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Does Plasma ß-Endorphin Influence Exercise-Induced Hypoalgesia in Healthy Adults?

Kathy Lemley
Marquette University

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Kathy Lemley
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Marquette University

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Anecdotal reports can be found in the literature of athletes who suffer from an injury, yet continue to participate in their sport with little or no pain. These reports have resulted in an interest in the possible role of stress, including exercise, in analgesia. Exercise-induced hypoalgesia (EIH), a decrease in pain perception following exercise, has been found to occur in healthy adults. In the 1970's opioid peptides with analgesic properties were discovered (Dalayeun, Nores & Bergal, 1993). One of these peptides, β-endorphin, is believed to be released from the anterior pituitary into the circulation under a variety of stressors, including exercise. Investigations into the plasma β-endorphin response with exercise have confirmed an exercise related increase. While animal studies may bring additional perspective to the study of EIH, this review will focus on human studies only. The intent then of this literature review is to answer the question: Does plasma β-endorphin concentration influence the EIH response in healthy adults?

Exercise-Induced Hypoalgesia

Investigations into the role of exercise and analgesia have examined aerobic, resistance and isometric exercise, with the most information on aerobic and isometric exercise. Types of stimuli used to assess pain perception include electrical stimulation, thermal heat, mechanical pressure, ischemia and cold pressor pain (immersing the hand and forearm in ice water).

Aerobic Exercise

A number of investigators have examined the presence of an attenuated pain perception response to aerobic exercise. Experimental design has varied considerably, including mode, intensity and duration of exercise, timing of pain assessments, pain perception measures (threshold, ratings or tolerance) and type of noxious stimulus presented, thus making direct comparisons between studies difficult. For example, Koltyn, Garvin, Gardiner, and Nelson (1996) utilized cycling at 75% VO_{2max} for

30 minutes whereas Guieu, Blin, Pouget, and Serratrice (1992) cycled for 20 minutes at approximately 50% of maximum and Paalasmaa, Kemppainen, and Pertovaara (1991) used four 8-minute stages with a progressive increase in workload. Others have used running (Hoffman, et al., 2004; Øktedalen, Solberg, Haugen, & Opstad, 2001) or track meet competition (Sternberg, Bokat, Kass, Alboyadjian, & Gracely, 2001) as the exercise stimulus. In addition to percent VO_{2max}, heart rate (HR) has been used to determine intensity (Padawer & Levine, 1992) or subjects have self-selected their exercise intensity levels (Bartholomew, Lewis, Linder, & Cook, 1996). See Table 1 for a summary of studies on aerobic exercise and EIH.

Despite these methodological differences, overall there does appear to be an alteration in pain perception to a variety of noxious stimuli following aerobic exercise with a number of investigators finding either a reduction in pain ratings (Droste, Greenlee, Schreck, & Herbert, 1991; Gurevich, Kohn, & Davis, 1994; Janal, Colt, Clark, & Glusman, 1984; Koltyn et al., 1996; Øktedalen et al., 2001; Sternberg et al., 2001), an increase in pain threshold (Droste et al., 1991; Guieu et al., 1992; Kemppainen, Paalasmaa, Pertovaara, Alila, & Johansson, 1990; Kemppainen, Pertovaara, Huopaniemi, Johansson, & Karonen, 1985; Koltyn et al., 1996; Olausson et al., 1986; Paalasmaa et al., 1991; Pertovaara, Huopaniemi, Virtanen, & Johansson, 1984) or an increase in pain tolerance (Bartholomew et al., 1996; Black, Chesher, & Starmer, 1979; Gurevich et al., 1994). However the EIH phenomenon may have a dose-response relationship. Hoffman et al. (2004) assessed the pressure pain response before and after treadmill running of various intensities and durations. They found decreased pain ratings at five minutes after the run only when running at 75% VO_{2max} for 30 minutes. No significant change in pain ratings were found with runs of shorter duration (10 minutes) or lower intensity (50% VO_{2max}).

Not all investigations show an EIH response. Padawer and Levine (1992) have suggested that the apparent EIH response is actually a response to the repeated pain testing and not a response to the

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exercise per se. Most early studies tested pain before and after exercise, and did not include a control group or control condition to assess the effect of the pain testing itself. Using a Solomon four-group design with cycling at 50% or 70% of age-predicted maximal heart rate for 20 minutes and the cold pressor test as their noxious stimulus, they found no exercise effect on pain. They did find a hypoalgesic effect for the pain testing.

In contrast to this and in support of an EIH response, Gurevich et al. (1994) also used a Solomon four group design and found no pain testing effect on pain responses. They used a step-climbing exercise for 12 minutes at an average of 63% $VO_{2\,max}$ and a pressure pain stimulus. Likewise both Bartholomew et al. (1996) and Koltyn et al. (1996) evaluated the pain response before and after quiet rest in addition to before and after exercise. While they failed to find a change in either pain ratings, pain threshold or pain tolerance after quiet rest, they did find decreased pain ratings and increased pain tolerance after exercise.

A possible explanation for the conflicting results may be the choice of pain stimulus. Gurevich et al. (1994), Bartholomew et al. (1996) and Koltyn et al. (1996) all used a pressure pain stimulus whereas Padawer and Levine (1992) used a cold pressor test. The EIH response has been found more consistently when presenting a noxious pressure or electrical stimulus than when the presenting stimulus is a cold pressor test (Cook & Koltyn, 2000). Additionally, exercise at 50% or 70% of $HR_{age-predicted\,max}$ as used by Padawer and Levine may not be a sufficient stimulus to induce changes in pain perception (Hoffman et al., 2004). Furthermore, several investigations have performed repeated pain tests during recovery with pain measurements initially attenuated and then gradually returning to baseline (Droste et al., 1991; Hoffman et al.; Olausson et al., 1986). This return to baseline in successive pain scores during recovery would argue against Padawer and Levine's hypothesis. Thus it appears that EIH does occur

after aerobic exercise of sufficient intensity and duration, and this response may be most consistent with a noxious pressure stimulus.

Resistance Exercise

There is very limited research into the pain response following resistance exercise. See Table 1 for a summary of the available literature. In a study examining the chronic response in pain perception to exercise training Anshel and Russell (1994) had sedentary male subjects perform an aerobic exercise training program, a strength training program, a combination of both types of exercise or no change in activity levels for 12 weeks. They found an increase in pain tolerance in the upper extremity, but not the lower extremity, to a pressure stimulus only in the two groups performing aerobic exercise. This would indicate that pain perception may be altered by a 12 week program of aerobic exercise, but is unchanged by a program of strength training. These investigators did not assess the acute impact of aerobic or resistance exercise on pain perception.

In contrast, the acute pain perception response to training was examined by Bartholomew et al. (1996). Male subjects, some of whom were body builders and others regular exercisers, performed a self-selected exercise program. Thirteen subjects chose to do weight lifting and four selected cycling. They found no group differences in pressure pain tolerance or pressure pain threshold leading to a pooling of the data. Their results showed that while no change in pain threshold occurred after exercise, pain tolerance was significantly increased after exercise compared with resting an equal time period.

Likewise an acute EIH response was found by Koltyn et al. (1998) following a 45 minute weight lifting session at 75% 1-repetition maximum (RM) in a mixed gender group of subjects. Increased pressure pain thresholds and decreased pressure pain ratings were present five minutes after the exercise, although these changes were no longer present at 15 minutes into recovery. Thus it appears

that resistance training produces an acute hypoalgesic response, but does not result in a chronic change in pain perception with training.

Isometric Exercise

In comparison to resistance exercise, isometric exercise has received more attention in the literature. A summary of the literature on isometric exercise and pain perception can be found in Table 1. Several investigators have found reductions in pain ratings (Hoeger Bement, Dicapo, Rasiarmos, & Hunter 2008; Koltyn & Umeda, 2007; Koltyn, Trine, Stegner, & Tobar, 2001; Staud, Robinson, & Price, 2005) or increases in pain thresholds (Hoeger Bement et al., 2008; Koltyn & Umeda, 2007; Koltyn et al., 2001; Kosek & Ekholm, 1995; Kosek & Lundberg, 2003; Kosek, Ekholm, & Hansson, 1996; Staud et al., 2005) following isometric exercise. As with aerobic exercise, there may be a dose-response relationship. Hoeger Bement et al. (2008) had male and female subjects perform elbow flexion at 25% maximal voluntary contraction (MVC) for two minutes, 25% MVC to task failure, 80% MVC to task failure or three reps 100% MVC. There was no significant difference in force between the three MVC contractions indicating that fatigue did not occur. Pain thresholds and pain ratings were assessed 30 minutes before and immediately after the exercises with a two minute pressure pain test on the contralateral index finger. Their results showed a decrease in pressure pain ratings after the contraction at 80% MVC to task failure and both a decrease in pain ratings and an increase in pressure pain threshold following the 100% MVC's and the contraction of 25% MVC to task failure. No change in pain ratings or pain threshold was found for a contraction of 25% MVC for two minutes. Furthermore, the greatest increase in pain threshold occurred following the contraction of 25% MVC to task failure, and this contraction was the only one to result in a decrease in peak pain ratings. Thus their results would indicate that for an EIH response to occur following isometric exercise, the dose must be such that it is either of high intensity or of prolonged duration when a lower intensity is used. Additionally,

as was shown with the 100% MVC task, fatigue is not a necessary component of the task at high intensity in order to have an EIH response.

