THE ANTIBRADYKININ ACTION OF FIBRINOLYSIN AND OTHER STUDIES ON CAPILLARY PERMEABILITY EMPLOYING DIFFERENT MEDIATORS AND SYNTHETIC BRADYKININ

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THIS presentation enlarges certain comments one of us (A. L. C.) made on several findings reported by Schachter[1] at this Symposium. We found also that plasmin has little or no significant effect in inducing capillary permeability. However, we noted that the precursor of plasmin or fibrinolysin, viz. plasminogen, present in the circulating blood, increased markedly capillary permeability in guinea-pigs and rats, the two species which we employed in our studies.

The electron microscopic observations of Schachter[1] appear to some extent to be similar to certain hitherto unpublished studies made recently by Palade and Majno.[2,3,4] A brief account of their work will be given together with that of our findings which led Copley to modify his concept of the endoendothelial fibrin film (EEFF) to include the basement membrane (BM). An attempt will be made to explain the antibradykinin effect of fibrinolysin on capillary permeability on the basis of this modified concept recently proposed[5,6] towards a better understanding of capillary permeability and fragility, two apparently antagonistic phenomena.

In an effort to elucidate the role of bradykinin on capillary permeability, we have extended a number of our previous studies recently reported on the integrity of the vascular wall and the antagonistic action of fibrinolysis to histamine and serotonin.[5,6] These observations of synthetic bradykinin are presented together with findings of its possible interaction with other mediators on capillary permeability.

METHODS

Albino guinea-pigs weighing from 150 to 250 g and albino rats from 120 to 250 g in weight were used. All animals were anesthetized with sodium pentobarbital (Veterinary Nembutal, Abbott Laboratories, North Chicago, Illinois). Because of the high sensitivity of the guinea-pig to the sodium pentobarbital, we found it convenient to use it in the following

concentrations in physiologic saline (0·9% NaCl): 6 mg/ml for the guinea-pig and 10 mg/ml for the rat; 0·35 ml of the above were injected per 100 g weight.

The skin on the ventral side between the shoulders and hips was closely shaved with a size 40, model # 2 animal clipper (Oster, Milwaukee, Wisconsin). Any chemical depilatory was thus avoided, and the above electric clipper secured very close shaving without damage to the skin.

Intradermal injections of the various substances in physiologic saline were made in 0·02 ml volumes with 12° bevelled intradermal needles, 1/2 in. (1·3 cm) in length and of # 27 gauge. The syringes used were of high accuracy (Hamilton Company, Inc., Whittier, California). Their Teflon tipped plunger is snugly fitted and the total volume of 0·1 ml is subdivided into increments of 0·001 ml volumes. For intravenous injections we used 1 ml tuberculin syringes.

Evans blue (National Aniline Division, Allied Chemical Corp., New York, N. Y.) was used in a concentration of 4 mg/ml physiologic saline and 0·2 ml of this stain solution was injected per 100 g weight into the brachial vein of the guinea-pig and the saphenous vein of the rat. Six minutes later the intradermal testing was begun. After the appearance of the last lesion and its proper recording, given test substances such as plasmin, bradykinin or histamine, were injected intravenously into the saphenous vein of the rat and the brachial vein of the guinea-pig, respectively. Ten minutes after such intravenous injection, testing on the other side of the ventral skin was started.

On the basis of control studies by Bhoola *et al.*,[7] we adopted the procedure of the intradermal injection of different substances in each one row of both shaved flanks of the guinea-pigs and rats. In a number of control studies we could confirm the results of the above authors who found no significant variation in the size of lesions, produced by the same concentration of a substance if the different intradermal injections were made between hip and shoulder.

Intradermal injections of 0·9% NaCl as control did not always result in blueing. However, when it occurred, the blueing measured usually about 1 mm and occasionally 2 mm in diameter and showed, at the most, a trace in intensity.

Intravenous injection of physiologic saline had been used at intervals of 10, 20, 30 and 40 min following the intradermal injection of the different test agents used in this study. Subsequent to the intravenous injection at the above intervals, the same test agents in the same amount and volume were injected intradermally. The resulting blueing reaction was found not to be altered, when compared to that obtained previous to the intravenous administration of the saline control.

Since lyophilized plasminogen solved in water had a pH of about 3·5, the following buffer was employed: 13·6 g KH_2PO_4, 9 g NaCl adjusted to pH 7·4 and diluted to 1 l. with distilled water. This isotonic saline 0·1M phosphate buffer was injected as intradermal or intravenous controls, similar to the above control studies employing physiologic saline. This never resulted in an effect which significantly altered the blueing reaction obtained with the buffer containing plasminogen preparation.

The diameter of the blue lesion, at the site of injection due to the dye from the leaking vessels, was recorded from its first occurrence until it obtained its largest size. Concomitantly, the intensity of the blueing was estimated by employing the following arbitrary grading: ± doubtful, (+) trace, + weak, ++ moderate, +++ strong, ++++ very strong. In charting our results for the Figures, we employed a method similar to that used by Miles.[8] The size of the lesion was taken as a mean of the largest diameter and the one at right angle to it.

Each point on the curves in the Figures represent the mean diameter of a minimum number of eight lesions in not less than three animals. It should be noted that although both the mean diameter and mean intensity of the lesion were always recorded simultaneously, the last points of both curves on the charts do not always coincide. The last point of the shorter curve shows a finding which thereafter remains stationary. In order to secure better visualization of our findings, the shorter curve was not drawn out to coincide with the last recorded time of the longer curve.

