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Antithrombin III: A Review

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Abstract

Antithrombin is a plasma glycoprotein that is made up of 432 amino acid residues integral in the control of the coagulation process in haemorrhage. Antithrombin often greatly binds to serine proteases factor II (thrombin). Antithrombin III inactivates thrombin, factor Xa and other enzymes in the intrinsic coagulation pathway, thereby reducing fibrin formation. As part of the normal physiological response to bleeding, platelets flowing in the plasma become initially activated by multiple factors produced by endothelial cells to aggregate and form a plug. Circulating fibrinogen is then converted into fibrin by thrombin through a series of protease activations, which constitute the reactions of the coagulation cascade pathway. Antithrombin III has two specific binding sites; the reactive site consisting of the reactive center loop which binds proteases such as thrombin, factor Xa, IXa, and the heparin-binding domain which binds heparin. Deficiency of antithrombin III may results to venous thrombosis especially the hereditary type.

Keywords: antihrombin III, sysnthesis, Function, antithrombin III deficiency, molecular basis

Introduction

Antithrombin is a plasma glycoprotein that is made up of 432 amino acid residues integral in the control of the coagulation process in haemorrhage. Antithrombin often greatly binds to serine proteases factor II (thrombin). Factor IXa, and factor Xa which hinders the blood coagulation steps involved in the coagulation cascade pathway. As part of the normal physiological reaction to haemorrhage, platelets flowing in the plasma become initially activated by multiple factors synthesized from endothelial cells to aggregate and form a plug (O'Donnell *et al.,* 2019; Okoroiwu *et al.,I 2021;* Okoroiwu *et al.,* 2014; Ifeanyi *et al.,* 2020; Obeagu and Obeagu, 2015; Nwovu *et al.,* 2018; Obeagu, 2022; Obeagu *et al.,* 2022*).*

AntithrombinIII is a plasma glycoprotein involved in thrombin inhibition in the blood coagulation. Antithrombin III inactivates thrombin, factor Xa and other enzymes in the intrinsic coagulation pathway, thereby reducing fibrin formation. As part of the normal physiological response to bleeding, platelets flowing in the plasma become initially activated by multiple factors produced by endothelial cells to aggregate and form a plug. Circulating fibrinogen is then converted into fibrin by thrombin through a series of protease activations, which constitute the reactions of the coagulation cascade pathway. Fibrin acts to stabilize the initial platelet-created plug which determines the completion of the clot formation (O'Donnell *et al.,* 2019).Deficiency in antithrombin has clinical links to increased risks of thrombosis, thromboembolism, and associated with hypercoagulable state (Bravo-Perez *et al*., 2019).

It is a protein in the blood that blocks abnormal blood clots from forming. Antithrombin serves mainly to hinder coaguation action from straying past an isolated injury site. In order to effectively carry out its roles, antithrombin assumes specific structural changes via associations with itself and other co-factors. Congenital antithrombin III deficiency is an inherited disease. Antithrombin is one of the coagulation cascade which provides a counter mechanism to clot formation. AT I refers to the absorption of thrombin onto fibrin after thrombin has activated fibrinogen. AT II refers to a cofactor in plasma, which together with heparin interferes with the interaction of thrombin and fibrinogen. AT III refers to a substances in a plasma that inactivates thrombin. AT IV refers to an antithrombin that becomes activated during and shortly after blood coagulation (Yin *et al*., 1971). The activity is increased by the anticoagulant drug heparin , which enhance the binding of antithrombin to factor IIa (Finley and Greenberg, 2013).AT III is generally referred to solely as Antithrombin.

Structure of antithrombin III

Antithrombin has a half-life in blood plasma of around 3 days. The normal antithrombin concentration in human blood plasma is high at approximately 0.12 mg/ml, which is equivalent to a molar concentration of 2.3 µM. Antithrombin has been isolated from the plasma of a large number of species additional to humans. Although its physiological state is typically a single peptide with only one subunit, antithrombin often crystallizes as a dimerthat includes both its latent and Da. The unactivated or native state of antithrombin refers to its conformation sans prior interaction with its cofactors- heparin or heparin sulfate. The secondary structure of this native state is comprised of three beta sheets and nine alpha helices interconnected by random coils. This core is referred to as the A-sheet and is an essential component of conformational changing (McCoy *et al*. 2003). The native tertiary structure adopted by this protein contains a domain specific for the heparin pentasaccharide ligand. Coordination of the N-terminal region of the protein, along with the N-terminal end of the helix A and all the helix D ultimately forms the binding site (Olson *et al*., 2010).

