ENDORPHINS: ENDOGENOUS OPIOID IN HUMAN CELLS

Dr. Archana Sharma*, Deepali Verma

Amity Institute of Pharmacy, Amity University, Uttar Pradesh, Noida, India.

ABSTRACT

Endorphins are endogenous opioids released from the pituitary gland that are believed to mediate analgesia, induce euphoria, and play a role in the reward system in the brain. It has been suggested that endorphins are responsible for creating the relaxed psychological state known as “runner’s high.” The relationship between vigorous exercise and blood plasma endorphin levels have produced conflicting results. Some indicate a significant increase of endorphins during or after exercise while others do not. Inconsistent methods and experimental techniques have made it difficult to determine a relationship between exercise and endorphin elevations. Research has shown that opioidergic activity plays a role in addictions by mediating the development of reinforcing qualities of certain activities and substances. A newly established condition known as exercise dependence defines exercise as an addiction, characterized by a compulsion to exercise excessively even when the consequences are harmful to an individual’s health, family relationships, and personal wealth. Various surveys and questionnaires have been validated for determining the level of an individual’s dependence on and need for exercise. A clear relationship between vigorous exercise and increased endorphin levels, causes of exercise dependence can be more concretely determined. Exercise dependence is not currently recognized by the DSM-IV[Diagnostic statistical manual of mental disorder], but its presence in certain human behaviours (similar to those of alcoholics and drug addicts) indicate that it should be precisely defined.

KEYWORDS: Endorphins, DSM-IV[Diagnostic, endogenous opioids.

INTRODUCTION

The current understanding of endorphins, specifically beta-endorphins, and how they relate to the field of surgery.
Beta-endorphins are neuro peptides involved in:-

a) pain management.

b) possessing morphine like effects, and are involved in natural reward circuits such as feeding, drinking, sex and maternal behaviour.

c) Their application to the field of surgery centres on their role in pain management. Since their discovery in the mid-1970s, the role of endorphins has been a widely studied but enigmatic topic within the science of physiology. Although it has been three decades, scientists are still searching for consistent answers as to why the body produces endorphins and how these peptides operate within the central nervous system.

d) The name endorphin is derived from two words, *endogenous* and *morphine*, because these hormones act similar to morphine (a natural opiate) within the natural opioid system. Researchers have found a correlation between vigorous exercise and elevated endorphin levels in blood plasma. While some evidence does suggest that exercise induces an increase in endorphin release, procedural, definitional, and observational inconsistencies have prevent consistently valid conclusions from being drawn.

e) The euphoric feelings generated by endorphins, which may result from strenuous exercise, are believed to play a role in addiction. While it is generally accepted that endorphins induce euphoria, it is unclear whether exercise causes an increase in endorphin levels. Additionally, if exercise increases endorphin levels, few studies have been performed to measure whether this increase plays a role in exercise dependence.

f) Individuals labelled as exercise-dependent show similar behaviours and hormone levels to those with alcoholism and drug addictions. Because findings of endorphin elevations are so inconsistent, researchers continually alter experimental strategies. Unfortunately, this makes it difficult to determine what, if any, strategies effectively measure endorphins and the physiological response to exercise. Based on the literature reviewed, it appears that endorphin activity maybe highly variable from one individual to the next, making this analysis even more complex many researchers have not found significantly elevated endorphin level exercise.

g) Endorphins also shows its effect on brain and other parts of the body. [6,43]

**Synthesis, Storage and Secretion of Beta-Endorphins** [39,41,49]

Beta-endorphins are primarily synthesized and stored in the anterior pituitary gland from their precursor protein pro opioid melanocortin (POMC). However, recent studies suggest cells of the immune system are also capable of beta-endorphin synthesis because immune cells possess
mRNA transcripts for POMC and T-lymphocytes, B-lymphocytes, monocytes and macrophages have been shown to contain endorphins during inflammation. POMC is a large protein that is cleaved into smaller proteins such as beta-endorphin, alpha-melanocyte stimulating hormone (MSH), adrenocorticotropic (ACTH), and others.\[^{36}\] The pituitary gland synthesizes POMC in response to a signal from the hypothalamus; that signal being corticotrophin-releasing hormone (CRH). The hypothalamus releases CRH in response to physiologic stressors such as pain, as in the postoperative period. When the protein products of POMC cleavage accumulate in excess, they turn hypothalamic CRH production off - that is, feedback inhibition occurs.

