PRESYNAPTIC α_2 -ADRENOCEPTOR MEDIATED REGULATION OF NOREPINEPHRINE RELEASE IN PERFUSED MESENTERIC VASCULATURES IN YOUNG AND ADULT SPONTANEOUSLY HYPERTENSIVE RATS

KAZUSHI TSUDA, M.D., MASATO KUCHII, M.D., ICHIRO NISHIO, M.D.
AND YOSHIAKI MASUYAMA, M.D.

The present study was designed to evaluate the role of the presynaptic α_2 -adrenoceptor in the pathogenesis of hypertension. Norepinephrine overflow during sympathetic nerve stimulation and its changes by presynaptic α_2 -adrenoceptor inhibition were examined in the perfused mesenteric vasculatures of young and adult spontaneously hypertensive rats (SHR) compared with age-matched Wistar Kyoto rats (WKY).

Electrical sympathetic nerve stimulation caused significantly greater overflow of endogenous norepinephrine from the adrenergic nerve terminals in young SHR than in age-matched WKY. Yohimbine, an α_2 -adrenoceptor blocking agent, facilitated norepinephrine overflow from the adrenergic nerve terminals. The effects of yohimbine on norepinephrine overflow and pressor responses to electrical nerve stimulation were less in young SHR than in age-matched WKY.

Norepinephrine overflow in adult SHR was similar to that in adult WKY, and differences in the effect of yohimbine on norepinephrine overflow between SHR and WKY were not marked at this chronic stage.

These results suggest that enhanced norepinephrine overflow in the mesenteric vasculatures can be observed only in young SHR; this may be due in part to an impaired negative feed-back mechanism on the nerve terminals by presynaptic α_2 -adrenoceptors.

THE role of the sympathetic nervous system in the regulation of blood pressure is well recognized. It has been reported that plasma norepinephrine concentration is higher in hypertension, especially at its early stage, than in normotensive controls¹. However, the mechanisms for an exaggerated sympathetic tone in

hypertension have not been fully elucidated. On the other hand, there is much evidence that neurotransmitter release from the sympathetic nerve endings can be modulated by several mechanisms, of which the autoregulatory system of presynaptic adrenoceptors seems the most important². Recent studies have shown that presynaptic α_2 -adrenoceptors have inhibitory effects on norepinephrine release from nerve terminals^{2,3}. This is one of the negative feed-back mechanisms in norepinephrine release. If the presynaptic α_2 -adrenoceptor mediated inhibition of norepinephrine release is attenuated

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Division of Cardiology, Department of Medicine, Wakayama Medical College, Wakayama, Japan

Mailing address: Kazushi Tsuda, M.D., Division of Cardiology, Department of Medicine, Wakayama Medical College, 1, 7-Bancho, Wakayama 640, Japan

in hypertension, it may contribute to the increase in peripheral sympathetic nerve activity.

Galloway and Westfall³ demonstrated that there was less enhancement of norepinephrine overflow by the α_2 -adrenoceptor blocking agent yohimbine in adult SHR, but not in young SHR in comparison with age-matched WKY by use of coccygeal arteries. Ekas et al⁴ reported that tramazoline (an α_2 -agonist) caused dose-dependent inhibition of stimulus-induced norepinephrine release in the perfused kidney of 18-week-old SHR, suggesting the supersensitivity of presynaptic α_2 -adrenoceptors. However, some reports indicate that no differences have been found in the relative presynaptic α_2 -adrenoceptor sensitivity between SHR and WKY.⁵ Thus, details of the inhibitory mechanism of presynaptic α_2 -adrenoceptors or their effect on hypertension are controversial.

The present study was designed to measure norepinephrine release and to evaluate the inhibitory activities of presynaptic α_2 -adrenoceptors in the mesenteric vasculatures of young and adult SHR compared with age-matched WKY.

