DOI: 10.23925/1984-4840.2017v19i3a3 **Review /** *Revisão*

Synthetic phosphoethanolamine as an inhibitor of tumor progression

A pesquisa com a fosfoetanolamina sintética como inibidor da progressão de tumores

Natália Aparecida Oliveira Caetano[1], Thamyres Cavajes Moreira[1], Leila Aidar Ugrinovich[1], Thais Adriana do Carmo[1], Patrícia Ucelli Simioni[1]

ABSTRACT

Introduction: Synthetic phosphoethanolamine (SP), known as "the cancer pill", was presented as a promising medicine for the treatment of tumors. This substance directs its mechanism of action towards the cell membranes by the transduction of signals and metabolism of lipids, which results in apoptosisinduction. **Objective:** The present study evaluated articles that indicated the use of SP as an inhibitor of the progression and dissemination of tumor cells. It also reviewed the possible mechanisms associated with the action of the molecule on the treatment of tumors. **Method:** The work is a narrative, exploratory and integrative bibliographic review, based on the following databases: Virtual Health Library, Google Academic, PubMed and Scientific Electronic Library Online (SciELO). Inclusion criteria: complete articles available in Brazilian and international literature, with the words: SP and tumors. **Results:** The search found a total of65 articles, and, after an analysis of the sources using the method described above, 19 articles describing the effects of synthetic phosphoethanolamine and the possible mechanisms associated with the action of SP on tumors were selected. **Conclusion:** Phosphoethanolamine is a lipid compound found in high concentration in tumors and is associated with a high rate of apoptosis. Preclinical research studies seek to validate the use of SP for tumor treatment. To date, there is no evidence that supports the efficacy of SP in neoplasms. Clinical studies showing the use of SP to treat tumors are essential for the validation of SP. In April 2017, as SP did not show any clinical efficacy in preliminary trials and clinical trials supported by São Paulo Cancer Institute, studies were suspended with the agreement of the Brazilian Health Regulatory Agency (ANVISA, Brazil).

Keywords: ethanolamines; drug evaluation; antineoplastic agents; neoplasms; apoptosis; drug screening assays, antitumor.

RESUMO

Introdução: A fosfoetanolamina sintética (FS), conhecida como pílula do câncer, foi apresentada como promissora do tratamento de tumores. Essa substância tem seu mecanismo de ação voltado para as membranas celulares pela transdução de sinais e metabolismo de lipídeos que resultam na indução da apoptose. **Objetivo:** O presente trabalho avaliou os artigos da literatura que relacionam o uso da substância fosfoetanolamina sintética (FS) como inibidor da progressão e disseminação de células tumorais no Brasil. Buscou-se também descrever os possíveis mecanismos associados com a ação da molécula para tratamento de tumores. **Método:** O trabalho é uma revisão bibliográfica, narrativa, exploratória e integrativa, nas bases de dados Biblioteca Virtual de Saúde, Google acadêmico, Pubmed e Scientific Electronic Library Online (SciELO). Critérios de inclusão: artigos completos disponíveis na literatura nacional e internacional, com palavras FS e tumores. **Resultados:** A partir de resultados de busca com 65 artigos, foram selecionados 19 artigos. Após análises das fontes de informações acima, foram selecionados os artigos que descreveram os efeitos da fosfoetanolamina sintética e os possíveis mecanismos associados com a ação da FS para tratamento de tumores. **Conclusão:** A fosfoetanolamina é um composto lipídico em elevada concentração em tumores, associada com elevada taxa de apoptose. Pesquisas pré-clínicas buscam validar a utilização da FS para tratamento tumoral. Até o presente não há dados que comprovem a eficácia da FS em neoplasias. Estudos clínicos relacionados ao uso da FS em tumores são essenciais para validação do uso da FS. Em abril de 2017, A FS não mostrou eficácia clínica em ensaios preliminares e os testes clínicos foram suspensos pela ANVISA.

Palavras-chave: etanolaminas; avaliação de medicamentos; antineoplásicos; neoplasias; apoptose; ensaios de seleção de medicamentos antitumorais.

