

The Effects of Losartan on Renal Function in the Newborn Rabbit

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ABSTRACT

The low GFR of newborns is maintained by various factors including the renin-angiotensin system. We previously established the importance of angiotensin II in the newborn kidney, using the angiotensin-converting enzyme inhibitor perindoprilat. The present study was designed to complement these observations by evaluating the role of angiotensin-type 1 (AT₁) receptors, using losartan, a specific AT₁-receptor blocker. Increasing doses of losartan were infused into anesthetized, ventilated, newborn rabbits. Renal function and hemodynamic variables were assessed using inulin and para-aminohippuric acid clearances as markers of GFR and renal plasma flow, respectively. Losartan 0.1 mg/kg slightly decreased mean blood pressure (−11%) and increased diuresis (+22%). These changes can be explained by inhibition of the AT₁-mediated vasoconstrictive and antidiuretic effects of angiotensin, and activation of vasodilating and diuretic AT₂ receptors widely expressed in the neonatal period. GFR and renal blood flow were not modified. Losartan 0.3 mg/kg decreased mean blood pressure significantly (−15%), probably by inhibiting systemic AT₁ receptors. GFR significantly decreased (−25%), whereas renal blood flow remained stable. The decrease in filtration fraction (−21%) indicates predominant efferent vasodilation. At 3 mg/kg, the systemic hypotensive effect of losartan was marked (mean blood pressure, −28%), with decreased GFR and renal blood flow (−57% and −51%, respectively), a stable filtration fraction, and an increase in renal vascular resistance by 124%. The renal response to this

dose can be considered as reflex vasoconstriction of afferent and efferent arterioles, rather than specific receptor antagonism. We conclude that under physiologic conditions, the renin-angiotensin is critically involved in the maintenance of GFR in the immature kidney. (*Pediatr Res* 51: 728–732, 2002)

Abbreviations

Angiotensin II
ACE, angiotensin-converting enzyme
ARI, acute renal insufficiency
AT₁, angiotensin type 1 receptor
AT₂, angiotensin type 2 receptor
BK, bradykinin
BW, body weight
EFP, effective filtration pressure
FF, filtration fraction
GFR, glomerular filtration rate
MAP, mean arterial blood pressure
NO, nitric oxide
PAH, para-aminohippuric acid
RAS, renin-angiotensin system
RBF, renal blood flow
RVR, renal vascular resistance
UV, urine flow rate
UVNa, urinary excretion of sodium

In all mammalian newborns, GFR is low, both in absolute and relative (compared with adult body surface area) terms (1–3). The reasons for a low neonatal GFR are multifactorial, with one of the main factors being a reduced EFP (4). Despite the low GFR, newborn human infants and newborn experimental laboratory animals have no signs of renal insufficiency as

evidenced by sustained growth and maturation. The low GFR of the newborn is even maintained at safe levels in the face of a variety of mild to moderate endogenous or exogenous pathophysiologic stresses such as hypoxemia, hypercapnia, or metabolic acidosis. Under stressful conditions, GFR is protected by various adaptive mechanisms, among which is the RAS (5–7).

Recent studies in our laboratory using blockade of the RAS with the ACE inhibitor perindoprilat in normoxemic and hypoxemic newborn rabbits clearly showed the importance of the RAS in maintaining a basic GFR in the newborn (8). The present study was thus designed to complement these observations in newborn rabbits by the administration of losartan, a specific antagonist of the endogenous AT₁.

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METHODS

Animal experiments. A total of 28 normoxemic newborn, 6.1 ± 0.2 (mean \pm SEM) d-old New Zealand White rabbits weighing 105.6 ± 2.5 g were studied. All animals were born in our own animal facilities by spontaneous vaginal delivery and breast-fed until the time of study. The animal studies were performed according to the guidelines of the Swiss National Research Foundation.

