Contribution of Bradykinin to Maintenance of Normal Blood Pressure

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SUMMARY The purpose of these experiments was to investigate whether the vasodilator tissue hormone bradykinin contributes to the maintenance of normal blood pressure. A newly synthesized peptide competitive antagonist of bradykinin, the compound Arg-Pro-Hyp-Gly-Phe-Ser-DPhe-Phe-Arg-trifluoracetic acid (B3852), capable of inhibiting the depressor effect of exogenous bradykinin by over 50%, was infused into 10 normotensive rats at a rate of 500 μg/0.1 ml/min. Blood pressure rose immediately, from a baseline of 104 ± 5 to 131 ± 7 mm Hg at the end of a 5-minute infusion, and returned to baseline within 2 to 3 minutes after discontinuation of the infusion. When similar doses were administered by continuous infusion to previously nephrectomized rats (n = 5) or as an acute bolus to adrenalectomized rats (n = 5), blood pressure rose from 111 ± 3 to 128 ± 5 mm Hg and from 112 ± 4 to 128 ± 5 mm Hg, respectively. The data suggest that a vasodepressor action of endogenous bradykinin contributes to maintenance of normal peripheral vascular tone, and that this action is not mediated through adrenal catecholamines or renomedullary prostaglandins.

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KEY WORDS • bradykinin antagonist • vasoregulation • normotensive rats • nephrectomized rats • adrenalectomized rats

THE strong vasodilator action of bradykinin has been demonstrated in the past by a number of pharmacological studies. However, the physiological role of this hormone in normal cardiovascular regulation remains elusive, partly because biochemical assays for its measurement in plasma have been fraught with methodological problems.

An alternative approach to this problem is to assess the effects of agents that inhibit bradykinin. Using antibodies to bradykinin, Carretero et al. demonstrated that bradykinin contributes to the antihypertensive effect produced in animals by angiotensin converting enzyme inhibition. Recently, we were able to demonstrate the same thing in hypertensive rats treated with an angiotensin converting enzyme inhibitor, by using instead a newly synthesized peptide analogue that is a competitive antagonist to bradykinin.

The present experiments were designed to investigate the possible contribution of bradykinin to the maintenance of normal blood pressure in normotensive rats, using a bradykinin-analogue competitive antagonist of this hormone.

Methods

Intact male Wistar rats weighing 225 to 255 g (Charles River, Wilmington, MA, USA) were used in the first set of experiments. One day before the experiment, all rats were cannulated under light ether anesthesia with two PE-50 catheters (Fisher Scientific, Medford, MA, USA), one into the iliac artery, for blood pressure measurements, and the other into the ascending aorta through the right carotid artery, for continuous infusion of the inhibitor. Rats used to test the capacity of the analogue to inhibit exogenous bradykinin had a third catheter introduced into the jugular vein for bolus injection of bradykinin. On the day of the experiment, the rats were maintained unanesthetized and unrestrained in plastic cages. Blood pressure and heart rate were monitored for a period of 60 minutes before the beginning of the experiment.

The drugs used in this study were bradykinin 50 μg/ml (Sandoz, Basel, Switzerland) in 5% dextrose solution and the bradykinin-analogue competitive antagonist B3852, 5 mg/ml, provided by Dr. John Stewart (University of Colorado) who has synthesized a number of bradykinin peptide analogues. The agent designated as B3852 has the following amino acid sequence: Arg-Pro-Hyp-Gly-Phe-Ser-DPhe-Phe-Arg-trifluoracetic acid (TFA).

The efficacy of B3852 in blocking the vasodilator
effect of exogenous bradykinin was tested in a pilot experiment on rats who were given bolus intravenous injections of 5 μg bradykinin before, during, and after a continuous 5-minute intra-arterial infusion of B3852. The first bradykinin injection was given 5 minutes before beginning infusion of the bradykinin antagonist, the second 2 minutes after initiation of the continuous B3852 infusion, the third at the end of the infusion, and the fourth 20 minutes later. Control rats were submitted to the same experimental procedures while receiving a continuous infusion of 5% dextrose in water instead of the bradykinin antagonist.

The actual experiment was conducted on two groups of intact rats. Group 1 (n = 10) received continuous infusion of B3852 at 500 μg/0.1 ml/min for a total of 5 minutes, and Group 2 (n = 6) received a control infusion of 0.1 ml/min of 5% dextrose. Blood pressure and heart rate were continuously recorded during infusion and for 2 hours after the end of the infusion.

