The Role of Renal Dopamine in the Reduction of High Blood Pressure by $\beta_1$-Selective $\beta$-Blocker with Intrinsic Sympathomimetic Activity in Spontaneously Hypertensive Rats

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The present experiments were undertaken to clarify the difference of renal dopamine production from $\beta_1$-selective $\beta$-blocker with and without intrinsic sympathomimetic activity (ISA). Either $\beta$-blocker with ISA, celiprolol (100 or 300 mg/kg/day; CEL-100 or CEL-300) or $\beta$-blocker without ISA, atenolol (50 mg/kg/day; ATE-50) was administered to the SHR from 19 to 26 weeks. Degrees of lowering blood pressure in CEL-300 SHR and in ATE-50 SHR were similar, but decrease in heart rate was significantly less in CEL-300 SHR than in ATE-50 SHR. Urine output, which was significantly less in control SHR than in control WKY, was significantly greater in CEL-100 SHR and CEL-300 SHR, but not in ATE-50 SHR. Urinary excretions of noradrenaline (u-NA) and dopamine (u-DA) were significantly higher in control SHR than in control WKY and a comparable u-DA/u-NA ratio was found in these two groups. U-DA and the ratio of u-DA/u-NA were significantly elevated in CEL-100 SHR and CEL-300 SHR, but not in ATE-50 SHR. There was a significant positive correlation between u-DA/u-NA ratio and urine output and a significant negative correlation between the ratio of u-DA/u-NA and change of blood pressure in control SHR, CEL-100 SHR and CEL-300 SHR. These results suggest that an enhancement of renal dopamine production by ISA ($\beta_2$ stimulation) of $\beta_1$-selective $\beta$-blocker may contribute, at least in part, to the antihypertensive effect of this drug. (Hypertens Res 1995; 18 Suppl. I: S215–S219)

Key Words: $\beta$-Blocker, Intrinsic Sympathomimetic Activity, Renal Dopamine, Spontaneously Hypertensive Rats

$\beta$-blockers have been recommended as first-step treatment in patients with hypertension (1). Some newer agents appear to have differential agonist effects on $\beta_1$- or $\beta_2$-receptors. Vasodilating $\beta_1$-selective $\beta$-blocker with intrinsic sympathomimetic activity (ISA) exhibits blocking properties at the $\beta_1$-receptors that mediate the antihypertensive and anti-anginal actions of $\beta$-blockers and agonist effects at $\beta_2$-receptors (2). When stimulated, $\beta_2$-subtype receptors, found in the arterial circulation, mediate vasodilation. The stimulatory action of $\beta_1$-selective $\beta$-blocker with ISA on vascular $\beta_2$-receptors reduces renal vascular resistance associated with preservation of renal blood flow and function (3).

Dopamine has been suggested as playing a role in the regulation of renal water and electrolyte excretion and has a potent vasodilative and natriuretic action in the kidney (4). Abnormal renal sodium handling has been known to be one of the major factors involved in the initiation and maintenance of high blood pressure in several models of hypertension, including genetic hypertension (5, 6). Endogenous kidney dopamine plays an important role in regulation of renal sodium excretion, so it has been proposed that impaired renal sodium handling in spontaneously hypertensive rats (SHR) may partly be due to a malfunction or a defect in the renal dopaminergic system (7, 8).

The interrelationship between the antihypertensive effect of vasodilating $\beta$-blocker with ISA and its effect on the production of renal dopamine is not well known. Therefore, the present experiments were undertaken to clarify the role of renal dopamine production in the mechanism of antihypertensive effects in $\beta_1$-selective $\beta$-blocker with ISA. The effects of $\beta_1$-selective $\beta$-blocker with ISA on high blood pressure and renal dopamine production were examined compared with those of $\beta_1$-selective $\beta$-blocker without ISA in SHR.

Methods

Animals
Male normotensive Wistar-Kyoto rat (WKY / NCrj, Charles River Japan Inc.) and SHR (NCrj, Charles River Japan Inc.) aged 19 weeks were divided into control WKY, control SHR, $\beta_1$-selective $\beta$-blocker with ISA, celiprolol-treated SHR (100 or 300 mg/kg/day) and $\beta_1$-selective $\beta$-blocker without ISA, atenolol-treated SHR (50 mg/kg/day). Either celiprolol or atenolol was administered through a gastric tube to the SHR from 19 to 26 weeks of age. Tap

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water was given to control WKY and control SHR. All rats were housed under the same conditions and were fed rat chow (Nihon Clea, CE-2).

**Experimental Design**

Systolic blood pressure and heart rate were measured in the conscious state at 19 weeks and 26 weeks of age by the tail plethysmography (Narco, PE-300) after 20 min of prewarming at 37°C.