[1]Faculdade de Americana (FAM) – Americana (SP), Brasil.
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INTRODUCTION

Tumors are formed by an accumulation of genetic mutations that occur mainly by the action of external agents.[1] These alterations appear mainly in specific genes called oncogenes, which are inactive in normal cells. When activated, they become responsible for transforming normal cells into tumors.[2] All tumors have chromosomal and genetic alterations, as well as the ability to transmit, during their multiplication, malignant mutated genes[1]. Tumor development is characterized by manifestations of physiological changes such as insensitivity to growth inhibition, escape from apoptosis and self-signaling to growth, causing uncontrolled replication, angiogenesis and metastasis formation.[3]

The most common treatments for tumors are radiotherapy, chemotherapy and surgery with a focus on eliminating tumor cells in order to begin the regression of tumors, usually through the association of more than one type of treatment[2]. However, studies are being carried out with the purpose of finding new methodologies for the treatment of tumors, as well as to better understand the mechanism of action of these therapies in the eradication of the disease.[4]

Organic phosphoethanolamine, found in the brain in normal amounts and in tumors in 10-fold greater amounts, is involved in phospholipid metabolism. It is a precursor of phosphatidylethanolamine and phosphatidylcholine, compounds of the cell membrane.[5] These molecules are involved in the regulation of cell division, signaling, activation, autophagy and phagocytosis. Phosphatidylethanolamine and phosphatidylserine translocate themselves from the inner portion to the outer region of the plasma membrane, thus generating a signaling mechanism of apoptotic cells for subsequent elimination by macrophages.[3]

Information disclosed by studies has indicated synthetic phosphoethanolamine (SP), known by the lay public as "the cancer pill", as a tumor cell marker. It indicates that it has an antiproliferative action that stimulates apoptosis and prevents tumor progression. Recent studies aim to evaluate the therapeutic potential of this molecule. They report that SP has antiproliferative and pro-apoptotic effects, inhibiting tumor growth without causing hepatic or hematological toxicity.[6] This molecule was proven promising for the treatment of tumors, since, unlike conventional methods, its mechanism of action is directed toward cell membranes (and not to DNA) through the transduction of signals and metabolism of lipids that result in the induction of apoptosis.[3]

However, it is known that this experimental substance has not yet been extensively tested in clinical trials since it needs approval from the Brazilian Health Regulatory Agency (ANVISA), the agency responsible for the regulation of health-related products and services. This substance caused much controversy that led to the emergence of several questions related to the release and use of SP by the public. Moreover, the manifestation of several researchers and health professionals who have divergent opinions about preventing or encouraging the use of the drug has also generated wide debate. At present, studies aim to prove the benefits or disprove the prejudices of the substance in the treatment of tumors. For this reason, the objective of this study was to evaluate articles that describe the benefits and prejudices of the use of SP as an inhibitor of the progression and dissemination of tumor cells. The present work aimed to evaluate the scientifically based state of the art of the research with phosphoethanolamine and describe the possible mechanisms of action of SP in tumor treatment.

METHODS

The present work is a bibliographic review, that is narrative, exploratory and descriptive in nature, where information available in scientific databases is presented and discussed, aiming to analyze and evaluate articles published in scientific journals related to SP. A retrospective study was carried out through bibliographic review of publications, scientific articles and government institutes which have been written about the subject, preferring articles published from 2012 to 2016, in Brazilian and international journals. Content-based analyzes were carried out by consulting the Virtual Health Library, Google Academic, PubMed and Scientific Electronic Library Online (SciELO).

The articles of greatest relevance to the study were selected based on the following descriptors: SP, phosphoethanolamine. Information collection took place from March to November, 2016. The inclusion criteria was published papers, preferably from 2012 to 2016, which approached subjects pertinent to the research. A total of 65 articles were found, of which 19 papers were selected according to their partial relevance to the focus of the present study. A thorough reading of the articles was performed. After analysis of the sources aforementioned, the articles that presented the terms SP and treatment of tumors and the possible mechanisms associated with the action of SP for the treatment of tumors were selected. Articles older than 5 years were excluded.

RESULTS

Neoplasia is defined as changes in bodily cells causing them to grow disorderly and to form a mass of tissue with no apparent function for the body. These changes result from mutations in DNA, causing changes in factors that control growth, development and cellular behavior.[5] In most cases, this process of altering cellular DNA is due to external factors such as radiation, food and stress that affect the cellular renewal and differentiation of the organism. This causes a disorder in its multiplication without the activation of the cellular apoptosis.[3] Malignant tumors, in general, may present the capacity to invade other tissues beyond which the process of formation. This migration and proliferation of tumor cells to another site is termed metastasis.[3,5]

Phosphoethanolamine and its role in the body

Cells need energy to survive and, for this, they use metabolic processes. The most used and effective one is oxidative phosphorylation (OP), through the Krebs cycle pathway. In eukaryotes, most of the ATP produced by catabolism

comes from OF in the mitochondria. Therefore, OF is of extreme importance for the regulation of ATP in order to adjust to the fluctuating cellular demand for energy.[5]

