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Evaluation of Anti-inflammatory Effects of Angiotensin Receptor Blockers in an Experimental Model of Acute Inflammation in Rats

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Abstract: There is a renewed interest in ARBs (angiotensin receptor blockers) for their effects on inflammation, as they are commonly used in the elderly suffering from disorders like arthritis, atherosclerosis which may have a potential inflammatory etiology. But there have been conflicting reports on the effect of ARBs on inflammation. The present study was aimed to evaluate the anti-inflammatory effect of ARBs in rat model of acute inflammation. Albino Wistar rats were randomly assigned to seven groups, i.e., Control (1% CMC (carboxy methyl cellulose)), Aspirin, Losartan, Telmisartan, Valsartan, Candesartan and Irbesartan groups. Rats were orally pretreated with drugs for three consecutive days. On the 3rd day, rats were challenged by a subcutaneous injection of 0.05 mL of 1% carrageenan into the plantar side of right hind paw, 30 min after drug administration. Paw edema was measured using a mercury plethysmograph and paw diameter by micrometer screw-gauge at 0, 3, 6 and 24 h after carrageenan challenge. Percentage inhibition of edema was also calculated. All the ARBs showed a significant anti-inflammatory effect at 3, 6 and 24 h as compared to control, although not comparable to that of aspirin. This anti-inflammatory effect, although not comparable to a known anti-inflammatory agent like aspirin, would perhaps prove beneficial in elderly patients routinely treated with these drugs.

Key words: Angiotensin receptor blockers, inflammation, carrageenan, paw edema.

1. Introduction

ARBs (Angiotensin receptor blockers), also known as angiotensin antagonists, are used in the therapeutics of hypertension, myocardial infarction and congestive cardiac failure [1]. However, there is a renewed interest in these compounds in terms of their effects on inflammation, as these drugs are commonly used as antihypertensives in elderly who are suffering from disorders like arthritis, atherosclerosis which may have a potential inflammatory etiology [2].

Ang II (Angiotensin II), the active principle of the RAAS (renin-angiotensin-aldosterone system), is a potent pro-hypertensive factor owing to its vasoconstrictor and sodium retentive properties [3]. Ang II increases adhesion molecules, cytokines and chemokines and exerts a pro-inflammatory effect on leucocytes, endothelial cells and vascular smooth muscle cells. Acting via the type 1 receptor, Ang II initiates an inflammatory cascade of reduced nicotinamide-adenine dinucleotide phosphate oxidase, ROS (reactive oxygen species) and nuclear factor-κB (NF-κB), which mediate transcription and gene expression and increase adhesion molecules and chemokines [4].

Kramer et al. [5] showed that a losartan metabolite

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EXP3179 is generated on cytochrome-P450 degradation of losartan. This metabolite demonstrated molecular homology to indomethacin, a cyclo-oxygenase inhibitor with anti-inflammatory and anti-aggregatory properties. Thus, they suggest that the anti-inflammatory properties of losartan are mediated via its metabolite EXP3179. In another study by Laudanno and Cesolari [6], they claimed that losartan, candesartan and valsartan show anti-inflammatory effect in carrageenan induced paw edema model. Similarly, Indumathy and Kavimani [7] also demonstrated that losartan, irbesartan and valsartan possess significant anti-inflammatory activity in carrageenan induced paw edema in rats.

In contrast, Raghavendra and Kulkarni [8] concluded that local administration of losartan significantly enhances carrageenan induced paw edema in a dose-dependent manner. They also showed that co-administration of sub-effective doses of losartan and Ang II significantly potentiated carrageenan induced inflammation.

Interestingly, a review of reports on ARBs [9, 10] also shows that the anti-inflammatory effects are not consistent across all ARBs. In a study conducted by Ichiki et al. [9], telmisartan, but not valsartan, attenuated IL-6 mRNA expression induced by TNF-α (Tumor Necrosis Factor-α). Another study [10] showed that valsartan attenuated the expression of MCP-1 (Monocyte Chemo attractant Protein-1), TNF-α, IL-6 (Interleukin-6), IL-1β (Interleukin-1β) and infiltration of leucocytes and macrophages in injured arteries.

