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Enhanced Presynaptic β_2-Adrenoceptor–Mediated Facilitation of the Pressor Responses in the Prehypertensive SHR

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Summary: The effects of β-adrenoceptor agonists and antagonists on pressor responses of the isolated perfused mesenteric arteries to periarterial nerve stimulation (PNS) in the prehypertensive 4-week-old spontaneously hypertensive rat (SHR) and the age-matched Wistar Kyoto rats (WKY) were examined. The systolic arterial blood pressure (SBP) of SHR and WKY were not significantly different at this young age. The pressor responses of the mesenteric arteries to PNS at various stimulating frequencies, however, were significantly greater in SHR than WKY. Cocaine, isoproterenol (a nonselective β-adrenoceptor agonist) and salbutamol (a selective β_2-adrenoceptor agonist) significantly enhanced the pressor responses to PNS in SHR and WKY, with significantly greater increase in SHR than WKY. The nonselective β-adrenoceptor antagonist (propranolol) and the selective β_2-adrenoceptor antagonist (ICI 118,551) significantly inhibited the pressor response to PNS in SHR without affecting that in WKY. The selective β_1-adrenoceptor antagonist (practolol) was without effect on the PNS-induced pressor responses in both SHR and WKY. These results demonstrate that the presynaptic β_2-adrenoceptor–mediated facilitation of neurogenic pressor response in mesenteric arteries already are enhanced in 4-week-old SHR. In view of the higher concentration of circulating epinephrine (Epi) in prehypertensive SHR, the enhanced facilitatory modulation via presynaptic β_2-adrenoceptors in prehypertensive SHR may be involved in development of hypertension. **Key Words:** Spontaneously hypertensive rats—Wistar Kyoto rats—Presynaptic β_2-adrenoceptor—Periarterial nerve stimulation—Mesenteric vasculature.

The spontaneously hypertensive rat (SHR) has been widely used as a model for study of human essential hypertension. In this animal model, hypertension has been suggested to result from multiple factors, such as increased neurohumoral vasoconstrictors (1), changes in central noradrenergic control mechanisms (2,3), and altered adrenergic neuroeffector transmission through presynaptic receptors (4). In particular, focus on the modulation of transmitter release by presynaptic receptors has gained increasing attention. In adult SHR, an increased facilitatory modulation by angiotensin II receptors (5,6) and β_2-adrenoceptors (7–9), and a decreased inhibitory modulation by α-adrenoceptors (10,11), P1 purinergic receptors (12,13), and serotonin receptors (14,15) have been reported. As a result of changes in presynaptic modulation of norepinephrine (NE) transmitter release, the peripheral vascular resistance increases. Receptor mechanisms involved in altered presynaptic modulation related to hypertension, however, have not been entirely clarified. Whether these changes are secondary to chronic high blood pressure (BP) and/or occur before the onset of high BP have not been determined. Furthermore, the concentration of circulating epinephrine (Epi) has been shown to be higher in prehypertensive SHR than in age-matched normotensive Wistar Kyoto rats (WKY) (16). The present study was therefore designed to examine the functional significance of presynaptic β_2-adrenoceptors in modulating the neurogenic pressor responses in isolated mesenteric arteries from

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young prehypertensive SHR and age-matched WKY.

MATERIALS AND METHODS

General procedure

Studies were performed on male, prehypertensive 4-week-old SHR (Harlan Sprague-Dawley, Indianapolis, IN, U.S.A.) and age-matched WKY. The body weights of SHR and WKY were 50.2 ± 2.3 g (n = 40) and 56.6 ± 2.5 g (n = 40), respectively. The systolic tail arterial BP was measured in the conscious state by the tail-cuff plethysmographic methods with a photosensor detector (KN210-1, Natume, Peninusula Lab, Belmont, CA, U.S.A.). The mesenteric vascular bed was isolated from animals under pentobarbital anesthesia [50 mg/kg, intraperitoneally (i.p.)]. The end of the superior mesenteric artery was tied off, and only four main arterial branches from the superior mesenteric artery running to the terminal ileum were perfused, according to the method of McGregor (17). After being gently washed out with 5-ml Krebs solution, the mesenteric vascular bed was placed in a 20-ml water-jacketed organ bath maintained at 37°C, and perfused with modified Krebs bicarbonate solution by a Buchler polystalic perfusion pump at a rate of 1.5 ml/min. The mesenteric vascular preparation was concomitantly superfused with the same Krebs solution at a rate of 1 ml/min to keep it moist. The modified Krebs solution was maintained at 37°C, equilibrated with a mixture of 95% O_2 and 5% CO_2. The Krebs solution had the following composition (in m*M*): NaCl 120, KCl 5.0, $CaCl_2 \cdot 2H_2O$ 2.4, $MgSO_4 \cdot 7H_2O$ 1.2, $NaHCO_3$ 25, EDTA · Na_2 0.027, dextrose 11 (pH 7.4).