AGENTS

Synthetic Bradykinin (Sandoz Inc., Hanover, New Jersey) was used in physiologic saline and intradermal injections were made with 0·02 μg/0·02 ml in the guinea-pig and 0·2 μg/0·02 ml in the rat. For intravenous injections, 0·01–0·5 μg/100 g weight were used both for guinea-pigs and rats.

Histamine Dihydrochloride (Amend Drug and Chemical Co., Inc., New York, N. Y.) was employed as 2 μg/0·02 ml physiologic saline for intradermal injection and from 0·01 μg to 0·5 μg for intravenous administration.

Serotonin Creatine Sulfate (Nutritional Biochemicals Inc., Cleveland, Ohio). 20 μg/0·02 ml in physiologic saline was injected intradermally.

Fibrinolysin (Ortho Research Foundation, Raritan, New Jersey). Human streptokinase-activitated plasmin was used as follows: 200 u/0·02 ml in physiologic saline for intradermal injection and 250 u, 500 u and 1000 u/100 g weight for intravenous injections.

Plasminogen (Merck, Sharp and Dohme, West Point, Pennsylvania). 0·2 mg/0·02 ml for intradermal injection and 1·25 mg/100 g weight for intravenous administration were employed.

RESULTS

For better orientation, our observations are described under the headings of those agents which were administered intravenously with prior and subsequent intradermal injection of different mediators.

1. *Fibrinolysin*

Figure 1 shows marked inhibition of capillary permeability, induced by intradermal injection of 0·02 μg bradykinin, following intravenous injection of 250 u and 1000 u of fibrinolysin. As can be seen, the higher the unitage of fibrinolysin, the more is its inhibitory effect on brady-

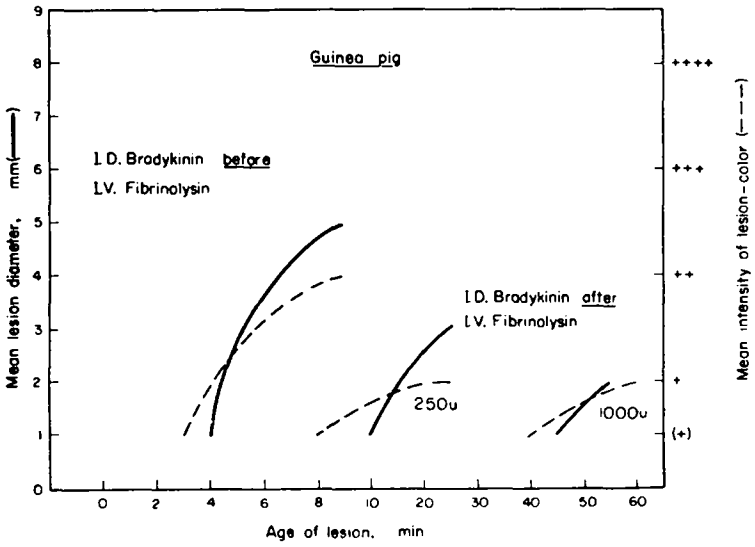

FIG. 1.

kinin-induced capillary permeability. The same holds true in the rat in which the intradermal bradykinin is 0·2 μg. Bradykinin thus behaves similarly as does the intradermal injection of histamine or of serotonin following intravenous fibrinolysin.[5,6]

The antagonistic effect of fibrinolysin to bradykinin was studied when the two substances were mixed together for intradermal tests, similar to our earlier reported observations regarding histamine and serotonin.[5,6] Saline solutions containing 0·02 and 0·2 μg bradykinin for guinea-pigs and rats respectively, were mixed with 200 u of fibrinolysin. These mixtures, comprising the total volume of 0·02 ml for intradermal injection, resulted always in a decrease of capillary permeability when

compared to bradykinin control, injected intradermally in the same animals. This effect was noted both in guinea-pigs and rats. The inhibitory action of fibrinolysin on bradykinin was further augmented follow-

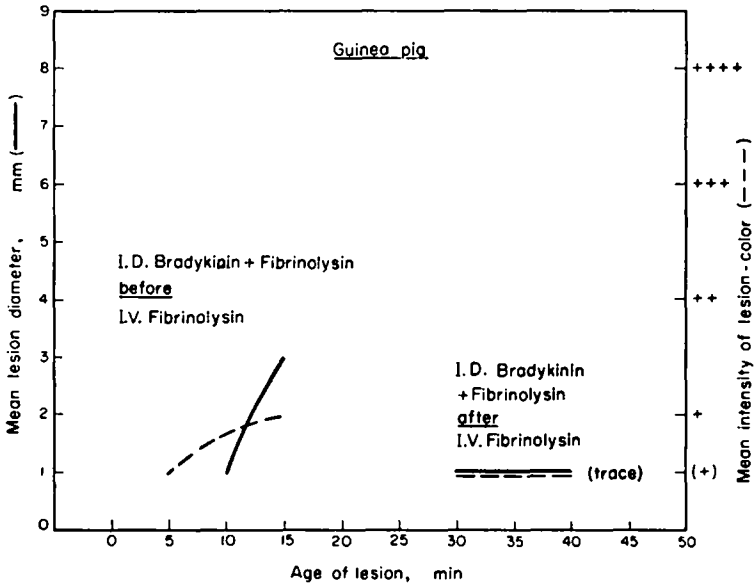

FIG. 2.

ing the intravenous injection of fibrinolysin resulting merely in traces occurring from 40 to 46 min later in rats and in guinea-pigs (Fig. 2) respectively.

