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Research Topic

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Abstract
A Study Of Fibrinolysis

According to present concepts, the enzyme responsible for the dissolution of fibrin both intra - and extra - vascularly is generated by the action of an “activator” upon the enzyme precursor plasminogen. Plasminogen is a B-globulin, of molecular weight of the order of 143,000, and a normal constituent of human plasma. It is known to possess a high affinity for both fibrin and fibrinogen, a property fundamental to the Sherry hypothesis of the physiological function of plasminogen where any fibrin clot is visualised as having an intrinsic plasminogen content sufficient to ensure its lysis when activated. The activation is achieved by activator either trapped within the clot at the moment of polymerisation, or diffusing subsequently into the clot from the surrounding liquid phase.

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RESEARCH TOPIC

A Study Of Fibrinolysis

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Abundant evidence now exists to suggest that plasminogen activator is released locally by blood vessels into the circulation in response to acute vascular changes[1,2,3] In a series of straightforward "in vitro" experiments in which tissue slices were placed upon a layer of preformed fibrin and local areas of fibrinolysis related to overlying anatomical structures, Todd[4] presented evidence which suggests that the human vascular endothelium serves as a labile pool for this activator. However, so far the majority of studies on fibrinolytic phenomena "in vivo" have been conducted with regard to the general circulation; thus it has been demonstrated that in normal subjects systemic levels of circulating activator will increase substantially in response to various physiological stimuli, notably exercise [5] and mental stress.

An intriguing question arises as to the gross anatomical origins of all this activator, and in an attempt to elucidate such a source I embarked, in the summer of 1966, upon an investigation of the human uterus[6].

The subjects were fifteen female patients undergoing surgery involving lower abdominal incisions. Blood samples were taken from the uterine artery, uterine vein, and for control purposes from a vein in the cubital fossa. The majority of the plasma so obtained was treated with acetic acid to precipitate the euglobulin fraction. This moiety is relatively free from plasmin inhibitors, which "in vivo" are excluded from formed clots, but which are present in plasma. The remainder was used for inhibitor estimations.

A proportion of the euglobulin was clotted and incubated at 37°C., and the time taken for the spontaneous lysis of the euglobulin clot was taken as a measure of activator concentration. Other aliquots were used for the estimations of plasminogen and fibrinogen levels. Parallel measurements of fibrin degradation products (F.D.P.), the result of "in vivo" plasmin activity in the subject, were carried out using a technique in which inhibition of antiserum agglutination of fibrinogen — coated red blood cells by these F.D.P.'s — bears a quantitative relationship to their concentration.

It was found that the uterine venous samples had a significantly ($0.001 < P < 0.002$) greater content of plasminogen activator than the arterial samples. Plasminogen, fibrinogen and plasmin inhibitor concentrations bore neither qualitative nor quantitative correlation to this fibrinolytic activity, there being no significant difference in these parameters between venous and arterial groups. The arterio - venous comparison of fibrin degradation products showed a significantly ($P < 0.001$) higher concentration in the uterine vein than the artery.

These results show that under the conditions of the study, the uteri were contributing to the fibrinolytic potential of the circulating blood. This contribution must be in the form of activator, since no complimentary difference in any of the other parameters could account for the present findings. The discovery of F.D.P.'s coming from the human uterus makes it conceivable that normally a constant consumption of the factors of fibrinolysis is taking place, with the enzymatic breakdown of fibrin, thus necessitating their continual maintenance.

Experiments on human blood by Buluk & Furman [7] in which an arterio - venous activator difference was demonstrated across the

kidney suggested to these authors that the kidneys might be the organs responsible for activator maintenance. The evidence presented above must throw doubt upon any assumption that, in females at least, the kidney is the sole candidate for this role.

The fact that no significant reduction in plasminogen or fibrinogen levels was found on passage through the uterus is interesting in that active fibrin disintegration can apparently proceed without detectable consumption of these factors. Such a consumption must be real, but the quantities involved are presumably below the detection threshold of our present techniques, quite apart from being insignificant within their total plasma concentrations.

One could say that it is hardly surprising that an organ so highly vascular and constantly involved in the process of coagulation and fibrinolysis should be found to have a high activator potential, but when a definite contribution by this organ to systemic activator levels is evident, one must consider not only the local processes involved with menstruation and pregnancy, but also the part played by this, and conceivably a number of other organs in the complex fibrinolytic picture of the body as a whole.

In order to further these existing lines of thought I hope, this coming summer, to carry investigations to dogs, where experimental scope is wider.

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