BLOCKING OF BETA ADRENERGIC RECEPTORS AS POSSIBLE APPROACH IN CANCER THERAPY

Amal Ajaweed Sulaiman*

*Department of pharmacology and Toxicology, College of pharmacy, University of Baghdad (Iraq).

ABSTRACT
Later evidence attributed the poor outcome of cancer development and progression to over activity of endogenous stress hormones epinephrine (EP) and nor-epinephrine (NE). Since, activation of β-adrenoceptor (βADRs) signaling pathways, can enhance cell division, proliferation and metastasis. Therefore, blocking of (βADRs) and their downstream events may serve as new strategy to suppress cancer and reduce cell invasion. However the exact impact on cancer cell survival and development still need to be illustrated. Therefore in this article, we try to prospect on the role of beta adrenergic receptor blockers, as a possible future adjuvant therapy that may lend pharmacological supports for conventional treatments to achieve better management of cancer.

KEYWORDS: Cancer, stress hormones, beta blockers, adrenaline.

1-INTRODUCTION
1.1 Stress and Cancer
Misery a common sensation of stress which impair human physical and social activities. Where, individuals being unable to cope or control their daily responsibilities and routine events. However, physiologic stress comprise both emotional and mental pressure. Since, both environmental and psychosocial factors can initiate a complex cascade of information processes at both central, and peripheral nervous systems.[1] Normally, stress may occur from time to time, while, frequent stress may cause physiological disturbances manifested as a health problem.
Continuous release of stress hormones; norepinephrine (NE) and epinephrine (E) known to be increased under acute or chronic stressful conditions, initiating a series of downstream events at different sites. Release of these hormones is often associated with a marked increase in blood pressure, heart rate, blood sugar levels, and free fatty acids to support an individual under stress with greater strength so that can escape a perceived threat. On the other hand, people who suffer from chronic stress showed signs of indigestion, infertility, immune deficiency, sleep disturbance, anxiety, depression and aid in development and progression of cancer. This result from activation of several body systems including autonomic nervous system and hypothalamic–pituitary–adrenal (HPA) axis, and the adrenal medulla by stress hormones.[2,3]

1.2 Hallmarks of cancer Development
Later cancer study reported that tumorogenesis usually controlled by a network of biological events mediated through activation of catecholamine receptors which highly expressed in cancer cells, to conduct relevant regulation on tumor cells to have the following properties; i- Proliferation, ii- continuous replication with Angiogenesis, iii- Evasion & metastasis and Insensitivity to immune destruction.[4]

1.3 Pathways of stress response
Stress response started by the secretion of stress hormones (corticosteroids and catecholamines), in response to the activity of hypothalamic-pituitary-adrenocortical (HPA) axis and the autonomic nervous system (ANS) respectively, to consequently affect every system of the body. The sympathetic neural fibers innervate most major organ systems, where they can release micromolar concentrations of norepinephrine neurotransmitter in response to physiologic, psychologic, and environmental threats to homeostasis.[5] Moreover, acute activation of SNS, rapidly elevates the levels of both, circulating epinephrine released from chromaffin cells of the adrenal medulla, and norepinephrine which spill-over from vascular neuro-muscular junctions.[6] The sympathetic neural outflow, generally modulated by local regulatory events mediated by uptake and degradation processes as well as by central nervous system (CNS), which can modulate secretion by involvement of the nicotinic/acetylcholine system at central and peripheral levels. As a result, it has been found that NE and EP concentrations can differ substantially in solid tissues versus blood, as well as across different tissue environments at the same point in time.[7]
In chronic psychosocial stress, the aspects of the stress response may continue for extended period, associated with prolonged secretion of stress hormones and biological subsequent events, which constitute as risk factor for Alzheimer disease, type 2 diabetes, cardiovascular disease, cancer and posttraumatic stress disorder (PTSD).\[^{8-10}\] however, the clinical importance remains controversial due, at least to difficulties associated with conducting standardized human behavioral studies. Recent studies further disclose that some tumor cells contain all the enzymes for the adrenaline synthesis and are capable to secrete adrenaline after stimulation. Others, suggest that various stress-related persistent stimulations might accelerate cancer progression, by adrenergic system activation.\[^{11,12}\]

2. THE ROLE OF ADRENERGIC MEDIATORS ON PERIPHERAL ORGANS

Physiologically both NE and E have a significant roles in regulating the microenvironment of peripheral organs. Therefore, the function of peripheral tissues can be modulated by different stress mediators. For example, ovarian tissue which being a common example for most conditions of reproductive system cancers, in which, the overall concentrations of catecholamines are substantially higher than in plasma. In addition, the levels of catecholamines in ovaries are known to be elevated in response to stress due to increased sympathetic activity, which aid in the appearance of precystic follicles. Similarly, high levels of catecholamines are found in bone marrow microenvironment, secreted from both nerve endings and bone marrow cells. They contribute in modulation of hematopoiesis within the bone marrow microenvironment through activation of adrenergic receptors (ADRs).

