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Arachidonic acid products-mediated contraction induced by bradykinin in relaxed mesenteric arterial rings from Holtzman rats

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Abstract

This study describes the contractile action of bradykinin on rat isolated mesenteric arterial rings and a possible mechanism responsible for this action. Bradykinin induced dose-dependent contraction of relaxed mesenteric arterial rings from Holtzman rats, but not from Wistar rats. A second bradykinin challenge in the same ring induced a very small effect or no effect at all. Destruction of the endothelium did not modify the response to bradykinin. des-Arg^9-[Leu^8]bradykinin failed to antagonize bradykinin's action. HOE 140 (D-Arg-[Hyp^3,Thi^5,D-Tic^7,Oic^8]bradykinin) reduced bradykinin-induced contractions. Indomethacin abolished the contractile response to bradykinin; prostaglandin $F_{2\alpha}$ induced a long-lasting contraction, dissimilar from that induced by bradykinin; L-655,240 (3-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-indol-2-yl]-2,2-dimethyl propanoic acid), an antagonist of the thromboxane receptor, inhibited bradykinin-induced contractions. These results suggest that bradykinin-induced contraction in mesenteric arterial rings is indirect, through activation of bradykinin B_2 receptors, resulting in liberation of prostanoids from outside the endothelium. Thromboxane A_2 is probably an intermediate in this response but we cannot exclude the participation of other prostanoids.

Keywords: Bradykinin; Arachidonic acid; Thromboxane; Arterial ring, mesenteric; Smooth muscle, vascular

1. Introduction

Bradykinin is known as a potent vasoactive polypeptide that has an important role in the modulation of cardiovascular function. Vasodilation with a fall in blood pressure is the typical in vivo response to systemic infusion of bradykinin (Regoli and Barabé, 1980), but when blood vessels are studied in vitro the responses to bradykinin are not the same under different circumstances. Thus, on different isolated vessels, this polypeptide was shown to induce relaxation as well as contraction (Briner et al., 1993).

Bradykinin has a direct action on some smooth muscles, including vascular smooth muscle, via its action on two receptor subtypes: B_1 and B_2 (Boschcov et al., 1984; Berguer et al., 1993; Field et al., 1994). Activation of these receptors leads to relaxation, contraction, or a biphasic response, depending on the organ or species under study (Boschcov et al., 1984; DeWitt et al., 1994; Field et al., 1994). Bradykinin has also an indirect action on vascular smooth muscle due to its ability to release intermediate agonists from the smooth muscle itself or from adjacent tissues. Bradykinin induces endothelium-dependent relaxation in renal and pulmonary arteries of the mongrel dog (Altura and Chand, 1981; Chand and Altura, 1981), in renal vein of the mongrel dog (Pawloski and Chapnick, 1991), and in the pulmonary vascular bed of the cat (DeWitt et al., 1994). Other studies indicated that bradykinin increases arterial blood pressure and induces vasoconstriction of vascular preparations by liberation of endothelium-derived contracting factors (EDCF). The nature of EDCF varies with the species and the anatomical site of its production, but thromboxane A_2 (Shirahase et al., 1987), superoxide anion (Vanhoutte and Katusic, 1988; Auch-Schwelk et al., 1990), endothelin (Yanagisawa et al., 1988) and prostaglandin H_2 (Kato et al., 1990) have been suggested as EDCFs.

Recently bradykinin was described as producing constriction of perfused rat mesenteric bed precontracted with norepinephrine (Fasciolo et al., 1990). As to our knowledge the in vitro effect of bradykinin on mesenteric arterial rings has not yet been described, we wondered whether

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this response would be a contraction instead of a relaxation as found in other arterial rings. We started using Holtzman rat arterial rings but after a few experiments we assayed also Wistar rat arterial rings. We found that the responses of relaxed arterial ring to bradykinin were different for each of these rat strains, although their responses to norepinephrine and KCl were similar. Relaxed Holtzman rat mesenteric arterial rings contracted in response to bradykinin but relaxed Wistar rat mesenteric arterial rings did not.