The EIH response following isometric exercise has been most consistent with the use of a pressure pain stimulus. Thermal pain threshold responses have been less consistent. While Staud et al. (2005) found a decrease in thermal pain ratings at end exercise during a 90 second handgrip contraction at 30% of MVC, Paalasmaa et al. (1991) failed to find a significant difference in heat pain threshold after two-minute static plantarflexion contractions of 30% and 70% MVC.

Inconsistency in the findings of these two studies may be related to the intensity and/or duration of the contractions. A two-minute contraction at 30% MVC may be insufficient to induce EIH (Hoeger Bement et al., 2008). However Staud et al. (2005) also used 30% MVC intensity with an even shorter duration with handgrip and did see a decrease in heat pain ratings, thus contraction parameters are not the primary reason for the conflicting results. The use of different measures of pain perception may account for the conflicting results as Staud et al. reported thermal pain ratings while Paalasmaa et al. assessed thermal pain threshold. It is possible to have changes in one parameter of pain perception, but not in another (Bartholomew et al., 1996; Hoeger Bement; Koltyn et al., 2001).

Another likely explanation for the different outcomes may be the gender of the subjects. While Staud et al. (2005) had all female subjects; the subjects in the Paalasmaa et al. (1991) study were all males. Indeed gender differences in the pain perception response to isometric exercise have been found. Both Hoeger Bement et al. (2008) and Koltyn et al. (2001) found women to have lower pressure pain thresholds at rest. Hoeger Bement et al. also noted that women had higher pressure pain ratings at rest than men. However while Hoeger Bement et al. found the magnitude of increase in pressure pain threshold and decrease in pressure pain ratings following MVC's of the elbow flexors to be equal across genders, Koltyn et al. found that pressure pain threshold increased only for the women. Furthermore

they noted that while decreases in pressure pain ratings after handgrip MVC's occurred in both genders, only the women showed a decrease in pressure pain ratings following submaximal efforts. Thus while it appears that women may have lower pressure pain thresholds than men at rest, gender differences in resting pain ratings and in the pain perception response to isometric exercise are as yet unclear.

A final physiological response that may impact thermal pain perception is the possible alteration in skin and subcutaneous temperature and blood flow with exercise. This in itself could result in differences in findings when using a heat stimulus as the measure of pain perception and may decrease the usefulness of thermal noxious stimuli in assessments of EIH.

Overall isometric exercise does appear to result in an EIH response. This response is most consistent for mechanical pressure pain and may require contractions of high intensity or long duration. Fatigue does not appear to be a necessary component per se. There may also be gender differences in pain perception at rest with women having lower resting pain thresholds, however gender differences in resting pain ratings and exercise related changes in pain ratings and pain threshold are not yet clear.

Local versus Central or Systemic Mechanisms for EIH

The EIH response appears to be mediated by central or systemic mechanisms. A change in pain perception would be expected only at the site of exercise if the response was mediated by a local mechanism. However several studies using both aerobic and isometric exercise have found a reduction in pain perception at sites distant to the exercising limb(s). For instance Hoffman et al. (2004) and Koltyn et al. (1996) used a pressure pain device on the index finger to assess pain perception after running and cycling exercise respectively, while Droste et al. reported increased pain tolerance of tooth pulp and finger tip electrical stimulation following cycling. And Anshel and Russell (1994) found increased pain tolerance in the upper extremity following a program of cycling or cycling plus weight training. Additionally, during the study of isometric exercise, Hoeger Bement et al. (2008) assessed

pressure pain on the contralateral limb while both pressure pain (Koltyn & Umeda, 2007; Kosek & Lundberg, 2003) and thermal heat pain (Staud et al., 2005) have been assessed bilaterally, all with a positive EIH response at the distant sites. While a greater EIH response magnitude is noted on the exercising limb (Kosek & Lundberg), decreased pain perception found distant to the exercising limb is consistent with a systemic or central mechanism of analgesia.

Summary

An EIH response has been found with all types of exercise. This response is most consistent with higher intensity aerobic exercise or isometric exercise of high intensity or prolonged duration and may be dependent upon the type of noxious stimulus presented. Pressure and electrical stimulation demonstrate the most consistent responses, whereas the responses to cold pressor and thermal stimuli are more equivocal. The measure used to assess pain perception may also vary the results, as pain threshold, pain ratings and pain tolerance do not always respond in an identical fashion. The EIH response appears to be centrally or systemically mediated, with reductions in pain perception occurring at sites distant from the exercising limb. Additionally there may be gender differences in pain perception, both at rest and in response to exercise.

Plasma β-endorphin Response to Exercise

The discovery of opioid receptors and the opioid peptides with their analgesic and mood elevating properties has led to significant interest in the role of these peptides in exercise and their possible role in EIH. Several investigators have examined the plasma β-endorphin response to exercise with the greatest amount of research involving aerobic exercise.

Aerobic Exercise

Results of numerous studies consistently show an increase in plasma β-endorphin levels following aerobic exercise of higher intensities (Angelopoulos 2001; Bortz et al., 1981; Bullen et al., 1984; Carr et al., 1981; Carrasco, Villaverde, & Oltras, 2007; Colt, Wardlaw, & Frantz, 1981; Fraioli et al., 1980; Goldfarb, Hatfield, Armstrong, & Potts, 1990; Goldfarb, Hatfield, Potts, & Armstrong, 1991; Goldfarb et al., 1998; Heitkamp, Schmid, & Scheib, 1993; Heitkamp et al., 1990; Howlett et al., 1984; Maresh et al., 2006; McMurray, Forsythe, Mar, & Hardy, 1987; Oleshansky, Zoltick, Herman, Mougey, & Meyerhoff, 1990; Oltras, Mora, & Vives, 1987; Piacentini et al., 2002; Rahkila, Hakala, Alen, Salminen, & Laatikainen, 1988; Rahkila, Hakala, Salminen, & Laatikainen, 1987; Sanchez-Garcia et al., 2004; Shen, Chin, Fullerton, Jennings, & Dart, 1992; Taylor et al., 1994; Viswanathan, Van Dijk, Graham, Bonen, & George, 1987). This increase in β-endorphin occurs in a non-linear fashion with a sharp increase in concentration at the end of exercise or into recovery (Droste et al., 1991; Goldfarb et al 1987; Heitkamp et al., 1993; Heitkamp et al., 1990; McMurray et al., 1987). One contradictory result of note is that of Farrell, Gates, Maksud, & Morgan (1982). While showing an increase in β-endorphin after running at 60% VO_{2max}, they failed to find an increase at 80% VO_{2max}. This result has not been replicated, thus an increase at higher workloads can be expected.

On the other hand exercise of low intensity does not appear to stimulate an increased release of β-endorphin. For example no increase was found in plasma β-endorphin levels following cycling at 60% VO_{2max} by Goldfarb et al. (1990, 1991, 1998). β-endorphin levels were also unchanged with cycling at 40% or 60% VO_{2max} (McMurray et al., 1987), 45% VO_{2max} (Viru & Tendzegolskis, 1995), and 25% or 50% VO_{2max} (Donevan & Andrew, 1987). Nor was plasma β-endorphin concentration altered by cycling or arm ergometry at 60% VO_{2peak} (Maresh et al., 2006) or running at 50% or 60% VO_{2max} (Rahkila et al., 1988; Farrell, Kjaer, Bach, & Galbo, 1987).

