

## Beta-Endorphins – A Novel Anticancer Agents

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### ABSTRACT

Endorphins are an endogenous morphine neuropeptides produced from pituitary gland in response to stress and pain. There are three types of endorphins beta-endorphins, enkephalins and dynorphins binds to mu ( $\mu$ ), kappa ( $\kappa$ ) and delta ( $\delta$ ) receptors situated on nervous system and immune cells. Beta endorphin is an abundant endorphin synthesized and stored in the anterior pituitary gland. It has got various activities such as immune stimulatory, anti-inflammatory, analgesic, anti-aging, stress buster activity involved in holistic preventive, promotive, therapeutic and palliative treatment of inflammation associated cancer without adverse effects. This article briefs about the recent basic research findings of beta endorphins. A novel holistic preventive, therapeutic, health promotive and palliative treatment of cancer.

**Keywords:** Cortisol, Noradrenaline, ACTH, IL-1 $\beta$ , IL-6, TNF- $\alpha$ , COX-2, NF-KB, STAT-3

### INTRODUCTION

Endorphins are endogenous morphine, neuropeptides produced in the pituitary gland in response to stress and pain [1-7]. 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 [8,9]. Holistic healing is a whole person healing. Human body works as a whole. If we consider human body as a whole rather than as parts in treating any disease with reductionist chemical drugs yields better results without adverse effects. Human body has an excellent capacity to combat against any disease.

Cancer is a major threat to mankind. Majority of cancers more than 90% of all cancers are due to external environmental factors such as tobacco, alcohol, chemical ingestion such as arsenic, silica, bismuth, lead and benzene. One of a cause for cancer is human environment that is human mind is a part of consciousness. Chronic inflammation is considered as a seventh hallmark of cancer. Chronic infection or chronic inflammation accounts 25% of all cancer. Chronic inflammatory conditions or injury that are associated with malignancy are Lichen planus, Oral submucous fibrosis, chronic periodontitis associated oral squamous cell carcinoma, sialadenitis related salivary gland carcinoma, Gastric acid associated Barrett's metaplasia and reflux esophagitis associated esophageal carcinoma, Sjogren's syndrome and Hashimoto's thyroiditis associated mucosa associated lymphoid tissue lymphoma, UV radiation associated skin inflammation mediated malignant melanoma. Silica, asbestosis, smoking associated silicosis

and bronchitis associated lung carcinoma, Prostatitis induced prostate carcinoma, chronic pancreatitis induced pancreatic cancer, Hepatitis B induced hepatocellular carcinoma and HPV induced cervical cancer and pharyngeal cancer. Human herpes virus 8 (HHV8) induced Kaposi's sarcoma [3].

Advanced cancer treatment modalities such as surgery, chemotherapy and radiotherapy fails to improve the prognosis of cancer with increasing morbidity, mortality, adverse drug reactions and decreasing survival rate [10-17].

I do not know any treatment, which can kill cancer cells without killing normal cells. Normal cells and cancer cells work alike (Albert Zen gyorgi) [18-20].

Beta-endorphins are abundant endorphins, more potent than morphine, synthesized and stored in the anterior pituitary gland; it is a precursor of POMC (Proopiomelanocortin) [21-26].

Most of all immune cells produce endorphins. In inflammatory state recruitment of immune cells to the site of

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inflammation by chemokines produce endorphins reduce inflammation by binding of endorphins to the receptors on peripheral nerves results in inhibition of substance p a neurotransmitter of pain and inflammation, production of IL-18, IL-10, IFN- $\gamma$  anti-inflammatory cytokines [27-30].

Endorphins produced during yoga, intense physical exercise creates a psychological relaxed state known as "Runner's High", mindful meditation, pranic healing, pranayama, chi therapy, acupuncture, music therapy, tender, love, care, sympathy, empathy in caring the patient [31-33].

### Mechanism of action of beta endorphins in anticancer activity

Chronic psychological stress induced release of CRH from hypothalamus activates HPA-axis through ANS release neuropeptides such as cortisol, noradrenaline and ACTH activates IL-1 $\beta$ , TNF- $\alpha$ , IL-6 and COX-2, inflammatory mediators, which activates NF-KB, STAT-3 transcription factors involved in chronic inflammation and cancer by induced expression of inflammatory mediators such as (BCL-2, BCL-XL, survivin, IAP1/2) involved in cell survival (MHC-1, MHC-11, cytokines) involved in chronic inflammation (IL-8, VEGF, COX-2) involved in angiogenesis (Cyclin D, C-Myc, P21) involved in cell proliferation (ICAM-1, VCAM-1, ELAM-1, UPA, fibronectin, E-selectin, Mmp-2,9, CXCR4) involved in invasion and metastasis [1-7,29,31-33].