Our study in the present paper tries to elucidate the contraction mechanism of bradykinin in relaxed mesenteric arterial rings from Holtzman rats by searching for a direct action on bradykinin receptors, the production of intermediate substances and the participation or not of the endothelium in the observed contraction.

2. Materials and methods

The experiments were performed in arterial rings of male Holtzman and Wistar rats from the Medicine Faculty of our University and weighing 250–350 g. The animals were killed by decapitation and a portion of the superior mesenteric artery about 1 mm in diameter was immediately excised and placed in a Petri dish containing nutritive solution at room temperature. Then, under a Zeiss magnifying lens the preparation was carefully cleaned from its surrounding fat and connective tissues and an arterial ring measuring about 2 mm wide was prepared. In some experiments only one arterial ring was prepared from each artery segment, but in the largest number of experiments, in order to perform comparative experimental protocols, two or three neighboring rings from the same artery were prepared. From a few animals a portion of thoracic aorta was also excised and an arterial ring was prepared from it.

Each arterial ring was suspended in a vertical 10 ml organ chamber, between two stainless steel hooks, and connected to a Grass FT-03 force displacement transducer. In a few arterial rings the endothelium was mechanically rubbed off in order to allow the evaluation of an effect of endothelium-derived substances in the responses to bradykinin. At the end of the experiments the integrity of the endothelium or the effectiveness of its intentional destruction was confirmed by the presence or absence of relaxation to 10^{-6} M acetylcholine in 2×10^{-7} M norepinephrine-precontracted rings.

The organ chambers were filled with Krebs solution (composition mM: NaCl 118, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25 and glucose 10) maintained at 37°C and continuously bubbled with a gas mixture of 95% O_2 and 5% CO_2. Isometric contraction forces were recorded on a Grass model 7 polygraph. A basal tension of 1.0 g was applied to each ring at the beginning of an experiment. The rings were equilibrated in the organ chambers for 90 min with replacement of nutritive solution each 15 min before any drug addition. Drugs studied were added to the muscle chamber in small volumes (0.1–0.2 ml). Drugs suspected to modify the action of bradykinin were left in contact with the biological preparation in the muscle chamber for 10–15 min before the addition of the agonist (bradykinin). After addition of a drug to the organ chamber and registration of its direct action on the biological preparation or its effect on the action of another drug, the organ chamber was drained and washed. The arterial rings were then left to rest for at least 60 min, with washing every 10–15 min, before a new drug assay was started. The contractile response of each ring to 60 mM KCl at the beginning of an experiment was taken as a standard to evaluate the magnitude of the responses to other drugs.

Drugs used: des-Arg^9-[Leu^8]bradykinin (kindly provided by Dr. M.A.R. Vieira), bradykinin acetate, des-Arg^9-bradykinin, acetylcholine chloride, (−)-arterenol hydrochloride (norepinephrine), imidazole, indomethacin, and prostaglandin $F_{2\alpha}$ were purchased from Sigma (St. Louis, MO, USA); D-Arg-[Hyp^3,Thi^5,D-Tic^7,Oic^8]bradykinin (HOE 140) from Hoechst-Roussel Pharmaceutical (Frankfurt, Germany), was kindly provided by Dr. R.A.S. Santos; 3-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-indol-2-yl]-2,2-dimethyl propanoic acid (L-655,240) from Merck Frosst (Canada), was kindly provided by Dr. J.N. Francischi. Each experimental procedure was repeated with at least 5 animals. Where appropriate, means, standard error of means (S.E.M.) and comparison of means through Student's *t*-test or paired *t*-test were calculated. Values (in % of response to KCl) given in Section 3 are means ± S.E.M.

