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Bradykinin B_1 receptors in human umbilical vein

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Abstract

The present study was undertaken to demonstrate the presence of bradykinin B_1 receptors mediating contraction of human umbilical vein. The bradykinin B_1 receptor selective agonist, des-Arg^9-bradykinin, produced a dose-dependent contractile response of human umbilical vein rings. Furthermore, des-Arg^9-bradykinin-mediated response increased in a time-dependent manner in vitro. The maximal response to des-Arg^9-bradykinin, expressed as percentage of the maximum elicited by serotonin, was: 10 ± 2 at 15 min, 55 ± 5 at 120 min and 80 ± 3 at 300 min. Des-Arg^9-bradykinin-mediated contractions were inhibited by the specific bradykinin B_1 receptor antagonist des-Arg^9-[Leu^8]bradykinin which produced parallel shifts in the dose-response curve to the selective bradykinin B_1 receptor agonist. Schild regression analysis of data established a pA_2 value of 6.16 ± 0.06. Kinin-induced contraction was not modified by pre-treatment with indomethacin (10 μM), a cyclo-oxygenase inhibitor. On the other hand, continuous exposure to the anti-inflammatory steroid dexamethasone (100 μM) or to the protein synthesis inhibitor cycloheximide (70 μM) largely prevented the sensitization to des-Arg^9-bradykinin in incubated human umbilical vein rings. These results confirm the presence of bradykinin B_1 receptors which mediate contraction in isolated human umbilical vein. These responses are up-regulated in a time- and protein synthesis-dependent process.

Keywords: Des-Arg^9-bradykinin; Des-Arg^9-[Leu^8]bradykinin; Umbilical vein, human; Bradykinin B_1 receptor; Sensitization

1. Introduction

Two mammalian bradykinin receptor subtypes, B_1 and B_2 receptors, have been pharmacologicaly defined (Regoli and Barabé, 1980; Farmer and Burch, 1992). Both bradykinin receptor genes have been cloned from human tissues (Hess et al., 1992; Menke et al., 1994). The endogenous agonists for the B_1 and B_2 bradykinin receptors are the nonapeptide bradykinin and the decapeptide Lys-bradykinin (kallidin). Bradykinin and kallidin are equipotent agonists at the B_2 receptor. Kallidin is also active at B_1 receptors (Regoli and Barabé, 1980); in contrast, bradykinin is a weak agonist of these receptors (Butt et al., 1995). Degradation of the B_2 receptor agonists by a carboxypeptidase produces the selective B_1 receptor agonists, des-Arg^9-bradykinin and des-Arg^{10}-kallidin. Bradykinin B_1 receptors are further characterised by the ability of des-Arg^9-[Leu^8]bradykinin to antagonize solely responses mediated by these receptors (Regoli and Barabé, 1980).

The B_1 receptor was originally discovered through a contractile response to des-Arg^9-bradykinin that was observed in the rabbit anterior mesenteric vein only after a prolonged in vitro incubation (Regoli et al., 1978). B_1 receptor-mediated responses are up-regulated in a time- and protein synthesis-dependent process (Regoli et al., 1978; Bouthillier et al., 1987). It has been proposed that the up-regulated responses to des-Arg-kinins result from inflammation, or from trauma during tissue isolation and incubation (Marceau et al., 1983). The bradykinin B_1 receptor pharmacology and its physiopathological applications have recently been reviewed (Marceau, 1995).

In vitro studies have implicated a different number of cytokines, most notably interleukin-1β and interleukin-2, as mediators that induce the expression of B_1 receptors (DeBlois et al., 1988, 1991; Levesque et al., 1993; Schneck et al., 1994; Galizzi et al., 1994). Furthermore, DeBlois et al. (1988, 1991) have seen that the increase in sensitivity to des-Arg^9-bradykinin in the incubated rabbit aorta is inhibited by the anti-inflammatory steroid dexamethasone.

