EFFECT OF BRADYKININ ON MICROVESSELS DEPENDING ON THEIR INITIAL TONE

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The distribution of kinins in the body and their high biological activity and broad spectrum of action suggest an important role for them in adaptation reactions and in the pathogenesis of cardiologic diseases [2, 3].

One of the biologically most active substances of the kallikrein–kinin system is the nonapeptide bradykinin.

The physiological effects of bradykinin on the central and peripheral circulation have been reasonably well studied [2, 6, 11, 13]. However, information on the effect of bradykinin on the microcirculation is contradictory. According to some workers, bradykinin causes dilatation of microvessels [4, 9], according to others it causes constriction [8, 9, 14], or it does not change the lumen of microvessels [1, 4].

This difference in the action of bradykinin can tentatively be explained by the state of the original tone and receptors of the microvessels, depending on the presence of other vasoactive substances.

The object of this investigation was to study the action of bradykinin on different sectors of the microcirculation and the connection between this action and the initial state of microvascular tone and changes in the central hemodynamics.

EXPERIMENTAL METHOD

Experiments were carried out on 17 male Wistar rats weighing 240-430 g, anesthetized with amobarbital (0.125 g/kg). Biomicroscopy of the mesenteric microvessels of the small intestine was carried out in the usual way [5]. The internal diameter of the microvessels was measured with an ocular micrometer. The response of arterioles from 11 to 22 μ in diameter and of venules from 18 to 40 μ in diameter was studied. Bradykinin was applied to the mesenteric microvessels in doses of 0.01 to 10 μg in 0.1 ml physiological saline.* The length and shape of the microvessels were studied from microprints and photomicrographs. The arterial pressure, pulse rate, and respiration rate were measured by means of an electromanometer connected to a catheter introduced into the femoral artery.

EXPERIMENTAL RESULTS

The threshold dose of bradykinin application of which was followed by changes in the lumen of the microvessels and changes in their permeability for blood cells was 0.01 μg in 0.1 ml physiological saline.

Bradykinin in doses of 0.01-10 μg caused three types of responses of the arterioles (constriction in 54% of cases, dilatation in 15%, no change in the lumen in 31%) and of the venules (constriction in 31% of cases, dilatation in 46%, no change in the lumen in 23%) of the mesentery. The type of response of the microvessels depended on the dose given. After application of 0.01-0.1 μg bradykinin constriction of the arterioles by 8.6%

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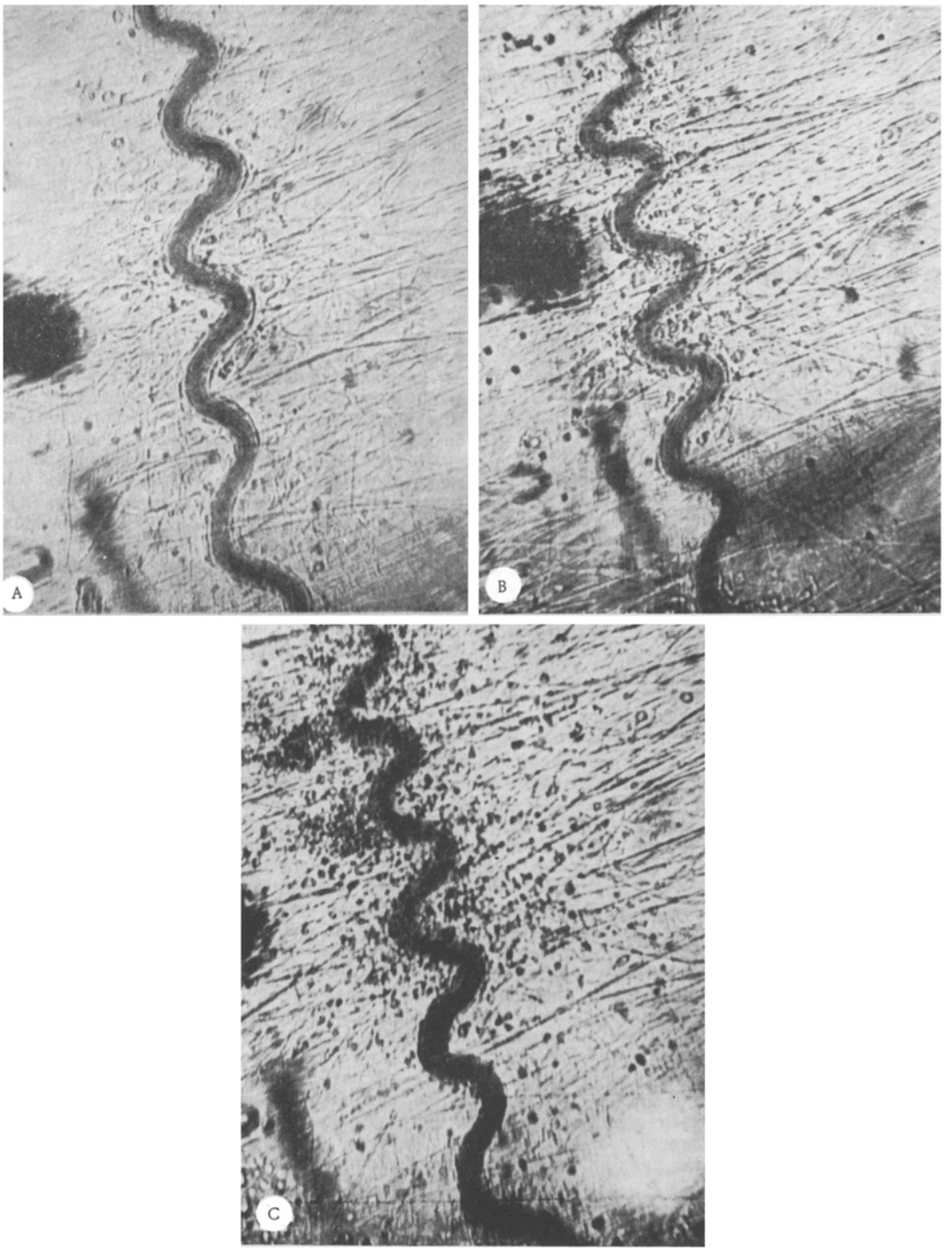

