Influence of enalapril, quinapril and losartan on lipopolysaccharide (LPS)-induced serum concentrations of TNF-α, IL-1β, IL-6 in spontaneously hypertensive rats (SHR)

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Abstract: Immunopharmacological studies of drugs used in cardiovascular diseases provide new data concerning their modulating effect on the levels of proinflammatory cytokines, chemokines and adhesion molecules. Therefore, we have made an attempt to find out whether enalapril, quinapril and losartan (drugs used in the treatment of arterial hypertension) are able to modulate lipopolysaccharide (LPS)-induced proinflammatory cytokine serum concentrations (tumor necrosis factor alpha – TNF-α, interleukin-1β – IL-1β, interleukin-6 – IL-6) in spontaneously hypertensive rats (SHR). The animals were divided into four groups as follows: SHR + M (control rats receiving 1% solution of methylcellulose), SHR + E (rats receiving enalapril – 10 mg/kg), SHR + Q (rats receiving quinapril – 10 mg/kg) and SHR + L (rats receiving losartan – 20 mg/kg). 1% solution of methylcellulose and hypotensive drugs were administered by a gavage for 21 days. Arterial blood pressure was measured in conscious rats, using the tail-cuff method. Twenty four hours after the last administration of enalapril, quinapril, losartan or 1% solution of methylcellulose, the rats received a single dose of LPS (ip; 0.1 mg/kg). After 2 h, the rats were anesthetized with ether and the blood samples were collected by heart puncture. Serum TNF-α, IL-1β and IL-6 concentrations were measured with enzyme-linked immunosorbent assay kits. Additionally, total cholesterol and high density lipoprotein (HDL) cholesterol were evaluated. Enalapril, quinapril and losartan significantly decreased LPS-stimulated TNF-α and IL-1β level after 21 days. Three-week administration of quinapril lowered IL-6 serum concentration after LPS stimulation. Enalapril and losartan did not affect the IL-6 level. The results were accompanied by a statistically significant decrease in systolic, diastolic and mean blood pressure. Hypotensive drugs also showed no effect on lipid level. The latest data indicate additional properties of hypotensive drugs. However, further studies are necessary to elucidate precisely the role of proinflammatory cytokines in arterial hypertension.

Key words: enalapril, quinapril, losartan, proinflammatory cytokines, SHR


Introduction

There is a lot of evidence supporting the participation of inflammatory mechanisms in the pathogenesis of
cardiovascular diseases, including atherosclerosis [29, 49]. Among numerous mediators, proinflammatory cytokines are thought to exert adverse actions, which could aggravate the course of the disease [35]. Recently, some studies have focused on the role of cytokines in the pathogenesis of hypertension. It is a complex and multifactorial phenomenon affected by genetic predisposition and environment. Several studies have demonstrated raised level of proinflammatory cytokines in hypertensive or apparently healthy patients. Bautista et al. [5] found elevated level of tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 and Chae et al. [9] suggested similar results for intercellular adhesion molecule-1 (ICAM-1) and IL-6. Dalekos et al. [16] recorded an increased level of IL-1β in hypertensive patients and a slight correlation between its concentration and mean blood pressure. Differences in C-reactive protein (CRP), TNF-α, but not IL-6 were found in pre-hypertensive and hypertensive patients in the ATTICA study [11]. It should be noted that not all studies confirm these observations. Peeters et al. [46] reported lack of statistically significant differences in concentration of TNF-α, IL-1β and IL-6. The increased levels of cytokines have been found in cases of pre-eclampsia-related hypertension in females [13]. Also studies in pregnant rats suggested a role of TNF-α and IL-6 in the increase in peripheral resistance and blood pressure [2, 42]. Obesity is one of the characteristic features of a metabolic syndrome, where proinflammatory cytokines are elevated, as well [1, 17, 62].

However, the scarce cytokine-related data in hypertension are confusing and clear evidence is still lacking. It has not been fully elucidated yet, whether the elevated level of cytokines precedes or follows the development of hypertension [33, 45].

