNA). We therefore recorded multi-fiber post-ganglionic SNA to skeletal muscle at rest from the peroneal nerves of nine young men with borderline hypertension before and after 45 min of treadmill exercise (43). Four subjects were also studied before and after "sham" exercise (i.e., normal ambulatory activity). "Sham" exercise had no effect on resting blood pressure or SNA. However, treadmill exercise lowered resting systolic blood pressure in seven subjects by an average of 13 mm Hg. Sympathetic nerve activity 60 min after exercise was lowered in all seven of these subjects (Fig. 3) but was unchanged, or slightly increased, in two subjects without post-exercise hypotension. In contrast, when infused in five subjects to produce a reduction in systolic blood pressure similar to that seen after exercise, nitroprusside increased sympathetic nerve activity significantly. These observations demonstrated that rhythmic exercise could lower blood pressure in men with borderline hypertension and that this post-exercise hypotension was associated with a decrease, rather than the predicted reflex increase, in SNA. We therefore concluded that post-exercise hypotension might be mediated in part by inhibition of sympathetic nerve activity.

Results from studies of prolonged sciatic nerve stimulation in SHR tempt us to speculate that the fall in blood pressure and reduction in sympathetic nerve activity seen in our hypertensive subjects might be blocked by naloxone, and indeed we are currently involved in studies to specifically investigate this hypothesis. The observation that the depressor response following exercise is greater in magnitude and duration in hypertensive than in normotensive humans and rats raises the intriguing possibility that altered central opioid activity or receptor number, or altered activity of neurotransmitter systems which can be modulated by endorphins, may contribute to the pathogenesis of "neurogenic hypertension" in both SHR (85) and man (94). Since hypertension can be temporarily inhibited by prolonged rhythmic exercise in both humans and SHR, any such central alterations in endogenous opioid activity or function would appear reversible—an observation with important therapeutic implications.

POTENTIAL THERAPEUTIC ROLES FOR EXERCISE AND ENDORPHIN ACTIVATION

A potential therapeutic role for exercise in the management of selected patients with essential hypertension was presented in the previous section. Our hypothesis suggests that exercise may also influence pain perception and immune function and be beneficial in the management of alcoholism, addiction, depression, and anorexia nervosa.

Pain perception. Some of the reported effects of exercise on pain perception have been discussed earlier. Results of previous experiments (63,163,164) indicate that pain threshold can be increased acutely by both sciatic nerve and gastrocnemius muscle electrical stimulation and that these effects can be blocked by naloxone. Spontaneous running also increases the squeak (pain) threshold in SHR (131). This increase will last

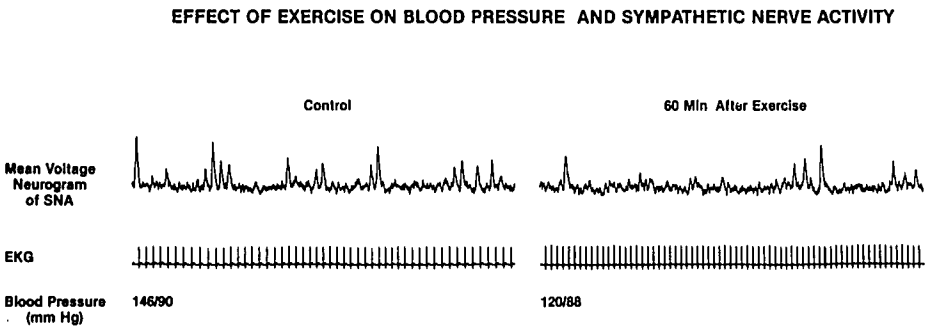

Figure 3—Muscle sympathetic nerve activity (SNA) and the electrocardiogram in one subject with borderline hypertension before and 60 min after treadmill exercise. The sympathetic nerve activity, recorded from the peroneal nerve, and blood pressure are lower after exercise, whereas heart rate is increased.

up to 4 h after these animals stop running. Naloxone (1–2 $mg \cdot kg^{-1}$) rapidly reversed the analgesic effect of spontaneous running in these experiments. In human studies, Haier et al. (55) and Janal et al. (69) showed an increased pain threshold after long-lasting exercise. The analgesic effect of exercise could be partially influenced by naloxone. Low frequency transcutaneous nerve stimulation (TNS) and ergometer cycling give very similar effects on dental pain perception. The pain threshold is elevated about 30% compared to control, and the elevation lasts about 60 min (105). These latter experiments are intriguing since they suggested that the endogenous opioid system may be involved in the analgesic effects of both acupuncture and jogging.

Acupuncture. Acupuncture has been used by Chinese physicians as a method of treating disease for over 2000 yr. Only in the last 30–40 yr has acupuncture been used as an effective means of controlling pain during surgical procedures. To review the analgesic effects of acupuncture is beyond the scope of this paper, and well-written reviews on the mechanisms of acupuncture and the involvement of opioids in acupuncture analgesia are provided by Chang (21), Han and Terenius (56), and He (57). Experimental studies in rats (110) and man (122,137) indicate that acupunction activates central opioid systems.