2. *Bradykinin*

Fibrinolysin in dosages from 200 to 1000 units, when injected intradermally, resulted only in slight or insignificant blueing, thus corroborating the findings by Schachter *et al.*[1,7] Intravenous bradykinin administration did not augment the blueing due to intradermal fibrinolysin. However, when the latter was substituted by plasminogen, the blueing reaction was very strong and nearly as strong as that obtained with histamine in the dosage we employed. The dosage of 0·2 mg of human plasminogen for intradermal injection corresponded, on a weight basis, to one-fifth of the amount of human plasmin which we used for intradermal injections.

Intravenous administration of bradykinin decreased the capillary permeability induced by plasminogen, as seen in Fig. 3.

Bradykinin, when injected intradermally, always increased capillary permeability in spite of the low dosage employed in comparison to that of histamine injected intradermally. On a weight basis, this amounted in the guinea-pig to one-hundredth and in the rat to one-tenth of the

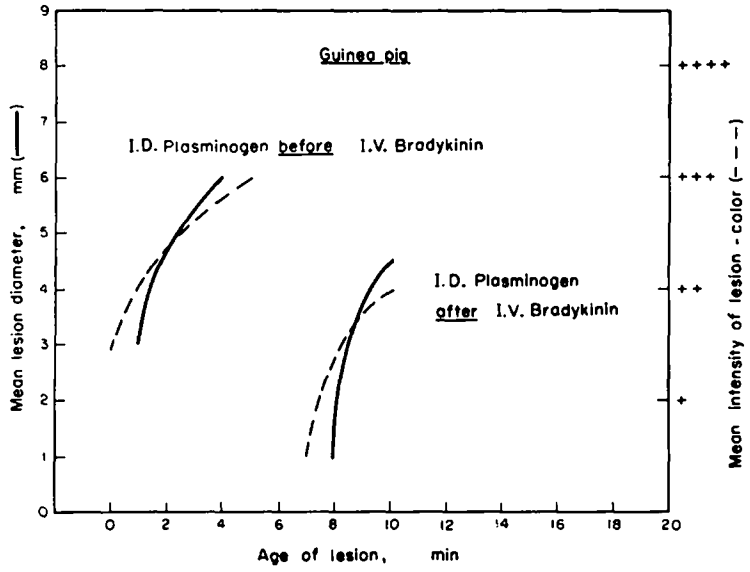

FIG. 3.

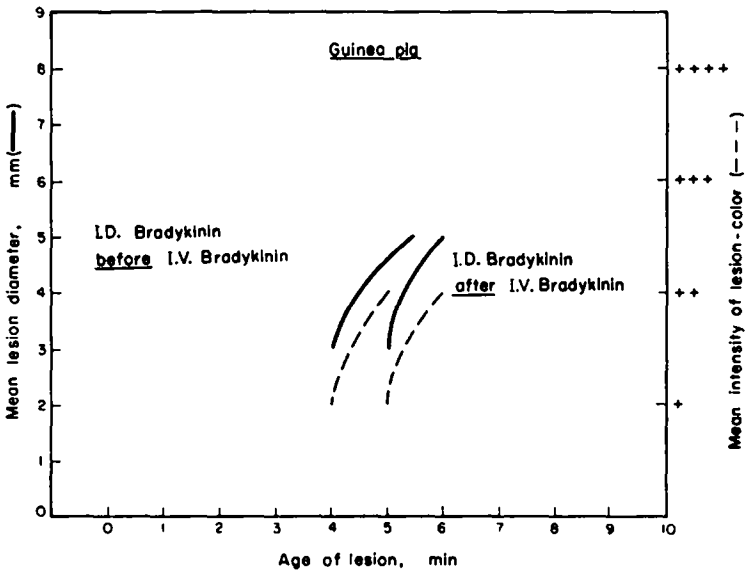

FIG. 4.

injected histamine. The bradykinin preparation which we used can be therefore considered a highly active one.

Following intravenous administration of bradykinin, the capillary permeability, induced by intradermal injection of bradykinin, was found in rats decreased, but guinea-pigs did not exhibit significant decreases as demonstrated in Fig. 4.

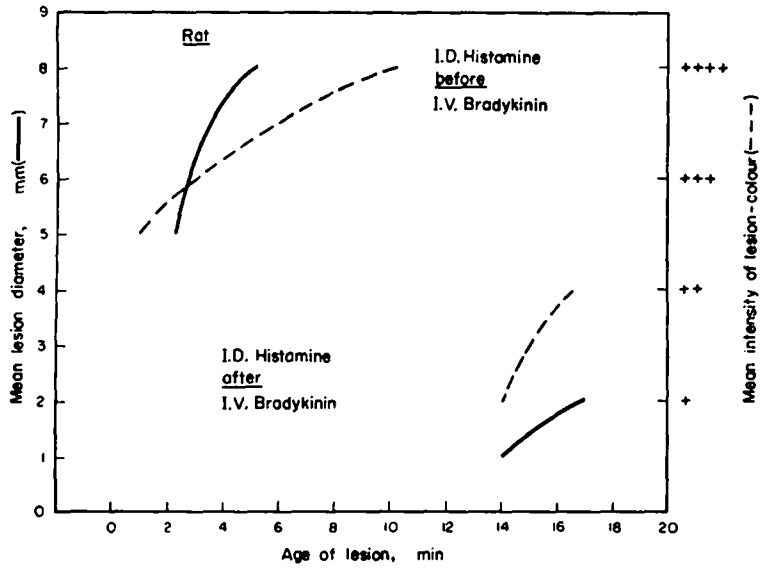

FIG. 5.