Immunopharmacological studies show that medicines used in cardiovascular diseases may exert modulating effects on cytokines. In our previous study in hypertensive rats, amlodipine decreased TNF-α, increased IL-6 and did not affect IL-1β level after lipopolysaccharide (LPS) challenge. Atenolol did not influence TNF-α and IL-1β concentration, but raised IL-6 level [3]. Since additional properties of hypotensive drugs could be very beneficial (decrease in the proinflammatory cytokines), we have decided to investigate whether angiotensin converting enzyme inhibitors (ACEIs): enalapril and quinapril or angiotensin II type 1 (AT₁) receptor blocker (ARB), losartan, can also modulate the proinflammatory cytokine level in spontaneously hypertensive rats (SHR) after stimulation with LPS. Literature data indicate that ACEIs and ARBs may have a potential modulating effect on endothelium [10], cytokines, adhesion molecules and chemokines [47, 53]. Additional properties of cardiovascular drugs could be very beneficial in decreasing complications accompanying hypertension.

Materials and Methods

Animals

The study was conducted on male SHR with initial body weight ranging between 240–290 g, which had free access to standard food and water. Their body weight was monitored during the experiments. The animals were housed in standard plastic cages at a constant temperature of 22°C and under a 12 h light-dark cycle. All experiments were conducted between 8 a.m. and 4 p.m. The rats had been familiarized with the environment and the equipment for three weeks before the study. Preliminary examinations were carried out in the second and third week in order to select the animals. The rats with high blood pressure fluctuations were excluded from the study. All experimental procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals and were approved by the Local Ethics Committee for the Experiments on Animals (no. L/BD/206).

The following preparations were used in the experiments: enalapril (Polfa, Warszawa, Poland), quinapril (ICN Polfa Rzeszów, Poland), losartan (Adamed, Poland), methylcellulose (Sigma, USA), LPS from Escherichia coli serotype 055:B5 (Sigma, USA).

Experimental design

Rats were divided into 4 experimental groups as follows:
1) SHR + M (control hypertensive rats receiving methylcellulose)
2) SHR + E (hypertensive rats receiving enalapril – 10 mg/kg)
3) SHR + Q (hypertensive rats receiving quinapril – 10 mg/kg)
4) SHR + L (hypertensive rats receiving losartan – 20 mg/kg)
Control rats (SHR + M) received 1% solution of methylcellulose (1 ml/kg) by a gavage as a vehicle. Hypotensive drugs were suspended in 1% solution of methylcellulose and administered by a gavage in a 1 ml/kg volume. All compounds were administered for 21 days. Control arterial blood pressure measurement was carried out after the first, the second and the third week of drug administration.

Twenty four hours after the last administration of enalapril, quinapril, losartan or 1% solution of methylcellulose, the rats received a single dose of LPS (ip; 0.1 mg/kg in a 1 ml/kg volume of saline). After 2 h, the rats were anesthetized with ether and the blood samples were collected by heart puncture. The blood was allowed to clot overnight at 4°C before centrifuging for 20 min at 2000 × g. The serum was removed and stored at −20°C until the assay. Preliminary studies showed no detectable values of cytokines in serum of SHR. LPS was administered in order to achieve a measurable cytokine levels. The time of blood sample collection after LPS administration was chosen according to Dredge et al. [18].

**Blood pressure determination**

Arterial blood pressure was measured in conscious rats with a manometer manufactured by LETICA (Panlab S.L., Spain), using tail-cuff method. Before the measurements, the animals were placed inside a warming chamber (about 34°C) for 30 min. The aim of the procedure was to calm the animals and dilate the tail blood vessels. Arterial blood pressure was measured at least three times for each animal. Changes in pressure were expressed as the percentage of baseline values.

**Lipid profile determination**

Total cholesterol levels were determined with the cholesterol oxidase method using a commercially available kit (Cholesterol CHOD PAP, Biolabo, Maizy, France).

HDL cholesterol was measured with the cholesterol kit after low density lipoproteins, very low density lipoproteins and chylomicrons from the samples had been precipitated by phosphotungutic acid and magnesium chloride (HDL-cholesterol – PTA, Biolabo, Maizy, France).

**Serum cytokine levels**

Serum TNF-α, IL-1β and IL-6 concentrations were measured in duplicate with a commercially available enzyme-linked immunosorbent assay kit (Quantikine, R&D Systems, USA) according to the manufacturer’s instructions.

