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Inhibitors of proteinases in physiological processes of a human being

V.A. Divocha*

Odessa International Medical University (OIMU), Ukraine

Abstract

In the review presented they give the data of modern domestic and foreign literature on structure, ability and function of proteinases inhibitors of blood plasma. It has been established that anti- plasmin abilities possess: α-2- antiplasmin, α-2- macroglobulin, α-1- antitrypsin, antitrombin-III, C1- inactivator, inter-α-antitrypsin. Receptors proteinases inhibitors have been found both on a surface of all types of cells, and on internal membranes cellular organellae. Proteinases inhibitors of blood plasma provide: free plasmin inhibition, inhibition of fibrinolysis, inhibition of an induction of a complex plasminigene- monoclonal body, slowing of apoptosis, participation in blood coagulation, kininogenesis, immune reactions (inhibition of reaction immunoglobulin anti-immunoglobulin). Regulation of activity of these inhibitors can be carried out by expression genes which code them, which the help of the TNF-factor of tumours necrosis and, directly, through reduction in synthetic function of liver. .

Introduction

Serum is an important source of proteinase inhibitors. Inhibitors are an integral component of the fibrinolytic system. It has been established that at least six inhibitors have antiplasmin properties: α-2-antiplasmin, α-2-macroglobulin, α-1-antitrypsin, antithrombin-III, C1 - inactivator, inter- α-antitrypsin.

α-2-antiplasmin is a single-chain glycoprotein that belongs to α--2-globulins (a family of serine protease inhibitors - "serpins") and has a molecular weight of 67000-70000 Da. It was opened in 1975-1976. and contains 13% carbohydrates [1]. The inhibitor is unstable in solution, during lyophilization and repeated freezing-thawing. The concentration of α-2-antiplasmin in blood plasma is 1 μM (50-70 mg / L) [2]. The inhibitor forms complexes only with plasmin and trypsin. α-2-antiplasmin inhibits free plasmin at a very high rate. The half-life of plasmin in the presence of α--2-antiplasmin is 0.1-0.5 sec. The interaction of α-2-antiplasmin and fibrin with the same lysine-binding site 1 of plasmin is one of the mechanisms providing the selectivity of plasmin action [3].

The interaction of plasmin and α-2-antiplasmin proceeds in 2 stages: the stage of rapid reversible formation of an enzyme-inhibitory complex and the stage of its slow transformation into an irreversible complex. As a result, a stoichiometrically stable complex (1: 1) is formed, devoid of any enzymatic activity and not dissociating in the presence of reducing and denaturing reagents.

It was found that the formation of a complex of plasmin with α-2-antiplasmin involves the lysine-binding sites of kringles 1-3,4, 5 and a region in the serine-proteinase domain of the enzyme molecule. The multicenter interaction ensures the specificity and effectiveness of the inhibitor. Using a specific chromogenic substrate plasmin C2251, the kinetics of inhibition by b-2-antiplasmin of the amidolytic activity of plasmin and its functionally active derivatives: mini- and micro-plasmin was studied. The results obtained indicate that the Kringle domains of the plasmin molecule are not necessary for the inhibition process, but they control the rate of the reaction of the enzyme with the inhibitor [4].

α-2-antiplasmin also prevents the binding of plasminogen to fibrin and thus has an additional antiplasmin effect (since the binding of plasminogen to fibrin accelerates its activation many times over). As a result of the formation of this complex, fibrin clots become less sensitive to fibrinolysis by plasmin. Fibrinolysis is carried out in the presence of fibrin-stabilizing factor (trans-glutaminase, factor XIII), thrombin and Ca2 +. The inhibition of fibrinolysis is proportional to the amount of a2-antiplasmin combined with fibrin [2].

However, other researchers have shown that b-2-antiplasmin, without the participation of activated factor XIII, interacts with fibrinogen. The studies were carried out using the principle of enzyme immunoassay and biotin-labeled proteins. The inhibitor reveals an affinity for fibrinogen, des AA-, des AA BB fibrinogen, D- and X-fragments of fibrinogen, D-fibrin dimer, but does not bind to the E-fragment [4]. Another functionally important plasmin inhibitor is α-2-macroglobulin, in contrast to α-2-antiplasmin, reacts with plasmin relatively slowly, but has a higher antiplasmin capacity than α-2 [2,5]. Therefore, with large amounts of plasmin and depletion of the supply of α-2 -antiplasmin, α-2 macroglobulin performs inactivation.

α-2 - macroglobulin - inhibitor of a number of proteolytic enzymes (trypsin, chymotrypsin, thrombin, plasmin, kallikrein), which is synthesized outside the liver. This inhibitor is a glycoprotein with a molecular weight of 725,000 Da. It consists of 2 subunits linked by non-covalent bonds and capable of reversible dissociation. Each

Correspondence to: V.A. Divocha, Odessa International Medical University (OIMU), Ukraine, E-mail: divocha09@ukr.net

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of the subunits contains 2 almost identical polypeptide chains. The content of α-2-macroglobulin in blood plasma is 2-4 mg / ml and is significantly higher in women than in men. α-2-macroglobulin is the main member of the human macroglobulin family. This protein is found in all biological fluids and is synthesized by many cells [6,7]. Knem receptors are found not only on the surface of almost all types of cells, but also on the inner membranes of cell organelles [8]. The high informational plasticity of this protein, as well as the presence of an additional hydrophobic binding site, allows it to participate in various, often functionally opposite, immune reactions [6]. This protein is the main carrier of many proteins, enzymes, and cytokines [6, 7], and its various conformational forms are capable of both stimulating and inhibiting the processes of apoptosis [9]. Finally, it is α-2-macroglobulin that participates in the presentation of most antigens to the cells of the immune system [10]. A number of authors propose to consider α-2-macroglobulin as a separate, ancient and evolutionarily conservative link of innate immunity.