3. Results

Mesenteric arterial rings from Holtzman rats responded with a dose-dependent contraction to a single dose of bradykinin added to the organ chamber. Contractions were observed with bradykinin concentrations ranging in the order of 10^{-7}–10^{-6} M and were not dependent of any previous treatment. The maximum observed contractile response to bradykinin was about 70% of the contraction induced by 60 mM KCl in the same preparation (Fig. 1). Dose dependency was observed when in parallel experiments neighboring rings from the same animal, mounted in different muscle chambers, were challenged with different doses of bradykinin. The mean magnitudes observed for each bradykinin concentration (given as percentage of the contraction induced by KCl in the same preparation) were: for [bradykinin = 2.5×10^{-7} M]: 15.4 ± 3.1 ($n = 7$); for [bradykinin = 5.0×10^{-7} M]: 27.0 ± 2.4 ($n = 8$); for [bradykinin = 1.0×10^{-6} M]: 46.6 ± 3.4 ($n = 8$); and for [bradykinin = 2.0×10^{-6} M]: 70.2 ± 4.2 ($n = 12$) (Fig. 1). As seen in Fig. 1, contractions elicited by bradykinin were short-lasting, fading in a few minutes.

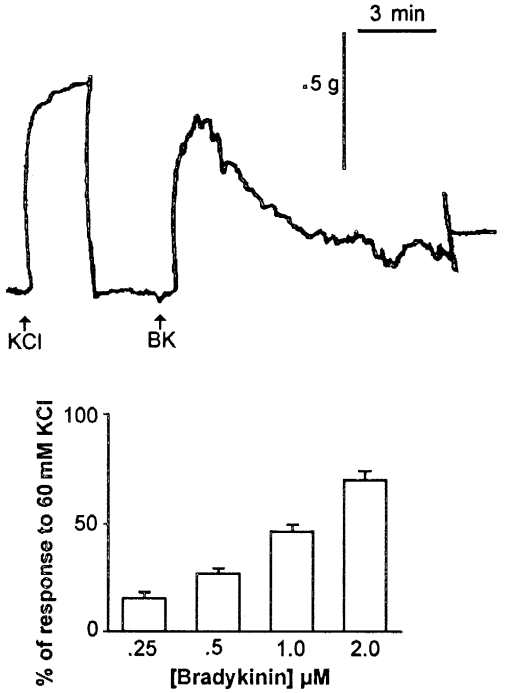

Fig. 1. Top: typical record showing a contraction elicited by bradykinin (BK) [2.0×10^{-6} M] in Holtzman rat mesenteric arterial ring and the corresponding contraction to 60 mM KCl. Bottom: graphic representation of the dose-response relationship for bradykinin in the preparation. Each column represents the mean ± S.E.M. for 7 to 12 animals.

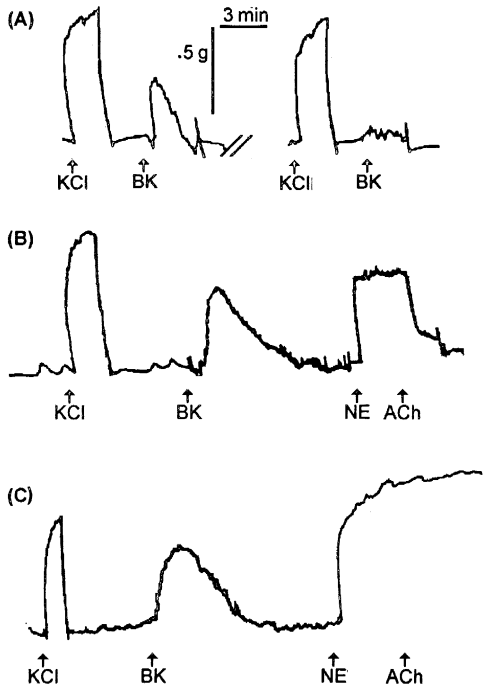

Fig. 2. (A) Bradykinin (BK) [10^{-6} M] generates a contraction in relaxed mesenteric arterial ring from Holtzman rat (left) but fails to produce a second contraction in the same preparation (right). Contractions in response to bradykinin (BK) [2.0×10^{-6} M] are observed in preparations with intact endothelium, as shown in (B), where 10^{-6} M acetylcholine (ACh) relaxes a pre-contraction produced by 2×10^{-7} M norepinephrine (NE). Identical results are observed in endothelium-denuded preparations, where acetylcholine does not relax a norepinephrine pre-contraction, as shown in (C). $n \geq 5$ animals for each experimental situation.

