

BETA ENDORPHINS – HOLISTIC THERAPEUTIC APPROACH TO CANCER

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ABSTRACT

Aim: Endorphins are endogenous morphine, neuropeptides, produced in the pituitary gland in response to stress and pain. There are three types of endorphins beta-endorphins, enkephalins, and dynorphins binds to mu, kappa, and delta receptors situated on nervous system and immune cells. Cancer is a major threat to mankind killing millions of people around the world annually. There has been recent advancements in the field of surgery, chemotherapy, and radiotherapy, still the prognosis of cancer patients not improved much with increasing morbidity. We can't kill cancer cells without killing normal cells. Cancer cells and normal cells work alike. The aim of the review was to determine the anticancer activities of beta-endorphins.

Materials and methods: Articles regarding endorphins and its therapeutic application in cancer were searched on PubMed and Google scholar. This review includes studies, reviews, clinical trials and key findings of my research were included in the manuscript.

Results: Beta-endorphin is an abundant endorphin, potent than morphine, synthesized and secreted in the anterior pituitary gland, it is a precursor of POMC (proopiomelanocortin). It has got various mechanisms of action such as analgesic activity, anti-inflammatory activity, immune stimulatory activity, stress buster activity, and euphoric activity.

Conclusion: Beta endorphin is an abundant endogenous morphine used for natural holistic preventive, therapeutic, promotive, and palliative treatment of cancer without adverse effects and inexpensive.

Keywords - IL-1 β ; IL-6; TNF- α ; Stress; Cortisol; Meditation; NF-Kb; STAT-3; HPA-axis.

INTRODUCTION

Cancer is a major cause of death worldwide¹. Cancers are mainly due to external environmental factors such as tobacco in the chewable and non-chewable form, chemical ingestion, alcohol consumption, dietary factors and viruses such as HPV (Human Papilloma virus).¹ Chronic inflammation is considered as a seventh hallmark of cancer.^{1,4} Cancer cells work like normal cells, "I do not know how to kill the cancer cells without killing normal cells said" by a Nobel laureate hungarian biochemist, Albert Szent-Gyorgyi.^{1,29}

Advanced treatment modalities such as surgery, radiotherapy, and chemotherapy fail to improve the cancer prognosis, which is around 50% with an increasing morbidity and mortality rate. The present concept of holistic healing rather than healing a part of the body yields better results without complications. Endorphins are endogenous morphine, more potent than morphine acts as neuropeptides produced by the pituitary gland through hypothalamus in response to

psychological stress, pain, sex, intense physical exercise, yoga, meditation, acupuncture, quantum healing, music therapy.^{14,16,20,21,22,25,26,29} It is also responsible for euphoria after vigorous exercise, creating a psychological relaxed state known as "runner's high".^{2-7,15,16,29}

Endorphins are mainly of three types, β -endorphins, enkephalins and dynorphins binds to mu, delta and kappa receptors respectively present on the immune cells and nervous system. β -endorphins are the abundant endorphins, more potent than morphine, synthesized and stored in the anterior pituitary gland, it is a precursor of proopiomelanocortin (POMC) which binds to the μ receptors and their ligands present on the immune cells and nervous system.^{13,26}

Neuroendocrinal pathway connects between nervous system, endocrinal system, and immune cells in human body. Neuroendocrinal system, which connects CNS (central nervous system) to PNS (peripheral nervous

system) via HPA (Hypothalamo-pituitary axis) and ANS (Autonomic nervous system) through direct nerve fiber connections with cells or the organs of the immune cells.

Chronic psychological stress is one of the predisposing factor for cancer along with depression, frustration, fear, hatred results in release of CRH (corticotrophic releasing hormone) from hypothalamus activates hypothalamo-pituitary adrenal axis (HPA-axis) through sympathetic nervous system activity of ANS release neurohormones such as cortisol, ACTH, and noradrenaline. These neurohormones induced inflammatory mediators such as IL-1 β , TNF- α , IL-6 and COX-2 inflammatory mediators activate key transcription factors NF-KB and STAT-3 promotes cell proliferation, angiogenesis, immunosuppressant, cell survival, invasion and metastasis leads to cancer.^{2,3,6,7,10,11,17,19,21,22,23,29,31,32,33} Chronic inflammation is considered as a seventh hallmark of cancer. Disassociation of beta-catenin from E-cadherin is an indicator of epithelial to mesenchymal transition.³⁰

As the process of blocking the release of neurohormones such as cortisol, ACTH, and noradrenalin is due to opioid receptor mediated hyperpolarization of neuronal cells. Increased levels of free beta-Catenin are demonstrative of a loss of cell adhesion.^{1,9,10,11,12,30}

DISCUSSION

Holistic approach of beta-endorphins in treatment of cancer:

Endorphins are natural morphine like substances, mainly β -endorphins, which is an abundant endorphins binds to μ receptors present on the immune cells such as macrophages, T and B lymphocytes, monocytes, and NK cells results in production of anti-inflammatory cytokines such as IL-18, IL-10, IFN- γ . NK cells are the natural first line of defense against cancer and antiviral activity by producing IFN- γ , opsonin and granzyme-B.^{14,17,18,19,20,25,29}

β -endorphins produce analgesia by inhibiting substance P, a neurotransmitter of pain in the peripheral nervous system through presynaptic μ (mu)-receptor binding. β -endorphins produce euphoria, rewarding and analgesic effect by inhibiting GABA neurotransmitter and stimulating dopamine release after binding to μ receptors in the central nervous system.^{21,22,23,26,27,34}

Betaendorphin inhibit chronic psychological stress by binding of betaendorphin to the μ receptors situated on the central nervous system results in inhibition of GABA inhibitory neurotransmitter and produce

dopamine neurotransmitter involved in analgesic activity, euphoria, and stress buster activity.

