

Late Blood Pressure Reduction in SHR Subjected to Transient Captopril Treatment in Youth: Possible Mechanisms

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Summary

Spontaneously hypertensive rats (SHR) are characterized by enhanced nifedipine-sensitive component of sympathetic vasoconstriction. Our study tried to elucidate the mechanisms responsible for long-term reduction of blood pressure (BP) in SHR subjected to early transient captopril treatment. Adult untreated SHR aged 30-34 weeks were compared with animals subjected to chronic captopril treatment for 6 weeks either in youth (between 4 and 10 weeks of age) or in adulthood (between 24 and 30 weeks of age). Antihypertensive effects of captopril were more pronounced in young than adult SHR. This was due to greater attenuation of sympathetic and nifedipine-sensitive BP components and prevention of residual BP rise in young captopril-treated SHR in which the reductions of nifedipine-sensitive BP component and residual BP persisted for 20 weeks after captopril withdrawal. The magnitude of nifedipine-sensitive component of sympathetic vasoconstriction is decisive for BP maintenance not only in untreated SHR but also in SHR during active captopril treatment by or after its withdrawal.

Key words

Genetic hypertension • Late effects of early treatment • Captopril • Nifedipine

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Spontaneously hypertensive rats (SHR) are characterized by sympathetic hyperactivity (Head 1989, De Champlain 1990) that is associated with enhanced contribution of nifedipine-sensitive vasoconstriction to BP maintenance (Paulis *et al.* 2007). It seems that this alteration is caused by increased stimulation of alpha-

adrenergic receptors because norepinephrine (NE) activates L-type voltage-dependent Ca^{2+} channels (VDCC) in vascular smooth muscle (Nelson *et al.* 1988).

The mechanisms of BP reduction induced by chronic blockade of renin-angiotensin system also involve a considerable reduction of sympathetic vasoconstriction (Berecek *et al.* 1987, Hojná *et al.* 2007, Paulis *et al.* 2007). Our earlier studies on salt hypertension (Zicha *et al.* 2001, Dobešová *et al.* 2002) revealed that sympathetic hyperactivity was more pronounced in salt-sensitive Dahl rats, which were exposed to high salt intake since weaning, than in those influenced by the same hypertensive stimulus only in adulthood. It is well known that the antihypertensive treatment is generally more efficient if applied in young prehypertensive rats (prevention of hypertension development) than in animals with established hypertension (therapy of hypertension) (for review see Zicha and Kuneš 1999). Moreover, antihypertensive treatment of young but not adult SHR with angiotensin-converting enzyme (ACE) inhibitors or AT_1 receptor blockers usually causes profound BP reduction which partially persists for a long time after drug withdrawal (Harrap *et al.* 1990, Adams *et al.* 1990, Morton *et al.* 1992), but the mechanisms responsible for this long-term BP reduction are not completely understood yet.

Our study was aimed to reveal possible mechanisms of long-term BP reduction persisting after the withdrawal of captopril treatment in young SHR and to determine the contribution of changes in sympathetic and nifedipine-sensitive BP components induced by early or late transient captopril treatment.

Table 1. Blood pressure and its particular components in untreated SHR (aged 30-34 weeks) and age-matched SHR treated for 6 weeks with captopril (100 mg/kg b.w./day) in youth or adulthood.

Captopril treatment At the age of Drug withdrawal for	Untreated – (n = 8)	Young group 6 weeks 4-10 weeks 20 weeks (n = 6)	Adult group 6 weeks 24-30 weeks 4 weeks (n = 6)
Mean arterial pressure (mm Hg)	203±5	167±4**	184±4* [#]
Δ MAP _{captopril} (mm Hg)	–21±6	–4±2*	–6±2
Δ MAP _{pentolinium} (mm Hg)	–89±4	–78±4	–92±3 [#]
Δ MAP _{L-NAME} (mm Hg)	96±6	99±6	80±7
Vasodilator deficit (mm Hg)	–19±5	–23±4	–21±3
Residual MAP (mm Hg)	79±3	66±2**	64±2**
Δ MAP _{nifedipine} (mm Hg) [§]	–82±4	–58±5 **	–68±7

Data are means ± SEM. [§] - additional group of animals with similar basal mean arterial pressure. Significantly different: *, ** from untreated SHR (p<0.05, p<0.01); [#] from young SHR (p<0.05).