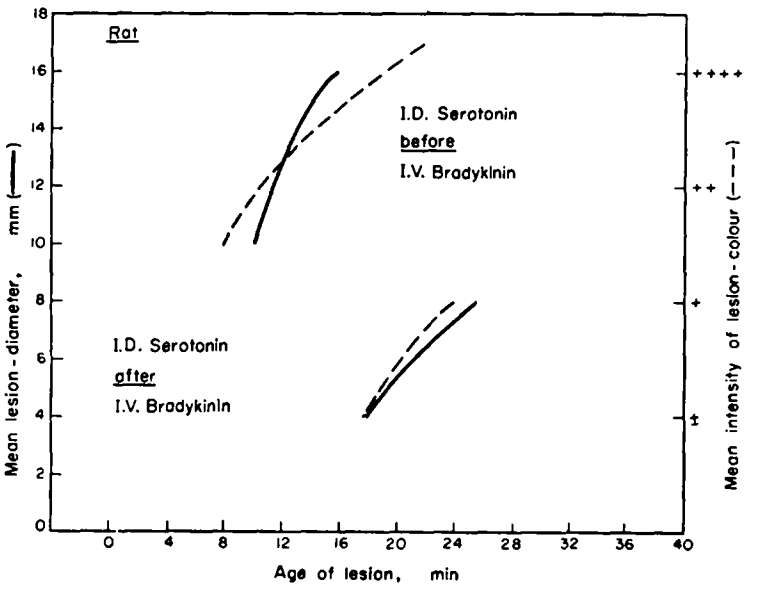

FIG. 6.

By using histamine intradermally, intravenous bradykinin decreased the histamine induced capillary permeability in both guinea-pigs and rats (Fig. 5).

Serotonin following intravenous bradydkinin in the guinea-pig and in the rat (Fig. 6) also resulted in decrease of capillary permeability. However, in the guinea-pig this decrease was found to be slight.

3. *Plasminogen*

The action of intravenous administration of plasminogen in guinea-pigs followed by intradermal injection of bradykinin (Fig. 7) or of a mixture of plasminogen and bradykinin (Fig. 8) resulted always in decrease of capillary permeability. If both Figs. 7 and 8 are compared, it

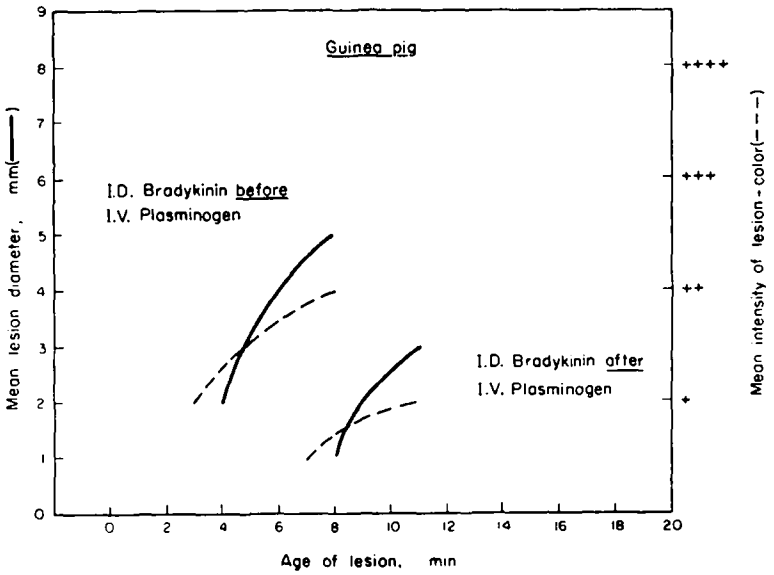

FIG. 7.

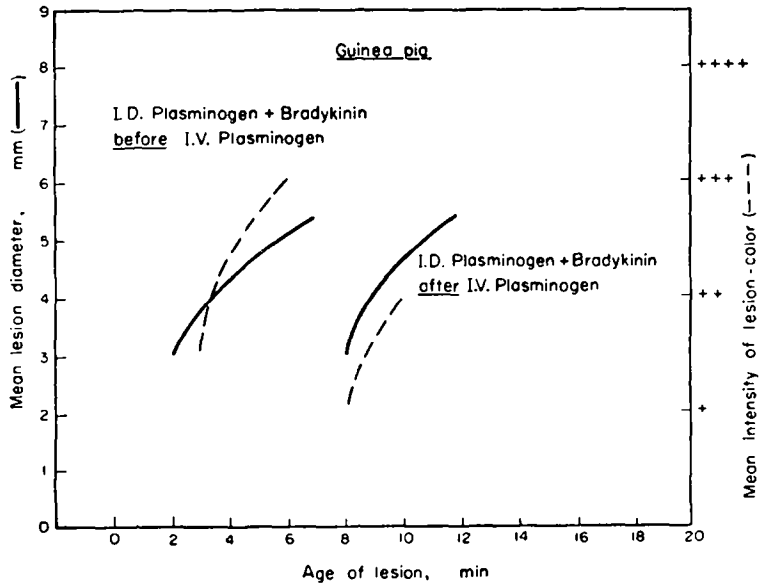

FIG. 8.

will be noted that the mixture of plasminogen and bradykinin (i.d.) does not inhibit permeability, whether prior or subsequent to the intravenous administration. There appears to be rather an increase in permeability. These findings are in contrast to those when mixtures of plasmin and bradykinin were used as intradermal test agents (Figs. 1 and 2).

