Beneficial Effects of Angiotensin II AT1 Blocker on Cardiovascular Adverse Remodeling Due to Nitric Oxide Synthesis Blockade

Efectos Beneficiosos del Bloqueador AT1 de la Angiotensina II en la Remodelación Cardiovascular Adversa Causada por el Bloqueo de la Síntesis de Óxido Nítrico

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SUMMARY: We studied with morphological tools the effects of different doses of Losartan upon the cardiovascular remodeling in nitric oxide deficient rats. At 15 weeks of age, thirty Wistar rats were separated in six groups: control (C), L-NAME (LN), and four groups were LN was given plus Losartan at different doses (1, 5, 20 and 40 mg/kg/day). The L-NAME was given for 9 weeks, the Losartan administration starting on the 2nd week of experiment. We studied the heart, thoracic aorta and superior mesenteric artery with light microscopy and stereology. The blood pressure (BP) increased since the first week of L-NAME administration, the Losartan treatment at doses of 20 and 40 mg/kg/day was efficient to reduce BP after the 7th week of treatment. The cardiac adverse remodeling in the LN group was characterized by intense interstitial fibrosis, impairment of the myocardial microvascularization, cardiomyocyte hypertrophy and consequent loss of cardiomyocytes. The aortic wall structure (density per area of smooth muscle cell nuclei and surface density of lamellae), and the superior mesenteric artery media/lumen ratio were also strongly affected by L-NAME administration. Only in the dose equal or higher than 20 mg/kg/day Losartan showed beneficial effects treating these alterations. In conclusion, both the heart and the arterial wall of NO deficient rats suffer a marked adverse remodeling process that is efficiently treated by a dose-dependent Losartan administration. The efficiency of Losartan treatment in this model of NO synthesis blockade correlates with the hypotensor effect of the drug mainly in the high dose treatment.

KEY WORDS: Losartan; Angiotensin II; L-NAME; Hypertension; Renin-angiotensin system; Stereology.

INTRODUCTION

The nitric oxide (NO), a paracrine vasodilator, plays an important role in the regulation of vascular tone, the inhibition of platelet aggregation, and the suppression of smooth muscle cell proliferation, and therefore may be critical in the developing of arterial hypertension and atherosclerosis (Furchgott & Zawadzki, 1980; Ignarro et al., 1987; Rees et al., 1989). The blood pressure (BP) shows a sustained elevation after a long-lasting inhibition of NO synthase by administering L-NAME in drinking water to rats and the NO-deficient hypertension is now considered an experimental model of hypertension besides Goldblatt renal hypertension, Okamoto spontaneous hypertension, and DOCA-salt hypertension (Baylis et al., 1992; Ribeiro et al., 1992). Chronic inhibition of NO biosynthesis causes cardiac ischemia associated with a mechanical dysfunction which is similar to those seen in some patients suffering from chronic arterial hypertension (Moreno et al., 1996) and we know that changes in the arterial and heart structure in hypertension are a risk factor for cardiovascular morbidity and mortality, independently of the BP levels (Mahmud & Feely, 2004).

Although the contribution of sympathetic nervous system to BP maintenance in L-NAME hypertension is more important than that of renin-angiotensin system (RAS) (Pechanova et al., 2004), and a direct link between activation of RAS and development of endothelial dysfunction in experimental hypertension was still not proved (Artigues-Varin et al., 2002), anti RAS agents, angiotensin-converting enzyme (ACE) inhibitors and the angiotensin II (Ang II) Type I receptor (AT₁R) antagonists improve endothelium-dependent vasodilation through an increase in NO bioavailability, by an increase in NO production and a
decrease in NO inactivation (Higashi et al., 2005). Ang II and NO have many antagonistic effects, as well as influencing each other's production and functioning. In the short-term, Ang II stimulates NO release, thus modulating the vasoconstrictor actions of the peptide. In the long-term, Ang II influences the expression of all three NO synthase (NOS) isoforms, while NO downregulates the Ang II AT₁R, contributing to the protective role of NO in the vasculature (Millatt et al., 1999; Zhou et al., 2004).

Losartan was the first orally acting nonpeptide AT₁R antagonist. It has provided the opportunity to obtain the benefits of selectively blockade the RAS at the level of the AT₁R avoiding the nonspecificity of the ACE inhibitors (Timmermans, 1999a, 1999b). The present study was designed to determine the differential effects of different doses of Losartan upon the cardiac and arterial remodeling in NO-deficient rats.