![Beta endorphin.](image)

So the basic portion for the synthesis of endorphins and its derivatives is pituitary gland which was secreted by the brain. The given flow chart will help to understand the basic synthesis and what kind of function they will be performing.

A. Firstly nervous system divided into two parts:-
   1.) Central nervous system
   2.) Peripheral nervous system

B. Then peripheral nervous system further divided into three parts:-
   1.) Parasympathetic nervous system
   2.) Sympathetic nervous system
   3.) Enteric nervous system

C. In the peripheral nervous system the discussion takes place regarding the receptors and their pharmacological actions on the body. In this we generally discuss about the different
Types of dosages form which are useful for treatment of a particular diseases. The central nervous system the brain and spinal cord functioning and their pharmacological actions takes place. In the given flow chart we can see that the central nervous system under which the brain and spinal cord in functioning, in the brain the pituitary gland in the sella tunica in the anterior part of the is situated and from there one of the fine hormone called as endorphin is released. Generally the endorphin is the secretion of morphin endogenously in the body and we all know the morphine is used as a good analgesic in the post operative functions. It also helps in improving cardiovascular, gastrointestinal, genitourinary function of the body and any disturbance in these areas may cause disease.\textsuperscript{[13,20]} It also helps in the emotional and behavioural improvement from stress coping. It improves the visceral functioning of the organs and also very useful in maintaining the homeostasis and vital like blood pressure, respiratory rate, cardiac cycle etc.
Mechanism of Action

In the peripheral nervous system (PNS), beta-endorphins produce analgesia by binding to opioid receptors (particularly of the mu subtype) at both pre- and post-synaptic nerve terminals, primarily exerting their effect through pre-synaptic binding. When bound, a cascade of interactions results in inhibition of the release of tachykinins, particularly substance P, a key protein involved in the transmission of pain. In the PNS, mu-opioid receptors are present throughout peripheral nerves and have been identified in the central terminals of primary afferent neurons, peripheral sensory nerve fibres and dorsal root ganglia. In the central nervous system, beta-endorphins similarly bind mu-opioid receptors and exert their primary action at pre-synaptic nerve terminals. However, instead of inhibiting substance P, they exert their analgesic effect by inhibiting the release of GABA, an inhibitory neurotransmitter, resulting in excess production of dopamine. Dopamine is associated with pleasure. In the CNS, mu-opioid receptors are most abundant in descending pain control circuits including the amygdala, mesencephalic reticular formation, periaqueductal gray matter (PAG) and rostral ventral medulla. β-endorphin has the highest affinity for the μ₁ opioid receptor, slightly lower affinity for the μ₂ and δ opioid receptors, and low affinity for the κ₁ opioid receptors. μ-Opioid receptors are the main receptor through which morphine acts. In the other sense, μ opioid receptors are presynaptic, and inhibit neurotransmitter release. Through that mechanism, they inhibit the release of the inhibitory neurotransmitter GABA, and dis inhibit the dopamine pathways, causing more dopamine to be released. By hijacking this process, exogenous opioids cause inappropriate dopamine release, and can lead to aberrant synaptic plasticity, which can cause dependency. Opioid receptors have many other and more important roles in the brain and periphery; however, modulating pain, cardiac, gastric and vascular function as well as possibly panic and satiation. Also, receptors are often found at postsynaptic locations as well as at presynaptic locations.
Role of Beta-Endorphin in Surgery