In another series of experiments in which plasminogen was injected as the intradermal test agent, it was found that there appears to be no difference in the size and intensity of the lesion, although the occurrence was 2 min later following the intravenous administration, but this difference is considered insignificant.

Similar results as obtained with intradermal plasminogen were secured with histamine as the intradermal test agent.

4. *Histamine*

An increase in bradykinin induced capillary permeability was observed following intravenous administration of histamine in all guinea-pigs studied (Fig. 9), but a decrease was found consistently in rats.

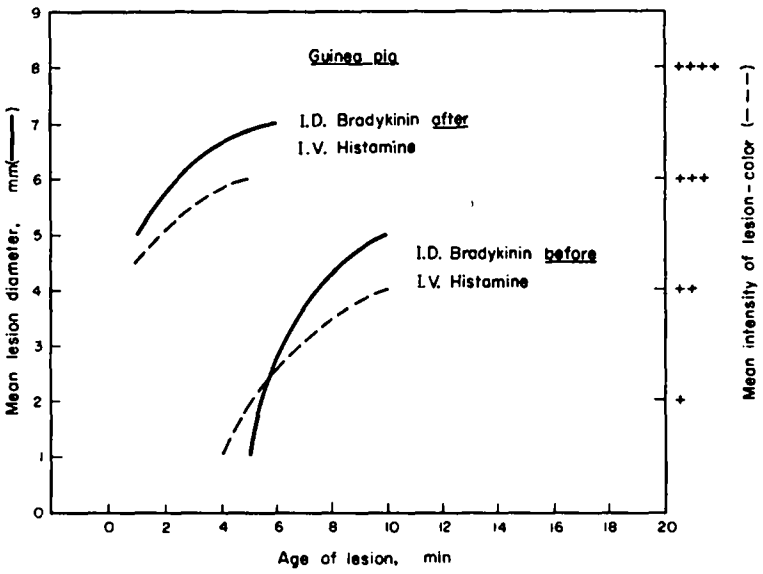

FIG. 9.

Histamine induced capillary permeability was always augmented following intravenous injection of 0·5 μg histamine in all guinea-pigs (Fig. 10) and rats studied. If the intravenous histamine dosage was lowered to 0·01 μg, both guinea-pigs and rats showed a decrease in capillary permeability.

The graphs on the preceding figures followed the course of the actual experimental data. In order to facilitate the comparisons of the

semiquantitative results, they are presented in Table I. The differential of the final points of the graphs of all experiments described above are tabulated, in an effort to establish certain patterns of response to the intravenous administration of the four agents.

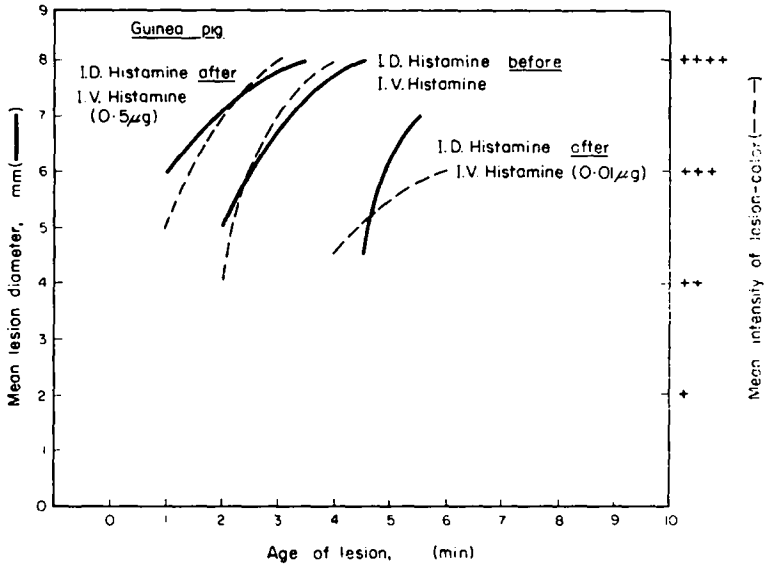

FIG. 10.

It appears that the intravenous injection of fibrinolysin inhibits markedly the optimal development of lesions regarding the time, size and intensity induced by bradykinin, with or without the admixture of fibrinolysin both in guinea-pigs and rats.

The antihistamine action on capillary permeability due to intravenously administered bradykinin was particularly marked in the rat, but somewhat less in the guinea-pig. Serotonin induced capillary permeability was affected similarly by intravenous bradykinin. This administration of bradykinin is antagonistic also to intradermal bradykinin in rats, but no differences were observed in guinea-pigs. Plasminogen which was only tested intradermally in the guinea-pig, showed some lowering in permeability.

Intravenously administered plasminogen affected merely intradermal bradykinin with or without admixture of plasminogen by decreasing slightly the permeability. Intradermal plasminogen or histamine did not demonstrate any significant differences.

The intravenous administration of histamine has been already referred to earlier in some detail. Of interest are the findings of bradykinin as intradermal test agent, showing increase of capillary permeability in the guinea-pig, but decrease in the rat.

