FURTHER STUDY OF THE REFLEX ACTION OF RENIN ON THE BODY

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It has been shown recently that in the development of a certain stage of hypertensive disease the formation of renin by the kidneys plays an important part [5, 7, 8]. The majority of workers think that renin by itself has not the power to alter vascular tone and only by its interaction with the α_2-globulin fractions of the serum proteins is the active vasoconstrictor hypertensin formed, which acts by the humoral route [6, 9].

However, during recent years facts have been brought to light showing that in the mechanism of the pressor action of renin a nervous factor [1, 3, 4] is important in addition to the humoral action. In particular, O.S. Merkulova and M.Ia. Ratner [3], using a method of perfusion of internal organs isolated from the vascular system, showed that renin is a sufficiently strong stimulator of the chemoreceptors of the kidney and small intestine.

The object of the present investigation was the further study of the special features of the action of renin on the receptors of internal organs. In particular it was necessary to ascertain whether the excitability of the chemoreceptors to such substances as nicotine was affected by renin. In addition, in a series of experiments an attempt was made to explain the role of the interoceptors in the mechanism of production of tachyphylaxis.

EXPERIMENTAL METHOD

In acute experiments on cats under urethane or urethane-chloralose anesthesia, a loop of small intestine was perfused with Ringer-Locke solution. The pressure in the carotid artery and the respiration were recorded in the usual way. The test substances were injected into the perfusing fluid by means of a syringe.

The renin used in the experiments was obtained by the method of Iu.D. Vadkovskaia [2]. The renin was prepared from the kidneys of pigs or cats. The preparation was considered suitable if no ammonium sulfate could be found in it after completion of dialysis (barium chloride test) and if it had no local action on the vessels. The latter was tested by recording the rate of flow of the perfusate. The renin was considered to be active enough if 1 ml of it, injected intravenously, resulted in prolonged (for 10-15 minutes) increase of the blood pressure by 30 to 40 mm of mercury. To avoid interaction of renin with the protein fractions of the blood the preparation was injected into the perfusing fluid only after the perfused organ had been thoroughly washed free from blood. Altogether 68 experiments were made.

EXPERIMENTAL RESULTS

In all the experiments the injection of 0.5 to 2 ml of renin into the perfusing solution of the isolated intestinal loop caused a clear rise in the blood pressure and, less commonly, changes in respiration. The degree of this reaction depended to some extent on the anesthesia.

Thus under urethane-chloralose anesthesia the injection of 1.5 ml of renin into the perfusing solution caused an increase of blood pressure of 18 to 40 (most commonly 20) mm of mercury, while under urethane anesthesia the same dose of renin raised the pressure by 10-12 mm mercury. Under combined anaesthesia, respiration on injection of renin into the perfusing solution, was not altered in most cases, and only in a small number of experiments was it slowed. With urethane anesthesia injection of renin into the perfusing solution led in half the cases to an increase in the rate and amplitude of respiration.

Investigation of the effect of renin on the excitability of the chemoreceptors to nicotine. In experiments by O.S. Merkulova and M.Ia. Ratner [3] it was shown that as a result of the action of renin on the chemoreceptors of the small intestine and kidneys their reaction to acetylcholine was modified. Injection of acetylcholine after renin in all the experiments caused, in place of a brief rise in the blood pressure, a more prolonged pressor effect, continuing for 2 minutes and even longer. It remained unexplained whether the sensitivity of the receptors was changed by the action of renin only to acetylcholine or to other chemical stimulants also. For this reason we tested the action of nicotine on the chemoreceptors of a loop of small intestine before and after injection into the perfusing solution of 2 to 4 portions of renin.

In the majority of experiments the action of any one concentration of nicotine was studied, but in some experiments both before and after the injection of renin, nicotine was injected several times in increasing concentrations (1 ml of solutions $1 \cdot 10^{-6}$ to $1 \cdot 10^{-4}$). With repeated injections of nicotine the interval between them was not less than 10 minutes.