Inhibitor α-2-macroglobulin plays an important role in the body as one of the regulators of the activity of enzymes involved in blood coagulation, fibrinolysis, kininogenesis, and immune reactions. It is assumed that, in addition to regulating the activity of proteinases, one of the functions of α-2-macroglobulin is the removal of activated enzymes from the bloodstream.

It has been established that α-2-macroglobulin can bind to the inner surface of the endothelium. This inhibitor also has the ability to bind to the cell membranes of the reticuloendothelial system (lymphocytes, polymorphonuclear leukocytes, macrophages) and inhibit protease-dependent reactions of immune processes.

α-I-antitrypsin, a thermo and acid labile inhibitor (molecular weight 45000-54000 Da. This inhibitor was isolated in 1955 and is a 3,5 S- α-1-glycoprotein with 12.2% carbohydrates) has a clear antiplasmin activity [1].

α-1-antitrypsin provides up to 92% of the antitryptic activity of plasma [11], also inhibits chymotrypsin, plasmin, thrombin, elastase, proteolytic enzymes of leukocytes, bacterial proteinases, but has almost no effect on plasma callecriin. This inhibitor is a fast acting inhibitor of trypsin. The reaction of α-1-antitrypsin binding with plasmin is rather long ("slow antiplasmin"), the rate of which depends on temperature. α-1-antitrypsin is polyvalent, since it protects the body from endogenous and exogenous (bacterial, fungal) proteinases

α-1-antitrypsin is a glycoprotein synthesized in the liver and exists in various phenotypic variants. Distinguish, at least 21 phenotypes of α-1-antitripsn. In the heterozygous state, the Z allele causes a decrease in protein in the blood, and in the homozygous state, an almost complete absence of protein in the blood.

It is assumed that the regulation of α-1-antitrypsin synthesis can be carried out by TNF-tumor necrosis factor [12]. Clinical studies have shown that contraceptives can indirectly, through a decrease in the synthetic function of the liver, have a negative effect on the content of α-1-antitrypsin.

Antithrombin-III also belongs to the active inhibitors of the proteolytic and esterolytic activity of plasmin.

Antithrombin -III (AT-III), one of the main components of the anticoagulant system, is synthesized mainly in the liver, but some of it is also synthesized by the endothelium. Contained in the blood at a concentration of 150-180mcg / ml. The half-life of AT-III is 2-3 days. AT-III consists of 432 amino acids, has 3 disulfide bridges and 4 glycosylation sites. The molecular weight of AT-III is 58000 Da. Almost 90% of all antithrombin activity of the blood is associated with AT-III. It contains 13.4% carbohydrates [1].

It inhibits all coagulation proteases (except factor VII), plasmin, trypsin, and the C1s component of complement. The inhibitory activity of AT-III is significantly increased in the presence of sulfated oligosaccharides, one of which is heparin. The high rate of inhibition of factor X a is due to the fact that in this reaction heparin not only activates AT-III, but also binds to thrombin, acting as a matrix that ensures the effective interaction of the protease with the inhibitor. When highly purified plasmin is incubated with antithrombin III, the enzyme activity is gradually inhibited: within 15-30 minutes. inhibited by 24-38% of plasmin. In the presence of heparin, this reaction is accelerated up to 30 s. The antiplasmin effect of antithrombin III is based on the formation of a non-dissociating complex with plasmin, which is a stoichiometric combination of an enzyme and an inhibitor in a 1: 1 ratio.

The formation of the inactivated thrombin / antithrombin-III complex occurs relatively slowly, which enables the coagulation factors to perform their main function - the formation of a fibrin clot - before they are inactivated [13].

In addition to thrombin, this interaction is realized by inhibition of factors X a and X11a and kallikriin. A number of plasma factors affect the interaction of thrombin with glycoproteins of the luminal surface of the endothelium and the vascular wall. Histidine-rich glycoprotein and factor 4 secreted from platelet granules, as well as vitronectin, bind to heparin-like structures and prevent the inactivation of thrombin and factor X a [14].

Conclusions

Antiplasmin property Possess: α-2-antiplasmin, α-2-macroglobulin, α-1-antitrypsin, antithrombin-III, C1-inactivator, inter- α-antitrypsin. Receptors for proteinase inhibitors are found both on the surface of all types of cells and on the inner membranes of cell organelles.

Inhibitors of blood plasma proteinases provide: inhibition of free plasmin, inhibition of the induction of fibrinolysis, inhibition of the plasminogen-monoclonal body complex, inhibition of apoptosis, participation in blood coagulation, kininogenesis, and immune responses (inhibition of the immunoglobulin / anti-immunoglobulin reaction).

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