

Effects of Stress on Colorectal Cancer and Related Medications

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Abstract: Colorectal cancer (CRC) ranks among the highest commonly diagnosed cancers globally. Meanwhile, with the acceleration of modern life rhythms, people's mental health is deteriorating. This article aims to explore the connection between mental stress and the genesis and development of CRC as well as discuss relevant medications. Through literature analysis, it is found that chronic stress has capacity of triggering not only the sympathetic nervous system (SNS) but also the hypothalamic-pituitary-adrenal (HPA) axis, giving rise to enhanced levels of cortisol and catecholamines, which promotes tumor and angiogenesis metastasis, resulting in the genesis and development of CRC through all kinds of mechanisms, including dysbiosis of intestinal flora, triggering of inflammatory responses, and stimulation of colorectal epithelial-mesenchymal transition. In addition, stress-related behavioral changes, such as dietary habits, may cause an increased risk of cancer. In terms of drug research, beta-blockers such as propranolol and antidepressants such as tricyclic antidepressants (TCAs) have shown certain anti-CRC potential. In conclusion, new approaches to CRC prevention and treatment have been developed with the help of a thorough comprehending of the link between mental stress and the disease as well as the enhancement of CRC patients' quality of life.

Keywords: Mental stress, CRC, gut flora, antidepressants, propranolol

1. Introduction

One of the most prevalent cancers is colorectal cancer (CRC), and today it is the third most prevalent and deadly cancer in the world, accounting for about 1/10 of all cancers diagnosed globally, according to data field [1]. CRC is made up of tumor cells, non-tumor cells (such as stromal cells) as well as a substantial amounts of microorganisms, and the genes that transform healthy mucosa into cancer are brought about by mutations in genes that suppress tumors (APC, CTNNB1, p53) and the oncogene (KRAS) [2].

At the same time, mental stress acts as an important factor during the genesis and progress of CRC. Mental stress is also known as psychological stress. The concept of “stress” was first introduced by physiologist Selye in 1985. He discovered how stress affects the body's physiological processes and stated that when the body is exposed to stress, it produces specific physiological in addition to psychological reactions like tense muscles, raised blood pressure, and an accelerated heartbeat. When these stressors exceed the body's ability to respond, health problems such as depression, anxiousness, hypertension, coronary artery disease, etc., occur. Selye called this “General Adaptation Syndrome” (GAS).

Whereas stress is usually categorized as acute stress, which typically lasts anywhere from a few minutes to a few hours and is associated with sudden, short-term, single, non-repetitive offenses, chronic stress, in contrast, typically lasts for weeks or years and is the result of prolonged and often repetitive exposure to psychological or physiological stressors, is regulated by a variety of neurochemical systems, leads to endocrine and behavioral responses, and is strongly associated with the ability to fight cancer closely related [3]. Chronic stress promotes cancer growth and spread when CRC develops.

This paper systematically compiles and analyzes how mental stress (especially chronic stress) affects the development of CRC and how psychotropic drugs improve it thus prevent people from developing cancer.

2. Chronic stress effects the mechanism of CRC development

2.1. Mental stress dysregulates gut flora that leads to CRC development

The intestinal microbiota, which facilitates the digestion of nutrients and protects the body from food-originated gastrointestinal flora in the human body, is very rich in number and type, and so far, the bacteria found in the human intestinal tract consist of the following nine phyla: Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria, Verrucomicrobia, Unclassified Bacteria similar to Cyanobacteria, Spirochaete, and VadinBE97. Through long-term evolution and mutual adaptation with the host, the intestinal microbiota maintains a balance among the environment, bacteria, and the host. However, any changes in the host's immunity or environmental factors can disrupt this balance, alterations in the intestinal microbiota's structure can also alter the intestinal milieu, harm intestinal epithelial cells, and eventually result in cancer and inflammatory bowel disease [4].

At the same time, the human intestinal microbiota has three major characteristics: diversity, stability, and self-repair ability. Among them, diversity helps maintain the stability of the microbiota structure, making the ecosystem less likely to be disturbed by external factors under normal physiological conditions; when the microbiota is imbalanced due to environmental changes, host immune abnormalities, and other factors, its inherent restorative mechanism can restore the microbiota to its original balanced state or reach a new dynamic balance. In the process of the occurrence and development of CRC, the imbalance of the intestinal microbiota is not a random phenomenon but a passive adaptive adjustment to the pathological environment [4,5].

