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Review paper

Is Stress a Causative Agent of Cancers?: A Mini Review

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Abstract

Background and Aim: Stress has long been considered a potential influencer of cancer, but its role remains complex and uncertain. This review aims to comprehensively evaluate stress as a causative factor for cancer, a perspective that has not been thoroughly explored. The innovative aspect of this study lies in its holistic assessment of stress as a potential cancer inducer.

Method: This review systematically gathered and analyzed scientific literature to investigate stress as a potential cancer inducer. It focused on stress's impact on cancer initiation, progression, and metastasis. Inclusion criteria ensured study quality and relevance. Stress-related variables and molecular mechanisms were assessed, adhering to systematic review guidelines.

Results: While stress appears to have substantial effects on cancer processes, the research landscape has yielded ambiguous results, often showing weak or no correlation between stress and cancer incidence, metastasis, or progression. This raises the question of whether stress is a critical biological agent in cancer etiology, a topic that demands further investigation.

Conclusion: The relationship between stress and cancer remains intricate and inconclusive. While stress seems to exert significant influences on cancer processes, the existing body of research has produced mixed findings. More studies are essential to determine whether stress plays a pivotal role as a causative factor in cancer development. Further research can potentially provide clarity on this complex interplay between stress and cancer.

Keywords: *Chronic, Acute, Stress, Neuroendocrine, Cancer*

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Introduction

Since many years ago, researchers have considered stress as an important effector of cancer initiation and progression [1]. Based on Hans Selye study, stress is a body response for returning to homeostasis which occurs through induction of the sympathetic nervous system (SNS) as well as the hypothalamic–pituitary–adrenal (HPA) axis. This lead to local release of adrenergic agents like adrenaline (also called epinephrine) as well as systemic release of these factors from sympathetic nerve axons and the adrenal medulla ,frequently noradrenaline (norepinephrine), the glucocorticoids secretion (like cortisol) from the adrenal cortex, as well as the opioids, oxytocin and other stress-mediating agents secretion [2]. Table 1 has summarized the neuroendocrine hormones and related receptors in different cancers.

Table 1. Neuroendocrine hormones and related receptors in different cancers

Neuroendocrine Hormones	Neuroendocrine Receptors	Cancer Type	References
NE	β2-AD	Breast, prostate, ovarian, and colon tumors	[3], [4], [5], [6]
EPI	β2-AD	Ovarian tumor	[3], [4]
Cortisol	Glucocorticoid receptor	Breast and prostate tumors	[7], [8], [9]
Prolactin	Prolactin receptor	Endometrial, breast, and prostate tumors	[10], [11], [12]
Oxytocin	Oxytocin receptor	Small cell lung (SCLC) tumor and Kaposi's sarcoma	[13], [14]
Dopamine	D2-receptor	Neuroblastoma, melanoma, breast, head and neck tumors	[12], [15], [16], [17], [18], [19], [20]

Stress responses start processing of various stressors by the central nervous system (CNS). It can contain inner-body responses to different situations, like tissue damage under anesthesia and surgery, or being at inconvenient temperature; extrinsic stimulating agents include happening something offensive, or being known of giving a life threatening disease like cancer; or even continuous CNS activities, because of being worried or thoughtful about financial problems, social isolation, problematic relationships, or suffering from tumors. It is important that depression and social isolation lead to stimulation as well as/or deregulation of the HPA axis, and can be specified by pro-inflammatory factors [21], which induces pathways alike stress responses [22]. These changes lead to cancer initiation and progression.

In this regard, it is very important to notice that based on some definitions, stress has been divided into two main types which lead to completely different kinds of responses; acute and chronic. Acute stress is defined as a short time one lasting from minutes to maximum hours, but chronic one last more, maybe days to months or even more [23]. But, the distinction acute stress from chronic one is very difficult in most cases as chronic stress induction in animal models are usually based on alternative or repeated acute stressors not long term ones. Beside this, there is no unique definition for these two expressions in medicine or psychology [24]. For example, 3–5 continuous days of acute stress considered as both acute [24] as well as chronic [25] stress. Furthermore, chronic social isolation as a chronic stress elevates reaction to acute stress such as short time restraint, which shows mutual reciprocal association between them. Acute stressors may produce chronic stress perceptions and/or responses in humans especially with pre-occur expectation as well as post-occur ruminations [26]. In the tumor-leading mechanisms, this overlapped nature of acute as well as chronic stressors, and their psychology results, can distort the distinction between

them as well as their effects on cancer behaviors [27]. Therefore, in the context of cancer any generalizations for acute and chronic stress responses need special caution.