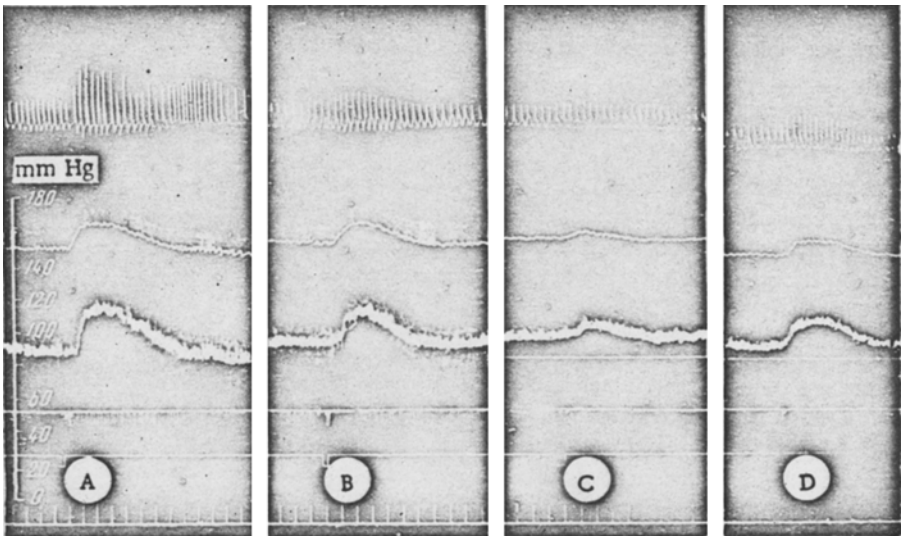

Fig. 1. The effect of renin on the excitability of the chemoreceptors to nicotine. A) 13 hours 10 minutes – injection into the perfusing solution of 1 ml of $1 \cdot 10^{-4}$ nicotine; B) 13 hours 20 minutes – the same; C) 13 hours 30 minutes – injection into the perfusing solution of 1.5 ml of renin; D) 13 hours 35 minutes – injection into the perfusing solution of 1 ml of nicotine solution in a concentration of $1 \cdot 10^{-4}$. (Experiment dated November 20, 1956.) The curves represent (from above downwards): respiration, heart rate, blood pressure, zero line, rate of perfusion in drops, record of stimulation, time marker (5 seconds). Note: In the kymogram of the experiment dated November 20, 1956 the tracing of the blood pressure follows that of the heart rate.

In contrast to the results with acetylcholine [3], we were unable to observe any significant change in the excitability of the chemoreceptors to nicotine after administration of renin. The height of the pressor reflex on injection of nicotine after renin was diminished in 16 out of 34 experiments in comparison with the original value of this reflex. However, this reduction, as a rule, was insignificant.

In 11 cases the height of the pressor reflex remained unchanged, and only in six experiments was a slight increase in the pressor effect observed. In the great majority of experiments the latent period of reflex reaction to nicotine and its duration suffered no change after the administration of renin (Figure 1).

Investigation of the role of the chemoreceptors of the internal organs in the development of tachyphylaxis. Repeated injections of renin into the general circulation are known to cause the development of tachyphylaxis, expressed as a progressive diminution of the hypertensive reaction to each following injection of the drug, until it finally disappears. Since, in addition to its humoral effect, renin also has a reflex action, it might be supposed that tachyphylaxis is to some extent the result of change in the excitability of the interoceptors as a result of the frequent appearance of renin in the general circulation.

In order to test this hypothesis experiments were set up in which renin was repeatedly injected into the perfusing solution at short intervals of time.

In these experiments the renin used was prepared from the kidneys of both pigs and cats. Renin was injected 4 or 5 times in doses of 1.5 to 2 ml with intervals of 2 to 2½ minutes between the injections.

Irrespective of whether the renin used was prepared from pigs or cats, in all 26 experiments of this series the pressor reflex arising from injection of renin into the perfusing solution repeatedly and often in close succession was unchanged (Figure 2).

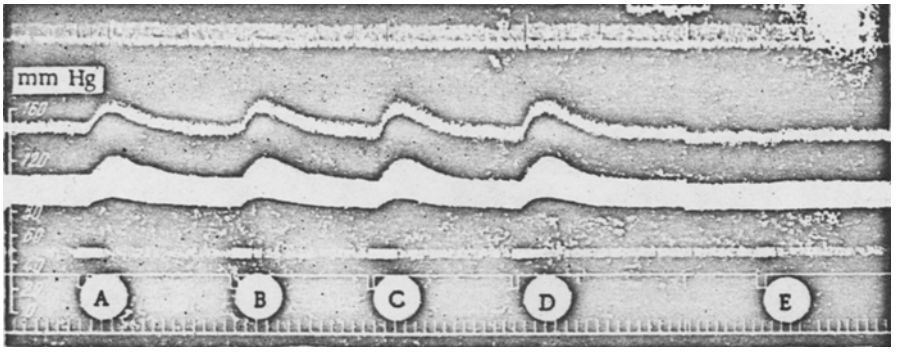

Fig. 2. Reflex action of renin injected repeatedly into the perfusing fluid of an isolated loop of intestine. A,B,C,D) Injection of renin into the perfusing solution in a dose of 1.5 ml; E) injection of 1.5 ml of inactivated renin. Significance of the curves as in Figure 1.