Actually, β-adrenergic receptors (ADRBs), have been identified on several cancer cell types, including breast and ovarian cancer cells, where they mediate many effects of catecholamines on target cells.\[^{13}\] Recently, a study using preclinical models of chronic stress reported that both NE and E are elevated in a sustained fashion in ovarian and other peritoneal tissues, and such elevation was related to greater tumor burden and increased angiogenesis in response to adrenergic signaling pathway induce an increase of intracellular cAMP.\[^{14,15}\]

2.1 Beta Adrenergic Signaling and Cancer

A distinct biochemical pathways of catecholamine signaling are mediated through α, and β-adrenergic receptor (BADR) families.\[^{16}\] There are three subtypes of (BADR) categorized as β1, β2, and β3, which have been identified at many sites of tumor growth and metastasis, including adrenal gland, brain, lung, liver, kidney, bone marrow, breast, ovary, prostate, lymphoid tissues, and vasculature. Signaling through β-adrenergic receptors, was reported to
perform regulatory functions of several cancer-related cell types, as vascular myocytes and pericytes, fibroblasts, epithelial cells, neural and glial cells, and most lymphoid and myeloid immune cells. Where, ligation of β-receptors by their specific ligands (NE and Ep), activates the G as guanine nucleotide-binding protein and stimulation of adenylyl cyclase occur to yield cyclic AMP (cAMP). Transient flux of cAMP subsequently regulates a range of diverse cellular processes by two main downstream effector systems (Fig. 1).

1- Protein Kinase (PK) pathway; Activation of (PKA) phosphorylates several target protein molecules involved in different levels of cellular functions, ranging from general metabolism and growth to cell specific processes, including differentiation, morphology, motility, secretion, neurotransmission, and gene transcription.\textsuperscript{[17]} The transcription process and expression of genes are mediated by PKA-induced phosphorylation of transcription factors which gathered approximately 20% of human genes.\textsuperscript{[18]}

2- Mitogen-activated protein kinase (MAPK) pathway; this pathway also could be activated by PKA. Accordingly, processes as inflammation, angiogenesis, and invasion mediated predominantly by PKA pathway inducing genes encoding cytokines and growth factors. whereas, (MAPK) pathway effects involve cell morphology and motility.\textsuperscript{[19]}

\textbf{Figure 1. The β-adrenergic signaling pathway in cancer}\textsuperscript{[17]}
2.2 Regulation of tumor by β-adrenergic

Recent evidence indicated that tumor progression, induced by several cellular and molecular processes, in which the activated β-adrenergic system is the major player. Where, Its involved in recruitment of macrophages into the site of primary tumor,\textsuperscript{[20]} expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and IL-8 by tumor cells and immune cells,\textsuperscript{[21]} angiogenesis, tissue invasion by matrix metalloproteinase (MMP), tumor cell mobilization and motility. However, some evidence suggest that β-adrenergic signaling can also suppress DNA repair signaling pathway, and immune functions of cytotoxic T-lymphocyte and natural killer cell responses.\textsuperscript{[22]} In this way, the SNS activation can regulate a wide range of cancer-related molecular pathways via direct regulation of (BADR) bearing cells including both tumor cells, those present in the tumor microenvironment, such as macrophages and vascular cells, by both circulating norepinephrine/epinephrine as well as, via local norepinephrine release from SNS nerve fibers, however, growing evidence suggests that the final dynamic plays a dominant role in this situation.

As previously documented, that human ovarian carcinomas substantially showed higher norepinephrine levels in tumor tissue than its level in blood.\textsuperscript{[23]} Moreover, intratumor norepinephrine levels rather than blood levels correlate with patient psychosocial risk factors and with tumor gene expression profiles. Such observations indicated the primary role for local nerve fiber derived norepinephrine in driving β-adrenergic effects on tumor biology. This was supported by histologic analyses of catecholaminergic fibers of human breast and ovarian carcinomas, where extensive perivascular innervation and nerve fibers into the tumor parenchyma were observed. Others, showed similarities in the pattern of SNS innervation with that present in other solid tissues like lymph nodes, where, chronic stress increase spreading of SNS nerve fibers within parenchymal tissue, suggesting the direct regulatory effect of NE to β-adrenergic receptors on cancer biology by affecting; i- tumor cells in primary tumor microenvironment, ii- the activities of stromal cells mainly tumor-associated monocytes and/or macrophages and iii- gene expression. This beside their systemic action at metastatic target sites. However, activated macrophages can also synthesize catecholamines. Therefore, some β-adrenergic influences on tumor biology may originate outside the tumor via SNS innervation. Accordingly, blocking of beta adrenergic receptor may suppress systemic support for tumor progression and provide adjuvant potential for Chemotherapy.\textsuperscript{[24-26]} Recent studies focused on the relationship between adrenergic system and tumorigenic
processes like proliferation and apoptosis in addition to angiogenesis and vasculature normalization which are important for cancer cell invasion and metastasis.