MATERIALS AND METHODS

Male Wistar rats (body weight 220–300g) were used in this study. Male spontaneously hypertensive rats (SHR, Okamoto & Aoki) were examined at the ages of 7–8 weeks (young) and 20–22 weeks (adult) in comparison with age-matched Wistar Kyoto rats (WKY). Systolic blood pressures, measured by the tail-cuff method, were 170.6 ± 4.0 mmHg ($n = 9$) in young SHR and 121.6 ± 3.4 mmHg ($n = 8$) in young WKY ($p < 0.005$). In adult rats, blood pressures were 208.0 ± 3.7 mmHg ($n = 8$) in SHR and 138.5 ± 4.1 mmHg ($n = 8$) in WKY ($p < 0.005$).

Animals were anesthetized with pentobarbital (40 mg/kg, intraperitoneal injection) and mesenteric intestinal loop preparations were prepared by the method of Castellucci et al.⁶ Four main branches of the mesenteric artery and their dominating intestine were used for the experiment. The preparation was perfused with modified Ringer-Locke solution (mmol/L: NaCl 120.7, KCl 5.9, CaCl₂ 2.5, MgCl₂ 1.3, NaHCO₃ 15.5, NaH₂PO₄ 1.2 and glucose 11.5, pH 7.4, 37°C). The solution was bubbled with a 95% O₂, 5% CO₂ mixture and maintained at a constant flow rate of 0.8 ml/min by a peristaltic pump (Harvard apparatus Model 1200). Perfusion

pressure was recorded via a side arm with a pressure transducer connected to a polygraph (Nihon Kohden Model CP-620G). Platinum electrodes were placed around the periarterial plexus at the proximal end of the mesenteric artery. After the preparation was set up, a 30-min equilibration period was allowed before the following experiment. The intramural sympathetic nerves of the artery were stimulated at supramaximal voltage (40 V) for 1 min with biphasic rectangular pulses of 5 msec duration at 10 and 15 Hz, using an electrical stimulator (Nihon Kohden Model SEN-3201).

Exogenous l-norepinephrine (3.3 μ g) was given as a bolus injection (in 0.1 ml of the buffer) into the preparation through the arterial cannula. Pressor responses to electrical nerve stimulation and exogenous norepinephrine were determined as an increase in the perfusion pressure.

For the measurement of norepinephrine overflow from the sympathetic nerve terminals in the vascular beds, the perfusate through the mesenteric preparation was collected into tubes containing a mixture of EGTA (90 mg/ml) and glutathione (60 mg/ml), in the ratio of 20 μ l/ml of the perfusate, for 3 min before and after electrical nerve stimulation. The latter collection period consisted of a 1 min secretory period and a following 2 min period. Norepinephrine in the perfusate was absorbed on alumina and extracted in 200 μ l of 0.1 mol/l perchloric acid (recovery through alumina approximately 80%). It was then assayed by high pressure liquid chromatography (HPLC) with an electrochemical detector (Bioanalytical System, Model LC-4A, carbon electrode, 700 mV). The HPLC unit was equipped with a delivery system (Waters Assoc. Model 510, flow rate 1.0 ml/min), an automatic injector (Waters Assoc. Model 710B, injected volume 100 μ l) and 5 μ m column (Biophase ODS). The solvent for the separation of norepinephrine was 0.1 mol/l of monochloric acid with 2 mmol/l of EDTA, 300 mg/l of sodium octyl sulfate and 9% (v/v) of acetonitrile. Norepinephrine overflow induced by electrical nerve stimulation was defined as the differences between the norepinephrine contents of the pre- and post-stimulatory periods, and was then calculated per wet tissue weight of each preparation.

The experiment was performed first in male normotensive Wistar rats (body weight 220–300g) to evaluate the pressor responses as well as the endogenous norepinephrine overflow

Fig.1. Effects of yohimbine (an α_2 -adrenoceptor blocker) on the pressor responses to electrical nerve stimulation (10, 15 Hz), and to exogenous norepinephrine (3.3 μ g) in the mesenteric vasculatures of normotensive Wistar rats (body weight 220–300g). The responses are represented as the increases in perfusion pressure. When the concentration of yohimbine was changed, a 10-min-equilibration time elapsed before the next stimulation.

during electrical nerve stimulation in the presence of yohimbine, an α_2 -adrenoceptor blocker. The effects of yohimbine on the vasoconstrictor responses to exogenous norepinephrine were also investigated.