Betaendorphin inhibit chronic psychological stress mediated inhibition of HPA-axis through autonomic nervous system (ANS) inhibits release of stress releasing neurohormones such as cortisol, ACTH, and noradrenalin. These neurohormones activate inflammatory mediators such as IL-1, TNF- α , IL-6, which further activate NF-KB and STAT-3 transcription factors involved in tumor progression.

It is also involved in suppression of sympathetic neuronal function and the parasympathetic neuronal stimulation by beta-endorphin neurons results in activation of anti-inflammatory cytokines and peripheral immunity involved in inhibition of tumor growth and progression. Anti-inflammatory activity by suppressing proinflammatory cytokines such as IL-1, IL-6, and TNF- α , free radicals release such as ROS and RNS by cytokines, immune cells, which is involved in tissue injury, cell aging, cell death, genetic mutation, and immunosuppression. Betaendorphins also activate anti-inflammatory cytokines such as IL-18, IL-10 and INF- γ .^{25,26,30,31}

Beta-endorphins mediated reduced cortisol secretion results in increases innate immune cell activity such as NK cells and macrophages.^{8,13,14,15,16,17,20,21,22,23,24,25,26} It also inhibits sympathetic neuronal excitatory activity and activates para sympathetic nervous system activity, improves peripheral immune activity by macrophages and NK cells. Immune cells such as T and B lymphocytes, monocytes, macrophages, produce beta-endorphins. In inflammation recruitment of immune cells to the site of inflammation by chemokines produce endorphins especially beta-endorphins involved in anti-inflammatory activity by reducing inflammatory mediators such as TNF- α , IL-1, IL-6, IL-8, and inhibiting key transcription factor NF-KB induces cell proliferation, cellular apoptosis, angiogenesis, chronic inflammation, invasion and metastasis. Receptors of opioid peptides are increases in periphery during inflammation. (Anti-inflammatory and analgesic effect of betaendorphin by inhibiting the release of substance P, a neurotransmitter of pain and inflammation and noradrenaline at the peripheral nervous system, which activate inflammatory mediators such as IL-1, TNF- α , IL-6). Decrease in psychological stress level by inhibiting HPA-axis through sympathetic neuronal activity and activating parasympathetic neuronal activity, decreases cortisol and nor-adrenaline secretion, improves activity of innate immune cells such as NK cells, macrophages, produce interferon-gamma, opsonin, and granzyme-b involved in anti-tumor and anti-viral activity.^{30,32,33}

Beta-endorphins involved in alteration of environment of genes and gene expression in tumor microenvironment. It also prolong human life span by lengthening telomeres, which shortens with aging and anti-inflammatory activity by neutralizing free radicals such as ROS, RNS responsible for cell aging during oxidative stress. Beta-endorphins suppress the release of ROS, RNS, free radicals and NO (nitric oxide) from inflammatory cells and cytokines such as TNF- α , IL-8, and tumor associated macrophages, tumor associated neutrophils, dendritic cells, involved in genetic mutation of tumor-suppressor gene p53, which is altered in more than 50% of all cancers, immune suppression, cell injury and cell death. Alteration of tumor micro-environment by suppressing catecholamine's induced inflammatory cytokines (IL-1, TNF- α , IL-6) and increase in anti-inflammatory cytokines such as IL-10, IL-18. IFN-Gamma). Beta-endorphins suppress tumor progression by suppressing the release of catecholamine's such as nor-adrenaline and cortisol mediated suppression of inflammatory mediators such as TNF- α , IL-1, COX-2, IL-6, involved in tumor progression by activating key transcription factors NF-KB, STAT-3, in tumor micro-environment, which involved in cell proliferation, cell survival, angiogenesis, genomic instability, immune suppression, invasion and metastasis. Beta-endorphin helps in e-cadherin expression and inhibiting the activity of proteolytic enzymes matrix-metalloproteases -2,9 (mmp-2,9), upA (urokinase plasminogen activator) involved in extracellular matrix degradation, invasion and metastasis results in cell adhesion, prevents invasion and metastasis.³⁰

Endorphins especially β endorphins acts as a natural preventive, therapeutic and palliative holistic therapeutic approach to cancer without any adverse reactions.^{24,28}

Many in-vivo and in-vitro studies have shown that β -endorphins have antitumor activities at an early and later stages of cancer on animal and human cancer cells.^{8-10,29}

Tenderness, love, care for the patient. Practice of sympathy, empathy, compassion for caring patient produce endorphins is the ultimate treatment of choice.

Comments: Thorough understanding of mechanism of action of beta-endorphin, duration of action, dose dependent action, prognosis related to stages of cancer will be useful for future therapeutic approach to cancer.

CONCLUSION AND FUTURE PERSPECTIVE

Endorphins are endogenous opioids, Beta-endorphins secreted by anterior pituitary gland in response to certain

stress and painful conditions of our body. It has a natural stress buster, analgesic, euphoric and immune-stimulatory activity to combat against cancer without any adverse effects. Quantity of secretion of beta-endorphins, dose dependent effects of beta-endorphins on cancer-related to prognosis; need to be known for future preventive, promotive, therapeutic and palliative holistic treatment of cancer.

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