Simultaneously the effect of a state of tachyphylaxis on the interoceptive reflexes caused by injection of renin was investigated. For this purpose renin was injected into the perfusing solution in a volume of 1.5 ml before and after repeated injections of this substance had been given in order to induce tachyphylaxis.

The experiments showed that the state of tachyphylaxis does not influence the reflex action of renin: in six experiments out of eight the pressor effect of introduction of renin into the perfusing fluid in a state of tachyphylaxis was practically indistinguishable from the reflex caused before the induction of tachyphylaxis (Figure 3). Only in two cases did we observe an insignificant increase in the pressor reflex to injection of renin in the state of tachyphylaxis.

The results of our experiments thus confirmed the possibility of reflex action of renin. This is supported also by the fact that, irrespective of the type of anesthesia, the latent period of the hypertensive reaction amounted to not more than 2½ to 5 seconds, and the duration of the reaction usually varied in the neighborhood of 40 seconds.

It is important to emphasize that the reflex changes in the blood pressure and respiration which we observed were due to the specific activity of the renin itself. This was confirmed by control experiments in which injection into the perfusing solution of renin inactivated by boiling or by storage for a day at room temperature

did not produce any change in the blood pressure or respiration (Figure 2).

In evaluating the results of the first series of experiments it must be remembered that repeated injections of nicotine into the perfusing solution in general reduce the excitability of the receptors to this drug. Evidently the diminution in the pressor reflex observed in some experiments was due in the first place to this fact and not to the specific action of renin. This view is supported by the fact that the duration of the pressor reaction to nicotine was not changed after the action of renin, in contrast to the results obtained by the use of acetylcholine [3].

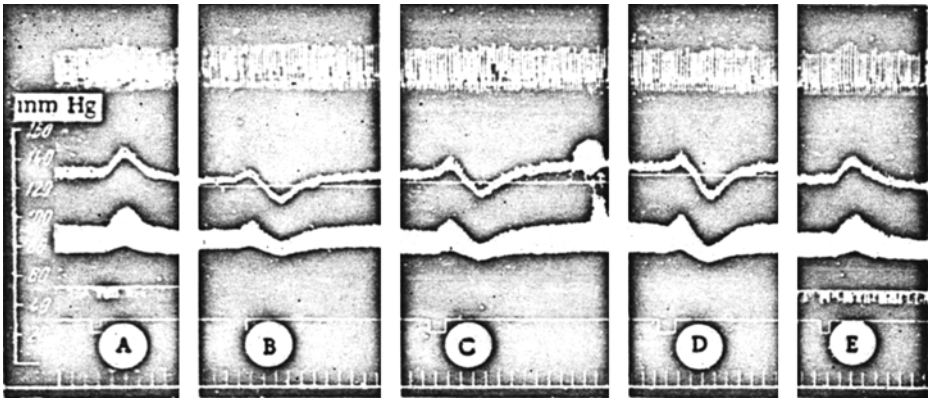

Fig. 3. The reflex action of renin during a state of tachyphylaxis. A) 14 hours 15 minutes – injection of 1.5 ml renin into the perfusing solution; B) 14 hours 20 minutes – injection of 1.5 ml renin into the femoral vein; C) 14 hours 23 minutes – the same; D) 14 hours 26 minutes – the same; E) 14 hours 30 minutes – injection of 1.5 ml of renin into the perfusing solution. Significance of the curves as in Figure 1.

We were unable to discover any manifestations of tachyphylaxis after the repeated action of renin on the receptors of the isolated loop of intestine.

SUMMARY

Acute experiments were performed on cats. The loop of the small intestine isolated with respect to the vessels was perfused by renin prepared from the kidneys of pigs or cats. It was established that renin, thus introduced, caused an increase of the blood pressure.

Preliminary introduction of renin into the perfusate does not change the sensitivity of the chemoreceptors of the organ to nicotine.

In difference to the administration of renin into the general circulation, numerous and frequent (with the intervals of 2 to 2.5 minutes) introductions of renin into the perfusate never caused tachyphylaxis.

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