In the human umbilical vein, bradykinin promotes a potent and effective vasoconstrictor response (Altura et al., 1972). It has been demonstrated that this pharmacological

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action depends on bradykinin B_2 receptor stimulus (Marceau et al., 1994; Félétou et al., 1995; Gobeil et al., 1996). On the other hand, in isolated human umbilical veins, we have observed a vasoconstricting action of the selective bradykinin B_1 receptor agonist, des-Arg^9-bradykinin (Sardi et al., 1993). Recently, Gobeil et al. (1996) have shown the presence of a kinin B_1 receptor in this tissue. The aim of this work was to pharmacologicaly characterise this selective kinin B_1 receptor agonist action as well as to evaluate the possible existence of an up-regulation phenomenon of bradykinin B_1 receptors in the isolated human umbilical vein.

2. Materials and methods

2.1. Preparation of the tissues for tension measurements

Approximately 15–35 cm of human umbilical cords ($n = 78$) excised midway between the placenta and infant were obtained from normal deliveries and immediately placed in modified Krebs solution (of the following mM composition: NaCl 119, KCl 4.7, $NaHCO_3$ 25, KH_2PO_4 1.2, $CaCl_2$ 2.5, $MgSO_4$ 1.0, EDTA 0.004, D-glucose 11). The veins were dissected out of the cords and cut into rings of approximately 3 mm width. The preparations were suspended in 10 ml organ baths and stretched with an initial tension of 2 g as described previously (Elgoyhen et al., 1993). Changes in tension were measured with Grass isometric transducers (FT 03C, Grass Instrument, Quincy, MA, USA) and displayed on Grass polygraphs (Model 7D). The time from delivery until the tissue was set up in the organ baths was approximately 3 h.

The Krebs solution was maintained at 37°C and at pH 7.4 by constant bubbling with 95% O_2/5% CO_2. During the incubation period, the bath solution was replaced every 15 min with fresh warmed Krebs. Thirty or 15 min before any peptide stimulation, the tissues were incubated with captopril (10 μM), in order to avoid peptide degradation by kininase II (angiotensin converting enzyme).

2.2. Kinin receptor stimulation

Cumulative concentration–response curves were obtained for bradykinin after a 120 min equilibration period. Furthermore, complete cumulative concentration-response curves to des-Arg^9-bradykinin were constructed after a 15, 120 or 300 min incubation time, in order to determine a possible tissue sensitization to kinins. Only one agonist concentration-response curve was performed on a single ring.

The effects of B_1 (des-Arg^9-[Leu^8]bradykinin, 1–30 μM) or B_2 (Hoe 140, 10–100 nM) receptor antagonists were also evaluated. The antagonist was applied 30 min before the cumulative addition of agonists (des-Arg^9-bradykinin or bradykinin), to ensure that equilibrium was obtained. Experiments were performed in parallel in the rings from the same tissue.

Some human umbilical vein rings were pre-treated with indomethacin (10 μM) 30 min before the concentration-effect curve to des-Arg^9-bradykinin was constructed, in order to inhibit the fatty acid cyclo-oxygenase.

In another series of experiments, human umbilical vein rings were continuously exposed to either cycloheximide (70 μM) or dexamethasone (100 μM) for a 300 min incubation period, before addition of des-Arg^9-bradykinin (0.3 μM).

In all experiments, serotonin (5-HT, 10 μM) was applied in order to determine the tissue maximal response.

2.3. Chemicals

All chemicals were purchased from Sigma (St. Louis, MO, USA), except Hoe 140 (D-Arg[Hyp^3,Thi^5,D-Tic^7,Oic^8]-bradykinin), which was obtained from Bachem (Torrance, CA, USA).

2.4. Expression of results and statistical analysis

All data are presented as means ± S.E.M. Responses are expressed as g of developed contraction or as percentage of maximal response to 5-HT obtained at the end of each experiment. The pD_2 values, negative logarithm of the agonist concentration that produces 50% of the maximum effect, were determined using ALLFIT, a nonlinear curve-fitting computer program (De Lean et al., 1978). The pA_2 values were calculated for des-Arg^9-[Leu^8]bradykinin and Hoe 140 (Arunlakshana and Schild, 1959). Statistical analysis was performed either by means of unpaired Student's *t*-test or by one way analysis of variance where appropriate. P values lower than 0.05 were taken to indicate significant differences between means.

