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Dynamics of pathologic clot formation: A mathematical model

Evgeny A. Shavlyugin [a,*], Leonid G. Hanin [b], Mikhail A. Khanin [a]

[a] Mathematical Modeling Laboratory, Center for Theoretical Problems of Physicochemical Pharmacology, Russian Academy of Sciences, Kosygina Street 4, Moscow 119991, Russia

[b] Department of Mathematics, Idaho State University, 921 S. 8th Avenue, Stop 8085, Pocatello, ID 83209-8085, USA

HIGHLIGHTS

- Mathematical model of dynamics of pathological clot formation is developed.
- The case of slow clot formation (time window: 3–6 h).
- Kinetic constants of the initiating biochemical reactions were evaluated.
- Influence of different inhibitors on clot dynamics was studied.
- Simultaneous inhibition of factors XI and XII for clot prophylaxis is proposed.

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ABSTRACT

Recent studies have provided evidence of a significant role of the Hageman factor in pathologic clot formation. Since auto-activation of the Hageman factor triggers the intrinsic coagulation pathway, we study the dynamics of pathologic clot formation considering the intrinsic pathway as the predominant mechanism of this process. Our methodological approach to studying the dynamics of clot formation is based on mathematical modelling. Activation of the blood coagulation cascade, particularly its intrinsic pathway, is known to involve platelets. Therefore, equations accounting for the effects of activated platelets on the intrinsic pathway activation are included in our model. This brings about a considerable increase in the values of kinetic constants involved in the model of the principal biochemical processes resulting in clot formation.

The purpose of this study is to elucidate the mechanism of pathologic clot formation. Since the time window of thrombolysis is 3–6 h, we hypothesize that in many cases the rate of pathologic clot formation is much lower than that of haemostatic clot. This assumption is used to simplify the mathematical model and to estimate kinetic constants of biochemical reactions that initiate pathologic clot formation. The insights we gained from our mathematical model may lead to new approaches to the prophylaxis of pathologic clot formation. We believe that one of the most efficient ways to prevent pathologic clot formation is simultaneous inhibition of activated factors XII and XI.

1. Introduction

Pathologic thrombosis is among the most common causes of mortality and disability. It leads to cardiac infarction, stroke, obstruction of pulmonary artery, as well as to stenosis and occlusion in other arteries. Despite numerous studies, the mechanism of pathologic clot (PC) formation is not well understood yet. It is clinically proven that atherosclerotic plaque rupture leads to activation of the processes that result in thrombosis (Hechler and Gachet, 2011). Thus, these complicated atherosclerotic plaques are the main risk factor for acute thrombosis.

Previous studies of therapeutic thrombolysis (Donnan et al., 2003) suggest that in most cases pathologic thrombosis results from relatively slow biochemical processes. This manifests in considerable duration (3–6 h) of therapeutic time window during which thrombolytic treatment is efficient. The main goal of the present work is to study the mechanism and kinetics of slow PC formation based on a mathematical model. Such a model can help elucidate the mechanism of this process and find the most effective targets for prophylaxis of PC formation. Our approach emphasizes the effects of activated platelets on the dynamics of pathologic clot formation that manifest through the following positive feedback loop: "thrombin production → platelet activation → expression of

* Corresponding author. Tel.: +7 926 3697840.
E-mail addresses: eshavlyugin@gmail.com (E.A. Shavlyugin), hanin@isu.edu (L.G. Hanin).

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phospholipids by platelets→increase in the values of the kinetic constants of biochemical reactions."

The system of blood coagulation is activated by two principal mechanisms: extrinsic and intrinsic pathways. Extrinsic coagulation pathway (ECP) is initiated through the exposure to blood of the tissue factor (TF) secreted by endothelial cells. The physiological role of the ECP is to minimize blood loss after blood vessel injury (Dahlbäck, 2000).

By contrast to the extrinsic pathway, physiological function of the intrinsic coagulation pathway (ICP) has not been well understood so far. Recent studies (Renné et al., 2005; Gailani and Renné, 2007) have shown that ICP is an essential player in the process of pathologic clot formation. They have also revealed that the first step in ICP activation is the initial activation of the contact system (CS). It was reported in Renné et al. (2005) that no pathologic clots were observed in factor XII knockout mice. This suggests that activation of the ICP involves activation of the Hageman factor (factor XII).

