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Commentary on Molecular Dynamic and Pharmacological Studies on Protein-Engineered Hirudin Variants of Hirudinaria Manillensis and Hirudo Medicinalis

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Commentary

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DESCRIPTION

Hirudins are direct thrombin inhibitors. Historically, hirudin was the first anticoagulant used for parenteral anticoagulation prior to the use of heparin, as well as the first anticoagulant for haemodialysis in humans. Heparin, on the other hand, induces a potentially fatal adverse immune reaction known as Heparin-Induced Thrombocytopenia (HIT), which is caused by the expression of Immunoglobulin G (IgG) antibodies that bind to the complex formed by heparin and platelet factor. It activates endothelial cells and platelets and enhances the formation of thrombi. In a deep carotid injury animal model, hirudin but not heparin significantly reduced platelet deposition and eliminated mural thrombosis.

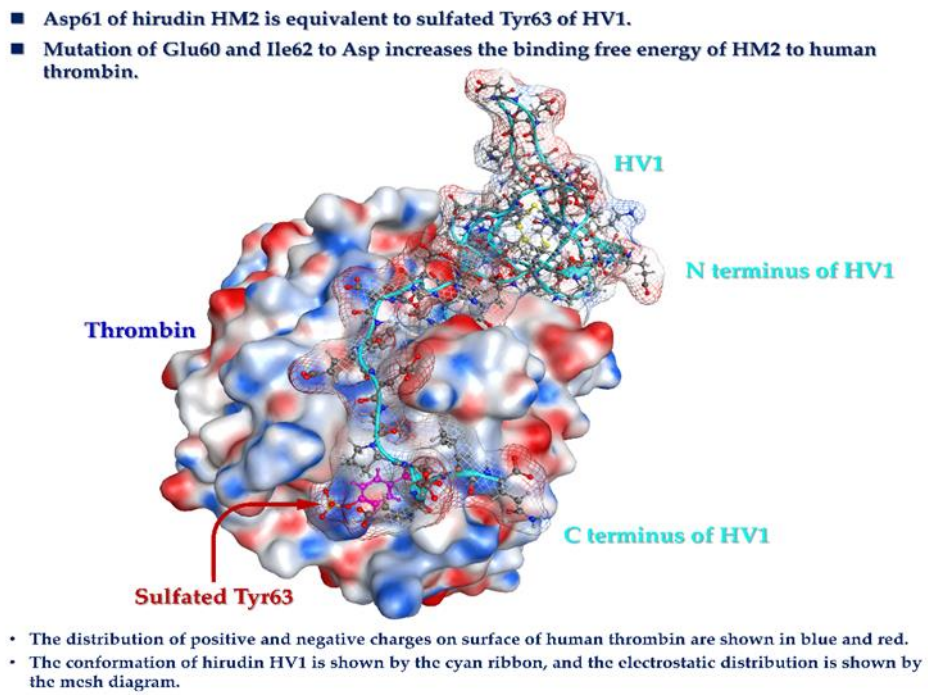
Hirudinaria Manillensis and Hirudo Medicinalis. RRJ Pharm Anal. 2023;12:001

Two medicines derived from hirudin, bivalirudin and desirudin, are currently used in clinical practice. Bivalirudin is commonly used for anticoagulation in patients undergoing Percutaneous Coronary Intervention (PCI). It is also indicated for PCI with provisional use of glycoprotein IIb/IIIa antagonist therapy and for patients undergoing PCI who have, or are at risk of having, HIT or HITTS. Desirudin is primarily used to prevent deep vein thrombosis after hip replacement surgery, which can result in pulmonary embolism. Before Bayer discontinued production in 2012, lepirudin was also available for anticoagulation in patients with HIT and adult patients with Acute Coronary Syndromes (ACS) such as unstable angina and acute myocardial infarction without ST elevation. Lepirudin is produced in yeast cells and is identical to natural hirudin with the exception of the absence of sulfate on the tyrosine residue (Tyr63) and the substitution of leucine for isoleucine.

Thrombin is the core enzyme in the coagulation cascade and an appealing target for anticoagulant medication development. The most powerful thrombin inhibitor identified so fat is native hirudin. The N-terminus of hirudin binds to the active site of thrombin, whereas the C-terminus binds to the fibrinogen recognition site, exosite I. The sulfation of Tyr63 in Hirudin Variant 1(HV1) of Hirudo medicinalis causes a conformational shift in the Lys81 side chain of thrombin, resulting in a salt bridge and a hydrogen connection between the phenolic hydroxyl of thrombin Tyr76 and the sulfate group of HV1. Because tyrosine O-sulfation is not inherent in microorganism expression systems, gene-recombinant hirudin medicines applied in clinical practice are much weaker than natural hirudin.

An integrative analytical approach was employed in a study published in the British Journal of Pharmacology by Yan to clarify the anticoagulant effects of C-terminus-modified hirudins, HV1 and hirudin variant 2 of *Hirudinaria Manillensis* (HM2) [1]. In umbrella sampling of the changes in the Gibbs free energy in the molecular system when the C-terminus of hirudin was pulled away from human thrombin, it was found that the Asp61 mutation of HM2 to Ala decreased the binding free energy of the HM2 C-terminus to thrombin, with the Coulombic potential energy playing a substantial role, whereas the Glu-60Asp (E60D) and Ile-62Asp (I62D) double mutation enhanced the binding free energy. The E60D and I62D double mutation of HM2 increased hirudin-thrombin affinity *in vitro*; the Ki value of HM2-E60D-I62D was lower than that of both secreted and gene-recombinant wild type HM2.

Proteins produced in yeast cells have high levels of glycosylation with mannose, which is not only immunogenic but also influences protein folding. The use of recombinant HM2-E60D-I62D hirudin produced by bacteria may help to reduce allergy reactions associated with yeast glycosylation that differs from that of humans. Hirudin, on the other hand, has a relatively short half-life. Protein engineering, albumin conjugation, or appropriate delivery forms, such as PEGylation, nanoparticle carriers, and so on, could all aid in increasing hirudin's blood stability.



Highlights

- Asp61 of hirudin HM2 is equivalent to sulfated Tyr63 of HV1.
- Mutation of Glu60 and Ile62 to Asp increases the binding free energy of HM2 to human thrombin.
- The use of recombinant hirudin produced from bacteria may reduce allergy reactions related with yeast glycosylation that differs from that of humans.

REFERENCES

1. Yan S, et al. Molecular dynamic and pharmacological studies on protein-engineered hirudin variants of Hirudinaria manillensis and Hirudo medicinalis. Br J Pharmacol. 2022;179:3740-3753.