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The substrate of the biopsychosocial influences in the carcinogenesis of the digestive tract

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Abstract

Digestive cancer represents a severe public health problem, being one of the main causes of death. It is considered a multifactorial disease, with hereditary predisposition, environmental factors, and other factors involved in carcinogenesis. Both the evolution and the pathogenesis of digestive neoplasms remain incompletely elucidated. As a multifactorial disease, it can be approached by taking into account the biopsychosocial influences via enteric nervous system. Many peptides and non-peptides having a neurotransmitter role can be found in the enteric nervous system, which can influence the neoplastic process directly or indirectly by affecting some angiogenic, growth, and metastasis factors. However, neurotransmitters can also cause directly, through intercellular signalizing, the angiogenesis, the proliferation, and the digestive neoplasms' metastasis. This new approach to neoplasms of the digestive tube assumes broader psychosocial factors can play an important role in the understanding the ethiopathogenie, the evolution of the disease, and determination of possible molecular targeted therapies; it also suggests that behavioral strategies may be important for maintaining a healthy state with respect to the digestive tract.

Keywords: enteric nervous system, neurotransmitters, carcinogenesis, biopsychosocial influences

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Introduction

Digestive cancer represents a serious public health problem. Epidemiologically 20% of the cancers involve the digestive tract, and this represents over 25% of the deaths caused by cancer (1). Digestive cancer is considered a multifactorial disease, with hereditary predisposition, environmental factors and other factors involved in carcinogenesis. Both the evolution and the pathogenesis of digestive neoplasms remain incompletely elucidated.

On the other hand, currently there is a trend of replacing the disease's classic etiological pattern with a view that assumes a biopsychosocial approach. Although the idea of the mind playing a role in the etiology of diseases was initially marginalized, Western medicine is increasingly viewing the mind and the body as linked within an integrated system, the disorder of which causes pain (the way a person detects changes in his health condition) and disease (2). According to biopsychosocial view, symptoms, despite the fact they can have a multiple pathophysiological determinism, can be affected by both the sociocultural and psychological influences (3). This idea is not new: the approach of making connections between the psychological influences and cancer originates from the Greek doctor Galen, who in the Ian century before Christ observed that so called melancholic women developed breast cancer more frequently than those with the other behavioral types (4).

Many studies have described both the involvement of the nervous system in the modulation of tumor progression and the possible signalizing mechanisms from tumors to nervous system (5,6,7). Despite this, much remains unexplained. Here we attempt to highlight some of the interactions between the central nervous system and digestive tract carcinogenesis. This new way of understanding the initiation, progression and tumor metastasis, represents in biopsychosocial terms, a new way to approach and manage the disease. This paper attempts to demonstrate the pathophysiologic substrate which is under the influence of the nervous system, the center of all mental activities/processes.

Discussion

Brain-gastrointestinal tract axis

The gastrointestinal tract has its own nervous system called the enteric nervous system. This system is entirely disposed in the intestinal wall, starting from the esophagus to the anus. About 100 million neurons are part of the enteric nervous system, almost the same number as in the spinal cord (8). However, there are also other neuronal networks which control the digestive functions, networks that are ordered in four main levels of

integrative organization (2). If the first level is represented by the enteric nervous system, the second level is the paraspinal sympathetic ganglia, where peripheral reflex arcs are influenced by sympathetic preganglionic fibers, which originate from the spinal cord. The next two levels are part of the central nervous system. At the third level, sympathetic and parasympathetic efferents towards the intestine are caused, at least partially, by reflexes with the afferent arc represented by sensory fibers which follow the path of autonomous nerves. The fourth level is represented by superior nervous centers that generate descendant signals, which are integrated with the sensory afferent signals at the third level (9).

Neurotransmitters and digestive cancer

Many peptides and non-peptides having a neurotransmitter role are found in the enteric nervous system (10). Recent studies usingimmune-histochemicalmethods have identified neurotransmitters for some neurons in gastrointestinal tract, their presence or their absence representing a method of classifying the enteric neurons (11). In attempt to deepen the understanding of the multiple functions of the enteric nervous system, researchers worldwide have identified more than twelve substances acting as neurotransmitters, substances that are being released from the different enteric neurons endings (8). Among these are: acetylcholine, norepinephrine, adenosine triphosphate, serotonin, dopamine, cholecystokinin, P substance, vasoactive intestinal polypeptide, somatostatin, leuenkefalina, metenkefalina and bombesin. The actions of many of theseare not sufficiently well known (8).

Due to the link between nervous elements and blood vessels in tumor tissues, and to the influence of certain neurotransmitters on tumor cells, some authors refer to a neuro-neoplasic synapse (12,13,14). Via some neurotransmitters, locally released stimulating or inhibitory influences over the activity of neoplastic cells may exist. On the other hand, changing the balance between stimulating and inhibitory neurotransmitters can confirm this assumption (15).

The influence of neurotransmitters on the neoplastic process can be exercised directly or indirectly by affecting elements of angiogenic, growth and metastasis factors. But neurotransmitters can cause directly, through intercellular signalizing, the angiogenesis, the proliferation and the digestive neoplasm’s metastasis (15).