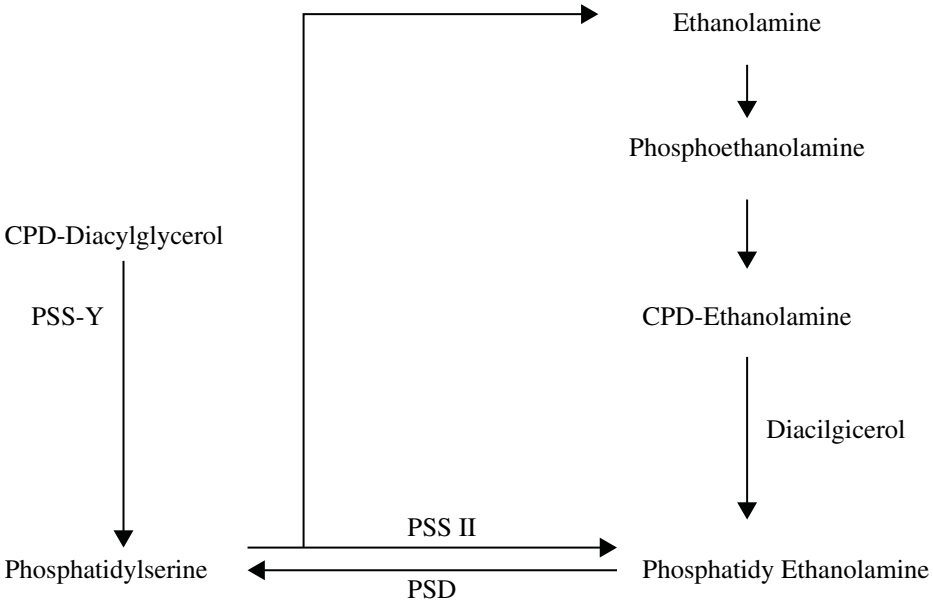
When a carcinogen injures the mitochondrial membrane, electrons escape, feeding the generation of free radicals, consequently causing DNA damage and the tumor initiation phase.[5] Tumor cells are able to reprogram the metabolic energy in order to stimulate cell division and proliferation. In order to satisfy their energetic demand, tumor cells prefer the glycolytic pathway of energy production compared to OP.[7] With mitochondrial membrane injury, OP also decreases, thus predominating anaerobic glycolysis.[5] In tumor cells, an ATP reduction can be observed in the cytoplasm. This is because OP provides energy to cytosol while the glycolytic pathway provides ATP to the nucleus. This behavior results in a process of perpetual cell division, the main characteristic of tumor cells.[5] Also, apoptosis plays an important role in the maintenance of tissue homeostasis and resistance to apoptosis is a characteristic of tumor cells.[8]

Phosphoethanolamine, also known as 2-aminoethanol-dihydrogenphosphate, is a monoester whose R group corresponds to NH2-CH2-CH2.[9] It is present in all animal tissues and organs and is a precursor of the synthesis of phosphatidylethanolamine (PE), one of the main components of the membranes.[10,11] PE, on the other hand, is associated with several stages of cellular metabolism, such as mitochondrial metabolism, acetylcholine synthesis and hormonal synthesis.[12] Eukaryotic cells have three mechanisms for the phospholipid biosynthesis of ethanolamine, phosphatidylethanolamine and plasmogen. Cells do not synthesize ethanolamine. Therefore, the Kennedy pathway, responsible for the synthesis of ethanolamine phospholipids, uses this molecule obtained from exogenous lipids supplied by food or even through its metabolic production. Ethanolamine is phosphorylated in phosphoethanolamine by ethanolamine kinase.[13] So, the conversion of phosphoethanolamine into CDP-ethanolamine by CTP produces phosphoethanolamine cytidyltransferase. Finally, CDP-ethanolamine: 1,2-diacylglycerol ethanolamine phosphotransferase catalyzes the formation of phosphatidylethanolamine through CDP-ethanolamine and DAG.[14] Phosphatidylethanolamine and serine generate phosphatidylserine (PS) and ethanolamine, through a reaction catalyzed by phosphatidylserine synthase II, as described in Figure 1.[15]

When phosphatidylserine, a compound commonly found in the internal lamina, is exposed on the outer surface of the membrane, it starts the programmed cell death. The first demonstration of the existence of phosphoethanolamine, a product of the hydrolysis of phosphatidylethanolamine in the free state, was in 1936 when phosphomonoester was isolated from bovine malignant tumors.[16] In 1993, a high concentration of phosphoethanolamine was also found in tumor cells.[17]

Synthetic Phosphoethanolamine

In the early 1990s, Ferreira et al. synthesized phosphoethanolamine based on previous research.[18] The synthesized substance has a simple chemical structure (Figure 2) with a lipid head region corresponding to polar phosphocholine, followed by an ethyl chain terminated with an amine. These authors report that the substance acts as a cell marker that signals



PS: Phosphatidylserine; PE: phosphatidylethanolamine; PSS II: phosphatidylserine synthase II; PSS Y: CDP-diacylglycerol: L-serine O-phosphatidyltransferase.