All methods have been described previously (5, 9). Briefly, the rabbits were anesthetized with 25 mg/kg BW of sodium pentobarbital i.p. and artificially ventilated via tracheostomy with an oxygen-enriched (approximately 40%) gas mixture. The respiratory rate was kept constant at 40 breaths/min, and tidal volume was adjusted for age and weight. Body temperature was kept constant at approximately 39°C. The femoral vessels had catheters implanted for solute infusion, arterial blood sampling, and continuous monitoring of MAP and heart rate. Urine was sampled by bladder catheterization. After completion of the surgical procedure (approximately 1 h), inulin and PAH clearances were measured throughout the experiments. From this point onward, all animals received a constant infusion of a modified rabbit Ringer solution at a rate of $1 \text{ mL} \cdot \text{h}^{-1} \cdot 100 \text{ g BW}^{-1}$. A 90-min equilibration period was allowed, followed by a 60-min control period (C) consisting of two 30-min urine collections with 0.4 mL of blood withdrawn at the midpoint. The red blood cells were reconstituted in diluted human albumin and reinfused. Eighty microliters of plasma were used for immediate measurements of blood gases, hematocrit, and plasma protein levels. The remainder of the plasma was frozen for later determination of electrolytes and renal function tests. Thereafter, a 30-min equilibration period was performed to ensure that each animal could serve as its own control.

Experimental protocol. The animals were then randomly divided into three groups receiving increasing doses of i.v. losartan (Merck Research Laboratories, Rahway, NJ, U.S.A.), 0.1, 0.3, or 3.0 mg/kg BW, administered within 2 min and flushed with heparinized saline for an additional 3 min. This

was followed by two additional 30-min experimental (E1, E2) urine collections with 0.4 mL of blood withdrawn at the midpoint; the red blood cells were again reconstituted and reinfused.

Analytical procedures. UV was assessed gravimetrically, and blood gas determinations were performed with a pH/blood gas analyzer. The automatic anthrone method of Wright and Gann (10) and the Bratton and Marshall (11) method were used for the determination of inulin and PAH concentrations, respectively. Sodium was measured by flame photometry. The plasma protein concentration was estimated by refractometry.

Inulin and PAH clearances were calculated from standard equations representing GFR and renal plasma flow, respectively. RBF, FF, RVR, and UVNa were derived from standard equations as previously reported (5, 7). The PAH extraction ratio used for the calculation of RBF was 0.55 ± 0.04 ; this is the usual value found in normoxemic neonatal rabbits in our laboratory.

Statistical analysis. All results are given as mean \pm SEM. Intergroup comparisons were made only for the C period data with the nonparametric Kruskal-Wallis rank-sum test, and ANOVA for repeated measurements followed by Fisher's paired least-significant difference test was used for repeated measurements. Intragroup comparisons between the C period and E1 or E2 were performed on the absolute individual data with the nonparametric Friedman and Wilcoxon signed-rank tests. A $p < 0.05$ was considered statistically significant.

RESULTS

The general baseline control data were comparable in the three animal groups, except for hematocrit, protein levels, arterial Po_2 , UV, and RBF. Absolute changes in these variables are indicated in Table 1. In view of these findings and to minimize possible inaccuracies, the experimental data were only compared within the same group of animals.

During the experiments, relatively minor, albeit statistically significant, changes in plasma protein levels and hematocrit

Table 1. The effects of losartan on MAP, HR, Hct, Prot, and blood gas variables in three groups of newborn rabbits