In general, the adrenergic system involve in progression of cancer by several ways including;

A- Promotion of cell proliferation and evasion of apoptosis
A growing investigations suggested that stress hormones NE/E display a tumor-promoting function. As they induce migratory activity of different cancer cells, pancreatic, colonic, mammary, and prostate carcinoma cells. Furthermore, norepinephrine up regulates the release of vascular endothelial growth factor (VEGF) and interleukin-6 and -8 in melanoma cells pointing to a more aggressive potential of the cells.\(^{27-29}\)

B- Induction of angiogenesis
The pathological condition of cancer usually distract the balance towards more stimulatory angiogenic factors, so that result in uncontrolled angiogenesis from normal blood vessels that give rise to immature vascular structures. Adrenergic mediators were proven to up regulate the expression of pro-angiogenic vascular endothelial growth factor VEGF to induce tumor angiogenesis and aggressive growth. Other, identified that other factors contribute in angiogenesis; as interleukin 6 (IL-6), IL-8, matrix metalloproteinase (MMP)-2 and MMP-9 also can be elevated by catechols-induced adrenergic receptor signaling in a diversity of cancer cells. Which indicated that an amplified cascade of events might exist among these factors which may synergistically fortify angiogenesis and aggressive development of tumors.\(^{30-32}\)

C- Enhancement of invasion and metastasis
Studies conducted on cancer cell lines and experimental models of metastasis suggested that, activation of adrenergic system seems to involve in each step of the cancer invasion-metastasis cascade. As they found a significant increase in extracellular matrix degradation by stress hormones, which accelerate cancer cell invasion and migration. A process mediated by induction of the release of MMP-2, MMP-7 and MMP-9.\(^{33}\)

3- ACCUMULATION OF DNA DAMAGE BY βAR-MEDIATED STRESS RESPONSE PATHWAY
Adrenergic receptors are prototypical G-protein-coupled receptors (GPCRs) that are identified in different sites of the body including brain, skeletal muscle and bone marrow.\(^{34,35}\) where they regulate numerous physiological processes mediated through Gs-
cAMP-PKA pathway. However, continuous stimulation of these receptors suggested to be the underlying cause behind receptor desensitization as a part of adaptation to their excessive activation. Desensitization carried out by G-protein-coupled receptor kinase (GRK)-dependent phosphorylation, which usually followed by the recruitment of β-arrestins, an independent signal transducers which have roles in receptor desensitization and subsequent internalization.\(^{[36,37]}\)

Recent molecular study identified a novel molecular mechanisms by which chronic stimulation of βAR activates signaling pathways, which trigger DNA damage and degrade pro-apoptotic gene p53, that finally leads to accumulation of DNA damage (Fig. 2), one of important mechanisms involve in DNA damage due to stimulation of βAR; is the production of reactive oxygen species by NAD(P)H oxidase, activation of adenylyl cyclase (AC) and PKA signaling (the downstream targets of the β2AR-Gprotein signaling cascade) and the promotion of oxidative stress via the suppression of antioxidative mechanisms. Thus, upon chronic secretion of catecholamines and stimulation of βARs, G-protein cascades lead to increased oxidative stress and also there is possible decrease of p53 levels through β-Arrestin 1 (βArr1)-mediated activation of PI3K/AKT signaling that lowering genome maintenance and increasing DNA damage.\(^{[38,39]}\)

Figure 2. Schematic diagram of β2AR-dependent regulation of DNA damage in the catecholamine-mediated stress response.
Catecholamine released in response to stress activate β2AR and its downstream signaling pathways which initiate activation of both Gs-PKA signaling and cytosolic β-arrestin-1 (βArr1)-mediated activation of PI3K/AKT signaling, that subsequently phosphorylate and activate Mdm2. within nucleus facilitate Mdm2-mediated nuclear degradation of apoptotic factor p53. Meanwhile, stimulation of β2AR leads to production of reactive oxygen species by NAD(P)H oxidase, and activation of adenylyl cyclase and PKA signaling promotes oxidative stress. Thus, these two independent G-protein and β-arrestin-mediated pathways synergistically increase accumulation of DNA damage.[38]