MATERIAL AND METHOD

Sample and procedures. The protocol of this experiment was conducted under the guideline of “Care Use of Laboratory Animals” published by the US National Institutes of Health.” Only male Wistar rats were used (from colonies maintained at the State University of Rio de Janeiro), all with 15 weeks old at the beginning of the study. The systolic BP was measured weekly by the non-invasive method of tail-cuff plethysmography (Letica LE 5100, Panlab, Barcelona, Spain). All animals were individually housed in a controlled room (12 h light/12 h dark) and air exhaustion extensions (Gundersen, 1977)). Length density was estimated for ima, \( L_{ima} \): \( Q_s \text{ima} \text{ mm/m}^3 \) and the mean cross-sectional area was estimated for cmy, \( A_{cmy} \): \( V_{cmy} / 2 \cdot Q_s \text{cmy} \text{ µm}^3 \) (Mandarim-de-Lacerda, 2003).

Thirty rats were used in this study separated into six groups of five animals each: control group (C), l-NAME group (LN) and four groups where l-NAME was given plus Losartan (LN+Lo) at different doses. The animals from control group received water and food ad libitum. The animals from LN group received l-NAME 20 mg/kg/day dissolved in the drinking water during nine weeks (N°-Nitro-L-arginine Methyl Ester Hydrochloride, Sigma-Aldrich Co., St. Louis, MO, USA, Lot 034K0674). The animals from the LN+Lo groups received LN for one week followed by LN plus Losartan for 8 weeks at the dosages of 1, 5, 20, and 40 mg/kg/day (LN+Lo1, LN+Lo5, LN+Lo20 and LN+Lo40 groups, respectively).

Finished the experiment period (9 weeks), the animals were deeply anesthetized with 50 mg/kg intraperitonial Thiopental and their vascular system was perfused with a constant pressure (90 mmHg, Minipuls 3, Gilson, Villiers le Bel, France) through the left ventricle (LV), firstly with physiologic solution, followed by a fixative solution (freshly prepared 1.27 mol/l formaldehyde in 0.1 M phosphate buffer, pH 7.2) (Carson et al., 1973). The atria were separated from the ventricles and the right ventricle from the LV. The volume of the entire heart and the LV (including the interventricular septum) were determined according to the submersion method of Scherle (Scherle, 1970) in which the water displacement due to organ volume is recorded by weighing (W). As the isotonic saline specific density (d) is of 1.0048 the respective volumes were obtained by \( V_s = W(d/\rho) \) or simply \( V_s = W(d) \) (Weibel, 1979). The thoracic aorta and the superior mesenteric artery were also excised and fixated with the same fixative solution for 24 h at room temperature.

Myocardium. The estimation was carried out by cutting the LV with the orientator method (Mattfeldt et al., 1990). Fragments of the LV were fixed for 24 h in the same fixative and then embedded in ParaPlast plus (Sigma-Aldrich Co., St. Louis, MO, USA), sectioned 5 µm thick, and sections were stained with hematoxylin-eosin and trichrome methods (Masson and picro sirius red). The myocardium was analyzed considering the cardiomyocytes (cmy) and the cardiac interstitium (intramyocardial arteries, ima, and the connective tissue, ct). The volume density was estimated for cmy, ima and ct: \( V_s = P_s / \rho_s \) (Pp is the number of points that hit the structure; \( \rho_s \) is the total test-points inside the test-system). The ratio between ima/cmy was used to study the amount of myocardial vascularization and was estimated as the ratio \( V_s = \rho_s(I-a_{cmy}) \). Density per area was estimated for cmy and ima, \( Q_s \text{cmy} \text{ mm/mm}^3 \) and the mean cross-sectional area was estimated for cmy, \( A_{cmy} \): \( V_{cmy} / 2 \cdot Q_s \text{cmy} \text{ µm}^3 \) (Mandarim-de-Lacerda, 2003).

The disector method used in the present study to estimate the number of cmy is a three-dimensional probe that samples structures proportional to their number without regard to the size or shape of the structures (Sterio, 1984). In a disector, two sections are used to create a sampling volume with an upper, reference section, containing a test frame. Sections were viewed with a 100x planachromatic immersion oil objective on a Leica DMRBE microscope (NA=1.25) to identify cmy nuclei. For each frame, the thickness of the section was measured by focusing on the
upper and lower section surfaces verified objectively by employing an auto-focus device and read-out (the microscope was equipped with a z-axis motorized focus controller microcator with a resolution of 0.1 μm). Light microscopy was performed using a microscope Leica DMRBE (Wetzlar, Germany), a Kappa videocamera (Gleichen, Germany) and a Sony Trinitron monitor (Pencoed, UK).

