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A Mathematical Model of the Kinetics of Blood Coagulation

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Linear mathematical models of the kinetics of blood coagulation have previously been presented (Levine, 1966, *Science, N.Y.* **152**, 651; Martorana & Moro, 1974, *Math. Biosci.* **21**, 77). In this paper a non-linear mathematical model of the extrinsic pathway of blood coagulation is presented to take into account a positive feedback. The feedback is due to factor V_a as a co-factor involved in thrombin formation. The extrinsic pathway is shown to function as an amplifier cascade if a vessel wall injury exceeds a threshold value. For sub-threshold stimulation, the extrinsic pathway does not function.

1. Introduction

The problem of modeling the kinetics of blood coagulation has first been considered by Levine (1966). This system has been shown to function as an enzyme amplifier cascade, thus supporting the hypothesis of Macfarlane (1964).

Additional equations have been incorporated in the models to describe some interaction effects (fibrinolysis, absorption of thrombin onto fibrin) (Martorana & Moro, 1974; Martorana, 1978). These models, however, are linear, whereas the kinetics of blood coagulation seems to exhibit distinct non-linear effects.

The purpose of this paper is to present a mathematical model of the kinetics of the extrinsic pathway of blood coagulation taking into account the non-linear effects. Fibrinolysis is not considered.

2. Enzyme Cascade Scheme

An enzyme cascade for the extrinsic pathway of blood coagulation is schematically shown in Fig. 1. Only the enzymic reactions important for the activation of this system are included. Feedback mechanisms due to fibrinolysis are therefore not considered. Also included is the positive feedback essential to the acceleration of thrombin formation. The activated factor V serves as a co-factor. A substance released from injured tissue is assumed to be a stimulating factor of the extrinsic pathway. The substance activates factor VII and thus initiates the extrinsic pathway.

3. Mathematical Model of the Kinetics of the Extrinsic Pathway

The enzymic reactions involved are shown in Fig. 1. A co-factor participates in reaction (4). The equation describing the reaction kinetics is

$$\frac{d[II_a]}{dt} = K_4[X_a]\frac{[V_a]}{K_a+[V_a]} - H_4[II_a], \tag{1}$$

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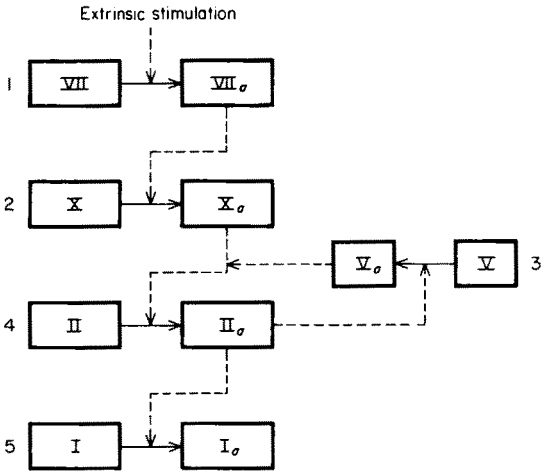

FIG. 1. Extrinsic pathway of blood coagulation as an enzyme cascade.

where K_4, K_a, H_4 are kinetic constants (H_4 is the thrombin breakdown constant).

From now on the concentrations of blood coagulation factors are denoted by the same symbols as the factors.

With the above assumptions, the system of equations describing the kinetics of the extrinsic pathway can be written as

$$\frac{d[VII_a]}{dt} = \alpha K_1 - H_1[VII_a] \tag{2a}$$

$$\frac{d[X_a]}{dt} = K_2[VII_a] - H_2[X_a] \tag{2b}$$

$$\frac{d[V_a]}{dt} = K_3[II_a] - H_3[V_a] \tag{2c}$$

$$\frac{d[II_a]}{dt} = K_4[X_a]\frac{[V_a]}{K_a + [V_a]} - H_4[II_a], \tag{2d}$$

where K_n is the n-th reaction rate constant, H_n the n-th reaction product breakdown constant and α the concentration of a substance released from injured vessel wall to activate factor VII: α will be called the stimulation intensity.

Since the initial process is considered, the kinetics of fibrin formation and changes in substrate concentrations are neglected. If the activation of fibrinogen is taken into account, then an increase in gain of the extrinsic pathway occurs.

