RELATIONSHIP BETWEEN VASCULAR FRAGILITY AND STATE OF THE MUCOPOLYSACCHARIDES IN THE SKIN

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Hyaluronidase, if injected intradermally into humans, rabbits, guinea pigs, and rats, does not reduce the resistance of the skin vessels despite the decrease in viscosity of the mucopolysaccharides.

The mechanical strength of the skin vessels is reduced in some pathological states (scurvy, thrombocytopenia, radiation sickness, etc.), so that hemorrhagic manifestations appear. The mechanism of this decrease in resistance of the vessels has not been adequately explained. The decrease in number of the blood platelets, in their adhesiveness, and in their ability to aggregate undoubtedly leads to a decrease in vascular resistance [1]. Disturbance of the formation of definitive fibrin [8] also evidently plays an important role. At the same time, in some diseases vascular fragility is connected with changes in the vessels themselves and with disintegration of the ground substance of the perivascular connective tissue [7]. However, as investigations [3] have shown, structural changes in the skin vessels of rabbits and rats characteristic of an inflammatory reaction (exposure to a moderate temperature, application of xylol to the skin, intradermal injection of histamine and bradykinin) and the accompanying increase in permeability do not lower the resistance of the vessels to mechanical action.

The object of this investigation was to study the relationship between mechanical strength of the blood vessels and the state of the perivascular connective tissue, especially the state of the mucopolysaccharides of the connective tissue ground substance.

EXPERIMENTAL

Experiments were carried out on rabbits, guinea pigs, rats (August), and human volunteers. The resistance of the skin vessels was determined from the number of petechiae arising in the course of 5 min at the site of application of a suction cup (internal diameter 10 mm in experiments on animals, 20 mm in experiments on volunteers) inside which the pressure was negative. The atmospheric pressure was reduced for rabbits by 200-250 mm Hg, for guinea pigs by 200 mm Hg, for rats by 300-375 mm Hg, and for the humans by 100-260 mm Hg. The hair was removed by an electric shaver 24 h before the experiment began. The measurements were made in animals on the skin of the abdomen and sides of the trunk, and in the human volunteers on the medial surface of the forearms.

Hydrolysis of the mucopolysaccharides of the skin was produced by intradermal injection of bovine testicular hyaluronidase (Reanal, Budapest; lyophically dried, and 1 mg = 300 units). The animals were injected with a dose of 1500 units in 0.5 ml physiological saline over a period of 20-30 sec at a pressure of 50 mm Hg. The human subjects were injected intradermally with 600 units hyaluronidase in 0.2 ml physiological saline from a syringe. The resistance of the vessels was studied 30 min after injection of the

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TABLE 1. Effect of Hyaluronidase on Resistance of Skin Vessels

Animal	Intact skin	Number of petechiae after min (M ± m)	
		Injection of physiological saline	Injection of physiological saline and hyaluronidase
Rabbit	3,0±0,37(20)*	2,0±0,31†(25)	3,0±0,29(25)
Guinea pig	3,0±0,65(10)	2,0±0,35(15)	2,0±0,38(15)
Rat	3,0±0,54(11)	2,0±0,25(10)	2,0±0,65(10)

*Here and subsequently, number of determinations shown in parentheses.

†Difference significant ($P < 0.05$).

hyaluronidase. Control tests were carried out on symmetrically opposite areas of intact skin into which physiological saline was injected under identical conditions.

Hyaluronidase activity was determined from the area of spread of a 0.25% solution of trypan blue, injected with or without 600 units hyaluronidase in 0.2 ml physiological saline by the standard method [6]. The area of spread was measured at once and 30 min after the injection.

The permeability of the skin vessels was determined in some animals at the end of the experiment by a modified Menkin's method [2].

The results were subjected to statistical analysis using Student's criterion.

EXPERIMENTAL RESULTS

Intradermal injection of hyaluronidase by the method used caused a more rapid spread of the dye in all cases, the action ceasing after 30 min. The ratio between the areas of spread of the dye in the presence and absence of hyaluronidase was 2.5 in the rabbits, 2.6 in the guinea pigs, and 2.4 in the rats. In the presence of hyaluronidase the papule quickly became flattened after injection of the solution, while after injection of physiological saline alone, it persisted for a long time. In human subjects and rabbits, injections of hyaluronidase produced a mild inflammatory reaction, persisting in rabbits for 24 h and in man for 48 h. Clinical manifestations of inflammation in rats and guinea pigs were not apparent. However, in these animals, just as in rabbits, inflammation developed. This was shown by the onset of disturbances of vascular permeability. The blue coloration of the skin as a result of exudation of the protein–dye complex was more clearly visible when the inner surface of the skin was examined. The duration of the disturbances of vascular permeability were greatest in the rabbits (over 2 h) and least in the guinea pigs and rats (under 1 h).

The actual decrease in atmospheric pressure was so chosen that 2-5 petechiae appeared on areas of intact skin in the course of 5 min. The same reduced pressure was applied to the experimental areas of skin of that particular animal (Table 1).

In the tests on animals, intradermal injection of hyaluronidase caused virtually no change in the resistance of the skin vessels. No changes in their resistance through the action of hyaluronidase likewise could be detected in the human subjects.

Experiments showed that intradermal injection of hyaluronidase caused a definite increase in the area of spread of the dye, reflecting liquefaction and reduction in viscosity of the mucopolysaccharides of the skin. Despite this fact, the resistance of the skin vessels was not lowered. The view that the ground substance of connective tissue plays the role of a factor determining the mechanical strength of the vessels thus required reexamination [5, 7].

According to data in the literature [4], under the influence of x rays the mucopolysaccharides of the skin undergo depolymerization, and this is partly responsible for the development of radiation hemorrhages. The results of the experiments described above demonstrate the need for a critical approach to such views regarding the pathogenesis of the radiation syndrome.

Intradermal injection of hyaluronidase caused the development of inflammatory changes in all the animal species studied and in man, and in particular, it increased vascular permeability. These effects

are evidently unconnected with the specific action of hyaluronidase, but are due to the presence of impurities in an insufficiently purified preparation. The absence of changes in resistance of the vessels, while their permeability was obviously disturbed, confirms data published previously [3] and emphasizes once again the difference between the two fundamental properties of the blood vessels: permeability and mechanical strength.

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