Effects of drugs and periarterial nerve stimulation (PNS)

The mesenteric vascular bed was perfused for 60 min to allow basal perfusion pressure to stabilize before commencing the experiment. The perfused mesenteric vascular bed was then subjected to electrical periarterial nerve stimulation (PNS). The PNS was elicited at 3-min intervals with bipolar platinum-ring electrodes placed around the mesenteric artery. Trains of 200 square-wave pulses of 2-ms duration and at supramaximal voltage (60 V) were applied at 6, 10, 14, and 18 Hz by means of a Grass stimulator (model S44). To study effects of drugs on PNS-induced pressor responses, drugs were added directly to the perfusate reservoir. Perfusion of the drug with the aid of an infusion pump (Harvard, model 975, South Natic, MA, U.S.A.) was completed within 2 min by changing from drug to nondrug-containing reservoirs. Two minutes after the first series of frequency–response curves to PNS was obtained, perfusion of drugs was started and continued throughout the second frequency–response curves to PNS. Changes in the perfusion pressure were monitored with a pressure transducer (Statham, model P23DC, Oxnard, CA, U.S.A.) and recorded on a Grass polygraph (model 179, Quincy, MA, U.S.A.).

Drugs used

The following drugs were used: L-NE bitartrate, tetrodotoxin (Sigma Chemical, St. Louis, MO, U.S.A.), L-isoproterenol bitartrate (Sigma), DL-propranolol hydrochloride (Sigma), practolol (Ayerst Laboratories, New York, NY, U.S.A.), ICI 118,551 hydrochloride (Imperial Chemical, Cheshire, U.K.), salbutamol sulfate (Glaxo Group Research, Ware, U.K.). All drugs were initially dissolved in distilled water containing ascorbic acid (2 mg/100 ml) and diluted in modified Krebs solution.

Statistics analysis

All data are expressed as mean ± SEM. Comparisons of effects of certain concentration of drugs within strains were made by Student's *t* test for paired and unpaired samples when appropriate. Effects of drugs on dose–response and frequency–response relationships were analyzed by an analysis of variance (ANOVA) (18). A p value <0.05 was considered statistically significant.

RESULTS

The mean tail arterial BP of 4-week-old SHR and WKY was 128.5 ± 4.2 mm Hg (n = 40) and 118.8 ± 3.7 mm Hg (n = 40), respectively, and was not significantly different ($p > 0.05$, Table 1). The mean basal perfusion pressures, however, were greater in SHR (20.2 ± 1.3 mm Hg, n = 40) than in WKY (17.0 ± 0.8 mm Hg, n = 40) ($p < 0.05$).

As shown in Fig. 1, response of mesenteric arteries to PNS is frequency-dependent in both SHR and WKY. There was no significant difference between the first and second control frequency–response curves to PNS. Therefore, the second frequency–response curve was constructed in the presence of drugs to be examined. The response to PNS was abolished by tetrodotoxin (10^{-7} *M*) (Fig. 1) and guanethidine (10^{-5}*M*, not shown) in both SHR (n = 5) and WKY (n = 5).

The pressor response of the mesenteric vascular bed to exogenously applied NE was not significantly different between the first and second set of control responses in either SHR or WKY ($p > 0.05$, Fig. 2); neither were the NE dose–response curves significantly different between SHR and WKY (Fig. 3). The responses to PNS at 14 and 18 Hz, but not at 6 and 10 Hz, were significantly greater in SHR than in WKY (Fig. 3), suggesting a greater release of neurotransmitter at higher frequencies of stimulation.

Effects of β-adrenoceptor agonists

As shown in Fig. 4A, the nonselective β-adrenoceptor agonist, isoproterenol (10^{-7} *M*) significantly

TABLE 1. *Systolic blood pressure, body weight, and basal perfusion pressure of 4-week-old SHR and age-matched WKY*

Parameters	SHR (n = 40)	WKY (n = 40)
BP (mm Hg)	128.5 ± 4.2	118.8 ± 4.2
Body weight (g)	50.2 ± 2.3	56.6 ± 2.5
Basal perfusion pressure (mm Hg)	20.2 ± 1.3[a]	17.0 ± 0.8

SHR, spontaneously hypertensive rats; WKY, Wistar Kyoto rats; BP, blood pressure.

Data are mean ± SE.

[a] Significantly different from WKY (unpaired *t* test, $p < 0.05$).

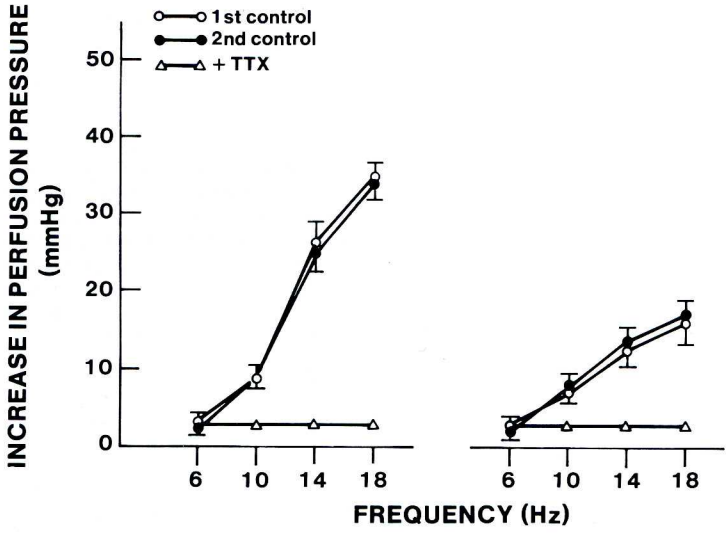

FIG. 1. Frequency–response curve to periarterial nerve stimulation on arterial perfusion pressure of the mesenteric vascular bed in spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY). Fifteen minutes elapsed between the first curve (first control) and the second curve (second control). There was no significant difference between two control curves in either SHR or WKY (paired *t* test). Tetrodotoxin (TTX, 10^{-7} *M*) abolished pressor responses in both SHR and WKY. SHR, n = 5; WKY, n = 5; n, number of experiments.

increased the pressor response to PNS at 14 and 18 Hz in SHR preparations ($p < 0.05$) and at 14 Hz in WKY preparations ($p < 0.05$). The control and the isoproterenol-treated frequency–response curves were significantly different in SHR ($p < 0.05$), but not in WKY ($p > 0.05$). The frequency–response curve in SHR was significantly shifted to the left of that in WKY, indicating a greater facilitation of pressor response by isoproterenol in SHR. Isoproterenol at a similar concentration (10^{-7} *M*) did not affect the basal perfusion pressure (not shown) and NE-induced pressor responses (Fig. 4B) in either SHR or WKY.

