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Short Communication

Actual Problems of Immunotoxicology. The Main Mechanisms of Xenobiotics Immunotoxicity

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As a result of the rapid development of immunology during the last quarter of the last century, a certain system of views on the mechanisms of interaction of a multicellular organism with living bodies and substances bearing signs of genetic foreignness, based on the idea of the immune system as a multicomponent system responsible for maintaining the genetic homogeneity of the organism. However, at present, the concept of "immunity" has undergone fundamental changes. By immunity they mean a special biological property of multicellular organisms, designed to protect against infections and other external pathogens that, when ingested, enter into strong bonds with cells and/or intercellular substance. When this occurs, the recognition of a variety of different molecules (antigens) with the subsequent destruction of damaged tissues and their elimination from the body [1-4].

Currently, there is a process of penetration of immunological ideas and research methods into related fields of science, which leads to the revision and refinement of existing ideas about the mechanisms of many processes in the human body and animals in health and pathology. This process can be considered as one of the applied aspects of modern immunology [4-7].

In the last 30-40 years, a new scientific direction has been formed, which is studying the effect of xenobiotics on the nonspecific resistance of the organism (inborn immunity) and the immune system - immunotoxicology. Within this promising direction, such sections as general, special, industrial, military, and environmental immunotoxicology are distinguished. In general, the differentiation of this area corresponds to the main sections of toxicology. The subject of immunotoxicology is the study of the effect on the immune homeostasis of xenobiotics: toxic chemicals (TCh), pharmacological agents and biological agents [3-5]. At the same time, damage to the immune system can be the result of both direct and indirect effects of xenobiotics and/or their metabolites. In addition, xenobiotics (or their metabolites) can develop an immune response with the formation of antibodies. It should be noted, and the possibility of modification of toxic compounds, as a result of which they acquire the properties of antigen. It is also possible the formation of antibodies to the complex toxicant – antigen [3-5,8].

The study of the effect of xenobiotics on immune homeostasis is one of the most pressing problems of toxicology. This is due, firstly, to the colossal pollution of the environment with various compounds that distort immune reactions and cause various diseases associated with a violation of the immune status; secondly, the need to correct disorders of the immune homeostasis, both in the case of chronic intoxication, and in case of poisoning, accidents at chemical plants, industrial accidents, in everyday life, during the destruction, storage and transportation of stocks of chemical warfare agents; thirdly, there may still be a need for immunocorrection of affected people with the use of toxic substances (TCh, chemical warfare agents) for terrorist and military purposes [2-4,7,9].

The positive steps taken by the international community in the destruction and complete prohibition of chemical weapons did not reduce the reality of their use for terrorist and criminal purposes [4,7]. Probably, research into the effectiveness of methods for degassing chemical warfare agents, searching for highly effective antidote drugs when they are damaged, research on biomarkers for differential diagnosis between skin lesions with mustard gas or lewisite, studying the features of damage to brain structures with organophosphorus toxic substances (and their long-term effects) [6,10-12].

Toxic substances have a multidirectional effect of varying intensity on different parts of the immune system. Therefore, the selection of a group of toxicants for their predominant action on the pre-immune biological mechanisms of resistance to infections (innate immunity), T, B cells, various subpopulations of immune competent cells, humoral and cellular immune responses are very relative [2-4]. TCh differ in predominant damage of Th1, Th2 lymphocytes and the dysfunction of these lymphocyte subpopulations equally [13-15]. It is necessary to take into account the fact that the data of a number of authors with respect to the immunotropic properties of TCh are contradictory [2-4].

Acute poisoning with toxicants can be accompanied by infectious complications associated with a decrease in innate and adaptive immunity (pre-immune biological mechanisms of resistance to

infections, non-specific resistance of the organism, humoral and cellular immune reactions). The development, along with antidote remedies, of ways to reduce the damage to the immune system by various TCh suggests further study of their immunotropic effects [2-5,7].

Immunotoxicity is the property of xenobiotics to cause suppression of immune reactions, the manifestation of hypersensitivity reactions (immediate or delayed types) or autoimmune reactions. The possibilities to realize the immunotoxic (immunotropic) effect of xenobiotics are very diverse. When considering their influence on the innate and adaptive immunity at the level of the organism, it is necessary to note the close connection between the action of toxicants on these systems and the function of the central nervous system and the endocrine system. Thus, the mediated effect of xenobiotics through the central nervous and endocrine systems is combined with their direct effect of xenobiotics on the morphological and functional systems of the immune system [2-4,16,17].

When xenobiotics act on immunocompetent cells and other cells involved in the immune response, the following options are possible: exposure through the central and peripheral nervous systems, the endocrine system, in particular, due to the effect of various mediators (acetylcholine, catecholamines, neuropeptides, etc.), as well as the action of hormones of the pituitary, adrenal glands, thyroid and other endocrine organs; direct effects of a toxicant on immune cells; the effect of biotransformation products (in the liver, lungs, skin, lymphocytes) the immunotropic effect of a toxic substance as an antigen; the interaction of the toxicant, which is a hapten, with proteins with the formation of a complex that acts on immunocytes and other cells involved in the immune response, as an antigen; the effect of xenobiotics as tolerogen (in this case, the toxicant abolishes or reduces the implementation of humoral or cellular immune responses) [3,4,8].