A second challenge with bradykinin in a same arterial ring elicited a much smaller response, or no response at all (Fig. 2A), independently of the concentration of the first bradykinin challenge. Attempts to induce a step-up contraction using cumulative doses of bradykinin did not succeed. Cumulative amounts of bradykinin were ineffective to increase the contraction produced by the first dose. No significant difference was observed between the responses to bradykinin of intact mesenteric arterial rings and of endothelial-denuded vessels from the same animal (Fig. 2B,C).

Aortic rings from Holtzman rats showed also contractile responses to bradykinin but the relative magnitudes of the maximum responses were only about 20% of the responses to 60 mM KCl. Neither mesenteric arterial rings nor aortic arterial rings from Wistar rats showed contraction in response to bradykinin under the same experimental conditions.

Mesenteric arterial rings from Holtzman rats did not contract in response to des-Arg^9-bradykinin in concentrations up to 2.0×10^{-6} M.

To find out whether the contractile action of bradykinin was through a direct action on bradykinin receptors we assayed the bradykinin B_1 receptor antagonist des-Arg^9-[Leu^8]bradykinin and the bradykinin B_2 receptor antagonist HOE 140 in the preparation. Responses to 2.0×10^{-6} M bradykinin in the presence of these receptor antagonists are shown in Fig. 3. The mean response to bradykinin (in percentage of response to 60 mM KCl) in the presence of 10^{-6} M des-Arg^9-[Leu^8]bradykinin was 61.5 ± 8.7, not significantly different from the paired control: 71.6 ± 5.0 ($n = 7$). No significant decrease in the response to bradykinin was observed in the presence of HOE 140 in

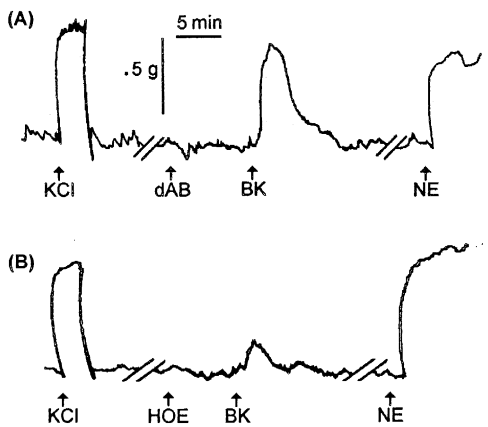

Fig. 3. The bradykinin B_1 receptor antagonist, des-Arg^9-[Leu^8]bradykinin, in a concentration of 10^{-6} M, (dAB) shown in (A), does not inhibit the contraction produced by 2.0×10^{-6} M bradykinin (BK). HOE 140, in a concentration of 10^{-7} M, (HOE) shown in (B), inhibits the contraction produced by bradykinin without affecting contractions produced by norepinephrine (NE). $n \geq 5$ animals for each experimental situation.