4. Reduction of the System (2)

By using Tikhonov's theorem, the system (2) can be essentially simplified. The theorem permits us to reduce the system of equations, thus decreasing their number significantly. In this way the characteristic times required to reach steady states in

specific processes are evaluated. Two kinds of approach to this problem are possible. One is based on the evaluation of the time required to reach a steady state in a specific process. The other is based on an analysis of biochemical data. The available data (Suttie & Jackson, 1977) strongly suggest that the slowest reaction in a sequence of the enzymic reactions involved in the extrinsic pathway is the one resulting in thrombin formation [reaction (4)]. The rate of this reaction increases about 10^4 times in the presence of activated factor V (Rosing *et al.*, 1980). In the initial period, however, the concentration of factor V_α is relatively small and hence reaction (4) is the slowest.

The above considerations permit us to reduce the system (2) assuming these equations to be quasi-stationary except for (2c) and (2d). We then obtain the following system of equations:

$$\alpha K_1 - H_1[\mathrm{VII}_a] = 0 \tag{3a}$$

$$K_2[\mathrm{VII}_a] - H_2[\mathrm{X}_a] = 0 \tag{3b}$$

$$\frac{\mathrm{d}[\mathrm{V}_a]}{\mathrm{d}t} = K_3[\mathrm{II}_a] - H_3[\mathrm{V}_a] \tag{3c}$$

$$\frac{\mathrm{d}[\mathrm{II}_a]}{\mathrm{d}t} = K_4[\mathrm{X}_a]\frac{[\mathrm{V}_a]}{K_a + [\mathrm{V}_a]} - H_4[\mathrm{II}_a]. \tag{3d}$$

By solving eqns (3a) and (3b) we get

$$\frac{\mathrm{d}X}{\mathrm{d}\tau} = Y - X; \frac{\mathrm{d}Y}{\mathrm{d}\tau} = a\frac{X}{1+X} - bY, \tag{4}$$

where $X = [\mathrm{V}_a]/K_a$; $Y = K_3[\mathrm{II}_a]/H_3K_a$; $\tau = H_3t$; $b = H_4/H_3$; and $a = \alpha K_1K_2K_3K_4/H_1H_2H_3^2K_a$.

In eqns (4) the dimensionless variables X and Y are the concentrations of factors V_a and II_a respectively.

5. Steady-state Solutions and their Stability

A qualitative theory of differential equations can be used to determine the behavior of solutions of the system (4).

There exist two steady-state solutions of the system (4): $\mathrm{d}X/\mathrm{d}\tau = 0$; $\mathrm{d}Y/\mathrm{d}\tau = 0$. Since factor concentrations are positively definite, a non-zero steady state solution exists if

$$a > b. \tag{5}$$

With the previous notation, the condition (5) becomes

$$\alpha > \alpha_{\mathrm{thres}} = K_a\frac{H_1H_2H_3H_4}{K_1K_2K_3K_4}. \tag{6}$$

α_{thres} will be called the threshold stimulation intensity. If extrinsic stimulation exceeds α_{thres}, then the system (4) has two steady-state solutions. For a sub-threshold

stimulation, the system (4) has only one zero steady-state solution. The next step is to analyze the stability of steady-state solutions. For this purpose, we linearize the system (4) near stationary points. The corresponding characteristic equation is

$$\lambda^2+\lambda(1+b)+b-\frac{a}{(1+\bar{X})^2}=0, \tag{7}$$

where $\bar{X}$ is the stationary point.

For a zero stationary point, one easily sees that if $a<b$, i.e. there exists one stationary point, then the characteristic roots are negative and hence the point is stable. If the inequality ($a>b$) is satisfied, i.e. there exist two stationary points, then

$$\lambda_1<0; \qquad \lambda_2>0$$

and hence the point is unstable (saddle).

Now consider the stability of a non-zero stationary point. In this case the characteristic equation is

$$\lambda^2+\lambda(1+b)+b-\frac{b^2}{a}=0. \tag{8}$$

From eqn (8)

$$\lambda_1<0; \qquad \lambda_2<0,$$

and hence the point is stable.

The results obtained can be summarized as follows. If the extrinsic pathway is under sub-threshold conditions, then there exists only one zero stationary point. In this case the system does not function as an amplifier cascade. The solutions tend to a zero stationary point. If stimulation intensity exceeds the threshold one, then there exists a non-zero stationary point. The zero stationary point becomes unstable. In that case the extrinsic pathway will function as an enzyme amplifier cascade.

6. The Simplest Solution of the Problem

To obtain the simplest solution of the system (4), we note that eqn (4a) describes a more rapid process than does eqn (4b). This fact permits us to use again Tikhonov's theorem and to reduce the system (2) to one eqn:

$$\frac{dY}{d\tau}=a\frac{Y}{1+Y}-bY. \tag{9}$$

Integration of eqn (9) is readily performed. The solution can thus be expressed in terms of elementary functions

$$Y^{(1/a-b)}\left(\frac{a-b}{b}-Y\right)^{-(a/(a-b)b)}=Y_0^{(1/a-b)}\left(\frac{a-b}{b}-Y_0\right)^{-(a/(a-b)b)}e^{\tau}, \tag{10}$$

where Y_0 is the initial factor II_a concentration.