Two other groups of rats were used for similar studies after prior bilateral nephrectomy or adrenalectomy. Unilateral nephrectomy was performed a few days before the experiment and was followed, on the eve of the experiment, by placement of catheters as described above. On the day of the experiment, under ether anesthesia, the remaining kidney was removed and the rats were allowed to regain consciousness and were observed for about 3 hours before the study was initiated. Bilateral adrenalectomy was performed under ether anesthesia on the morning of the experiment on rats that had had catheters placed, as described above, on the previous day. They were then observed for 3 hours before initiation of the study. Vital signs were continuously monitored and were shown to be stable for at least 60 minutes before the infusion began.

The nephrectomized rats received a continuous infusion of B3852 at 500 μg/0.1 ml/min for 5 minutes (n = 5) or the same amount of 5% dextrose (n = 4). The adrenalectomized rats received a bolus injection of 500 μg of B3852 in 0.1 ml dextrose (n = 5) or the vehicle alone (n = 4).

All results were expressed as the mean ± SEM. Statistical comparisons were made by one-way analysis of variance followed, whenever F was significant, by unpaired or paired t test. Results were considered significant at p < 0.05.

Results

The pilot study demonstrated the inhibitory effect of B3852 on the depressor effect of exogenous bradykinin. The hypotensive effect of 5 μg of intravenous bradykinin was inhibited by an average of 60% during the continuous infusion of B3852, 500 μg/min (i.e., bradykinin produced average decrements of 12 mm Hg during the infusion, as compared with decrements of 29 and 32 mm Hg before and after infusion, respectively) but was not affected by the vehicle, 5% dextrose. Mean blood pressure was increased in these rats throughout the infusion of B3852 by an average of 26 mm Hg, which constituted the new baseline from which the effects of bradykinin were calculated.

Figure 1 summarizes the changes in blood pressure during the main experiment in intact rats. In the B3852-infused group (Group 1), there was a sharp rise during the first minute of the B3852 infusion, from 104 ± 5 to 121 ± 6 mm Hg (p < 0.001), with a gradual further elevation reaching the highest point at the end of the infusion (131 ± 7 mm Hg). Upon discontinuation of the infusion, blood pressure returned almost to baseline within the first minute and completely in less than 5 minutes. Heart rate tended to decrease during the infusion from a baseline of 418 ± 22 to 386 ± 20 beats/min at the end of the infusion and return to baseline 5 minutes later, but these changes were not statistically significant. In the dextrose-infused group (Group 2), mean arterial pressure and heart rate remained stable throughout (from a baseline of 110 ± 4 to 111 ± 4 mm Hg at the end of the infusion).

Figure 2 summarizes the changes in blood pressure during bradykinin inhibition in the nephrectomized group of rats. This group displayed a curve similar to that of the intact rats, with a maximal blood pressure rise of 14 ± 5 mm Hg toward the end of the infusion. The adrenalectomized group exhibited an immediate rise in blood pressure of 16 ± 5 mm Hg, (from 112 ± 4 to 128 ± 5 mm Hg, p < 0.001), lasting for a little over 1 minute and returning gradually to baseline. None of the control infusions produced any change in blood pressure. There was no consistent pattern of heart rate changes during these experiments.

Discussion

The maintenance of blood pressure within a certain range is the result of the influence of several opposing vasoconstrictor and vasodilator factors. Our present experiments indicate that the vasodilator bradykinin contributes to this equilibrium, since its temporary inhibition induced a consistent rise in blood pressure that averaged 27 mm Hg. This rise was sustained for the duration of the infusion of the bradykinin antagonist, and the blood pressure returned to baseline within 2 to 3 minutes after discontinuation of the infusion. In nephrectomized or adrenalectomized animals, the bradykinin antagonist produced average increases of blood pressure of 14 and 16 mm Hg, respectively.
As with other tissue hormones, the physiological role of bradykinin has not yet been clearly determined. Kinins that are both generated and bound by tissues of the vascular wall are probably more relevant to the regulation of vascular tone than kinins that circulate in plasma. Moreover, tissue-bound bradykinin is subject to slower degradation by kininases than is the circulating hormone and may therefore have a more sustained effect.

In a previous set of experiments, we found that a similar bradykinin antagonist, infused at a rate of 40 \( \mu \text{g/min} \), could inhibit the depressor effect of exogenous bradykinin by more than 60%, and that doubling the dose of that antagonist made no difference in its inhibitory capacity. These doses had no effect on the blood pressure of intact normotensive animals, although they were sufficient to reverse by 30% the pressor action of bradykinin plays an important role in the maintenance of normal blood pressure, probably by counteracting the pressor influence of other vasoactive mechanisms. It is therefore possible that loss of this action may well contribute to high blood pressure or other systemic or regional vasoregulatory abnormalities.

**References**

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