In the second series of experiments, the pressor responses and norepinephrine overflow during electrical nerve stimulation were measured in young (7–8 weeks) and adult (20–22 weeks) SHR in comparison with age-matched WKY. The effects of yohimbine on these responses also were determined in SHR and WKY at both ages.

Some experiments were performed with an uptake-blocker of norepinephrine, desipramine (4.1×10^{-8} M), in the medium.

Drugs were perfused 10 min prior to electrical nerve stimulation or exogenous norepinephrine application. For each preparation, the result was evaluated by comparing the response before (control) and during infusion of the drugs (experimental), and then expressed as percentage ratios of the control response for each experiment. A value greater than 100% indicated an enhanced response and one less than 100% represented an inhibitory response.

Values were represented as mean $\pm$ SEM. Statistical significance was determined by Student's t-test and analysis of variance. Differences

of $p < 0.05$ were considered to be significant.

L-norepinephrine and yohimbine were obtained from Sigma Chemical Co., Ltd. Desipramine was kindly donated by Ciba Geigy Co., Ltd.

RESULTS

1) Fundamental studies in normotensive Wistar rats

In normotensive Wistar rats (body weight 220–300g), the initial perfusion pressure was 21.5 ± 0.8 mmHg ($n = 12$) and the basal norepinephrine content in the perfusate during the unstimulated period (3 min) was 0.08 ± 0.01 ng/g of wet tissue weight ($n = 12$). The increase in norepinephrine overflow by electrical nerve stimulation was 0.69 ± 0.10 ng/g at 10 Hz stimulation and 1.07 ± 0.08 ng/g at 15 Hz stimulation ($n = 12$).

The pressor responses and norepinephrine overflow by electrical nerve stimulation were completely blocked by adding guanethidine (2.0×10^{-6} M) into the perfusion medium. These observations provided evidences that periarterial stimulation, but not direct stimulation of the vascular smooth muscles, is mainly neuronal in nature. In preliminary studies, it has been established that pressor responses and norepi-

TABLE I NOREPINEPHRINE OVERFLOW DURING ELECTRICAL NERVE STIMULATION (10, 15 Hz) FROM THE SYMPATHETIC NERVE ENDINGS IN MESENTERIC VASCULATURES OF SHR AND AGE-MATCHED WKY. VALUES ARE EXPRESSED AS THE DIFFERENCE IN NOREPINEPHRINE CONTENT IN THE PERFUSATES BEFORE AND AFTER ELECTRICAL NERVE STIMULATION, AND CALCULATED AS ng/g OF WET TISSUE WEIGHT IN EACH PREPARATION

	10 Hz	15 Hz
Young SHR	1.23 ± 0.14 ng/g** (n = 8)	2.20 ± 0.22 ng/g* (n = 8)
Young WKY	0.44 ± 0.07 ng/g (n = 8)	1.19 ± 0.21 ng/g (n = 8)
Adult SHR	0.86 ± 0.11 ng/g (n = 8)	0.97 ± 0.06 ng/g (n = 8)
Adult WKY	1.13 ± 0.13 ng/g (n = 8)	1.21 ± 0.14 ng/g (n = 8)

mean ± SEM, **p* < 0.02, ***p* < 0.005, Significant differences between SHR and WKY.