Various models of ICP were proposed on the basis of experimental data (Chatterjee et al., 2010; Xu et al., 2010; Danforth et al., 2009; Kramoroff and Nigretto, 2001; Guo, 2006). A review of the existing blood coagulation models was recently published in Hemker et al. (2012). In the present work, we used these known models to develop an alternative mathematical model of the mechanism of PC formation. In the previously published models, the mechanism of platelet activation by thrombin and its effects on the functioning of the ICP enzymatic cascade was not considered in detail. The existing theoretical models of ICP are unable to explain a substantial prolongation of the therapeutic time window as they consider only relatively high thrombin concentrations like those associated with the ECP. Also, these models disregard the platelet activation process and assume that all platelets are already activated when ICP is launched. By contrast, our model takes into account the impact of platelet activation process on ICP dynamics through the dependence of enzymatic kinetic constants on the fraction of activated platelets inferred from experimental data.

We believe that a detailed description of the initial stage of PC formation is crucial. Therefore, in this work we emphasize the kinetics of platelets activation and aggregation. Our model of ICP including the enzymatic cascade (see Section 2), consists of a system of ordinary differential equations, some of which are linear and some non-linear, representing the mass balance of ICP reagents and equations that describe the kinetics of platelet activation by thrombin.

Biochemical reactions of ICP take place on the membrane of activated platelets and involve phospholipids, such as phosphatidylserine, phosphatidylethanolamine and phosphatidylcholine, expressed on the platelet surface. These phospholipids play a role of cofactors in a series of enzymatic reactions during blood coagulation, most notably, activation of prothrombin and factor X. This results in a significant (up to 1000 times) increase in the values of some of the kinetic constants of these reactions (Rawala-Sheikh et al., 1990). Platelets also play a critical role in activation of the ECP (Hemker et al., 2012).

PC formation via ICP is a considerably slower process than haemostatic clot formation. This is particularly evident from the observed long (3–6 h) therapeutic time window of the thrombolysis (Donnan et al., 2003). By contrast, haemostatic clots are known to be formed within minutes after blood vessel wall injury. A relatively slow pace of PC formation enabled considerable simplification of the mathematical model utilized in our work. In particular, we neglected such processes as depletion of substrates as well as convection and diffusion of coagulation factors. One of the most likely biochemical mechanisms of PC formation via ICP is auto-activation of factor XII on the surface of atherosclerotic plaques (Schmaier, 2008). In the present study, we also consider proteolytic activation of prekallikrein as one of the ICP-initiating biochemical reactions.

Using our model we found the range for an unknown aggregate kinetic constant of contact system activation that allows for PC formation within 3–6 h, which corresponds to the observed duration of thrombolytic time window. As expected, only relatively low values of this activation constant satisfy such a constraint (see Section 3). Our model predicts that slow PC formation occurs for low thrombin concentrations (0.01–0.1 nM). A relatively wide variation of thrombin concentration may serve as an explanation for a considerable range in the duration of therapeutic time window.

Our model deals with a spatially localized process of PC formation that takes place *in vivo*. Consequently, it does not take into account the loss of coagulation factors in plasma, for such a loss would be naturally compensated. However, when dealing with an *in vitro* system, such loss should be taken into consideration because of its substantial influence on the dynamics of thrombin and fibrin generation and thereby on the rate of clot formation.

Unfortunately, the authors of this work were unable to find published experimental data that could directly validate the proposed mathematical model. Known experimental studies deal only with the processes of fast clot formation under high thrombin concentrations; such processes are completed within a few minutes. Also, many of these studies simulated the effects of platelet activation by artificial injection of phospholipids. Such an approach prohibits assessment of the effects of platelet activation kinetics, which are central to this work. We note, however, that our mathematical model of pathologic thrombosis is based on well-established equations of enzymatic and second-order reactions that are known to adequately describe relevant biochemical processes while our description of platelet activation and aggregation is based on fitting recognized experimental data (White et al., 1981). This may serve as an indirect validation of our model.

2. Mathematical model

The scheme of biochemical reactions of ICP is presented in Fig. 1. Biochemical reactions of ICP are described mathematically by the kinetic equations given in Appendix A. These equations are well established in the literature (see e.g. Khanin et al., 1998). The key additional features that distinguish our mathematical model of ICP from the existing models are as follows:

(i) We assumed ICP to be the main mechanism that activates pathologic clot formation and therefore did not include reactions of ECP and its factors in our model;
(ii) Because pathologic clot formation is a relatively slow process we assumed that depletion of substrates is negligible, which resulted in a much simpler model;
(iii) We included platelet activation reactions as a critical component of the model. In particular, apart from known feedback loops, the model incorporates another positive feedback loop, namely "thrombin production→platelet activation→expression of phospholipids by platelets→increase in the values of the kinetic constants of biochemical reactions" which we believe is the key feature of the process of slow clot formation that distinguishes it from fast clot formation.

Sections 2.1 and 2.2 below describe in detail the model of the contact system while Section 2.3 describes our model of platelet activation.