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Angiotensin II potentiates inflammatory edema in rats: Role of mast cell degranulation

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Abstract

The aim of this study was to evaluate the effect of angiotensin II on models of acute inflammation. This study shows that angiotensin II potentiates the carrageenan- and dextran-induced paw edema. The administration of angiotensin II does not change the myeloperoxidase activity, neither the tissue content of interleukin-1 beta and tumor necrosis alpha nor the neutrophil migration to the peritoneal cavity, but induces significant enhancement of mast cell degranulation. The anti-histamine, mepyramine, and the anti-serotonin, metisergyde, reduce the angiotensin II-facilitated dextran-induced edema. Our results suggest that angiotensin II increases the vascular permeability through induction of mast cell degranulation and that this effect is mediated by the angiotensin AT_2 receptor, since the angiotensin AT_1 receptor antagonist and the angiotensin AT_2 receptor agonist potentiated the paw edema.

Keywords: Angiotensin II; Edema; Mast cell; Carrageenan; Dextran

1. Introduction

Angiotensin II is an effector hormone of the renin–angiotensin system, which plays a major role in the control of peripheral vascular resistance, blood pressure, and fluid and electrolyte homeostasis through its multiple effects on the vasculature, adrenal glands, kidneys, and brain (Reid, 1992). These actions of angiotensin II are mediated by specific receptors located on target tissues. Two distinct angiotensin II receptors subtypes (AT_1 and AT_2) have been identified by their sensitivity to dithiothreitol (Chiu et al., 1989; Whitebread et al., 1989). Most of the hypertensive actions of the angiotensin II, such as vasoconstriction, stimulation of aldosterone secretion, and increased renal tubular sodium resorption, have been shown to be mediated by the angiotensin AT_1 receptor (Dzau et al., 1993). The angiotensin AT_2 receptor appears to be important in fetal development, cell differentiation, apoptosis, and regeneration of various tissues (Cao et al., 2000; Chung et al., 1998; Csikos et al., 1998). Up-regulation of angiotensin AT_2 receptors can be observed in myocardial infarction, cardiac hypertrophy and skins wounds (Ichiki et al., 1996; Viswanathan and Saavedra, 1992; Viswanathan et al., 1996; Walsh et al., 1997). Recent evidence has revealed that the function of angiotensin AT_1 and AT_2 receptors are mutually antagonistic (De Gasparo et al., 2000; Horiuchi et al., 1999).

In additional to the effects on the cardiovascular system, recent studies have investigated a role for the rennin–angiotensin system in the modulation of inflammatory responses. Brasier et al.

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demonstrated that the angiotensinogen gene was transcriptionally activated in hepatocytes during the acute-phase response and the mechanism involves the activation of nuclear factor-κB (Brasier et al., 1990, 1994; Brasier and Li, 1996). Another study reported that angiotensinogen is an acute phase protein, because its plasma concentration increases during some forms of acute inflammation (Klett et al., 1993). Additionally, it has been described that some drugs of the angiotensin-converting enzyme inhibitors group, a major class of antihypertensive drugs, have anti-inflammatory effects, which include inhibition of tumor necrosis factor alpha and interleukin-1 production (Schindler et al., 1995).

Clinical observations also suggest a link between renin–angiotensin system activity and the development of cardiac ischemic events (Brunner et al., 1972; Cambien et al., 1992). Angiotensinogen II has been implicated in the pathogenesis of the vascular injury associated with hypertension (Williams et al., 1995) and it is becoming increasingly apparent that hypertension, as well as atherosclerosis, is associated with the presence of an inflammatory response in the arterial wall. The initial phase of this inflammatory response is characterized by the accumulation of macrophages in the arterial wall (Alexander, 1995; Chobanian et al., 1989) and it has been demonstrated that angiotensin II is a potent stimulator of monocyte chemoattractant protein-1 (Chen et al., 1998), a macrophage chemoattractant that has been previously implicated in the development of atherosis (Capers et al., 1997; Clozel et al., 1991; Haller et al., 1995).