There is a close relationship between the adverse effects of mental state and intestinal microbiota dysbiosis, which can cause microbial community disorders. Some related neurotransmitters produced in the intestine, including serotonin, glutamate, and gamma-aminobutyric acid (GABA), are closely related to mental stress. In contrast, both acute and chronic stress can influence the gut microbiota's overall biomass and composition. Even just 2 hours of contact with acute stress can significantly change some colonic mucosa-associated microbiota and reduce the relative proportion of major microbiota phyla [6]. It is well known that chronic stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis, prompting cortisol to be generated continuously, which increases intestinal permeability and makes it easier for metabolites of germs to penetrate the intestinal mucosal barrier. Studies have shown that chronic stress may exacerbate intestinal dysfunction by altering colonic motility and further upsetting the homeostasis of the intestinal microbiota [7]. At the same time, under mental stress, the abundance of *A. muciniphila* and its related metabolite butyrate in the intestinal microbiota significantly decreases, and the supplementation of such substances can greatly reverse the cancer stem cells caused by mental stress [8]. Besides, chronic stress may additionally hinder the central amygdala from becoming active and reduce the regulation of vagal neurons on the Brunner's

glands of the duodenum, leading to a decrease in *Lactobacillus* and weakening the intestinal barrier function, ultimately increasing the risk of infection [9].

Moreover, chronic stress can also cause intestinal microbiota dysbiosis and lead to CRC by affecting dietary habits and lifestyles. According to studies, chronic stress triggers the HPA axis, which results in continuous cortisol release. This suppresses satiety signals and increases desires for foods high in fat and sugar. At the same time, the function of the lateral habenula nucleus of the brain is suppressed under chronic stress, leading to the continuous activation of reward signals and driving "comfort eating" behavior [10]. Extended intake of high-fat diets might reduce the quantity of beneficial microbes which produce short-chain fatty acids (SCFAs), such as *Clostridium leptum*, while increasing the abundance of cancer-promoting bacteria such as *Fusobacterium nucleatum* [11]. The paragenetic link between the intestine and the microbiota can be upset by such environmental changes, which can lead to inflammatory bowel illness or CRC [2].

Overall, mental stress can contribute to CRC by disrupting the gut microbiota.

2.2. Chronic stress triggers an inflammatory response that leads to CRC

Cancer cells may secrete more pro-inflammatory cytokines in response to mental stress, and inflammation can accelerate the development of cancer by causing DNA mutations, oxidative stress damage, and cytokine release. Similar to this, immunological alterations brought on by stress can also promote the migration and synthesis of numerous pro-inflammatory substances in the tumor microenvironment, these consist of interleukin (IL)-6 and tumor necrosis factor (TNF- α). Besides, there are some prolonged inflammatory conditions related to cancer, such as ulcerative colitis (UC) and chronic gastritis, which indicate a close connection between stress and CRC.

Inflammatory indicators can be raised through chronic and acute stress, although chronic stress is more detrimental. Chronic stress can permanently stimulate the sympathetic nervous system (SNS) and HPA axis, promoting the secretion of hormones as well as neurotransmitters like catecholamines (typically including norepinephrine, epinephrine, and dopamine) and glucocorticoids, thereby disrupting the physiological microenvironmental homeostasis and affecting immune cell function, leading to increased intestinal permeability and local immune dysregulation [12,13]. At the same time, continuous HPA activation leads to high cortisol levels, which disrupts the "brain-gut axis" (BGA) in the gastrointestinal tract, ultimately leading to irritation and inflammation of the mucosal inner wall and poor food digestion and absorption. The resulting mucosal inflammation can cause immune system disorders, which over time can evolve into chronic inflammation [14]. Moreover, under chronic stress stimulation, the hypothalamus is stimulated to secrete corticotropin-releasing hormone (CRH), and CRH, whether as a product of long-term activation of the HPA axis or as a peripherally secreted neuropeptide, comes to play a crucial role in regulating intestinal immune responses by way of neuroimmune crosstalk regulating BGA function.