But, in general, we can say the stress has great effects on cancer initiation, progression, and metastasis which are mediated through β-adrenergic signaling and a lesser HPA axis signaling [28]. Stress even affect the tumor cells and their niches and microenvironment; such as immune and stromal cells [2]. So, it is necessary to do a comprehensive study to evaluate the role of stress in cancer progression.

- *Catecholamines, α and β- Adrenergic Receptors*

Effector molecules such as norepinephrine (NE) and epinephrine (EPI) as catecholamines effects on tumor development, progression, as well as metastasis [29], [30], via α and β-adrenergic receptors, especially the β2-adrenergic receptor [30].

Some of the most important sources of catecholamines are the sympathetic nervous system, adrenal medulla [30], and keratinocytes which attach to adrenoceptors as the G protein-coupled receptors. Adrenoceptors are divided into two main subgroups, α and β, that each one categorizes into three subtypes according to their pharmaceutical and structural characteristics, as well as mechanism of action [31]. The first one is the α1-adrenoceptor subtype that plays key role in the cardiac and smooth muscle investment, blood pressure regulation, muscle contraction, nasal congestion, as well as prostate activity. In the most cases, the α1- adrenoceptors (α1A, α1B and α1D) induce phospholipase C via the Gq/11 proteins which lead to release of accumulated calcium, as well as finally, stimulate protein kinase C [32].

α1-adrenoceptors exist in the SK-Mel23 human melanoma cell line whereas α2-, β1- and β2-adrenoceptors exist in normal human melanocytes [33]. It also apply mitogenic functions on human as well as rodent vascular smooth cells, rodent hepatocytes, human cardiomyocytes as well as pheocromocitoma PC12 [34]. Along with this finding, Zhao et al. showed that metaproterenol can enhance melanocyte proliferation, tyrosinase function as well as, TRP-1 production as a β2-adrenergic agonist. Although the α2-adrenergic antagonist yohimbine reduced the tyrosinase activity, without influencing on cell growth [35].

In contrast, some of studies show that catecholamines inhibit tumor cell proliferation maybe via the adrenergic receptor or the dopamine transporter [36]. For example, α1-adrenoceptors may reduce proliferation in human hepatoma, astrocytes, embryonic kidney as well as CHO cells [37]. melanoma cell treatment with the 1-adrenergic agonist phenylephrine reduced proliferation in a dose-dependent manner that could be compensated by prazosin, 1-adrenergic antagonist [36]. Based on study of Pifl et al. , norepinephrine stimulated neuroblastoma cells to produce the dopamine transporter to block proliferation via entering into the G0/G1 phase [38].

On the other hand, β-adrenergic signaling can elevate apoptosis resistance as a cancer hallmark and β-adrenergic antagonists can stimulate pro-apoptotic pathways. For example, propranolol as a non-selective β-blocker in cultured liver cancer cell lines of HepG2 as well as HepG2.2.15, led to apoptosis, poly ADP–ribose polymerase cleavage, caspase 3 down-regulation, and S-phase arrest [39].

β-Adrenergic signal transduction can also cause cell motility as well as trafficking as well as induce invasion and metastasis. For instance, NE treatment led to invasiveness of many breast cancer cell lines. But, in contrast, NE decreased the invasiveness as well as migration of oral squamous cell carcinoma cell lines (SCC-9 and SCC-25) in a dose-dependent manner [40]. Rivero et al. represented ambiguous results, because after treating human breast cancer cell lines with salbutamol as a β2-agonist, and propranolol, anti-migratory and anti-metastatic effects were observed [40]. In another study, agonists of β-adrenergic signal transduction decreases the

deformation of various tumor cells like solid and metastatic human breast cancer cells, ovarian, melanoma, prostate, and leukemia cells as an invasion marker. EPI and NE also elevated gastric cancer cell proliferation as well as invasion *in vitro*. In the other word, EPI and NE elevated the migration of gastric cancer via an up-regulation of metastasis protein [41].

Moreover, Behavioral stress activates β-adrenergic signaling that leads to tumor angiogenesis via histone deacetylase-2 (HDAC2) as an epigenetic suppresser of Thrombospondin-1. HDAC2 is also necessary for angiogenesis induced by β-adrenergic signaling. β-adrenergic signaling activates HDAC2 as a target of cAMP response element binding protein (CREB) in vitro and in prostate cancer xenograft mice [42]. β-Adrenergic signaling can lead to vascular remodeling and angiogenesis as a key prerequisites for tumor progression, because tumor cells need an adequate amount of oxygen and nutrient, as well as the repel of their wastes. A lot of pro- and anti-angiogenic agents like; vascular permeability factor (VPF), interleukin (IL)-8, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-α and β, platelet-derived growth factor (PDGF), angiogenin, fibroblast growth factor (FGF), and β-adrenergic signaling adjust angiogenesis. Chronic stress can also change lymphatic vessels in a way that lead to tumor escape. These vessels also help tumor dissemination [43].