Although several lines of experimental and clinical evidence suggest a potential role of angiotensin II in chronic inflammatory conditions (Hirayama et al., 1990; Jaszewski et al., 1990; Martín et al., 1984), its role on the acute inflammatory response is not well studied.

In view of this, the present study was conducted to evaluate the effect of angiotensin in carrageenan- and dextran-induced edema in rats and to examine the mechanisms involved in this effect.

2. Materials and methods

2.1. Animals

Wistar rats weighing 180–200 g were housed in temperature-controlled rooms and received water and food ad libitum until use. All experiments were conducted in accordance with NIH guidelines on the welfare of experimental animals and with approval of the Committee of Ethics in Animal Research and Care of the Federal University of Ceará.

2.2. Drugs

Angiotensin II, dextran, Nicotinic acid-Tyr-*N*-benzoxyl-carbonyl-Arg-Lys-His-Pro-Ile-OH (CGP 42112A), mepyramine and metisergyde were purchased from Sigma-Aldrich (St. Louis, MO, USA). The carrageenan used is a product of FMC Corporation (Philadelphia, PA, USA). Losartan was obtained from Merck Research Laboratories (Rahway, NJ, USA). Sheep anti-rat interleukin-1 beta and tumor necrosis alpha was obtained from the National Institute for Biological Standards and Control (NIBSC; UK).

2.3. Carragenan- and dextran-induced paw edema

Paw edema was induced by subplantar injection of carrageenan (100 μg/paw) or dextran (100 μg/paw). Angiotensin II (1 μg/paw), losartan (angiotensin AT_1 receptor antagonist; 62.5 μg/paw) or CGP 42112A (angiotensin AT_2 receptor agonist; 142.5 μg/paw) was administered immediately before the inflammatory stimulus (carrageenan or dextran) into the left hind paw. The same dose of angiotensin II was also administered alone in the left hind paw of another group of rats in order to study its effect per se on paw volume. Control groups consisted of animals that received only saline solution and that received saline co-administered with the inflammatory stimulus. The final volume injected into the left hind paw was 0.1 ml. Paw volume was measured with a hydroplesthysmometer (Ugo-Basile 7140 Plesthysmometer) immediately before (basal volume) and at 1, 2, 3 and 4 h after the dextran or carrageenan administration. Results were expressed as the variation in paw volume (ml), calculated by subtracting the paw basal volume from the hydroplesthymometer reading.

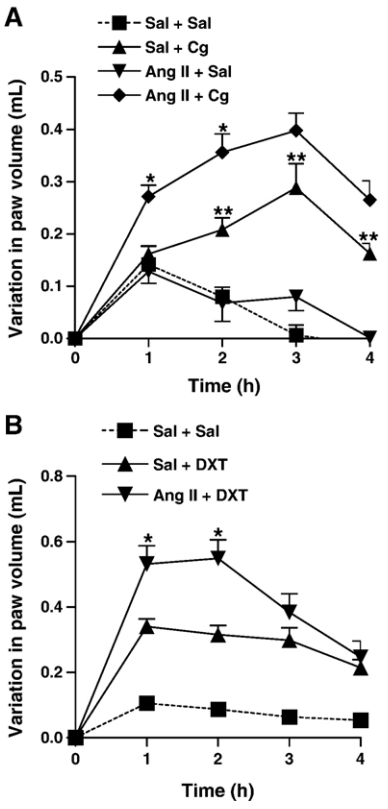

Fig. 1. Effect of angiotensin II (Ang II) on paw edema induced by carrageenan (Cg) (A) or dextran (DXT) (B). Ang II (1 μg, s.p.) or saline solution (Sal) was administrated immediately prior to Cg (100 μg, s.p.), DXT (100 μg, s.p.) or saline administration. Paw volume was measured immediately before and at 1, 2, 3 and 4 h after the injection of DXT or Cg and expressed as the increase in paw volume (ml) above its basal volume. The dots on the curve represent the mean ± SEM of the variation of paw volume. *$P<0.05$ vs. Sal+Cg group; **$P<0.05$ vs. Sal+Sal. ANOVA/Bonferroni.