The selective β_2-adrenoceptor agonist, salbutamol (10^{-6} *M*), which did not affect the basal perfusion pressure, caused facilitation of the pressor response to PNS in both SHR and WKY (Fig. 5A). The responses to PNS were significantly enhanced by salbutamol (10^{-6} *M*) at 10, 14, and 18 Hz in SHR ($p < 0.05$) and at 14 and 18 Hz in WKY ($p < 0.05$). ANOVA showed that the control and the salbutamol-treated frequency–response curves were significantly different in SHR ($p < 0.01$) but not in WKY ($p > 0.05$). This facilitation of pressor response was significantly greater in SHR than that in WKY ($p < 0.05$). Salbutamol at 10^{-6} *M* did not affect the NE-induced pressor responses in either WKY or SHR (Fig. 5B).

Effects of β-adrenoceptor antagonists

Effects of the nonselective β-adrenoceptor antagonist propranolol (10^{-7}–10^{-6} *M*) on the frequency–response curve to PNS are shown in Fig. 6. Propranolol at 10^{-6} *M* decreased the pressor responses to PNS at all frequencies examined in SHR ($p < 0.05$) but did not affect those in WKY. The control

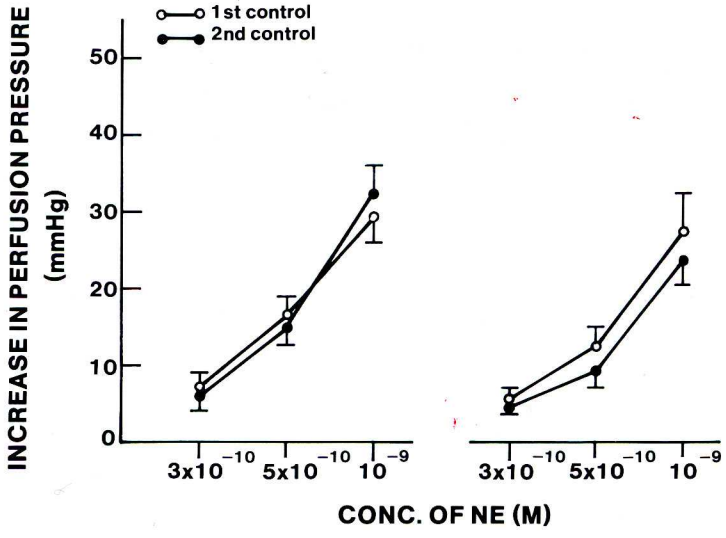

FIG. 2. Dose–response curve to exogenously applied norepinephrine (NE) on the arterial perfusion pressure of the mesenteric vascular bed in spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY). Fifteen minutes elapsed between the first curve (first control) and the second curve (second control). There was no significant difference between two consecutive curves in either SHR or WKY (paired *t* test); SHR, n = 5; WKY, n = 5; n, number of experiments.

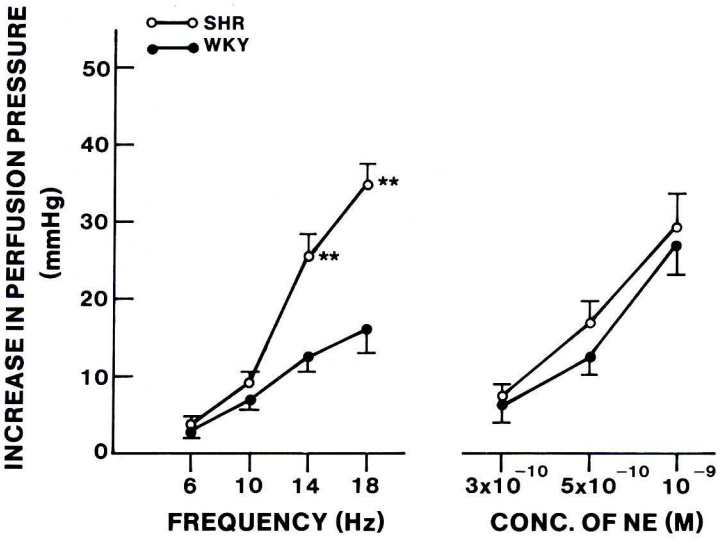

FIG. 3. Response to periarterial nerve stimulation was significantly greater in spontaneously hypertensive rats (SHR) than in Wistar Kyoto rats (WKY). However, dose–response curves to exogenously applied norepinephrine (NE) were not significantly different between SHR and WKY. **$p < 0.01$, significant difference from the respective frequency of stimulation in the control curve for WKY (paired *t* test). PNS, n = 5; NE, n = 5; n, number of experiments.