β-Adrenergic signaling can even affect cancer cell energy. Cancer cells can be characterized by their modified energetics because of their metabolic reprogramming such as the elevated glycolysis as well as the Warburg effect, which occurs even under anaerobic conditions. NE and EPI significantly affect the metabolic reprogramming of cells, specifically by modulating the production of HIF-1α, p53, as well as sirtuin 1 (SIRT1). NE and EPI also regulate glucose metabolism in a way that sufficient glycemia is kept off even during hypoxia in tumor macroenvironment, through signaling cascades which target transcriptional complexes that adjust the metabolic regulator genes expression [44].

- *Sources of Norepinephrine (NE) and Epinephrine (EPI) and Their Mechanisms of Action*

Psychosocial stress leads to adrenergic stimulation, tumor induction, and progression [29] via stimulation of several molecular and cellular procedures. For example; increase of NE and EPI hormones in the tumor microenvironment mostly leads to cancer progression. Nearly all tumor markers defined by Hanahan and Weinberg are affected by β-adrenergic signal transduction. On the other hand, the tumor microenvironment can synthetize NE [45]. Recently, novel cancer-specific sources have been discovered for NE; For instance, neuronal progenitor cells which are located in the central nervous system (CNS) infiltrate prostate cancer tissues. The very same neurons convert to adrenergic cells. Or sensory neurons among cancer tissues have the potential of the reprogramming to adrenergic ones. So, these neurons are the producers of NE or EPI in the tumor microenvironment [46].

The β-Adrenergic signaling of NE or EPI causes genome instability, mutation, and attenuation of DNA damage repair process which can lead to malignant transformation as a result of the DNA damage accumulation. Based on Lamboy-Caraballo et al. investigation, NE induced double-strand DNA damage but no single ones in epithelial ovarian cancer cells [29]. In an in vitro study, Flint et al. showed the molecular effects of short-term exposure (less than 30 min) of murine 3T3 cells to natural concentrations of EPI and NE lead to more than more DNA damage in these cells compared to control untreated ones [47]. Whereas alike Lamboy-Caraballo et al. [29], pre-treatment with propranolol decreased the damage. But, there was no significant effects of these two hormones on cell cycle control. At the end, targeted gene arrays confirmed that NE and EPI changed the transcription of DNA damage signaling pathways genes such as increase of checkpoint kinase 1 and 2, as well as the proto-oncogene cell division cycle 25 A in cell cycle

delay after DNA damage [47]. Hara et al. suggested the mechanisms of these compounds on genomic stability, which was the stimulation of Gs–protein kinase A (PKA) and β-arrestin-mediated pathways following the stimulation of β2-adrenergic receptors by EPI or NE, DNA damage trigger, and decrease of p53, so they synergistically caused the DNA damage [48].

β-Adrenergic signaling such as NE, EPI, and their agonists can also potentiates sustained proliferative signaling as an essential process in various tumor development or progression (e.g., gastrointestinal, prostate, melanoma, and glioblastoma [49]) in in-vitro and in-vivo studies [50]. NE and EPI induces the intracellular cyclic adenosine monophosphate (cAMP)/PKA signaling pathway that activates proteases and agents such as rat sarcoma viral oncogene homolog (Ras)-extracellular signal-regulated protein kinases 1 and 2, phosphoinositide 3-kinases/protein kinase B, activator protein 1, signal transducer and activator of transcription 3 (Stat3), nuclear factor-κB, p38 mitogen-activated protein kinase (P38/MAPK), cAMP-response element binding protein (CREB), VPF, interleukin 6 as well as 8, and metalloproteases that may influence cancer cell proliferation and differentiation following Gαs-coupled β-adrenergic receptors stimulation [49], [50]. However, NE and EPI do not stimulate all kinds of cancers' progression. The pro- or anti-proliferative influences of NE and EPI in breast tumor depends on at least two factors: first, the experimental cancer model and second, the type of stimulated adrenergic receptor [50]. Furthermore, in the tumor microenvironment, other types of stromal cells also have β-adrenergic receptors, so, they cause tumor cell proliferation [51].

Moreover, tumor cell treatment with NE or EPI over-expressed VFP in vitro. And propranolol reversed the NE- and EPI-pro-angiogenic effects. NE and EPI induced M2-polarized phenotype of macrophage which increased VEGF production and stimulated tumor angiogenesis [52].