**Statistical analysis**

Results are expressed as the mean ± SD. The normality of distribution was checked by means of Kolmogorov-Smirnov test with Lilliefors test. The statistical evaluation was performed using analysis of variance (ANOVA) and post hoc comparisons were performed by means of Least Significant Differences (LSD) test. If the data were not normally distributed, statistical evaluation was performed by using ANOVA (Kruskal-Wallis) and Mann-Whitney U test. Differences were considered significant when p < 0.05.

**Results**

**Blood pressure**

The SHR selected for the experiments had initial mean arterial blood pressure values as follows: systolic pressure 204.54 ± 14.93 mmHg, diastolic pressure 148.15 ± 12.82 mmHg, mean pressure 166.77 ± 11.35 mmHg. SHR did not show any significant changes in all values of pressure during administration of 1% solution of methylcellulose.

Enalapril at the dose of 10 mg/kg administered for 21 days caused a statistically significant decrease in the values of systolic, diastolic and mean blood pressure in comparison with the control group (SHR + M). Additionally, a significant decrease in mean blood pressure after the second week was noted. Quinapril (10 mg/kg) significantly decreased diastolic and mean blood pressure values in the second week of observation. The values of systolic, diastolic and mean blood pressure were found to be significantly lower in rats receiving quinapril than in the control group at the third week of observation. Losartan at the dose of 20 mg/kg also caused a significant decrease in all the measured values of blood pressure in the third week of treatment in comparison with the control. Additionally, a significant decrease in diastolic and mean
blood pressure after the second week was observed. The results are shown in Table 1.

### Lipid profile

The hypotensive drugs (enalapril, quinapril and losartan) did not cause statistically significant changes in comparison with the control group in the examined lipid parameters. Mean total cholesterol and HDL cholesterol levels were as follows: SHR + M: 63.38 ± 7.67 mg/dl, 29.43 ± 4.49 mg/dl; SHR + E: 56.83 ± 7.53 mg/dl, 30.94 ± 6.93 mg/dl; SHR + Q: 60.01 ± 6.57 mg/dl, 33.84 ± 6.44 mg/dl; SHR + L: 63.1 ± 10.9 mg/dl, 33.63 ± 6.98 mg/dl, respectively.

### Cytokine level

As shown in Figure 1, the hypotensive drugs caused a statistically significant decrease in serum concentration of TNF-α after 21 days in comparison with the control group. The following concentrations were found: SHR + M: 2895.74 ± 1194.81 pg/ml, SHR + E: 507.27 ± 463.71 pg/ml, SHR + Q: 235.68 ± 175.93 pg/ml, SHR + L: 247.30 ± 164.38 pg/ml. Quinapril

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**Tab. 1.** The influence of the repeated administration (by a gavage) of enalapril (SHR + E), quinapril (SHR + Q) or losartan (SHR + L) on arterial blood pressure in SHR

<table>
<thead>
<tr>
<th>Time after drug administration (week)</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SHR + M</td>
<td>SHR + E</td>
<td>SHR + Q</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>97.13 ± 8.47</td>
<td>95.65 ± 7.33</td>
<td>94.37 ± 6.72</td>
</tr>
<tr>
<td>2</td>
<td>102.81 ± 13.96</td>
<td>94.02 ± 8.67</td>
<td>93.10 ± 8.16</td>
</tr>
<tr>
<td>3</td>
<td>105.46 ± 14.12</td>
<td>91.36 ± 8.89*</td>
<td>89.51 ± 6.25*</td>
</tr>
</tbody>
</table>

Data are presented as the mean and standard deviation (SD); * p < 0.05 in comparison with SHR + M (control group receiving methylcellulose) (n = 14–16)

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**Fig. 1.** The influence of the repeated administration of enalapril (SHR + E), quinapril (SHR + Q) or losartan (SHR + L) on serum concentration of TNF-α. The animals received methylcellulose (SHR + M)/enalapril (SHR + E)/quinapril (SHR + Q) or losartan (SHR + L) for 21 days (n = 8–13). Data are presented as the mean and standard deviation (SD); * p < 0.05 in comparison with SHR + M

**Fig. 2.** The influence of the repeated administration of enalapril (SHR + E), quinapril (SHR + Q) or losartan (SHR + L) on serum concentration of IL-6. The animals received methylcellulose (SHR + M)/enalapril (SHR + E)/quinapril (SHR + Q) or losartan (SHR + L) for 21 days (n = 8–13). Data are presented as the mean and standard deviation (SD); * p < 0.05 in comparison with SHR + M
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caused a statistically significant decrease in IL-6 concentration as compared to SHR control group (330.00 ± 214.97 pg/ml vs. 1048.56 ± 910.07 pg/ml). Three-week administration of enalapril and losartan did not influence IL-6 level (1062.41 ± 839.40 pg/ml and 778.28 ± 640.96 pg/ml, respectively) (Fig. 2).