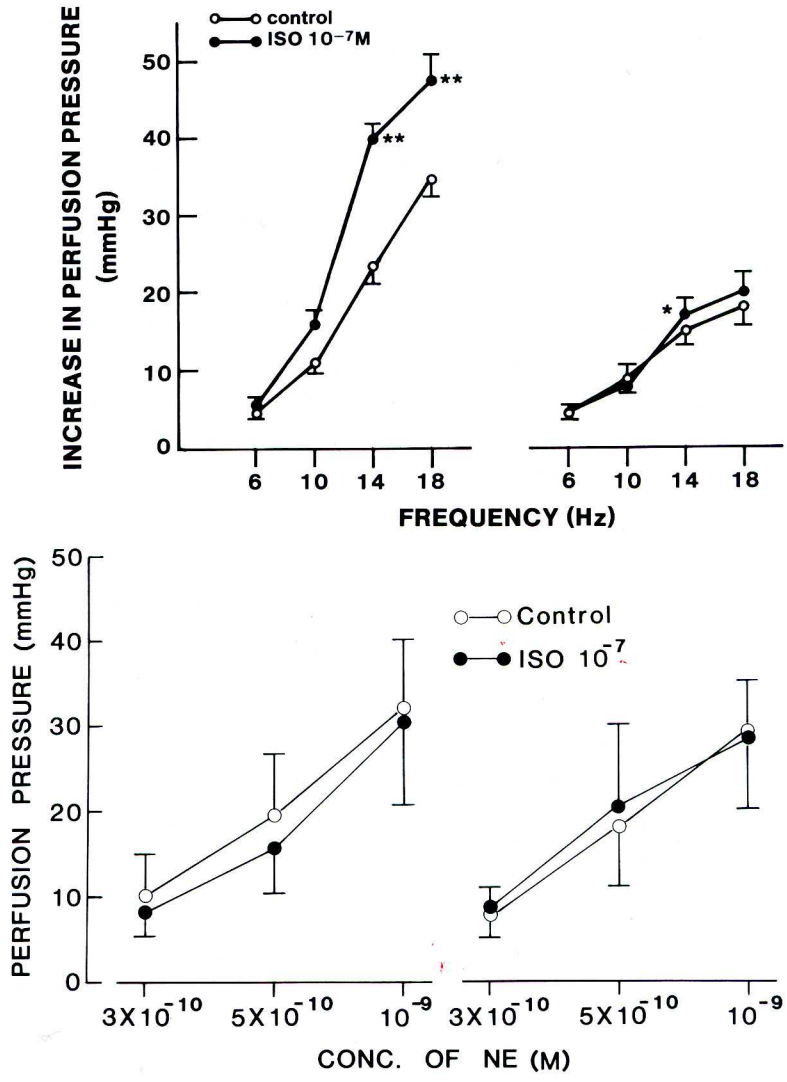

FIG. 4. Frequency–response curve to periarterial nerve stimulation **(A)** and norepinephrine (NE) **(B)** obtained before (control) and during infusion with isoproterenol (ISO, 10^{-7} *M*). The frequency–response curve in the presence of ISO 10^{-7} *M* was significantly different from the control curve in spontaneously hypertensive rats (SHR) but not in Wistar Kyoto rats (WKY). ISO at a similar concentration (10^{-7} *M*) did not affect the NE-induced pressor responses in either SHR or WKY. *$p < 0.05$ and **$p < 0.01$, significant difference from the respective frequency of stimulation in the control (paired *t* test); n, number of experiments. A: SHR, n = 5; WKY, n = 5. B: SHR, n = 4; WKY, n = 3.