Moderate intensity exercise has more equivocal results and may depend upon duration of the exercise program. While an increase in β-endorphin was found with cycling at 70-75% VO_{2max} by some investigators (Goldfarb et al., 1990, 1991; Donevan & Andrew, 1987), no change in β-endorphin was noted after running at the same intensity (Kraemer, Blair, Kraemer, & Castracane, 1989; Rahkila et al., 1988) and decreased levels were found after 30 minutes of running at either the individual anaerobic threshold (Di Luigi et al., 2003) or at 75% VO_{2max} (Di Luigi et al., 2001). Schwarz and Kindermann (1989) did note an increase in β-endorphin levels after cycling at approximately 63% VO_{2max}, the anaerobic threshold of their male subjects, but not until between 50 and 75 minutes of exercise. This may imply that aside from potential differences in the threshold intensity required to stimulate a β-endorphin response with different modes of exercise, the duration of moderate intensity exercise may need to be prolonged in order to stimulate the release of β-endorphin.

Another possible reason for the inconsistent findings at moderate intensity may be related to wide variability in individual responses. Several authors have identified an extremely large degree of interindividual variability in the β-endorphin response to aerobic (de Meirleir et al., 1986; Goldfarb, Hatfield, Sforzo, & Flynn, 1987; Donevan & Andrew, 1987; Howlett et al., 1984), resistance (Doiron, Lehnhard, Butterfield, & Whitesides, 1999; Pierce et al., 1994; Pierce, Eastman, Tripathi, Olson, & Dewey, 1993) or isometric (Melchionda et al., 1984) exercise. Thus studies that failed to find changes may have been underpowered considering the large degree of interindividual variation in this physiological response.

The effect of aerobic training on the β-endorphin response to exercise is not yet clear, with some reports of an attenuated β-endorphin response (Engfred et al., 1994) or no change in response (Kraemer et al., 1989) after training. However the majority of studies appear to support an augmentation in the β-endorphin response to exercise following training. Bullen et al. (1984) trained female prior athletes who

were currently sedentary by running four days a week at 85% HR_{max} for 8 weeks. They found the magnitude of the increase in β-endorphin was greater following the eight week training program than before the program. Likewise Carr et al. (1981) found a greater rise in plasma β-endorphin following four weeks of a cycling/running program in sedentary females than before training. There was no further increase in response magnitude after four weeks. In a cross-sectional study of trained Nordic skiers compared to recreational skiers, Mougin et al. (1987) found the highly trained skiers to have greater increases in β-endorphin levels than the recreational skiers after a long distance Nordic ski race. Similarly de Diego Acosta et al. (2001) found an increase in β-endorphin levels after a graded treadmill exercise test only in their trained subjects as well as finding higher basal levels of β-endorphin in the trained subjects than the sedentary subjects. This result was similar to that of Viru and Tendzegolskis (1995) who showed that the plasma β-endorphin concentration did not change in untrained male subjects following 2 hours of cycling at 60% VO_{2max}, but did increase in trained individuals; and those of Goldfarb et al. (1991) who found a trend for trained male subjects to have higher basal and post-exercise β-endorphin levels than untrained. Farrell et al. (1987) also found a larger increase in β-endorphin in the trained group compared to the untrained group, but only at supramaximal exercise. An important finding by Goldfarb et al. (1991) was that while the increase in the absolute levels of β-endorphin with exercise trended higher in the trained individuals, the relative change in β-endorphin was no different between the groups.

Gender differences have also been postulated to exist in the β-endorphin response to aerobic exercise, but the results remain equivocal.   Although Kraemer et al. (1989) failed to find any change in plasma β-endorphin in either gender after 30 min of running at 80% HR_{max}, they did note that males had higher β-endorphin levels at all time points. And both Heitkamp et al. (1990) and Goldfarb et al. (1998) found increases in plasma concentrations of β-endorphin after exercise with trends toward differences in

gender responses. However while Heitkamp et al. saw a trend for women to have a greater β-endorphin response to exercise than the men, Goldfarb et al. saw a trend in the opposite direction, with women trending toward a lower response magnitude than men. No gender differences in the β-endorphin response were identified after running by Rahkila et al. (1987) or cycling by McMurray et al. (1987). Thus a gender difference may exist in the basal and exercise response of β-endorphin, but a definitive statement in this regard cannot be made at this time.

It has also been postulated that the β-endorphin response in females differs at different phases of the menstrual cycle and that this may be a confounder when assessing gender differences. Goldfarb et al. (1998) assessed the β-endorphin response to cycling in both genders, assessing the female subjects twice, once in the follicular phase of their menstrual cycle (2-6 days after menses onset) and once in the luteal phase (22-26 days after menses onset). While basal β-endorphin levels trended toward being lower in the luteal phase of the menstrual cycle, they found no phase difference in the response to exercise. Thus the menstrual cycle does not influence gender differences that may exist in the β-endorphin response to aerobic exercise.

Resistance Exercise

The β-endorphin response to resistance exercise has received much less attention than that of aerobic exercise and results have included an increase (Doiron et al., 1999; Elliot, Goldberg, Watts, & Orwoll, 1984; Kraemer et al., 1993), decrease (Pierce et al., 1994; McGowan, Pierce, & Eastman, 1993) or no change (Petraglia et al., 1988; Kraemer et al., 1993; Pierce et al., 1993) in β-endorphin concentrations. An increase in β-endorphin concentration was found in male subjects after a hypertrophy weight training protocol of 10-RM with 1 min rest between sets, however, no change in β-endorphin was found following resistance exercise of higher resistance (5-RM) or longer rest times (3 min) by Kraemer et al (1993). Additionally no change in males was seen following resistance exercise

consisting of 3 sets of 8 reps at 40%-60% 1-RM with 3 minutes between sets (Pierce et al., 1993) and a decrease in plasma β-endorphin in both genders was noted after resistance exercise of 3 sets of 8 reps at 80% of 1-RM with 3 minutes between sets by Pierce et al. (1994)

Petraglia et al. (1988) examined discus throwers and runners during a national athletic competition. While they did find elevations in plasma β-endorphin concentrations in the runners, with the greatest elevations occurring in the endurance runners and less marked elevations in the sprinters, no change in concentration was found in the discus throwers. It would appear that there may be a threshold for intensity of resistance exercise and that the rest period between exercises may be critical in determining the threshold requirement.

Isometric Exercise

There is an extreme paucity of information on the plasma β-endorphin response to isometric exercise. Melchionda et al. (1984) examined the response to fatiguing knee extension MVC's in male and female elite kayak paddlers and untrained individuals. They found no difference in the basal levels of β-endorphin with training status. Neither the trained nor the untrained subjects revealed a change in β-endorphin concentrations following the exercise session. Furthermore, no correlation was found between resting β-endorphin concentration and strength, fatigue or body size. The authors did note a very large degree of individual variability in β-endorphin levels at rest, particularly amongst the trained athletes.

Summary

Table 2 provides a synopsis of investigations into the release of β-endorphin with exercise. In summary, β-endorphin levels in the plasma rise considerably in a non-linear fashion with aerobic exercise of higher intensity and a dose-response relationship may exist. Consistent elevations in

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β-endorphin appear to take place with exercise intensities of greater than 70% - 80% VO_{2max} and may be related to the mode of exercise. The response to resistance exercise is much more equivocal, and may be dependent upon exercise protocol with short rest periods necessary for an increase in β-endorphin to occur. Isometric exercise does not appear to result in an increase in plasma β-endorphin levels, but a paucity of information in the literature leaves this in question. Additionally, there is great inter-individual variation in the β-endorphin response to all types of exercise.   Finally, training status and gender may influence the β-endorphin response to exercise, but there are conflicting results in the literature in regard to both of these issues. It may be that training produces absolute differences, but not relative differences in the β-endorphin response, and while gender differences may exist, they do not appear related to the menstrual cycle.

Exercise-Induced Hypoalgesia and Plasma β-endorphin Relationship

Considering the similarity in the pain perception and β-endorphin responses to aerobic exercise, it would be easy to infer a relationship between these two physiological responses. Surprisingly little research has looked directly into the relationship between them. Only three groups of researchers have measured both β-endorphin levels and pain perception during and following exercise. All three investigators examined the responses to aerobic exercise with all male subjects, limiting generalizability to other forms of exercise or to female participants. See Table 3 for a summary of these investigations.

The first to investigate the possible role of exercise induced increases in plasma β-endorphin with altered pain perception was Janal et al. in 1984. These investigators had 12 trained runners run a 6.3 mile city street course at racing pace (~85% VO_{2max}). Blood samples and pain and mood assessments were performed both before and after the run. Pain stimuli included thermal heat pain, ischemic pain and a cold pressor test. Each runner ran twice, once receiving an injection of naloxone, an

opioid antagonist, immediately post-run and once receiving a placebo injection. The injection order was

counterbalanced in a double-blind fashion. The order of presentation of mood and pain stimuli was

varied between individuals and was consistent across runs.