2.4. Effect of mepyramine and metisergyde in the dextran-induced paw edema

In order to investigate whether histamine and serotonin were involved in the mediation of dextran-induced paw edema, rats were injected intraperitoneally with the anti-histamine mepiramine (10 mg/kg) or the anti-serotonin metisergyde (1 mg/kg) 1 h prior to the dextran injection (100 μg/paw). Angiotensin II or saline was locally injected immediately prior to dextran injection.

2.5. Effect of angiotesin II on mast cell degranulation in paw tissue

Angiotensin II (1 μg/ml) or saline solution was administered in the left hind paws of the animals immediately prior to the local injection of carrageenan (100 μg) or dextran (100 μg). The same concentration of angiotensin II was also co-administered with saline to study its effect per se on mast cell degranulation. A control group received two injections of saline into the subplantar region of the left hind paw. One hour later, the animals were sacrificed and the paw tissues were fixed with 10% neutral buffered formalin. Fixed tissues samples were rinsed in PBS and embedded in paraffin according to standard techniques. Sections (5 μm) were collected on microscope slides. The hydrated tissue sections were immersed in a solution of 0.1% toluidine blue (in 0.9% sodium chloride) for 60 s followed by extensive rinsing in deionized water as described previously (Zhong et al., 2001). The percentage of degranulated mast cells was determined by counting one hundred stained cells per tissue section.

2.6. Myeloperoxidase activity

Angiotensin II (1 μg/paw) or saline was administered immediately before the inflammatory stimulus (Cg;100 μg/paw) or saline into the left hind paw. Three hours after the administration of carrageenan, animals were sacrificed and the whole skin from the plantar region of the left paws was harvested. After homogenization and centrifugation (4500 rpm, 20 min), myeloperoxidase activity, an enzyme found in azurophil neutrophil granules, was determined by a colorimetric method described previously (Souza et al., 2003) and expressed as units of myeloperoxidase activity per 5 mg of tissue.

2.7. Stimulation of neutrophil migration into peritoneal cavities

Carrageenan (100 μg/0.5 ml) or saline (0.5 ml) was injected intraperitoneally (i.p.) in rats pretreated 1 hour earlier with angiotensin II (0.5 μg/0.5 ml, i.p.) or saline (0.5 ml; i.p.). Three