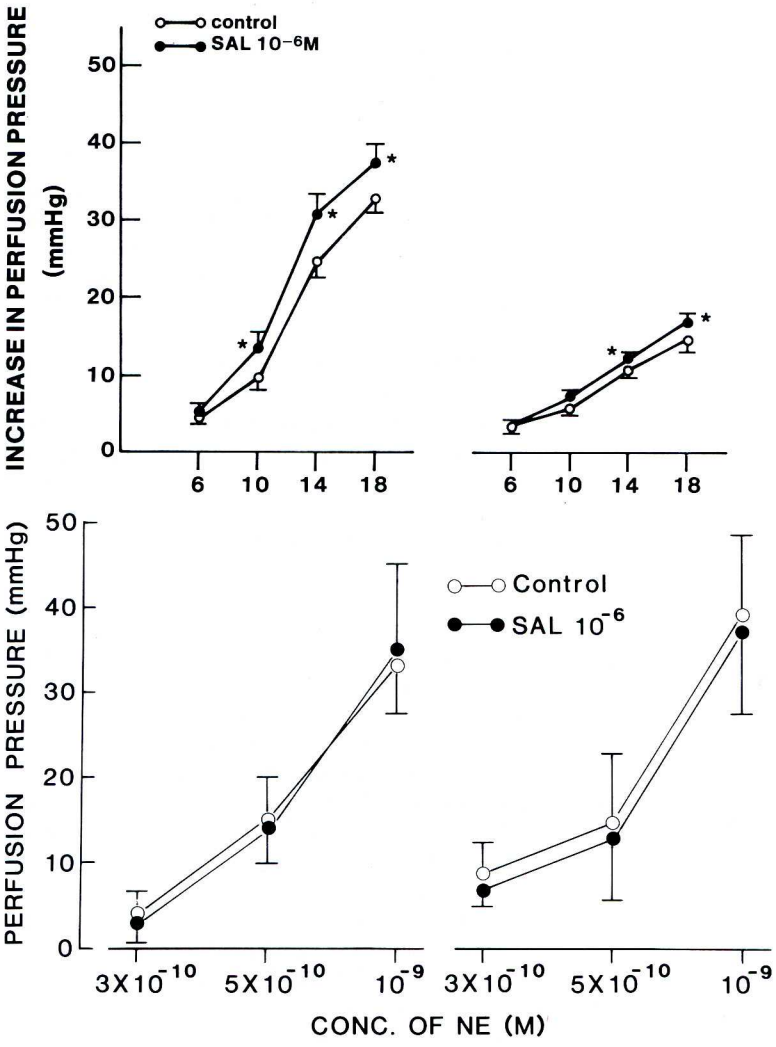

FIG. 5. Frequency–response curve to periarterial nerve stimulation **(A)** and norepinephrine (NE) **(B)** obtained before (control) and during infusion with salbutamol (SAL 10^{-6} *M*). The frequency–response curve with SAL 10^{-6} *M* added was significantly different from control curves in spontaneously hypertensive rats (SHR) but not in Wistar Kyoto rats (WKY). SAL at 10^{-6} *M* did not affect the NE-induced pressor responses. *$p < 0.05$ and **$p < 0.01$, significant difference from the respective frequency of stimulation in the control (paired *t* test); A: SHR, n = 5; WKY, n = 5. B: SHR, n = 3; WKY, n = 3; n, number of experiments.

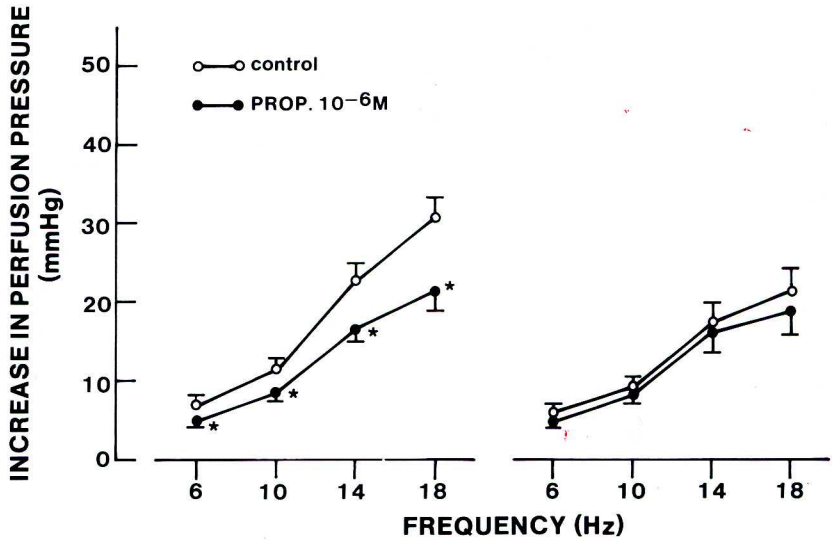

FIG. 6. Frequency–response curve to periarterial nerve stimulation obtained before (control) and during infusion with propranolol (PROP 10^{-6} *M*). The pressor responses in the presence of PROP 10^{-6} *M* were significantly decreased at all frequencies examined in spontaneously hypertensive rats (SHR) but not in Wistar Kyoto rats (WKY) (paired *t* test). Two-way analysis of variance split-plot also showed the significant difference between the control and PROP-treated curves in SHR ($p < 0.05$) but not in WKY ($p > 0.05$). *$p < 0.05$ and **$p < 0.01$, significant difference from the respective frequency of stimulation in the control curve (paired *t* test). SHR, n = 5; WKY, n = 5; n, number of experiments.

and propranolol-treated frequency–response curves were significantly different in SHR ($p < 0.05$) but not in WKY ($p > 0.05$). These concentrations of propranolol (10^{-7}–10^{-6} *M*) did not affect the NE-induced pressor responses in either strain (not shown).

The selective β_2-adrenoceptor antagonist ICI 118,551 (ICI, 10^{-6} *M*) (19) significantly decreased the pressor response to PNS at 10, 14, and 18 Hz in SHR ($p < 0.05$) but not in WKY (Fig. 7). ANOVA showed that the control and ICI 118,551-treated frequency–response curves were significantly different in SHR ($p < 0.01$) but not in WKY ($p > 0.05$). This inhibition of pressor responses in SHR was significantly greater than that in WKY ($p < 0.01$). Similar concentration of ICI (10^{-6} *M*) did not affect the NE-induced pressor responses in either WKY or SHR (not shown).

The selective β_1-adrenoceptor antagonist, practolol (10^{-6} *M*) did not affect the pressor response in either SHR or WKY, as shown in Fig. 8. ANOVA showed no significant difference in practolol effects between SHR and WKY ($p > 0.05$).

Effects of nonneuronal and neuronal uptake blockers

Corticosterone (4×10^{-5} *M*) alone did not affect the pressor responses to PNS (Fig. 9) or intraluminally applied NE (not shown) in either SHR or WKY. In the presence of corticosterone, cocaine (3×10^{-7} *M*) significantly enhanced the pressor responses to PNS at 14 and 18 Hz in SHR but did not affect that in WKY (Fig. 10). Cocaine at higher concentrations (4×10^{-6} *M*), however, enhanced the pressor responses to PNS at all frequencies examined in SHR and that to PNS at 14 and 18 Hz in WKY. Cocaine (4×10^{-6} *M*), in the presence of corticosterone (4×10^{-5} *M*), also enhanced the pressor responses to the intraluminally applied NE in both SHR and WKY (Fig. 11). The degree of potentiation was comparable between the two strains.