Opioid medications (e.g. Vicodin, Morphine, Fentanyl) are commonly prescribed in the postoperative period. These medications exert their effect by mimicking natural endorphins, binding to mu-opioid receptors in both the CNS and PNS with variable specificity. This is accomplished by sharing a beta-phenylethylamine group, the moiety that binds the opioid receptor. Acute administration of exogenous opioids inhibits the production of endogenous opiates (e.g. beta-endorphins). Patients undergoing general anaesthesia have shown a significant increase in beta-endorphins during surgery. This increase was effectively inhibited by the co-administration of fentanyl. In similar studies, showed that patients who underwent dental surgery and were given local anesthetic (lidocaine) alone had increased plasma beta-endorphin levels during and after surgery. However, when fentanyl was co-administered, plasma beta-endorphin levels were significantly reduced. Chronic administration of exogenous opioids inhibits the production of both endogenous opiates and mu-opioid...
receptors. Multiple studies have demonstrated the down regulation of POMC gene expression and subsequent decrease in endorphin production in rats given chronic morphine. Surgical patients occasionally require treatment for pain over an extended period of time. However, chronic administration of opioid analgesics carries significant risks of opioid induced hyperalgesia (OIH), tolerance and addiction. Patients who experienced hyperalgesia (increased sensitivity to painful stimuli) and allodynia (pain elicited from a normally non painful stimulus) upon the cessation of morphine use. While down regulation of both endorphins and mu receptors associated with chronic exogenous opioid use likely play a role in OIH, anti opioid peptides are also likely involved. The anti-opioid peptides described thus far include cholecystokinin (CCK), neuropeptide FF (NPFF) and orphanin FQ/nociceptin. These anti-opioid peptides are thought to exert their action by binding mu receptors thereby decreasing their affinity for endorphins and similar opioids. Both the down regulation of endorphins and mu receptors, as well as the production of anti-opioid peptides, are processes that occur over time.\textsuperscript{[16,30,38]} As these processes occur, patients require increasing amounts of opioids to induce the same level of analgesia, a process known as tolerance. Addiction is described as a brain disease resulting in a loss of control over drug taking or in compulsive drug seeking, despite noxious consequences. While the aforementioned mechanisms associated with OIH and tolerance are likely key contributors to opioid addiction, a discussion of addiction would not be complete without briefly discussing the association between the dopaminergic reward system and opiates. As mentioned previously, opioids in the CNS exert their analgesic effect by increasing dopamine release by disinhibiting GABA’s effect on dopaminergic neurons. The dopaminergic neurons most associated with addiction are those of the “reward center” including the ventral tegmental area, nucleus accumbens system, prefrontal cortex and extended amygdala. To maintain normal dopamine levels, patients who develop tolerance require increased amounts of exogenous opioids. Conversely, when the patient who is reliant on exogenous opioids to maintain dopamine homeostasis attempts to cease opioid use, they frequently suffer severe withdrawal symptoms and may employ drug-seeking behaviour. The degree of pain experienced by the surgical patient during and after a procedure correlates with plasma beta-endorphin level.\textsuperscript{[30,38]} A study of pre- and postoperative beta-endorphin levels was conducted for various major surgeries. It was found that both pre- and postoperative plasma beta-endorphin levels correlated positively with postoperative pain severity. In a similar study comparing plasma beta-endorphin levels between open- and laparoscopic cholecystectomies, an invasive and minimally invasive procedure respectively, concluded that endorphins are most likely excreted in response to
postoperative pain. Earlier studies have also found a negative correlation between intra-operative plasma beta-endorphin concentration and postoperative pain severity. Non-opioid medications affect plasma beta-endorphin levels through unknown mechanisms. In a study of osteoarthritis of the knee, both acetaminophen and rofecoxib (a COX-2 inhibitor) were administered to patients with symptomatic osteoarthritis. Additionally, the decreased postoperative pain severity and opioid requirements following preoperative administration of celecoxib plus gabapentin. In the future, more research may reveal the dynamics between beta-endorphins and other non-opioid medications to provide more effective analgesia without the risks associated with opioid medications.

