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Beta endorphins: The natural opioids

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Abstract
Endorphins (endogenous morphine) are endogenous opioid neuro-peptides and peptide hormones in humans and animals. They are produced by the central nervous system and the pituitary gland. The term "endorphins" consists of two parts: *endo-* and *-orphin*; intended to mean "a morphine-like substance originating from within the body". The principal function of endorphins is to inhibit the communication of pain signals and produce a feeling of euphoria very similar to that produced by other opioids β-endorphins are the best in pain relief and its production is hereditary, due to this, its production level varies from animal to animal. Endorphins are naturally produced in response to pain but their production can also be triggered by various activities This review aims to focus on how higher concentrations of β-endorphins decreases stress and maintain homeostasis resulting in pain management and are involved in natural reward circuits such as feeding, drinking, sex and maternal behavior.

Keywords: Opioids, analgesic, antistressor, immunomodulator and anti-inflammatory agent

Introduction
Our body produces hundreds of chemicals to make sure the body works properly. Of these many hormones are one of the most important one because these hormones must be present in the exact amount in the blood, as hypo-secretion or hyper-secretion of hormones may cause diseases and abnormalities. There are various hormones that some people even don't know. Without hormones the body will not work properly or will not do its functions normally. There are hormones which act on target organs and not other organs. Even the release of these hormones is based on the typical stimuli by typical organ or any parameter. But there is a hormone which is released on several different stimuli or moods or stress which is known as endorphins.

Endorphins (endogenous morphine) are endogenous opioid neuro-peptides and peptide hormones in humans and animals. They are produced by the central nervous system and the pituitary gland. The term "endorphins" implies a pharmacological activity (analogous to the activity of the corticosteroid category of biochemicals) as opposed to a specific chemical formulation. It consists of two parts: *endo-* and *-orphin*; these are short forms of the words *endogenous* and *morphine*, intended to mean "a morphine-like substance originating from within the body". Endorphins, a multi-functional chemical, are emitted to counteract and deal with sensations by transmitting electrical impulses through the body to the nervous system. The principal function of endorphins is to inhibit the communication of pain signals and they may also produce a feeling of euphoria very similar to that produced by other opioids. Endorphins are naturally produced in response to pain but their production can also be triggered by various activities. Vigorous aerobic exercise can stimulate the release of β-endorphins, a potent μ-opioid receptor agonist, in the human and animal brain, which contributes to a phenomenon known as a "runner's high". Laughing may also stimulate endorphins production. β-endorphins are the best in pain relief and its production is hereditary, due to this, its production level varies from animal to animal. High concentrations of endorphins in the brain produce a sense of euphoria, enhance pleasure and suppress pain both emotionally and physically. Low concentrations of endorphins in the animal's brain feel troubled and more aware of pain causes reduced the performance of the animals.

Endorphins inhibit pain perception. It is commonly called body's natural analgesic or endogenous opioid. It is produced at the time of physical or emotional stress such as parturition. It binds to the same receptors that bind exogenous opiates. It affects animal emotions and responsible for body feeling pleasure and produce a sense of euphoria.

Endorphins are morphine like in structure and has same binding site in the brain cells or receptors. Endorphins are released during different exercises, eating food, sex and meditation, etc. Anxiety or nervousness in animals can be treated with this endogenous endorphins without using any medication or tablets, only the thing is that we must know how and when endorphins is released. β-endorphins are related to decreasing bodily stress and maintaining homeostasis resulting in pain management, reward effects and behavioral stability.

History of endorphins, synthesis, storage and secretion of β-endorphins

Pert and Snyder, (1973) [27] discovered the "endogenous opioid system". In the year 1976, Simantov and Snyder isolated endogenous opioid from the brain of a calf and term is given "endorphin" (i.e. Endogenous morphine). Guillemin and Schally, (1977) [16] won Noble price for their research and findings on endorphins. Human and animals body produces at least 20 different endorphins. Special four types are as follows: (made all by 16 to 31 amino acids) Alpha (α) endorphin, Beta (β) endorphin, Gamma (γ) endorphin and Sigma (σ) endorphin β-endorphins are primarily synthesized and stored in the anterior pituitary gland from their precursor protein Proopiomelanocortin (POMC). However, recent studies suggest that cells of the immune system are also capable of β-endorphin synthesis because immune cells possess mRNA transcripts for POMC and T-lymphocytes, B-lymphocytes, monocytes and macrophages which have been shown to contain endorphins during inflammation. POMC is a large protein that is cleaved into smaller proteins such as β-endorphin, alpha-melanocyte stimulating hormone (α-MSH), adrenocorticotropin (ACTH) and others. The pituitary gland synthesizes POMC in response to a signal from the hypothalamus that signal being corticotropin-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.

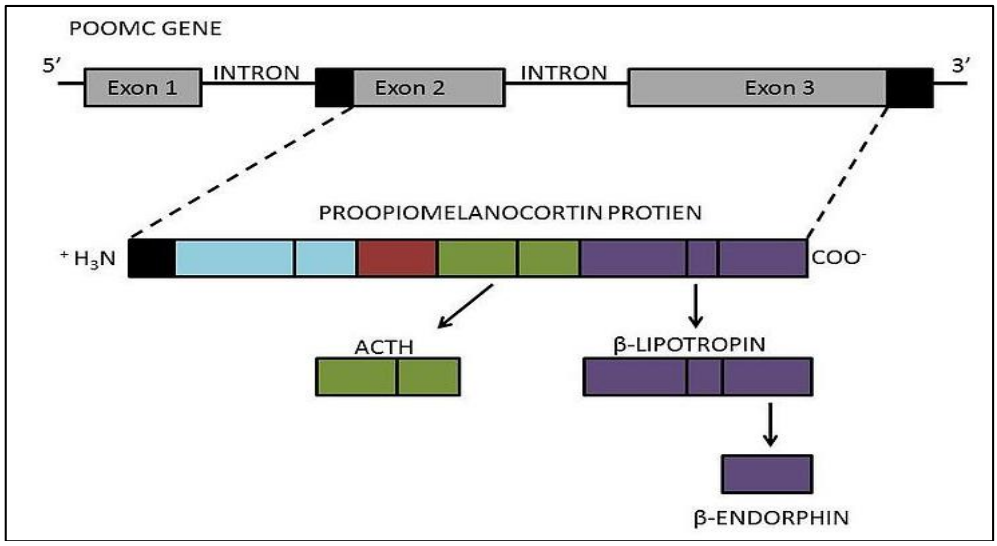

Fig 1: Depicts the formation of β-endorphin from the POMC gene in the pituitary gland. Portions of the second and third exon of this gene make up the POMC protein. The cleavage of the C-terminal end of this protein produces β-lipotropin, which is then cleaved again to form β-endorphin. The POMC protein is also a precursor to other neuropeptides and hormones, such as adrenocorticotropic hormone.