Group	Period	MAP (mm Hg)	HR (per min)	Hct (%)	Prot (g/L)	Pao ₂ (mm Hg)	Paco ₂ (mm Hg)	pH
Losartan 0.1 mg/kg	C	27.6 \pm 0.7	286.2 \pm 7.2	28.6 \pm 0.7	28.4 \pm 1.3	131.2 \pm 5.0	36.4 \pm 0.5	7.51 \pm 0.01
	E1	24.3 \pm 1.1*	278.2 \pm 8.4	26.1 \pm 1.0*	25.6 \pm 1.2**	130.0 \pm 4.0	34.8 \pm 1.0	7.50 \pm 0.01
	E2	24.6 \pm 1.1*	273.1 \pm 9.9	25.9 \pm 1.0*	26.2 \pm 1.1**	124.7 \pm 2.2	34.2 \pm 0.9	7.50 \pm 0.02
Losartan 0.3 mg/kg	C	30.9 \pm 1.0	270.6 \pm 7.0	31.2 \pm 1.4††	32.8 \pm 1.4§	116.6 \pm 3.0§	36.2 \pm 0.4	7.51 \pm 0.01
	E1	26.7 \pm 1.7**	264.8 \pm 9.2	29.9 \pm 1.2**	30.2 \pm 1.4**	124.9 \pm 5.7	36.5 \pm 1.0	7.50 \pm 0.01
	E2	26.1 \pm 1.1**	261.5 \pm 9.7	29.6 \pm 1.2**	30.3 \pm 1.4**	117.5 \pm 4.0	34.0 \pm 0.9	7.50 \pm 0.01
Losartan 3 mg/kg	C	29.5 \pm 1.1	294.2 \pm 6.0	26.5 \pm 0.7	26.1 \pm 1.1	130.0 \pm 3.5	34.8 \pm 0.7	7.50 \pm 0.01
	E1	20.8 \pm 1.3***	279.1 \pm 5.5***	24.4 \pm 0.5**	22.9 \pm 1.1**	124.6 \pm 4.5	32.4 \pm 0.5	7.48 \pm 0.02
	E2	21.8 \pm 1.3***	274 \pm 8.4***	23.9 \pm 0.8**	23.4 \pm 1.2**	125.4 \pm 2.0	33.1 \pm 0.6	7.48 \pm 0.01

* $p < 0.05$ compared with C period of same group of animals.

** $p < 0.01$ compared with C period of same group of animals.

*** $p < 0.001$ compared with C period of same group of animals.

†† $p < 0.05$ compared with C period of group losartan 3 mg/kg.

§ $p < 0.05$ compared with C period of both groups losartan 0.1 and 3 mg/kg.

Abbreviations: HR, heart rate; Hct, hematocrit; Prot, plasma protein; Pao₂, arterial Po₂; Paco₂, arterial Pco₂.

were observed. These are recurrent findings in the neonatal animal experiments as a result of repeated blood sampling.

The hemodynamic and renal functional responses to i.v. losartan in the three animal groups can be found in Tables 1 and 2 (absolute data) and Figure 1 (values of percentage changes from the C period to the E1 and E2 periods averaged to simplify presentation).

In group 1 (losartan 0.1 mg/kg BW), the mean fall in MAP was -11% ($p < 0.01$). FF decreased slightly (-11%), but only significantly in period E1 ($p < 0.05$); there were no significant changes in all other renal function variables. UV increased by 22%, although not reaching statistical significance (SEM = 14).

In group 2 (losartan 0.3 mg/kg BW), the mean decrease in MAP was -15% ($p < 0.01$). This slight additional fall in MAP caused, however, a fall in GFR of approximately -25% ($p < 0.05$) without significant changes in RBF, RVR, UV, and UVNa. FF obviously decreased (-21% ; $p < 0.01$).

The major renal functional changes were observed in the animals of group 3 with the highest dose of losartan (3 mg/kg BW). The mean decrease in MAP was -28% ($p < 0.001$) with a fall in GFR and RBF of -57% and -51% , respectively (both $p < 0.01$). With the almost identical change in GFR and RBF, FF remained unchanged. Diuresis decreased by -41% ($p < 0.05$). RVR rose by an average of 124%, with a maximum of +151% in period E1 ($p < 0.05$).

DISCUSSION

The use of the potent AT₁ antagonist losartan confirms that AII plays a key role in the preservation of systemic blood pressure and glomerular filtration in the neonatal period.