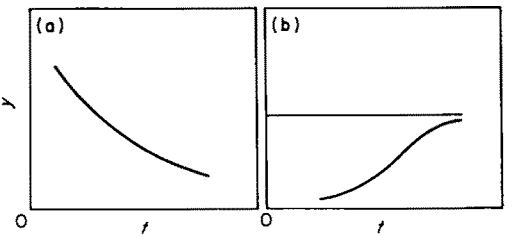

FIG. 2. Thrombin concentration as a function of time: (a) sub-threshold stimulation; (b) supra-threshold stimulation.

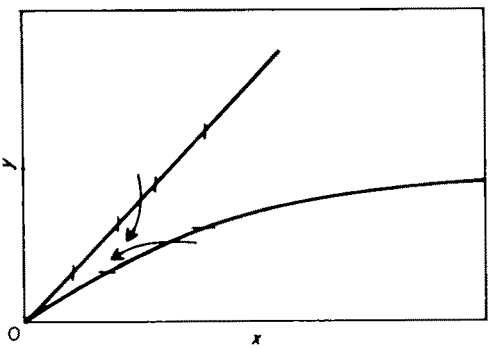

FIG. 3. Phase-plane diagram of the system (4) for sub-threshold stimulation. Continuous lines are principal isoclines. Short lines are tangents to phase trajectories at certain points on principal isoclines. Arrows are phase trajectory directions near stationary points.

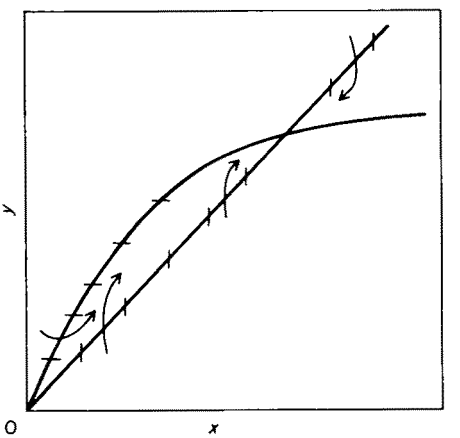

FIG. 4. Phase-plane diagram of the system (4) for supra-threshold stimulation. Notation is the same as in Fig. 3.

The thrombin concentration as a function of time for sub- and supra-threshold stimulation is shown in Fig. 2. As can be seen from this figure, there is an essential difference in the solutions.

The phase-plane diagrams of the system (4) are shown in Figs 3 and 4.

In dimensionless variables the system (2) can be written as

$$\begin{aligned}
\frac{dX_1}{d\tau} &= 1 - X_1 \\
\frac{dX_2}{d\tau} &= X_1 - X_2 \\
\frac{dX_3}{d\tau} &= X_4 - X_3 \\
\frac{dX_4}{d\tau} &= X_2 \frac{X_3}{d + X_3} - X_4,
\end{aligned} \tag{11}$$

where

$$X_1 = \frac{[\mathrm{VII}_a]H}{\alpha K_1}; \qquad X_2 = \frac{[\mathrm{X}_a]H^2}{\alpha K_1 K_2}$$

$$X_3 = \frac{[\mathrm{V}_a]H^4}{\alpha K_1 K_2 K_3 K_4}; \qquad X_4 = \frac{[\mathrm{II}_a]H^3}{\alpha K_1 K_2 K_4}$$

$$d = \frac{K_a H^4}{\alpha K_1 K_2 K_3 K_4}; \qquad \tau = Ht.$$

In eqns (11) H_i $(i = 1, 2, 3, 4)$ are assumed to be equal. Therefore eqns (11) is the system with one parameter d. The value of d is determined by the threshold-to-extrinsic stimulation intensity ratio.

In dimensionless variables the concentrations of activated factors as functions of time for sub- and supra-threshold stimulation are shown in Figs 5 and 6. As can be

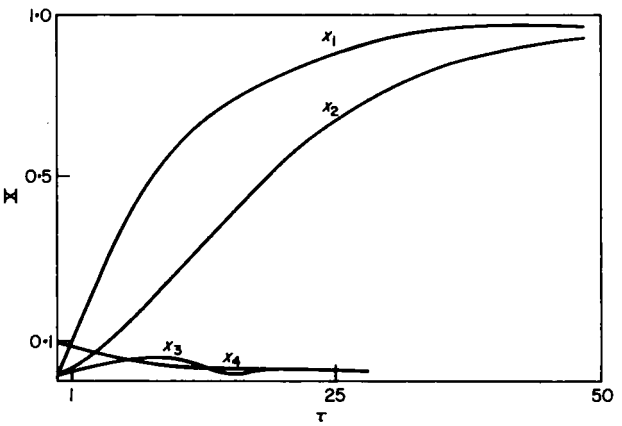

FIG. 5. Factor concentrations as functions of time for sub-threshold stimulation.