4-THE ROLE OF β-BLOCKERS IN CANCER

The β-blockers, which are antagonists of β1- and/or β2-adrenergic receptors, are widely prescribed therapeutic agents for the chronic treatment of heart failure, in which they act via poorly understood mechanisms to afford cardioprotection.[40]

Interestingly, clinical and epidemiological studies suggest that β-blockers have additional therapeutic benefits. For example, chronic β-blocker therapy is associated with lower incidences of prostate cancer and reduced metastasis, tumor recurrence and specific mortality in breast cancer.[41] In addition they found that treatment with propranolol after trauma provided potential inhibition of either or both downstream signaling cascades. While, genetic deletion of G prorein or arrestin mediated singnaling pathways revealed effects similar to that produced by β-blockade.[42,43]

Preclinical animal study showed that behavioral stress in mice increases ovarian tumor growth, and this effect is inhibited by administering β-blocker propranolol. Other study showed a significant decrease of post-ischemic brain injury in a mouse stroke model for middle cerebral artery occlusion (MCAO), administering the β2AR-selective β-blocker or genetic deletion of β2AR decrease post-ischemic brain injury.[42] These effects are, at least in part, mediated through inhibition of a β2AR-β-arrestin-1 signaling cascade pathway. Actually, β-blockers have been developed as antagonists for βARs, mainly targeting G-protein signaling.

Later findings indicated the therapeutic potential of β-blockers, also targeting effects of β-arrestin-1 signaling that affects p53 levels and genome integrity during chronic stress. Treatment with the β-blocker propranolol has been recently used as an effective therapy for an infantile vascular tumor, hemangiomas, causing regression of tumor.
In clinical situation, Within the last two years, a number of retrospective epidemiological studies have found that chronic use of beta-blocking drugs is associated with lower recurrence and mortality of breast cancer or reduced progression and mortality of breast cancer and malignant melanoma. Three earlier studies also suggested beneficial effects from prolonged use of beta blockers on general cancer risk or on prostate cancer risk. [44,45]

It was reported that non-selective blocker propranolol significantly reduced the primary tumor development, nodal/metastatic occurrence and breast cancer-specific mortality but not for beta1-blocker atenolol. The finding also suggests that beta2-adrenergic pathway is a predominant mediator for the therapeutic action of propranolol.

Collectively, these findings are both provocative and encouraging. They are provocative because beta blockers, which have been used clinically for decades worldwide, are typically taken to treat heart-related disorders, such as arrhythmias and hypertension, not cancer. They are encouraging because beta blockers may represent a “new,” and relatively safe, category of drugs for the prevention and possible treatment of a range of cancers, while also shedding light on the pathophysiological basis of some types of cancer. [46]

However, all such studies take into account the historical record of beta-blocker usage by the patient, regarding the use of different beta-blocking drugs, which vary in their specificity for different beta adrenoceptors, such as beta1 and beta2, may differentially affect cancer outcome in both preclinical and clinical settings.

One beta blocker that has been used in a number of preclinical oncology studies, propranolol, blocks both beta1 and beta2 receptors.

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are responsible for extracellular matrix remodeling in a dose-dependent manner, which could be blocked by an MMP inhibitor and propranolol that showed significant decrease in MMP-2 activity in a phorbolmyristate acetate-activated human leukemic cell line.

Propranolol-induced growth inhibition was associated with cell cycle arrest, and repressed gastric cancer cell growth through the downstream inhibition of MMP-2 and MMP-9. This finding was supported by previous study which was reported that NE induced expression of MMP-2 and MMP-9, and these effects were inhibited by propranolol in model of pancreatic cancer cells, as well as in human colon adenocarcinoma cells. [47] suggesting the role of β-
adrenergic antagonists in the pathological process of cancer by downregulating the level of MMPs and regulating the level of tissue inhibitors of metalloproteinases.

The MAPK pathways; a signaling pathway that affect gene expression and involve in cell division. This pathway significantly activated in renal cancer specimens compared to control group specimens, with considerable increase in tumor diameter and grade indicating a direct correlation with MAPK expression.

Propranolol was found to suppress hemangiomas and angiogenesis associated with cancer progression by interrupting the cAMP/MAPK pathway and the inflammatory process induce cancer.\[48\]

5. CONCLUSION
Catecholamine hormones secreted during chronic stress activate β2ARs and activate downstream molecular events of both G-protein and β-arrestin-1 signaling pathways. A process that may result in development of human disorders as cancer. In this direction later studies showed that the β-blockers can inhibit DNA damage accumulation in response to stress. Accordingly, blocking of beta adrenergic receptors may represent an attractive therapeutic approach to prevent/block/ameliorate the negative consequences of stress. So beta blockers as a class of well-defined conventional drugs used for cardiovascular diseases in the past decades, may hold a considerable promise to treat patients with some cancers in the future.

REFERENCES