Beta-endorphins are proteins that are primarily synthesized by the pituitary gland in response to physiologic stressors such as pain. They function through various mechanisms in both the central and peripheral nervous system to relieve pain when bound to their mu-opioid receptors. Opioid medications function by mimicking natural endorphins, competing for receptor binding. In the acute setting, exogenous opiates inhibit the production of endogenous opiates while in the chronic setting, exogenous opiates inhibit the production of both endogenous opiates and mu-opioid receptors. Risks associated with chronic opiate use include opioid induced hyperalgesia, tolerance and addiction. In the future, to understand the dynamics between beta-endorphins and non-opioid pain medications to offer patients maximal pain management with minimal associated risk.
Role of Beta Endorphin in Depersonalization Disorder, Acupuncture & Pregnancy

1.) Depersonalization Disorder

Endorphins are known to play a role in depersonalization disorder. The opioid antagonists naloxone and naltrexone have both been proven to be successful in treating depersonalization. To quote a 2001 naloxone study, "In three of 14 patients, depersonalization symptoms disappeared entirely and seven patients showed a marked improvement. The therapeutic effect of naloxone provides evidence for the role of the endogenous opioid system in the pathogenesis of depersonalization." [11,36]

2.) Acupuncture

In clinical researchers reported that inserting acupuncture needles into specific body points triggers the production of endorphins. In another study, higher levels of endorphins were found in cerebrospinal fluid after patients underwent acupuncture. In addition, naloxone appeared to block acupuncture’s pain-relieving effects.31

3.) Pregnancy

A placental tissue of fetal origin i.e., the syncytiotrophoblast excretes beta-endorphins into the maternal blood system from the 3rd month of pregnancy. A recent study proposes an adaptive background for this phenomenon. The authors argue that foetus make their mothers endorphin-dependent then manipulate them to increase nutrient allocation to the placenta. Their hypothesis predicts that:

1. Anatomic position of endorphin production should mirror its presumed role in foetal-maternal conflict.
2. Endorphin levels should co-vary positively with nutrient carrying capacity of maternal blood system.
3. Postpartum psychological symptoms (such as postpartum blues, depression, and psychosis) in humans are side-effects of this mechanism that can be interpreted as endorphin-deprivation symptoms.
4. Shortly after parturition, placentophagy could play an adaptive role in decreasing the negative side-effects of foetal manipulation.
5. Later, breast-feeding-induced endorphin excretion of the maternal pituitary saves the mother from further deprivation symptoms.
Endorphins: Natural Pain and Stress Fighters

Endorphins are among the brain chemicals known as neurotransmitters, which function to transmit electrical signals within the nervous system. At least 20 types of endorphins have been demonstrated in humans. Endorphins can be found in the pituitary gland, in other parts of the brain, or distributed throughout the nervous system. Stress and pain are the two most common factors leading to the release of endorphins. Endorphins interact with the opiate receptors in the brain to reduce our perception of pain and act similarly to drugs such as morphine and codeine. In contrast to the opiate drugs, however, activation of the opiate receptors by the body's endorphins does not lead to addiction or dependence.

In addition to decreased feelings of pain, secretion of endorphins leads to feelings of euphoria, modulation of appetite, release of sex hormones, and enhancement of the immune response. With high endorphin levels, we feel less pain and fewer negative effects of stress. Endorphins have been suggested as modulators of the so-called "runner's high" that athletes achieve with prolonged exercise. While the role of endorphins and other compounds as potential triggers of this euphoric response has been debated extensively by doctors and scientists, it is at least known that the body does produce endorphins in response to prolonged, continuous exercise. Endorphin release varies among individuals. This means that two people who exercise at the same level or suffer the same degree of pain will not necessarily produce similar levels of endorphins. Certain foods, such as chocolate or chili peppers, can also lead to enhanced secretion of endorphins. In the case of chili peppers, the spicier the pepper, the more endorphins are secreted. The release of endorphins upon
ingestion of chocolate likely explains the comforting feelings that many people associate with this food and the craving for chocolate in times of stress. \cite{1,2,3} even if you don't participate in strenuous athletics, you can also try various activities to increase your body's endorphin levels. Studies of acupuncture and massage therapy have shown that both of these techniques can stimulate endorphin secretion. Sex is also a potent trigger for endorphin release. Finally, the practice of meditation can increase the amount of endorphins released in your body.