Structure of β -Endorphins

β -Endorphin is peptide hormones (consist of chains of amino acids), consist of 31 amino acid polypeptide

Sequence: Ac - Tyr - Gly - Gly - Phe - Met - Thr - Ser - Glu - Lys - Ser - Gln - Thr - Pro - Leu - Val - Thr - Leu - Phe - Lys - Asn - Ala - Ile - Ile - Lys - Asn - Ala – His - Lys - Lys - Gly - Gln – OH.

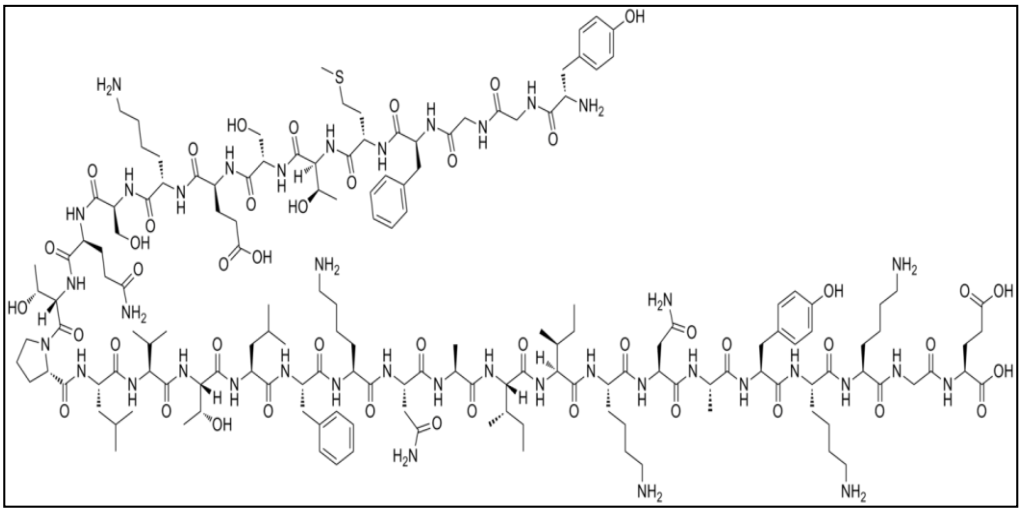

Fig 2: Structure of β -Endorphins

Receptors of β –endorphins and Factors stimulating the release of β -endorphins

All of the endorphins bind to the μ-opioid receptors in the brain. These analgesia- producing receptors are located in brain, spinal cord and other nerve endings. β-endorphin containing nerve fibers spread widely from neurons in the hypothalamus to make inhibitory contacts with target neurons to reduce pain. Receptors of endorphins are increased during stressful conditions located on nervous system and immune cells. Most of all immune cells produce endorphins.

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Mechanism of action of β -endorphins

β-endorphins is released by pituitary (into blood) and hypothalamus (into the spinal cord and brain). β-endorphins containing nerve fibers spread widely from neurons in the hypothalamus, to make inhibitory contacts with target neurons to reduce pain. Free hormones are rapidly eliminated from circulation through kidney or liver. The actions of β-endorphins have been associated primarily with the central nervous system and pain modulation. It may also be involved in reproduction, exercise, stress and regulation of immune function. The physiologic effects of the β-endorphins are mediated through interactions with highly specific membrane receptors. In the peripheral nervous system (PNS), β-endorphins produce analgesia by binding to μ-opioid receptors 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 substance P, a key protein involved in the transmission of pain. In the PNS, μ-opioid receptors are present throughout peripheral nerves and have been identified in the central terminals of primary afferent neurons, peripheral sensory nerve fibers and dorsal root ganglia. In the central nervous system, β-endorphins similarly bind μ-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.

Role of β -endorphins in cancer

β-endorphins are natural neuropeptides secreted by anterior pituitary gland through hypothalamus in response to stress. Stress is also a one of the predisposing factor for cancer by activating inflammatory mediators such as IL-1 and TNF-α, involved in tumor progression. β -endorphins can be used for natural antitumor activity by activating NK cells, macrophage innate immune cells. Binding of β-endorphins to the receptors on the immune cells, activates immune cells. β-endorphins have an anti-carcinogenic activity by activating IFN-gamma, NK cells and macrophages, which involve in antiviral activity, apoptotic activity, decrease cellular proliferation and alters the environment of gene expression in tumor microenvironment (Zhang, 2015) [34]. Supplementation of β-endorphin neurons through transplants prevented carcinogen-induced mammary tumorigenesis and tumor metastasis. When the β-endorphins transplants were given at the early stage of tumor development, many tumors were destroyed, possibly because of increased innate immune activity and the surviving tumors lost their ability to progress to high-grade cancer owing to β-endorphins cells' suppressive effects on epithelial–mesenchymal transition regulators. Another remarkable effect of the β-endorphin transplantation was that it promoted the activation of the innate immune (NK cells and macrophages) activity, following tumor cell invasion, to such an extent that tumor cell migration to another site was completely halted. NK cells and macrophages are critical components of the innate immune system and play a vital role in host defense against tumor cells. Hence, the increased level of innate immunity may have caused unfavorable conditions for cancer cell survival. In the β-endorphin cell–treated animals, the lower inflammatory milieu that was achieved by the higher level of anti-inflammatory cytokines and the lower level of inflammatory cytokines may have also been involved in inhibiting cancer growth and transformation. β-endorphins suppress the sympathetic neuronal function and stimulate the parasympathetic neuronal activity results activation of peripheral immunity and anti-inflammatory cytokines to control tumor growth and progression.