Among them, the most prevalent prolonged idiopathic inflammatory disease is inflammatory bowel disease (IBD), which is capable of affecting the lower gastrointestinal tract, leading to chronic colitis. This condition is intimately linked to a high risk of acquiring CRC that also rises with the length of IBD. At the same time, IBD, which may take the form of Crohn's disease (CD) or UC, is also a significant risk factor for CRC development. In contrast to the general public, people who suffer from IBD have a multiple times higher risk of developing CRC [15]. In addition, chronic stress is capable of causing loss of intestinal homeostasis and inappropriate immune activation, leading to the development of IBD and ultimately CRC.

Generally, immune imbalance in the intestinal milieu is thought to be the primary cause of the development and spread of cancer, particularly CRC. Certain pro-inflammatory cytokines can promote reactive nitrogen intermediates (RNI), reactive oxygen species (ROS), and other gene-toxic substances in the chronic inflammatory milieu of the colon, which can lead to carcinogenesis. These

can eventually show up as damage to DNA or as stimulation of the ability to survive signaling networks of inflammatory mediators, especially Akt, STAT3, and NF- κ B [16].

2.3. Chronic stress stimulates colorectal epithelial-mesenchymal transition that leads to CRC development

Numerous adrenergic receptor types can be found on the surface of CRC cells, and these types of receptors might play a role in mediating the biological modulation of catecholamine-related hormones on CRC cells. Tumor cells undergo the trans-differentiation mechanism known as epithelial-mesenchymal transition (EMT), causing them to change from epithelial to mesenchymal phenotype, which enhance the tumor's invasive and metastatic abilities. The majority of CRC exhibits infiltrative growth, which is closely related to EMT, and EMT often occurs at the infiltrative front of CRC. During EMT, different transcription inhibitors regulate the transcription of epithelial cadherin (E-cadherin), such as ZEB1, the most significant component in inducing EMT in CRC. Research has demonstrated that EMT triggers the endoplasmic reticulum (ER) stress response mechanism, whereby long-term stress can indirectly activate β -catenin or HIF1 α , therefore inducing ZEB1, the EMT phase, and ER stress, all of which raise the tumor cells' survival rate [17].

P53 is one of the most important cancer suppressor genes and is involved in regulating the EMT process in tumor cells. According to studies, chronic stress stimulates the increase in adrenaline secretion, activating β -adrenergic receptors, which suppresses p53 protein expression. At the same time, colorectal tumor formation is facilitated by the β 2-adrenergic receptor (ADRB2) on the surface of CRC cells. Thus, chronic stress may encourage tumor cells to undergo EMT by inhibiting the expression of p53 protein in cells [18].

Therefore, chronic stress can induce and stimulate the EMT transformation of tumor cells, ultimately affecting the development of CRC.

3. Application of psychotropic drugs

Common psychotropic drugs include non-selective beta-adrenergic receptor antagonists such as propranolol and antidepressants such as tricyclic antidepressants. Current research has demonstrated their influence on the occurrence and development of CRC to a certain extent.

3.1. The role of beta-receptor antagonists in CRC

As a non-selective retardant of beta-1 and beta-2 receptors for adrenergic substances, propranolol (prop), exerts its effect by competitively antagonizing these receptors. The blocking-up of receptors for beta-adrenergic affects fundamental signaling pathways that regulate the tumor microenvironment, with the core mechanism being the inhibition of sympathetic nerve activity. Research has demonstrated that prop inhibits tissue from producing p-AKT, p-ERK, and p-MEK from tumors and activates autologous CD8⁺ T lymphocytes to prevent the formation of CRC [19].

Additionally, in recent years, some studies have confirmed the resistance influence of prop on CRC. Prop no more demonstrated anti-tumor benefits in immunodeficient naked mice, but it has been demonstrated to greatly reduce T cell fatigue in animals with strong immune capacity in the tumor specimens of two well-established CRC models [20].