Thus, there have been conflicting reports on the effect of ARBs on inflammation.

Hence, we decided to evaluate the anti-inflammatory effect of ARBs in rat model of acute inflammation. In our study, we aim to evaluate the anti-inflammatory activity of ARBs in carrageenan induced paw edema model of acute inflammation in rats, and try to assess whether the anti-inflammatory effect, if any, is a class property or an individual drug effect. We will also compare the anti-inflammatory effect of ARBs with aspirin.

2. Materials and Methods

2.1 Ethical Statement

The animal experiments were carried out in accordance with the guidelines set by the "CPCSEA" (Committee for the Purpose of Control and Supervision on Experiments on Animals). The study was approved by the Institutional Animal Ethics Committee.

2.2 Experimental Animals

Albino Wistar rats of 6-8 weeks age and weighing around 100-150 g were used. These animals were sourced from Haffkine Institute, Mumbai, India. Animals were accommodated in polypropylene cages with grill on top. Identification of animals was done using cage tags. Food and water was given ad libitum. The animals were allowed acclimatization for a period of 1 week in the animal laboratory, at a temperature of 25 ℃, 60% humidity and 12 h light-and-dark cycle.

2.3 Test Substances: (Pure Form)

Losartan (Cipla pharmaceuticals), Telmisartan (Cipla pharmaceuticals), Valsartan (Lupin pharmaceuticals), Candesartan (Medley pharmaceuticals), Irbesartan (Sun pharmaceuticals), Aspirin (Penta Pharmaceuticals Ltd.) and Carrageenan powder (Sigma Chemicals) were used in our study. Freshly prepared 1% (*w*/*v*) solution of carrageenan in normal saline was used for inducing inflammation. 1% suspension of CMC in distilled water was used as a vehicle and also fed to the control group. The suspensions of test drugs were made in 1% CMC.

2.4 Carrageenan Induced Paw Edema Model

After acclimatization for a period of 7 days, all animals were randomly divided into seven groups, i.e., Control viz. 1% CMC (1 mL), Aspirin (360 mg/kg), Losartan (9 mg/kg), Telmisartan (7.2 mg/kg), Valsartan (14.4 mg/kg), Candesartan (1.44 mg/kg) and Irbesartan (27 mg/kg). The control/test drugs were

given by oral feeding for 3 days. On the 3rd day, 30 minutes after drug administration, rats were challenged by a subcutaneous injection of 0.05 mL of 1% solution of carrageenan into the plantar side of right hind paw. Paw was marked using an ink marker at the level of the lateral malleolus, and immersed in the mercury in one arm of a mercury plethysmograph up to this mark to measure the paw volume [11]. The paw diameter was measured using a micrometer screw gauge [12]. These measurements were performed at 0 (baseline), 3, 6 and eventually at 24 h after the carrageenan challenge.

2.5 Parameters Assessed

Paw diameter was recorded at baseline, i.e., 0 h, then at 3, 6 and 24 h

Paw volume was recorded at baseline, i.e., 0 h, then at 3, 6 and 24 h

Percentage inhibition of paw edema is calculated as follows: % inhibition = $(1 - V_t/V_c) \times 100$,

Where,

V_t —paw volume in drug treated group

V_c —paw volume in control group [12].

2.6. Statistical Analysis

Plethysmographic readings of the paw volume and micrometer readings of the paw diameter between study groups, were compared using one way analysis of variance, followed by Tukey's post test, separately at 0, 3, 6 and 24 h.

Plethysmographic readings of the paw volume and micrometer readings of the paw diameter, within group, were compared using Repeated Measures Analysis of Variance, followed by Dunnett's post test.