TABLE II PRESSOR RESPONSES TO ELECTRICAL NERVE STIMULATION (10, 15 Hz, 40 V, 1 min, 5 msec DURATION, RECTANGULAR PULSES) IN MESENTERIC PREPARATIONS FROM SHR AND AGE-MATCHED WKY. VALUES ARE REPRESENTED AS THE INCREASE IN PERFUSION PRESSURE

	10 Hz	15 Hz
Young SHR	40.3 ± 3.3 mmHg** (n = 9)	86.3 ± 4.3 mmHg** (n = 8)
Young WKY	13.1 ± 2.3 mmHg (n = 8)	30.6 ± 5.6 mmHg (n = 8)
Adult SHR	62.8 ± 8.7 mmHg* (n = 8)	94.1 ± 3.8 mmHg** (n = 8)
Adult WKY	32.9 ± 8.4 mmHg (n = 8)	58.0 ± 10.0 mmHg (n = 8)

mean ± SEM, **p* < 0.02, ***p* < 0.005, Significant differences between SHR and WKY.

nephrine overflow during sympathetic nerve stimulation in the same preparation do not vary significantly for at least seven repeated stimuli. Therefore, all experiments were performed within this stable period.

2) Effects of yohimbine on pressor responses and norepinephrine overflow by electrical nerve stimulation in normotensive Wistar rats.

Yohimbine, an α_2 -antagonist, increased norepinephrine overflow by electrical nerve stimulation (10 Hz stimulation, yohimbine 5.0×10^{-8} M, $253 \pm 30\%$ of the control value in the absence of yohimbine, *p* < 0.005, yohimbine 1.0×10^{-7} M, $290 \pm 42\%$, *p* < 0.01, *n* = 6). A high concen-

tration of yohimbine showed a smaller increase in norepinephrine overflow than did a low concentration of the drug.

The enhancement of norepinephrine overflow at 15 Hz stimulation was less than that observed at 10 Hz stimulation (15 Hz stimulation; yohimbine 5.0×10^{-8} M, $163 \pm 32\%$ of the value in the absence of yohimbine, *n* = 4, yohimbine 1.0×10^{-7} M, $120 \pm 35\%$, *n* = 5). Pressor responses to electrical nerve stimulation were also enhanced by a low concentration of yohimbine, but they were suppressed in the presence of a high concentration of yohimbine (Fig. 1).

Vasoconstrictor responses to exogenous norepinephrine were depressed dose-dependently by yohimbine ($3.3 \mu\text{g}$ of 1-norepinephrine admin-

Fig.2. Effects of yohimbine on norepinephrine overflow during electrical nerve stimulation (10 Hz) from the sympathetic nerve endings in mesenteric vasculatures of SHR and age-matched WKY (a. young, 7–8 weeks; b. adult, 20–22 weeks). Values are expressed as the percent changes of the controls in the absence of yohimbine in SHR and WKY, respectively. Experiment numbers are shown in the figure.

Fig.3. Effects of yohimbine on the pressor responses to electrical nerve stimulation (10 Hz) in mesenteric vasculatures of SHR and age-matched WKY (a. young, 7–8 weeks; b. adult, 20–22 weeks). Values are represented as the percent changes of the control responses in the absence of yohimbine in SHR and WKY, respectively. Experiment numbers are shown in the figure.

istration, yohimbine $5.0 \times 10^{-8} \text{ M}$, $75.0 \pm 6.0\%$ of the control value in the absence of yohimbine, $n = 4$, $p < 0.05$, yohimbine $5.0 \times 10^{-8} \text{ M}$, $61.0 \pm 3.0\%$, $n = 3$, $p < 0.01$) (lower part of Fig. 1).

The facilitatory effect of yohimbine on norepinephrine overflow and pressor responses was more evident with the lower concentration of yohimbine. Therefore we employed $5.0 \times 10^{-8} \text{ M}$ and $1.0 \times 10^{-7} \text{ M}$ of yohimbine to investigate the alterations of presynaptic α_2 -adrenoceptors in SHR.