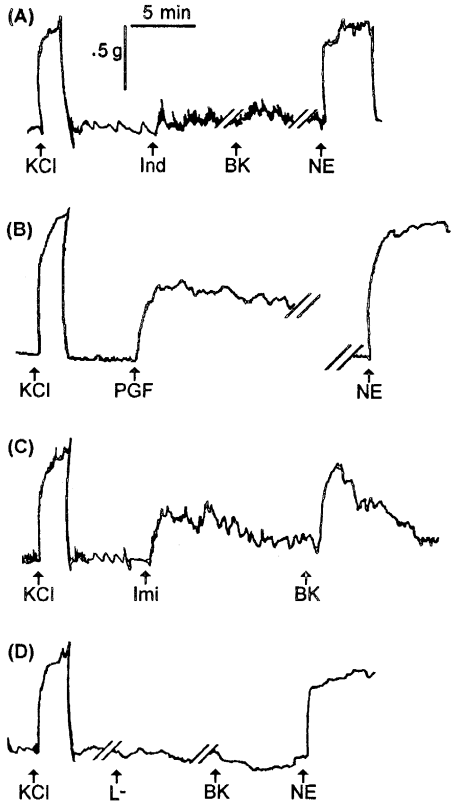

Fig. 4. (A) Indomethacin (Ind) [10^{-6} M] blocks the contractile action of bradykinin (BK) [2.0×10^{-6} M] in mesenteric arterial rings of Holtzman rats without affecting the contraction induced by 2.0×10^{-7} M norepinephrine (NE). (B) Prostaglandin $F_{2\alpha}$ (PGF) generates a sustained contraction of the preparation, distinct from the short-lasting contractions elicited by bradykinin. (C) Imidazole (Imi) [10^{-4} M] does not affect the action of bradykinin in mesenteric arterial rings. (D) The thromboxane inhibitor L-655,240 (L-) [2.5×10^{-7} M] prevents the contraction induced by bradykinin without affecting the contraction produced by norepinephrine. $n \geq 5$ animals for each experimental situation.

concentrations up to 3.0×10^{-8} M, but in the presence of 10^{-7} M HOE 140 the mean response to bradykinin was 19.9 ± 2.0, significantly lower ($P < 0.005$) than that of the paired control: 65.3 ± 5.1 ($n = 5$).

Indomethacin (10^{-6} M) abolished the contractile responses to bradykinin without changing the responses to norepinephrine or KCl (Fig. 4A).

Mesenteric arterial rings from Holtzman rats and from Wistar rats were assayed with prostaglandin $F_{2\alpha}$ in the concentration range of 10^{-6} M; both responded with sustained, long-lasting contractions, different from the fading contractions elicited by bradykinin (Fig. 4B). The contraction elicited by prostaglandin $F_{2\alpha}$ was stronger in Holtzman than in Wistar rat mesenteric arterial rings, and in both rat strains repetitive contractions in response to prostaglandin $F_{2\alpha}$ were observed on subsequent challenge of the same arterial ring.

Imidazole (10^{-4} M) induced a phasic long-lasting contraction of Holtzman rat mesenteric arterial rings and did not inhibit the contractile effect of bradykinin (Fig. 4C). The mean response to 2.0×10^{-6} M bradykinin in the presence of imidazole was 66.6 ± 4.4, not significantly different from the paired control: 64.5 ± 3.2 ($n = 6$).

In the presence of the thromboxane A_2 inhibitor L-655,240 (2.5×10^{-7} M) bradykinin failed to induce contraction in Holtzman rat mesenteric arterial rings (Fig. 4D). In 2 out of 6 experiments we observed weak responses to 2.0×10^{-6} M bradykinin, with values of less than 15% of the response to 60 mM KCl and in the other 4 experiments no response at all was observed.

4. Discussion

Bradykinin is known to induce relaxation of most arterial vessels (Regoli and Barabé, 1980; Cherry et al., 1982; Chand et al., 1987). In the rat mesenteric vascular bed bradykinin is described as a relaxant of arteries (Berguer et al., 1993) and as an arterial vasoconstrictor of norepinephrine-precontracted preparations (Fasciolo et al., 1990). In our experiments we found that bradykinin contracts relaxed mesenteric arterial rings isolated from Holtzman rats. In contrast to the results of Fasciolo et al. (1990), we found that with rat isolated perfused mesenteric arterial preparations there was no need for norepinephrine precontraction to observe the contractile effect of bradykinin.