β-endorphins neuronal cells in the hypothalamus control the neoplastic growth and progression of tumor cells, likely by modulating one or more of the factors indicated. Effects include the activation of parasympathetic nervous system control of lymphoid organs, causing activation of innate immune cells (macrophages and NK cells) and an increase in anti-inflammatory cytokine levels in the circulation. The HPA axis and subsequent stress hormones released from the adrenal gland and sympathetic nerve terminals (glucocorticoids and catecholamines) may also be suppressed. In a tumor microenvironment, these hormonal and cytokine changes down regulate inflammation-mediated epithelial–mesenchymal transition (EMT) and thereby, suppress cancer progression. Collectively, these effects create an unfavorable environment for tumor initiation, growth and progression. neoplastic growth and progression of tumor cells, likely by modulating one or more of the factors indicated. Effects include the activation of parasympathetic nervous system control of lymphoid organs, causing activation of innate immune cells (macrophages and NK cells) and an increase in anti-inflammatory cytokine levels in the circulation. The HPA axis and subsequent stress hormones released from the adrenal gland and sympathetic nerve terminals (glucocorticoids and catecholamines) may also be suppressed. In a tumor microenvironment, these hormonal and cytokine changes down regulate inflammation-mediated epithelial–mesenchymal transition (EMT) and, thereby, suppress cancer progression. Collectively, these effects create an unfavorable environment for tumor initiation, growth, and progression.

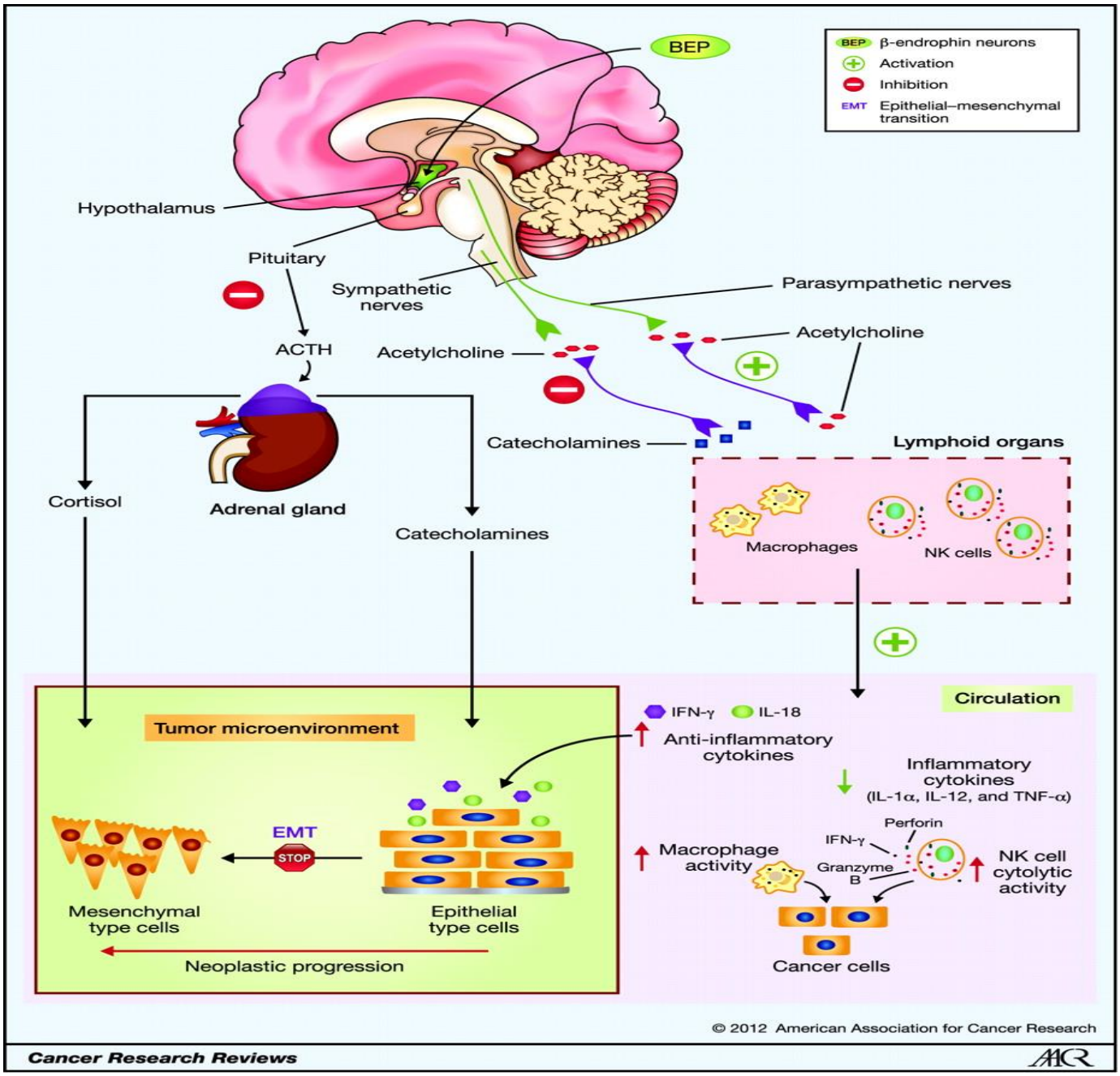


Fig 3: β-Endorphin neuronal cells in the hypothalamus control the

Role of β -endorphins in inflammation

In inflammatory condition recruitment of immune cells to the site of inflammation by chemokines produce endorphins, acts as Anti-inflammatory activity of β-endorphins by activating anti-inflammatory cytokines such as IL-18, IL-10, IFN-Gamma and decreasing pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α mediated release of COX-2 inflammatory mediator activates key transcription factors NF-KB and STAT-3 involved in tumor progression by cellular proliferation, cell survival, angiogenesis, genomic instability, immune suppression, invasion and metastasis. β-endorphins suppress NF-KB transcription factor activity, there by inhibiting the mutation and suppression of P53 tumor suppressor gene. It also involved in epithelial expression of E-Cadherin induced cell adhesion, loss of E-Cadherin involved in epithelial to mesenchymal transition induced tumor invasion. The stress of inflammation triggers the release of corticotrophin-releasing hormone (CRH). The endorphin-producing cells have receptors for CRH, which then facilitate the release of endorphins. Immune cells also have receptors for endorphin indicating an autocrine/paracrine effect of endorphin on the immune cells modulating signal transmission of inflammation, the production of cytokines and its progress. The increased level of endorphins, in the systemic circulation during inflammation may originate from the pituitary as well as from peripheral immune cells. Resting plasma β-endorphins levels as a clinically useful predictor of opioid analgesic responses. The evaluation of β-endorphins levels in body fluids might be useful as a marker for disease diagnosis and treatment (Mousa *et al*., 2004) [23].