3) Norepinephrine overflow and pressor responses to electrical nerve stimulation in SHR and WKY

There were no differences between SHR and WKY in basal perfusion pressure and norepinephrine content during the unstimulated period (3 min) (basal perfusion pressure: young SHR $26.3 \pm 1.6 \text{ mmHg}$, $n = 9$, young WKY $24.3 \pm 1.4 \text{ mmHg}$, $n = 8$; adult SHR $17.9 \pm 0.8 \text{ mmHg}$, $n = 8$, norepinephrine overflow: young SHR $0.36 \pm 0.06 \text{ ng/g}$ of wet tissue weight, $n = 8$, young WKY $0.35 \pm 0.06 \text{ ng/g}$, $n = 8$; adult SHR $0.13 \pm$

0.02 ng/g, $n = 8$, adult WKY 0.18 ± 0.07 ng/g, $n = 8$).

Electrical nerve stimulation caused significantly greater overflow of endogenous norepinephrine from the sympathetic nerve endings in the mesenteric vasculatures of young (7–8 weeks) SHR than in age-matched WKY (Table I). The inhibition of norepinephrine-uptake by desipramine produced a significant increase in transmitter overflow compared to control stimulation without the uptake-blocker in young SHR and age-matched WKY. Percentage ratios of the control responses were $121.3 \pm 5.7\%$ in young SHR ($n = 8$), and $122.1 \pm 4.6\%$ ($n = 4$) in WKY, and there were no significant differences between them (10 Hz stimulation).

The pressor responses to electrical nerve stimulation were also more enhanced in young SHR than in age-matched WKY (Table II).

In adult rats, the amount of norepinephrine overflow from the nerve terminals during electrical stimulation was not significantly different between SHR and WKY, though the pressor responses were greater in SHR than in WKY (Table I, II).

4) *The effects of yohimbine on norepinephrine overflow and pressor responses in SHR*

As shown in Fig. 2a, yohimbine facilitated norepinephrine overflow during electrical nerve stimulation significantly less in young SHR than in age-matched WKY (10 Hz stimulation, yohimbine 5.0×10^{-8} M, SHR $88 \pm 19\%$ of the corresponding control value without yohimbine, $n = 8$, WKY $253 \pm 30\%$, $n = 6$, $p < 0.001$). This experiment was performed without uptake-blocker in the medium.

The pressor responses also were less potentiated in young SHR than in young WKY (10 Hz stimulation, yohimbine 5.0×10^{-8} M, SHR $99 \pm 16\%$ of the control value, $n = 9$, WKY $183 \pm 34\%$ of the control value, $n = 6$, $p < 0.05$, Fig. 3a).

On the other hand, differences in the effect of yohimbine on norepinephrine overflow and pressor responses during electrical nerve stimulation were not so marked between adult SHR and WKY (Figs. 2b and 3b).

DISCUSSION

It has generally been accepted that norepinephrine release from sympathetic nerve endings can be modulated by several factors, including the negative feedback mechanism of presynaptic

α_2 -adrenoceptors on the nerve terminals? Blocking of the presynaptic α_2 -adrenoceptors by yohimbine, a selective α_2 -antagonist, exerted an increase in norepinephrine release during electrical nerve stimulation^{7,8}. In vitro study has shown that yohimbine increases the plasma norepinephrine concentration in intact animals⁹.

In this study, we examined whether presynaptic α_2 -adrenoceptor mediated inhibition on norepinephrine release might be changed in SHR, using yohimbine. In fundamental studies of mesenteric vasculatures from normotensive Wistar rats, yohimbine (5.0×10^{-8} M and 1.0×10^{-7} M) facilitated norepinephrine overflow during electrical nerve stimulation. High-concentration yohimbine (5.0×10^{-7} M) showed a smaller increase in norepinephrine overflow and pressor responses were not potentiated. A high concentration of yohimbine could have a variety of actions other than that of an α_2 -adrenoceptor blocking agent^{7,10}. Therefore, we used 5.0×10^{-8} M and 1.0×10^{-7} M of yohimbine to examine the function of presynaptic α_2 -adrenoceptors in the mesenteric vasculatures from SHR.

