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PHARMACOLOGICAL PROPERTIES OF ACTIVE SUBSTANCES IN THE SALIVA OF THE HIRUDO MEDICINALIS LEECH

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Abstract: Medical leeches Hirudo medicinalis are used in medicine in a procedure known as hirudotherapy, which involves the external use of leeches to treat various diseases. The components of leech saliva are believed to help reduce inflammation, thin the blood, and improve circulation. Today, it is of greatest relevance to study the composition of the saliva of medicinal leeches, since if it is proven that specific components of saliva have medicinal properties, this may lead to the development of new drugs or therapeutic methods.

Keywords: leech, hyaluronidase, hirudin, bdellin, apyrase, eglin, destabilize.

Hirudotherapy, or treatment with medicinal leeches, is a method that has been used in traditional medicine for many centuries. Some supporters of traditional medicine and hirudotherapy claim that this method has its advantages, such as improved microcirculation, antithrombotic effects, anti-inflammatory properties, and pain relief. One of the main effects of hirudotherapy is the improvement of blood microcirculation in the area of the leech used. This can promote better supply of oxygen and nutrients to the tissues. The saliva of a medicinal leech also contains hirudin, an antithrombotic substance that helps prevent blood clotting. This property is actively used in the treatment of conditions associated with the formation of blood clots. In addition, the components of leech saliva have an anti-inflammatory effect, which can be useful in the treatment of various inflammatory processes, such as arthritis. In some cases, hirudotherapy can help reduce pain, possibly due to the combination of anesthetic and anti-inflammatory effects of biological substances contained in leech saliva.

Purpose of the study: Meta-analysis of scientific works and research in the field of studying the composition of medicinal leech saliva.

Materials and methods of research: We studied 27 scientific papers on hirudotherapy in which the composition of the saliva of a medicinal leech was described. Search engines for scientific works such as elibriary, pubmed, web of science were used as sources for the study.

Results and discussions: To date, the main active ingredients of leech saliva have been identified and studied: hyaluronidase, a histamine-like substance, hirudin, pseudohirudin, bdellin,

apyrase, eglin and destabilize.

Hyaluronidase is an enzyme that destroys hyaluronic acid, one of the main components of the intercellular substance in the body. Hyaluronic acid plays an important role in maintaining tissue elasticity and hydration. The main function of hyaluronidase is to break down hyaluronic acid into smaller fragments. This leads to a decrease in viscosity and the level of hyaluronic acid in the intercellular space. In addition, the action of hyaluronidase helps maintain a certain level of viscosity in the intercellular space, which is important for the normal structure and function of tissues. Hyaluronidase is also involved in cell migration processes, facilitating the movement of cells through the intercellular space, playing an important role in physiological processes such as growth and development, as well as in pathological conditions including inflammation and cancer. The degree and nature of the action of hyaluronidase are important for maintaining the health of tissues and organs. Histamine-like substances have properties similar to the action of histamine, which is a biologically active amine. Histamine-like compounds have the ability to act on histamine receptors, causing histamine-like effects. Histamine and histamine-like substances can cause allergic reactions. This includes vasodilation, increased vascular permeability, which can lead to edema, and stimulation of mucus secretion. The action on histamine receptors can cause vasodilation, which leads to increased blood flow and redness of the skin. Histamine and histamine-like substances may play a role in the regulation of inflammatory processes by participating in inflammatory mediators. In addition, some histamine-like substances can stimulate smooth muscle contraction, which may be associated with some types of symptoms such as cramping and pain. An example of a histamine-like substance would be certain drugs or chemical compounds that can have similar effects to histamine when interacting with its receptors. It is important to note that such substances may also be used medicinally to treat certain conditions such as allergies and asthma.

