Beta Endorphins – Novel Holistic Therapeutic Approach to Chronic Inflammation Associated Cancer

Shrihari T. G.

Assistant Professor, Department of Oral Medicine and Oral Oncology , Krishna Devaraya College af Dental Sciences and Hospital , Bangalore -562157, Karnataka, India.

ABSTRACT

Endorphins are neuropeptides produced by pituitary gland in response to pain and stress. They release CRH from hypothalamus, activate HPA-Axis, release cortisol, cause nor-epinephrine mediated activation of the inflammatory mediators of IL-1ß, TNF-α, IL-6, from the inflammatory cells, and activate NF-KB, STAT-3, and transcription factors which are involved in tumor progression, auto-immune diseases, and infectious diseases. Beta-endorphins are synthesized and stored in the anterior pituitary gland involved in the immune stimulatoy, anti-inflammatory, stress buster activity, and analgesic activity. Chronic inflammation is a basis for most of diseases. Because of anti-inflammatory activity of beta-endorphins, they are used to treat diseases such as cancers, auto-immune diseases, and infectious diseases. This article has briefly reviewed the basic research findings of beta endorphins in holistic treatment of the inflammation associated cancers.

Key Words: Cortisol, Noradrenaline, ACTH, IL-1β, IL-6, TNF-α, COX-2, NF-KB, STAT-3.

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INTRODUCTION

Cancer has been a major threat to mankind, and it kills many people every year. Despite many advanced treatment modalities, the prognosis of cancer has not been improved much. The majority of cancers are due to the external environmental factors such as tobacco, alcohol, infectious agents such as HPV (Human pappiloma virus), chemical agents such as silica, arsenic and other factors such as obesity and nutritional insufficiency. Chronic inflammation accounts for 25% of all cancers. Chronic inflammation can be considered as the seventh hallmark of cancers. In extrinsic pathway of inflammation related cancers, some inflammatory conditions or injuries that are associated with malignancy are: Lichen planus, Oral submucous fibrosis, gingivitis and chronic periodontitis associated oral squamous cell carcinoma, Sialadenitis related salivary gland carcinoma, Gastric acid associated barrett's metaplasia and reflux oesophagitis associated oesophageal carcinoma, Sjogren's syndrome, and Hashimoto's thyroiditis associated, mucosa associated lymphoid tissue lymphoma, UV radiation associated skin inflammation melanoma, Silica, asbestose, smoking associated silicosis, and bronchitis associated lung carcinoma, Prostatitis induced prostate carcinoma, chronic pancreatitis induced pancreatic cancer, Hepatitis B induced hepatocellular carcinoma, HPV induced cervical cancer, and pharyngeal cancer. Human herpes virus 8 (HHV8) induce kaposis sarcoma. Inflammation is the complex biological response to the physical or chemical, or infectious stimuli. Acute inflammatory response to the tissue injury results in tissue repair by various mediators such as neutrophils , macrophages, and dendritic cells release mediators such as COX-2, ROS, TGF-Beta . If the inflammation is aggravated chronically, non-resolving , chronic smoldering inflammation results in dysregulated immunity mediated release of cytokines ,chemokines, growth factors, proteolytic enzymes by innate and adaptive immune cells such as macrophages and neutrophils involved in tumor progression. Human

Corresponding author: Shrihari T.G
Address: Assistant Professor, Department of Oral medicine and Oral oncology , Krishna devaraya college of dental sciences and hospital , Bangalore -562157, Karnataka, India .
E-mail: ✉ drshrihariomr@gmail.com

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environment is one of the causes of cancer , human environment is human mind that involves consciousness. Chronic psychological stress induces the activation of HPA-axis which causes the release of neuropeptides such as cortisol, ACTH, and noradrenaline activate inflammatory mediators such as IL-β,TNF-α,COX-2, and IL-6 ,which activate NF-KB and STAT-3 key transcription factors involved in tumor progression [1-8].

The mechanism of beta-endorphins on inflammation associated cancers

Endorphins are natural opioids, potent endogenous morphines, and neuropeptides produced in the anterior pituitary gland in response to stress and pain, through the release of corticotrophin releasing hormone(CRH) from hypothalamus. Endorphins are of three types including: β-endorphins, Dynorphins, Enkephalins. Enkephalins have an affinity with mu, delta, kappa receptors present in nervous system, brain and immune cells. Beta- endorphins are abundant endorphins, synthesized and stored in the anterior pituitary gland, which are more potent than morphine, and are precursors of POMC (Proopimelanocortin). The inflammation receptors of endorphins are increased in peripheral nerves , binding of β-endorphins produced by the immune cells binds to any of the receptors such as mu, kappa, delta on the peripheral nerves activated by the anti-inflammatory cytokines such as IL-18, IL-10, IFN-Gamma. The intense physical exercise creates a psychologically relaxed state known as "Runner's high"; and pranayama, mindful meditation , yoga, music therapy, acupuncture, tranquility of mind, pranic healing, love, tender, care can cause the endorphins release [3, 4, 9-18].