Their results indicated that discriminability of the thermal pain stimulus was significantly

decreased following exercise and was not modified by naloxone. Pain ratings during the ischemic pain

test were also lower after exercise; however this effect was reversed by naloxone. There was no overall

change in pain perception with the cold pressor test following exercise and no effect of naloxone.

β-endorphin levels were increased after exercise, however there was no co-variation of pain and

β-endorphin levels either before or after exercise.

Seeing as naloxone failed to reverse the effects of exercise on the response to the thermal

stimulus, but did reverse the effect of ischemic pain, it is possible that there may be different

mechanisms involved with different types of pain stimuli and that exercise may activate both opiate and

non-opiate mediated analgesia systems. Furthermore, the failure to find a correlation between plasma

β-endorphin levels and pain would indicate that the opiate-mediated system is either centrally rather than

peripherally located or involves other peripheral opioids such as enkephalins or endomorphins.

Naloxone is not limited to the periphery and unlike β-endorphin is able to cross the blood-brain barrier,

thus affecting both peripheral and central opioid receptors (Fichna, Janecka, Costentin, & Do Rego,

2007; O'Connor & Cook, 1999).

There are several significant limitations to the Janal et al. (1984) study. First of all is the large

number of assessments performed, some of which were quite lengthy. Test times were 15 minutes to

complete the thermal test and 20 minutes for the ischemic test. The cold pressor test took 5 minutes and

blood sampling took another 10 minutes. The authors also assessed mood, adding yet another five

minutes for this assessment. Thus there were only 3 subjects who received any given test (pain or mood)

first and this was always preceded by a 10-12 min time lapse between the end of exercise and start of the assessment for blood sampling and drug injection. Indeed the authors discuss the time lag issue and show results for the different tests depending upon the time between exercise and testing. This design issue significantly reduces the power for any given test, as most studies indicate a return back to baseline of pain perception within 5-15 minutes (Hoffman et al. 2004; Koltyn & Arbogast, 1998; Kosek et al., 1996) or between 15 and 30 minutes (Kosek & Lundberg 2003; Kemppainen et al., 1985) of completing exercise.

Another limitation of this study was the timing of the blood draws. Blood draws were performed immediately before the administration of the pain and mood tests. The pain and stress of the blood draw itself may have resulted in an alteration in the response to the pain assessments. Likewise, performing pain assessments in a consecutive fashion is likely to alter the results of the latter assessments (O'Connor & Cook, 1999; Padawer & Levine, 1992). In addition, the failure to take blood samples and test pain perception during the run or at different time intervals during recovery does not allow for a time course to be plotted for both plasma β-endorphin concentration and pain perception.

Lack of a control group presents yet another limitation of the Janal et al. (1984) study. This was a common limitation in many of the earliest studies. While each subject was tested both with naloxone and with saline, no group was tested without an exercise intervention. Thus test-retest changes may have confounded the results and cannot be ruled out.

And finally, the assay used for determining β-endorphin concentration shows a high degree of cross-reactivity with β-lipotropic hormone (β-LPH), so the numbers reported are for a combination of both peptides rather than just for β-endorphin and may not adequately reflect the true change in β-endorphin levels.

Despite these limitations, the correlation results of Janal et al. (1984) are consistent with those of Droste et al. (1991). Ten male regular, non-competitive exercisers participated in this study. The subjects cycled in supine with either naloxone or placebo, starting at 100 W and increasing the workload 50 W every 3 minutes to exhaustion. Pain threshold and plasma β-endorphin concentrations were assessed at rest, during submaximal exercise, at maximal exercise and during recovery. Pain stimulus was electrical stimulation to tooth pulp and to the tip of the middle finger. Their findings included a gradual increase in tooth pulp pain threshold during exercise that peaked at or near exercise termination. This is in contrast to the time course of plasma β-endorphin which showed a peak 10 minutes into recovery, a finding consistent with that of several other investigators (de Meirleir et al., 1986; Farrell et al., 1987; Goldfarb et al., 1990, 1991; Hatfield, Goldfarb, Sforzo, & Flynn, 1987; Taylor et al., 1994). In addition, pain ratings for tooth pulp suprathreshold stimuli were decreased after exercise. Likewise fingertip pain threshold increased at maximum exercise and was further increased in the session with naloxone. Naloxone had no effect on pain ratings for either area. As with Janal et al. (1984), no correlation was found between plasma β-endorphin and pain threshold. Furthermore, there was a positive correlation between plasma β-endorphin and cortisol and between plasma β-endorphin and blood lactate, yet neither cortisol nor lactate showed a significant correlation with pain thresholds.

Thus Droste et al. (1991) was able to show that while both plasma β-endorphin and dental pulp and finger tip electrical stimulation pain thresholds increased following aerobic exercise, their time courses differed from each other. Pain thresholds peaked at or near maximal exercise, while β-endorphin levels peaked at 10 minutes into recovery. At this time pain thresholds were still elevated above baseline, but were beginning to decrease. Furthermore, if pain threshold was mediated by plasma β-endorphin, then a reversal of the increased pain threshold would be expected with naloxone, rather than a further increase in threshold or no effect.

Similar to other early studies, including that of Janal et al. (1984), limitations of this study included the cross-reactivity with β-LPH of the hormonal assay and the lack of a non-exercise control group.

Consistent with the two previous studies, Øktedalen et al. (2001) also failed to find a significant correlation between β-endorphin and pain ratings pre- or post-exercise. Two experiments were performed to examine this relationship as well as to assess the effect of meditation on the two responses. In the first experiment they performed a cross-sectional study with a group of 20 trained males and 9 sedentary controls. An ischemic pain test was performed on the non-dominant arm before and after a graded treadmill VO_{2max} test. There were no group differences in either the basal or post-exercise β-endorphin levels. Likewise there were no group differences in pain ratings during the ischemic test, with both the trained and untrained demonstrating both decreased intensity and a slower rise in pain ratings following exercise.

In their second experiment Øktedalen et al. (2001) undertook a longitudinal study on the effects of mediation on the β-endorphin and pain responses. The trained group was subdivided into a group trained in and practicing daily meditation and a group not trained in or practicing mediation. Both groups continued with their regular athletic training programs. Follow-up six months later revealed resting plasma β-endorphin and pain ratings to be less than pre-meditation intervention with no difference between those that practiced meditation and those that did not. The original sedentary control group was not reassessed at the six month interval, so the reason for these changes cannot be adequately determined. They may represent simply a learning effect or a reduction in testing anxiety being familiar with the testing procedure. It cannot be assumed to be due to six months of training as all of the subjects in the second experiment had been training regularly before the start of the experiment and there was no

change in their training regime during the intervening 6 months. Aside from lower basal β-endorphin

levels, no other differences from pre-intervention were found.

Other investigators have indirectly assessed the exercise induced β-endorphin – pain perception

relationship. Pertovaara et al. (1984) examined tooth pulp pain responses following cycling exercise.

While plasma β-endorphin was not measured in this study, plasma adrenocorticotropin (ACTH) levels

were assessed. Since ACTH and β-endorphin are released concomitantly from the anterior pituitary

(Dalayeun et al., 1993; Fraioli et al., 1980), the ACTH response may be indicative of the β-endorphin

response as well. An increased pain threshold was noted at the highest workload employed (200 W).

This workload amounted to approximately 71% of maximal aerobic capacity. While pain threshold did

increase at the highest workload, no increase in ACTH level occurred with the exercise and there was no

correlation between ACTH and pain threshold, either before or during exercise. One confounding factor

may have been the timing of the venous catheter placement for blood sampling. The catheter was

inserted 10 minutes prior to exercise and the first blood draw. This was probably too short of a period of

time, as the pain of the catheterization may itself have altered hormonal and pain responses. Indeed, a

higher than normal ACTH level at all time points in this study may be due to an inadequate rest time

between catheter placement and the start of data collection.

While not examining hypoalgesia in response to exercise, Matejec et al. (2005) did examine the

relationship of acute thermal and pressure pain and plasma opioids. Corticotropin-releasing hormone

(CRH) or placebo was infused via an intravenous line accompanied by either naloxone or placebo 40

minutes later. The infusion of CRH resulted in an increase in β-endorphin, β-lipotropin and

β-endorphin-immunoreactive material. No change in thermal heat pain tolerance was found under any

condition; however pressure pain tolerance was increased in the two CRH conditions and was not

reversed by naloxone. Neither heat nor pressure pain thresholds significantly correlated with any of the

plasma opiates indicating that the increase in the plasma opioids was not related to the change in pressure pain tolerance and this is confirmed by the failure of naloxone to reverse the pressure pain tolerance response.