In 1884, a substance extracted from leeches that slows blood clotting was first isolated from leech extract by Highcraft and subsequently named hirudin. Before the discovery of heparin, extracts from the head part of leeches were widely used as an anticoagulant. In the 40s, Kirsanov and Bystritskaya developed a preparation of raw hirudin. A method of fractionating the extract from the head part of the medicinal leech was used by Marquardt to isolate pure hirudin. Hirudin, being a specific inhibitor of the thrombin enzyme, forms a strong non-covalent stoichiometric complex with thrombin. This enzyme has high specificity for thrombin and differs from other natural inhibitors of this enzyme, such as antithrombin III, heparin and α2-macroglobulin. Compared to a number of synthetic thrombin inhibitors, hirudin is considered an ideal inhibitor of this enzyme. In addition to inhibiting thrombin activity, hirudin also slows down the reaction of thrombin activation of coagulation factors V, VIII and XIII. It prevents the release and aggregation of platelets, and also causes the dissociation of the thrombin complex with specific receptor proteins on platelets. Oxidation of disulfide bonds leads to loss of antithrombin activity of hirudin. Chemical modification of the free carboxyl groups in hirudin reduces its affinity for thrombin, indicating ionic interactions between the molecules during complexation of hirudin with thrombin. Pseudogirudin: When hirudin is isolated from whole medicinal leeches, it is accompanied by an inactive component from the bodies of leeches, called pseudohirudin. Unlike hirudin, which contains isoleucine at the N-terminus, pseudohirudin contains valine at the N-terminus.

The amino acid composition of pseudohirudin is somewhat different from hirudin. Hirudin is characterized by a higher content of aspartic and glutamic acids, lysine, isoleucine and tyrosine. The cysteine content in pseudohirudin is 3 times lower than in hirudin. Scientifically known as a hirudinoid, pseudohirudin is a man-made analogue of hirudin, a thrombin inhibitor derived from leeches. Pseudohirudin has some similar properties, but it is synthetic and intended for use in medical applications. Like hirudin, pseudohirudin is a thrombin inhibitor. It forms a complex with thrombin,

preventing blood clotting. Pseudohirudin, like hirudin, has high specificity for thrombin, making it an effective inhibitor of this enzyme. Pseudohirudin, like hirudin, is able to maintain antithrombotic properties, preventing the formation of blood clots. Studying pseudohirudin can also be used to better understand the molecular interactions between inhibitors and thrombin, which in turn could help in the development of new antithrombotic drugs.

Bdellins, inhibitors of trypsin and plasmin, were first discovered in 1969 in commercial preparations of hirudin, which had the ability to inhibit the amidolytic activity of plasmin and trypsin. Scientifically known as bdellins, bdellins are a group of proteins that were isolated from the saliva of the medicinal leech (Hirudo medicinalis). These proteins have a number of unique properties and functions: Bdellins have an antithrombotic effect, that is, they can reduce blood clotting. They are able to inhibit the activity of thrombin and other coagulation factors. Research suggests that bdellins may have anti-inflammatory properties. This is due to their effects on various components of the inflammatory cascades in the body. Some bdellins may have an anesthetic effect, which may help reduce pain at the site of a leech bite and influence pain receptors. Bdellins can affect blood flow at the site of the bite, helping to dilate blood vessels and improve blood flow to the area. Bdellins are generally considered biologically safe for the human body, making their use in medical procedures relatively accessible. Research into bdellins is ongoing, and their precise mechanisms of action and potential medical applications may be the subject of further research. Eglins were first identified in commercial hirudin preparations together with bdellins. Eglins are a group of polypeptides with a molecular weight of 6600 to 6800 Da. They have the ability to inhibit α-chymotrypsin, subtilisin and neutral proteases of human granulocytes, such as elastase and cathepsin G. Eglins form strong complexes with these proteases, and their dissociation constants are approximately (2-3) x 10-10 M.

Eglins have been successfully obtained in pure form, and their composition and physicochemical properties have been well studied. Eglin C, for example, has a primary structure of 70 amino acid residues. One of the features of these proteins is the absence of disulfide bonds and methionine, isoleucine and tryptophan residues. This highlights their unique structure among proteins, which may have important implications for their functionality and potential medical applications.