Losartan 0.1 mg/kg slightly decreased MAP (-11%) and increased diuresis ($+22\%$) without any modification in GFR and RBF. These minor changes can be explained by inhibition of the vasoconstricting and antidiuretic effects of AII mediated by the systemic and tubular AT₁, as well as the activation of the vasodilating and diuretic AT₂ (12). Indeed, the vast majority of the actions of AII are thought to be mediated by AT₁, which is

highly expressed in renal glomeruli, tubules, and vasculature (13, 14). However, the expression of the AT₂ is markedly increased in the neonatal period (14–16). The AT₂ mediates counterregulatory vasodilation and protects against a further increase in blood pressure in a rat model of AII-dependent renal wrap hypertension (17). This protective vasodilator response is mediated by the renal production of BK and NO (12, 18, 19) as well as epoxyeicosatrienoic acids (20, 21). During normal sodium intake, exogenous AII administration increased cGMP acutely, a response blocked by the specific AT₂ antagonist PD 123319 but not by losartan (19). Addition of the NO synthase inhibitor *N*^ω-nitro-L-arginine methyl ester to PD 123319 completely blunted the AII-mediated increases in cGMP without potentiation of PD 123319 inhibition by *N*^ω-nitro-L-arginine methyl ester, suggesting that all of the cGMP production via AII stimulation of AT₂ could be accounted for by increased NO production (22). AT₂ stimulation is also directly linked to BK release (19, 23). Studies in genetically engineered mice lacking AT₂ have confirmed the concept that AT₂ mediates a BK-NO-cGMP vasodilator cascade (18).

Losartan 0.3 mg/kg decreased MAP significantly (-15%), probably by inhibiting systemic AT₁. GFR decreased (-25%) but RBF remained stable. The decrease in FF (-21%) indicates predominant efferent vasodilation and strongly suggests that AII acts via its AT₁ predominantly on the efferent arterioles. We can assume that AT₁ blockade by losartan blunted the AII vasoconstrictive response in our model. Similar results were found with the potent ACE inhibitor perindoprilat in the same model (24). Again, AT₁ inhibition with losartan may also have revealed the AT₂-mediated dilatatory potential of AII. Actions of the unopposed AT₂ may contribute as AT₁ antagonists do not affect AT₂ but even expose it to increased levels of AII. The latter is owing to the loss of the negative feedback exerted by AII via AT₁ on renin release, and hence on its own generation. It is thus conceivable that under blockade of AT₁, AII interactions with AT₂ are intensified (25).

The most potent effects were seen with losartan at 3 mg/kg. The systemic hypotensive effect was marked, MAP decreasing

Table 2. The effects of losartan on renal function variables in three groups of newborn rabbits

Group	Period	UV (mL/kg per min)	UVNa (mmol/kg per min)	GFR (mL/kg per min)	RBF (mL/kg per min)	FF (%)	RVR (mm Hg/mL per kg per min)
Losartan 0.1 mg/kg	C	0.062 ± 0.004	1.87 ± 0.56	1.63 ± 0.11	14.7 ± 0.9†	15.6 ± 0.7	1.96 ± 0.14
	E1	0.071 ± 0.008	1.70 ± 0.38	1.43 ± 0.15	13.7 ± 1.4	13.7 ± 0.7*	1.91 ± 0.20
	E2	0.075 ± 0.007	1.64 ± 0.32	1.42 ± 0.16	13.5 ± 1.2	14.2 ± 1.0	1.91 ± 0.15
Losartan 0.3 mg/kg	C	0.081 ± 0.003§	1.37 ± 0.38	1.96 ± 0.09	19.9 ± 1.1	14.6 ± 0.6	1.60 ± 0.09
	E1	0.074 ± 0.011	1.22 ± 0.21	1.50 ± 0.25	17.6 ± 2.2	11.6 ± 0.7**	1.71 ± 0.19
	E2	0.081 ± 0.008	1.31 ± 0.17	1.46 ± 0.15*	18.0 ± 1.0	11.5 ± 1.0**	1.47 ± 0.07
Losartan 3 mg/kg	C	0.061 ± 0.005	0.93 ± 0.20	1.83 ± 0.22	17.3 ± 1.4	14.8 ± 1.6	1.81 ± 0.16
	E1	0.033 ± 0.011*	0.51 ± 0.08	0.76 ± 0.25**	7.54 ± 2.7**	14.8 ± 1.3	4.66 ± 0.82*
	E2	0.043 ± 0.013	0.60 ± 0.11	0.98 ± 0.31**	10.7 ± 2.7**	11.4 ± 1.3*	3.38 ± 0.94