Role of β -endorphins in immunity

β-endorphins receptors are present on most of all immune cells such as neutrophils, T-lymphocytes, B-lymphocytes, macrophages, NK cells, dendritic cells binds with β-endorphins results in activation of innate and adaptive immune cells such as NK cells, macrophages, T cell proliferation, B cells results in release of IFN-Gamma, Perforin, Granzyme-B and antibodies.

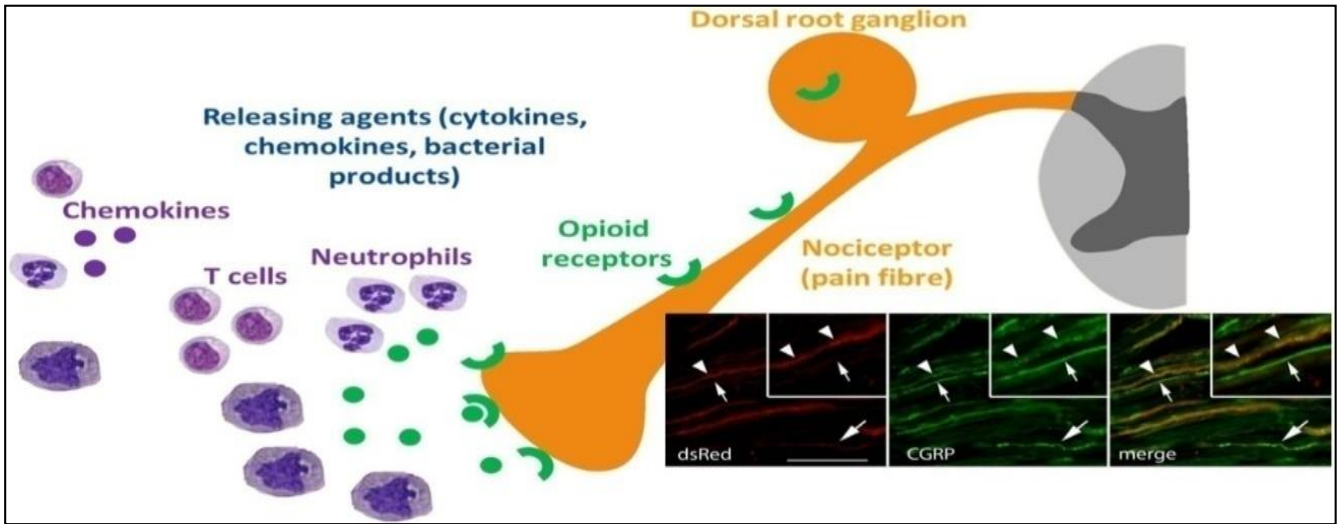


Fig 4: Schematic depiction of β-endorphins release from immune cells of the innate and adaptive immune system. Neutrophils, monocytes/macrophages and T-cells migrate into inflamed tissue in response to chemokines. Release of β-endorphins (green circles) is triggered by cytokines, chemokines and bacterial products. β-endorphins bind to opioid receptors (green) expressed in peripheral sensory neurons (yellow). This cascade causes peripheral antinociception.

Receptors for endorphin have been identified on leukocytes. A number of *in vitro* studies have demonstrated the ability of opioids to influence immune function, such as lymphocyte proliferative responses, natural killer cell activity and granulocyte activity. Recent research has also demonstrated the production of β-endorphin and ACTH by cells of the immune system, along with the expression of the endorphin genes. Although it appears that endogenous opioids are released in response to various forms of stress and in turn interact with cells of the immune system thereby modulating immune function (Mambretti *et al.*, 2016) [22].

Role of β-endorphins in pain modulation

β-endorphins had a potent analgesic effect and 18 to 33 times more potent compared to morphine on a molar basis (Loh *et al*., 1976) [21]. β-endorphins is packaged in membrane-bound secretory vesicles ready to be released when required**.** In the peripheral nervous system β-endorphins binds to μ-opioid receptors results in decreased release of substance P, a neurotransmitter of pain and inflammation results in analgesic activity and reduce inflammation.

In the central nervous system, β-endorphins binds to μ-opioid receptors results in decrease GABA neuro-inhibitory transmitter and release of dopamine neurostimulatory neurotransmitter results in analgesic, euphoric, self-reward, cognitive development of brain.