3. Results

3.1. Effects of bradykinin and des-Arg^9-bradykinin on human umbilical veins

After a 120 min incubation period, bradykinin as well as des-Arg^9-bradykinin produced a concentration-related contraction of human umbilical vein rings. However, bradykinin was more effective and potent than the B_1 selective agonist (Fig. 1). The maximal response for bradykinin was 10.4 ± 0.9 g while that for des-Arg^9-bradykinin was 4.5 ± 0.6 g ($P < 0.001$). Furthermore, the pD_2 of bradykinin was 8.96 ± 0.06 and the one of des-Arg^9-bradykinin was 6.80 ± 0.08 ($P < 0.001$).

3.2. In vitro sensitization to des-Arg^9-bradykinin

As shown in Fig. 2, in vitro incubated human umbilical veins increased their contractile response to des-Arg^9-

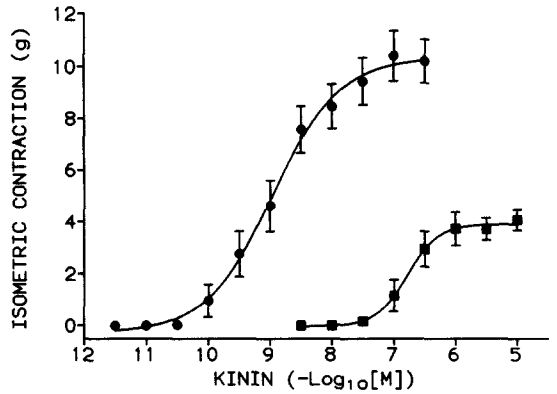

Fig. 1. Concentration–effect curves for bradykinin (●) and des-Arg^9-bradykinin (■) on human umbilical vein rings. The points represent the mean of 15 determinations for bradykinin and 13 for des-Arg^9-bradykinin made after 120 min of incubation and the vertical lines show S.E.M. The responses are expressed in g of developed contraction. Abscissa scale: $-\log_{10}$ of molar concentration.

bradykinin as a function of time. The maximal response was 0.6 ± 0.2 g ($10 \pm 2\%$ of 5-HT max) at 15 min, 4.5 ± 0.6 g ($55 \pm 5\%$ of 5-HT max) at 120 min and

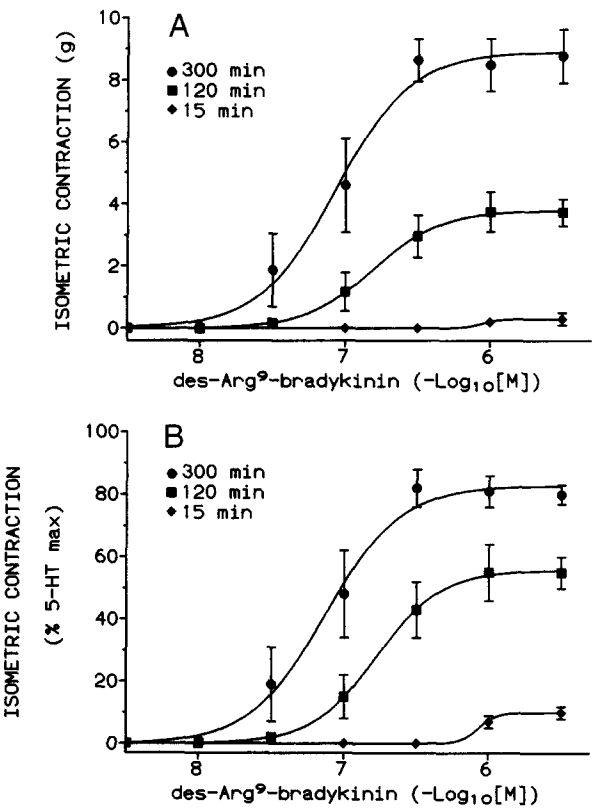

Fig. 2. Concentration–effect curves for des-Arg^9-bradykinin at 15 min (♦, $n = 10$), at 120 min (■, $n = 13$) and at 300 min (●, $n = 10$) of incubation on human umbilical vein rings. The points represent the mean of n determinations and the vertical lines show S.E.M. The data are expressed as (a) g of developed contraction or as (b) percentage of maximal response to 5-HT obtained at the end of each experiment. Abscissa scale: $-\log_{10}$ of molar concentration. All curves were significantly different compared to each other using ALLFIT (De Lean et al., 1978).