Why suggest that similar mechanisms may be involved in mediating analgesic effects of acupuncture and prolonged exercise? Detailed studies of the neurophysiology and neurochemistry of acupuncture indicate that the acupuncture needle stimulates somatic muscle nerve afferents (probably the A-delta (Group III) afferents discussed previously, and possibly Group IV (unmyelinated C) afferent fibers as well) (21,56). About 70% of the so-called acupuncture points in the body are motor points (87), i.e., the point where the nerve goes through the fascia and enters the muscle. Local anesthesia of the skin over the acupuncture point will not prevent the acupuncture effect, but anesthesia deep down in the muscle totally blocks it (22). Thus, responses to acupuncture and prolonged exercise might both be mediated by excitation of slow-conducting muscle afferents and the consequent activation of central opioid systems.

Immune function. Many joggers firmly believe that exercise gives them protection against common infections and that they will become ill if their regular exercise pattern is interrupted. We are unaware of epidemiological evidence to support these opinions, but there are experimental data indicating that exercise can influence immune function (136).

Interestingly enough, several recent studies have demonstrated that opioids modulate (enhance or suppress) immune function; for review, see Fischer and Falke (40). Of special interest is the enhancement of natural killer (NK) cell activity by very low (physiologic) doses of beta-endorphin and enkephalin (19,33,92). However, it must be stressed that there is no evidence directly linking exercise to endogenous opioids and immune function.

Addiction and alcoholism. Alcohol can affect central neurotransmitter systems involved in morphine abstinence (4), and recent work suggests that central opioid systems are also involved in the addiction to alcohol. Ethanol dependence in mice is associated with decreases in hypothalamic and midbrain beta-endorphin concentration (156), and some fractions of CSF opioids are decreased during early alcohol withdrawal (15). One clinical application of this has been the use of parenteral naloxone, which can abruptly awaken patients who are somnolent due to alcohol intoxication (6,88). Thus, alcohol may stimulate the release of opioids from central nervous system sites, and abstinence syndromes may be due to decreased levels of central opioids during periods of withdrawal.

Can a program of regular exercise benefit patients with drug or alcohol addiction? The efficacy of acupuncture in the management of patients with both alcohol and opiate addiction (18,23,44,138,141,149,154) raises the very interesting and important theoretical possibility that a vigorous exercise program, together with psychiatric treatment and psychosocial interventions, might assist the conversion of the addict from one who is dependent upon exogenous sources of opioids to an "endogenous endorphinist".

Depression and anxiety. Prolonged regular exercise can also induce changes in mood. Farrell et al. (36) found a decrease in psychological tension in healthy volunteers after 40–80 min of running at intensities above 40% of maximal oxygen uptake. Other mood alternations reported after exercise include joy and euphoria, which could be reversed, in part, by intravenous naloxone (69).

Exercise appears to be almost as effective as antidepressive therapy in treating selected types of anxiety and depression (7,51,101,102,161). Although the mechanism of these mood changes might be via the endogenous opioid system, not all investigators have been able to block these exercise-induced mood changes with naloxone (90). However, as discussed earlier, the dose used in this study (0.8 mg) may have been insufficient to block endogenous opioid systems (25,118).

As summarized earlier, voluntary running and sciatic nerve stimulation both can change the behavioral patterns of SHR (11,62,163). In an open field test, for example, Hoffmann et al. (62) found that following exercise SHR showed only half the locomotor activity of their sedentary controls; i.e., the sedentary hypertensive controls were actually "hyperactive" compared to their running counterparts. The exercising rats also appeared to be less aggressive than the controls. One might speculate that such behavior may contribute to

the elevated blood pressure in sedentary SHR. Finally, these animals showed an "abstinence reaction" with a considerable elevation in their aggressive behavior if, after 6 wk of daily exercise, they were prevented from running by having the wheels on their cages locked. Since central opioid release triggered by activation of muscle afferents may be responsible for many of the hemodynamic and behavioral changes seen in exercising SHR, mood changes seen in man after exercise may be due to similar mechanisms. Thus, prolonged regular exercise together with psychological support might be therapeutic in selected patients with mild psychological or psychiatric diseases and preferable, at least as an initial therapy, to pharmacological approaches to such problems.

Eating disorders. Fasting can induce changes in central endorphin systems which result in both elevations in pain threshold (95) and decreases in blood pressure in SHR (162). Indeed, Kaye et al. (77) found that CSF opioid activity was increased in severely underweight anorectics, as opposed to patients who had chronic anorexia nervosa but who were not severely underweight. CSF opioid activity returned to normal levels in the former group of patients after weight restoration.

However, interpretation of clinical and experimental data is not straightforward. Decreases, not increases, in plasma beta-endorphin levels have been reported in patients with bulimia (153), and in a more recent study Kaye et al. (76) reported findings opposite to those in their 1982 report; namely, a decrease in CSF concentration of beta-endorphin and other POMC fragments in underweight anorectics and an increase in the CSF concentration in these peptides after weight gain.