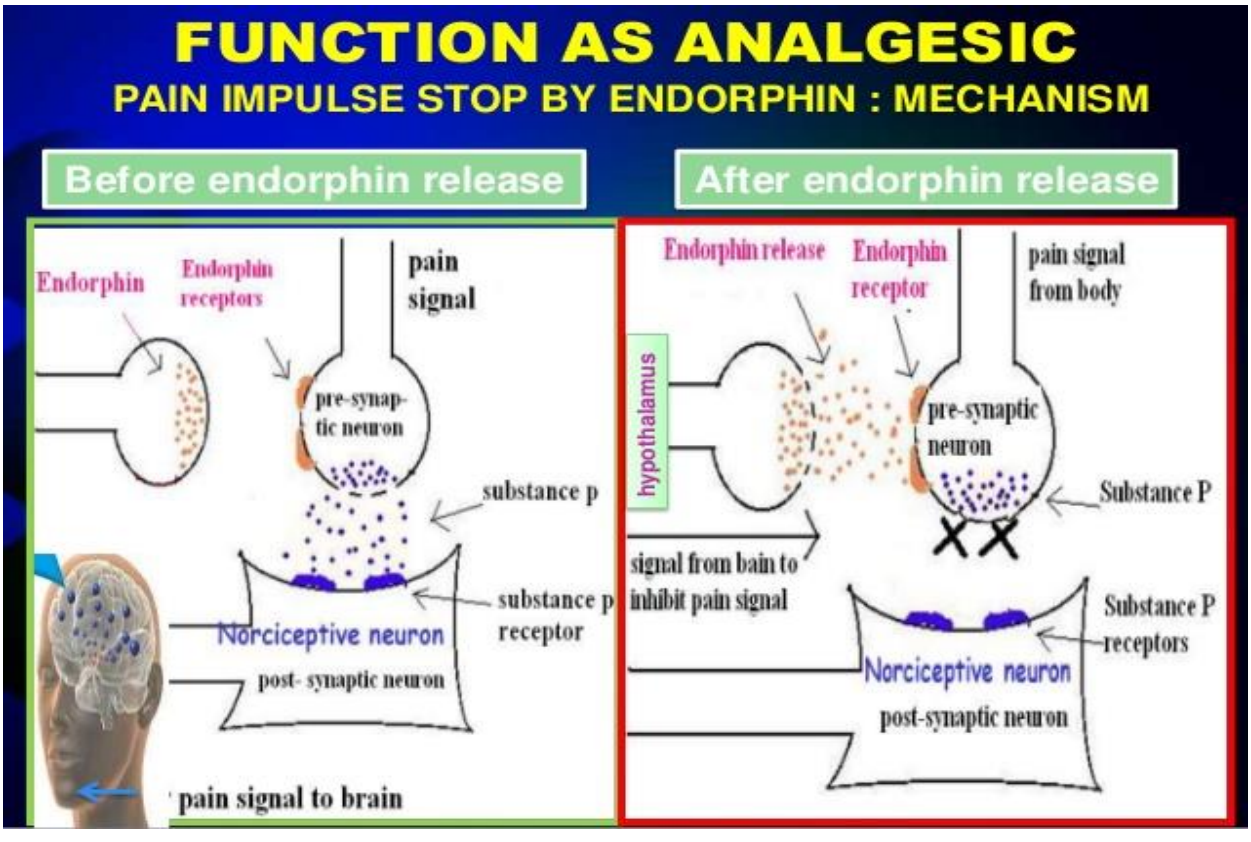


Fig 5: β-endorphins and pain modulation

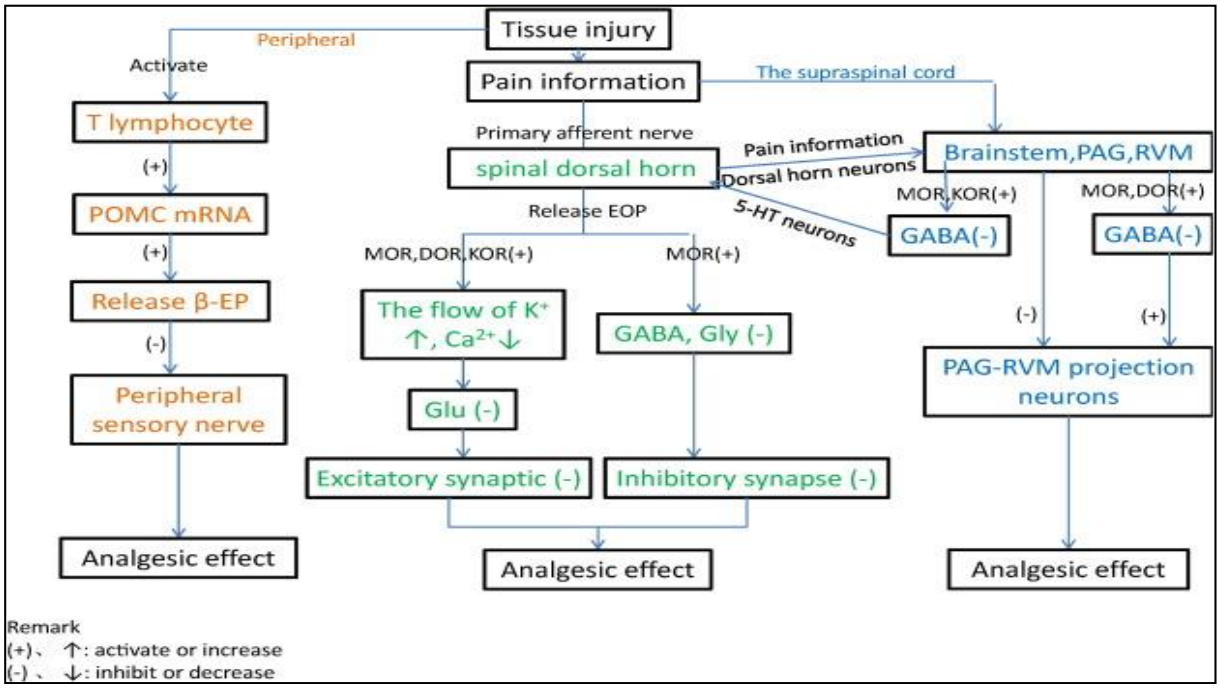


Fig 6: Analgesic effect of β-endorphins.

Role of β-endorphins in stress

Endorphins may play a role in the defensive response of the organism to stress. It may function as trophic hormones in peripheral target organs such as the adrenal medulla and the pancreas and mediate adrenaline and glucagon release in response to stress. It plays a role in the control of the pituitary gland during stress. It plays a role in the behavioral concomitants of stress. It has the ability to inhibit stress hormone production and produce analgesia and a feeling of well-being. It has a stress reducing activity by suppressing hypothalamic pituitary adrenal (HPA)-axis activated in response to stress, release corticotropic releasing hormone and norepinephrine and neuropeptides through sympathetic nervous system activity.β-endorphins neuronal cell bodies are primarily localized in the arcuate nuclei of the hypothalamus and its terminals are distributed throughout the CNS, including the paraventricular nucleus of the hypothalamus. In the paraventricular nucleus, these neurons innervate CRH neurons and inhibit CRH release. During stress, secretion of CRH and catecholamine stimulates secretion of hypothalamic β-endorphins and other pro-opiomelanocortin-derived peptides, which in turn inhibit the activity of the HPA axis. β-endorphins are known to bind to μ-opioid receptors to modulate the neurotransmission in neurons of the ANS via neuronal circuitry within the paraventricular nucleus (Guillemin *et al*., 1977) [15].