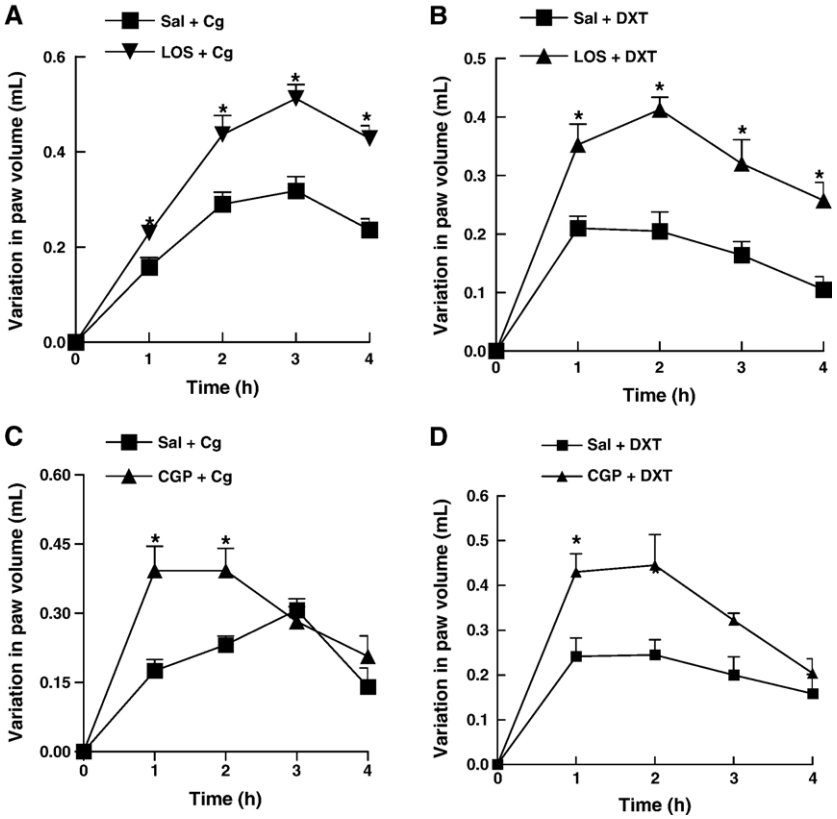

Fig. 2. Effect of the angiotensin AT1 receptor antagonist losartan (LOS) and the angiotensin AT2 receptor agonist CGP 42112A (CGP) on paw edema induced by carrageenan (Cg) (A and C) or dextran (DXT) (B and D). LOS (62.5 μg/paw), CGP (142.5 μg/paw) or saline solution (Sal) was administrated immediately prior to Cg (100 μg, s.p.) or DXT (100 μg, s.p.) administration. Paw volume was measured immediately before and at 1, 2, 3 and 4 h after the injection of DXT or Cg and expressed as the increase in paw volume (ml) above its basal volume. The dots on the curve represent the mean±SEM of the variation of paw volume. *$P<0.05$ vs. Sal+Cg (A and C) or Sal+DXT (B and D). Student t test.

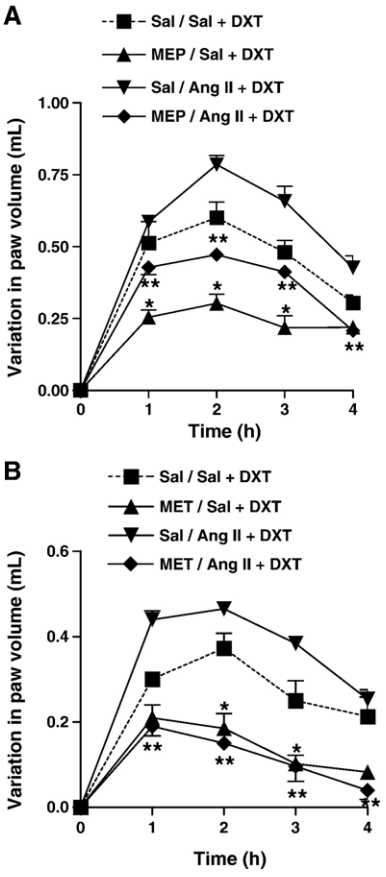

Fig. 3. Effect of the anti-histamine mepyramine, (MEP; A) and the anti-serotonin metisergyde (MET) on the Ang II modulation on the dextran (DXT; B) induced paw edema. Rats were injected intraperitoneally with MEP (10 mg/kg), MET (1 mg/kg) or saline solution (Sal) 1 h prior to the DXT injection (100 μg). Ang II (1 μg, s.p.) or saline was locally injected immediately prior to DXT injection. Paw volume was measured immediately before and at 1, 2, 3 and 4 h after the DXT injection and expressed as the increase in paw volume (ml) above its basal volume. The dots on the curve represent the mean±SEM of the variation of paw volume. *$P<0.05$ vs. Sal/Sal+DXT; **$P<0.05$ vs. Sal/Ang II+DXT. ANOVA/Bonferroni.

hours after the carrageenan injection, the animals were sacrificed and peritoneal fluid was collected. Total and differential cell counts were performed as described elsewhere (Souza and Ferreira, 1985).