Molecular basis of antithrombin III

Antithrombinis part of a family of serine protease inhibitors known as serpins. Serpins generally consist of a highly conserved structure of amino acid chains organized into three beta-sheets, nine alpha-sheets, and a reactive center loop (RCL) designated as the sequence of amino acids which serve as the reactive site for protease interaction (Ersdal-Badju*et al*., 1997). The reactive center loop (RCL) in antithrombin exist along the amino acid chain sequence at the 393 arginine residue and 394 serine residue near the carboxyl-terminal of the amino acid sequence. It is the region within the antithrombin that creates the antithrombin-protease complex for inhibition (Ersdal-Badju*et al*., 1997). Depending on the number of occupied glycosylation sites, anti-thrombin further subcategorizes into two isoforms: alpha antithrombin and beta antithrombin (Karlaftis*et al*., 2014).

Alpha antithrombvin refers to antithrombin in which oligosaccharides bind all four glycosylation sites. It is the predominant configuration of antithrombin, presenting as around 90% of the antithrombin in the plasma (Pol-Fachin*et al*., 2014). Beta antithrombin, however, refers to antithrombin with three of the four sites occupied, with oligosaccharide chain at Asn135 missing (Pol-Fachin*et al*., 2014). This change in configuration increases the affinity of beta antithrombin binding to heparin at a designated heparin-binding domain (Amiral and Seghatchian, 2011). The binding of heparin dramatically increases the affinity for antithrombin to bind to serine protease, enhancing the functional efficiency of antithrombin to inhibit clot formation.

Mechanism of antithrombin III

Antithrombin III has two specific binding sites; the reactive site consisting of the reactive center loop which binds proteases such as thrombin, factor Xa, IXa, and the heparin-binding domain which binds heparin. Strands from beta-sheet A of the antithrombin site separate halfway along the length and the reactive center loop(RCL) subsequently rearranges at the point of entry into the sheet A along with various other conformational changes, which serve to increase the mobility of the reactive center loop (RCL). The increased mobility provides a docking site of the protease, which in turn creates an irresistible complex. The inhibitor-protease complex is then rapidly removed from the circulation no more than 5 minutes after formation, which removes thrombin from the circulation, disrupting the clotting effect of the coagulation cascade. The formation of antithrombin-protease complex, while irreversible, is a naturally slow and inefficient reaction. The prcess can be rapidly increased up to 1000-fold with the presence of

sulfated polysaccharides in the form of heparin and heparin sulfate (Perry, 1994).

Heparin contains a unique pentasaccharide sequence within its glycosaminoglycan chain consisting of negatively charge sulfate groups, which is responsible for its high-affinity towards the antithrombin heparin-binding domain. The heparin-binding domain located on the surface of antithrombin contains positively charged arginine and lysine which bind to the negatively charged domains of the heparin pentasaccharide sequence through partially an allosteric mechanism (Roth *et al*., 2015). The successful binding of heparin activates a conformational change within the antithrombin, which increases its affinity towards protease, promotes the formation of the antithrombin-protease complex, and ultimately inhibits blood coagulation (Van Amsterdam*et al*., 1995). Allosteric activation induced by heparin to the antihrombinserpin structure has been the object of extensive study, and while the kinetics of the reaction is quite complex, generally the allosteric activation of antithrombin induces structural changes within the RCL, the heparin-binding site, and the hydrophobic core that constitutes the antithrombin (Roth *et al*., 2015).

Function of antithrombin III

Antithrombin is the major inhibitor of thrombin, factor IXa and factor Xa in plasma, but it also inactivates the other serine protaeses of the intrinsic coagulation pathway, factors Xia and XIIa, as well as some noncoagulation serine proteases, such as plasmin, kallikrein and the complement enzyme C1. Most proteases are inactivated much more slowly than thrombin. Inhibition by antithrombin involves the formation of a stable 1:1 complex between the active domain of the serine protease and the reractive site of antithrombin, which proteases initially recorgnize as a substrate. During the cleavage of the reactive site bond in antithrombin conformational changes occurs in the inhibitor that traps the protease.

Antiangiogenic antithrombin III

Angiogenesis is a physiological process involving the growth of new blood vessels from pre-existing vessels. Under normal physiological conditions angiogenesis is tightly regulated and is controlled by a balance of angiogenesis stimulators and angiogenic inhibitors. Tumor growth is dependent upon angiogenesis and during tumor development a sustained production of angiogenic stimulatory factors is required along with a reduction in the quantity of angiogenic inhibitory factors tumor cells produce (O'Reilly. 2007).The cleaved and latent form of antithrombin potently inhibit angiogenesis and tumor growth in animal models. The prelatent form of ofantithrombin has been shown to inhibit angiogenesis in-vitro.Antithrombin functions as a principal plasma protein inhibitor of blood coagulation proteinases and belongs to a family of serine protease inhibitors (serpins) which have common mechanism of inhibition. Antithrombin acquires a potent antiangiogenic activity upon conversion of the native molecule cleaved or latent conformation (Azhar *et al*., 2013). The native form of antithrombin binds with high affinity to vascular heparin sulfate proteoglycans containing a specific pentasaccharide sequence and it is this cofactor interaction that activates antithrombin to maximal rate of thrombin inhibition (Azhar *et al*., 2013).