**Endorphins as Exercise Dependence and Addiction**

The role of endorphins has been a widely studied but enigmatic topic within the science of physiology. Although it has been three decades, scientists are still searching for consistent answers as to why the body produces endorphins and how these peptides operate within the central nervous system. The name endorphin is derived from two words, *endogenous* and *morphine*, because these hormones act similar to morphine (a natural opiate) within the natural opioid. Researchers have found a correlation between vigorous exercise and elevated endorphin levels in blood plasma. While some evidence does suggest that exercise induces an increase in endorphin release, procedural, definitional, and observational inconsistencies have prevented consistently valid conclusions from being drawn. The euphoric feelings generated by endorphins, which may result from strenuous exercise, are believed to play a role in addiction. While it is generally accepted that endorphins induce euphoria, it is unclear whether exercise causes an increase in endorphin levels. Additionally, if exercise increases endorphin levels, few studies have been performed to measure whether this increase plays a role in exercise dependence. \cite{1,3,4} Individuals labelled as exercise-dependent show similar behaviours and Endorphins, Exercise, and Addictions hormone levels to those with alcoholism and drug addictions. Because findings of endorphin elevations are so inconsistent, researchers continually alter experimental strategies.

Endorphins are part of a general class of hormones known as endogenous opioids, a group which also includes enkephalins and dynorphins. The endorphin opioid consists of a specific 31-amino acid sequence, cleaved from a larger peptide known as pro opiomelanocortin (POMC). Endorphins are released from the pituitary gland into the circulatory system. Neurons producing endorphins are located mainly in the ventromedial arcuate nucleus, which projects to the hypothalamus and limbic system (Oswald & Wand, 2004). Opioid peptides activate three different types of receptors, mu (μ), kappa and delta receptors, all of which act through a second messenger. \cite{30,45,26} The affinity with which each opioid binds to the three
different receptors can vary; endorphins primarily operate via the μ-opioid receptor. This is a receptor known to mediate analgesic effects as well as play a role in the reward system within the brain. Evidence showing that endorphins can interfere with the release of other neurotransmitters, including nor epinephrine, dopamine, and acetylcholine, have led to a belief that they work by modulating the presynaptic membranes of synapses other than their own. Opioid antagonists, including Naloxone, Naltrexone, and Nalmefene, have all been shown to block opioid receptors in both animal models and human studies. Naloxone is the most commonly used opioid antagonist in clinical studies as well as addiction treatment. The relationship between exercise and endorphin release studying the role of these peptides in exercise-induced euphoria as well as the reduction of pain. Endorphins are often implicated in the euphoria known as “runner’s high,” the relaxed psychological state sometimes experienced during or after vigorous exercise such as running. Inconsistent evidence for a significant rise in endorphin release, however, makes it very difficult to simply deduce that endorphins released due to exercise are the cause of euphoric feelings. In addition, Dishman (1985) maintains that the so-called “runner’s high” has not been systematically nor thoroughly documented. Similar to the euphoria data, results from studies on pain reduction are also conflicting due to inconsistent experimental methods and results. In one study, subjects who ran 1.6 km at a self-selected pace took significantly longer to report pain on their fingertip from a 1.2-kg weight. The analgesia, however, was reduced when a 2-mg dose of naloxone was administered; a 10-mg dose of the drug eliminated the analgesic effects altogether. This indicates that the endorphins released as a result of running could be responsible for the reduced pain sensitivity. However, this experiment has not been replicated and follow-up studies have not examined this exact response. Non-replicated experiments, such as this one, and minimal data make it difficult to confidently formulate a relationship between running and analgesia. Clinical research studies measuring endorphin levels before, during, and after exercise are conflicting, some show significant increase where others do not. Additional complications occur when researchers differ in their definitions as to what constitutes acute, vigorous exercise. It is possible that a specific VO2max threshold must be met or maintained, a certain distance or length of time must be completed, or a specific form of exercise must be performed in order for the physiological response of endorphin release to occur assessed the threshold by looking at the effects of intensity and distance of running on endorphin-release in male subjects by compiling results from multiple studies with varied time and distances of running. Analyses of these data
indicated a trend of elevated endorphin levels after exercise in all studies, although not all were significant performed a study measuring plasma endorphin levels before and after endurance exercise, defined as 45 minutes of high-intensity aerobics. Results indicated a significant increase in endorphin levels after the exercise as compared to levels before. Such findings support the idea that opioid peptides may be released as a result of exercising vigorously for a specific amount of time. A study agrees with the conclusion, but claims that a critical intensity of exercise must be attained to induce elevations in plasma endorphin levels. However, the data evidence infers that the increases in endorphin release did not appear to be dependent on the intensity of running chose to assess endorphin levels during an exercise test where subjects experienced an increase in bicycle resistance every 3 minutes until fatigue or their individual VO2max was attained. Endorphins were measured before, during, and after exercise. The endorphin response in each individual varied greatly, making it difficult for relationships to be discovered and validated. Some indicated a significant increase early in the test, others late in the test, and some not at all. While overall endorphin level increases did not prove significant during exercise and at varying intensities, investigators found a significant elevation following the exercise period. However, the large amount of variability between subjects may indicate different individual responses to different types of exercise. While much data has been published about the relationship between endorphins and intensity of exercise, other researchers tested different forms of exercise – mostly the difference between running and bicycling sought to determine whether bicycling or running at 60% VO2max at fixed time (1 hr) would significantly elevate endorphin levels and, if so, which form of exercise was more effective. While a trend of increased endorphin levels was observed, statistical analyses did not reveal significance. One might question, however, if this is due to the fact that an intensity of 60% VO2max is possibly insufficient to significantly increase endorphin release; perhaps a greater effort would be necessary. In fact, Pierce et al. (1993) have asserted that a 70% VO is required to significantly elevate endorphin levels in the blood plasma. All these studies demonstrate a variety of measurements on human participants examining endorphin activity. None indicate strong evidence of increased endorphin release as a result of vigorous exercise, although many suggest trends of such a response. This trend is evidence enough to compel researchers to continually question if such a response exists. Unfortunately, experimental inconsistencies make it nearly impossible to draw a distinct relationship between exercise and elevations in endorphin blood plasma levels. Another factor that may cause variability in measurement of endorphin levels is the technique used to measure levels of the hormone in blood plasma.
Generally, radioimmunoassay (RIA) is the accepted method of measurement. Increased endorphin levels and exercise may indicate that blood plasma levels are not the best measure of endorphin levels. Thus, the methods of testing blood plasma may not be sufficient for determining the amount of endorphin released by the pituitary.