A contractile effect of bradykinin was not observed in relaxed mesenteric arterial rings from Wistar rats, under identical experimental conditions. Considering that both rat strains have probably the same kind of smooth muscle in their arterial walls, this observation was a first suggestion that bradykinin could be acting not directly in arterial smooth muscle but rather indirectly, through the liberation of some intermediate contractile factor from the preparation. The non-repetitiveness of the bradykinin contractile effect suggested a depletion of some source of an intermediate substance, reinforcing the idea of an indirect effect. In spite of such suggestions of an indirect effect of bradykinin, we had to consider that this peptide has been described as having a direct action in resistance arteries (Berguer et al., 1993; Nakhostine et al., 1993; Nossaman et al., 1994). Therefore we decided to inhibit eventual bradykinin-contracting receptors in the mesenteric arterial rings, to see whether this had any influence on bradykinin's action. It is known that the bradykinin B_1 receptor antagonist des-Arg^9-[Leu^8]bradykinin has an agonistic effect when large doses are used in other smooth muscle preparations containing bradykinin B_1 receptors, e.g., the rat uterus. The failure of large doses of this antagonist either to contract the arterial rings or to inhibit bradykinin-induced contractions was an almost conclusive indication of an indirect effect of bradykinin in promoting contraction of Holtzman rat mesenteric arterial rings. The absence of a contractile response to des-Arg^9-bradykinin suggests that bradykinin B_1 receptors are not involved in the contractile

response of mesenteric arterial rings from Holtzman rats to bradykinin and reinforces the indication of an indirect action.

Bradykinin is known to release prostaglandins from various vascular preparations (Cherry et al., 1982; Fasciolo et al., 1990; Lüscher et al., 1992). Therefore we decided to investigate a possible mediation of bradykinin-induced contraction of Holtzman rat mesenteric arterial rings by products of the arachidonic acid cascade. Inhibition of cyclo-oxygenase by Indomethacin abolished the contractile effect of bradykinin, suggesting that bradykinin-induced contractions might be mediated by prostaglandins or other eicosanoids derived from arachidonic acid.

Considering that prostaglandin $F_{2\alpha}$ was shown to be a contractile prostanoid in other arterial vessels (Dorn et al., 1992; Rapoport, 1993), we assayed this agonist in mesenteric arterial rings. Our results show that the Holtzman rat mesenteric arterial ring contracts in response to prostaglandin $F_{2\alpha}$ but the contraction is long-lasting, different from the short-lasting contraction observed with bradykinin. Relaxed Wistar rat mesenteric arterial rings also contracted in response to prostaglandin $F_{2\alpha}$, in spite of not responding to bradykinin. These observations suggest that prostaglandin $F_{2\alpha}$ may not be the intermediate prostanoid liberated by bradykinin in the Holtzman rat mesenteric arterial ring. Nevertheless, we cannot discard completely the participation of this prostanoid in the response elicited by bradykinin.

Imidazole, a well-known inhibitor of thromboxane synthesis, did not prevent the contractile effect of bradykinin. This could suggest that thromboxanes are not intermediate eicosanoids in the observed bradykinin contractile effect. But the selective thromboxane/prostaglandin endoperoxide receptor antagonist L-655,240 (Hall et al., 1987) prevented the contractile effect of bradykinin, suggesting strongly the participation of thromboxane A_2 as an intermediate. The exact meaning of this observation cannot be explained by our studies but it might be possible that: (1) prostaglandin H_2, which also activates the thromboxane receptor, is released instead of thromboxane A_2 (Lüscher et al., 1992); or, (2) thromboxane synthesis has an alternative route, not mediated by thromboxane synthetase and therefore not inhibited by imidazole.

Since contractions of relaxed mesenteric arterial rings from Holtzman rats were not modified by removal of the endothelium, we conclude that endothelial cells are not the target of bradykinin to produce the contractile prostanoid. Under different circumstances and with different animals, bradykinin-induced relaxation mediated by prostanoids was found to be independent of the endothelium (Toda, 1974; Regoli et al., 1982). These and our findings indicate that prostanoids released by bradykinin may be formed outside the endothelium and probably in smooth muscle cells. The hypothesis that smooth muscle cells might be the source of contractile prostanoid(s) liberated by bradykinin is supported by the finding that in cultured mesenteric smooth muscle cells bradykinin increases the synthesis of 6-keto PGE_1 (Takeuchi et al., 1988).