2.8. Quantification of tumor necrosis alpha and interleukin 1 beta

Angiotensin II (1 μg, subplantar injection) or saline was injected immediately prior to carrageenan (100 μg, s.p.) administration. One and two hours later, the paw tissue was harvested for tumor necrosis factor alpha and interleukin-1 beta determination , respectively, by ELISA, according to a previous description of time course production of these cytokines after carrageenan injection (Cunha et al., 2003). Briefly, paw skin was homogenized in 500 μl of the appropriate buffer containing protease inhibitors. Microtiter plates (Nunc-Maxisorb) were incubated overnight at 4 °C with a sheep anti-rat interleukin-1 beta or tumor necrosis alpha polyclonal antibody. After blocking the plates, samples and standards at various dilutions were added in triplicate and maintained at room temperature for 2 h. The plates were washed three times with buffer and a second biotiny-lated polyclonal antibody against interleukin-1 (1:500 dilution) or tumor necrosis alpha (1:1000 dilution) was added followed by incubation at room temperature for 1 h. Finally, 100 μl of avidin-HRP (1:5000 dilution) was added to each well and, after 30 min, the plates were washed and the color reagent o-phenylenediamine (40 μl well^{-1}) was added. After 15 min, the reaction was terminated with H_2SO_4 (1 M, 50 μl well^{-1}) and the optical density measured at 490 nm. The results were adjusted to 500 μl, the volume used to extract the cytokine from the paw skin, and were expressed as nanograms of respective cytokine per paw.

2.9. Statistical analysis

Results were presented as means and standard errors of the mean for groups of six animals each. The differences between the experimental groups were compared by Analysis of variance (ANOVA) followed by Bonferroni's t-test. The level of significance was set at $P<0.05$.

3. Results

3.1. Paw edema

Subplantar injection of carrageenan or dextran induced significant paw edema with peak at 3 h for carrageenan and 1 h for dextran. Local injection of angiotensin II resulted in a significant increase of paw edema in the first 2 h after the injection of carrageenan ($P<0.05$; Fig. 1A) and dextran ($P<0.05$; Fig. 1B). However, the local administration of angiotensin II alone did not induce any significant change in paw volume (Fig. 1A) compared to the saline group. Local administration of losartan enhanced the carrageenan- and dextran-induced increase in paw volume (Fig. 2A and B). CGP 42112A also potentiated carrageenan- and dextran-induced edema within the first 2 h of treatment (Fig. 2C and D).

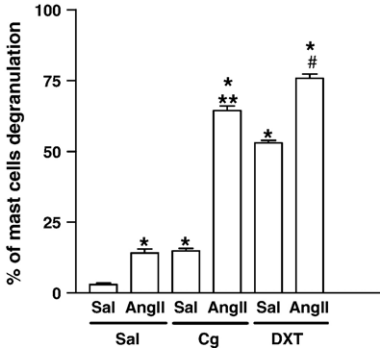

Fig. 4. Effect of angiotensin II (Ang II) on mast cell degranulation in paws injected with carrageenan (Cg) or dextran (DXT). Ang II (1 μg/ml) or saline solution (Sal) was administered immediately prior to the local injection of Cg (100 μg), DXT (100 μg) or saline. One hour later, the animals were sacrificed and the skin and subcutaneous paw tissue samples were stained with toluidine blue. The percentages of degranulated mast cells was determined by counting one hundred stained cells in different fields (×400). The dots on the curve represent the mean±SEM of the percentage of mast cells degranulation. *$P<0.05$ vs. Sal+Sal; **$P<0.05$ vs. Sal+Cg; $^{\#}P<0.05$ vs. Sal+DXT. ANOVA/Bonferroni.