If these latter observations are correct, regular exercise might counter the effects of anorexia or bulimia by restoring central endorphins to their normal levels. Interestingly enough, rat strains that normally do not exercise spontaneously will run up to 8 $km \cdot d^{-1}$ when they are deprived of only 10% of their normal food intake (121). Since exercise may reinforce anorectic behavior by substituting exercise for food as a mechanism of central opioid activation, controlled prospective studies will be needed to determine whether regular exercise will be beneficial or detrimental to patients with these disorders.

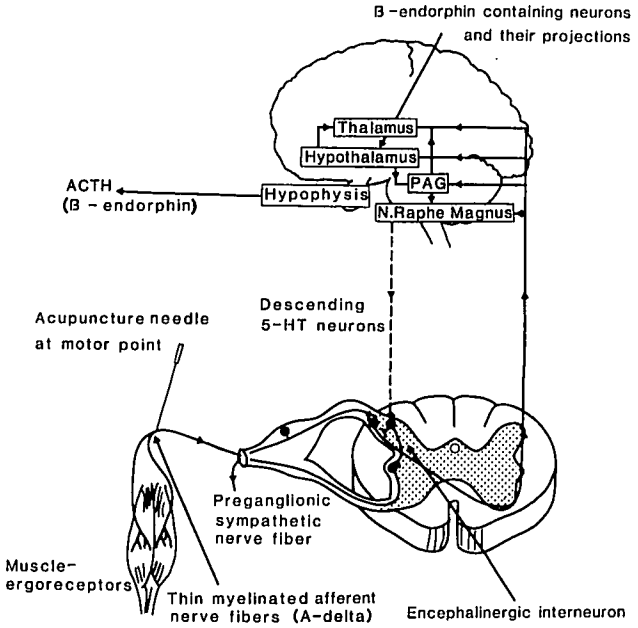

Figure 4—Hypothetical scheme: how muscle exercise and acupuncture might influence central (and peripheral) opioid concentrations and exert its effects on nociception and blood pressure. Exercise activates "ergoreceptors" located in skeletal muscle which react to both stretch and contraction. Impulses are transmitted to the spinal cord by thin myelinated nerve fibers (Group III or A-delta afferents) and reach the thalamus but also the nucleus raphe magnus (NRM) and the periaqueductus gray nucleus (PAG) via ascending spinal pathways. The thalamus, which is involved in pain perception, has opioid receptors of several types and contains enkephalinergic nerve cells. The PAG and the NRM are a part of the descending pain modulatory system, and the ventral PAG and the raphe nuclei also are involved in CNS control of blood pressure. Both the midbrain PAG and the brain stem NRM are rich in opioid receptors, and the PAG has dynorphinergic and enkephalinergic nerve cells. In the NRM, the descending inhibitory serotonergic (5-HT) neurons are activated and spinal enkephalinergic interneurons are stimulated, and possibly preganglionic sympathetic nerve fibers are influenced. The ascending signals also continue up to the hypothalamus, where beta-endorphin, enkephalin, and dynorphin are released. The hypothalamus, which is involved in autonomic control, including blood pressure, behavior, reward, and pain modulation, contains the N. Arcuatus, which is the major (extrapituitary) beta-endorphinergic nerve cell site in the CNS. The N. Arcuatus has endorphinergic projections to the thalamus, the PAG, and the brain stem. The released beta-endorphin probably acts as neuromodulator or neurotransmitter. Also, the hypophyseal, beta-endorphin containing system is activated as beta-endorphin is co-released with ACTH from the adenohypophysis into the circulation.

SUMMARY

The experimental and clinical findings discussed here lead us to propose that prolonged rhythmic exercise can activate central opioid systems by triggering increased discharge from (Group III or A-delta) thin, mechanosensitive afferent nerve fibers arising from contracting skeletal muscle. We have reviewed evidence that supports the concept that many of the cardiovascular, analgesic, and behavioral effects of either a single bout of prolonged rhythmic exercise or chronically performed exercise are mediated by this mechanism. We believe that some of the controversy in this area has arisen from two methodological errors: the assumption that plasma beta-endorphin concentrations will reflect changes in central opioid activity and the assumption that low dose naloxone will block these central opioid systems.

We have also reviewed evidence in support of the concept that the same mechanisms may be responsible for the central and peripheral responses to both prolonged rhythmic exercise and acupuncture. A schematic suggestion of common opioidergic mechanisms appears as Figure 4.

We acknowledge that many of the points raised in this paper are purely speculative and obviously require further research before firm conclusions can be reached. One of our major objectives in preparing this paper has been to stimulate research activity in this physiologically important and clinically relevant area. Hitherto, the concept that exercise (or acupuncture) is useful in treating or preventing disease has been rather diffuse and based primarily upon anecdotal observations and studies in small numbers of subjects rather than upon strong experimental evidence. Greater understanding of the relationship between exercise and the actions of central opioid release could lead to appropriately designed clinical studies of the role of rhythmic exercise alone or as an adjunct to other conventional therapies in the treatment of a variety of disorders.

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