Another study that indirectly looked at the β-endorphin – pain perception relationship involved the use of naloxone. Olausson et al. (1986) had subjects perform 20 minutes of cycling and arm ergometry at workloads sufficient to achieve a heart rate of 150 bpm. They received either naloxone or saline and pain thresholds to dental pulp stimulation were assessed every 5 minutes during a 50 minute recovery. While there was large interindividual variability in thresholds, pain thresholds did increase following arm exercise and trended toward an increase in leg exercise. The threshold changes following arm exercise were attenuated with naloxone at 5 minutes recovery, but not thereafter. No effect of naloxone was found with leg exercise. Thus based on the short-term attenuated response to naloxone, the increased pain thresholds after arm ergometry may be at least partly opiate mediated. However, the location of the analgesic effect in the periphery versus the central nervous system cannot be ascertained from this study.

Likewise the location of possible opioid activity cannot be elucidated from the study by Paulev et al. (1989). Naloxone versus saline was used to assess opioid involvement in the assessment of muscle pain following a Cooper Test (12 minute track run to exhaustion). β-endorphin was found to increase similarly in both conditions and while performance was not affected, the perception of muscle pain was augmented by naloxone. This would indicate that a reduction in the perception of muscle pain with exhaustive exercise may be opiate mediated, however the role of peripheral versus central β-endorphin activity is unclear.

Post-exercise muscle pain was also examined by Gordon, Duncan, & Kohl (1989) using a Wingate test and by Cook and Koltyn (2000) using dynamic graded handgrip to task failure. In contrast

to Paulev et al. (1989), however, in neither study did the opioid antagonist result in a change in pain threshold or pain ratings relative to the placebo condition. Thus the role of opioids in post-exercise muscle pain remains controversial.

Summary

Overall, the failure to find any significant correlation between plasma β-endorphin concentration and exercise induced hypoalgesia along with the finding of different time courses for the two physiological responses would indicate that the peripheral release of β-endorphin is not responsible for the analgesic response following exercise. This is further supported by the lack of a significant correlation between ACTH and changes in pain perception. Furthermore while no change in plasma β-endorphin has been found after isometric exercise, there is a rather robust reduction in pain thresholds and pain ratings following this type of exercise.

While the use of naloxone at times may be indicative of an opioid-mediated mechanism to EIH, studies to date in humans have not specifically addressed a peripheral versus a central mechanism. Additionally, the responses to opioid antagonists have been inconsistent, with some studies finding an augmented pain response, some no change and still others an attenuated pain response. Thus it is possible that the mechanism of EIH may vary with different types of pain stimuli and may involve both opiate and non-opiate pathways.

Conclusion

In conclusion, exercise does produce a hypoalgesic response, particularly with aerobic exercise of high intensity or isometric exercise of high intensity or prolonged duration. This response is most consistent with the noxious stimuli of pressure pain and electrical stimulation. There is much less consistency with thermal or cold pressor pain. The exact mechanisms behind the EIH response are

unknown and may vary with the presenting noxious stimulus. Continued research in this area is clearly needed. Plasma β-endorphin also increases at the end of exercise or within the first few minutes of recovery, with this response being most consistent with aerobic exercise of high intensity. The β-endorphin response is less consistent with resistance exercise and may be dependent upon duration of rest periods between sets. There does not appear to be a change in plasma β-endorphin concentration with isometric exercise. While hypoalgesia may have differing mechanisms for different pain stimuli, failure to identify a significant correlation between changes in pain perception and changes in plasma β-endorphin levels in any study, the differing time courses between the hormonal and pain responses, failure to identify a change in plasma β-endorphin with isometric exercise despite a robust decrease in pain perception and the inconsistent response to opioid antagonists all suggest that plasma β-endorphin does not directly influence exercise induced hypoalgesia in healthy adults.

Table 1. Studies examining the pain perception response to exercise

Author and Year	Subjects	Exercise Mode	Intensity and Duration	Pain Stimulus	EIH Response?
Aerobic					
Hoffman et al. 2004	7 female 5 male	Treadmill (TM)	75% VO_{2max} x 10 min 50% VO_{2max} x 30 min 75% VO_{2max} x 30 min	Pressure	No, Ratings No, Ratings Yes, Ratings
Sternberg et al. 2001	10 female 10 male	Treadmill Track meet	85% predicted HR_{max} x 10min	Cold Pressor	Yes, Ratings, females only Yes, Ratings, both genders
Øktedalen et al. 2001	29 male	Treadmill	Graded VO_{2max} test	Ischemic	Yes, Ratings
Koltyn et al. 1996	2 female 14 male	Cycling	65-75% VO_{2max} x 30 min	Pressure	Yes, Ratings and Threshold
Bartholomew et al. 1996	17 male	Cycling	Self-Selected	Pressure	No, Threshold Yes, Tolerance
Gurevich et al. 1994	60 male	Step Exercise Solomon 4-group	75% $VO_{2submax}$ x 12 min	Pressure	Yes, Ratings and Tolerance
Padawer & Levine 1992	91 both genders	Cycling Solomon 4-group	70% predicted HR_{max} x 20min	Cold Pressor	No, Ratings
Guieu et al. 1992	2 female 4 male	Cycling	200W (~50% of max) x 20 min	Electrical Stimulation	Yes, Threshold
Droste et al. 1991	10 male	Supine Cycling	Progressive to exhaustion	Electrical Stimulation	Yes, Threshold and Ratings
Paalasmaa et al. 1991	11 male	Cycling	100W (~36.5% VO_{2max}), 150W (~54.5% VO_{2max}), 200W (73% VO_{2max}), 250W (~91% VO_{2max})	Thermal	Yes, Threshold, 250W only
Kemppainen et al. 1990	6 male	Cycling	100W (~37% VO_{2max}), 150W (~56% VO_{2max}), 200W (~74% VO_{2max}) x 10 min each	Electrical Stimulation	Yes, Threshold All workloads
Olausson et al. 1986	3 female 8 male	Cycling leg Cycling arm	HR > 150 bpm x 20 min	Electrical Stimulation	Trend yes Yes, Threshold
Kemppainen et al. 1985	7 male	Cycling	100W (~30% VO_{2max}), 200W (~61% VO_{2max}), 250W (~76% VO_{2max}), 300W (~91% VO_{2max})	Electrical Stimulation	Yes, Threshold Final two workloads only
Janal et al. 1984	12 male	6.3 mile road run	~85% VO_{2max} x ~44 min	Ischemic Thermal Cold Pressor	Yes, Ratings Yes, Discriminability No, Ratings
Pertovaara et al. 1984	6 male	Cycling	50W, 100W, 150W, 200W (~71% VO_{2max}) x ~8 min each	Electrical Stimulation	Yes, Threshold 200W only
Resistance					
Koltyn & Arbogast 1998	6 female 7 male	Weight Training	45 minutes 3 sets 10 reps 75% 1RM	Pressure	Yes, Threshold and Ratings
Bartholomew et al. 1996	17 male	Weight Training	Self-Selected	Pressure	No, Threshold Yes, Tolerance
Anshel & Russell 1993	48 male	Weight Training	12 week strength training	Pressure	Increased pain tolerance arm only (chronic response)

Table 1 Continued

Author and Year	Subjects	Exercise Mode	Intensity and Duration	Pain Stimulus	EIH Response?
Isometric					
Hoeger Bement et al. 2008 (experiment 1)	14 female 13 male	Elbow Flexion	MVC's x 3	Pressure	Yes, Threshold and Ratings
Hoeger Bement et al. 2008 (experiment 2)	11 female 11 male	Elbow Flexion	25% MVC to fatigue	Pressure	Yes, Threshold and Ratings
			25% MVC x 2 min		No, Threshold or Ratings
			80% MVC to fatigue		Yes, Threshold only
Koltyn & Umeda 2007	14 female	Handgrip	40%-50% MVC x 2 min	Pressure	Yes, Threshold and Ratings
Staud et al. 2005	11 female	Handgrip	30% MVC x 90 sec	Thermal Pressure	Yes, Ratings Yes, Threshold
Kosek & Lundberg 2003	12 female 12 male	Quadriceps Infraspinatus	MVC to fatigue	Pressure	Yes, Threshold Yes, Threshold
Koltyn et al. 2001	16 female 15 male	Handgrip	MVC	Pressure	Yes, Threshold female only, Ratings both genders
			40%-50% MVC x 2 min		Yes, Threshold and Ratings female only
Kosek et al. 1996	14 female	Knee Extension	25% MVC to fatigue (max 5 min)	Pressure	Yes, Threshold
Kosek & Ekholm 1995	14 female	Knee Extension	25% MVC to fatigue (max 5 min)	Pressure	Yes, Threshold
Paalasmaa et al. 1991	11 male	Plantarflexion	30% MVC x 2 min 70% MVC x 2 min	Thermal	No, Threshold No, Threshold