TABLE I

Compilation of data on the blueing reaction induced with different mediators in guinea-pigs and rats before and after intravenous administration of various agents

Intravenous agent	Intradermal agent	Differentials of optimally developed blueing lesions					
		Time of occurrence (min)		Mean diameter (mm)		Mean intensity of color (degree)	
Dosage/100 g weight		guinea-pig	rat	guinea-pig	rat	guinea-pig	rat
Fibrinolysin 250 μ	Bradykinin	16	15	2	2	−	+
1000 μ		46	40	3	2	+	±
250 μ	Bradykinin + Fibrinolysin	>120*	>120*	3	3	+	+
1000 μ		>120*	>120*	3	3	+	±
Bradykinin 0·01 mg	Bradykinin	1	5	0	2	0	±
	Histamine	1	12	3	6	++	+++
	Serotonin	2	8	3	8	++	++
	Plasminogen	6		2		+	
Plasminogen 1·25 mg	Bradykinin	3		2		+	
	Plasminogen	2		0		0	
	Plasminogen + Bradykinin	5		0		±	
	Histamine	2		0		0	
Histamine 0·05 μg	Bradykinin	4**	4	2**	2	+**	+
0·05 μg	Histamine	1**	0	0	0	0	+
0·01 μg	Histamine	1	3	1	0	+	±

* No lesion was observed for more than 2 hr.

** In this case, the difference means that the permeability is increased following intravenous administration.

DISCUSSION

A. *Bradykinin and Capillary Permeability*

The term "blood capillary" is used throughout to denote any microscopic blood vessel in a capillary bed between arterioles and venules.[5,6]

Increased capillary permeability by the action of crude bradykinin in the guinea-pig and rabbit was reported in 1957 by Holdstock *et al.*,[9] and in man by Herxheimer and Schachter.[10] Bhoola, *et al.*[7] who found fibrinolysin (plasmin) to be without significant effect on capillary permeability in the three animals which they tested, noted that bradykinin was more effective than histamine in inducing capillary permeability. Pure bradykinin was reported by Elliott *et al.*[11] to increase markedly capillary permeability in guinea-pigs and rabbits. The above references may suffice to show that this permeability increasing action of bradykinin is well established, and it is not our intention to review the entire literature.

In our studies, employing different mediators, a pattern, shown in Table I, is emerging that all the tested mediators affecting capillary permeability are capable of interfering with the activity of the other. To explain the pattern, one may postulate the existence of a common receptor in the vascular wall for which these mediators compete and which is slowly reconstituted.

Regarding our findings with plasminogen (profibrinolysin), it is not clear whether it has a direct effect on capillary permeability or whether it induces increased permeability by liberating bradykinin or other mediators.

Our findings of the antibradykinin action of fibrinolysin, which are similar to our previous results with histamine or serotonin, appear to be of physiologic significance as we shall develop later. This work was begun with studies on capillary permeability and fragility in the capillary bed of the cremaster muscle, a new preparation developed by Majno and Palade.[3,4] In employing various tracers in their method, we found an antagonistic action of histamine, serotonin or bradykinin to fibrinolysin. Majno and Palade studied the action of histamine and serotonin on the blood capillary wall, but not of bradykinin. In their electron microscopic studies, which we shall discuss in some detail, they found a gap between the endothelial cells, as Schachter reported on bradykinin at this Symposium. The work by Majno and Palade represents a fundamental, detailed study on the microstructure of the blood capillary wall.

The extent of blueing may be considered a function of both increased capillary permeability and blood flow to the affected area. Inhibition of blueing, as reported in this study, could conceivably result from decrease of blood flow to the injected site. This possibility seems unlikely in view of the fact that the inhibition of the blueing reaction is obtained

not only if fibrinolysin is administered intravenously, but also when it is injected locally together with the mediator.

The results that fibrinolysin opposes increased capillary permeability, induced by bradykinin, histamine or serotonin, have not merely been established by us with the rat's cremaster preparation and the blueing reaction in guinea-pigs and rats. This is being done also by the use of the more sensitive method of measuring protein extravasation which has been published recently by Aschheim and Zweifach.[12] The course of the inflammatory reaction can be followed with this method by assaying radioactive changes of the skin of rats injected intravenously with radioiodinated human serum albumin. We found, with Aschheim, in preliminary experiments, that fibrinolysin, when injected together with either histamine or bradykinin, inhibits the local inflammation response up to 90 per cent. These studies, which are now in progress, will be reported later.

The anti-inflammatory action was observed by us not solely with different preparations of plasmin, activated by streptokinase or by chloroform, and of streptokinase, but also with other proteolytic enzymes, such as trypsin, chymotrypsin and papain in relation to histamine and serotonin.[5,6] Such studies with bradykinin, which are contemplated, may yield similar results.

B. *Fibrin, a "Physiologic Cement" in the Microstructure of the Blood Capillary Wall*

On the basis of the electron microscopic and topographic studies by Majno and Palade[2,3,4] on the effect of histamine and serotonin on capillary permeability and of the reported findings by Copley[5,6] on vascular integrity, the latter modified his concept of the endoendothelial fibrin film (EEFF) to include the basement membrane (BM). In Fig. 11, the diagram illustrates this concept. Recent work has shown that there can be little doubt that the EEEF actually exists.[14] According to this concept, fibrin in submicroscopic dimensions, is produced steadily during life in the more or less immobile layer of the plasmatic zone next to the endothelium, deposited preponderantly on the endothelial cells facing the vascular lumen and the maintenance of this fibrin film is controlled by fibrinolysis.