Our results showing that the bradykinin B_2 receptor antagonist HOE 140 inhibits the contractile action of bradykinin suggest that the triggering of the arachidonic acid cascade by bradykinin, yielding the contractile prostanoid, might be achieved by activation of bradykinin B_2 receptors. This suggestion agrees with observations of other investigators showing an indirect action of this polypeptide through activation of bradykinin B_2 receptors (Berguer et al., 1993; Molimard et al., 1994, 1995)

A logical question remains in the face of such results: what is the explanation for the absence of contraction of Wistar rat mesenteric arterial rings to bradykinin? Our results do not explain such question, but we suggest that bradykinin does not liberate the contractile eicosanoid in this preparation, or that the amount liberated is too small to elicit an effect, or, finally, that this preparation is not sensitive to the liberated eicosanoid.

In summary, our study showed that bradykinin induces dose-dependent contraction of relaxed mesenteric arterial rings from Holtzman rats. The effect is not mediated by bradykinin B_1 receptors. It is an indirect effect, through the liberation of a product from the arachidonic acid cascade, probably thromboxane A_2, although the participation of other eicosanoids cannot be excluded. The source of the contractile eicosanoid is not the endothelium. The bradykinin-induced contraction could not be re-elicited by subsequent challenge of the same arterial ring, probably as a consequence of depletion of arachidonic acid from the preparation. Relaxed mesenteric arterial rings from Wistar rats did not contract in response to bradykinin, either because the eicosanoid was not liberated by bradykinin in this preparation or because the arterial smooth muscle was insensitive to the contractile eicosanoid liberated by bradykinin.

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References

Altura, B.M. and N. Chand, 1981, Bradykinin-induced relaxation of renal and pulmonary arteries is dependent upon intact endothelial cells, Br. J. Pharmacol. 74, 10.

Auch-Schwelk, W., Z.S. Katusic and P.M. Vanhoutte, 1990, Thromboxane A_2 receptor antagonists inhibit endothelium-dependent contractions, Hypertension 15, 699.

Berguer, R., O.D. Hottenstein, T.E. Palen, J.M. Stewart and E.D. Jacobson, 1993, Bradykinin-induced mesenteric vasodilation is mediated by B_2-subtype receptors and nitric oxide, Am. J. Physiol. 264, G492.

Boschcov, P., A.C.M. Paiva, T.B. Paiva and S. Shimuta, 1984, Further

evidence for the existence of two receptor sites for bradykinin responsible for the diphasic effect in the rat isolated duodenum, Br. J. Pharmacol. 83, 591.

Briner, V.A., P. Tsai and R.W. Schrier, 1993, Bradykinin: potential for vascular constriction in the presence of endothelial injury, Am. J. Physiol. 264, F322.

Chand, N. and B.M. Altura, 1981, Acetylcholine and bradykinin relax intrapulmonary arteries by acting on endothelial cells: role in lung vascular diseases, Science 213, 1376.

Chand, N., T.P. Mahoney, Jr., W. Diamantis and R.D. Sofia, 1987, Pharmacological modulation of bradykinin-, acetylcholine-, and calcium ionophore A23187-induced relaxation of rabbit pulmonary arterial segments, Eur. J. Pharmacol. 137, 173.

Cherry, P.P., R.F. Furchgott, J.V. Zawadzki and D. Jothianandas, 1982, The role of endothelial cells in relaxation of isolated arteries by bradykinin, Proc. Natl. Acad. Sci. 79, 2106.

DeWitt, B.J., D.Y. Cheng, T.J. McMahon, B.D. Nossaman and P.J. Kadowitz, 1994, Analysis of responses to bradykinin in the pulmonary vascular bed of the cat, Am. J. Physiol. 266, H2256.

Dorn, G.W., II, M.W. Becker and M.G. Davis, 1992, Dissociation of the contractile and hypertrophic effects of vasoconstrictor prostanoids in vascular smooth muscle, J. Biol. Chem. 267, 24897.

Fasciolo, J.C., L. Vargas, M.C. Lama and H. Nolly, 1990, Bradykinin-induced vasoconstriction of rat mesenteric arteries precontracted with noradrenaline, Br. J. Pharmacol. 101, 344.