Cleaved and latent antithrombin III

Cleavage at the reactive site results in entrapment of the thrombin protease, with movement of the cleaved reactive site loop together with the bound protease, such that the loop forms an extra sixth strand in the middle of beta sheet A. Antithrombin (AT), a member of the serine protease inhibitor family, is the key regulator of thrombin activity in vivo. Thrombin inhibition is accomplished by the formation of covalent thrombin-AT (TAT) complex. The rate of inhibition is accelerated by heparin, which also leads to the formation of a substantial amount of cleaved AT. Will produce a murine monoclonal antibody (mAb) (M9) that is specific for the two forms of AT, in which the reactive center loop is inserted into the beta-sheet A, i.e cleaved and latent AT. The antibody has no measurable affinity for native AT (Kjellberg*et al*., 2006). Native antithrombin can be converted to latent antithrombin by heating alone or heating in the presence of citrate. However, without extreme heating and at 37°C 10% of all antithrombin circulating in the blood is converted to the L-antithrombin over a 24-hours period. Not only is the latent form of antithrombin inactive against its target coagulation proteases, but its dimerization with an otherwise active nature antithrombin molecule also results in the native molecules inactivation. A form of antithrombin that is an intermediate in the conversion between native and latent forms of antithrombin has also been isolated and this has been termed prelatentantithrombin (Larsson *et al*., 2001).

Antithrombin III deficiency

Antithrombin III is a nonvitamin k-dependent protease that inhibits coagulation by neutralizing the enzymatic activity of thrombin. Antithrombin III activity is marked potentiated by heparin, the principal mechanism by which both heparin and low-molecular-weight heparin results in anticoagulation. This deficiency may be inherited or acquired. It is a rare hereditary disorder that generally comes to light when a patient suffers recurrent venous thrombosis and pulmonary embolism and repetitive intrauterine fetal death (Kurman, 2002).

Hereditary antithrombin III deficiency results in a state of increased coagulation which may lead to venous thrombosis (Khor and Van, 2010).Inheritance is usually autosomal dominant, though a few recessive cases have been noted. AT III may occur if too much of the protein is being used up.It is a type of multifactorial disease where both genetics and environment affect the procoagulant and anticoagulant forces, finally leading to antithrombin III deficiency. Various mutations in genes, such as deletion or addition of genes, for anticoagulant proteins such as protein C, antithrombin or protein S are one of the risk factors (Dahlback, 2008). The deficiency maybe caused by adhesion of platelets with immobilized fibrinogen (Loncar*et al*., 2006).

Acquired antithrombin deficiency

Acquired antithrombin deficiency occurs as a result of three distinctly different mechanisms. The first mechanism is increased excretion which may occur with renal failure associated with proteinuria nephrotic syndrome. The second mechanim results from decreased production as seen in liver failure or cirrhosis or an immature liver secondary to premature death. The third mechanism results from accelerated consumption which is most pronounced as consequences of severe injury trauma. The causes of acquired antithrombin III deficiency are easier to find than the hereditary deficiency (Khor and Van, 2010).

Congenital antithrombin III deficiency

This is a genetic disorder that causes the blood to clot more than normal. It is an autosomal dominant disorder in which an individual inherit one copy of the SERPINC1 gene on chromosome 1q25.1, which encodes antithrombin III. This condition leads to increased risk of venous and arterial thrombosis, with an onset of clinical manifestations typically appearing in young adulthood. Antithrombin III is a protein in the blood that blocks abnormal blood clots from forming. Congenital antithrombin III deficiency is an inherited disease, it occurs when a person receives one abnormal copy of the antithrombin III gene from a parent with the disease.

When is an antithrombin III test performed?

If blood clot develops in blood vessels. Deep vein thrombosis occurs when a clot develops in one of the veins deep in the body. This type of clot can develop anywhere, but most likely to form in the legs. If the clot breaks free, it can travel to other parts of the body, if it travels to the lungs, it can cause a pulmonary embolus, or a clot in the lungs. Recurring blood clots indicates that there isn't enough antithrombin III or other clotting factors to prevent clots from forming.

Diagnosis

Different laboratory tests can be performed to investigate for antithrombin III deficiency.

1. Numerical analysis for antithrombin can be performed. A lower antithrombin III level increases the risk of venous thrombosis and pulmonary embolism (Gaman and Gaman., 2014).
2. Anticardiolipin antibodies can be injected.
3. Antigen activity and total tests for Protein C and Protein S can be checked to see if the genes of their proteins have been mutated.
4. Prothrombin time (PT) and partial thromboplastin (aPTT) time can be calculated.
5. Factor V Leiden test can be performed to check blood clotting and adhesion of platelets (Jennings and Kotha., 2013).