Fig. 1. Biomicroscopy of rat mesentery before and after application of bradykinin. A) Venule before application, B) diapedesis of erythrocytes and deformation of the same venule after application of 0.1 μg bradykinin, C) dilatation, increased congestion, diapedesis of erythrocytes, and hemorrhages from curved segments of the same venule after application of 1 μg bradykinin. 140×.

and of the venules by 10% compared with the initial measurement of the lumen was observed ($P < 0.05$). Application of 0.1-1.0 μg bradykinin led to dilatation of the arterioles by 12.9% ($P < 0.02$) and venules by 8.1% ($P < 0.05$). After application both of the largest (10 μg) and of the smallest (0.01 μg) of the doses of bradykinin used, no response of the vessels was observed. A response of the microvessels developed immediately after application of bradykinin and reached a maximum after 1-2 min. After 5-7 min the diameter of the micro-

vessels was restored to its initial value except in isolated cases when, despite rinsing of the mesentery with physiological saline, the changes persisted for 10-20 min.

A characteristic feature of the action of bradykinin is a change in permeability of the microvessels [14]. The degree of increase in permeability and the time of its manifestation in the present experiments corresponded sufficiently strictly to the dose of bradykinin. In half of the cases 7-8 min after application of 0.01 μg bradykinin diapedesis of single erythrocytes was observed, chiefly from postcapillaries and venules. In a dose of 0.1 μg bradykinin caused the formation of collections of erythrocytes around the venules after 3-5 min (Fig. 1B). Application of 1.0 μg bradykinin led after 1-2 min to massive hemorrhages from the venules (Fig. 1C). Similar changes in permeability appeared a few seconds after application of 10 μg bradykinin.

Diapedesis of erythrocytes and hemorrhages occurred mainly at junctions between capillaries, postcapillaries, and small venules, and also in regions of their greatest curvature (Fig. 1C).

Another characteristic feature of the action of bradykinin was that massive diapedesis of erythrocytes was accompanied in the present experiments by an increase and not a decrease in the velocity of the blood flow in the microvessels. In no case was thrombus formation or a disturbance of integrity of the vessel wall observed, except deformation of venules, expressed as a closer distribution of the undulating waves of the blood vessels (Fig. 1B, C).

Measurement of the length of the venules showed that they were shortened on average by 10% under the influence of bradykinin. Diapedesis of the erythrocytes was most marked in segments of maximal shortening. An increase in permeability of the microvessels was observed not only at the site of application of bradykinin, but also in other loops of the mesentery. These observations point to a generalized, yet unequal change in permeability of the microvessels under the influence of bradykinin and they reveal the most vulnerable regions from this respect: the junctions between the vessels and the crests of the waves formed by the convoluted venules.

Repeated application of bradykinin was often accompanied by a reflex movement of the animal, evidently due to the nociceptive action of bradykinin [7, 12]. It was noted that the animal's reflex movement occurred as a rule at the time of maximal change in permeability of the vessel wall.

Local application of bradykinin was followed by changes in the central hemodynamics: The systemic arterial pressure fell on average by 25% ($P < 0.01$), the pulse rate increased by 13% ($P < 0.05$), and the respiration rate increased by 20% ($P < 0.01$).

Noradrenalin, applied in a dose of 2 μg to the mesenteric microvessels caused constriction of the arterioles by 16.8% ($P < 0.01$) but virtually no change in the diameter of the venules (constriction by 1.4%; $P > 0.1$). The velocity of the blood flow in the arterioles was slowed and frequently the flow stopped for a short time. The blood flow in the venules was disturbed less severely. Rinsing the mesentery led to restoration of the blood flow in the venules and, a little later, in the arterioles. In response to repeated application the sensitivity of the microvessels to noradrenalin decreased.