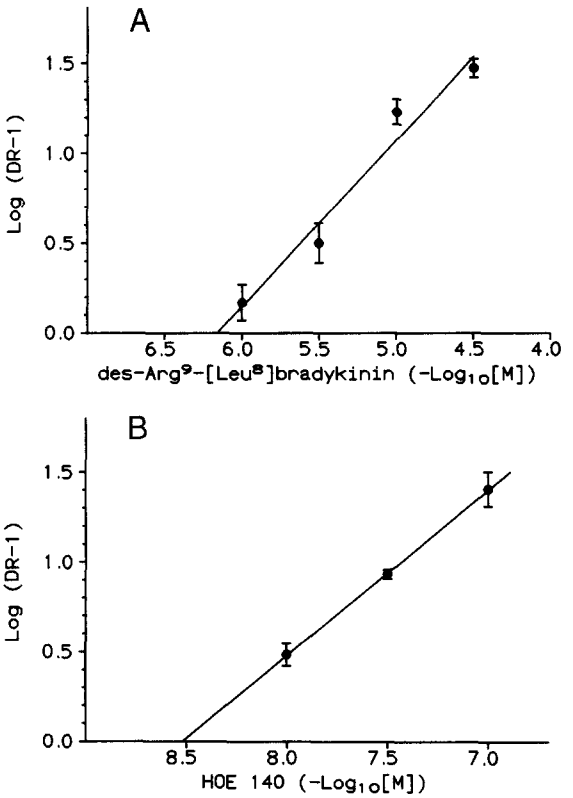

Fig. 3. Schild regressions for antagonism of responses to (a) des-Arg^9-bradykinin by the selective B_1 antagonist, des-Arg^9-[Leu^8]bradykinin or to (b) bradykinin by the selective B_2 antagonist Hoe 140 in human umbilical vein rings. The estimates for des-Arg^9-[Leu^8]bradykinin were: $pA_2 = 6.16 \pm 0.06$, $b = 0.89 \pm 0.10$, $r = 0.938$ ($n = 19$) and for Hoe 140, $pA_2 = 8.52 \pm 0.04$, $b = 0.92 \pm 0.09$, $r = 0.942$ ($n = 14$).

9.1 ± 0.9 ($80 \pm 3\%$ of 5-HT max) at 300 min. In addition, the pD_2 at 120 min was 6.80 ± 0.08 ($n = 13$) and the one at 300 min was 7.07 ± 0.05 ($n = 10$; $P < 0.05$). On the other hand, contractile responses to 5-HT also increased as a function of incubation time but this sensitization was markedly different from the increasing responses to des-Arg^9-bradykinin.

3.3. Effect of kinin receptor antagonism

The specific B_1 receptor antagonist des-Arg^9-[Leu^8]bradykinin was used to determine if the contractile response to des-Arg^9-bradykinin could be attributed to B_1 kinin receptor activation. Increasing concentrations of des-Arg^9-[Leu^8]bradykinin (1–30 μM) produced a parallel rightward shift of the des-Arg^9-bradykinin dose-response curve without affecting the maximal response, suggestive of competitive antagonism. Analysis of the data by Schild regression gave a slope which was not significantly different from unity and a pA_2 value of 6.16 ± 0.06 ($n = 19$, Fig. 3a). On the other hand, the concentration-response curve to bradykinin at 120 min was not shifted by des-Arg^9-[Leu^8]bradykinin (10 μM) (data not shown).

To further determine the bradykinin B_1 receptor identity, the B_2 receptor antagonist Hoe 140 has been tried against des-Arg^9-bradykinin. The concentration–response curve to this bradykinin B_1 receptor agonist at 300 min was not shifted by Hoe 140 (100 nM, data not shown). On the other hand, increasing concentrations of the B_2 receptor antagonist Hoe 140 (10–100 nM) produced a competitive shift of the bradykinin dose-response curve. Analysis of the data by Schild regression gave a slope which was not significantly different from unity and a pA_2 value of 8.52 ± 0.04 ($n = 14$, Fig. 3b).