Image experiments can be studied to evaluste the antithrombin III deficiency. First of all, echocardiography is performed to all patients suffering from antithrombin III deficiency. These patients will first go through the blood test to find a sign of arterial thrombus, then echocardiograghy can be done (Hayirogl*et al*., 2016).

Second, doppler ultrasonography is usually performed at earlier stage than echocardiograpghy. It is used to find the resolution of an acute thrombus (Hassan., 2018).

Finally, ventilation-perfusion scanning is tested to check for images of pulmonary thrombosis.

Risks of the antithrombin III test

- Difficulty obtaining a blood sample, resulting in multiple needle sticks
- Pain, discomfort, throbbing at the site of puncture
- Excessive bleeding at the puncture site
- An accumulation of blood under the skin at the puncture site
- Development of an infection at the puncture site
- Fainting
- Lightheadedness

Management

Heparin enhances ATIII activity and neutralizes activated serine protease coagulation factors (Edward, 2011). Patients with ATIII deficiency requiring anticoagulant therapy with heparin will need higher doses of heparin. ATIII binds to thrombin and then forms the thrombin-anti thrombin complex of TAT complex. The binding of thrombin to AT is greatly enhanced in the presence of heparin. Heparin does not affect Vitamin K metabolism, so giving vitamin K1 will not reverse the effects of heparin.

Clinical significance

Hereditary antithrombin deficiency categorizes into Type I Type II. Type I results in a complete deficiency of antithrombin gene products if in a homozygous state. A heterozygous genotype results in approximately 50% of functional antithrombin activity. Type II deficiencies characteristically demonstrate the production of altered antithrombin protein, which results in the loss of its function (Maclean and Tait, 2007). The location in which the protein undergoes alteration can affect the reactive site, heparin-binding domain, or both. The lack of antithrombin activity or production most commonly presents as a deep vein thrombosis. The first instance of thrombosis occurs at relatively young ages, initial treatment for thrombosis in these patients is heparin, and maintenance treatment is generally ongoing with an oral anticoagulant. For asymptomatic incidences, primary prophylaxis is currently not recommended due to the increased risk of fatal hemorrhage on the long-term anticoagulation versus the lesser risk fatal VTE. Acquired antithrombin deficiency is generally associated with either decreased production as a part of impaired synthesis in the instance of acute liver failure, cirrhosis, malnutrition, a direct loss of antithrombin in conditions including nephrotic syndrome, or due to an increase in consumption (Maclean and Tait, 2007).

Antithrombin gets lost through consumption coagulopathies, including disseminated intravascular coagulation system (DIC), microangiopathies with thrombosis, malignancies, and hematologic transfusion reactions (Maclean and Tait, 2007). The loss of antithrombin in sepsis is in part due to the increase in plasma turnover, and the down regulation of antithrombin production. The degree of deficiency also correlates with the severity of the illness. The effects of antithrombin on the body are extensive, and an understanding of the structure and function provides foundational knowledge to integrate treatments and clinical practices for patients with antithrombin disorders (Perry, 1994).Antithrombin has been studied in sepsis to reduce diffuse intravascular coagulation and other outcomes (Allingstrup*et al*., 2016).

The role of antithrombin III in diseases,Antithrobin deficiency generally comes to light when a patient suffers recurrent venous thrombosis and pulmonary embolism.

1. Acquired antithrombin deficiency.
2. Inherited antithrombin deficiency
3. Type I antithrombin deficiency:

- Mutations may produce unstable antithrombins that either may not be exported into the blood correctly upon completion biosynthesis or exist in the blood for a shortened period of time.
- Mutations may affect mRNA processing of the antithrombin gene.
- Minor insertions or deletions may lead to frame shift mutations and premature termination of the antithrombin gene.
- Point matuations may also result in the premature generation of a termination or ctop codon.
- Type II antithrombin deficiency:
- Subgroup IIa - Decreased thrombin inactivation, decreased factor Xa inactivation and decreased heparin affinity.
- Subgroup IIb – Decreased thrombin inactivation and normal heparin affinity.

- Subgroup IIc – Normal thrombin inactivation, normal factor Xa inactivation and decreased heparin affinity.

Conclusion

Antithrombin is a plasma glycoprotein that is made up of 432 amino acid residues integral in the control of the coagulation process in haemorrhage. Antithrombin often greatly binds to serine proteases factor II (thrombin). Antithrombin III inactivates thrombin, factor Xa and other enzymes in the intrinsic coagulation pathway, thereby reducing fibrin formation. Deficiency of antithrombin III may results to venous thrombosis especially the hereditary type.

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