Noradrenalin significantly altered the response of the microvessels to bradykinin. The most characteristic effect was a shift toward dilatation of the microvessels. The constrictor responses to bradykinin disappeared completely. All doses of bradykinin used dilated the arterioles on average by 9.6% ($P < 0.05$), whereas dilatation of the venules by 1% was not significant ($P > 0.1$).

The action of bradykinin after preliminary administration of noradrenalin, like the action of bradykinin alone, was thus accompanied by an increase in microvascular permeability. However, diapedesis of the erythrocytes and hemorrhages from the venules occurred 5-10 min later. The number of foci of hemorrhage was increased almost twofold (up to 21) in the later stages after application of noradrenalin and bradykinin (on average after 20-25 min) compared with their number after application of bradykinin alone (up to 12 foci).

The results are evidence that the character of response of the mesenteric microvessels to bradykinin if the initial tone is changed may differ significantly from responses observed under ordinary conditions.

In view of evidence that β-adrenoreceptor blockade potentiates the depressor action of bradykinin [2], it might be expected that the depressor action of bradykinin would be reduced in the presence of noradrenalin. Yet the facts observed are evidence to the contrary. When the noradrenalin concentration was increased the dilator effect of bradykinin and its effect on permeability of the microvessels also were increased. Since noradrenalin hyperproduction is characteristic of stress situations, the counter-regulatory action of bradykinin is of adaptive importance, helping to protect the tissues against ischemia and metabolic exhaustion. An im-

portant role in the mechanisms of action of bradykinin is probably played by its stimulating effect on synthesis of prostaglandins and histamine [10].

LITERATURE CITED

1. A. Ya. Bunin, in: On Microcirculation Problems [in Russian], Moscow (1977), pp. 191-192.
2. A. A. Dzizinskii and O. A. Gomazkov, Kinins in the Physiology and Pathology of the Cardiovascular System [in Russian], Novosibirsk (1976).
3. A. A. Nekrasova, "Humoral depressor factors in arterial hypertension," Author's Abstract of Doctoral Dissertation, Moscow (1973).
4. B. V. Tsveifakh, Patol. Fiziol., No. 2, 6 (1964).
5. A. M. Chernukh, P. N. Aleksandrov, and O. V. Alekseev, The Microcirculation [in Russian], Moscow (1975).
6. A. M. Chernukh, P. N. Aleksandrov, and M. I. Timkina, Byull. Éksp. Biol. Med., No. 3, 259 (1976).
7. D. Armstrong, J. B. Jepson, C. A. Keele, et al., J. Physiol. (London), 135, 350 (1957).
8. R. P. Bobbin and P. S. Guth, J. Pharmacol. Exp. Ther., 160, 11 (1968).
9. J. N. Diana, Am. J. Physiol., 212, 456 (1967).
10. L. Grodzinska, Folia Med. Cracov., 20, 211 (1978).
11. E. Haberman, in: B. I. Roka, Generalisierte intervasculäre Gerinnung. Beeinflussung der Hämostäse durch gefessactive Pharmaka, Stuttgart (1971), p. 193.
12. J. L. Marx, Science, 190, 544 (1975).
13. A. M. Northover and B. J. Northover, J. Pathol., 101, 99 (1970).
14. D. A. Rowley, Brit. J. Exp. Pathol., 45, 56 (1964).

PROSPECTS FOR THE STUDY OF MYOCARDIAL CONTRACTILITY IN HUMAN AUTOPSY MATERIAL

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To study the mechanisms of electromechanical processes in the myocardium in most cases strips of myocardium from experimental animals or biopsy specimens from patients undergoing operations for various heart diseases are used [2, 4, 7]. However, in view of the well-known structural and functional differences between the myocardium of experimental animals and man, some caution must be exercised in the interpretation of the experimental material, whereas results obtained on strips of myocardium taken at biopsy during operations reflect only the function of the pathologically changed myocardium. Moreover, the choice of strips of myocardium removed during surgical operation by the experimenter is very limited. For this reason the possibility of working with strips of myocardium from the heart of patients with diseases not suitable for operative treatment and also of working on strips of heart from clinically healthy subjects is of great interest.

The object of this investigation was to determine whether it is possible to record isometric contraction of strips of myocardium from human autopsy material, to attempt to reproduce the most elementary experiments in chrono- and inotropism, and also to determine the sensitivity of the myocardium to adrenalin, noradrenalin, and acetylcholine.

EXPERIMENTAL METHOD

Strips of the right atrium 0.5-0.8 cm long and 1 × 2 mm thick and the papillary muscles of the right ventricle were placed in a constant-temperature chamber with a volume of 5 cm^3 through which Ringer's

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