Changes in serum concentration of IL-1β after 21 days of drug administration are shown in Figure 3. In the present study, we observed a decrease in IL-1β values in enalapril-, quinapril- and losartan-treated SHR in comparison with the control group (130.11 ± 102.06 pg/ml and 43.95 ± 30.76 pg/ml and 81.66 ± 67.83 pg/ml vs. 264.60 ± 133.73 pg/ml, respectively).

Discussion

Among the numerous disorders observed in primary hypertension, dysfunctions of the renin-angiotensin-aldosterone system, increased activity of the sympathetic nervous system, and disturbances of renal function should be mentioned [41]. Besides, endothelial dysfunction and related imbalance between vasodilating and vasoconstricting factors is emphasized [24, 44]. Increasing attention is also paid to changes in the immune system observed in arterial hypertension [19]. In this aspect, the studies describing increased levels of proinflammatory cytokines in subjects with elevated blood pressure or hypertension seem interesting. Of course, it is difficult to determine unequivocally whether the elevated proinflammatory cytokines are only a marker of secondary, pathophysiological changes or the evidence of cytokine involvement per se.

In our study, enalapril, quinapril and losartan administered for 21 days significantly decreased LPS-stimulated serum TNF-α concentration in SHR. Several studies demonstrated similar cytokine-modulating capabilities of ACEIs and ARBs in various experimental models. Niimi et al. [38] observed that enalapril suppressed LPS-induced TNF-α and IL-6 mRNA levels in the kidneys of Wistar rats. In another study, administration of this drug significantly inhibited enhanced TNF-α mRNA expression in the lung of C57BL/6 mice in a model of pulmonary hypertension induced by bleomycin [43]. Schindler et al. [53] in a study of human peripheral blood mononuclear cells found that captopril, enalapril and cilazapril decreased the synthesis of TNF-α and IL-1α induced by IL-1β. Other drugs of that group: lisinopril, perindopril and ramipril exerted no significant effect on the synthesis of TNF-α. Interestingly, Cominacini et al. [12] showed that zofenoprilat, but not enalaprilat, was effective in reducing the expression of vascular cell adhesion molecule-1 (VCAM-1), ICAM-1 and E-selectin in monocytic U-937 cells and activated human coronary artery endothelial cells. The authors conclude that sulfhydryl-containing ACEI may be useful in inhibiting foam cell formation. Lindmark and Siegbahn [34] noted that enalapril reduced TNF-α expression in monocytic U-937 cells and activated human coronary artery endothelial cells. Similar results of modulating influence on TNF-α were observed with quinapril. Bachetti et al. [4] observed that quinapril reduced LPS-stimulated serum TNF-α levels in normotensive rats. In Wistar rats with congestive heart failure after myocardial infarction, quinapril reduced the increased expression of cytokines, such as: TNF-α, IL-1β, IL-5, or IL-6 in the myocardium [60]. Anti-inflammatory activity of quinapril was also observed in mice with collagen-induced arthritis. Quinapril administered at the moment of induction, or after development of symptomatic arthritis caused alleviation of symptoms of the disease, accompanied by reduced expression of TNF-α in joints. The potential to modulate cytokine levels was confirmed by reduction of LPS-stimulated TNF-α production in splenocytes obtained from mice with arthritis in comparison with control animals [15]. In our experiments, losartan decreased the level of
TNF-α, which is consistent with the immunopharmacological data for that drug, confirming the ability of AT1 receptor antagonists to modulate cytokine levels in various experimental models. Losartan administered at 50 mg daily dose to subjects with essential hypertension decreased the levels of TNF-α, bFGF and PDGF after 3 months of the therapy [14]. Reduced TNF-α levels were also found in patients with heart failure receiving a therapy including losartan at the dose of 50 mg a day [22]. Different data were presented by Sardo et al. [52], who did not demonstrate any effect of this drug on the level of TNF-α. Only the level of ICAM-1 decreased in the fourth week of treatment and returned to baseline values in the subsequent weeks of the therapy in patients with hypertension. It should be noted that enalapril, quinapril and losartan significantly decreased systolic, diastolic and mean blood pressure after the third week of administration in the present study. Additionally, quinapril and losartan lowered diastolic and mean blood pressure after 14 days of the study. Favorable hemodynamic actions could have an impact on the observed TNF-α changes. Nevertheless, ACE inhibitors and angiotensin receptor blockers probably may exert anti-inflammatory effects by inhibiting proinflammatory