- *Glucocorticoids*

Behavioral stress can stimulate glucocorticoid secretion which lead to tumor growth [25]. Glucocorticoids (like cortisol) are secreted from the adrenal cortex as a result of stress-induction of the SNS and the HPA axis through hypothalamic corticotropin-releasing hormone (CRH) and the CNS which process physiological and psychological stressors, trigger responses which lead to release of endorphins, oxytocin, prolactin, vasopressin, adrenocorticotropic hormone (ACTH) as well as systemic ACTH release causes glucocorticoids' secretion [2].

Some stressors lead to DNA damage, jeopardize DNA repair, and lead to malignant transformation. Specifically, stressed mice serum, or adrenaline, noradrenaline and cortisol (separately or in combination), increased DNA damage and/or reduced DNA repair after UV exposure of a mouse fibroblast cell line. Glucocorticoid response can also lead to p53 down regulation and increase apoptosis resistance after ionization irradiation [53]. Some of human tumor cell lines showed DNA damage after β-adrenergic as well as glucocorticoid signaling [29], via the ATR–p21 pathway activation. Merely DNA damage will not cause cancer initiation, mutations which transmit to next generation and lead to apoptosis resistance can lead to cancer [2].

Figure 1 has summarized the mode of action of chronic stress on cancer progression.

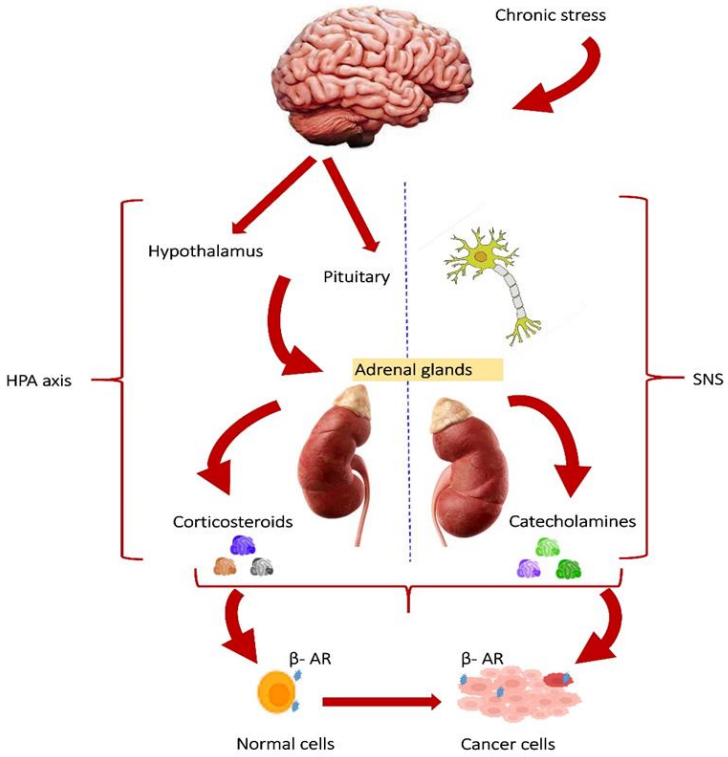

Figure 1. Stress-mediated neuroendocrine response in cancer (β-AR: β-Adrenergic receptors)

Conclusion and Future Perspective

Clinical trials as well as epidemiological investigations represented ambiguous results, or found weak or no correlation between stress and cancer incidence, metastasis, or its progression. Therefore, in the present, physicians do not regard to stress prevention as a means in controlling cancer. This may be an important subject that whether stress is a critical biological agent causing cancer etiologically. Recent animal studies have approved that stress can accelerate growth and metastasis of a lot of cancer types via presenting solid evidence and in this regard, countless molecular, cellular, and endocrine mechanisms have been recognized. For instance, based on animal studies, stressors induce most significant cancer hallmarks [1], and that responses to different stresses can lead to more cancer progression and metastasis through directly changing molecular biology and the microenvironment, tumor cells [54], immune system activity and even indirect mediators in this way. Furthermore, some of the natural responses to acute stress elevated the metastasis risk in animal models [2]. In people suffering from cancer, stress activates a lot of mentioned events [55], [56], bolding the clinical importance of current outcomes.

To sum up, tumors can produce nerve growth factors which can elevate the sympathetic innervation and noradrenaline to make a feed forward loop. Tumor, stromal, as well as immune cells express the membrane-embedded β-adrenergic receptors (β-ARs) that bind to EPI, NE, as well as intracellular glucocorticoid receptors (GRs). Stress factors can stimulate most tumor hallmarks. In addition, active β-ARs and GRs also activate the E3-ubiquitin ligase MDM2 which degrade p53, leading to accumulation of DNA damage. With regards to the importance of the role of stress in different pathways, more investigation like metaanalyses and clinical trials is highly recommended to understand the role of stress in human cancer.

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Conflict of interests
Authors declare no conflict of interest.

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