Majno and Palade proposed that the blood capillary wall is composed of an outer discontinuous stratum of cells and fibers, the adventitial tunic (AT), and two continuous layers, the cellular endothelium and the acellular BM. The latter persists as an uninterrupted layer while the two cellular layers may differ from one type of capillary to another and be discontinuous or even absent. They found the BM to be a fibrillar, fuzzy, felt-like structure of 400–600 Å in thickness. To the above three layers comprising in general the capillary wall, Copley[5,6] proposed

(see Fig. 11) the addition of a fourth and fifth layer, one being the EEFF next to the endothelium and the other the exoendothelial space (EXES), possibly containing a film of plasma mixed with tissue fluid, between the endothelial cells and the BM. A sixth layer, the more or less

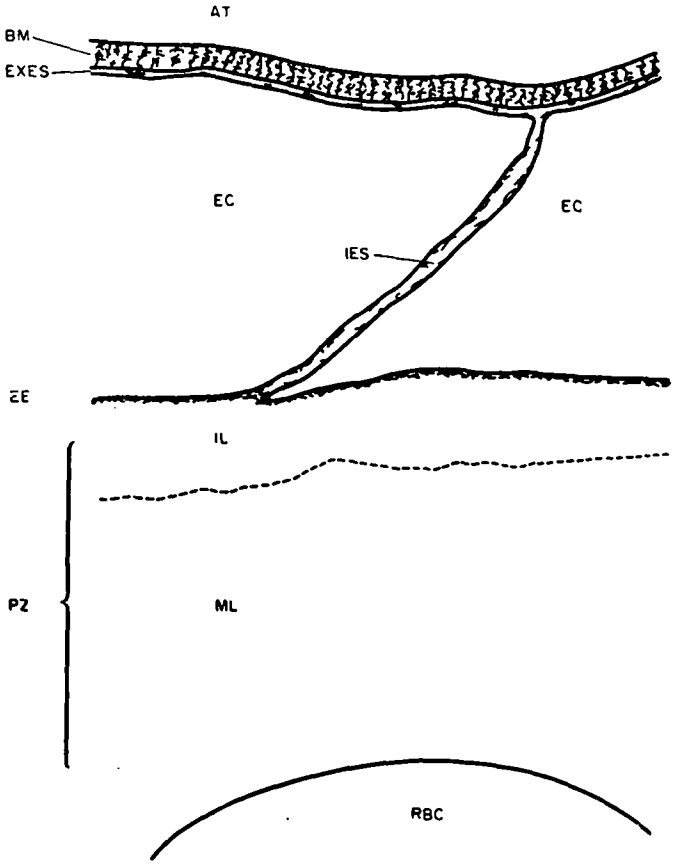

FIG. 11. Diagram illustrating Copley's concept of fibrin as a physiologic constituent of the blood capillary wall.

The drawing is meant to convey a general idea without giving scale or dimensions and without simulating the appearance of elements in the microstructure of the vessel wall.

AT = adventitial tunic. BM = basement membrane; the signs indicate the presence of fibrin (f) and of its breakdown products (fb) due to fibrinolysis, and of channels or pores in this felt-like structure. EXES = exoendothelial space; note short strokes indicate presence of f and fb. EC = endothelial cell. IES = interendothelial space; short strokes indicate presence of f and fb. EEFF = endoendothelial fibrin film; the lining of strokes next to the endothelial cells denotes a porous film of f and fb. PZ = plasmatic zone, composed of the more or less immobile layer (IL) separated by a dotted line from mobile layers (ML); the dotted line indicates changes in width of the IL. Not illustrated in the diagram are changes in the width of the ML, due to changes in the velocity of blood flow and to other factors. RBC = red blood cell.

immobile layer (IL) of the plasmatic zone (PZ) might be considered.[15] However, this layer may not be properly counted as a morphologic constituent of the capillary wall. The EEFF may extend around the endothelial cells (EC) and in some cases may be part of what Chambers and Zweifach[16] referred to as the cement substance. The EEFF may fulfil and anticoagulant function because it has been demonstrated by Copley *et al.*[16,17] that native plasma in contact with fibrin surfaces inhibits coagulation. This action of fibrin surface appears to be an essential one for transport through the endothelial layer, be it, as demonstrated by Palade *et al.*, through vesicles in the endothelial cells or be it between the endothelial cells (IES). The earlier concept of Copley on the homeostatic equilibrium of fibrin formation and fibrinolysis for maintaining the EEFF was amended to include the BM in view of the recent morphologic findings by Palade *et al.*, and the fact that hemorrhages only occur at certain sites of the vessel wall.

Renkin and Pappenheimer[18] have shown the capillary wall to be more permeable to lipid soluble molecules than to water soluble molecules of equal diameter and have postulated a different pathway across the endothelial cells for lipids. Since the experimental studies of Majno and Palade suggested that the BM is the main filtration barrier of the capillary wall, it might well be that the BM thus favors penetration by lipid soluble molecules. Therefore, the entrance of coagulation-promoting lipids such as thromboplastin, contained in so-called "tissue-juice" by inward filtration into the exoendothelial space and further into the immobile layer of the plasmatic zone could act upon the trapped coagulation factors present, resulting in non-gelated fibrin formation in the BM, in the EXES and finally in the formation of the EEFF.