All the quantitative data was expressed as Mean ± SEM (standard error of mean).

$P < 0.05$ was considered as statistically significant.

3. Results and Analysis

Comparison of various groups with aspirin at various time intervals was done by one way anova followed by Tukey's post test.

Control group showed a significant increase in paw volume at 3, 6 and 24 h compared to 0 h.

Aspirin group showed a significant increase in paw volume at 6 h and 24 h as compared to 0 h. Also, paw volume in aspirin group at 3, 6 and 24 h was significantly lower as compared to that in the control group at 3, 6 and 24 h, respectively.

Losartan, telmisartan, valsartan, candesartan and irbesartan groups showed a significant increase in paw volume at 3, 6 and 24 h as compared to 0 h.

Also, paw volume in these groups at 3, 6 and 24 h was significantly lower as compared to that in the control group at 3, 6 and 24 h, respectively.

However, paw volume in losartan, telmisartan, valsartan, candesartan and irbesartan groups was significantly higher as compared to that in aspirin group at 3 h and 6 h but not at 24 h.

Control group showed a significant increase in paw diameter at 3, 6 and 24 h compared to 0 h.

Aspirin group showed a significant increase in paw diameter at 3, 6 and 24 h as compared to 0 h Also, paw diameter in the aspirin group at 3, 6 and 24 h was significantly lower as compared to that in the control group at 3, 6 and 24 h, respectively.

Losartan, telmisartan, valsartan, candesartan and irbesartan groups showed a significant increase in paw diameter at 3, 6 and 24 h as compared to 0 h.

Also, paw diameter in these groups at 3, 6 and 24 h was significantly lower as compared to that in the control group at 3, 6 and 24 h, respectively.

However, paw diameter in losartan, telmisartan, valsartan, candesartan and irbesartan groups was significantly higher as compared to that in the aspirin group at 3 h and 6 h but not at 24 h.

4. Discussion

Angiotensin receptor blockers are a class of drugs which act on renin-angiotensin-aldosterone axis and are used for the treatment of hypertension. Angiotensin II is an octapeptide, generated in plasma from a

precursor plasma α2 globulin with a variety of effects including vessel inflammation [1]. It stimulates the release of pro-inflammatory cytokines, activates NF-kB, increases oxidant stress, suppresses nitric oxide synthesis and behaves as an inflammatory molecule [13]. It also induces inflammation through the production of reactive oxygen species, adhesion molecules, and inflammatory cytokines such as MCP-1 [14]. COX-2 (Cyclooxygenase-2) synthesis and release are also induced by Angiotensin II [5]. However, conflicting reports were found in studies evaluating the effect of ARBs in inflammation, so the present study was carried out to evaluate this role.

In this study, we compared the anti-inflammatory effect of ARBs with the standard anti-inflammatory drug, aspirin, which is a potent and irreversible inhibitor of COX (Cyclo-oxygenase). Aspirin was used at a dose of 360 mg/kg, equivalent to a human dose of 4 g. This dose is in the normal therapeutic dose range, when aspirin is used for anti-inflammatory therapy in humans.

Carrageenan induced paw edema model was used to evaluate acute inflammation in rats as it is simple, easy, reproducible and one of the most commonly used models to study acute inflammation [15].

In this study, we found that there was no significant difference in the paw volume and paw diameter among the control, aspirin and the ARBs' group at baseline (Table 1). This indicates that the groups were comparable at baseline. Paw volume in the aspirin group was significantly lower as compared to that in the control group at 3, 6 and 24 h, respectively (Table 2 and Fig. 1), indicating that aspirin exerts a strong anti-inflammatory effect. Paw volume in losartan, telmisartan, valsartan, candesartan and irbesartan groups was also significantly lower as compared to that in the control group at 3, 6 and 24 h, respectively. This indicates that losartan, telmisartan, valsartan, candesartan and irbesartan show a good anti-inflammatory effect. The anti-inflammatory effect of these ARBs is significantly different from aspirin at 3 h and 6 h. This indicates that although the ARBs have a significant anti-inflammatory effect of their own, it is not comparable to that of an established anti-inflammatory drug like aspirin.