DISCUSSION

There is general consensus that the SBP of SHR increases significantly between the sixth and eighth week of age (20,21). The 4-week-old SHR used in the present study exhibited low SBP similar to that of WKY of the same age, indicating that the SHR at this young age are prehypertensive. The pressor response to PNS of the isolated mesenteric arteries from the prehypertensive SHR, however, was already enhanced as compared with that of WKY (Fig. 3). Several possible mechanisms may be responsible for this alteration in SHR: (a) increased NE release through altered presynaptic modulation, (b) enhanced inhibition of neuronal NE uptake, (c) increased postsynaptic contractile characteristic of NE, and (d) structural abnormalities of blood vessel wall (22,23). Although the increase in perfusion pressure in mesenteric arteries in 4-week-old SHR, as shown in the present study, may reflect an increase in wall–lumen ratio in these arteries (23), the pressor response of the mesenteric arterial preparation to exogenously applied NE is not different between SHR and WKY (Fig. 3). Thus, enhanced NE release through presynaptic modulation is most likely responsible for the enhanced PNS-induced pressor responses. Results from the present study in mesenteric artery preparations indicate that uptake$_2$ or nonneuronal uptake blockade with corticosterone (4×10^{-5} *M*) did not affect the pressor responses to PNS or intraluminally applied NE in either WKY or SHR (4-week-old). Uptake$_1$ or neuronal uptake blockade with cocaine (3×10^{-6} *M*), on the other hand, significantly increased the pressor responses to PNS in SHR and WKY, with

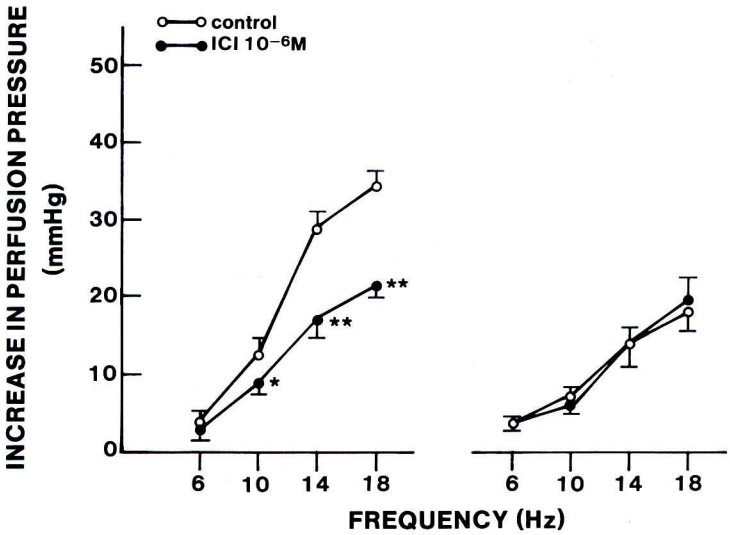

FIG. 7. Frequency–response curve to periarterial nerve stimulation before (control) and during infusion with ICI 118,551 (ICI 10^{-6} *M*). The frequency–response curve with ICI 10^{-6} *M* added was significantly different from the control curve in spontaneously hypertensive rats (SHR) but not in Wistar Kyoto rats (WKY). *$p < 0.05$ and **$p < 0.01$, significant difference from the respective frequency of stimulation in the control curve (paired *t* test); SHR, n = 5; WKY, n = 5; n, number of experiments.

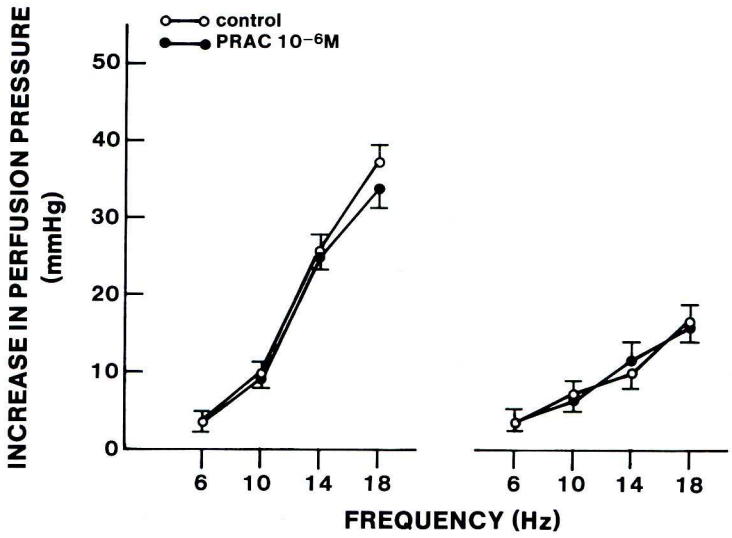

FIG. 8. Frequency–response curve to periarterial nerve stimulation obtained before (control) and during infusion with practolol (PRAC 10^{-6} *M*). There was no significant difference between the control and experimental curves in either spontaneously hypertensive rats (SHR, n = 5) or Wistar Kyoto rats (WKY, n = 5); n, number of experiments.

greater enhancement in SHR than WKY. Cocaine (3×10^{-6} *M*) also potentiated the pressor responses to intraluminally applied NE in both WKY and SHR; potentiation, however, was comparable between the two strains. This result further suggests that the enhanced PNS-induced pressor responses in 4-week-old SHR are primarily due to altered presynaptic rather than postsynaptic mechanisms. Kubo and Su (24) also demonstrated that inhibition by adenosine of [^{3}H]NE release from the isolated perfused mesenteric arteries was significantly diminished in prehypertensive 5-week-old SHR as compared with age-matched WKY. This result further supports an altered presynaptic modulatory mechanism on adrenergic transmission in young SHR.