The numerical density (Nv) of cardiomyocyte nuclei (cmyn per mm²) was determined from 10 random disector pairs for each rat. This sampling design was based on a pilot experiment to determine the inter-animal variability. Estimates of relative variance (= variance/mean = coefficient of variation²) of around 10% was considered acceptable (Gundersen & Osterby, 1981). Centers of nuclei were measured, rather than tops of nuclei. The center of nuclei was defined by focusing on the clear nuclear edge and the most clearly defined nuclear chromatin to prevent constraint on section thickness (Gundersen et al., 1988).

\[ N_{v_{cmyn}} = \frac{Q_{cmyn}}{t \cdot A_T} \]

The absolute parameters were estimated multiplying the density by the LV volume. For example, the total cardiomyocyte nuclei number in the LV was estimated as the product of \( N_{v_{cmyn}} \) and LV volume.

**Aorta and superior mesenteric artery.** The descending thoracic aorta and the superior mesenteric artery (at level of the first jejunal branch) were excised and then immersed in the same fixative for 24 h. In both arteries, two rings were perpendicularly cut and placed on the cut surface, embedded in Paraplast plus (Sigma-Aldrich Co., St. Louis, MO, USA), and cut at 3 μm thick sections (in aorta, vertical section was obtained according to the previously described) (Pereira et al., 2004). The sections were stained with trichrome methods (Masson and picro sirius red) staining collagen fibers, smooth muscle and nuclei.

Five non-consecutive aortic sections were analyzed per animal. A test-system with 16 cycloid arcs was put on the video screen and calibrated (Leitz micrometer 1 mm/100). The cycloids’ minor axes were arranged in parallel with the defined vertical axis. The smaller thickness of tunica intimae and tunica media in four fields, located at 0, 90, 180, and 270 degrees, were examined in each section. The number of hits of the lamellae with cycloid arcs ([I/Im]) were counted to estimate the lamellae surface density ([Sv[lm]] = 2[I/Im]/L_t). LT is the test-line length based on the system calibration. The smooth muscle cell nuclei number was counted in a two-dimensional test frame of 6,400 μm² allowing the estimation of its numerical density per area (Q_d/smcn) (Mandarim-de-Lacerda, 2003).

Five digital images of superior mesenteric artery per animal were acquired (TIFF format, 36-bit color, 1280 x 1024 pixels) with a LC Evolution camera and a Olympus BX51 microscope, and analyzed with the Image Pro Plus version 5.0 (Media Cybernetics, Silver Spring, USA). The images were segmented using the same semitone’s level in order to obtain an uniform microscopic pattern of color and intensity and were transformed into pixels. The lumen perimeter was drawn upon the image and the software automatically gave the lumen area (A). The lumen diameter (D) was determined from the equation \( D = 2 \cdot \sqrt{A/\pi} \), assuming that the vessels cross-sections were practically circular in vivo. Tunica media was defined as the region between the inner and the external elastic laminae. Two polygons were drawn; one upon the inner elastic lamina and other upon the external elastic lamina, and the average linear distance between these two polygons was automatically given by the software. This value was used as the tunica media thickness. The lumen diameter and the tunica media thickness were used to calculate the media-to-lumen ratio (M/L ratio).

**Data analysis.** The differences of the biometrical parameters were tested by the one way ANOVA and the post-hoc test of Newman-Keuls. The quantitative differences were tested using the non-parametric ANOVA of Kruskall-Walliss followed by the Mann-Whitney test. In all cases the significant level of 0.05 was considered for significant statistics (Glantz, 2002). All analyses were performed using GraphPad Prism version 4.03 for Windows (GraphPad Software, San Diego, CA, USA).

**RESULTS**

**Blood pressure.** Compared to control rats, the BP increased since the first week of L-NAME administration (mean±SD) from 115±5 mmHg to 152±9 mmHg, p<0.001. After 9 weeks of L-NAME administration the BP reached 190±8 mmHg (plus 70% than the control group level at this week, p<0.0001). The treatment with Losartan was efficient to control the BP increase in rats taken L-NAME. The Losartan at doses of 1 and 5 mg/kg/day reduced the BP to intermediary levels between the control group and the LN group. The Losartan treatment at doses of 20 and 40 mg/kg/day was more efficient than the previous doses reducing...
BP similar to the control group level after the 7th week of treatment (Fig. 1).