Similar results were obtained when paw diameter was compared among these groups (Table 3 and Fig. 2).

The percentage inhibition of paw edema by aspirin was 62.3%, 65.6% and 25.45% at 3, 6 and 24 h, respectively. Among the ARBs, maximum percentage inhibition was seen with losartan which was 43% and 41.6% at 3 h and 6 h respectively. At 24 h, maximum percentage inhibition was seen with telmisartan, i.e., 21.8% (Table 4).

Similar findings were reported by Indumathy and Kavimani [7] who evaluated the effect of losartan, irbesartan and valsartan on carrageenan induced paw edema in rats. In their study, diclofenac was used at a dose of 20 mg/kg intraperitoneally and losartan, irbesartan, valsartan were used at a dose of 10 mg/kg each intraperitoneally. ARBs showed a significant reduction in paw edema when compared to that in control. The percentage inhibition of increase in paw volume at 120 min was 88.9% for diclofenac, whereas for ARBs, the percentage inhibition of increase in paw volume at 120 min was found to be 77.8%.

Table 1 Baseline comparability of paw volume and paw diameter in ARBs.

Groups	Vehicle control	Aspirin 360 mg/kg	Losartan 9 mg/kg	Telmisartan 7.2 mg/kg	Valsartan 14.4 mg/kg	Candesartan 1.44 mg/kg	Irbesartan 27 mg/kg
N	6	6	6	6	6	6	6
Paw volume (cm)	0.33 ±0.02	0.33 ±0.02	0.33 ±0.02	0.35 ±0.02	0.35 ±0.02	0.33 ±0.02	0.35 ±0.02
Paw diameter (mm)	4.27 ±0.01	4.27 ±0.01	4.27 ±0.01	4.27 ±0.01	4.26 ±0.01	4.28 ±0.01	4.2 ±0.01

Values expressed as mean ± SEM, *n* = no. of animals in each group. The test applied here was one-way ANOVA followed by Tukey's multiple comparison test. There was no significant difference in the paw volume and paw diameter between the groups. (p = 1.0 for paw volume and p = 0.85 for paw diameter).

Table 2 Comparison of paw volume of ARBs at 0, 3, 6 and 24 h.

		Paw volume in cm			
Groups	*N*	0 h	3 h	6 h	24 h
Control (Ctrl)	6	0.33 ±0.02	0.93 ±0.02***	1.25 ±0.02***	0.55 ±0.02***
Aspirin (Asp)	6	0.33 ±0.02	0.35 ±0.02	0.43 ±0.02**	0.41 ±0.01*
Asp V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.01$)
Losartan (Los)	6	0.33 ±0.02	0.53 ±0.02***	0.73 ±0.02***	0.45 ±0.02***
Los V/s Ctrl			s ($P < 0.001$)	s ($P < .001$)	s ($P < 0.05$)
Los V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns
Telmisartan(Tel)	6	0.35 ±0.02	0.63 ±0.02***	0.83 ±0.02***	0.43 ±0.02***
Tel V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.01$)
Tel V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns
Valsartan (Val)	6	0.35 ±0.02	0.65 ±0.02***	0.85 ±0.02***	0.45 ±0.02***
Val V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.05$)
Val V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns
Candesartan(Can)	6	0.33 ±0.02	0.67 ±0.02***	0.85 ±0.02***	0.45 ±0.02***
Can V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.05$)
Can V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns
Irbesartan (Irb)	6	0.35 ±0.02	0.65 ±0.02***	0.85 ±0.02***	0.45 ±0.02***
Irb V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.05$)
Irb V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns

Values expressed as mean ±SEM, s = significant, ns = not significant, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$;*indicates within group comparison; s/ns–indicates intergroup comparison. Within group comparison was done by repeated measures ANOVA followed by Dunnett's test. Comparison of various groups with control at various time intervals was done by one way anova followed by Tukey's post test.