Field, J.L., S.K. Butt, I.K.M. Morton and J.M. Hall, 1994, Bradykinin B_2 receptors and coupling mechanisms in the smooth muscle of the guinea-pig taenia caeci, Br. J. Pharmacol. 113, 607.

Hall, R.A., J. Gillard, Y. Guindon, G. Letts, E. Champion, D. Ethier, J. Evans, A.W. Ford-Hutchinson, R. Fortin, T.R. Jones, A. Lord, H.E. Morton, J. Rokach and C. Yoakim, 1987, Pharmacology of L-655,240 (3-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-indol-2-yl]-2,2-dimethyl propanoic acid); a potent, selective thromboxane/prostaglandin endoperoxide antagonist, Eur. J. Pharmacol. 135, 193.

Kato, T., Y. Iwama, K. Okumura, H. Hashimoto, T. Ito and T. Satake, 1990, Prostaglandin H_2 may be the endothelium-derived contracting factor released by acetylcholine in the aorta of the rat, Hypertension 15, 475.

Lüscher, T.F., C.M. Boulanger, Y. Dohi and Z. Yang, 1992, Endothelium-derived contracting factors, Hypertension 19, 117.

Molimard, M., C.A.E. Martin, E. Naline, A. Hirsch and C. Advenier, 1994, Contractile effects of bradykinin on the isolated human small bronchus, Am. J. Respir. Crit. Care Med. 149, 123.

Molimard, M., C.A.E. Martin, E. Naline, A. Hirsch and C. Advenier, 1995, Role of thromboxane A_2 in bradykinin-induced human isolated small bronchi contraction, Eur. J. Pharmacol. 278, 49.

Nakhostine, N., C. Ribuot, D. Lamontagne, R. Nadeau and R. Couture, 1993, Mediation by B_1 and B_2 receptors of vasodepressor responses to intravenously administered kinins in anaesthetized dogs, Br. J. Pharmacol. 110, 71.

Nossaman, B.D., C.J. Feng and P.J. Kadowitz, 1994, Analysis of response to bradykinin and influence of HOE-140 in the isolated perfused rat lung, Am. J. Physiol. 266, H2452.

Pawloski, J.R. and B.M. Chapnick, 1991, LTD4 and bradykinin evoked endothelium-dependent relaxation of the renal vein: dissimilar mechanisms, Am. J. Physiol. 261, H88.

Rapoport, R.M., 1993, Potentiation of norepinephrine-induced contraction by primary prostaglandin receptor activation in rat aorta, Eur. J. Pharmacol. 243, 207.

Regoli, D. and J. Barabé, 1980, Pharmacology of bradykinin and related kinins, Pharmacol. Rev. 32, 1.

Regoli, D., J. Mizrahi, P. D'Orleans-Juste and S. Caranikas, 1982, Effects of kinins on isolated blood vessels. Role of endothelium, Can. J. Physiol. Pharmacol. 60, 1580.

Shirahase, H., H. Usui, K. Kurahashi, M. Fujiwara and K. Fukui, 1987, Possible role of endothelial thromboxane A_2 in the resting tone and contractile responses to acetylcholine and arachidonic acid in canine cerebral arteries, J. Cardiovasc. Pharmacol. 10, 517.

Takeuchi, K., K. Abe, H. Yasujama, M. Sato, K. Omata, Y. Kasai, M. Komazahua and K. Yoshinaga, 1988, The cellular action of bradykinin in vascular smooth muscle, Am. J. Hypertens. 2, 105A.

Toda, N., 1974, The action of vasodilating drugs on isolated basilar coronary arteries of the dog, J. Pharmacol. Exp. Ther. 191, 139.

Vanhoutte, P.M. and Z.S. Katusic, 1988, Endothelium-derived contracting factor: endothelin and/or superoxide anion?, Trends Pharmacol. Sci. 9, 229.

Yanagisawa, M., H. Kurihara, S. Kimura, Y. Tomobe, M. Kobayashi, Y. Mitsui, Y. Yazaki, K. Goto and T. Masaki, 1988, A novel potent vasoconstrictor peptide produced by vascular endothelial cells, Nature 332, 411.