The 26 week-old rats were housed in individual metabolic cages and a 24 h urine collection was made in flasks containing 1 ml of 6 N-HCl for determination of catecholamines contents and creatinine content after a 24 h period of acclimatization.

Urinary noreadrenaline (NA) and dopamine (DA) contents were determined using high performance liquid chromatography with electrochemical detection (9, 10). Urinary creatinine content was measured enzymatically.

Urinary excretions of NA (u-NA) and DA (u-DA) were calculated as the product of urinary concentration and urinary output divided by g creatinine (µg/g creatinine).

**Statistics**

All values are expressed as the mean ± SE. Analysis of variance was used for multiple group comparisons, using either Student’s t test or the Dunnett multiple range test, as appropriate. Statistical significance was defined as p<0.05.

**Results**

**Effects of Celiprolol and Atenolol on Body Weight, Systolic Blood Pressure and Heart Rate**

In 19 week-old WKY and SHR, body weights of all SHR groups were significantly lower than those of WKY, and systolic blood pressure and heart rate of all SHR groups were significantly higher than those of WKY (Table 1).

In 26 week-old rats, body weights of all SHR groups were significantly lower than those in control WKY. Both systolic blood pressure and heart rate in control SHR were significantly higher than in control WKY. Treatment with either celiprolol (100 or 300 mg/kg/day) or atenolol (50 mg/kg/day) for 7 weeks significantly decreased systolic blood pressure and heart rate in SHR. The degrees of fall in blood pressure in celiprolol-treated SHR (300 mg/kg/day) and atenolol-treated SHR were similar, but decrease in heart rate was significantly less in celiprolol-treated SHR (300 mg/kg/day) than in atenolol-treated SHR.

**Effects of Celiprolol and Atenolol on Urine Output, u-NA and u-DA**

Urine output was significantly less in control SHR than in control WKY (Table 2). Treatment with celiprolol (100 or 300 mg/kg/day) significantly increased urine output in SHR, but treatment with atenolol did not.

U-NA and u-DA were significantly higher in control SHR than in control WKY and a comparable u-DA/u-NA ratio was found in the two groups (Table 2 and Fig. 1). Treatment with either celiprolol (100 or 300 mg/kg/day) or atenolol significantly increased u-NA to the same degree. Treatment with celiprolol (100 or 300 mg/kg/day) significantly increased u-DA and u-DA/u-NA ratio in SHR in a dose-dependent manner, but treatment with atenolol did not.

**Relationship between Urine Output, Change of Blood Pressure and u-DA/u-NA Ratio in Control SHR and Celiprolol-Treated (100 or 300 mg/kg/day) SHR**

Change of systolic blood pressure in each rat was calculated using systolic blood pressure measured at 19 weeks and 26 weeks of age in control SHR and celiprolol-treated (100 or 300 mg/kg/day) SHR. There was a significant positive correlation between u-DA/u-NA ratio and urine output (Fig. 2) and a significant negative correlation between u-DA/u-NA ratio and change of blood pressure (Fig. 3) in control SHR and celiprolol-treated (100 or 300 mg/kg/day) SHR.

**Discussion**

In patients and rats with hypertension, either higher or lower levels of DA concentration in plasma or

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**Table 1. Effects of Celiprolol and Atenolol on Body Weight, Systolic Blood Pressure and Heart Rate**

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>Control (n=8)</th>
<th>CEL-100 (n=7)</th>
<th>CEL-300 (n=6)</th>
<th>ATE-50 (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>19 weeks: 373±3</td>
<td>331±6*</td>
<td>323±5*</td>
<td>319±3*</td>
<td>349±4*</td>
</tr>
<tr>
<td></td>
<td>26 weeks: 415±3</td>
<td>354±5*</td>
<td>364±6*</td>
<td>378±6*</td>
<td>368±3*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>19 weeks: 125±3</td>
<td>192±4*</td>
<td>195±3*</td>
<td>191±5*</td>
<td>197±4*</td>
</tr>
<tr>
<td></td>
<td>26 weeks: 118±2</td>
<td>197±3*</td>
<td>174±2**</td>
<td>160±4**</td>
<td>159±2**</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>19 weeks: 333±8</td>
<td>383±11*</td>
<td>383±11*</td>
<td>398±16*</td>
<td>396±11*</td>
</tr>
<tr>
<td></td>
<td>26 weeks: 335±5</td>
<td>404±11*</td>
<td>346±11*</td>
<td>331±7*</td>
<td>300±6**†</td>
</tr>
</tbody>
</table>

CEL-100 SHR; celiprolol-treated (100 mg/kg/day) SHR, CEL-300 SHR; celiprolol-treated (300 mg/kg/day) SHR, ATE-50 SHR; atenolol-treated (50 mg/kg/day) SHR, *p<0.05 vs. control WKY, **p<0.05 vs. control SHR, †p<0.05 vs. CEL-300 SHR.
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urine than in normotensive subjects have been reported in the literature (11\textendash{}13). These conflicting data may be caused by the DA levels in plasma or urine at the different stages of hypertension and / or the different subtypes of hypertension.