3.4. Cyclo-oxygenase inhibition

The possible involvement of cyclo-oxygenase products in the selective B_1 receptor agonist mediated responses has been assessed by testing the effect of indomethacin (10 μM) on the concentration–response curve to des-Arg^9-bradykinin. Pretreatment with the cyclo-oxygenase inhibitor did not modify the human umbilical vein contractile response to des-Arg^9-bradykinin at 300 min (treated tissues: pD_2, 7.1 ± 0.1, max. response, 9.0 ± 1.5 g, $n = 5$; control tissues: pD_2, 7.07 ± 0.05, max. response, 9.1 ± 0.9 g, $n = 10$; Fig. 4).

3.5. Effect of protein synthesis inhibition on sensitization to des-Arg^9-bradykinin

Exposition to cycloheximide (70 μM) throughout the 300 min incubation period, largely inhibited the sensitization to des-Arg^9-bradykinin. The response to 0.3 μM B_1 receptor agonist in tissues continuously exposed to cycloheximide was 3.5 ± 1.6 g, significantly different from control (8.8 ± 0.7 g, $P < 0.05$, Fig. 5). In addition, the maximal response to 5-HT was not modified by this treatment.

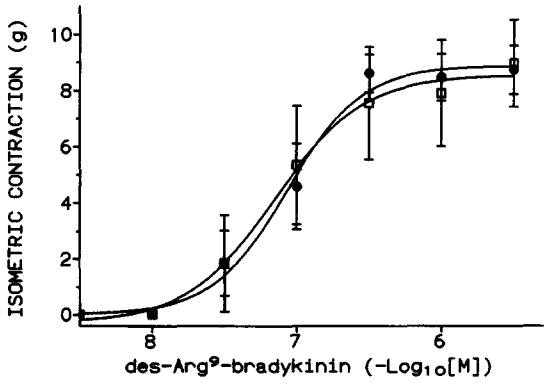

Fig. 4. Concentration–effect curves for des-Arg^9-bradykinin on control human umbilical vein rings (●, $n = 10$) and on tissues exposed to indomethacin (10 μM, 30 min, □, $n = 5$). The points represent the means of n determinations made after 300 min equilibration period and the vertical lines show S.E.M. The responses are expressed in g of developed contraction. Abscissa scale: $-\log_{10}$ of molar concentration.

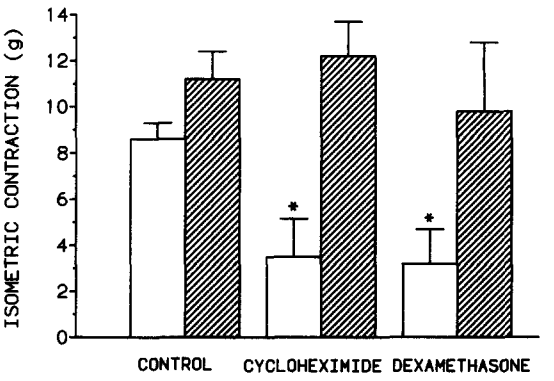

Fig. 5. Effect of continuous exposure to cycloheximide (70 μM, $n = 6$) or dexamethasone (100 μM, $n = 5$) on the submaximal response to des-Arg^9-bradykinin (0.3 μM, open columns) of human umbilical vein rings. The tissues were treated with the protein synthesis inhibitor or the glucocorticoid throughout the 300 min incubation period. One untreated group ($n = 10$) of tissues was also stimulated with des-Arg^9-bradykinin (0.3 μM) after 300 min of incubation. Responses are shown as the means of n determinations and the vertical bars show the S.E.M. Statistically significant differences between responses of treated and control tissues were determined by one way analysis of variance followed by Dunnett's test. Maximal responses to serotonin (10 μM, hatched columns) were not affected by any of those treatments. Significance from control is denoted: $^*P < 0.05$.

