

Redefining Approaches to Asthma: Bridging the Gap Between Heparin and Its Anti-inflammatory Activities

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Abstract Heparin is widely used as an anticoagulant. Currently, this macromolecule is at the forefront in the field of glycobiology because of the recognition of its therapeutic potential in a wide range of medical conditions including inflammation. Heparin is composed of anticoagulant and non-anticoagulant molecules. A large body of evidence suggests that the anti-inflammatory activities of heparin are attributed to its non-anticoagulant molecules and are therefore independent to its anticoagulant effect. However, the potential therapeutic use of heparin in inflammatory conditions is hindered by the presence of anticoagulant molecules causing the risk of bleeding. Therefore, there is an emerging interest in identifying non-anticoagulant molecules of heparin responsible for the anti-inflammatory effects of the parent molecule. The present editorial commentary focuses on the non-anticoagulant applications of heparin for the management of asthma. The commentary concisely describes the plausible mechanisms of action of heparin involved in the therapy of asthma. It also discusses various approaches that are utilised for the development of novel non-anticoagulant analogues of heparin that possess the potent anti-asthmatic activity of the parent

molecule but are devoid of anticoagulant effect. We also briefly outline potential future approaches for the use of this molecule as an effective anti-inflammatory agent.

Keywords Heparin · Inflammation · Asthma · Anticoagulant molecules · Bleeding · Non-anticoagulant molecules · Anti-inflammatory

Heparin, a naturally occurring glycosaminoglycan, was discovered more than 100 years ago, and since then, enormous progress has been made in identifying its true physiological role. In clinical practice, heparin is widely used as an anticoagulant drug and, in fact, the identification of the molecular mechanism via which heparin exerts its characteristic anticoagulant effect represented a landmark in this field of biological research. It is now known that only a small sequence (generally referred to as pentasaccharide structure) within this macromolecule is responsible for its potent anti-coagulant effect.

The complete physiological role of heparin in the body is still unclear. Heparin is present in a wide range of different species, including some invertebrates that do not even have a blood coagulation system. In addition, anticoagulation is physiologically achieved mostly by heparan sulphate proteoglycans derived from the endothelial cells. Heparin, an intricate mixture of anticoagulant and non-anticoagulant molecules, encompasses a high degree of structural heterogeneity and complexity, making it one of the most information-dense molecules in biology. Heparin is produced by mast cells and released into the vasculature; it is therefore believed that heparin plays an important role in regulating the inflammation cascade. Heparin has indeed been shown to interact with a wide range of biological molecules,

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thereby playing a pivotal role in modulating inflammatory responses associated with several disorders, including asthma.

Although heparin possesses anti-inflammatory activities, the presence of anticoagulant molecules can increase the risk of bleeding when used for the management of asthma or other inflammatory conditions. However, interestingly, the anti-inflammatory effects of heparin are reported to be due to the presence of molecules that are not related to its anticoagulant effect (also referred to as non-anticoagulant molecules of heparin). Therefore, it is imperative to differentiate the anticoagulant and non-anticoagulant molecules of heparin when examining its potential to be utilised as a safe and effective anti-inflammatory agent.

Several chemically or enzymatically modified non-anticoagulant analogues of heparin have been developed and tested for their anti-asthmatic potential. However, these processes are carried out at extreme temperatures and cause structural modification within the parent heparin, resulting in non-anticoagulant analogues of heparin with impaired anti-inflammatory activities. To avoid this, attempts have been made to separate the anticoagulant and anti-inflammatory molecules of heparin via sophisticated separation science techniques. New and emerging analytical approaches have permitted the identification and isolation of heparin derivatives responsible for the potent anticoagulant and anti-inflammatory properties of the parent macromolecule. Such technological advances represent a cornerstone, allowing the isolation of non-anticoagulant molecules of heparin and their subsequent pharmacological testing in various biological applications including asthma.

To understand the complex biological effects that heparin mediates, proper understanding of its sequence-structure-function relationship is required. Anti-inflammatory activities of heparin are known to be sequence-dependent. The length of repeating disaccharide units of heparin is known to be one of the vital features that allow it to bind and inhibit the activity of proteins involved in the process of inflammation. Importantly, conformationally defined patterns of sulphate groups within the repeating disaccharide units are known to be critical for regulating the interaction between heparin and various inflammatory markers. For instance, desulfation of heparin has been reported to contribute to its potential to bind and inhibit the release of inflammatory mediators associated with asthma. Otherwise, the knowledge of the precise anti-asthmatic effects of heparin is still incomplete.

Several potential pathways have been proposed to explain the therapeutic effectiveness of heparin in asthma. For instance, it has been suggested that mast cell-

derived heparin possesses a protective role in the regulation of inflammatory responses, hence limiting the extent of airway inflammation during asthma. In experimental models, heparin inhibited the degranulation of mast cells and consequent release of inflammatory mediators associated with asthma. This effect of heparin was shown to be due to the inhibition of inositol triphosphate signalling and immunoglobulin E synthesis.

Adhesion molecules like selectins are known to play a major role in asthma. Calcium-dependent binding of heparin to lectins via the NH₂-terminal domain of lectins has been reported to reduce the extent of asthmatic inflammation. Recent *in-vitro* and *ex-vivo* studies suggested that the interaction between 6-*O*-sulfated heparin derivatives and T cell- as well as protease-activated receptor(s) inhibited the release of potent inflammatory mediators associated with asthma. Likewise, several animal studies have revealed a similar protective role of heparin in asthma. For instance, heparin confers benefits against allergen-induced airway hyper-responsiveness by preventing nitric oxide signalling. In addition, heparin has also shown potential in several controlled clinical studies where it attenuated exercise-, histamine- and allergen-induced bronchoconstriction and can be a valuable add-on treatment in bronchial asthma. Possible reported mechanisms of action for such anti-inflammatory response are (i) inhibition of mast cell activation and mast cell mediators via blockade of 1,4,5 triphosphate receptors, (ii) inhibition of eosinophil cell migration and eosinophil cationic proteins and (iii) modification of inflammatory cell influx (decreased percentages of eosinophils and lymphocytes in bronchoalveolar lavage).

It is evident from basic science investigations, as well as clinical observations, that heparin possesses anti-inflammatory activities. However, questions regarding its true pharmacologic potential, clinical limitations, safety and efficacy when utilised for the management of inflammatory disorders, including asthma, still need to be answered. Importantly, it should be noted that heparin preparations are commercially standardised for its use as an anticoagulant and not as non-anticoagulant. A close examination has suggested significant structural differences between non-anticoagulant molecules present in different heparin preparations. Therefore, before attempting to answer the preceding questions, characterisation of the structural elements within heparin that account for its anti-inflammatory response, via the development of novel characterisation techniques, is warranted.

Continuous research efforts have assisted in solving a few mysteries behind the use of heparin as an anti-inflammatory agent. However, much remains to be identified. The complexity of this macromolecule greatly

complicates the detailed understanding of its protective character in inflammation. Although by no means a trivial undertaking, further knowledge of the structural, chemical and biological aspects of heparin during inflammation would help us develop a myriad of heparin derivatives for various inflammatory disorders, including asthma. Moreover, future research should also focus on the route of delivery that best confines the distribution of heparin molecules to target asthma and other inflammatory disorders. With rapid advances in science and

technology, we look forward to expanding and establishing the use of heparin as an anti-inflammatory drug.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.