History and prospects of medical use of animal raw materials origin on the example of organopreparations from the spleen of a pig

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History and perspectives of medical use of raw materials of animal origin on the example of porcine spleen organic preparations

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SUMMARY

The development of new immunomodulatory drugs is an urgent task of modern healthcare. Of great interest are drugs that stimulate the immune system, of natural origin, prepared on the basis of spleen tissues. The spleen is involved in the production of specific antibodies and nonspecific immunoglobulins, the formation of biologically active substances that affect various links of immune homeostasis. In world practice, several preparations from the spleen are used, such as: solkosplen, splenin, polyegra, splenopid, etc. However, the search for new organopreparations of the spleen is of great interest.

Key words: immunomodulatory drugs, organopreparations, spleen, biologically active substances.

RESUME

The actual problem of modern health care is the creation of new immunomodulatory drugs. The most interesting are drugs that stimulate the immune system, natural origin, prepared from spleen tissue. The spleen is involved in the production of specific antibodies and nonspecific immunoglobulins, production of biologically active substances that affect different parts of the immune homeostasis. In the world practice there are some preparations of the spleen, such as: solkosplen, splenin, poliegra, splenopid and others. However, the search for new spleen drugs is of great interest.

Keywords: immunomodulatory drugs, animal extracted drug, spleen, biologically active substances.

Efficient and safe pharmacological correction of immune processes occupies a special place among the urgent problems of modern healthcare [14]. One of the solutions to this problem is the use of so-called organopreparations - preparations made from organs and tissues of healthy animals and their embryos [30].

In modern medicine, various organopreparations are used from xenogenic (non-human, animal) organs and tissues, the spectrum of which is very wide. They are made on the basis of organs, tissues, cells, organelles, biomolecules, cell extracts, hydrolysates, filtrates and ultrafiltrates,

also developed analogues of organopreparations obtained by biotechnology using genetic engineering methods [26].

The use of animal organs in medicine has a long tradition [26]. But starting in 1850, under the influence of natural science medicine, it began to lose importance, and only by the end of the 19th century, preparations from organs of animal origin were again used in official medicine. The great French physiologist, founder of endocrinology, Claude Bernard (1813–1878) introduced the concept of internal secretion, confirming experimentally that the liver can produce sugar and supply it with blood [31]. Subsequently, Charles Edouard Brown-Séquard (1817-1894) transferred the concept of internal secretion to the activity of another organ - the testicle. He tried to inject under the skin extracts obtained from crushed testicles of puppies or guinea pigs, mixed with blood from the veins of the testicles and seminal fluid. Despite, that the injections were accompanied by significant and rather prolonged pain, after which there was an increase in general muscle strength, an improvement in the administration of the rectum, bladder and genitals, as well as an increase in mental activity. With this experience Sh. E. Brown-Sekar went down in history as the founder of organotherapy [21]. Extracts were also obtained from organs of other animals, such as the spleen, kidney, pancreas, thyroid, lung, liver, salivary gland, adrenal cortex, brain and spinal cord. According to Sh. E. Brown-Séquard, all the glands of external secretion have internal secretion. They are organs that communicate “important principles” to the blood either directly or by resorption as a result of their secretion [22]. One of the therapeutic developments of Sh. Brown-Séquard was the use of an organopreparation in the treatment of myxedema due to hypothyroidism. In 1894, two English researchers: George Oliver (1841-1915) and Edward Schaeffer (1850-1935) laboratory revealed the regulatory role of extracts of the thyroid gland and the posterior pituitary gland, thereby confirming the theory of internal secretion [27].

At the beginning of the 20th century, under the influence of the work of Brown-Séquard, St. Petersburg doctor of pharmacy A.V. Pel (1850–1908) established the production of organopreparations - spermine and opovarin, which soon became widely known. The successor to the Pel business was the Soviet scientist I.N. Kazakov (1891-1938). Based on the idea of the leading role of dysfunction of the endocrine glands in aging and the development of various diseases, he proposed a new method of treatment using endocrine gland lysates, the so-called lysate therapy [13].

A great scientific achievement was the isolation from the adrenal glands, and then the synthesis of the corresponding hormone - adrenaline in 1905. Patients suffering from Addison's disease, along with high doses of adrenaline, were also given per os doses of the corresponding organ [27]. At the same time, there were reports of successful therapeutic experiments with extracts from the adrenal cortex [32].

In 1901, A. Beer (1861–1949), based on the results of his own experiments, came up with the idea of using animal organs as a stimulant. Thus, he wanted to achieve "the stimulation of the production of new, healthy blood" [20].

