



Immunostimulatory and immunomodulatory functions of a novel phenothiazine derivative

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Abstract

Immune cells are involved in every part of the human body and are affected by many factors such as nutrition, exercise and sleep. In reactions called immune response, the body is basically protected from the microorganisms and their harmful soluble products. The decrease in the functions of cells in the immune system increases the susceptibility to infectious diseases. The immune system, which is the body's security force; also acts as a means of interaction between the central nervous system, the cardiovascular system and the digestive system. Phenothiazine derivatives have high affinity for many receptors, enzymes and proteins and play an important role in medicinal chemistry field. Many studies have been carried out on phenothiazine derivatives and positive outcomes have been obtained as a result of those studies for their drug potential. The immune system, on the other hand, is a defense system that creates the reactions of living things. During autoimmune or inflammatory disorders, it is imperative to have drug molecules that can modulate the immune reaction to prevent harmful excessive inflammation. Our studies aim to generate novel drug candidates that can be utilized against inflammatory and autoimmune diseases.

Introduction

Our body has an immune system made up of cells and molecules to protect itself against infections and foreign substances. The task of the immune system is preventing organisms that try to enter the body or harmful substances formed in the body, or not allowing them to spread throughout the body [1].

Immune system cells secrete a large number of protein messengers. These protein messengers regulate host cell division and are involved both in the innate and adaptive immune responses. These messengers are called cytokines, and each has its own name. The general purpose of the cytokines is to provide communication between the cells. Cytokines are among the glycoprotein products of immune cells such as lymphocytes and macrophages. Cytokines mediate defense functions through effectors. They generally do not show cytotoxic properties against the cells themselves. Among the cytokines; Interleukins, interferons (IFN), colony -stimulating factors and TNF are involved in the immune responses. They have a very important role in the immune reactions, inflammatory and infection conditions. Cytokines are related to the growth, development, differentiation, activation and orientation of the immune system cells [2,3]. Phenothiazine derivatives are involved in various biological processes. They are used as popular medicine to treat various diseases as they are characterized by low toxicity. In previous studies, it was investigated that phenothiazine and its derivatives have anti- psychotic, antibacterial, anti- fungal, and anti - oxidant properties [4-6]. Phenothiazine and its derivatives have been used in the treatment of various diseases. In this study, the immunomodulatory and immunostimulatory effects of phenothiazine on the immune system cells will be examined.

Results

We know that immune system cells play an important role against different kinds of danger signals or sources in our body. The immune system is examined under two main umbrellas as the innate immune system (the inherited immune system) or adaptive immune system. The components of the innate immune system are the specialized cells called natural killer cell (NK), the epithelial barriers of the skin, respiratory and digestive systems that prevent the entry of microbes, phagocytic leukocytes called neutrophils and macrophages. Macrophages, one of the innate immune system cells, can recognize danger and produce different types of inflammatory signals. It also has the ability to present the antigen to the other immune system cells to produce an appropriate immune response. Researchers are focusing on regulating the immune system cells to eliminate chronic inflammation due to infections or autoimmune reactions, to create longer lasting cure compared to the current treatment methods [6].

Phenothiazine consists of a tricyclic nucleus of two benzene rings. A central ring joins these two benzene rings and this central ring contains a sulfur and nitrogen atom. We know that the chemical structure of phenothiazine, which can interact with a range of biological processes, is very important [7]. Phenothiazines and its derivatives have very different etiology and symptomatology. In addition to being useful as therapy agents for versatile diseases, these molecules are currently used clinically mostly because they show stark antipsychotic effects and are also useful as antihistamine drugs. In other words, they show antiallergic, antiemetic, sedative and antipruritic activities. Some derivatives have exerted anti-inflammatory, antioxidants, antispasmodics, antitussive, and radioprotective effects.

When we examine the work done; in the study of [6] phenothiazine-based cyanoacrylamide was synthesized from phenothiazine by a multi-step synthetic strategy. Antioxidant and anticancer properties of the synthesized compounds were investigated by *in vitro* methods. As a result of that study, it had high antioxidant properties and *in vitro* anti-cancer effects on pancreatic tumor cells [8].

Alzheimer's, which is among the neurodegenerative diseases, occurs with the accumulation of beta-amyloid plaques in the brain, which has also been used as disease diagnosis marker. Phenothiazine derivatives seem to inhibit the beta-amyloid aggregation and fluorescence. In the study of Dao et al., beta-amyloid, which provides NIRF imaging of amyloid plaques. The phenothiazine derivative that they utilized prevented the formation of those plaques and also resolution of the fibrils. With this system, they showed that a phenothiazine derivative could bind beta-amyloid in the brain of the mice with the Alzheimer's disease model [9].

In the study of Kışla et al.; for the synthesis of phenothiazine derivative compounds, phenothiazine core structures were generated either in non-substituted form or as 2-chlorophenothiazine with acetyl chloride/propionyl chloride and as phenothiazine 10-yl acyl chlorides. They reacted with amines in the presence of K_2CO_3 and NaI and obtained phenothiazine 10-carboxamides. As a result of the studies, they found twelve phenothiazine derivatives and stated in their studies that the obtained compounds showed anticancer properties [10].

Discussion

In summary; above studies strongly suggest that phenothiazine derivatives have anticancer properties and may be effective against Alzheimer's disease. Based on some other studies, phenothiazine derivatives may exert immunomodulatory and immunostimulatory effects on the immune system. In addition, these results also imply that phenothiazine derivatives will play an important role in the development of new drug candidates and more research should be done in the field to fully decipher their drug potentials.

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