As the BM, according to Majno and Palade, is a felt-like structure with many fibers of unknown chemical nature, it is quite possible that one of the constituents of the BM may be fibrin. Such fibrin could readily form in those parts of the BM which may contain trapped plasma proteins including fibrinogen and other coagulation factors. Fibrin may therefore be contained as a normal constituent in the BM in different stages of polymerization and in different dimensions up to those large enough to be seen by light microscopy. The very large sized fibrin constituents of the BM were pictured to be rather far apart and wherever they were lysed by fibrinolysin the BM will break. Through such a breach, whole blood could leave the blood vessel and exhibit true extravasation or bleeding. This property of the blood vessel to break through such sites by the action of fibrinolysin is proposed to be closely associated with capillary fragility.

The microstructure underlying increased capillary permeability produced by histamine and serotonin has been studied by Majno and Palade in the rat's cremaster. Since these authors found changes in the

smallest capillaries only after extremely high dosages of histamine or serotonin, the permeability of these vessels may be affected by mediators other than histamine and serotonin. Further electron microscopic studies may well establish that different mediators affect different vessels in the capillary bed.

The general picture found by Majno and Palade suggests that the plasma may be leaking out in discrete areas through gaps in the endothelium and that the BM, acting as a filter, retains the tracer particles, employed by these investigators, while allowing the passage of the water or small molecular components of the plasma. Majno and Palade thought that the accumulation of plasma proteins is partly responsible for the intramural pools of amorphous material in which they found filaments of fibrin polymerized. They suggested that the amorphous material may in part be fibrin at an early stage of polymerization.

C. *The Inhibitory Action of Fibrinolysin on Capillary Permeability*

Capillary permeability and fragility are two quite different phenomena which appear to be antagonistic. Such antagonistic action was recently demonstrated by us in scorbutic guinea-pigs.[5,6] Fibrinolysin and other proteolytic enzymes increase capillary fragility resulting in hemorrhage.

We reported earlier that trypsin, chymotrypsin, streptokinase-activated plasmin as well as chloroform-activated plasmin produce hemorrhages, but, when injected together with histamine, the permeability is markedly decreased as shown by the small amount of blueing.[5,6] These findings demonstrated that this kind of antihistamine action is not limited to fibrinolysin and streptokinase, but appears to be a general activity of proteolytic enzymes. Nevertheless, since fibrinolysis is a physiologic process assumed to occur in the more or less immobile layer of the plasmatic zone and in the exoendothelial space, the physiologic response to inflammation resulting in the action of mediators, is thus being controlled by fibrinolysis. This appears to be also true with bradykinin, as our results demonstrate the latter mediator to be antagonistic to fibrinolysin.

Of great interest are the findings of the decreasing action of intradermal histamine following the intravenous administration of the smaller dosages of histamine, as well as, to a lesser extent, of intradermal bradykinin following intravenous bradykinin. Similar observations, as reported above, were made with intradermal histamine or serotonin following the intravenously administered bradykinin. Although it must be considered premature to give a satisfactory explanation for these results, a tentative explanation may be offered. It is quite conceivable that the intravenous administration of histamine or bradykinin may

activate the plasminogen present in the circulating blood and therefore, ultimately, the action would be similar to that following the intravenously administered fibrinolysin. Such a possibility appears to be suggested to some extent by the observations of Rocha e Silva *et al.*[19] who found in anaphylactic and peptone shock activated fibrinolysin in blood. These authors thought that kinins might be produced by fibrinolysin in such conditions. The actual course of events in the occurrence of histamine and kinins and of activated fibrinolysin in the blood in anaphylactic or peptone shock will need to be clarified in future experiments. The above mediators may then be found to precede the activation of the plasminogen in the circulation and subsequently form fibrinolysin.

The antagonistic action of fibrinolysis to increased capillary permeability induced by bradykinin or other mediators may be explained by the breakdown of fibrin. The resulting molecular fragments or particles may then obstruct the pores or channels in the BM. Although cellular proteolytic enzymes may produce such breakdown of fibrin as well, fibrinolysis would be more likely to do so in accordance with Copley's concept on fibrin as a physiologic cement of the vascular wall. The recent electron microscopic studies by Bang[20] on fibrinolysis, resulting in defective fibrin polymerization, suggest that breakdown products may well be formed by the action of fibrinolysin on non-gelated fibrin and obstruct the BM with resulting decrease in capillary permeability.

There might be a molecular effect to impede the action of bradykinin or of other mediators. The pore size may be diminished due either to a direct action of the fibrinolysin or indirectly due to some metabolites from the breakdown of fibrin. Such breakdown products may then not be able to pass the existing pores.

In physics, permeability is defined as the coefficient which characterizes the resistance of the membrane to liquid flow across it (or the capacity of the membrane to permit passage of flow). Permeability is therefore *a property of the membrane* and not, as often referred to by biologists, a movement of material across a barrier.

The fact that the permeability characteristics are maintained, e.g., in vascular purpura, a condition in which there are gross discontinuities in the vascular wall but in which there is no edema, is an indication that the aggregated surface of the defects is negligible as compared to the surface of the entire vascular system.

In capillary fragility in which the defect is gross, widely spaced and of very small total surface, the dimension of the openings are of the order of more than 1 μ. In capillary permeability the structural failure, manifested by the size of pores or channels, is minute and closely spaced from a few to hundreds of Ångstrom units in dimension.

CONCLUSION

The "fibrinolysin versus mediator concept", which physiologically may mirror a homeostatic equilibrium, has been proposed to interpret the integrity of the vascular wall. Vascular integrity includes such opposing physical properties as capillary fragility and capillary permeability. The physiologic and pathologic significance of bradykinin and other mediators in their affecting the vascular wall may thus be better understood.

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