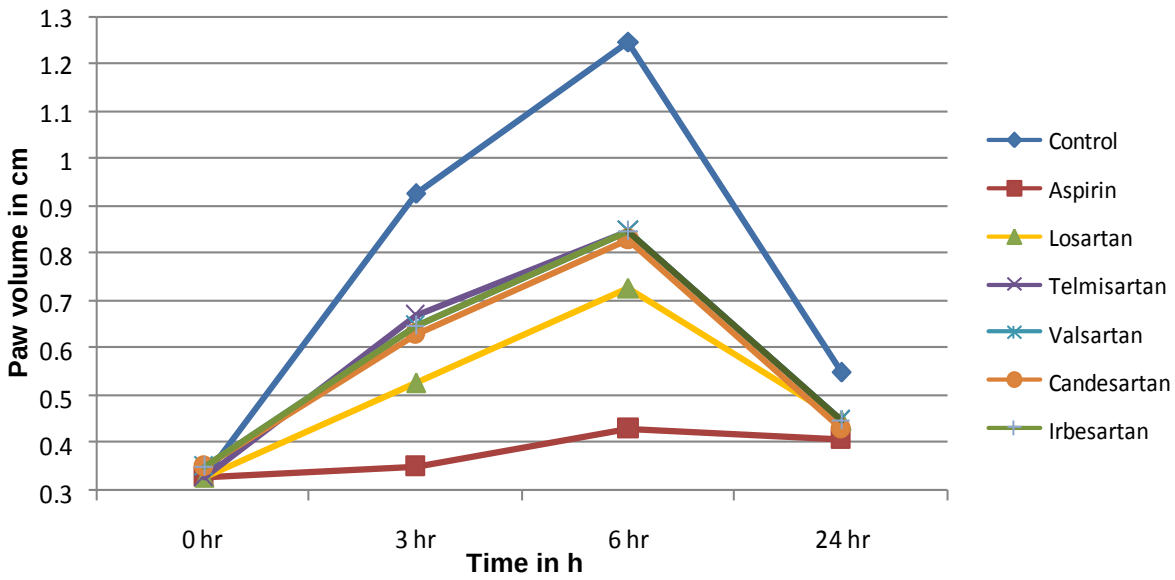

Fig. 1 Graph showing comparison of paw volume of ARBs at 0, 3, 6 and 24 h.

However, a study conducted by Raghvendra and Kulkarni [8] has shown contradictory results. They showed that losartan enhances Ang II (angiotensin II) facilitated carrageenan induced paw edema. In their study, local administration of losartan (10-50 micrograms/paw) or Ang II (0.2-1 microgram/paw) did not induce any inflammation when administered individually, but both significantly enhanced the edema

Table 3 Comparison of paw diameter of ARBs at 0, 3, 6 and 24 h.

		Paw diameter in mm			
Groups	*n*	0 h	3 h	6 h	24 h
Control (Ctrl)	6	4.27 ±0.01	8.34 ±0.04***	11.84 ±0.01***	6.82 ±0.01***
Aspirin (Asp)	6	4.27 ±0.01	4.54 ±0.01***	6.43 ±0.02***	6.61 ±0.01***
Asp V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.001$)
Losartan (Los)	6	4.27 ±0.01	5.35 ±0.01***	7.85 ±0.02***	6.60 ±0.01***
Los V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.001$)
Los V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns
Telmisartan (Tel)	6	4.26 ±0.01	5.70 ±0.01***	8.05 ±0.01***	6.64 ±0.01***
Tel V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.001$)
Tel V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns
Valsartan (Val)	6	4.26 ±0.01	5.63 ±0.008***	8.02 ±0.02***	6.61 ±0.009***
Val V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.001$)
Val V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns
Candesartan (Can)	6	4.28 ±0.01	5.69 ±0.01***	8.07±0.01***	6.65 ±0.01***
Can V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.001$)
Can V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns
Irbesartan (Irb)	6	4.26 ±0.01	5.63 ±0.008***	8.04 ±0.01***	6.63 ±0.01***
Irb V/s Ctrl			s ($P < 0.001$)	s ($P < 0.001$)	s ($P < 0.001$)
Irb V/s Asp			s ($P < 0.001$)	s ($P < 0.001$)	ns