The following main mechanisms should be highlighted when considering the effect of xenobiotics on immunocompetent cells (and other cells involved in the immune response) at the cellular and subcellular levels: initiation of cell membrane lipid peroxidation by toxicant (xenobiotics), in particular, by inactivating antioxidant enzymes and vitamins (superoxide dismutase, catalase, peroxidase, glutathione transferase, glutathion peroxidase, alpha-tocopherol, beta-carotene, vitamins E, A, C); combining polyaromatic chlorinated hydrocarbons (dibenzaparadioxins, dibenzfurans) with the cytosol Ah-receptor (AhR, Ahr) of the immunocyte with subsequent entry into the cell nucleus and interaction with DNA; the effect of mediators and hormones of the central and peripheral nervous and endocrine systems on immunocyte membrane receptors; inactivation of the enzymes of the cytosol and the membrane of lymphocytes (acetylcholinesterase, coenzymes of the pyruvate oxidase system, etc.), as well as enzymes of the tissue respiration system in the mitochondria of immunocytes; induction or inhibition of the synthesis of P-450-dependent monooxygenases localized predominantly in natural killer cells and T lymphocytes; impact on the cell membrane, its damage, followed by the formation of autoantibodies interacting with the immunocyte. In the process of immunogenesis, xenobiotics can affect on various immunocytes and their precursors up to a polypotent hemopoietic stem cell [3,4,8,18-32].

During the interaction of macrophages, T (Th2 cells) and B lymphocytes, as a result of which T-dependent antibody production takes place (the synthesis of immunoglobulins of B cells (plasma cells). Xenobiotics can affect both the cells involved in this cooperation and the production of various cytokines by macrophages, dendritic cells and lymphocytes, resulting in reduced synthesis of different classes of immunoglobulins. During hypersensitivity reactions production of IgE is induced. Toxic chemicals can affect mainly T lymphocytes (most xenobiotics) [3,4,16,17]. Some immunosuppressants (rapamycin) and toxicants (methanol, formaldehyde, formic acid) [33,34], a number of pharmacological agents (methotrexate) related to immunosuppressants affect mainly B lymphocytes (plasma cells), reducing their production of immunoglobulins [33].

Thus, the immunotoxicity of xenobiotics can be considered at various levels of organism integration: systems and organs, cellular, subcellular, and molecular. In addition, it is necessary to take into account that the realization of the immunotropic effects of toxicants occurs at various stages of immunogenesis, as well as in the process of cell cooperation in inducing a humoral or cellular immune response. Depending on the predominant changes in the nonspecific resistance of the organism (factors of innate immunity), humoral and cellular immune reactions, or the characteristics of their combined damage, various types of infringement of the nonspecific resistance of the organism (innate immunity), humoral and/or cellular immune response can be distinguished [2-5,7].

As a rule, xenobiotics inhibit, to varying degrees, the nonspecific resistance of the organism (factors of innate immunity), humoral and cellular immune responses. At the same time, various hypersensitivity reactions are not excluded (1-5 types, when certain reactions of the immune system are increased). These reactions, as well as suppression of the immune response, can be a manifestation of the immunotoxicity of xenobiotics. There are options when one of the components that provide immune homeostasis, increases with the suppression of others [4,5,8,16,17].

Mostly xenobiotics cause contact and respiratory allergic reactions. Contact allergens activate Th1 lymphocytes, which, using cytokines (IL-2, γ-interferon, TNF-β, etc.) recruit macrophages and monocytes to implement type IV hypersensitivity reactions (delayed-type hypersensitivity). This reaction involves Langerhans cells and keratinocytes. In addition, contact allergens, producing IL-2, γ-interferon and TNF-β, inhibit the synthesis of IgE. Respiratory allergens, acting on Th2 lymphocytes, activate the production of IL-4, IL-5, IL-6, IL-10, which promote the synthesis of IgE of plasma cells (B cells). These immunoglobulins, localized on mast cells, interacting with antigens (allergens), cause a respiratory allergic reaction (type I hypersensitivity reaction). Pharmacological agents can cause drug intolerance due to allergic reactions of type I, II, III, connecting with various components of the body (in particular, with blood cells) and turning from hapten into a full-fledged antigen. When interacting with blood cells, cytotoxic antibodies are formed and is realized by an allergic reaction of type II. Drugs, binding to whey proteins, can cause reactions III, due to the formation of immune complexes [4,5,8,16,17].

Xenobiotics can cause autoimmune reactions (autoimmune processes and autoimmune diseases) related to immunotoxicity. A number of authors describe them as V type hypersensitivity reactions. Thus, the reaction of type V (autosensitization due to antibodies) is possible when antibodies (xenobiotics) interact with key components of the cell surface (for example, with a hormone receptor, which leads to cell activation) [4,5,17].

Obtaining new and clarifying the already known data regarding the immunotoxicity of toxic chemicals will allow to substantiate the possibility use of the most promising drags from a large arsenal medicines (based on the results of the research) adequate to the nature of disorders of immune homeostasis for the prevention and treatment of post-intoxication infectious complications and diseases.

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