ACTION OF BRADYKININ ON THE MESENTERIC MICROCIRCULATION IN RATS

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Responses of the mesenteric microvessels of rats to application and intravenous injection of bradykinin were studied in acute experiments using intravital microscopy. No clear bioelectric response of the smooth-muscle cells of the microvessels to local application of bradykinin could be found in electrophysiological experiments. In another series of experiments the dynamics of vasomotor activity were studied after the same treatment by the split-image method. The response of the microvessels to bradykinin application was shown to vary in character depending principally on whether the preparation was being applied for the first or subsequent time. It is suggested that bradykinin acts on the mesenteric microvessels through the intermediary of other vasoactive substances.
KEY WORDS: *microcirculation; bradykinin; split-image method; application of drugs.*

In some pathological states and responses of the organism the blood level of vasoactive kinins is raised. The problem of the mechanism of action of the vasoactive kinins on human and animal organs and tissues has by no means been solved. Experiments have shown that the vasoactive effect of the plasma kinins, when injected into the blood stream, is well marked. For example, intravenous injection of bradykinin leads to a fall of the systemic arterial pressure both in man and in most animals [9, 12]. Meanwhile in some experiments the constrictor action of bradykinin has been demonstrated on isolated segments of arteries and veins [8, 13, 15]. Corresponding data for the action of bradykinin on microvessels are very few in number and contradictory in nature. According to one report, local application of bradykinin causes vasodilatation and opens the precapillary sphincters [11, 16]. However, most investigations have shown that bradykinin acts as a powerful vasodilator on the smallest vessels [7, 10, 13]. Microvessels of different organs and tissues have been shown to differ in their sensitivity to bradykinin [11]. Until recently it was not known how the response of the terminal vascular network to bradykinin develops in time. On the one hand, the action of bradykinin was considered to develop over a comparatively long period, but on the other hand, evidence obtained by the study of microcirculatory systems showed that application of 0.1 μg bradykinin leads to marked dilatation of the mesenteric microvessels of rats, starting 3-5 sec and ending 1 min after application [16]. At the same time, it must be remembered that bradykinin, injected into the blood stream, is quickly destroyed by kininases and that a similar phenomenon may evidently take place also after local application of bradykinin.

To study the mechanisms of maintenance of microvascular tone, an investigation was therefore carried out to study the effect of local application and intravascular injection of bradykinin.

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EXPERIMENTAL METHOD

In a series of electrophysiological experiments the dynamics of electrical activity recorded by a microelectrode from the wall of the mesenteric vessels of rats was used as an indicator of the functional state of the smooth-muscle cells [4, 5]. Synthetic bradykinin (Sandoz) was applied in doses of 1, 2.25, 3.4, 5.9, and 7 μg to the surface of the mesentery in 0.1 ml physiological saline or injected intravenously in the same volume in doses of 2, 3, 25, and 90 μg. The mesenteric vessels of the rats were examined by intravital microscopy in transmitted light and great attention was paid to changes affecting the whole microcirculatory network of the rat mesentery following administration of bradykinin.

EXPERIMENTAL RESULTS

The experiments showed that application of bradykinin in some cases led to a motor response of the animal consisting of tonic convulsions and spasms, the intensity of which depended on the depth of anesthesia. During repeated application of bradykinin no motor response was observed. This response can be attributed to the nociceptive effect of bradykinin [6]. Under these experimental conditions the blood flow in most vessels remained normal, but sometimes the lateral branches of the main vessels were empty.

No clear bioelectrical response of the smooth-muscle cells of the microvessels to local application of bradykinin to the surface of the mesentery in the doses used could be observed in the electrophysiological experiments. Whenever, as a result of application of a large dose of bradykinin, stasis developed in the microvascular system, complete and irreversible depression of electrical activity was recorded from the wall of the microvessels. Nevertheless, it could be concluded that under the experimental conditions used, because of technical limitations, the bioelectrical response of the microvessels to bradykinin could not be recorded. To continue the analysis of the experimental data a series of experiments was carried out to study the vasomotor response of the mesenteric microvessels over a period of time after application and intravenous injection of bradykinin.

The split image method [1] was used to study responses of 25 arterioles, from 11.8 to 52.5 μ in diameter, and of 13 venules from 12.9 to 45.7 μ in diameter. The results were subjected to statistical analysis by Peters' method [3]. Just as in the electrophysiological experiments, bradykinin was applied locally in the same doses and injected intravenously. The results showed that of the 38 vessels observed, 18 arterioles and six venules gave statistically significant responses to bradykinin application ($P < 0.05$ and $P < 0.014$ respectively). Following intravenous injection of bradykinin statistically significant responses occurred in four arterioles ($P \leq 0.03$) and five venules ($P < 0.05$). The character of the response of the microvessels to the first application of bradykinin to the mesenteric surface differed from that to subsequent application of the drug. For instance, in most cases the first application of bradykinin was followed by vasoconstriction (six of nine arterioles were constricted; $P < 0.006$). The initial constriction amounted to 4-6% of the original diameter of the vessel, whereas the maximal contraction reached 15-16%. The response began after a very short latent period (under 1 min) and reached a maximum as a rule by the 5th-7th minute after application of bradykinin to the surface of the mesentery. Constriction of the mesenteric vessels continued even after rinsing with physiological saline, but the degree of the contractile response was greatly reduced. In three cases (arterioles of comparatively small diameter, 13-16 μ) bradykinin caused lasting dilatation, amounting to 30% 15 min after application. The small venules were dilated by application of 1 μg bradykinin ($P \leq 0.014$); the dilatation reached a maximum 5 min after the beginning of application, i.e., during maximal constriction of the arterioles. No direct relationship could be observed between the dose of bradykinin applied and the degree of the vasoconstrictor response. Repeated administration of bradykinin to the same animal gave a response of the microvessels that was qualitatively opposite to that to the first application in five of seven cases ($P < 0.05$). In some experiments the response of the mesenteric vessels to subsequent applications was biphasic. The venules also responded variably to repeated administration of bradykinin: reversible constriction of the venules starting immediately after application of 3 μg bradykinin and reaching 2.1-5% developed in two of five cases ($P < 0.014$). In other cases, dilatation of venules 12-16 μ in diameter was observed. Just as after the first application, in this case also no definite relationship could be detected between the degree of the vasomotor response and the dose of bradykinin applied.

After intravenous injection of both small and large doses of bradykinin, dilatation of the arterioles developed during the first 30 sec, and in some cases it reached 20% ($P < 0.001$). After large doses of bradykinin, persistent dilatation and stasis sometimes developed in the arterioles. The venules also were dilated after intravenous injection of bradykinin, but their dilatation did not exceed 5-7% ($P < 0.002$). Only in three of nine cases was the blood flow in the vessels restored 6-10 min after intravenous injection of bradykinin.

It can thus be concluded from these experiments that with the techniques employed, bradykinin has no clearly demonstrable and consistent effect on the mesenteric microvessels of the rats. Nevertheless, the results suggest that when bradykinin is applied to the mesentery it, or at least much of it, does not reach the membranes of the vascular smooth muscles, and does not therefore have any direct action on them. Bradykinin can be destroyed by tissue kinases or, what seems more likely, the application of bradykinin leads to liberation of other biologically active substances which, in turn, mask the action of bradykinin. At the same time, it must be remembered that the response of the microcirculatory system to bradykinin is not confined to the vasomotor response. Application of bradykinin also leads to marked changes in permeability of the microvessels [14] and there is reason to suppose that this particular effect of bradykinin is not mediated through other vasoactive substances [2].

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