So far as the subtypes of essential hypertension are concerned, decreased dopaminergic activity in adrenal cortex and kidney has been reported in both patients with low-renin hypertension and in salt-sensitive patients. It has been suggested that the decreased dopaminergic activity may be involved in the pathogenesis of hypertension (14\textendash{}18). These patients are believed to have volume-dependent hypertension (16, 17), accompanied by a high plasma aldosterone level in proportion to a low plasma renin activity (14) and decreased urinary excretion of DA in response to salt loading (15) and to progression of overweight (18). As these patients may show decreased DA release into plasma or urine as compared with patients with normo- and high-renin hypertension or nonsalt-sensitive or nonobese patients (14\textendash{}18), the experiments from heterogenous groups of essential hypertension may yield different results.

In SHRs, urinary free DA excretion and tissue DA content were higher in the developing stage of hypertension as compared to those in normotensive animals, but these increases in the DA level or concentration were absent in the established stage of hypertension (12, 19). In the present study, urine output in control SHR was significantly less than in control WKY, and u-NA and u-DA in control SHR were significantly higher than in control WKY although a comparable u-DA/u-NA ratio was found in these two groups. These results indicate that SHR shows the enhancement of renal sympathetic activity, which is suggested by an increased urinary excretion of NA, while the increased urinary DA excretion is regarded as a compensatory mechanism to decrease blood pressure and increase sodium excretion. These data, including the present study, strongly suggest that DA plays an important role in the regulation of blood pressure by affecting depressor action against the enhancement on renal sympathetic nerve activity and sodium retenion.

The effects of \textbeta\textendash{}blockers on renal function vary (20). The tendency of most \textbeta\textendash{}blockers to produce constrictor effects in the arterial circulation could potentially impair renal blood flow; in contrast, inhibitory effects of these agents on intrarenal renin-angiotensin mechanisms may have a compensatory dilatory effect. Most clinical studies have reported little or no change in renal function during short-term \textbeta\textendash{}blocker therapy. Of all the \textbeta\textendash{}blockers, only nonselective \textbeta\textendash{}blocker, nadolol, maintains the renal blood flow while concomitantly diminishing cardiac output (21), but its effects on renal function have not been discussed.

A recent report describing the effects of celiprolol on renal function showed that the hemodynamic effects within the kidney were similar to those it produces in the systemic circulation (22). In patients with hypertension, celiprolol significantly decreases mean arterial pressure and decreases renal vascular resistance. Thus, despite the marked decrease in blood pressure, renal plasma flow remained within the normal range. Plasma renin activity fell significantly during the 1-month period of celiprolol treatment. However, it is not possible to determine whether the reduced renal vascular resistance in these patients resulted from the direct effects of celiprolol on vascular \textbeta_2\textendash{}receptors or whether the suppression of renin played a role in mediating this...
The interrelationship between the antihypertensive effect of vasodilating β-blocker with ISA and its effect on the production of renal dopamine is not well known.

In the present experiments, β₁-selective β-blocker with ISA, celiprolol or β₁-selective β-blocker without ISA, atenolol was administered to SHR for 7 weeks. Degrees of lowering systolic blood pressure in celiprolol-treated SHR and in atenolol-treated SHR were similar, but decrease in heart rate was significantly less in celiprolol-treated SHR than in atenolol-treated SHR. Urine output, u-DA and the ratio of u-DA/u-NA were significantly elevated in celiprolol-treated SHR, but not in atenolol-treated SHR. These results suggest that an enhancement of renal dopamine formation may play, at least in part, an important role in the antihypertensive effect of β₁-selective β-blocker with ISA, celiprolol. The possible mechanisms of an increase in urinary dopamine excretion induced by β₁-selective β-blocker with ISA are as: 1) an increase in delivery of L-dopa, precursor of dopamine, to renal proximal tubules due to ISA-induced renal vasodilation, and 2) ISA-induced acceleration of renal dopaminergic neural activity. However, the precise mechanism of ISA-induced enhancement of renal DA production has yet to be clarified. It largely depends upon future multilateral studies involving the interrelationships of dopaminergic system, nitric oxide system, kallikrein-kinin system, prostaglandins and other systems in the kidney.

In summary, increased renal dopamine excretion in control SHR may not be involved in the hypertensive mechanism in SHR, but ISA (β₂ stimulation) of β₁-selective β-blocker induces an enhancement of renal dopamine production and its effect may contribute, at least in part, to the anti-hypertensive effect of this drug.

References