The frequency–response curves in SHR, however, were shifted at high but not low frequencies (Fig. 3). The neurogenic responses at the lower frequencies would also be expected to be increased if there was an enhanced release of NE in SHR versus WKY. This observation bears a striking resemblance to the perfusion pressure in rat caudal arteries (25) and kidney (26) and the enhanced increase in BP observed at high, but not low, frequencies of stimulation in pithed rat preparations (27). This may be mediated by saturation of inactivation process. This is supported by results from the present study: Cocaine significantly enhanced the pressor responses of 4-week-old SHR mesenteric arteries to PNS at both high and low frequencies. The potential abnormality in presynaptic receptor functions involved in regulation of release of NE (28), however, cannot be ruled out.

In the present study, salbutamol (10^{-6} *M*) and isoproterenol (10^{-7} *M*) significantly enhanced pressor responses of the mesenteric arteries on PNS in SHR but not in WKY. Since isoproterenol (10^{-7} *M*) and salbutamol (10^{-6} *M*) did not affect the pressor response to exogenously applied NE in the mesenteric artery, the potentiating action by these drugs most likely resulted from modulation of presynaptic

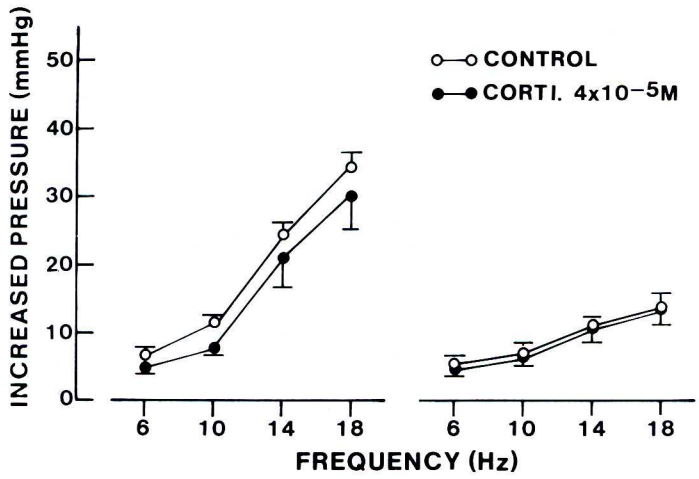

FIG. 9. Corticosterone (CORTI. 4×10^{-5} *M*) alone did not affect the pressor response of the mesenteric vascular bed to periarterial nerve stimulation in either spontaneously hypertensive rats (SHR, n = 3) or Wistar Kyoto rats (WKY, n = 3) aged 4 weeks; n, number of experiments.

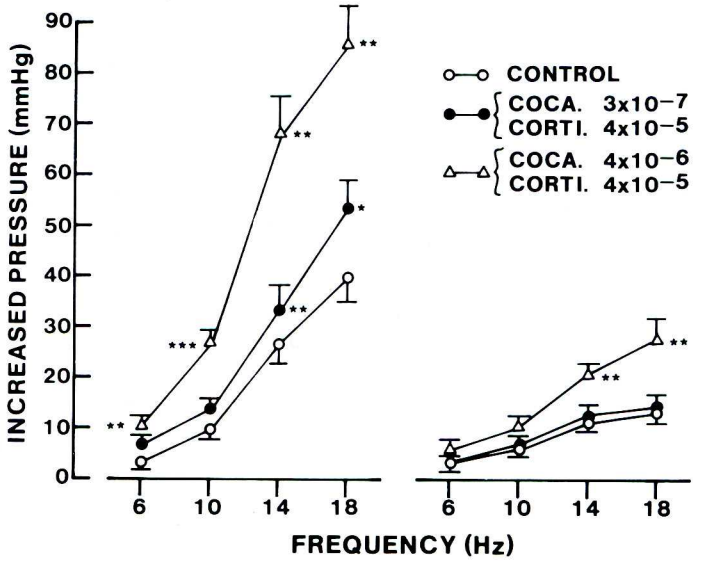

FIG. 10. Cocaine (COCA 3×10^{-7}–4×10^{-6} *M*), with corticosterone (CORTI. 4×10^{-5} *M*) added dose-dependently potentiated pressor responses toperiarterial nerve stimulation (PNS) in both spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY) aged 4 weeks, with greater effect in SHR than in WKY. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$, significant difference from the respective control of stimulation frequency; SHR, n = 10; WKY, n = 10; n, number of experiments.