Figure 1. Phosphatidylserine synthesis pathway. Adapted on Santos.[15]

the existence of the tumor cells to the immune system, so that they are destroyed.[6,18]

Since then, researchers have been trying to validate the use of SP as a therapeutic agent and as a new treatment option for patients. They claim it is a highly selective drug with reduced side effects as well as an affordable one.[18] In 2004, studies conducted by Arias-Mendoza et al. showed that the concentrations of phosphoethanolamine and phosphocholine were high in tumors. These molecules are related to apoptotic activity and can be used as a marker of prognosis in the treatment of cancer.[19] Research on the existence of phosphoethanolamine in the free state has aroused scientific interest in phosphorylated compounds in order to obtain information on the biochemical role of these substances in organic tissues.[5]

The study of SP in tumors shows that the substance, found in malignant tumors, would not be linked to the process of stimulating tumor growth. It is believed that this substance acts as a defense mechanism against neoplastic cells. Researchers, knowing that the phosphoethanolamine commercially available was expensive, developed a process to obtain the substance with a lower cost, high yield and high level of purity.[20]

Recent studies have been conducted to investigate the antitumor and cytotoxic effects of SP on normal human endothelial cells, fibroblasts and murine melanoma (B16F10 cells). They obtained results showing that the concentrations of the substance used to promote the cytotoxicity of tumor cells did not cause the death of healthyones. In relation to the cell cycle, it was observed the reduction of DNA synthesis capacity and reduction of mitosis cells, thus inhibiting cell proliferation.[18]

There are other methods to synthesize the substance phosphoethanolamine, which can be found in the international market. This substance has already been produced on an industrial scale for decades, has been commercialized and can be purchased freely. Calcium-EAP, a version of SP, has been on the market for more than 50 years as a food supplement in the US, replacing calcium and magnesium ions. In this case, phosphoethanolamine transports these minerals, in addition to acting in the correction of cellular dysfunctions.[21]

DISCUSSION

Studies were carried out to investigate the effects of SP in the treatment of some types of neoplasia. In *in vitro* and *in vivo* studies with B16F16 melanoma cells and in an experimental model, research showed that SP inhibited proliferation and tumor growth.[3] Another study focusing on this same type of neoplasia presented a significant reduction in metastasis formation, in addition to a decrease in mass and tumor density, reduction of neovascularization and a significant increase in apoptotic cells and survival rate of the treated animals. However, SP did not show inhibition of the lymphoproliferative response when tested on cultured T lymphocytes and activated by specific mitogens.[5]

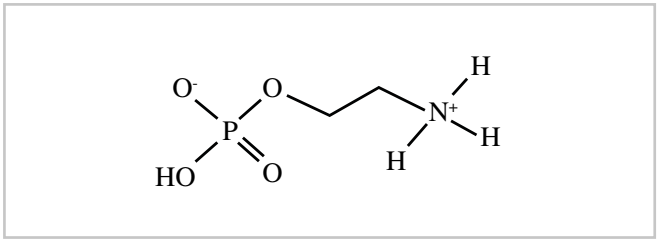


Figure 2. Chemical structure of synthetic phosphoethanolamine. Adapted on Ferreira.[18]

An article published in 2013 indicates SP as a precursor of selective cytotoxic effects for tumor cells, such as human melanoma (SK-MEL-28), renal murine carcinoma (RENCA) and non-small cell lung carcinoma (NSCLC). The authors report that SP exhibits antitumor effects due to induction of apoptosis caused by the structural modification of the cell, reduction of the electrical potential of the membrane and increased activation of caspase 3 and 8, as well as inhibition of the kinases that determine the antiproliferative effect of the substance.[18] Apart from the cited studies, the efficacy of SP has also been tested in the treatment of leukemia, showing that it is effective against more than just solid tumors. This research showed that the activation of caspase 3 led to the externalization of phosphatidylserine, which marks the cell for a programmed death.[6]

After the Chierice research group produced capsules of SP, patients with cancer started to have access to and receive from USP São Carlos, free of charge, these same capsules. However, at the end of 2015 this distribution was interrupted, as there was no scientific evidence of the efficacy of SP.[22] In order for SP to be released as medicine, ANVISA determined that clinical studies must be carried out to evaluate the efficacy and safety of the product based on globally accepted scientific criteria.[23]