Attempts have also been made to treat not only blood, but also injections of organopreparations of animal origin. For example, A. Gerke attempted to treat patients with tabes of the spinal cord, progressive paralysis and multiple sclerosis, using the organopreparation "Promonta" [24], which contained "substances extracted from the central nervous system, polyvalent vitamins, lime, iron, complete protein substances and easily assimilated carbohydrates ”[23]. The effect of the drug came only after the introduction of the "stimulating agent" (in this case, strychnine), due to which "the body accepted the organopreparation offered to it."

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Patients with diseases of the liver and biliary tract in a Berlin clinic were treated with a sterile preparation from the mucous membrane of the gallbladder, as well as from the elements of the liver parenchyma [28]. Later, this drug appeared on the market under the commercial name Choloton [25].

In 1926, the Soviet microbiologist and pathophysiologist M.P. Tushnov (1879-1935) developed the theory of tissue preparations, known as the theory of histolysates. Histolysates, according to M.P. Tushnov, are called organotherapeutic drugs, the active principle of which is the decay products of tissues of individual organs. He developed methods for the preparation of histolysate, in which, under the influence of various factors - autolysis, fermentolysis or hydrolysis - decomposition products are obtained that are close in chemical composition, but different in specific effect on the body, depending on the starting material for digestion. Tissue therapy was further developed in the studies of V.P. Filatov (1875-1956), who believed that the therapeutic effect of tissue drugs is provided by substances

Several years later I.P. Chukichev (1895-1973), by hydrolysis of fibrin with sulfuric acid, obtained a strong sympathomimetic substance - sympathomimetine. In a number of experimental and clinical observations, he proved the significant activity of this drug, as a tonic of the sympathetic and nervous system [4].

Paul Niehans (1882-1971) is rightfully considered the founder of cell therapy in 1931. In 1937, the professor first performed the implantation of brain cells (mainly cells of the hypothalamus and pituitary gland). Subsequently, he expanded the technique by introducing cells of the liver, pancreas, kidneys, heart, duodenum, thymus, spleen. In 1949 Niehans performed the first injections of lyophilized cells [6].

The manufacture of protein heteropreparations is associated with enormous difficulties in removing the properties of species specificity, primary toxicity, and anaphylactogenic factors from the heteroprotein. The first of the heterogeneous protein preparations, which withstood extensive testing in practice, was proposed and further improved by Academician NG Belenkiy (1908–1997).

In the early seventies, young employees of the Leningrad Military Medical Academy V.Kh. Khavinson and V.G. Morozov developed a new class of drugs - bioregulators with the ability to restore the specific functions of those organs and tissues from which they were isolated, and also became the creators of bioregulatory therapy - a new medical technology for restoring and preserving the basic functions of organs and tissues of the body within the genetically determined the life span of a person, involving the use of these same bioregulators [8]. In 1973 V.Kh. Khavinson and V.G. Morozov isolated peptides from the thymus of calves that can regulate the activity of the immune system. Then they managed to isolate peptide bioregulators (cytomedins) from the pineal gland and hypothalamus [5].

In modern medical practice, a wide range of preparations of animal origin from cell extracts from stem to mature cells of fetal organs and tissues of healthy animals grown in specialized nurseries in ecologically clean regions of the world are used [31].

One of the main properties of organopreparations is the pharmacological accuracy of the effect on the functions of a homologous organ or tissue - the effect of homology. Its essence lies in the increased tropism of the obtained biomolecular substance to homologous human organs or tissues. The 1999 Nobel Prize laureate, the American biochemist G. Blobel, made his contribution to the discovery of the mechanism of organotropism as an all-encompassing property of living things [31].

In addition to the homology effect, organopreparations are also characterized by a replenishment effect. Organopreparations, especially in relatively high concentrations, make up for the deficiency of cellular biomolecules. This effect is the starting one in the subsequent development of the chain of physiological regenerative reactions [20]. The effect of homology does not depend on the method and place of administration of organopreparations. This effect gives organopreparations the property of conductors of other drugs to a homologous organ, provided that they are jointly introduced into the body [29].

Currently, the list of indications for the use of drugs of animal origin is quite wide. So, they are used for the treatment of degenerative, dystrophic, atrophic diseases, complications of diabetes mellitus, hypertension, for rehabilitation in the post-stroke and post-infarction periods, for the treatment of inflammatory diseases and the normalization of the functions of some organs in case of hyperfunction. A number of organopreparations are used in the correction of immune disorders [18].

Of particular interest, along with the immunotherapeutic use of organopreparations, is their use in immunorehabilitation, in the complex restoration of the functions of the immune system to the physiological norm [9, 11, 12].