The experiments were carried out in 40 male SHR aged 30-34 weeks. Half of the rats were subjected to consecutive blockade of vasoactive systems, whereas remaining animals were used for acute VDCC blockade by nifedipine. We compared untreated SHR with SHR treated with captopril (100 mg/kg/day) for 6 weeks starting at the age of either 4 weeks (young group) or 24 weeks (adult group). Thus SHR treated with captopril in youth (4th – 10th week of age) were examined 20 weeks after drug withdrawal, whereas those treated in adulthood were studied 4 weeks after drug withdrawal.

SHR from our own colony were housed under standard conditions (temperature 23±1 °C, 12-h light-dark cycle, pelleted ST-1 diet with 1 % NaCl) and drank tap water *ad libitum*. The experimental protocol, which was approved by the *Ethical Committee of the Institute of Physiology AS CR*, conformed to *European Convention on Animal Protection*.

One day before BP determination, polyethylene catheters were inserted into the left carotid artery and jugular vein and exteriorized in the interscapular region. BP was recorded in conscious rats after 24-h recovery using PowerLab system (ADInstruments Ltd, Bella Vista, NSW, Australia). To eliminate the influence of circadian BP variation, the measurements were always done between 08:00 and 12:00 h a.m. Baseline values of systolic, diastolic and mean arterial blood pressures were monitored in conscious animals for 30 min. Thereafter a consecutive blockade of renin-angiotensin system (RAS), sympathetic nervous system (SNS) and NO-synthase (NOS) was

performed as described previously (Zicha *et al.* 2001, Hojná *et al.* 2007). Firstly, intravenous bolus of captopril (10 mg/kg b.w.) was injected to block ACE. Ten minutes later, ganglionic blockade was induced by pentolinium (Sigma, St. Louis, USA, 5 mg/kg b.w.), which caused rapid BP fall. After the temporary BP stabilization for about 5 min, NOS inhibitor L-NAME (30 mg/kg b.w.) was given and BP restoration was monitored for next 20 min. At the end of the experiment sodium nitroprusside (SNP, 20 µg/kg b.w.) was injected to determine minimal (residual) BP, which reflects structural changes of resistance vessels. The magnitude of vasodilator deficit was estimated from a comparison of BP level reached after SNP injection with that found after pentolinium administration. All drugs (Sigma, St. Louis, USA) were given as an intravenous bolus in a volume of 1 ml/kg b.w.

BP response to acute VDCC blockade by nifedipine was determined in separate subgroups of untreated and captopril-treated SHR. After monitoring baseline BP for 30 min, increasing doses of nifedipine (Sigma, St. Louis, USA, 0.05, 0.1, 0.2 and 0.4 mg/kg b.w., dissolved in 50 % ethanol, i.v. bolus 0.2 ml/kg b.w.) were injected in 10-min intervals. Relatively sharp BP decrease occurring after nifedipine administration was followed by BP stabilization, which was maintained for next 10 min. Stabilized BP values were used for the calculation of nifedipine-induced BP reduction. Results were expressed as means ± SEM. The data were evaluated by means of one-way analysis of variance with LSD *post-hoc* test. P<0.05 value was taken as significant.

