International Journal of Public Health Science (IJPHS)
Vol.2, No.1, March 2013, pp. 17~22
ISSN: 2252-8806

Tumors, Neurotransmitters and Pharmacology: Interactions and Implications

Abdelaziz Ghanemi
Department of Pharmacology, China Pharmaceutical University, Nanjing 210009, China
Department of Pharmacy, Faculty of Medicine, Mentouri University of Constantine, Constantine 25000, Algeria

Article Info

Article history:

Received Nov 21, 2012
Revised Jan 6, 2013
Accepted Jan 22, 2013

Keywords:

Tumor
Neurotransmitter
Pharmacology

ABSTRACT

Tumors represent a challenge for the modern therapies, and divers studies have shown that different factors are involved in both tumorigenesis and processes of tumor development. Therefore, further investigations and descriptions of inter-influences and interactions between the nervous system, the tumoral process and pharmacotherapies might lead to novel advances and applications, not only in the therapeutical approaches but also in the experimental design.

Corresponding Author:

Abdelaziz Ghanemi,
Department of Pharmacology China Pharmaceutical University, No. 24 Tong Jia Xiang, Nanjing, 210009, Jiangsu Province, The People's Republic of China.
Mobile : 008613776688144
E-mail: ghanemiabdelaziz@hotmail.com

1. INTRODUCTION

Tumors constitute a major health problem, and due to the complex mechanisms tumoral processes involve, this area remains full of challenges for both modern medical practice and pharmacological researches. However, biochemical and genetic descriptions of tumorigenesis and tumor development, similar to what has been suggested for normal organ homeostasis, should be regarded as a result of constant and mutual interactions between tumor cells and their surrounding microenvironment. In fact, in addition to the complex physiological and biochemical factors tumoral processes involve, numerous observations concluded that tumor cells, as biological entities, interact with their surrounding cells, lymphatic circulation, blood circulation and nervous system. For instance, lymphoangiogenic factors influence the metastatic process [1], whereas tumor cells have the ability to foster neoangiogenesis [2]. Thus, the concept of limiting the tumors development via drugs that stop blood supply [3, 4] came out.

Since novel neurological aspects of tumors were more elucidated, many evidences have further shown that tumors growth process is also related to the nervous system. Indeed, The existence of nerve endings within bladder [5], eye [6], prostate [7], breast [8, 9], pancreatic tumors [10] and also within other types of cancers like colon cancer [11, 12] illustrates well such concept. More important, numerous neurotransmitters influence tumor vascularization [13, 14] and cells migration[15, 16], in addition, they may also suppress the immune response in cancer [17]. These influences are increased by the ability of the cancer cells to secret neurogenic factors [18-20] which influences neurons development.

Among the known neurotransmitters, which are likely over 100 [21], some constitute important factors of tumoral processes such as cells migration, stimulation and proliferation. Moreover,

immunomodulation theories suppose that a potential targeting of those neurotransmitters' receptors by pharmakons might lead to new therapies especially if pharmacologic elements, such as the factors that influence the function of those receptors, including receptor surrounding chemical environment and the kind of cell junctions [22], are defined within a tumor context and then, taken into consideration during the related pathogenesis description and the drugs development approaches.