In the peripheral nervous system (PNS) binding of beta-endorphins to the  $\mu$  (mu) receptors on peripheral nerves results in inhibition of substance P a neurotransmitter of pain and inflammation, produce IL-10, IL-18 and IFN- $\gamma$  anti-inflammatory cytokines [31-34].

In the central nervous system (CNS) binding of beta endorphins to the  $\mu$  (mu) receptors on central nervous system instead of inhibiting substance p, it inhibits GABA (Gama amino butyric acid) inhibitory neurotransmitter, activates dopamine neurotransmitter involved in analgesic activity, euphoria, tranquillity of mind, self-reward, cognitive development and stress buster activity [31-34].

Endorphin receptors are situated on immune cells. Binding of beta endorphins to the  $\mu$  (mu) receptors on immune cells such as NK cells, DC's, neutrophils, macrophages, T cells and B cells results in activation and release of opsonin, granzyme-B and IFN- $\gamma$  involved in antibacterial, antiviral, antitumor and anti-inflammatory activity [31-33].

Beta-endorphins inhibits chronic psychological stress induced sympathetic nervous system activity and activates parasympathetic nervous system activity of ANS (Autonomic nervous system) mediated inhibition of release of neuropeptides such as cortisol, ACTH, noradrenaline, through HPA-axis results in inhibition of inflammatory mediators such as IL-1 $\beta$ , TNF- $\alpha$ , IL-6 and COX-2, which

activates NF-KB, STAT-3 transcription factors involved in chronic inflammation and cancer [8-14].

Beta-endorphins inhibits chronic psychological stress induced activation of NF-KB transcription factor involved in tumour progression, which antagonize the P53 tumour suppressor gene, a guardian of the genome mutated in more than 50% of all cancers by inflammatory mediators such as NO (nitric oxide), ROS, RNS free radicals, AID (Activated induced cytidine deaminase) enzyme [31-33].

Beta-endorphins express epithelial E-Cadherin involved in epithelial cell attachment, loss of epithelial E-cadherin involved in EMT (epithelial mesenchymal transition) induced tumor invasion.

Beta endorphins involved in reduction of cell proliferation, apoptotic activity by activating NK cells mediated release of apoptotic proteins such as granzyme A and B, perforins and FASL [15-20,29,31-33].

Beta-endorphins delay aging by lengthening telomeres, which otherwise shorten with aging and other mechanism is by inhibiting free radicals (ROS, RNS) release during oxidative stress via NADPH oxidase pathway produced by inflammatory cells such as neutrophils, macrophages and dendritic cells involved in cell aging, genetic mutation, tissue damage and cell death [21-28,31-33].

Beta endorphins inhibits NF-KB a key transcription factor involved in conversion of TH1 lymphocytic type to TH2 lymphocytic type release IL-4, IL-13, along with TH17 cells facilitate chronic inflammation, immune modulation and tissue damage, altered induced Tregs (Regulatory T cells) formed from TH1 cells mediated by TGF- $\beta$  inflammatory mediator release IL-10, IL-2, IL-17, IL-4, IL-13, IL-5 involved in immune modulation, otherwise normally involved in self-tolerance and immune homeostasis, growth factors such as (EGF, FGF, VEGF) involved in cell proliferation and angiogenesis, mmp's 2,9 (matrix metalloproteases 2,9) involved in extracellular matrix degradation, tumor invasion and metastasis [29-34].

### CONCLUSION AND FUTURE PERSPECTIVE

Beta-endorphins are an endogenous morphine acts as a holistic preventive, therapeutic, health promotive and palliative treatment of cancer by its analgesic, anti-inflammatory, immune stimulatory and stress buster activity without adverse effects and inexpensive. Thorough understanding of endorphins, activities that produce endorphins, mechanism of action, dose dependent duration of action, prognosis related to disease helpful for future therapeutic applications in treatment of cancer.

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