Cardiac remodeling. The Fig. 2 shows two major aspects of the myocardium in LN group and LN+Lo40 group. The l-NAME administration caused myocardial ischemic lesions and consequent interstitial fibrosis (Fig. 2A) while the Losartan administration treated these myocardial lesions (Fig. 2B). The cardiac remodeling was observed in both the non contractile and contractile components of the myocardium. In the non contractile myocardial component, the \( Vv[ct] \) was 7±2 % in the control group and 24±5 % in the LN group (more 240 %, p<0.001). Treatment with Losartan was efficient to prevent the \( Vv[ct] \) increase only in the doses equal or higher than 20 mg/kg/day, \( Vv[ct] \) was 13±6 % in LN+Lo20 (less 45 % than LN group, p<0.01) and 5±1 % in LN+Lo40 (less 80 % than LN group, p<0.01). The capacity of Losartan in decrease \( Vv[ct] \) was correlated with its efficiency in lowering systolic BP (R= 0.77, p<0.001) (Fig. 3). The myocardial vascularization was measured in the left ventricle by \([ima]/[cmy]\) ratio and \(Lv[ima]\). Compared to the control group the \([ima]/[cmy]\) ratio was lower in the LN group (by 60 %) and in the LN+Lo20 group (by 25 %), but no difference was seen in LN+Lo40 group (Fig. 4). The \(Lv[ima]\) was negatively correlated with the systolic BP control by Losartan (R= -0.83, p<0.001). The \(Lv[ima]\) was 8,200±350 mm/mm³ in the control group and 4,400±1,000 mm/mm³ in the LN group (less 45 %, p<0.001). Treatment with Losartan was efficient to prevent \(Lv[ima]\) decrease only in the doses equal or higher than 20 mg/kg/day, \(Lv[ima]\) was 6,200±810 mm/mm³ in LN+Lo20 group (plus 40 % than LN group, p<0.01), it was 9,220±670 mm/mm³ in LN+Lo40 group (plus 100 % than LN group, p<0.0001) (Fig. 5).

Fig. 1. Systolic blood pressure (mean±SD). Groups are: C- control, LN- l-NAME, LN+Lo- l-NAME+Losartan with different doses (1, 5, 20, and 40 mg/kg/day). In signaled cases, when compared, P≤0.05, if: a, when compared with C group; b, with LN group; c, with LN+Lo1 group; d, with LN+Lo5 group.

Fig. 2. Photomicrographs showing the myocardium in rats treated with l-NAME(A) and l-NAME plus Losartan 40mg (B). The ischemic areas characterized by cardio-myocyte hypertrophy and interstitial fibrosis (arrows in A) were not seen in animals treated with Losartan high dosage (B) (stain: picro Sirius red, bright field. Bar = 100µm).
In the left ventricle contractile component great alteration was seen in the $A_{cmy}$ that grew from 354±14 µm$^2$ in the control group to 600±107 µm$^2$ in the LN group (plus 70 %, p<0.001). Treatment with Losartan was efficient to reduce $A_{cmy}$ only in the doses equal or higher than 20 mg/kg/day (Fig. 6). The $N_{cmy}$ dropped from 38±4 million in the control group to 28±4 million in the LN group (less 25 %, p<0.02). The $N_{cmy}$ was different only between the LN and the LN+Lo40 groups (Fig. 7).


In signaled cases, when compared, $P \leq 0.05$, if: a, when compared with C group; b, with LN group; c, with LN+Lo1 group; d, with LN+Lo5 group; e, with LN+Lo20 group.

The beneficial effects of angiotensin II AT1 blocker on cardiovascular adverse remodeling due to nitric oxide synthesis blockade were observed in the left ventricle contractile component. The area of cardiomyocytes ($A_{cmy}$) increased from 354±14 µm$^2$ in the control group to 600±107 µm$^2$ in the LN group (70%, p<0.001). Losartan treatment was effective only at doses equal to or higher than 20 mg/kg/day (Fig. 6). The number of cardiomyocytes ($N_{cmy}$) decreased from 38±4 million in the control group to 28±4 million in the LN group (25%, p<0.02). The $N_{cmy}$ was different only between the LN and the LN+Lo40 groups (Fig. 7).
Arterial wall remodeling. In the aortic wall, both the QA[smcn] and the Sv[lamelae] were efficiently treated by Losartan. Between the control group and the LN group the Sv[lamelae] decreased by 40% and difference between untreated LN animals and Losartan treated ones was observed since the dose of 20 mg/kg/day (Fig. 9). The superior mesenteric artery M/L ratio grew 40% from control animals to untreated LN animals. The Losartan treatment was efficient to reduce the M/L ratio only in the dose of 40 mg/kg/day (Fig. 10).