3.6. Effect of dexamethasone on B_1 sensitization

Continuous exposure to dexamethasone (100 μM) during 300 min incubation, largely prevented the development of the sensitization to the kinin B_1 selective agonist. The response to 0.3 μM des-Arg^9-bradykinin of human umbilical vein rings treated with dexamethasone was 3.3 ± 1.7 g, significantly different from control at 300 min (8.8 ± 0.7 g; $P < 0.05$, Fig. 5). Furthermore, the maximal response to 5-HT was not modified by this treatment.

4. Discussion

Bradykinin is a potent agonist of B_2 bradykinin receptor and a very weak stimulant of kinin B_1 receptors (Regoli and Barabé, 1980; Butt et al., 1995). Des-Arg^9-bradykinin is an agonist more potent than bradykinin on B_1 receptors and in our preparations, of 120 min incubated human umbilical vein rings, it produced a maximal response approximately three times smaller than bradykinin. In similar experimental conditions, Marceau et al. (1994) have reported that this selective bradykinin B_1 receptor agonist exerts little effect on human umbilical vein rings. The nature of this discrepancy is not know. Furthermore, Gobeil et al. (1996) have recently demonstrated the presence of kinin B_1 receptors in human umbilical vein helical strips using a wide variety of synthetic peptides. The potency of des-Arg^9-bradykinin observed by these authors was 6.69, similar to that obtained in our preparations (6.82 at 120 min and 7.07 at 300 min).

Responses to the selective B_1 receptor agonist, des-Arg^9-bradykinin increased during human umbilical vein in vitro incubation. Moreover, des-Arg^9-bradykinin-mediated responses were competitively antagonized by the B_1 receptor-selective antagonist, des-Arg^9-[Leu^8]bradykinin (pA_2 6.16) with a similar affinity to that reported in human tissues (pK_B estimates of 6.14, 5.98 and 6.37 for coronary arteries, isolated ileum and umbilical vein, respectively; Drummond and Cocks, 1995; Zuzack et al., 1996; Gobeil et al., 1996). Furthermore, no appreciable interaction of the B_1 receptor-selective agonist with B_2 receptors was observed in human umbilical vein, since Hoe 140 (0.1 μM) was without activity in the des-Arg^9-bradykinin concentration-response curve (data not shown). On the other hand, the bradykinin concentration-response curve was not affected by des-Arg^9-[Leu^8]bradykinin (10 μM, data not shown). Furthermore, bradykinin-mediated responses were competitively antagonized by the B_2 receptor-selective antagonist, Hoe 140, as demonstrated by the linearity of the Schild plot and in accord with previous studies (Marceau et al., 1994, Félétou et al., 1995, Gobeil et al., 1996).

In rabbit anterior mesenteric vein, Regoli et al. (1978) were the first to describe that the B_1 receptor agonist response increases as a function of in vitro incubation time. In other tissues, different authors have confirmed the development of this sensitization in vitro and in vivo (see Marceau, 1995). It has been established that the sensitization process is dependent on the de novo synthesis of protein as it is blocked by continuous application of protein synthesis inhibitors, as cycloheximide or anisomycin (Regoli et al., 1978; Bouthillier et al., 1987; DeBlois et al., 1991). In the present study, continuous application of cycloheximide profoundly inhibited the sensitization to des-Arg^9-bradykinin in incubated human umbilical vein rings, indicating that the up-regulation process of B_1 receptors in this tissue is also dependent on the de novo synthesis of protein. Furthermore, in the rabbit aorta, Audet et al. (1994) have described the modulatory effect of a protein glycosylation inhibitor and a protein trafficking inhibitor on the B_1-sensitization. This evidence supports the idea that the de novo formation of membrane bradykinin B_1 receptors is the molecular basis of the up-regulation phenomenon.

In the rabbit mesenteric artery, the B_1 effects of des-Arg^9-bradykinin are inhibited by indomethacin, a fatty acid cyclo-oxygenase inhibitor (Churchill and Ward, 1986). In vitro, both the arteries and veins of the umbilical cord produce great amounts of prostanoids; indomethacin leads to a dramatic depression of the prostanoid concentration (Bjoro et al., 1986). The lack of effect of indomethacin on the vasoconstrictor responses to des-Arg^9-bradykinin in human umbilical vein, suggests that cyclo-oxygenase derived products are not involved in the mechanical response of this tissue. Although, in the rabbit isolated aorta, Levesque et al. (1993) have found that eicosanoid release occurs in response to B_1 receptor stimulation, but does not affect the mechanical response to the same stimulus.