Values expressed as mean ±SEM, s = significant, ns = not significant, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$;*indicates within group comparison; s/ns – indicates intergroup comparison. Within group comparison was done by repeated measures ANOVA followed by Dunnett's test. Comparison of various groups with control at various time intervals was done by one way ANOVA followed by Tukey's post test. Comparison of various groups with aspirin at various time intervals was done by one way ANOVA followed by Tukey's post test.

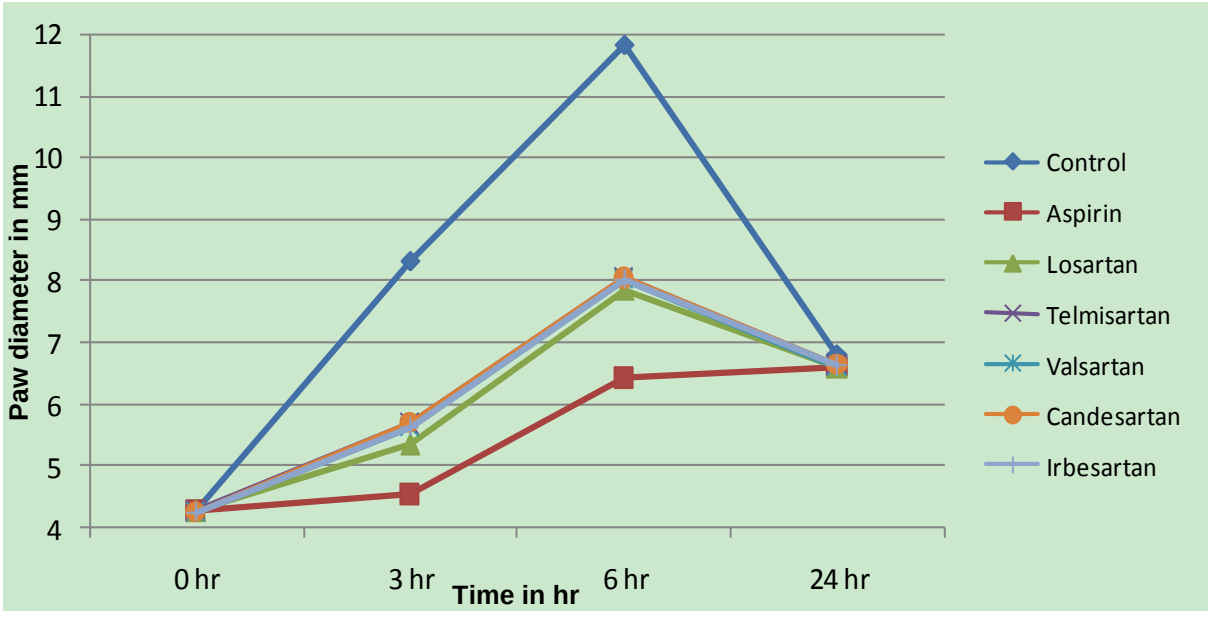

Fig. 2 Graph showing comparison of paw diameter of ARBs at 0, 3, 6 and 24 h.

induced by carrageenan in a dose-dependent manner. They proposed that Ang II might be formed locally during carrageenan-induced acute inflammation. They also proposed that the potentiation of Ang II effect by

Table 4 Percentage inhibition of paw edema by ARBs at 3 , 6 and 24 h.