effects of angiotensin II. The exact mechanism by which ACEIs or ARBs reduce cytokine synthesis is unknown. The decrease in TNF-α concentration noted in our study may be favorable in the context of reports concerning the negative effect of this proinflammatory cytokine. As indicated by research results, TNF-α may stimulate expression of the angiotensinogen-encoding gene in the liver, thus influencing the function of the renin-angiotensin-aldosterone system. The promoter region of angiotensinogen contains an APRE (acute-phase response element), whose binding to TNF-α induced nuclear factor κB (NF-κB) [7]. There are data indicating that TNF-α may limit the half-life of eNOS mRNA, which affects the NO availability and its level [39, 64]. Enalapril and losartan did not affect the IL-6 level in our experimental model. However, the concentration of this cytokine in the group receiving losartan seems to have a declining tendency at the used dose. Quinapril significantly decreased IL-6 level. The observed effects may be connected with the inhibition of angiotensin II action. Quinapril as a “tissue ACEI” could have higher potency in hindering proinflammatory actions of angiotensin II. Wei et al. [60] observed that treatment with quinapril significantly reduced the expression of the measured cytokines (e.g. IL-6) in the rat model of post-myocardial infarction congestive heart failure. As noted in patients with chronic congestive heart failure, enalapril administered at 40 mg daily dose caused a reduction of IL-6 level with a simultaneous increase in sIL-6R receptor level. Enalapril administered at 5 mg daily dose did not demonstrate such effect [21]. Niimi et al. [38] and Lindmark and Siegbahn [34] also observed the cytokine-modulating properties of enalapril in their experiments. Interestingly, losartan despite blockade of the action of angiotensin II exerted via AT1 receptors did not affect significantly the concentration of IL-6 in our study. Skurk et al. [54] showed that candesartan significantly counteracted the Ang II-stimulated IL-6 and IL-8 release, although this inhibition was not complete. Also Sanz-Rosa et al. [51] observed reduction of IL-6 plasma concentration in SHR after ten weeks of candeasartan treatment. The observed lack of losartan effect on IL-6 levels may have been associated with too short duration of treatment. Also an increase in the level of angiotensin II and its effects should be taken into consideration. It should be noted that a recent study by Lee et al. [32] showed that arterial hypertension induced by angiotensin II infusion and high-salt diet depended significantly on the presence of IL-6. The experiments were carried out on transgenic IL-6 knockout mice and wild-type C57BL/6J. High-salt diet did not affect mean blood pressure values in the experimental animals, whereas ang II infusion caused a statistically significant increase of mean blood pressure starting from day 6 in wild-type animals in comparison with IL-6 KO ones. It is noteworthy that a 10-fold increase in plasma IL-6 level was observed in wild-type mice receiving angiotensin II infusion as compared with strain-matched controls. According to the authors, this may indicate the involvement of that cytokine in the pressor effect of angiotensin II. It may be associated with the influence of IL-6 on renal sodium excretory capability. In rat vascular smooth muscle cell cultures, angiotensin II increased the transcription of mRNA for IL-6 by activation of NF-κB [23]. Similarly, stimulation of cultured human vascular smooth muscle cells from human saphenous veins with angiotensin II caused a dose- and time-dependent increase in IL-6 production [31]. The effect was associated with AT1 receptors, and activation of NF-κB was also noted. The authors suspect that the effect of ang II may be related to NF-κB stimulation by a superoxide radical associated with the stimula-
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Activation of NAD(P)H oxidase by ang II. IL-6 is a cytokine with pleiotropic effect, including the promotion of isolated rat aorta smooth muscle cell proliferation, which is a characteristic feature of early-stage hypertension and atherosclerosis. According to the authors, such an effect was associated with PDGF [25]. The activity of IL-6 has been discussed primarily in the context of atheromatous changes. However, we do not know whether similar changes may accompany the development of arterial hypertension. It should be emphasized that IL-6 may stimulate the expression of angiotensinogen [56]. It was also noted that in vitro stimulation of rat aorta smooth muscle cells with IL-6 led to up-regulation of AT1 receptor mRNA. Additionally, preincubation of smooth muscle cells with IL-6 was found to increase significantly angiotensin II-induced production of free radicals [59].