Norepinephrine overflow during electrical nerve stimulation as well as vasoconstrictor responses in young SHR were significantly greater than in age-matched WKY.

When norepinephrine uptake was blocked by desipramine, the increased degree of norepinephrine overflow was similar in young SHR and WKY, implying that the enhanced norepinephrine overflow in young SHR may be due to the abnormality of the release, but not to the re-uptake of norepinephrine in the nerve terminals.

Yohimbine caused a marked increase in norepinephrine overflow in young WKY, but this effect was blunted in young SHR. Pressor responses to electrical nerve stimulation also were less potentiated by yohimbine in young SHR than in young WKY. These findings suggest that presynaptic α_2 -adrenoceptor mediated inhibition is impaired in young SHR, resulting in an increase in norepinephrine overflow from the sympathetic nerve terminals.

Unlike that seen with in the young SHR, the amount of norepinephrine overflow during electrical nerve stimulation was not increased in adult SHR compared with age-matched WKY. Additionally, we could find no significant differences in the effects of yohimbine on norepinephrine overflow in adult SHR and WKY. It is possible that the presynaptic α_2 -adrenoceptor function did not change in adult SHR and

WKY, which is compatible with previous results that there were no differences in presynaptic α_2 -adrenoceptor function in the mesenteric arteries of 18-week-old SHR and WKY using phentolamine.⁵

The precise reasons for this alteration of the presynaptic α_2 -adrenoceptor activity in young and adult SHR remain to be found, though it has been reported previously that plasma norepinephrine content was increased only in young SHR,¹¹ which is compatible with the present result. The presynaptic alterations leading to an increase in norepinephrine release may be an important factor in the early development of SHR.

In other tissues, Ekas et al. showed the supersensitivity of presynaptic α_2 -adrenoceptors in the perfused kidney of SHR. In the isolated portal vein, Westfall et al.¹² demonstrated that presynaptic α_2 -adrenoceptor activity was attenuated in adult, but not in young, SHR. In the coccygeal arteries, Galloway and Westfall³ reported that there was less enhancement of norepinephrine release by yohimbine in adult SHR, suggesting that the presynaptic α_2 -adrenoceptor function might be decreased. It is likely that there were distinct differences in neurotransmission among the vascular beds used in each experiment. However, our results are consistent with the hypothesis that the decreased activities of presynaptic α_2 -adrenoceptors lead to a greater release of norepinephrine, which may contribute to the exaggerated vasoconstriction in young SHR.

It has been suggested recently that the inhibitory action of presynaptic α_2 -mediated inhibition of norepinephrine release is exhibited by reducing the availability of Ca for neurotransmitter release.^{13,14} Langer¹⁴ reported that the inhibition of neurotransmitter release by the stimulation of presynaptic α_2 -adrenoceptors was more pronounced when the extracellular Ca concentration was reduced. Therefore, the decreased sensitivity of presynaptic α_2 -adrenoceptors in young SHR shown in this experiment may be related to the increased Ca-influx into the sympathetic nerve cells.^{15,16}

As for the postsynaptic α_2 -adrenoceptors, Hicks et al. reported that α_2 -adrenoceptors could be demonstrated in arterial smooth muscle cells and were particularly evident in tail arteries from hypertensive animals. In our preparations of rat mesenteric vasculatures, yohimbine suppressed the vasoconstrictor responses to exogenous

norepinephrine, although there is virtually no evidence that postsynaptic α_2 -adrenoceptors exist in rat mesenteric vasculatures. Yohimbine may inhibit vasoconstrictor responses by its α_1 -antagonistic activity. The role of postsynaptic α_2 -adrenoceptors in rat mesenteric vasculatures and their contribution to the pathogenesis of hypertension remain to be defined.

In conclusion, the present study demonstrated that norepinephrine overflow from sympathetic nerve endings is increased in the mesenteric vasculatures of young SHR. This may be due in part to the impaired presynaptic α_2 -adrenoceptor activities on the nerve terminals, which would be an important factor in the early development of hypertension of SHR.

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