In vitro studies show that norepinephrine, dopamine and P substance increase the proliferation rate of cells in colon neoplasm (12,16). Catecholamines act on the digestive system by stimulating beta-adrenergic receptors. This binding is responsible for the activation of adenylatecyclase via Gs protein, which is responsible for the increasing the intracellular concentration of AMPc (17). This acts like a signal or second messenger

transducer which changes, in turn, the percentage of several enzyme-catalyzed reactions. The final result is represented by the upregulation of angiogenetic factors (18,19).

Angiogenesis is a complex process that includes several stages, each having an important role in the progression and metastasis of digestive neoplasms (20). Several factors initiate and sustain this process: VEGF (vascular endothelial growth factor), bFGF (basic fibroblast growth factor), aFGF (acidic fibroblast growth factor), PDGF (patelet-derived growth factor), HGF (hepatocyte growth factor), Ang-1 (angiopoietin-1), but also other factors which can be involved in the angiogenesis cascade (21). The most important factor is VEGF, with many studies indicating an overexpression of the vascular endothelial factor, which appears after the stimulation of beta2 adrenergic receptors (22-26).

Metalloproteinases represent another protein group with enzymatic activity which leads to the progression and metastatis of digestive neoplasms (27). Their primary role is to degrade the tissue from the tumoral microenvironment that allows, on one hand, tumoral progression and, on the other hand, remodeling tissues among blood vessels (28,29). Their level, as well as the level of VEGF, can be increased by stimulating beta-adrenergic receptors (17).

On the other hand, acetylcholine can cause directly or indirectly, the overexpression of some growth, angiogenic and proliferation factors in neoplastic cells (30,31,32). Noteworthy is that acetylcholine, by activating M3 muscarinic receptors and by stimulating metalloproteinase-7 (MMP-7), can cleave heparin binding epidermal growth factor receptors (HB-EGF) from Pro-HB-EGF (33). A way of intercellular signalizing is thus activated which results in the transcription of some genes responsible foruncontrolled proliferation and of the avoidance of apoptosis by neoplastic cells (34,35,36).

Besides the neurotransmitters mentioned above, others are also found. Several studies show that surgical or chemical denervation of different segments of the digestive tract negatively influence carcinogenesis at that level (37,38).

Psychological factors and neoplasm

Many neurotransmitters implicated in carcinogenesis are also associated with negative psychological factors, which themselves may be relevant factors for the patient's health. The past decades have been characterized by a progressing interest regarding stress' effects over the gastrointestinal tract, as explored in both human and animal studies (39). In rodents, stress affects hydric homeostasis and natural defense barriers, and it increases the permeability of mucous, allowing their penetration by bacteria (40). Clinical studies

show that negative psychological factors affect the onset, promotion, progression, and metastasis of tumors (41). Studies also show that through sympathetic nervous mechanisms and through the chronic activation of hypothalamic-pituitary-adrenal axis, the immune response is affected. In this way, deficiencies in the DNA repairing mechanisms appear, with the alteration of the function of some important genes implicated in cellular replication and in apoptosis (42). It has been observed that drugs such as adrenergic system blockers or prostaglandins reduce the effects mediated by stress in carcinogenesis (43).

Brain-mast cell axis in malignant tumors of digestive tract

Currently, the connection between brain and mast cell provides a more plausible mechanism to explain the evident relation between stress and defining symptoms of irritable bowel syndrome (2). Inflammatory mediators released by these cells access and influence ENS, via paracrine changes of electric and synaptic behavior of enteric neurons (44). Evidence of brain-mast cell connection is offered by the Pavlovian conditioning possibility of mast cells degranulation (45). The influence of the CNS over the mast cells from the superior digestive tract is also suggested by the increasing concentration of histamine at their level when the vagus nerve is being stimulated (46). Electrical stimulation of spinal afferents in the small intestine causes histamine releasing from mast cells, an effect mediated by P substance's action on neurokinin-1receptor, which is being expressed on the surface of mast cells (47, 48).

Studies have also demonstrated that mast cells play an important role in carcinogenesis by releasing inflammatory cytokines which affect tumor progression, angiogenesis, and metastasis (49). In 2009, research suggested that mast cells can be the target of neoplastic therapy (50). More recently in 2010, the infiltration of pancreatic tumors with mast cells has been associated with a poor prognosis (51). Another study performed in the same year showed that gastric cancer malignity is correlated with tumor and peritumoral infiltration degree with mast cells (52).

Conclusions

Cancer of the digestive tube represents one of the major problems currently facing society. This multifactorial disease and may be best studied by taking into account the biopsychosocial influencesvia enteric nervous system.The enteric nervous system is permanently linked not only with the central nervous system, but also with the other neuronal networks such as sympathetic and parasympathetic autonomic nervous system.

Influences of the central nervous system (both those sociocultural and psychological) can be reflected in the carcinogenesis process through both

the interaction with the enteric nervous system and through mast cells.This new approach to neoplasms of the digestive tube plays an important role in the understanding the ethiopathogenesis, the evolution of the disease, determination of possible molecular targeted therapies and also determination of some behavioral cues for sustaining good health status.

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