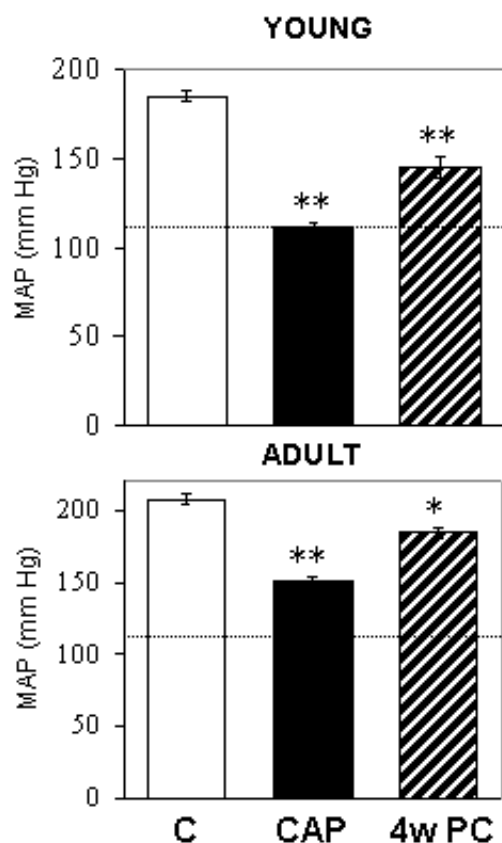


Fig. 1. Mean arterial pressure (MAP) in young SHR (aged 10-14 weeks; Paulis *et al.* 2007) and adult SHR (aged 30-34 weeks; Hojná *et al.* 2007) – untreated rats (C, open bars), rats treated with captopril for 6 weeks (CAP, full bars) and rats studied 4 weeks after drug withdrawal (4w PC, hatched bars). Dotted line indicates MAP level in normotensive WKY rats.

Early captopril treatment prevented the development of spontaneous hypertension in SHR, maintaining their BP at the level of normotensive Wistar-Kyoto (WKY) rats. Withdrawal of captopril treatment for 4 weeks was accompanied by a moderate increase of blood pressure (Fig. 1), but significant BP lowering persisted at least 20 weeks after treatment withdrawal (Table 1). On the other hand, the same antihypertensive treatment of adult SHR with established hypertension decreased their BP only moderately and BP rose rapidly during 4 weeks after captopril withdrawal (Fig. 1).

Early transient captopril treatment (from the 4th to the 10th week of age) induced considerable changes in the development of hypertension that can be disclosed even after 20 weeks of drug withdrawal (Table 1). BP was decreased by 20 % compared to untreated 30-week-old SHR due to borderline reductions in angiotensin II-dependent and sympathetic BP components. There was a considerable attenuation (30 %) of nifedipine-sensitive BP

fall in captopril-treated group. Both groups did not differ in NO-dependent vasodilation or vasodilator deficit. Residual BP was decreased by 16 % following early transient captopril treatment (Table 1). We can thus compare SHR subjected to transient captopril treatment in youth (studied after 20 weeks of drug withdrawal) with animals subjected to the same treatment in adulthood (studied after 4 weeks of drug withdrawal). It is evident that BP in the adult group (after a short-term drug withdrawal) was less attenuated than BP of the young group after a long-term drug withdrawal. Sympathetic vasoconstriction tended to be greater in the adult than in the young group. In addition, nifedipine-sensitive BP component was not significantly reduced in the adult group in contrast to its major reduction in the young group. Surprisingly, residual BP was lowered to the same extent in young and adult groups (Table 1).

The most important finding of our study concerns the hemodynamic changes responsible for long-term (20-week lasting) BP lowering after the withdrawal of captopril treatment of young SHR. We have observed that BP of 30-week-old SHR, which were subjected to a transient captopril treatment at the age of 4-10 weeks, was reduced by 20 % compared to untreated age-matched SHR. This BP decrease reflects a major reduction of nifedipine-sensitive BP component and a moderate lowering of residual BP. These two changes seem to represent the alterations induced by early captopril treatment, which persisted for a long time after drug withdrawal. As we already mentioned (Paulis *et al.* 2007), early captopril treatment of young SHR abolished the rise of residual BP, which is reflecting structural remodeling and/or basal tone of resistance vasculature. After drug withdrawal the value of residual BP did not surpass its level in age-matched control WKY rats. On the contrary, residual BP values decreased by chronic captopril treatment of adult SHR were still considerably elevated as compared to values found in age-matched WKY rats (Hojná *et al.* 2007). The same was also true for residual BP values found in adult SHR after captopril withdrawal, which was not accompanied by any significant changes of residual BP compared to active treatment period.

Long-term attenuation of BP after transient RAS inhibition in young SHR is in a good agreement with earlier studies (Harrap *et al.* 1990, Kost *et al.* 1995, Baumann *et al.* 2007) which also indicated significant improvement of structural remodeling of cardiovascular apparatus (Christensen *et al.* 1989, Adams *et al.* 1990, Morton *et al.* 1992) and attenuation of end-organ damage (Bergström *et al.* 2002). However, this study represents a

rare attempt to evaluate the mechanisms of this BP reduction on the basis of altered contribution of particular vasoactive systems and/or changes in residual BP (reflecting the remodeling of resistance vessels).

In conclusions, the magnitude of nifedipine-sensitive component of sympathetic vasoconstriction is decisive for BP level in SHR, including rats subjected to active antihypertensive treatment or its withdrawal.

Conflict of Interest

There is no conflict of interest.

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