To date, many methods and means have been developed and are actively used in practical medicine aimed at improving the functioning of the immune system. However, their choice should be based on an accurate clinical diagnosis of immunopathology and a thorough analysis of the patient's immune status, indicating the localization of disorders in the links of the immune system and their severity [7]. This position also applies to organopreparations with immunotropic action, since their arsenal is quite wide [7].

So, immunotropic drugs (organopreparations), depending on the feedstock, can be classified as follows:

- preparations of the thymus gland: T-activin, thymalin, vilosen, thymoptin, thymulin and others;
- embryonic tissue: erbisol [11];
- bone marrow: myelopid (B-activin) [15, 16];
- spleen: splenin, splenopid [17];
- placenta: placenta extract [11];
- blood: histaglobulin, pentaglobin and other immunoglobulin preparations [2].

In most cases, all of these immunotropic drugs have a complex effect on the immune system. Therefore, their division into groups according to the predominant effect on individual links of the immune system is conditional, but at the same time acceptable and convenient in clinical practice. So, for example, in case of dysfunction of the T-cell link of immunity, one of the following drugs can be used: T-activin, thymogen, thymalin, vilosen, erbisol. In case of dysfunction of the B-cell link of immunity, it is necessary to prescribe drugs such as myelopid, splenin [9, 19].

Preparations of animal origin prepared on the basis of spleen tissues are of great interest. The spleen is the source of a large amount of biologically active substances. Its cells produce a large complex of cytokines (interleukins: 1, 2, 3, 4, 6, 8, 10, interferon-gamma, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor), opsonins (tuftsin, fibronectin, etc.), which have of great importance for ensuring immune homeostasis, stimulating, first of all, the phagocytic and metabolic activity of leukocytes and macrophages, as well as

other peptides that are regulators of the body's immune system [1]. The presence in the spleen of 25% of all lymphoid tissue and 30% of the entire reticuloendothelium of the body, a large number of T- and B-lymphocytes, macrophages determines its role as an important immunocompetent organ [17].

It was found that an aqueous extract of the spleen of animals, containing high molecular weight protein molecules, has a protective and therapeutic effect in radiation sickness. It is relatively heat-resistant. Injections of it into irradiated animals significantly prolong their life [22].

It was also possible to isolate a high-molecular-weight protein substance from the spleen, which was attributed to keylons - factors that inhibit cell multiplication in the corresponding tissues. Keylon of the spleen inhibits immunological reactions in this organ after the introduction of foreign cells. Using ultrafiltration and chromatography, a low-molecular-weight immunosuppressive factor was isolated from a high-molecular-weight protein substance. This opened up a real opportunity to establish its structure, carry out synthesis and provide practical application [1, 22].

In the middle of the twentieth century, the American researcher G. Ungar attempted to develop preparations based on spleen tissue, namely, Splenin A and Splenin B. The first one reduces capillary permeability and promotes an increase in the resistance of erythrocytes to the action of anti-erythrocyte serum. The action of Splenin B has the opposite direction [17].

In 1932, the German professor E. Schlifake received the drug Splenotrat, aka Prosplen. The drug was widely used for the treatment of gastritis with disturbed acidity of gastric juice and for allergic diseases. [29]. A few years later, a drug called Solkosplen was obtained by Swiss researchers by dialysis of the spleen extract. It is a stimulant of sexual function, normalizing the activity of the gonads. It has been used to treat both men and women [28].

A new preparation for animal spleen is Splenolysate, which was developed and subsequently studied by F.P. Lehrer in the organo-therapeutic department of the Kazan Institute [3].

In 1945, in the Laboratory of Experimental Endocrinology (A.A.Bogomolets Institute of Experimental Biology and Pathology, Kiev), Academician of the Academy of Sciences of the Ukrainian SSR V.P. Komissarenko received the drug Splenin. The drug is a clear, colorless or yellowish liquid, salty in taste, with a characteristic odor. It contains peptides containing 13 amino acids, many fatty acids, lipids, trace elements and vitamins. The drug showed pronounced detoxification properties, as well as a therapeutic effect in the treatment of various forms of hepatitis and functional disorders of the liver, thyrotoxicosis, parathyroid gland insufficiency, schizophrenia and diabetes [17].

In various institutions in our country, tests were carried out on the action of Splenin in case of toxicosis in the early stages of pregnancy. The drug proved to be highly effective in the treatment of this pathology. Researchers have discovered another ability of the drug - to inhibit the manifestation of allergic

reactions. Splenin had a pronounced therapeutic effect in the treatment of allergic rhinitis, urticaria and allergic dermatitis.