* $p < 0.05$ compared with C period of the same groups of animals.

** $p < 0.01$ compared with C period of the same groups of animals.

† $p < 0.05$ compared with C period of group losartan 0.3 mg/kg.

§ $p < 0.05$ compared with C period of both groups losartan 0.1 and 3 mg/kg.

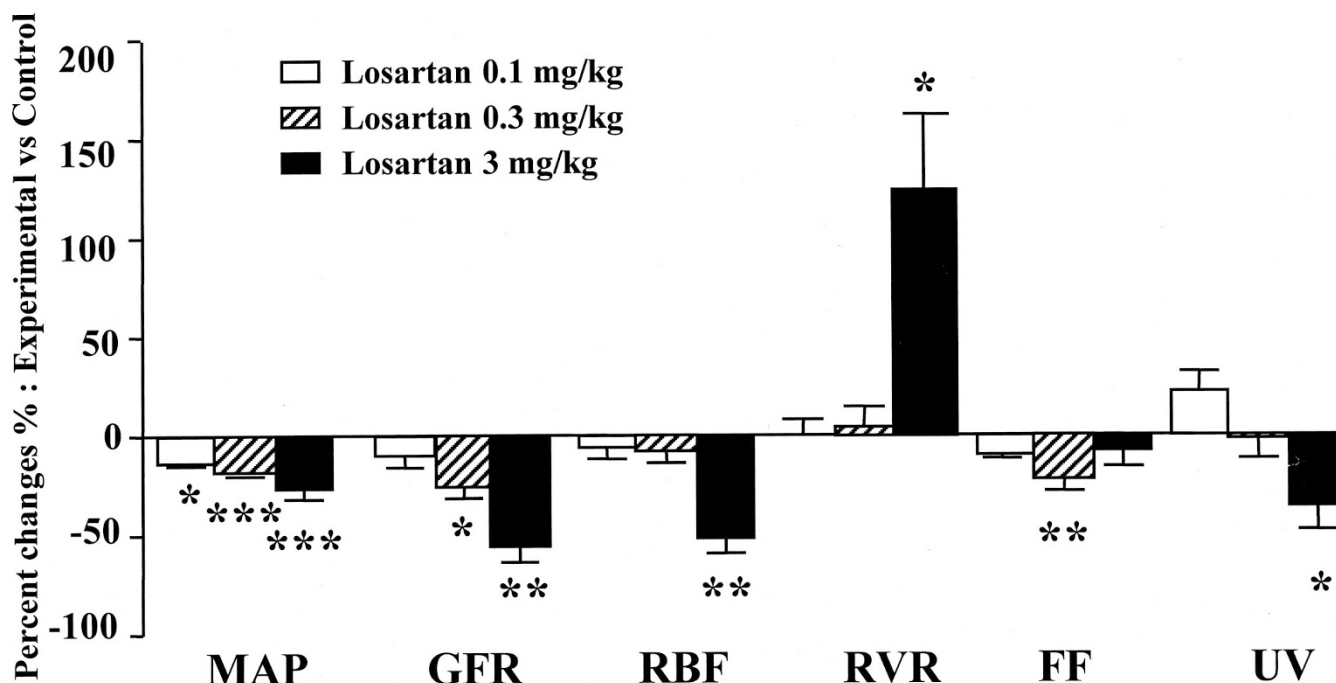


Figure 1. The percentage changes ($\Delta\%$) in UV, GFR, RBF, and RVR in three groups of newborn rabbits after the i.v. administration of 0.1 (open columns), 0.3 (striped columns), and 3 mg/kg (black columns) of losartan. The values presented are means \pm SEM of percentage changes for each group from the C period to the E1 and E2 periods (values averaged). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ when absolute values of E1 and E2 periods are compared with the values of the C period (absolute values presented in Tables 1 and 2).

by -28% as a result of losartan-induced systemic vasodilation. The renal response to this dose of losartan can thus be considered as a reflex vasoconstriction of both afferent and efferent arterioles rather than specific receptor antagonism (stable FF, increase in RVR by 124% , decrease in GFR and RBF by -57% and -51% , respectively).

In newborn infants and in particular in preterm babies, the EFP, the force that drives glomerular filtration, is far less than in adults (26). This situation predisposes the newborn to ARI when confronted with exogenous or endogenous stresses. However, in most cases ARI is prevented by a complex system of reinforcements aimed at minimizing changes in EFP. This is indeed what occurred in our experiments in newborn rabbits. When MAP fell because of the acute, high-dose i.v. administration of losartan, RVR rose with the consequent reduction in RBF and GFR. However, GFR was maintained at 50% of its normal level without signs of severe oliguric ARI as UV and UVNa fell only by -41% and -24% , respectively. Similar findings have been previously described in the neonatal rat (27). The regulatory mechanisms that minimize changes in GFR involve coordinated vasoconstriction or vasodilation of the afferent and efferent glomerular vasculature (7). One of the major mechanisms involved in the regulation of renal vascular tone, total and intrarenal distribution of RBF, and single nephron GFR appears to be the RAS. In our laboratory, Huet *et al.* (24) infused the ACE inhibitor perindoprilat into newborn rabbits. The renal hemodynamic reaction consisted of a fall in RVR and a rise in RBF without changes in GFR, except when MAP fell by approximately 20% and GFR followed with a -17% decrease. Basically the same was found by Robillard *et al.* (28), who used a continuous infusion of the ACE