This sensitization process is a spontaneous phenomenon of unknown mechanism. It has been postulated that this up-regulation phenomenon results from trauma during tissue isolation and incubation or from inflammation (Marceau et al., 1983). In the incubated rabbit aorta, the steroid dexamethasone inhibited the development of contractile responses to des-Arg^9-bradykinin (DeBlois et al., 1988). Moreover, several studies provided evidence that different cytokines, as interleukin-1β, are involved in B_1 receptor induction (DeBlois et al., 1988, 1991). DeBlois et al. (1991) have proposed that the inhibition of interleukin-1β synthesis by glucocorticoids may partially account for the effect of dexamethasone on up-regulated responses to des-Arg^9-bradykinin. In the human umbilical vein, the anti-inflammatory steroid dexamethasone also prevented the development of the kinin B_1 up-regulation.

In summary, our results demonstrated the presence of kinin B_1 receptors which mediate contraction in the human umbilical vein and exhibit an up-regulation phenomenon during in vitro incubation. Des-Arg^9-bradykinin-mediated sensitizated responses were competitively antagonized by the selective kinin B_1 receptor antagonist, des-Arg^9-[Leu^8]bradykinin, thus confirming that B_1 receptors are present in this tissue. The B_1 receptors of the human umbilical vein behaved as their counterparts in rabbit vascular tissue, since a protein synthesis inhibitor (cycloheximide) and the glucocorticoid (dexamethasone) both decreased the expression of responses to desArg^9-bradykinin without modifying the actions of other contractile agents. Thus, the isolated human umbilical vein could represent one interesting experimental model of up-regulation process based on a human tissue.

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References

Altura, B.M., D. Malaviya, C.F. Reich and L.R. Orkin, 1972, Effects of vasoactive agents on isolated human umbilical arteries and veins, Am. J. Physiol. 222, 345.

Arunlakshana, O. and H.O. Schild, 1959, Some quantitative uses of drug antagonists, Br. J. Pharmacol. Chemother. 14, 48.

Audet, R., E. Petitclerc, G. Drapeau, F. Rioux and F. Marceau, 1994, Further analysis of the up-regulation of bradykinin B_1 receptors in isolated rabbit aorta by using metabolic inhibitors, Eur. J. Pharmacol. 271, 551.

Bjoro, K., T. Hovig, K.T. Stokke and S. Stray-Pedersen, 1986, Formation of prostanoids in human umbilical vessels perfused in vitro, Prostaglandins 31, 683.

Bouthillier, J., D. DeBlois and F. Marceau, 1987, Studies on the induction of pharmacological responses to des-Arg^9-bradykinin in vitro and in vivo, Br. J. Pharmacol. 92, 257.

Butt, S.K., L.G. Dawson and J.M. Hall, 1995, Bradykinin B_1 receptors in the rabbit urinary bladder: induction of responses, smooth muscle contraction, and phosphatidylinositol hydrolysis, Br. J. Pharmacol. 114, 612.

Churchill, L. and P.E. Ward, 1986, Relaxation of isolated arteries by des-Arg^9-bradykinin stimulation of B_1 receptors, Eur. J. Pharmacol. 130, 11.

DeBlois, D., J. Bouthillier and F. Marceau, 1988, Effect of glucocorticoids, monokines and growth factors on the spontaneously developing responses of the rabbit isolated aorta to des-Arg^9-bradykinin, Br. J. Pharmacol. 93, 969.

DeBlois, D., J. Bouthillier and F. Marceau, 1991, Pulse exposure to protein synthesis inhibitors enhances vascular responses to des-Arg^9-braykinin: possible role of interleukin-1, Br. J. Pharmacol. 103, 1057.

De Lean, A., P.J. Munson and D. Rodbard, 1978, Simultaneous analysis of families of sigmoidal curves: application to bioassay, radioligand assay, and physiological dose-response curves, Am. J. Physiol. 235, E97.