Beta- endorphins have an anti-carcinogenic activity by activating IFN-gamma, perforin, granzyme-B from NK cells, neutrophils, Dendritic cells, NK cells, and macrophages immune cells, which involve in the antiviral activity, apoptotic activity , and decrease the cellular proliferation. The mindful meditation alters the environment of the gene expression in tumor microenvironment. The anti-inflammatory activity of Beta-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 INF-α mediated release of COX-2 inflammatory mediator activates the key transcription factors of NF-KB and STAT-3 involved in the tumor progression by cellular proliferation (cyclin D, C-myc, P21), cell survival (BCL-2, BCL-XL, CFLIP, survivin), angiogenesis (IL-8, VEGF, COX-2), genomic instability(ROS, RNS, NO), immune suppression (TGF-Beta,IL-10, iNOS), invasion and metastasis of (MMP-2, 9, E-selectin, CXCR4, uPA, Fibronectin, ICAM-1, ELAM-1,VCAM-1). NF-KB transcription factor antagonizes the action of P53 tumor suppressor gene , which is altered in more than 50 % of all the cancers by the inflammatory mediators such as NO (Nitric oxide),ROS,RNS, AID(Activation induced cytidine deaminase) enzyme. Beta- endorphins suppress NF-KB transcription factor's activity, by inhibiting the mutation and suppression of P53 tumor suppressor gene. They are also involved in the epithelial expression of E-Cadherin induced by the cell adhesion, the loss of E-Cadherin involved in epithelial to mesenchymal transition induced tumor invasion [2, 5, 6, 14-19].

Endorphin receptors are present in most of the immune cells such as neutrophils, T-lymphocytes, B-lymphocytes, macrophages, NK cells ,dendritic cells , macrophages. The binding of beta – endorphins to the receptors on the innate and adaptive immune cells results in the activation of the immune cells which cause the release of IFN- Gamma, perforin, granzyme-B, and antibodies involved in the anti-inflammatory, antiviral, anti-bacterial, and antitumor activities [10-13, 19-27].

In the peripheral nervous system, beta-endorphins binds to mu receptors, and results in the decreased release of substance P, neurotransmitter of pain and inflammation, and produces IL-10,IFN-γ anti-inflammatory cytokines which involve in the analgesic activities and reduce the inflammation [13-19].

In the central nervous system, beta endorphins bind to mu receptors and decrease GABA neuro-inhibitory transmitter, and release dopamine excitatory neurotransmitter which consequently result in analgesic , euphoria , self –reward , cognitive development and tranquility of mind. They have a stress busting activity by suppressing hypothalamic pituitary adrenal(HPA) axis activated in response to stress, anger, hatred, jealousy, frustration, depression, by the release of corticotrophin releasing hormone from hypothalamus and neuropeptides' cortisol, noradrenaline , and ACTH through the autonomic nervous system's mediated release of the inflammatory mediators such as IL-1, IL-6, TNF-α and COX-2 inflammatory mediators. And, they activate a key NF-KB,STAT3 transcription factor involved in the chronic inflammation, and tumor progression [4-6,14-16, 27-29].

Beta-endorphins inhibit NF-KB which is a key transcription factor that induces the expression of the inflammatory mediators such as cytokines, growth factors, and proteolytic enzymes involved in the conversion of TH1 lymphocytic type to TH2 lymphocytic type, and releases IL-4,IL-13,IL-5 proinflammatory cytokines along with TH17 cells involved in the chronic inflammation, tissue damage, and immune modulation. The growth factors such as EGF, FGF, VEGF are involved in the cell proliferation and angiogenesis. The altered induced regulatory T cells (Tregs) formed from TH1 cells mediated by TGF-β inflammatory mediator, release IL-10,IL-2,IL-17,IL-4,IL-13,IL-5, proinflammatory cytokines involved in the

immune modulation. Otherwise, the normal regulatory T cells (Tregs) are involved in self tolerance and immune homeostasis. Proteolytic enzymes such as Mmp's 2, 9 (Matrix metallo proteases2,9) are involved in tissue damages, and all these changes lead to tumor progression [1, 2, 5, 6, 14-16].

Beta-endorphins also have an anti-aging activity by inhibiting the 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 the oxidative stress via NADPH oxidase pathway , which is involved in DNA damage, genetic mutation, cell aging, cell death and beta-endorphins involved in lengthening telomeres, which get shortened with aging [13-16, 30].

CONCLUSION AND FUTURE PROSPECTIVE:

Endorphins are endogenous morphine and neuropeptide which are produced by pituitary gland in response to stress and pain. They are of 3 types, including: neta-endorphins, dynorphins, enkephalins, which bind to mu, kappa, delta receptors found in the immune cells and nervous system. Beta-endorphins are the most abundant endorphins which are synthesized and stored in the anterior pituitary gland. They have got various activities such as the immune stimulatory activity by the activating NK cells, macrophages, T-lymphocytes; the anti-inflammatory activity by producing cytokines, such as IL-18, 1L-10; the analgesic activity by inhibiting the substance-p; the anti-ageing activity by suppressing ROS, RNS, free radicals and lengthening telomeres; the stress busting activity by decreasing cortisol and nor-adrenaline, and releasing dopamine involved in the holistic, preventive, health promotive, therapeutic and palliative treatment of cancer which is inexpensive without any adverse effects. The understanding of beta-endorphins and their receptors, the mechanism of their activity, the dose dependent duration of their activity, and the prognosis related to diseases are useful for the future therapeutic purposes.

Abbreviations:

PNS- Peripheral nervous system
CNS- Central nervous system
ACTH- Adrenocorticotropic hormone
HPA- axis- Hypothalamic pituitary adrenal axis.
STAT 3- Signal transducer and activator of transcription protein 3
NF-kB – Nuclear factor kappa- light- chain –enhancer of activated B cells
CRH- Corticotropin releasing hormone
COX-2- Cyclooxygenase 2
TNF- α –Tumor necrosis factor – Alfa
IFN- γ- Interferon Gamma

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