inhibitor captopril in late fetal and newborn lambs. Captopril caused a fall in MAP and RVR whereas RBF remained unchanged; GFR and FF, however, decreased. The outstanding feature of these experiments was the near constancy or the relatively moderate decrease of GFR, despite major renal hemodynamic changes. The latter were probably offset by adjusted pre- and postglomerular dilation. In the present experiments, interference with the action of AII on its receptors by losartan induced a rather different response than with ACE inhibitors. One explanation could be that the divergent effects of perindoprilat and losartan are due to differences in the depression of circulating AII levels as well as in the plasma elimination of active AII. Although this may indeed occur, it seems far more likely that AT_1 blockade caused activation or suppression of different rescue mechanisms such as adenosine, BK (29), endothelin, NO, or sympathetic reflexes. Additional interactions are quite possible. However, in the newborn animal some of these mechanisms may differ, either because of the basic hyperactivity of the RAS and other vasoactive factors at a very young age, or because of developmental expressions of a variety of receptors. The abundant transient expression of AT_2 during fetal and postnatal life, compared with the limited expression of AT_2 in few organs in the adult, emphasizes the probable important role of this receptor type in fetal and early postnatal development (30).

Until further results with selective AT_2 antagonists, we can only conclude from our present, as well as previous, data that the neonatal rabbit kidney has the possibility to mobilize a large variety of vasoconstrictor and vasodilatory forces that are activated under conditions of stress such as hypotension, anoxia, and the administration of a variety of vasoactive drugs.

The present data reinforce the notion that the RAS is critically involved in the maintenance of GFR in the newborn period.

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