In the CNS, the β-endorphins have rewarding and reinforcing properties and to be involved in stress response. Stress has been associated with depression of the immune system. β-endorphins are one of the potential mediators of stress-induced immune-modulation. The role of stress in immune function appears to require an interaction between the brain and the immune system. Current research suggests that bidirectional communication exists between the immune and the central nervous systems.

β-endorphins influence adrenaline synthesis and storage and to stimulate adrenaline release from the adrenal medulla directly (Kvemansky, 1970) [20]. β-endorphins have been reported to stimulate *in vitro* corticosterone synthesis. Since some opiate receptor binding sites occur in the adrenal cortex. It is conceivable that endorphin, like ACTH, could exert some corticotropic effects in animals, when released into the circulation in response to stress (Shanker *et al*., 1979). β-endorphin, has been elevated due to exposure to stress. Sheep respond with elevated plasma β-endorphin following stressful procedures such as tail docking, castration, skin pinching and isolation. Dairy cows respond with elevated circulating levels of β-endorphin when placed in an unfamiliar room for milking. Surgical castration had a much greater effect on plasma β-endorphin and cortisol concentrations than the psychological stressors of weaning, isolation and shearing restraint (Bruckmaier *et al.*, 1994) [14].

Role of β-Endorphins in Puberty

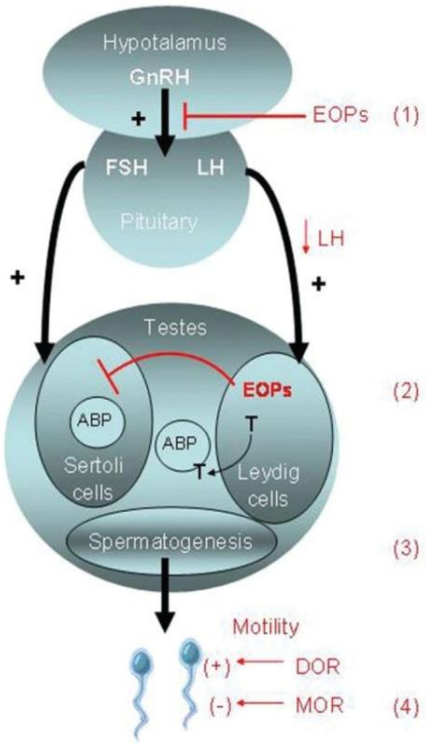
The onset of puberty initiates changes in somatic growth and gonadal maturation. It depends on the activation of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator, resulting in pulsatile GnRH secretion and subsequently pituitary gonadotropin secretion. Hypothalamus generates the pulsatile release of GnRH, resulting in the onset of puberty. β -endorphins influence to the onset of puberty. Studies suggest that maturation of the hypothalamic-pituitary-ovarian axis may be due to a decrease in hypothalamic pituitary sensitivity to the inhibitory effects of β -endorphins. Thus, β -endorphins, appears to provide a greater inhibitory influence on LH secretion before puberty than after the completion of puberty**.** Puberty in the female is accompanied by a marked attenuation of the opioid inhibition of luteinizing hormone secretion. One factor which may contribute to this altered role is a change in the metabolism of opioid peptides during sexual maturation **(**Wiemann *et al*., 1989) [33].

Role of β -endorphins in the testis

β-endorphins has a regulatory influence on the reproductive function at the level of the hypothalamic-pituitary gonadal axis. Immunohistochemical evidence shows that β-endorphin is present in the leydig cells of fetal, neonatal and adult animal. β-endorphins synthesis localized in the leydig cells leading to the hypothesis of a direct function of the peptide in the reproductive organs **(**Albrizio *et al.*, 2006) [1]. The

presence of high-affinity opioid binding sites in Sertoli cells of the testes. β-endorphins treatment of the Sertoli cells inhibits basal and FSH-stimulated androgen-binding protein production. No opiate binding on leydig cell. Acute or chronic β-endorphin treatment does not affect testosterone production by leydig cells *in vitro*, consistent with the absence of receptors on these cells **(**Nerea *et al*., 2011) [24]. A novel biochemical tool for the diagnosis and treatment of male infertility could be based upon components of the opioid system. The presence of the opioid system in sperm cells also represents a novel opportunity for reproductive management, for either enhancing the probability of fertilization or reducing it through the development of novel targeted contraceptives (Gerendai *et al*., 1984) [11].

At the level of the CNS, β -endorphins regulate reproductive function by inhibiting the secretion of GnRH, thereby suppressing the release of LH and sex hormonal steroids such as testosterone and estradiol. Because of the shortcomings of currently available methods of male contraception, opioid system may contribute to develop additional non-hormonal male contraceptive since currently available methods require the administration of exogenous testosterone (Amory, 2005). In the testis, β -endorphins are mainly synthesized de novo by leydig cells and Sertoli cells and it appear to be able to inhibit Sertoli cell function in an autocrine and paracrine manner. The detection in sperm cells of β -endorphins, specific enzymes for their degradation and opioid receptors suggests that the opioid system may contribute to sperm fertility, and β -endorphin may be used as a biochemical tool for the diagnosis and treatment of the human male fertility. These findings open up a novel area of therapeutic exploitation of the treatment of male infertility (Garrido, 2008) [12].



Control of male reproductive function by the opioid system at multiple levels.

(1) At the level of the CNS, β-endorphin inhibit the secretion of GnRH, thereby suppressing the release of LH from the pituitary.

(2) At the testes level, β-endorphin are synthesized mainly in Leydig cells after LH stimulation, and they exert an inhibitory effect on Sertoli cells. In particular, β-endorphin can regulate the levels of testosterone (T) indirectly, inhibiting the production of ABP that is stimulated by FSH in Sertoli cells.

(3) Genes encoding opioid peptide precursors are differentially expressed in germ cells, and somatic cells of the testes and their transcripts are not efficiently translated in spermatogenic germ cells.