Fig 7. Bar graph (mean±SE) of the differences found to the number of cardiomyocyte nuclei in the left ventricle among the groups (C- control, LN- L-NAME, LN+Lo- L-NAME+Losartan with different doses: 1, 5, 20, and 40 mg/kg/day). In signaled cases, when compared, P≤0.05, if: a, when compared with C group; b, with LN group; c, with LN+Lo1 group; d, with LN+Lo5 group; e, with LN+Lo20 group.

Fig 8. Bar graph (mean±SE) of the differences found to the surface density of the aortic lamellae among the groups (C- control, LN- L-NAME, LN+Lo- L-NAME+Losartan with different doses: 1, 5, 20, and 40 mg/kg/day). In signaled cases, when compared, P≤0.05, if: a, when compared with C group; b, with LN group; c, with LN+Lo1 group; d, with LN+Lo5 group; e, with LN+Lo20 group.

Fig 9. Bar graph (mean±SE) of the differences found to the numerical density per area of the aortic tunica media smooth muscle cell nuclei among the groups (C- control, LN- L-NAME, LN+Lo- L-NAME+Losartan with different doses: 1, 5, 20, and 40 mg/kg/day). In signaled cases, when compared, P≤0.05, if: a, when compared with C group; b, with LN group; c, with LN+Lo1 group; d, with LN+Lo5 group; e, with LN+Lo20 group.

Fig 10. Bar graph (mean±SE) of the differences found to the media-to-lumen ratio of the superior mesenteric artery among the groups (C- control, LN- L-NAME, LN+Lo- L-NAME+Losartan with different doses: 1, 5, 20, and 40 mg/kg/day). In signaled cases, when compared, P≤0.05, if: a, when compared with C group; b, with LN group; c, with LN+Lo1 group.
DISCUSSION

The NO synthesis inhibition by L-NAME resulted in the BP elevation and the consequent adverse cardiovascular remodeling, characterized by cardiomyocyte hypertrophy, interstitial fibrosis, impairment of the myocardial vascularization, tunica media hypertrophy of aorta and superior mesenteric artery, and a significant loss of cardiomyocytes. Losartan reduced BP and attenuated these adverse remodeling in NO deficient rats when used in high dose but not in low dose.

The Ang II AT1R mediates virtually all of the known physiological actions of Ang II in cardiovascular, renal, neuronal, endocrine, hepatic, and other target organs. These actions include the regulation of BP, electrolyte and water balance, thirst, hormone secretion, and renal function (Gasparo et al., 2000). The AT1R blockade increases circulating levels of Ang II that could in theory act on the unopposed AT1R. The ability of Ang II to stimulate AT1R in the presence of blockaded AT1R could provide additional complementary therapeutic benefit (Widdop et al., 2003). AT1R stimulation has been associated with increased production of bradykinin, nitric oxide (NO), and guanosine cyclic 3’,5’-monophosphate (cGMP) (Siragy & Carey, 1996, 1997; Campbell et al., 2005). Each of these substances has vasodilator actions, and it is possible that AT1R stimulation leads to vasodilation through this autacoid cascade (Carey et al., 2001). AT1R located on smooth muscle of rat aortic rings mediated vasorelaxation via stimulation of B2 receptors by bradykinin, which in turns results in the activation of the NO-cGMP pathway, vasodilator cyclooxygenase product(s), and voltage-dependent and Ca++-activated large-conductance K+ channels (Fukada et al., 2005). The BK-NO-cGMP vasodilator cascade mediated by the AT1R suggested the possibility that the AT1R may serve a protective role in BP regulation (Carey et al., 2000).

After oral administration, Losartan undergoes the first pass metabolism in the liver and is converted into active metabolites like EXP3174 and EXP3179. The EXP3174 metabolite has an affinity to the AT1R 10 times higher than that of Losartan (Sadoshima, 2002). The EXP3179 metabolite shows molecule homology to indomethacin, a cyclooxygenase inhibitor with antiinflamatory and antiaggregatory properties. EXP3179 is able to block the COX-2 mRNA upregulation and COX-2-dependent TXA2 and PGF2α generation in vitro (Kramer et al., 2002). Moreover, EXP3179 abolishes dose-dependently arachidonic acid (AA)-induced platelet aggregation, suggesting an inhibitory effect at the COX enzyme. This suggests that pharmacological effects of Losartan are mediated not only by Losartan itself but also by its metabolites. The EXP2179 action suggests an AT1R independent effect of Losartan.