Furthermore, combining various medications has already become a more viable therapeutic strategy to get increased effectiveness and decreased toxicity. For instance, prop and an oncolytic virus therapy together increased anti-angiogenic activity and produced a synergic lethal impact on CRC cells [21]. Prop and the COX-2 inhibitor etodolac simultaneously suppressed CRC from spreading to the liver [22]. Prop can also be combined with irinotecan hydrochloride (CPT-11), a sort

of first-line medication to treat CRC, which exerted the strongest inhibitory effect on the progression of CT26 tumors [20].

3.2. The role of antidepressants in CRC

Antidepressants are currently also known as "neuromodulators" and belong to the category of psychotropic drugs. Clinically, they are mainly classified into five categories: tricyclic antidepressants (TCAs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), atypical antidepressants, specific serotonin reuptake inhibitors, and norepinephrine.

The most common ones are TCAs, SSRIs, and SNRIs. TCA is named for its unique chemical structure, which consists of three rings with one side chain. It is further classified into tertiary and secondary amine subtypes. Following absorption in the small intestine, TCA undergoes further liver metabolism. They are widely bound to proteins and eventually interact with other protein-bound drugs. At the same time, they are widely distributed throughout the systemic circulation, leading to systemic effects, including central nervous system symptoms. Studies have shown that TCA can inhibit the development of CRC by regulating intestinal microorganisms, affecting the level of metabolites of the flora, and at the same time regulating the neuroendocrine level of the body through the medium of the BGA to maintain the normal microenvironment of the intestine [23].

In addition, SSRIs, as autophagy regulators for the growth of many types of cancer, are frequently utilized in cancer sufferers who experience chronic stress. SSRIs have anti-inflammatory properties and exert anti-inflammatory effects through three mechanisms: first, they have the ability to suppress the activity of transcription factors that promote inflammation, including NF- κ B and STAT3; second, by blocking cytokines like IL-6, IL-8, IL-1 β as well as TNF- α , they can reduce the destruction of lung tissue and the recruitment of pro-inflammatory cells; and finally, they can directly inhibit inflammatory cells, including T cells, thrombocytes, and macrophages [24]. Meanwhile, both SSRIs and SNRIs can improve intestinal motility, secretion, and sensory functions by increasing the local release of 5-hydroxytryptamine (5-HT) in the gastrointestinal tract, thereby affecting the occurrence and progress of CRC [23].

Regarding the three categories of norepinephrine and specific serotonin reuptake inhibitors and atypical antidepressants, some studies have revealed their therapeutic effects on gastrointestinal diseases and also demonstrated their potential anti-cancer and anti-tumor properties, but the specific mechanisms remain unclear.

4. Conclusion

This study has summarized that mental stress, especially chronic stress, facilitates the genesis and development of colorectal cancer (CRC) by causing gut microbiota imbalance, triggering inflammatory responses, and stimulating colorectal epithelial-mesenchymal transition (EMT). In response to these mechanisms, psychotropic drugs such as the beta-receptor antagonists like propranolol (prop) and antidepressants like TCAs and SSRIs can inhibit CRC through different mechanisms, thereby achieving preventive and therapeutic effects. However, the current research still has significant limitations. For instance, prop's ability to resist tumors in CRC is mainly based on animal models and small-sample clinical observations, lacking large-scale randomized controlled trials to verify its efficacy and safety; while SSRIs (such as fluoxetine) can indirectly affect CRC by relieving stress, the direct mechanism of their impact on CRC development remains unclear, and long-term use may cause complex metabolic interactions due to the regulation of gut microbiota.

Future research should break through in the following directions: Firstly, a systematic analysis of the molecular association network between mental stress and CRC should be conducted, especially

the interaction mechanism between stress signaling pathways (such as the HPA axis) and tumor EMT and immune escape. Secondly, multiple clinical trials should be carried out to evaluate the preventive potential of psychotropic drugs in high-risk CRC populations and their synergistic therapeutic effects in cancer patients, while paying attention to the accuracy of dosage and individualized medication differences. In addition, a multimodal intervention strategy combining gut microbiota regulation (such as probiotic intervention) and psychological behavioral therapy (such as mindfulness-based stress reduction) may be one of the options; ultimately, by integrating psychological, oncological, and pharmacological research, it is expected to provide innovative and clinically feasible intervention targets for the prevention and treatment of CRC.

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