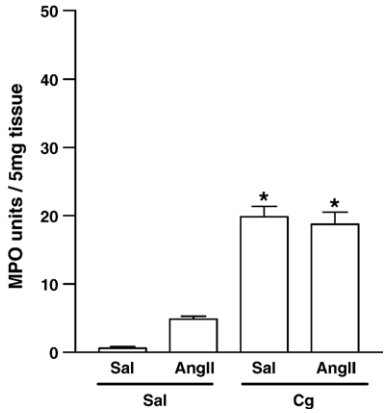

Fig. 5. Effect of angiotensin II (Ang II) on the myeloperoxidase activity in Wistar rat paw treated with subplantar (s.p.) injection of carrageenan (Cg) or saline (Sal). Ang II (1 μg, s.p.) or saline solution (Sal) was administered immediately prior to the injection of Cg (100 μg, s.p.). The control group received saline. After 2 h, samples of skin and subcutaneous tissue of the paws were harvested for determination of myeloperoxidase activity. The bars represent the mean ± SEM of units of myeloperoxidase per 5 mg of tissue. *$P<0.05$ vs. the Sal+Sal group. ANOVA/Bonferroni.

3.2. Effect of mepyramide and metisergyde in the dextran-induced paw edema

Pretreatment of animals with mepyramide or metisergyde 1 h prior to the administration of dextran produced a significant ($P<0.05$) suppression of dextran-induced edema (Fig. 4A and B). Similarly, mepyramide and metisergyde also significantly ($P<0.05$) reduced the angiotensin II-facilitated dextran-induced edema (Fig. 3A and B).

3.3. Effect of angiotensin II on mast cell degranulation in paws injected with carrageenan and dextran

Subplantar administration of dextran and carrageenan significantly ($P<0.05$) enhanced the percentage of mast cell degranulation on paw tissue compared with animals that received saline alone. Although it was not able to induce edema, subcutaneous

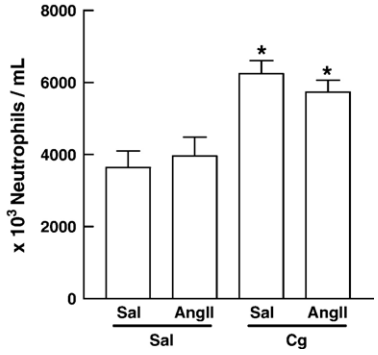

Fig. 6. Effect of angiotensin II (Ang II) on polimorphonuclear (PMN) migration to the peritoneal cavity induced by carrageenan (Cg). Carragenan (100 μg) or saline solution was injected in rats pretreated 1 hour earlier with Ang II (0.5 ml; i.p.). Control group (Sal) received two injections of 0.5 ml of saline (i.p.). Three hours after the Cg injection, the animals were sacrificed and the neutrophils that migrated to the peritoneal cavity were counted. The bars represent the mean ± SEM of the number of $10^3 \times$ neutrophil/ml from 5–6 rats in each group. *$P<0.05$ vs. the Sal+Sal group. ANOVA/Bonferroni.

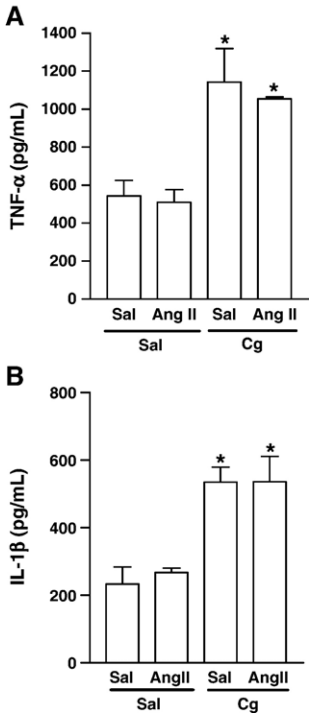

Fig. 7. Effect of angiotensin II (Ang II) on the tumor necrosis factor alpha (TNF-α ; A) and interleukin 1 beta (IL-1β; B) contents in paw tissue treated with subplantar (sp) injection of carrageenan (Cg) or saline (Sal). Ang II (1 μg, s.p.) or saline solution (Sal) was injected immediately prior to Cg (100 μg, s.p.) administration. One and two hours later the skin and subcutaneus tissue of the paw were harvested in order to measure the content of TNF-α and IL-1 β, respectively, through ELISA. Values represent the mean ± SEM of the TNF-α (A) and IL-1 β (B) content from 5 rats in each group. *$P<0.05$ vs. the Sal+Sal group (ANOVA/Bonferroni).