There are also known data on the ability of Splenin to have an render immunostimulating effect. So, in the complex therapy of patients with pulmonary tuberculosis, with the introduction of Splenin, stimulation of the fraction of T- and B-lymphocytes and an improvement in the general condition were observed. Stimulation of T-lymphocytes and improvement in the condition were also noted in patients with seroresistance after syphilis treatment. Many of Splenin's effects can be explained by its membranotropic properties, i.e. the ability to stabilize the cell membrane. So, erythrocytes treated with this drug are more stable in a hypoosmotic environment.

The chemical structure of 2 peptides isolated from the spleen with high biological activity was established: tuftsin, the biosynthesis of which occurs in the spleen in the form of leukokinin, and the final structure is formed on the surface of leukocyte membranes; a factor similar in structure to thymopoietin and called Splenin. Tuftsin, like thymopoietin, consists of 49 amino acids and has an active site of five amino acids, which was named splenopentin.

British company Merc was proposed highly efficient a drug called Polierga. The preparation contains oligopeptides obtained from pig spleen. Polyegra promotes the treatment of the tumor process, including after chemoradiation therapy, and also prevents the metastasis of tumors and is used in the prevention of cancer. [17].

Unitary Enterprise "Dialek" has developed an original technology of the Diasplena peptide preparation based on the spleen of embryos and young cattle. Diasplen contains biologically active compounds that have a multifunctional effect on various tissues and organs. They have an immunomodulatory effect, regulate energy processes in cells, have a normalizing effect on free-radical lipid peroxidation, and stimulate reparative and trophic processes. Clinical trials were carried out using Diasplen in patients with rheumatoid arthritis, putrefactive-necrotic diseases of the maxillofacial region (sialoadenitis of the large salivary glands), radiation osteonecrosis of the jaws, obliterating vascular diseases of the lower extremities, trophic disorders,

Another immunotropic agent is the Eni-Sala Peptide Complex 1, created using the unique Eni-Sala technology. The drug has shown high efficiency when used in complex treatment regimens for patients with chronic nonspecific lung diseases, acute bronchitis, respiratory diseases of the upper respiratory tract, pulmonary tuberculosis. In 90% of cases, a pronounced positive trend was obtained in the form of a quick normalization of general well-being and an improvement in blood counts, the absence of

tendencies to hardening of lung tissue, normalization of the immune status (positive effect on T-lymphocytes, blood immunoglobulin levels), decrease in the frequency of antibiotic therapy [10].

In Russia, at the Research Institute of Transplantology and Artificial Organs of the Ministry of Health of the Russian Federation, a method of extracorporeal connection of the xenospleen (porcine) was developed and introduced into wide clinical practice, as well as the introduction of splenoperfusate (saline, passed through the vascular bed of the xenosepleen) to the patient. This method was used in various pathologies associated with immune deficiency, namely, in autoimmune diseases, purulent-septic processes. However, despite the high efficiency of these techniques, they have limitations in use, due to the complexity of the procedure and the need for the participation of highly qualified personnel. Therefore, subsequently, a technology was created for obtaining a drug from the spleen tissue with immunocorrective properties. The drug was named Splenopid [17].

The drug is a peptide fraction isolated from the spleen tissue of pigs or cattle. It is successfully used in the complex treatment of multiple sclerosis, oncological pathologies, diabetic foot, pyelonephritis, hemorrhagic fever, multiple organ failure, purulent-septic complications in the postoperative period. Splenopid activates cellular and humoral immunity, increases the specific and nonspecific resistance of the organism [18].

In recent years, a highly effective method of treating stomach and duodenal ulcers using Splenopid has been developed. The prerequisite for its creation was the positive experience of treating patients with non-healing ulcers of splenoperfusate when taken orally. Injection of the spleen organopreparation directly in the ulcer zone turned out to be even more effective [17].

Considering high efficiency methods splenotherapy (extracorporeal connection of the xenospleen and the introduction of splenoperfusate) in the treatment of many pathologies, it should be assumed that Splenopid will find wide application in medical practice.

However, the widespread use and introduction in general of organopreparations and preparations from the spleen, in particular, is hindered by a number of factors:

- the need to carry out strict veterinary and sanitary and sanitary epidemiological measures to prevent the intake of infected raw materials and its contamination (including microbiological and prion);
- labor intensity of collection, preparation and storage of raw materials;
- features of the technology of organopreparations that require monetary costs and a large amount of time, a special culture of production, the specifics of equipment and specially trained personnel;
- the complexity of standardization of raw materials and finished products;
- difficulties in storage, use of organopreparations associated with instability when exposed to chemical, physical and microbiological factors;

- relatively poor knowledge of the mechanisms and features of the action, indications and contraindications for these drugs, etc.

These problems pose a number of fundamental and applied scientific problems for specialists in the development and study of these drugs. It should be noted that developments in these areas are being actively pursued all over the world and in our country in particular. This follows from scientific publications, many of which are presented in this review.

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