It is important to note that research into eglins and other components of leech saliva is ongoing, and scientists continue to explore their potential applications, including in medicine and biotechnology. Destabilization complex

Destabilase e-(g-Glu)-Lys isopeptidase was first discovered in the secretion of the salivary glands of Hirudo medicinalis in 1986. The enzyme carries out its fibrinolytic (thrombolytic) activity through the hydrolysis of isopeptide bonds formed during the stabilization of fibrin in the presence of blood coagulation factor XIII, causing an unconventional mechanism of fibrinolysis. Destabilase is capable of forming aggregates, which, thanks to the lipid component, can change their spatial orientation. This is supported by the fact that the destabilase exhibits its properties (i.e., hydrolysis of isopeptide bonds) in both aqueous and organic solvents. Destabilase aggregates formed in solution acquire the properties of a micelle, capable of changing its spatial orientation, depending on the physicochemical properties of the solvent, exposing either the hydrophilic or hydrophobic parts of its structure. However, the antithrombotic potential of destabilase is difficult to explain solely by the blockade of platelet aggregation caused by a prostacyclin analogue, the lipid component of destabilase. When analyzing the effect of destabilase on blood coagulation parameters, it was shown that in its presence the thrombin time and the time of recalcification of blood plasma are significantly extended. It is natural to assume that such an effect is provided by hirudin and the blood plasma kallikrein inhibitor, which were found in destabilase preparations. Destabilase is a fairly strong complex containing destabilase and prostaglandin components, hirudin and a plasma kallikrein inhibitor, which can be called the “destabilase complex”. The strength of this complex is evidenced by the fact that it

cannot be destroyed by common methods of biochemistry.

Naturally, the preventive antithrombotic effect of destabilase is due to both the blockade of the internal blood coagulation mechanism (inhibition of platelet adhesion and aggregation and the activity of plasma kallikrein) and the antithrombin activity of hirudin. The penetration of the destabilase complex into the blood is carried out by two mechanisms: conventional transport through intercellular contacts (passive transfer) and transmembrane (active transfer) transport, i.e. through the cell membrane due to integration into the membrane structure. And this is possible for such a high-molecular complex only if it has the properties of a liposome. The ability of the destabilase complex to change its spatial orientation depending on the nature of the solvent is clearly demonstrated by analyzing the activities of the components of the complex during the transition from the aqueous phase to the organic phase and vice versa. In the aqueous phase, all components of the destabilase complex exhibit their activity, while in ethyl acetate only the activity of destabilase (amidase) and prostaglandin (blockade of platelet aggregation); When the complex is transferred back into the aqueous phase, all components exhibit their activity. Thus, the ability of destabilase to aggregate into micelles, as well as to bind hirudin and the kallikrein inhibitor, provides the destabilase complex with the properties and structure of a liposome. All hirudin and kallikrein inhibitor in blood plasma are in a bound state, i.e. in the composition of the liposome, and only in the bacterium-symbiont of leeches these substances are in a free state.

Thus, destabilase, which is a strong protein-lipid complex, has a high aggregation ability. As a result of aggregation of destabilase monomers, a micelle is formed that is capable of changing its spatial orientation depending on the nature of the solvent or contacting substrate, exposing either the hydrophilic or the hydrophobic parts of its structure. Because of contact with blood, the micellar structure of destabilase binds free hirudin and the kallikrein inhibitor of blood plasma, forming a liposome, which in aqueous solvents exhibits the activity of all components of DC (i.e. destabilase, an analogue of prostacyclin, hirudin and IC), while in organic solvents it demonstrates activity only of destabilase and prostacyclin analogue. The monomeric form of the liposome is the DC fraction with a MW of 25 KD.

Conclusions: Based on the above, the following conclusions can be drawn about the biologically active substances produced by medicinal leeches:

It exhibits an antithrombotic effect, blocking various parts of the internal blood coagulation mechanism and preventing the formation of blood clots. In addition, it has a thrombolytic effect, especially on old fibrin clots, with a possible effect on newly formed blood clots. A normotensive effect of medicinal leech saliva associated with low molecular weight substances of prostaglandin nature was discovered. It has a regenerative effect on damaged vessels, helping to restore the atrombogenic surface. It exhibits an antiatherogenic effect, interfering with lipid metabolism and reducing the level of cholesterol and triglycerides in the blood.

It also exhibits an antihypoxic effect, which increases survival during hypoxia, which is important in conditions of pathological processes during pregnancy. An immunostimulating effect was discovered, activating the compliment system and increasing the phagocytic activity of the blood, which contributes to the anti-inflammatory effect. It exhibits an analgesic effect, providing pain relief both at the site of leeches and throughout the body.

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