(4) In spermatozoa, the opioid system regulates sperm motility in a distinct manner by the activation of distinct receptors

Fig 7: Effect of β-endorphins on male reproductive system

Role of β-endorphins in pregnancy

When measuring plasma concentrations in first, second, and third trimester pregnancies, we found a significant lowest during the second trimester and highest in third trimester pregnancies. Genazzani *et al.* (1981) [13] reported a significant decrease in maternal plasma β-endorphin at 9-12 weeks gestation and an increase near full term (36-37 weeks) gestation when compared with those found in non-pregnant controls. Maternal plasma β- endorphin concentrations higher in pregnant animal in comparison to non pregnant animals (Goland *et al*., 1981) [14]. During labour, maternal plasma β-endorphin concentrations rise and remain high during the early postpartum period. This is most consistent with the increase in secretion of ACTH that has been reported to occur during labour and to peak at delivery. Csontos *et al*. (1979) [8] reported parallel increases in maternal plasma β-endorphin and ACTH concentrations. Maternal plasma β- endorphin concentrations remain raised for some time after delivery, despite the short half life of β- endorphin, indicates that the maternal pituitary continues to secrete increased amounts of β-endorphins after delivery. β-endorphins increase during labour and peak at parturition. Endorphins are natural substances, which are released whenever the body is physically stressed. Once labour begins, the level of endorphins rises, helping the mother to cope with her contractions and to get some rest in between. β-endorphins is an endogenous anti-nociceptive neuropeptide and an important pain biomarker in pregnant cows (Csontos *et al*., 1979) [8].

Role of β- endorphins and the fetus

Plasma β-endorphin concentrations are a measure of stress not only in the mother but also in the fetus. β-endorphin increases in the fetal circulation in response to stress. Inverse correlation between umbilical plasma β-endorphin concentrations and Partial pressure of arterial oxygen (PaO_2) and pH, indicating that fetal hypoxia or acidosis, or both, may be related to endorphins release (Wardlaw *et al.,* 1979). Umbilical venous plasma endorphin concentrations are higher than umbilical arterial plasma endorphin concentrations suggesting that the placenta contributes to the pool of circulating fetal β-endorphins. In the presence of fetal distress,

however, umbilical arterial endorphin concentrations seem to rise more extensively than umbilical venous concentrations, suggesting that the fetal pituitary is capable of secreting β-endorphin in response to stress.
Fachinetti *et al.* (1982) [10] reported that β endorphin is present in the plasma of newborn animals during the first 24 hours of life. The fetus born at full term is capable of producing endorphins by release from the pituitary. That CRH secreted in response to stressful stimuli may not only initiate the selective cleavage of ACTH but also that of endorphins from their common precursor pro-opiomelanocortin in the fetus and newborn. Hypoxia may be the overriding stress stimulus in the fetus, and β-endorphin in the fetal central nervous system may act as neurotransmitters that modulate fetal heart rate patterns and decrease fetal heart rate variability.

Role of β-endorphins in aging
It also has an anti-aging activity by decreasing release of free radicals (ROS, RNS) from immune cells such as neutrophils, macrophages, dendritic cells and cytokines such as IL-1, IL-8, TNF-α during oxidative burst, which is involved in DNA damage, genetic mutation, cell aging, cell death and β-endorphins involved in lengthening of telomeres, which otherwise shorten with aging. Endorphin reduces or removes superoxide and retards aging process (Shrihari, 2017) [28].

β-endorphins and milking
β-endorphin is involved in the endocrinological response to suckling in animals. Elevated plasma β-endorphins concentrations in unfamiliar surroundings in dairy cows. When cows get acclimatize to the new surroundings, the concentrations of the hormones decreases. These observations β-endorphin that play a role within the mechanisms causing central inhibition of milk ejection; hence, the exogenous opioid morphine inhibited both oxytocin release and milk ejection. In emotional stress situations, the release of oxytocin from the pituitary is inhibited with simultaneously elevated β-endorphin levels in dairy cows. Moreover, a decrease of plasma β-endorphin concentrations during machine milking in cows. β-endorphin releases was not affected by milking frequency and not correlated with the magnitude of prolactin release (Bruckmaier, 1994) [14].

Role of β-endorphins during exercise
Physical activity is thought to induce significant β-endorphin release. During continuous exercise there is release of endorphin and the effect is called Runner's high. When the athlete crosses the limit of his exercise then endorphins are released which reduces the pain by stopping the pain signals and the athlete is able to work out for more time even after his threshold limit is over. In heart patients who had an attack before, are always advised to do regular exercise, the reason for this is during exercise endorphin is released and it protects the heart from an attack. And if, does the heart attack comes, instead of getting frightened and panic, it gives the patient the strength to fight against it for a long time till he is hospitalized and becomes healthy very soon. There is a very rare possibility that a man who is continuously exercising has an second attack. A positive attitude is generated by the release of these hormones (Hausenblas and Downs, 2002) [18].
When we exercise, our body releases chemicals called endorphins. These endorphins interact with the receptors in your brain that reduce your perception of pain. Endorphins also trigger a positive feeling in the body. Regular exercise has been proven to reduce stress and improve sleep. Exercise helps bump up the production of your brain's feel-good neurotransmitters, called endorphins. Although this function is often referred to as a runner's high, endorphins increases self-confidence, it relaxes you, and it can lower the symptoms associated with mild depression and anxiety. Endorphins can also improve your sleep, which is often disrupted by stress, depression and anxiety (Biddle and Mutrie, 1991) [3].

Fig 8: The brain before and after 20 minutes vigorous exercise

Role of β -endorphins in emotions
Endorphins are produced as a response to certain stimuli, especially stress, fear or pain. They originate in various parts of the body like pituitary gland, spinal cord and throughout parts of nervous system and interact mainly with receptors in cells found in regions of the brain responsible for blocking pain and controlling emotion (Dalayeun, 1993) [9]. Music releases endorphins in the blood and changes the mood. Change in mood is directly proportional to endorphin. Endorphin also protects us from stress, hypertension, depression and heart attacks. Endorphin is released during stress and hypertension and these endorphins bind to the μ-opioid receptors in neurons which block the release of neurotransmitters and in turn block the pain signals going to the brain (Chaudhary, 2004) [7]. Music has a role in reducing stress and inhibit the secretion of cortisol (Hebert, 2005). During coitus endorphins are released, it gives the blissful and happy feeling and due to release of endorphins females look too young and charming. It's the endorphins effect which is released during sex that brings the charm and shining on the face of the married girl. Laughing releases the endorphin which keeps you happy and healthy (Best, 2007) [5].