administration of angiotensin II alone induced a discrete but significant ($P<0.05$) increase in the percentage of degranulated mast cell on paw tissue compared with animals that received saline alone. The co-administration of angiotensin II significantly ($P<0.05$) enhanced both carragenan- and dextran-induced mast cell degranulation in paw tissue (Fig. 4).

3.4. Myeloperoxidase activity

Subplantar injection of carrageenan resulted in a significant ($P<0.05$) increase in myeloperoxidase activity measured 3 h after the stimulus when compared with control group (Saline). No significant difference was observed between the group pretreated with angiotensin II and the group injected with carrageenan alone. Angiotensin II alone did not change the tissue content of myeloperoxidase activity (Fig. 5).

3.5. Neutrophil migration into the peritoneal cavity

The intraperitoneal injection of carrageenan significantly stimulated neutrophil migration into peritoneal cavities ($P<0.05$). The pretreatment with angiotensin II did not modify the neutrophil migration in response to carrageenan. Similarly, no significant difference was observed between the group which received angiotensin II alone (without inflammatory stimulus) and the control group (saline) (Fig. 6).

3.6. Quantification of tumor necrosis alpha and interleukin-1

Paw tissue injected with carrageenan and harvested 1 h later exhibited a 100% increase in tumor necrosis alpha levels compared with animals that received saline injection alone (Fig. 7A). Similar results were obtained with interleukin 1 beta, harvested 2 h later (Fig. 7B), which also revealed a 100% increase. Angiotensin II alone did not have a significant effect on the tumor necrosis alpha or interleukin-1 beta levels, with or without carrageenan (Fig. 7A and B).

4. Discussion

In this study we demonstrated that angiotensin II potentiates the carrageenan and dextran induced paw edema, suggesting an activity of angiotensin II in inflammatory events. It has been previously reported that the renin–angiotensin system plays a role in the modulation of inflammatory response. Angiotensinogen is considered an acute phase protein, because its plasma concentration increases during acute inflammation (Klett et al., 1993). Moreover, it has been previously demonstrated that granuloma macrophages release angiotensin-converting enzyme, which produces angiotensin II, which in turn modulates monocyte/macrophage activity (Simon et al., 1991). Angiotensin II receptors (AT_1 and AT_2) and angiotensin-converting enzyme develop sequentially during angiogenesis in the rat subcutaneous sponge granuloma (Walsh et al., 1997). These findings suggest the possibility of expression of renin–angiotensin system within the tissue at the site of inflammation. Local production of angiotensin II occurs and modulates the ongoing inflammatory processes. However, in the current report the administration of angiotensin II alone did not induce edema, suggesting that triggering mechanisms are essential for angiotensin II to initiate inflammatory action.

The present study also showed that the locally administered angiotensin AT_1 receptor antagonist, losartan, potentiated carrageenan-induced paw edema. This data is in accordance with a previous report which shows that local administration of losartan, as well as angiotensin II, enhanced the carraggenan-induced increase in paw volume in a dose-dependent manner (Raghavendra and Kulkarni, 2000). It has been reported also that angiotensin AT_1 receptor antagonists cause elevated levels of angiotensin II, which selectively binds to unblocked angiotensin AT_2 receptors (Bernstein and Alexander, 1992). Thus, the potentiation of carrageenan-induced edema by losartan could be a consequence of the activation of angiotensin AT_2 receptors by endogenous angiotensin II produced during inflammation, since the angiotensin AT_1 receptors are blocked. Consistent with this hypothesis, we found that the angiotensin AT_2 receptor agonist CGP 42112A also potentiated the carrageenan-induced inflammation. According to our data, it has been demonstrated that stimulation of angiotensin AT_2 receptors are thought to activate prostaglandins, kinins and the nitric oxide system (Schiefer et al., 1994) which are known mediators of carrageenan-induced inflammation.