Table 2. Studies examining the β-endorphin response to exercise

Author and Year	Subjects	Exercise Mode	Intensity and Duration	Increased β-Endorphin?
Aerobic				
Carrasco et al. 2007	23 male	Swim Competition	Max Intensity	Yes
Maresh et al. 2006	8 male	Cycling Arm ergometry	60% VO_{2peak} x 30 min 80% VO_{2peak} x 30 min	No Yes
Sanchez-Garcia et al. 2004	15 both genders	18,500 m race	Race pace	Yes
Di Luigi et al. 2003	18 male twins	Treadmill	IAT x 30 min	No – Decreased
Piacentini et al. 2002	7 male	Cycling	Graded max test	Yes
Angelopoulos 2001	9 male	Treadmill	80% max x 30 min	Yes
de Diego Acosta et al. 2001	19 male	Treadmill	Graded exercise test	Yes trained only
Di Luigi et al. 2001	12 male	Treadmill	75% x 30 min	No - Decreased
Goldfarb et al. 1998	12 both genders	Cycling	60% VO_{2max} x 25 min 80% VO_{2max} x 25 min	No Yes
Viru & Tendzegolskis 1995	23 male	Cycling	45% VO_{2max} x 2 hrs 60% VO_{2max} x 2 hrs	No No
Engfred et al. 1994	9 female 12 male	Cycling	Graded max test	Yes, attenuated by training
Taylor et al. 1994	7 male	Treadmill	85% VO_{2max} x 20 min	Yes
Heitkamp et al. 1993	16 male	Treadmill Marathon run	Graded exercise test Non-race	Yes Yes
Shen et al. 1992	8 male	Cycling	50% of W_{max} x 25 min	Yes
Goldfarb et al. 1991	12 male	Cycling	60% VO_{2max} x 30 min 70% VO_{2max} x 30 min 80% VO_{2max} x 30 min	No Yes Yes
Heitkamp et al. 1990	7 female 20 male	Running Outdoors	6 km	Yes
Goldfarb et al. 1990	12 male	Cycling	60% VO_{2max} x 30 min 70% VO_{2max} x 30 min 80% VO_{2max} x 30 min	No Yes Yes
Oleshansky et al. 1990	17 male	Treadmill	Max test to exhaustion	Yes
Kraemer et al. 1989	10 female 13 male	Treadmill	80% HR_{max} x 30 min	No
Schwarz & Kindermann 1989	10 male	Cycling	63% VO_{2max} (anaerobic threshold) to exhaustion	Yes
Rahkila et al. 1988	10 male	Treadmill	50% VO_{2max} x 10 min 60% VO_{2max} x 10 min 70% VO_{2max} x 10 min 80% VO_{2max} x 10 min 90% VO_{2max} x 10 min 100% VO_{2max} x 10 min	No No No No Yes Yes
Petraglia et al. 1988	27 male	Track Meet	Variable	Yes run No discus
McMurray et al. 1987	10 female 10 male	Cycling	40% VO_{2max} x 20 min 60% VO_{2max} x 20 min 80% VO_{2max} x 20 min	No No Yes

Table 2 Continued

Author and Year	Subjects	Exercise Mode	Intensity and Duration	Increased β-Endorphin?
Viswanathan et al. 1987	12 female 6 male	Cycling	30% VO_{2max} x 20 min 60% VO_{2max} x 20 min 90% VO_{2max} to exhaustion	No Yes female only Yes
Rahkila et al. 1987	5 female 5 male	Treadmill	Graded max test	Yes No
Donevan & Andrew 1987	19 male	Cycling	25% VO_{2max} x 8 min 50% VO_{2max} x 8 min 75% VO_{2max} x 8 min	No No Yes
Farrell et al. 1987	14 male	Treadmill	60% VO_{2max} x 7 min 100% VO_{2max} x 3 min 110% VO_{2max} x 2 min	No Yes Yes
Goldfarb et al. 1987	9 male	Cycling	Graded max test	Yes
Mougin et al. 1987	17 male	Nordic Ski Race	Max	Yes
Oltras et al. 1987	9 male	22000 M marathon	Max	Yes
Hatfield et al. 1987	16 male	Cycling	Graded to exhaustion	Yes, recovery only
Howlett et al. 1984	13 female	Running	8 week training	Yes
Bullen et al. 1984	7 female	Cycling	50%, 70%, 80%, and 85% HR_{max} x 10 min each stage	Yes, augmented by training
Elliot et al. 1984	5 male	Treadmill	Max test	Yes
Farrell et al. 1982	1 female 5 male	Treadmill	60% VO_{2max} x 30 min 80% VO_{2max} x 30 min Self-Selected pace x 30 min	Yes No No
Colt et al. 1981	6 female 20 male	6.4-12.8 km run	Self-selected pace Near max effort	Yes, hard run > easy run
Bortz et al. 1981	34 both genders	161 km marthon	Max effort	Yes
Carr et al. 1981	7 female	Cycling	50%, 70%, 80%, and 85% HR_{max} x 10 min each stage	Yes, augmented by training
Fraioli et al. 1980	8 male	Treadmill	15 km/hr to exhaustion	Yes
Resistance				
Doiron et al. 1999	13 female	Weight Machines	12 exercises 65% 1-RM to fatigue	Yes
Pierce et al. 1994	10 female 10 male	Nautilus	4 upper body exercises 3 sets, 8 reps, 80% 1-RM	No - Decreased
Kraemer et al. 1993	8 male	Weight Training	10-RM, 1 min rest 5-RM, 1 min rest 10-RM, 3 min rest 5-RM, 3 min rest	Yes No No No
Pierce et al. 1993	6 male	Weight Training	3 sets, 8 reps, 40%-60% 1-RM, 3 min rest	No
McGowan et al. 1993	10 female 10 male	Weight Training	3 sets, 4 reps, 80% 1-RM	No – Decreased No
Elliot et al. 1984	5 male	Weight Training	3 sets, 8 reps, 80% 1-RM	Yes
Isometric				
Melchionda et al. 1984	9 female 11 male	Knee Extension	3 sets, 16 reps, MVC x 10 sec, 5 sec rest reps, 3 min rest sets	No

Table 3. Studies examining the EIH and β-endorphin relationship

Author and Year	Subjects	Exercise Mode Intensity and Duration	β-endorphin Response	Pain Stimulus	EIH Response?	β-endorphin-Pain Correlation?	Naloxone Reversed?
Øktedalen et al. 2001	29 male	Treadmill Graded VO_{2max} test	Increased	Ischemic	Yes	No	N/A
Droste et al. 1991	10 male	Supine Cycling Progressive to exhaustion	Increased Peaked 10 min post exercise	Electrical Stimulation	Yes Peaked end exercise	No	No
Janal et al. 1984	12 male	6.3 mile road run ~85% VO_{2max} x ~44 min	Increased	Ischemic Thermal Cold Pressor	Yes Yes No	No	Yes No No

References

Angelopoulos, T. J. (2001). Beta-endorphin immunoreactivity during high-intensity exercise with and without opiate blockade. *European Journal of Applied Physiology, 86*, 92-96.

Anshel, M. H., & Russell, K. G. (1994). Effect of aerobic and strength training on pain tolerance, pain appraisal and mood of unfit males as a function of pain location. *Journal of Sports Sciences, 12*, 535-547.

Bartholomew, J. B., Lewis, B. P., Linder, D. E., & Cook, D. B. (1996). Post-exercise analgesia: replication and extension. *Journal of Sports Sciences, 14*(4), 329-334.

Black, J., Chesher, G. B., Starmer, G. A., & Egger, G. (1979). The painlessness of the long distance runner. *The Medical Journal of Australia, 1*(11), 522-523.

Bortz, W. M., Angwin, P., Mefford, I. N., Boarder, M. R., Noyce, N., & Barchas, J. D. (1981). Catecholamines, dopamine, and endorphin levels during extreme exercise. *The New England Journal of Medicine, 305*(8), 466-467.

Bullen, B. A., Skrinar, G. S., Beitings, I. Z., Carr, D. B., Reppert, S. M., Dotson, C. O., et al. (1984). Endurance training effects on plasma hormonal responsiveness and sex hormone excretion. *Journal of Applied Physiology, 56*, 1453-1463.