In the heart, left ventricular hypertrophy and adverse remodeling primarily involve both the cardiomyocytes and the extracellular matrix (Weber & Brilla, 1991; Pessanha & Mandarim-de-Lacerda, 2000), and the collagen fibers are excessively deposited by fibroblasts, predominating the type I over the type III (Ritter & Neyes, 2003). This process begins in the perivascular region and progressively diffuses to the adjacent tissue. Additionally, reparative fibrosis due to cardiomyocyte loss for apoptosis or necrosis can occur (Mayet & Hughes, 2003). In this study, treatment with Losartan, mainly in high dose, reduced significantly the collagen interstitial myocardial production.

L-NAME-induced hypertension leads to myocardial injury (Pechanova et al., 1999) that is time and dose-dependent (Pereira et al., 1998, Pessanha et al., 1999). The cardiomyocyte loss in this model of hypertension seems to be mainly due to necrosis, although apoptosis is also present (Mandarim-de-Lacerda & Pereira, 2000) probably due to the impairment of the myocardial microvascularization (Pereira & Mandarim-de-Lacerda, 2000). Present findings are in favor of beneficial effects of Losartan on myocardial microvascularization and the loss of cardiomyocytes when administrated in high dose.

The hypertension alters the mechanical properties and morphology of the arteries. Large arteries exhibit increased lumen size and media thickening by compromise smooth muscle cells and elastic lamellae (Aguilu et al., 2004; Pereira et al., 2004). In small arteries, particularly in mild hypertension, smooth muscle cells are restructured around a smaller lumen, without true hypertrophy (eutrophic remodeling) (Mulvany, 1990, 2003). In more severe hypertension, hypertrophic remodeling with increased vascular stiffness can be found (Schiffrin, 2001). A well-active antihypertensive drug must not only reduce the BP levels but also reverse and/or impair target organs damage. Losartan showed a dose-dependent effect under BP in the L-NAME-induced model of hypertension and also was able to keep it at normal levels. This effect was similar regarding left ventricular and arterial adverse remodeling.

In conclusion, both the heart and the arterial wall of NO deficient rats suffer a marked adverse remodeling process that is efficiently treated by a dose-dependent Losartan administration. The efficiency of Losartan treatment in this model of NO synthesis blockade correlates with the hypotensor effect of the drug mainly in the high dose treatment.
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RESUMEN: Se estudiaron con herramientas morfológicas, los efectos de diferentes dosis de Losartan sobre el remodelamiento cardiovascular, en ratas deficientes en óxido nítrico. 30 ratas Wistar, con 15 semanas de edad, fueron separadas en 6 grupos: control (C), L-NAME (LN), y 4 grupos en que administró LN junto con Losartan, en diferentes dosis (1, 5, 20 y 40 mg/kg/día). El L-NAME fue administrado durante 9 semanas y la administración de Losartan se inició en la segunda semana de experimentación. Se estudiaron el corazón, la parte torácica de la aorta y la arteria mesentérica craneal, con microscopía de luz y estereología. La presión arterial (PA) aumentó desde la primera semana de administración de L-NAME. El tratamiento con Losartan, en las dosis de 20 y 40 mg/kg/día, fue eficiente para reducir la PA después de la séptima semana de tratamiento. El remodelamiento cardiaco adverso en el grupo LN se caracterizó por intensa fibrosis intersticial, disminución de la microvascularización miocárdica e hipertrofia y consecuente pérdida de cardiomiocitos. La estructura de la pared de la aorta (densidad por área de células musculares lisas y densidad de superficie de lamelas), y la relación media/luz de la arteria mesentérica craneal, también fueron muy alteradas por la administración de L-NAME. Sólo en una dosis igual o mayor que 20 mg/kg/día, Losartan tuvo efecto beneficio tratando estas alteraciones. En conclusión, tanto el corazón como la pared arterial de ratas deficientes en óxido nítrico, presentan un proceso de remodelamiento acentuado, y éste es eficientemente tratado con Losartan en diferentes dosis. La eficiencia del tratamiento con Losartan en el modelo de bloqueo de la síntesis de óxido nítrico se correlaciona con el efecto hipotensor de la droga, principalmente en las dosis más elevadas.

PALABRAS CLAVE: Losartan; Angiotensina II; L-NAME; Hipertensión; Sistema renina-angiotensina, Estereología.

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