β_2-adrenoceptors. Neither isoproterenol nor salbutamol affected basal perfusion pressure. This effect probably is not due to lack of active muscle tone of the arterial preparation, since luminal application of acetylcholine (10^{-7} *M*) decreased basal perfusion pressure (vasodilation) (T. Tsuji and T. J-F. Lee, unpublished observations). A similar result was obtained in adult mesenteric arteries of SHR and WKY (6). Our preliminary results, however, indicate that angiotensin II (Ang II 3×10^{-7} *M*) increases basal perfusion pressure in mesenteric arteries of 4-week-old SHR. One possibility, therefore, is that the postsynaptic β-adrenoceptor and/or its function in the mesenteric artery of young SHR and WKY are not fully developed. This conclusion is further supported by the observation that propranolol and the selective β_2-adrenoceptor antagonist ICI 118,551 (19), which did not affect the NE-induced pressor responses, significantly inhibited the pressor response to PNS in SHR but not in WKY. On the other hand, the selective β_1-adrenoceptor antagonist practolol failed to affect PNS-induced pressor responses in either SHR or WKY. These results demonstrate that a positive feedback mechanism through presynaptic β_2-adrenoceptors, but not β_1-adrenoceptors, is functional in the mesenteric arteries of the prehypertensive SHR. Isoproterenol, salbutamol, and ICI 118,551 affect the frequency–response curve at high but not low (6 Hz) frequencies. Apart from the possible explanatin of saturation of inactivation process as described above, this is different from the effect of propranolol. This β-adrenoceptor antagonist significantly decreased the PNS-induced perfusion pressure at all frequencies examined. The reason that propranolol is more effective than other β-adrenoceptor agonists and antagonists in changing the perfusion pressure on PNS is not known.

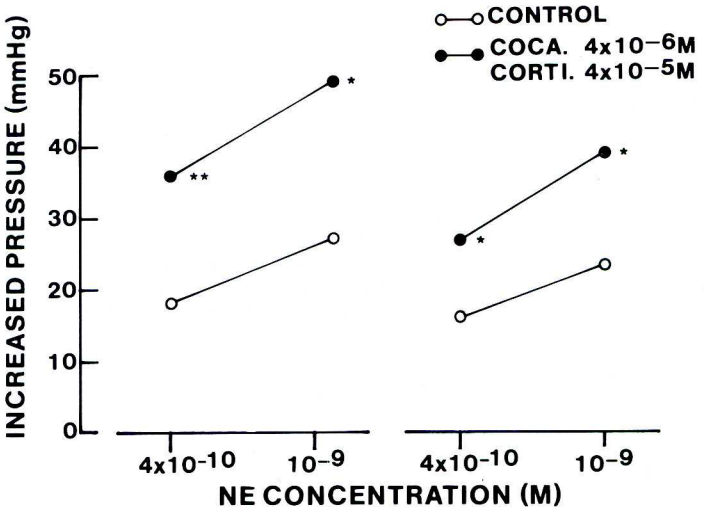

FIG. 11. Cocaine (COCA 4×10^{-6} *M*) and corticosterone (CORTI.) potentiated pressor responses to exogenously applied norepinephrine (NE 4×10^{-10}, 10^{-9} *M*) in both spontaneously hypertensive rats (SHR, n = 5) and Wistar Kyoto rats (WKY, n = 5) aged 4 weeks. *$p < 0.05$ and **$p < 0.01$, significant difference from the respective control.

Our present findings in young prehypertensive rats are consistent with previous reports that presynaptic β-adrenoceptors are of β_2 subtype (6). NE, which is a preferential β_1-adrenoceptor agonist (29), might be expected to be relatively ineffective in activating the presynaptic β_2-adrenoceptor–mediated facilitatory mechanism. However, the circulating Epi is ~100 times more potent than NE as a β_2-adrenoceptor agonist (30), and the concentration of circulating Epi is threefold higher in 5-week-old prehypertensive male SHR than the age-matched WKY (16). Furthermore, the circulating Epi is taken up into sympathetic adrenergic nerve terminals in the blood vessel wall and subsequently released as a cotransmitter to activate the presynaptic β_2-adrenoceptors (31). Thus, an enhanced positive feedback mechanism through presynaptic β_2-adrenoceptors in the mesenteric vascular bed of the prehypertensive SHR may result in an enhanced NE transmitter release and pressor response. Since this enhancement of the pressor response already occurs in prehypertensive rats, the facilitatory modulation through presynaptic β_2-adrenoceptors in SHR appears to be genetic in nature and may play a role in development of hypertension.

The significance of presynaptic β-adrenergic receptors in regulating vascular tone is becoming more evident, although evidence against an enhanced presynaptic β-adrenoceptor–mediated facilitation in adult SHR has been reported (26,32). The reason for these differences in findings is not known; use of different preparations and/or different ages of animals may explain them. Recently, isoproterenol-induced enhancement of pressor responses to sympathetic nerve stimulation has been reported to be attenuated by either [Sar^1-Ile^8]Ang II or captopril in isolated perfused adult rat mesenteric arteries (6). These results suggest potential involvement of the vascular renin–angiotensin system in the prejunctional β-adrenoceptor–mediated facilitation of noradrenergic neurotransmission. Indeed, the isoproterenol-induced enhancement of pressor responses to nerve stimulation was accompanied by an increase in Ang II release from mesenteric arteries (33). Although the origin of Ang II release from the vascular wall and the exact mode of interaction between β-adrenoceptors and Ang II have not been determined, Kawasaki and colleagues (6) showed that activation of the vascular renin–angiotensin system by β_2-adrenoceptors results in a greater facilitation of neurotransmission in mesenteric vascular preparations from SHR than in those from WKY. These results are consistent with the findings of enhanced presynaptic β_2-adrenoceptor–mediated facilitation of the pressor responses in hypertensive SHR. The effect of captopril on PNS-induced pressor responses by isoproterenol in 4-week-old prehypertensive SHR is currently under investigation.

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