The intraplantar injection of carrageenan elicits an inflammatory response characterized by a time-dependent increase in paw edema. Edema formation in rat hind paw following injection of carrageenan has been described as a biphasic event consisting of a relatively rapid early phase followed by a more sustained late phase (Vinegar et al., 1969). It is suggested that the early inflammation response of carrageenan-induced edema in rats results from the release of histamine and serotonin from mast cells (Kulkarni et al., 1986). On the other hand, the late phase of carrageenan-induced edema is known to be dependent on cytokine production by resident cells and neutrophil migration (DiRosa et al., 1971; Vinegar et al., 1969, 1982; Wedmore and Williams, 1981).

In the present study we demonstrated that angiotensin II potentiates the first 2 h of carrageenan-induced paw edema, known to be mediated by the release of mast cell derived mediators (Capasso et al., 1975; Kulkarni et al., 1986). Accordingly, we demonstrated that angiotensin II, as well as losartan and CGP 42112A, has potentiated the dextran-induced paw edema, which is also dependent of mast cell degranulation and release of several inflammatory mediators such as histamine and serotonin (Cahill et al., 1996; Chu et al., 1997; Kulkarni et al., 1986; Ribeiro et al., 1997). Consistent with these data, we showed that the pretreatment with a specific inhibitor of histamine H1 receptor, mepyramine, reduced both the dextran and angiotensin II-facilitated dextran induced paw edema. Similar results were observed with the pretreatment with the serotoninergic blocker, metisergyde. These results suggest that the release of histamine and serotonin appears to be involved in the angiotensin II potentiation of carrageenan- and dextran-induced paw edema.

These findings point toward the hypothesis that angiotensin II interferes with mast cell degranulation, which is mainly responsible for the dextran edema and for the early phase of carrageenan paw edema (DiRosa, 1971). In fact, we also demon-strated that the administration of angiotensin II induced significant enhancement of mast cell degranulation in the dextran and carrageenan-induced paw tissue. Similar result was obtained in the mesenteric tissue, where angiotensin II potentiated the mast cell degranulation induced by 48/80 compound (data not shown).

To further investigate the participation of angiotensin II in the late phase of carrageenan-induced inflammation, which is associated with cytokine production and neutrophil migration (DiRosa et al., 1971; Vinegar et al., 1969, 1982; Wedmore and Williams, 1981), we examined the effects of angiotensin II in the cytokine levels and myeloperoxidase activity in carrageenan-injected paw tissue, and in the neutrophil migration to peritoneal cavity in response to carrageenan. The local pretreatment with angiotensin II did not change the tissue content of the pro-inflammatory cytokines tumor necrosis alpha and interleukin 1 beta, suggesting that these cytokines are not involved in angiotensin II-potentiation of carrageenan-induced inflammation. Furthermore, pretreatment with angiotensin II did not modify the neutrophil migration to the peritoneal cavity in response to carrageenan and did not enhanced the increase in myeloperoxidase activity induced by carrageenan in paw tissue. Taken together, these data suggest that angiotensin II does not interfere with the late phase carragenan-induced paw edema.

In conclusion, the present study suggests an important role of angiotensin II in inflammatory response, increasing vascular

permeability through induction of mast cells degranulation. Furthermore, our results suggest that angiotensin II enhances edema response through the angiotensin AT_2 receptors, since the angiotensin AT_1 antagonist and angiotensin AT_2 agonist also potentiated the paw edema. Although, further investigation is required, these data provide basic information on the role of angiotensin II on acute inflammation and support future studies of ligands of angiotensin II receptors on the modulation of inflammatory conditions.

Acknowledgements

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