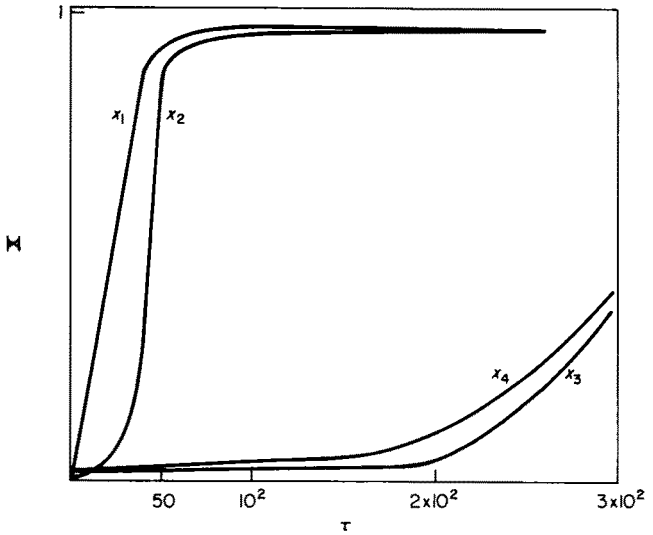

FIG. 6. Factor concentrations as functions of time for supra-threshold stimulation.

seen from Fig. 5, the concentrations of factors VII_a and X_a (X_1 and X_2) rapidly increase with time: $X_1, X_2 \to 1$ as $\tau \to \infty$. In dimensional variables an amplification effect in the activation of factors VII and X is observed. For sub-threshold stimulation, a non-linear chain due to the activation of factor II prevents the process from proceeding further. In this case the system does not function as an amplifier cascade.

In dimensionless variables the concentrations of activated factors as functions of time for supra-threshold stimulation are shown in Fig. 6. As can be seen from this figure, the concentrations of factors VII_a and X_a (X_1 and X_2) reach a steady state much more rapidly than do the concentrations of factors V_a and II_a (X_3 and X_4). In that case the system will function as an amplifier cascade.

7. Discussion

The main result obtained from the model is a non-linear response of the system to a vessel wall and tissue injury. If the initial concentrations of activated factors are not zero, then for sub-threshold stimulation the extrinsic pathway exhibits a transient rise in fibrin concentration. In this case the system does not function. For supra-threshold stimulation, the system will function as an amplifier cascade. The fibrin concentration tends to a non-zero steady-state value. In that case the response duration of the system is determined by the exposure time to substances released from injured tissue as well as the deactivating mechanisms not taken into consideration in the model.

The expression for α_{thres}, (6), permits us to analyze quantitatively the pathogenetic mechanisms of hypo- or hypercoagulation and to search for ways of normalizing the system.

From (6) we can conclude that hypercoagulation occurs in the following cases:
(1) the increase in stable substrate concentrations,
(2) the increase in K_a,
(3) the decrease in product breakdown constants,
(4) the increase in reaction rate constants.

The opposing effects in the system may result in hypocoagulation.

It should be noted that an increase in K_a may be due to humoral factors (Ca^{2+} ions, phospholipides).

The model also permits us to search for ways of preventing the system from hypercoagulation. The control link in the extrinsic pathway is the activation of thrombin formation. Therefore the most effective way of preventing the system from hypercoagulation (more precisely, inadequate blood coagulation) is to slow down the activation of factor V or to decrease the thrombin formation rate.

From eqn (6) we can also conclude that another way of doing it is to decrease substrate concentrations. This is realized by the hemosorption method. Unfortunately, in this way we can only transiently decrease the substrate concentrations.

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REFERENCES

LEVINE, S. N. (1966). *Science, N.Y.* **152,** 651.
MACFARLANE, R. G. (1964). *Nature, Lond.* **202,** 498.
MARTORANA, F. (1978). *J. Nucl. Med. All. Sci.* **22,** 181.
MARTORANA, F. & MORO, A. (1974). *Math. Biosci.* **21,** 77.
ROSING, J., TANS, G., GOVERS-RIEMSLAY, J. W. P., ZWAAL, R. F. A. & HEMKER, H. C. (1980). *J. biol. Chem.* **255,** 274.
SUTTIE, J. W. & JACKSON, C. M. (1977). *Physiol. Rev.* **57,** 1.