Diagram of the brain circuits involved in the motivation system that influences behaviour. This motivation system is responsible for the development of addictions. As described, it is believed that not only the dopaminergic, but also the opioidergic systems are involved in these processes.

**CONCLUSION**
The previous research on exercise, endorphins, and addictions provides a solid foundation based upon which several ideas can be established. Although further research is necessary, if endorphin release is increased as a result of exercise, it could play a possible role in the development of exercise dependence, seeing as endorphins are believed to facilitate
addiction. By expanding upon the research that indicates an increase in endorphin levels after exercise, well documented evidence will make a relationship much more apparent and credible. It appears that in some cases, exercise can elevate endorphin levels.

Methodical research is the next step to pinpointing the circumstances that cause such an increase. As exercise dependence becomes more clearly defined, there are two issues that must be addressed. First, the existence of such a condition must be assessed to determine if it is harmful or healthy. Second, it may prove necessary to devise a treatment plan for those addicted to exercise if the addiction is harmful to their health. Determining the genetic influence on people afflicted with such a condition can lead to prevention and early detection of exercise dependence for individuals believed to have a high risk for the development of exercise dependence. Solid evidence determining a relationship between endorphins and addictive behaviour may illustrate to society that addictions have neurobiological foundations and are not necessarily determined by will-power of an individual. A better understanding of the endogenous opioid system would greatly improve the understanding of endorphins and exercise dependence in humans.

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