2. NEUROPHARMACOLOGY AND ANTITUMOR THERAPIES

A number of illustrative findings and advances exemplify the increasing potentials that neuropharmacology has among the existent antitumor therapies. For instance, the study of serotonin, which is excessively synthesized by breast cancer cells to sustain their growth [23], and the corresponding signaling system, has led to new therapeutics such as the three serotonin receptor inhibitors paliperidone, pimozide and risperidone that might have an adjunctive role in glioblastoma treatment via growth factors deprivation[24]. As a second example, whereas the activation of the β-adrenergic receptors (βAR) could modulate both development and progression of ovarian cancer [13, 25] and mammary tumors cells [26, 27], it increases the metastasis process in breast, lung and colon cancer models [28-30]. Moreover, epinephrine and norepinephrine, which are βAR agonists, induce the secretion of vascular endothelial growth factor (VEGF) and interleukin-6(IL-6) by cancer cells [13, 31, 32] thus, illustrate the impact of the two βAR agonists on cell growth and proliferation. Importantly, a preventive effect of propranolol (a β-blocker) on the development of pancreatic ductal adenocarcinoma in mice [33] has been reported which, therefore, presents β-blockers as potential candidates for the treatment of some catecholaminergic system-related tumors. Other studies, on the effects of both nicotine and 4-(methylnitrosoamino)-1-(3-pyridyl)-1 butanone (NNK, a tobacco-specific nitrosamine) on human small cell lung cancer (SCLC), suggested a link between tumors processes and autonomic nervous system [34]. Consequently, laboratories are investigating the potential use of acetylcholine receptor antagonists as an anticancer therapy. The results showed that some muscarinic antagonists have the ability to stop tumor progression in nude mice [35], whereas NSCLC nicotinic acetylcholine receptor (n-AChRs) antagonists have a pro-apoptotic effect on NSCLC [36]. Furthermore, muscarinic acetylcholine receptor M_3 (M3R) antagonists might constitute an adjuvant for SCLC treatment [37] and, together with previous observations, strengthens the promising area of oncological neuropharmacology.

Additionally, many temporal cells express glutamate and glutamate receptor subunits. Such cells constitute tissues of colorectal cancer [38, 39], glioma cancer [40-42], gastric cancer [43], prostate cancer [44], oral squamous cell carcinoma [45], melanoma [46, 47] and osteosarcoma [48]. Importantly, glutamate has been shown to play a role in cancer [48, 49], thus we may target glutamate receptors to obtain an anticancer pharmacotherapy. Whereas cancers such as colon, gastric, ovarian and breast cancers have an increased gamma aminobutyric acid (GABA) content [50-53], numerous papers have pointed a correlation between the GABAergic system and both oncogenesis [54, 55] and tumor cells migration [56], indicating a local antitumor effect of GABA [57, 58]. Therefore, GABA and its analogues, such as baclofen, constitute candidates to anticancer therapy and drug development [59]. Another neurotransmitter, which is the dopamine, plays also an important role within the neuro-tumoral interactions and has effects on both cancer growth and anticancer drugs. Indeed, it blocks VEGF–induced angiogenesis of endothelial progenitors in the bone marrow [60, 61], in addition, dopamine contributes in the growth diminution of other cancers such as stomach, breast and colon cancers [60, 62]. Furthermore; dopamine, if given with conventional anticancer drugs, like doxorubicin or 5-fluorouracil (5-FU), produces synergistic effects [60] which shows the important role of dopaminergic pathway within cancer pathogenesis.

Another neuro-oncological interactions example is represented by tachykinins pathways. Tachykinins are synthesized by neuronal, endothelial, and epithelial cells, in addition of macrophages [63]. In human species, tachykinins system includes substance P (SP), neurokinin A, neurokinin B and their receptors that are NK1, NK2 and NK3 respectively [63]. Among tachykinins system constituents, SP and its receptor NK1 are overexpressed in several cancers including breast, ovarian, prostate, pancreas, thyroid cancers and glioblastoma [63]. While SP and its receptors confer oncogenic properties to breast cancer cells [64-67], the proliferation of the cancer cells has been shown to be the result of NK1 receptors' activation by SP. Therefore, the pharmacologic applications that inhibitors, of either NK1 binding to SP [68] or SP activity [69], are under investigation to provide new therapeutic arsenal [70].

Not only neurotransmitters, but also different active compounds (mainly drugs), interfere, either directly or indirectly, with the tumor process. Such compounds might interact with the neuronal networks as agonists, antagonists or other kind of neuro-activity modulators, thus influence the tumors prognoses in many ways depending on specific factors including the drugs' pathways and dosages, in addition of the nature of the neurotransmitters implicated within the drugs' mechanisms.

