OBSERVATIONS ON THE DEPRESSOR EXTRACTS OF HUMAN BLOOD AND ON THE VASCULAR ACTION OF EXTRACTS OF RABBIT AND DOG BLOOD

By IRVINE H. PAGE, M.D.

(From the Hospital of The Rockefeller Institute for Medical Research)

(Received for publication, October 12, 1934)

It has been shown that alcoholic extracts of human body fluids contain a substance or a group of substances which, when injected into cats or rabbits, markedly elevate the blood pressure level. The search for pressor extracts has been extended to other species with results which are at variance with those exhibited by human blood plasma. It was shown that extracts of plasma of rabbits always produced depression of the level of blood pressure of anesthetized cats, whereas extracts of dog blood had but the slightest degree of this action.

While extracts of fresh human plasma exhibit only pressor action it was found that when whole blood, plasma, ascitic or spinal fluid was allowed to stand for more than an hour or two, or if hemolysis occurred, the action of the extract from any one of these fluids was invariably powerfully depressor. We have attempted to learn more concerning this action by comparing the simultaneous effects of these extracts on the volume of the leg, the renal volume, and the blood pressure of the animal, with those of other extracts of tissue or adequately characterized depressor substances.

Method

The preparation of extracts of whole blood, plasma, and serum has been described in the previous paper. The method consists essentially in the precipitation of heparinized blood or plasma with alcohol, filtration, and removal of the alcohol at low temperature with the aid of a vacuum. The excess lipid...
Fig. 1. Comparison of plasma, corpuscle, and liver extract of rabbit with choline and histamine. Upper tracing = leg volume; middle = kidney volume; lower = carotid blood pressure. Time intervals = 10 seconds. (1) Saline 5 cc. (2) Choline 1.5 mg. (3) Extract of 3 cc. plasma. (4) Extract of 3 cc. corpuscles. (5) Extract of 3 cc. plasma. (6) Extract of 3 cc. corpuscles. (7) Choline 1.5 mg. (8) Extract of liver. (9) Same. (10) Histamine 0.001 mg.
was then removed by chilling the extract. Ultrafiltrates were prepared by filtration through collodion membranes at high pressure. Extracts of tissue were made by boiling the fresh minced tissue in 0.1 per cent acetic acid for 3 minutes, filtering, and adjusting the filtrate to pH 7.4 just before injection into the animal.

Cats anesthetized with either ether or ethyl urethane were employed for the testing. Vagotomy was performed, the right kidney inserted into a Livingston oncometer, the left leg into a plethysmograph, and either the right carotid or the right femoral artery cannulated for recording the blood pressure.

RESULTS

Whole blood, plasma, serum, or corpuscles of rabbits, whether the blood was removed by puncture of the heart or by puncture of a peripheral artery or vein, yielded extracts which were powerfully depressor in action (Fig. 1). The renal volume is markedly reduced and the leg vessels dilated simultaneously with the fall in pressure. This action is unaltered by preliminary atropinization of the animal. The depressor action of plasma extracts differs from that of choline not only in that it is not abolished by atropine but also in that the constriction of the kidneys is quantitatively much more powerful and the peripheral dilatation considerably weaker. Apparently choline contributes little or nothing to the depressor action of plasma extracts.

The powerful constrictor action in the kidneys is one of the most characteristic features of either corpuscle or plasma extracts of rabbit blood. From time to time, reversal of the usual depressor effect to a pressor one is observed. Even in these cases where the pressure rises instead of falling, the typical constriction of the kidneys is seen. This action on the kidneys resembles closely that resulting from the injection of adenylic acid. Histamine also produces constriction of the kidney but with the same degree of reduction in blood pressure, adenylic acid has a more powerful constrictor action.

Ultrafiltrates of rabbit blood plasma are actively depressant and also constrict the kidneys. Human plasma ultrafiltrates are inactive.

Extracts of plasma from dogs' blood plasma, whether arterial or venous, have almost no effect on the blood pressure of an etherized cat. Occasionally slight depressor action is observed. Extracts of whole blood, taken directly from the cannulated vessel into alcohol, exhibit very slight depressor action, while corpuscle extracts are moderately active depressants. The ultrafiltrates from plasma are uniformly without vascular action.
Comparison of Depressor Extracts of Human Blood with Other Depressor Substances and Extracts

Human blood plasma differs from that of the rabbit and dog in yielding extracts which are pressor. However, if the blood is allowed to stand at room temperature for an hour or two, or to hemolyze, the extracts are powerfully depressor. Human ascitic and spinal fluid also yield pressor extracts when fresh, but if allowed to stand the extract yielded is depressor.

Inspection of many graphic records shows that plasma extracts which exhibit depressor action produce marked renal constriction and relatively insignificant changes in the leg volume. In this respect plasma extracts resemble the action of corpuscle extracts.

Human corpuscle extracts, whether the extract has been prepared from intact or previously hemolyzed cells, are usually moderately strongly depressor. The depressor action is accompanied by marked constriction of the kidneys with an insignificant change in the leg volume. It is possible that the red cells liberate depressor substances into the plasma on standing. Many of our experiments indicate that this is true.

Comparison has been made of the action of depressor extracts of plasma with that of acetic acid extracts of kidney, liver, and histamine, adenosine, adenylic acid, and choline (Fig. 2). Ordinarily histamine depresses the level of the blood pressure to an extent out of proportion to its action on the renal volume when compared with plasma extracts. Adenosine also has a more marked action on the level of blood pressure than on renal volume but adenylic acid may exhibit extreme constrictor action on the kidneys without markedly affecting the level of the blood pressure.

Choline, on the other hand, may depress the blood pressure to the same extent as plasma extract without at the same time producing marked renal volume reduction. Peripheral dilatation is especially active. The effect of extracts of liver and kidney closely resembles that of depressor plasma extracts, especially as regards their powerful constrictor action on the kidneys.

2 The adenosine and adenylic acid were kindly supplied by Dr. P. A. Levene and Dr. S. A. Harris.
Fig. 2. Comparison of the action of various depressor substances with depressor extracts of plasma. Upper curve = leg volume; middle = renal volume; lower = carotid blood pressure. Etherized cat. Time intervals = 10 seconds. (1) Acetic acid extract of rabbit kidney. (2) Histamine 0.0007 gm. (3) Adenosine 6 mg. (4) Adenosine 10 mg. (5) Adenylic acid 2 mg. (6) Choline 4 mg. (7) Plasma extract equivalent to 4 cc. plasma. (8) Acetic acid extract of rabbit liver.
CONCLUSIONS

1. Alcoholic extracts of the plasma of rabbits obtained from arterial or venous blood differ from those of human plasma in having a marked depressor action on the blood pressure of anesthetized cats. This action is unantagonized on atropinization. Extracts of the plasma of dogs, on the other hand, are almost without vascular effect.

2. Ultrafiltrates of the plasma of rabbits are actively vasodepressor, while those of human and dog plasma are without action.

3. Extracts of the plasma of rabbits reduce the renal volume greatly and they have a relatively weak dilator action on the arteries of the periphery. These effects resemble those of adenylic acid more than those of histamine.

4. It is possible that the pressor-depressor substances of the blood are species-specific.

5. Human plasma, ascitic and spinal fluid which have been allowed to stand, yield extracts that are depressor and in their pharmacological action resemble closely extracts prepared from red blood cells and acetic acid extracts of tissues. Their constrictor effect on the kidneys is marked.

6. Histamine, choline, and adenosine depress the level of the blood pressure more effectively than they constrict the volume of the kidneys, while the reverse is true when adenylic acid is employed.