DRC 38/2013 establishes the program of compassionate use of medicines. In article 2 of the aforementioned standard, it is defined that it is possible to release a new drug considered promising, while not participating in an expanded access program or clinical research, provided it is for personal use by the patients under the authorization of ANVISA. In these cases, the drug, while still in the process of clinical development and without registration in ANVISA, can be given to patients with serious lethal or debilitating diseases, such as patients without satisfactory therapeutic alternatives already registered in the country.[24]

Due to the great repercussion in the media about the distribution of SP as a cancer treatment and in view of public hearings in the Chamber of Deputies and the Federal Senate, a working group was created by the Ministry of Health to carry out research on the efficacy and safety of the substance. [21] Through Ordinance GM/MS No. 1767/2015, the working group was formed by representatives of the Ministry of Health, National Cancer Institute, Oswaldo Cruz Foundation, ANVISA and researchers responsible to deposit the Patent application for the substance at the National Institute of Industrial Property. Also included were the Ministry of Science, Technology and Innovation (MCTI), CNPq and research laboratories, which received funding from federal agencies.[21]

In March 2016, the identification, characterization and synthesis of SP capsule components was performed. Directed by MCTI, the capsules produced at the Institute of São Carlos arrived at the Chemistry Institute of University of Campinas (UNICAMP). Of the 60 capsules identified as SP 500 mg, 16 were opened and weighed, with values that ranged from 233 mg to 368 mg. The results obtained in the identification of the organic and inorganic components indicated 32.2% of phosphoethanolamine; 18.2% of protonated monoethanolamine; 3.9% of phosphobisethanolamine; 34.9% of phosphates of calcium, magnesium, iron, manganese, aluminum, zinc and barium; 3.6% of calcium, magnesium, iron, manganese, aluminum, zinc and barium pyrophosphates; and 7.2% of water.[25]

Reports released by MCTI and issued by laboratories participating in clinical trials released results of research on the substance phosphoethanolamine with no human results to date. Studies on toxicity, cytotoxic evaluation, antiproliferative action, genotoxicity and cytotoxic hemolytic potential were made available to the public in order to maintain complete transparency of current research.[26]

In May 2016, one of the published reports on the effects of SP on Walker's 256 carcinosarcoma described that the drug did not show antiproliferative action in animals treated with the dose of 1g/kg of body weight per day, for 10 consecutive days. A published report on sarcoma 180 cells also showed no inhibitory effects at the same dose and administration period.[27]

A human trial was initiated on July 25, 2016 and in its first phase of research ten patients with tumors were evaluated. If no side effects were detected, 200 more people would be distributed among ten groups with different types of tumors: head and neck, lung, breast, colon and rectum, cervix, prostate, melanoma, pancreas, stomach and liver.[28] Research participants received three tablets a day and it was believed that within six months there would be a response on the effectiveness of the substance. After satisfactory results, 800 patients would be included in a second phase until a number of 1,000 participants were reached. If there was a serious toxicity, the research would be interrupted and a new safety dose would have to be found for the tests to be restarted.[29]

In April 2017, according to the director of the Cancer Institute, the substance had no clinical efficacy in preliminary studies[30] and clinical trials were suspended.[31] In addition, ANVISA determined, as a precautionary measure, the suspension of all advertisements and publicity that attribute therapeutic, health or functional properties to the product "Phospho 2-AEP immune system" and "Phosphoethanolamine Phospho Ethanolamine".[32]

FINAL CONSIDERATIONS

According to the studies reviewed in this work, SP was first described as a restorer of cellular signaling and a reverser of alterations that transform a normal cell into a malignant one. The present work shows that one of the hypotheses to explain the possible antitumor action of SP was related to the translocation of this substance in the cell membrane, leading to apoptosis. Thus, in tumor cell signaling, migration of the phosphoethanolamine molecule, a precursor of phosphatidylserine, occurs from the inner region of the plasma membrane to the outer region. A second hypothesis of action of SP on tumor cells was based on the restoration of mitochondrial membranes by this substance. Thus, the possibility of treatment with SP was because the organism does not produce this substance in sufficient quantity, necessitating the complementation for the treatment of tumors.

Importantly, clinical trials are essential for proving the efficacy of drugs in humans for the treatment of tumors. If a drug is effective in treating tumors in clinical trials, it can be released by ANVISA for use as a tumor therapy, without risk to the population. However, satisfactory results to date have not been obtained to substantiate the efficacy of SP for the treatment of tumors. Conversely, studies have shown that SP was not effective in humans.

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