Drummond, G.R. and T.M. Cocks, 1995, Endothelium-dependent relaxation to the B_1 kinin receptor agonist des-Arg^9-bradykinin in human coronary arteries, Br. J. Pharmacol. 116, 3083.

Elgoyhen, A.B., P.S. Lorenzo, R.P. Rothlin, D. Spaccavento and E. Adler-Graschinsky, 1993, Relaxant effects of benzodiazepines on isolated human umbilical arteries and veins, J. Auton. Pharmacol. 13, 373.

Farmer, S.G. and R.M. Burch, 1992, Biochemical and molecular pharmacology of kinin receptors, Annu. Rev. Pharmacol. Toxicol. 32, 511.

Félétou, M., C.A.E. Martin, M. Molimard, E. Naline, M. Germain, C. Thurieau, J.L. Fauchère, E. Canet and C. Advenier, 1995, In vitro effects of HOE 140 in human bronchial and vascular tissue, Eur. J. Pharmacol. 274, 57.

Galizzi, J.P., M.C. Bodinier, B. Chapelain, S.M. Ly, L. Coussy, S. Giraud, G. Neliat and T. Jean, 1994, Up-regulation of [^{3}H]-des-Arg^{10}-kallidin binding to the bradykinin B_1 receptor by interleukin-1β in isolated smooth muscle cells: correlation with B_1 agonist-induced PGI_2 production, Br. J. Pharmacol. 113, 389.

Gobeil, F., L.H. Pheng, I. Badini, X.K. Nguyen-Le, A. Pizard, A. Rizzi, D. Blouin and D. Regoli, 1996, Receptors for kinins in the human isolated umbilical vein, Br. J. Pharmacol. 118, 289.

Hess, J.F., J.A. Borkowski, G.S. Young, C.D. Strader and R.W. Ransom, 1992, Cloning and pharmacological characterization of human bradykinin (BK-2) receptor, Biochem. Biophys. Res. Commun. 184, 260.

Levesque, L., G. Drapeau, J.H. Grose, F. Rioux and F. Marceau, 1993, Vascular mode of action of kinin B_1 receptors and development of a cellular model for the investigation of these receptors, Br. J. Pharmacol. 109, 1254.

Marceau, F., 1995, Kinin B_1 receptors: a review, Immunopharmacology 30, 1.

Marceau, F., L. Levesque, G. Drapeau, F. Rioux, J.M. Salvino, H.R. Wolfe, P.R. Seoane and D.G. Sawutz, 1994, Effects of peptide and non peptide antagonists of bradykinin B_2 receptors on the venoconstrictor action of bradykinin, J. Pharmacol. Exp. Ther. 269, 1136.

Marceau, F., A. Lussier, D. Regoli and J.P. Giroud, 1983, Pharmacology of kinins: their relevance to tissue injury and inflammation, Gen. Pharmacol. 14, 209.

Menke, J.G., J.A. Borkowski, K.K. Bierilo, T. MacNeil, A.W. Derrick, K.A. Schneck, R.W. Ransom, C.D. Strader, D.L. Linemeyer and J.F. Hess, 1994, Expression cloning of a human B_1 bradykinin receptor, J. Biol. Chem. 269, 21583.

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

Regoli, D., F. Marceau and J. Barabé, 1978, De novo formation of vascular receptors for bradykinin, Can. J. Physiol. Pharmacol. 56, 674.

Sardi, S.P., H. Pérez, L.M. Zieher and R.P. Rothlin, 1993, Up-regulation de receptores a bradiquinina B_1 en vena umbilical humana, Medicina (Bs. As.) 53, 135.

Schneck, K.A., J.F. Hess, G.Y. Stonesifer and R.W. Ransom, 1994, Bradykinin B_1 receptors in rabbit aorta smooth muscle cells in culture, Eur. J. Pharmacol. 266, 277.

Zuzack, J.S., M.R. Burkard, D.K. Cuadrado, R.A. Greer, W.M. Selig and E.T. Whalley, 1996, Evidence of a bradykinin B_1 receptor in human ileum: pharmacological comparison to the rabbit aorta B_1 receptor, J. Pharmacol. Exp. Ther. 277, 1337.