IL-1β is thought to be one of the main regulators of the immune and inflammatory response. Its proinflammatory properties, including the increase in endothelial cell permeability, induction of adhesion molecules, procoagulant potential, may favor the development of atheromatous changes in arterial hypertension. However, the exact effect and role of IL-1β in development of arterial hypertension are unknown. The literature contains contradictory data concerning the influence of IL-1β on arterial blood pressure in animals and humans, with respect to its both hypotensive and hypertensive effect after systemic administration or infusion into the central nervous system (CNS) [20, 27, 55, 61]. This may be due to a variety of doses used for acute administration. Studies involving the administration of IL-1β to the CNS suggest its involvement in neurogenic blood pressure control [30, 37, 63]. In our study, all hypotensive drugs selected for experiments caused a significant decrease in its concentration. However, there is little data concerning the potential of quinapril, enalapril and losartan to modulate IL-1β concentration. Reduction of IL-1β level might be an additional advantage in hypertension treatment. Tikiz et al. [57] observed insignificant changes in this cytokine in patients with long-term rheumatoid arthritis after quinapril treatment. Wei et al. [60] noted that quinapril attenuated myocardial infarction-induced rise in IL-1β expression in rats. In the in vitro studies, Schindler et al. [53] demonstrated that enalapril suppressed IL-1β-induced synthesis of IL-1α. Decreased levels of IL-1β and interferon gamma (IFN-γ) were also noted in mice with experimental immune-mediated colitis, after subcutaneous administration of losartan [26]. In dehydrated Wistar rats, a single dose of losartan administered after LPS also attenuated the increase in IL-1β level in the liver [36]. Ufnal et al. [58], in experiments on Sprague-Dawley rats, observed a significant, but transient, increase in mean arterial blood pressure after intracerebroventricular (icv) administration of IL-1β. Interestingly, central administration of losartan inhibited the pressor effect of the cytokine. The authors suppose that IL-1β may increase the sensitivity to the central effect of angiotensin II, although different results were presented by Campese et al. [8]. In experiments on Sprague-Dawley rats, central administration of angiotensin II was associated with a decrease in the expression of IL-1β and nNOS mRNA in the brain. The decrease in NO level by ang II may increase activity of the sympathetic nervous system.

Our investigations of total cholesterol and HDL cholesterol levels did not demonstrate statistically significant changes in the groups of SHR receiving enalapril, quinapril and losartan in comparison with the control group. The above may indicate no involvement of lipid profile changes in the mechanism of development of this experimental hypertension in SHR. ACEIs and ARBs are usually characterized by neutral or favorable effect on the lipid profile [28, 40]. In hyperlipidemic Imai rats, enalapril treatment significantly reduced hypercholesterolemia at 38 weeks [50]. Additionally, use of the ACE inhibitor quinapril normalized proteinuria, cholesterol levels and glomurular lesions in obese Zucker rats [6]. Qin et al. [48] showed that losartan administered for eight weeks in experimental diabetes in Wistar rats did not influence plasma cholesterol concentration.

Conclusions

Some data indicate a potential involvement of proinflammatory cytokines in the disorders observed in the arterial hypertension, however, the results of such studies should be interpreted with considerable caution. We still do not have sufficient data which would indicate obvious cause-and-result relationship. In our studies, enalapril, quinapril and losartan acted as immunomodulators of LPS-stimulated proinflammatory cytokines in SHR. The observed decrease in TNF-α,
IL-1β and IL-6 (quinapril) serum concentrations in SHR may be connected with attenuation of angiotensin II actions. Cytokine-modulating properties of enalapril, quinapril and losartan may be beneficial to hypertension complications (i.e. atherosclerosis). Further studies, which will allow to elucidate the exact role of proinflammatory cytokines in arterial hypertension and the mechanisms of action of hypotensive drugs on proinflammatory cytokines, are necessary.

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