3. TUMORS AND PSYCHIATRY

As described above, there are both complex and deep reactions and interactions between several neurotransmitters and cancer processes. Moreover, among those neurotransmitters, some might either influence or be influenced by some therapies. Because neurotransmitters' concentration and secretion are strongly linked to the pschycological and the psychiatric profiles of the patient; the mood, for example, constitutes an important factor that can strongly influence tumoral processes [13, 71, 72]. Such influence is due to the changements of the neurotransmitters' activity that accompany the psychological or the psychiatric variations. These variations may also modify the anticancer drugs' effects and eventually, have an impact of the therapy efficacy. For example, the concentration of epinephrine and norepinephrine increases as a consequence of psychological and social pressures [73], which is likely to enhance the probability of the cancer initiation [25, 74]. Such approach needs further investigation, especially in the light of the different investigations that describe the psychiatric disorders as neural system dysfunctions [75], thus suggest that a factor (or a drug) that interfere with an element of this neural system (receptor, enzymatic pathway…etc) might influence the other elements of the same neural system's network that include the neurotransmitters and therefore, interfere with the tumoral process.

Following this line of thought, and due to the impact they have on tumoral process, pschycological and psychiatric profiles should be taken into consideration mainly during both drugs-testing investigations and therapeutical approaches [70] for oncology studies, especially that the same anti-tumor treatment may not have the same efficacy inside a population because the psychological or the psychiatric variations that exist between the individuals of this population.

4. PERSPECTIVES

Descriptions of both clinical and physiological aspects of the possible interactions between neurotransmitters, tumors evolution and therapeutic mechanisms, together with the new elements about the different onco-biological systems and their related molecular and enzymatic pathways, will surely contribute in further elucidating the related pathogenic and pharmacodynamical phenomena, therefore, lead to novel explanatory theories. Such approach might constitute the starting point of new therapies via screenings of potential chemical, natural or immunological agonists and antagonists of the different tumor-related neuroreceptors. Some chemicals, used in laboratories as regents or solvents, and for which biological and pharmacological properties have been reported [76] , could represent candidate to antitumor drug development as well and, thus might require more investigations.

On the other hand, the strong interactions between the pharmacological factors, the oncological profile and the neurological status, in addition to the complexity of the neuronal networks implicated within the different oncogenesis pathways, make that the understanding of the related pharmacovigilance requires a high level of expertise. Both a detailed description of such pharmakons' mechanisms of actions and whether they target and modify the tumor-related neuronal network system, remain highly important in any future drug design, on the one hand, and control the side effects due to the neural system complexity and interactions, on the other hand.

Following this line of thought, strong and continuous collaborations between different experts, including psychologists, pharmacologists, neuroscientists and oncologists, will lead to the emergence of a new field within the modern medical sciences that would combine the divers factors implicated in the tumoral process. Such field could provide data and assistance not only for clinicians, to design appropriate treatments schema, but also for researchers to optimize their experimental conditions.

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AUTHOR BIOGRAPHY

Abdelaziz GHANEMI was born on October, 11th, 1986 in Algiers (Algeria). He finished his elementary and high school education in Constantine (Algeria). In 2004, he graduated with the Secondary Education Baccalaureate Degree with honors (Good). In 2009, Abdelaziz GHANEMI graduated from the Medicine Faculty of Mentouri Constantine University (Algeria) with a Pharmacist Diploma (Valedictorian). From September 2009 to June 2010: Chinese language Class at China Pharmaceutical University (Nanjing city, Jiangsu Provence, China). From September 2010 to June 2013: Master's degree (Msc) candidate majoring in Pharmacology at China Pharmaceutical University (China). In addition to Arabic (mother tongue), Mr.GHANEMI has English, French and Chinese language proficiency certificates. The author does research and has publications about both pharmacology and neuroscience-related fields.