Role of β -endorphins in acupuncture therapy
In acupuncture therapy when needles are inserted at the fixed points in the body, there is pain while inserting not one but

several needles due to which endorphin is released, which releases the feeling of pain and subject easily goes through this therapy. Mechanisms how acupuncture stimulates the immune system through β-endorphin are the described as acupuncture stimulation of ST36 acupoint induces release of nitric oxide (NO). NO, a neurotransmiter, stimulates via the sensory nerves, spinal cord and medulla oblongata, gracile nucleus the lateral hypothalamic area (LHA), where it promotes secretion of opioid peptides such as β-endorphin. β-endorphin travels via blood circulation to the spleen and other body locations containing immune cells where it binds to opioid receptors expressed on the surface of NK cells and stimulates NK cells to amplify their expression of cytotoxic molecules and consequently tumoricidal activity, and production of IFN-γ. This cytokine induces the expression of NK cell receptors and cytokine receptors on NK cells and perhaps cytokine secretion by other immune cells, thereby orchestrating and further amplifying anticancer immune functions (Nopadow *et al*., 2008) [25].

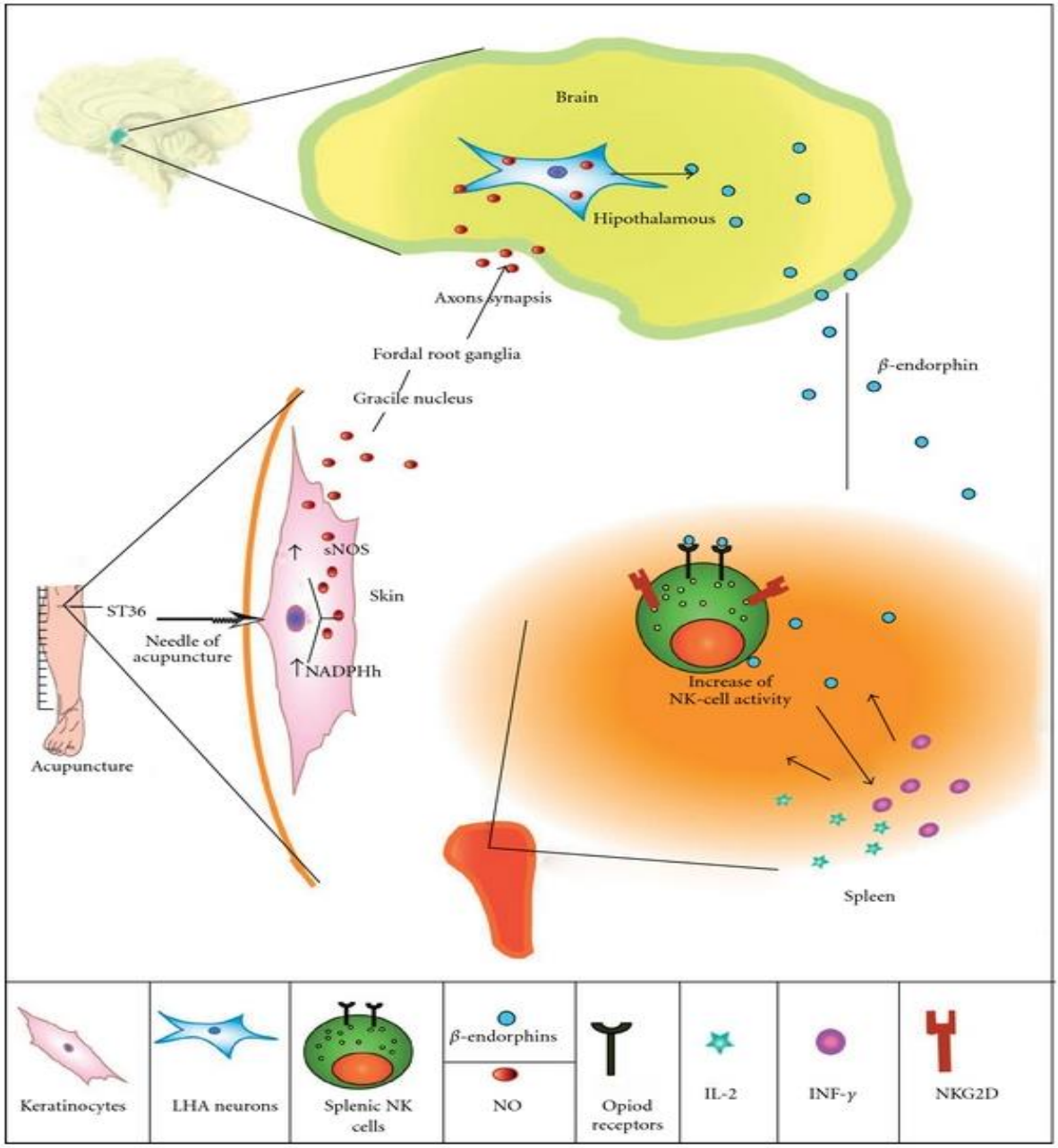


Fig 9: Mechanisms how acupuncture stimulates the β-endorphin production and affect the immune system

Conclusion

Exercises such as walking, running, workouts, laughing exercise, meditation, listening music and all these are responsible for the release of endorphins hormone or they are the stimuli to release this hormone which gives them strength, confidence and gives mood of well being and happy. In anxiety patients endorphin is given orally, but, instead of taking pills orally one can make use of original endorphins present in the body as a medicine. Only the thing is the subject must know how endorphins are released in his body and what he has to do for it. Also in anxiety patients music gives a great relaxation to their brain and mind and the patient feel more peaceful and happy. Medication and high dose tablets harm the immune system making us vulnerable to many diseases, but exercise releases endorphins which keeps us healthy happy curing many diseases and it never interrupts with the immune system. β-endorphins are one of the abundant type of endorphins has various activities such as immune-stimulatory, analgesic, stress reducer and anti-inflammatory activity. β-endorphins are neuropeptides

involved in pain management, possessing morphine like effects and are involved in natural reward circuits such as feeding, drinking, sex and maternal behavior. Therefore, more studies are necessary for understanding of β-endorphins and their dose dependent action is helpful for future preventive, therapeutic, and holistic treatment of various diseases such as autoimmune diseases, cancer and infectious diseases without adverse drug effects which is inexpensive.

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