Carrasco, L., Villaverde, C., & Oltras, C. M. (2007). Endorphin responses to stress induced by competitive swimming event. *Journal of Sports Medicine and Physical Fitness, 47*(2), 239-245.

Carr, D. B., Bullen, B. A., Skrinar, G. S., Arnold, M. A., Rosenblatt, M., Beitins, I. Z., et al. (1981). Physical conditioning facilitates the exercise-induced secretion of beta-endorphin and beta-lipotropin in women. *New England Journal of Medicine, 305*, 560-563.

Colt, E.W.D., Wardlaw, S. L., & Frantz, A. G. (1981). The effect of running on plasma β-endorphin. *Life Sciences, 28*, 1637-1640.

Cook, D. B., & Koltyn, K. F. (2000). Pain and exercise. *International Journal of Sport Psychology, 31*(2), 256-277.

Dalayeun, J. F., Nores, J. M, & Bergal S. (1993). Physiology of β-endorphins. A close-up view and a review of

the literature. *Biomedicine and Pharmacotherapy, 47*(8), 311-320.

de Diego Acosta, A. M., Garcia, J.-C., Fernandez-Pastor, V. J., Peran, S., Ruiz, M., & Guirado, F. (2001).

Influence of fitness on the integrated neuroendocrine resonse to aerobic exercise until exhaustion.

Journal of Physiology and Biochemistry, 57(4), 313-320.

de Meirleir, K., Naaktgeboren, N., Steirteghem, V., Gorus, F., Olbrecht, J., & Block, P. (1986). Beta-endorphin

and ACTH levels in peripheral blood during and after aerobic and anaerobic exercise. *European Journal

of Applied Physiology, 55*, 5-8.

Di Luigi, L., Guidetti, L., Baldari, C., & Romaelli, F. (2003). Heredity and pituitary response to exercise-related

stress in trained men. *International Journal of Sports Medicine, 24*, 551-558.

Di Luigi, L., Guidetti, L., Romanelli, F., Baldari, C., & Conte, D. (2001). Acetylsalicylic acid inhibits the

pituitary response to exercise-related stress in humans.

Doiron, B. A. H., Lehnhard, R. A., Butterfield, S. A., & Whitesides, J. E. (1999). Beta-endorphin response to

high intensity exercise and music in college-age women. *Journal of Strength and Conditioning

Research, 13*(1), 24-28.

Donevan, R. H., & Andrew, G. M. (1987). Plasma beta-endorphin immunoreactivity during graded cycle

ergometry. *Medicine and Science in Sports and Exercise, 19*, 229-233.

Droste, C., Greenlee, M. W., Schreck, M., & Herbert, R. D. (1991). Experimental pain thresholds and plasma

beta-endorphin levels during exercise. *Medicine and Science in Sports and Exercise, 23*(3), 334-342.

Elliot, D. L., Goldberg, L., Watts, W. J., & Orwoll, E. (1984). Resistance exercise and plasma beta-

endorphin/beta-lipotrophin immunoreactivity. *Life Sciences, 34*, 515-518.

Engfred, K., Kjaer, M., Secher, N. H., Friedman, D. B., Hanel, B., Nielsen, O. J., et al. (1994). Hypoxia and

training-induced adaptation of hormonal responses to exercise in humans. *European Journal of Applied

Physiology, 68*, 303-309.

Farrell, P. A., Gates W. K., Maksud, M. G., & Morgan, W. P. (1982). Increases in plasma β-endorphin/β-lipotropin immunoreactivity after treadmill running in humans. *Journal of Applied Physiology, 52*(5), 1245-1249.

Farrell, P. A., Kjaer, M., Bach, F.W., & Galbo, H. (1987). Beta-endorphin and adrenocorticotropin response to supramaximal treadmill exercise in trained and untrained males. *Acta Physiologica Scandinavica, 130*, 619-625.

Fichna, J., Janecka, A., Costentin, J., & Do Rego, J.-C. (2007). The endomorphin system and its evolving neurophysiological role. *Pharmacological Reviews, 59*, 88-123.

Fraioli, F., Moretti, C., Paolucci, D., Alicicco, E., Crescenzi, F. & Fortunio, G. (1980). Physical exercise stimulates marked concomitant release of β-endorphin and adrenocorticotropic hormone (ACTH) in peripheral blood in man. *Experientia, 36*(8), 987-989.

Goldfarb, A. H., Hatfield, B. D., Armstrong, D., & Potts, J. (1990). Plasma beta-endorphin concentration: response to intensity and duration of exercise. *Medicine and Science in Sports and Exercise, 22*(2), 241-244.

Goldfarb, A. H., Hatfield, B. D., Potts, J., & Armstrong, D. (1991). Beta-endorphin time course response to intensity of exercise: effect of training status. *International Journal of Sports Medicine, 12*, 264-268.

Goldfarb, A. H., Hatfield, B. D., Sforzo, G. A., & Flynn, M. G. (1987). Serum β-endorphin levels during a graded exercise test to exhaustion. *Medicine and Science in Sports and Exercise, 19*(2), 78-82.

Goldfarb, A.H., Jamurtas, A. Z., Kamimori, G. H., Hegde, S., Otterstetter, R., & Brown, D. A. (1998). Gender effect on beta-endorphin response to exercise. *Medicine and Science in Sports and Exercise, 30*(12), 1672-1676.

Gordon, N., Duncan, J. J., & Kohl, H. W. (1989). Effect of opioid anatgonsim on the ability to tolerate maximal anaerobic exercise. *South African Medical Journal, 76*(6), 268-269.

Guieu, R., Blin, O., Pouget, J., & Serratrice, G. (1992). Nociceptive threshold and physical activity. *Canadian Journal of Neurological Science, 19*, 69-71.

Gurevich, M., Kohn, P. M., & Davis, C. (1994). Exercise-induced analgesia and the role of reactivity in pain sensitivity. *Journal of Sports Science, 12*, 549-559.

Hatfield, B. D., Goldfarb, A. H, Sforzo, G. A., & Flynn, M. G. (1987). Serum beta-endorphin and affective responses to graded exercise in young and elderly men. *Journal of Gerontology, 42*(4), 429-431.

Heitkamp, H.C., Schmid, K., & Scheib, K. (1993). β-endorphin and adrenocorticotropic hormone production during marathon and incremental exercise. *European Journal of Applied Physiology, 66*, 269-274.

Heitkamp, H. C., Schrode, M., Bornemann, A., Wurster, K. G., & Jeschke, D. (1990). Beta-endorphin during mearathon running. . *In: Sports, Medicine and Health, GPH Hermans (Ed.).* 532-537.

Hoeger Bement, M. K., Dicapo, J., Rasiarmos, R., & Hunter, S. K. (2008). Dose response of isometric contractions on pain perception in healthy adults. *Medicine & Science in Sports & Exercise, 40*(11):1880-1889.

Hoffman, M. D., Shepanski, M., Ruble, S. B., Valic, Z., Buckwalter, J. B., & Clifford, P. S. (2004). Intensity and duration threshold for aerobic exercise-induced analgesia to pressure pain. *Archives of Physical Medicine and Rehabilitation, 85*(7), 1183-1187.

Howlett, T. A., Tomlin, S., Ngahfoong, L., Rees, L. H., Bullen, B. A., Skrinar, G. S., et al. (1984). Release of β-endorphin and met-enkephalin during exercise in normal women: response to training. *British Medical Journal, 288*(6435), 1950-1952.

Janal, M. N., Colt, E. W., Clark, W. C., & Glusman, M. (1984). Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. *Pain, 19*(1), 13-25.

Kemppainen, P., Paalasmaa, P., Pertovaara, A., Alila, A., & Johansson, G. (1990). Dexamethasone attenuates exercise-induced dental analgesia in man. *Brain Research, 519*, 329-332.

Kemppainen, P., Pertovaara, A., Huopaniemi, T., Johansson, G., & Karonen, S. L. (1985). Modification of dental pain and cutaneous thermal sensitivity by physical exercise in man. *Brain Research, 360*, 33-40.

Koltyn, K. F., & Arbogast, R. W. (1998). Perception of pain after resistance exercise. *British Journal of Sports Medicine, 32*, 20-24.

Koltyn, K. F., & Umeda, M. (2007). Contralateral attenuation of pain after short-duration submaximal isometric exercise. *Journal of Pain, 8*(11), 887-892.

Koltyn, K. F., Garvin, A. W., Gardiner, R. L., & Nelson, T. F. (1996). Perception of pain following aerobic exercise. *Medicine and Science in Sports and Exercise, 28*(11), 1418-1421.