Groups	3 h	6 h	24 h
Control			
Aspirin	62.3%	65.6%	25.45%
Losartan	43%	41.6%	18%
Telmisartan	32.2%	33.6%	21.8%
Valsartan	30.1%	32%	18%
Candesartan	27.9%	32%	18%
Irbesartan	30.1%	32%	18%

losartan in carrageenan-induced inflammation may be mediated through over-stimulation of unblocked AT2 receptors or due to stimulation of inflammatory pathways by unknown mechanisms.

Losartan is known to inhibit many pro-inflammatory cytokines like TNF-α [16], IL-1β [16-18], IL-8 (Interleukin-8) [19], IL-6 (Interleukin-6) [17] and increase the levels of Interleukin-10 (IL-10), which is an anti-inflammatory cytokine [20]. It is also known to reduce the levels of ICAM-1 (Intercellular Adhesion Molecule-1), VCAM-1 (Vascular Cell Adhesion Molecule-1) [21], MMP-9 (Matrix Metalloproteinase-9), COX-2 and MCP-1 and inhibit the expression of CCR-2 (C-C Chemokine Receptor-2) [13]. Also, Kramer et al. [5] proposed that losartan metabolite EXP3179 is generated on cytochrome-P450 degradation. This metabolite shows molecular homology to indomethacin, a cyclooxygenase inhibitor with anti-inflammatory and antiaggregatory properties. It acts by abolishing COX-2 mRNA upregulation and COX-dependent TXA2 (thromboxane-A2) and PGF2α (prostaglandin-F2α) generation. Thus, anti-inflammatory properties of losartan may also be mediated via its EXP3179 metabolite.

Telmisartan is known to decrease the levels of inflammatory markers like IL-6, MMP-9, MMP-2 and PTX3 (plasma pentathrix-3), a marker of vascular inflammation [22]. It is also known to attenuate the expression of MCP-1 and CCR-2 (13). It is found to decrease the release of pro-inflammatory cytokines such as PGE2 (prostaglandin E2), VCAM-1, NF-κB activation and inhibit ROS formation through its PPAR-γ (peroxisome-proliferator-activated-receptor-γ) agonistic activity [23]. ROS and NF-κB are known to initiate inflammatory process and increase the transcription of pro-inflammatory cytokines, adhesion molecules and NADPH oxidase [24].

Valsartan is known to decrease the levels of inflammatory mediators like IL-6 [25], TNF-α [26], NF-κB, CRP (C-reactive protein) [4], MCP-1, IL-1β, ROS and inhibit infiltration of leucocytes and macrophages [10]. CRP is an acute-phase reactant which is downstream of a number of inflammatory triggers. It plays a role in the innate immune response by opsonizing bacteria and activating complement.

Candesartan is also known to decrease the levels of IL-1β, IL-6, TNF-α and ROS [27, 28]; and that of NF-κB, CRP and MCP-1 [29]. Irbesartan is known to decrease the levels of IL-6, MMP, VCAM-1, TNF-α and superoxide levels and increase the level of anti-inflammatory cytokine, IL-10 [20, 30].

Additionally, angiotensin II is known to promote oxidative stress and to be a pro-inflammatory molecule. Leukocytes are known to express angiotensin II receptors. Thus, ARBs which block angiotensin II actions may be expected to inhibit inflammation [31]. This might also be a possible mechanism of action of anti-inflammatory activity of ARBs.

5. Conclusions

From our study, we have found enough evidence to put forward the view that all the five Angiotensin receptor blockers viz. Losartan, Telmisartan, Candesartan, Valsartan and Irbesartan have a significant anti-inflammatory effect, indicating that it might be a class property of ARBs. This anti-inflammatory effect, although not substantial and comparable to a known anti-inflammatory agent like aspirin, would perhaps prove beneficial in elderly patients, who are routinely and preferentially treated with these drugs for their cardiovascular etiologies.

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