Koltyn, K. F., Trine, M. L., Stegner, A. J., & Tobar, D. A. (2001). Effect of isometric exercise on pain perception and blood pressure in men and women. *Medicine and Science in Sports and Exercise, 33*, 282-290.

Kosek, E., & Ekholm, J. (1995). Modulation of pressure pain thresholds during the following isometric contractions. *Pain, 61*, 481-486.

Kosek, E., & Lundberg, L. (2003). Segmental and plurisegmental modulation of pressure pain thresholds during static muscle contractions in healthy individuals. *European Journal of Pain, 7*(3), 251-258.

Kosek, E., Ekholm, J., & Hansson, P. (1996). Modulation of pressure pain thresholds during and following isometric contraction in patients with fribromyalgia and in healthy controls. *Pain, 64*(3), 415-423.

Kraemer, W. J., Blair, S., Kraemer, G. R., & Castracane, V. D. (1989). Effects of treadmill running on plasma beta-endorphin, corticotropin and cortisol levels in male and female 10K runners. *European Journal of Applied Physiology, 58*, 845-851.

Kraemer, W. J., Dziados, J. E, Marchitelli, L. J., Gordon, S. E., Harman, E. A., Mello, R., et al. (1993). Effects of different heavy-resistance exercise protocols on plasma beta-endorphin concentrations. *Journal of Applied Physiology, 74*(1), 450-459.

Maresh, C. M., Sokmen, B., Kraemer, W. J., Hoffman, J. R., Watson, G., Judelson, D. A., et al. (2006). Pituitary-adrenal responses to arm versus leg exercise in untrained man. *European Journal of Applied Physiology, 97*, 471-477.

Matejec, R., Uhlich, H., Hotz, C., Mühling, J., Harbach, H.-W., Bödeker, R.-H., et al. (2005). Corticotropin-releasing hormone reduces pressure pain sensitivity in humans without involvement of β-endorphin (1-31), but does not reduce heat pain sensitivity. *Neuroendocrinology, 82*, 185-197.

McGowan, R. W., Pierce, E. F., & Eastman, N. (1993). Beta-endorphins and mood states during resistance exercise. *Perceptual Motor Skills, 76*, 376-378.

McMurray, R. G., Forsythe, W. A., Mar, M. H., & Hardy, C. J. (1987). Exercise intensity-related responses of beta-endorphin and catecholamines. *Medicine and Science in Sports and Exercise, 19*, 570-574.

Melchionda, A., Clarkson, P. M., Deriko, C., Fredson, P., Graves, J., & Katch, F. (1984). The effect of local isometric exercise on serum levels of beta-endorphin/beta-lipotropin. *The Physician and Sports Medicine, 12*, 103-109.

Mougin, C., Baulay, A., Henriet, M. T., Haton, O., Jacquier, M. C., Turnhill, D., et al. (1987). Assessment of plasma opioid peptides, β-endorphin and met-enkephalin, at the end of an international ski race. *European Journal of Applied Physiology, 56*, 405-410.

O'Connor, P. J., & Cook, D. B. (1999). Exercise and pain: the neurobiology, measurement, and laboratory study of pain in relation to exercise in humans. *Exercise and Sport Sciences Reviews, 27*, 119-166.

Øktedalen, O., Solberg, E. E., Haugen, A. H., & Opstad, P. K. (2001). The influence of physical and mental training on plasma beta-endorphin level and pain perception after intensive physical exercise. *Stress and Health, 17*, 121-127.

Olausson, R., Eriksson, E., Ellmarker, L., Rydenhag, B., Shyu, R. U., & Andersson, S. A. (1986). Effects of naloxone on dental pain threshold following muscle exercise and low frequency transcutaneous nerve stimulation: a comparative study in man. *Acta Physiologica Scandinavica, 126*, 229-305.

Oleshansky, M.A., Zoltick, J. M., Herman, R. H., Mougey, E. H., & Meyerhoff, J. L. (1990). The influence of fitness on neuroendocrine responses to exhaustive treadmill exercise. *European Journal of Applied Physiology, 59*, 405-410.

Oltras, C. M., Mora, F., & Vives,, F. (1987). Beta-endorphin and ACTH in plasma: effects of physical and psychological stress. *Life Sciences, 40*, 1683-1686.

Paalasmaa, P., Kemppainen, P., & Pertovaara, A. (1991). Modulation of skin sensitivity by dynamic and isometric exercise in man. *European Journal of Applied Physiology, 62*, 279-285.

Padawer, W. J., & Levine, F. M. (1992). Exercise-induced analgesia: fact or artifact? *Pain, 48*, 131-135.

Paulev, P. E., Thorboll, J. E., Neilson, U., Kruse, P., Jordal, R., Bach, F. W., et al. (1989). Opioid involvement in the perception of pain due to endurance exercise in trained man. *Japanese Journal of Physiology, 39*, 67-74.

Pertovaara, A., Huopaniemi, T., Virtanen, A., & Johansson, G. (1984). The influence of exercise on dental pain thresholds and the release of stress hormones. *Physiology & Behavior, 33*, 923-926.

Petraglia, F. C., Barletta, C., Facchinetti, F., Spinazzoli, F., Monzani, A., Scavo, D., et al. (1988). Response of circulating adrenocorticotropin, beta-endorphin, beta liptrophin and cortisol to athletic competition. *Acta Endocrinologica, 118*, 332-336.

Piacentini, M.F., Meeusen, R., Buyse, L., De Schutter, G., Kempenaers, F., Van Nijvel, J., et al. (2002). No effect of a noradrenergic reuptake inhibitor on performance in trained cyclists. *Medicine and Science in Sports and Exercise, 34*(7), 1189-1193.

Pierce, E. F., Eastman, N. W., McGowan, R. W., Tripathi, H. T., Dewey, W. L., & Olson, K. G. (1994). Resistance exercise decreases β-endorphin immunoreactivity. *British Journal of Sports Medicine, 28*(3), 164-166.

Pierce, E. F., Eastman, N. W., Tripathi, H. T., Olson, K. G., & Dewey, W. L. (1993). Plasma beta-endorphin immunoreactivity: response to resistance exercise. *Journal of Sports Science, 11*(6), 499.

Rahkila, P., Hakala, E., Alen, M., Salminen, K., & Laatikainen, T. (1988). Beta-endorphin and corticotrophin release is dependent on a threshold intensity of running exercise in male endurance athletes. *Life Science, 43*, 551-558.

Rahkila, P., Hakala, E., Salminen, K., & Laatikainen, T. (1987). Response of plasma endorphins to running exercises in male and female endurance athletes. *Medicine and Science in Sports and Exercise, 19*(5), 451-455.

Sanchez-Garcia, J., Villaverde-Gutierrez, C., Ramirez-Rodrigo, J., Ruiz-Villaverde, G., Arroyo-Morales, M., &
Ruiz-Villaverde, R. (2004). ACTH, β-endorphin, and levels of anxiety in middle-aged athletes.
International Journal of Sport Psychology, 35, 149-156.

Schwarz, L., & Kindermann, W. (1989). Beta-endorphin, catecholamines, and cortisol during exhaustive
endurance exercise. *International Journal of Sports Medicine, 10*(5), 324-328.

Shen, A., Chin, J., Fullerton, M., Jennings, G., & Dart, A. (1992). Increases in plasma β-endorphin
concentrations during exercise do not contribute to increases in heart rate following autonomic blockade
in man. *British Journal of Clinical Pharmacology, 33*, 89-92.

Staud, R., Robinson, M. E., & Price, D. D. (2005). Isometric exercise has opposite effects on central pain
mechanisms in fibromyalgia patients compared to normal controls. *Pain, 118*, 176-184.

Sternberg, W. F., Bokat, C., Kass, L., Alboyadjian, A., & Gracely, R. H. (2001). Sex-dependent components of
the analgesia produced by athletic competition. *Journal of Pain, 2*(1), 65-74.

Taylor, D.V., Boyajian, J. G., James, N., Woods, D., Chicz-Demet, A., Wilson, A. F., et al. (1994). Acidosis
stimulates β-endorphin release during exercise. *Journal of Applied Physiology, 77*(4), 1913-1918.

Viru, A., & Tendzegolskis, Z. (1995). Plasma endorphin species during dynamic exercise in humans. *Clinical
Physiology, 15*(1), 73-79.

Viswanathan, M., Van Dijk, J. P., Graham, T. E., Bonen, A., & George, J. C. (1987). Exercise and cold-induced
changes in plasma β-endorphin and β-lipotropin in men and women. *Journal of Applied Physiology,
62*(2), 622-627.