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ORIGINAL PAPER

Endogenous angiotensin II has fewer effects but neuronal nitric oxide synthase has excitatory effects on renal sympathetic nerve activity in salt-sensitive hypertension-induced heart failure

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Abstract The effects of endogenous angiotensin II (Ang II) and neuronal nitric oxide synthase (nNOS) on tonic sympathetic activity were studied in salt-sensitive hypertension-induced heart failure. Dahl salt-sensitive rats were fed 8% NaCl diet for 9 weeks to induce chronic heart failure (CHF-DSS). The effects of intravenous administration of a selective nNOS inhibitor, *S*-methyl-L-thiocitrulline (SMTC), and an Ang II type 1-receptor blocker, losartan, on renal sympathetic nerve activity (RSNA) were examined in chronically instrumented conscious rats. Baroreceptor (baro)-unloaded RSNA was obtained by decreasing arterial pressure with caval occlusion to determine tonic RSNA. SMTC significantly decreased baro-unloaded RSNA, and subsequent losartan recovered baro-unloaded RSNA to the control level in CHF-DSS rats. To compare the effects of the inhibitors between low- and high-activity states of the renin–angiotensin system (RAS), Sprague–Dawley rats were fed low (0.04%)- or high (8%)-salt diets. A significant difference was found in the effects of SMTC and/or losartan on RSNA between the high- and low-RAS states, which suggested that there is a difference in the effect of endogenous Ang II on RSNA between salt-induced and other-type heart failure. To examine the effects of heart failure on brain-tissue nNOS activity, we measured the activities of the diencephalon in heart-failure rats. Heart failure significantly suppressed diencephalon nNOS activity, which was significantly different from the results in salt-sensitive hypertension without heart failure. These results suggest that endogenous Ang II has fewer effects, but nNOS has excitatory effects on tonic RSNA in salt-sensitive hypertension-induced heart failure.

Keywords Chronic heart failure · Salt-sensitive hypertension · Neuronal nitric oxide synthase · Angiotensin II · Sympathetic activity

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Introduction

It is generally accepted that nitric oxide (NO) and angiotensin II (Ang II) play important roles in regulation of the sympathetic nervous system. Some studies have shown that NO suppresses sympathetic activity [1–3] and that Ang II enhances sympathetic activity [4, 5]. However, the effects of NO or Ang II on sympathetic activity are still controversial. Some studies have indicated that NO enhances sympathetic activity [6] and that Ang II suppresses sympathetic activity [7, 8]. The interaction of and balance between NO and Ang II have been discussed [9]. Katoh et al. [10] reported that cardiac Ang II receptors are up-regulated at an early phase in the chronic inhibition of NO synthesis in rats. Liu et al. [11] reported that the blockade of NO synthesis resulted in only an increase in renal sympathetic nerve activity (RSNA) when plasma Ang II levels were elevated. Hence, NO and Ang II interact with each other in various ways. In chronic heart failure (CHF), central and peripheral Ang II has been reported to be activated [12, 13], which results in an abnormal sympathotonic state [13]. In pacing-induced CHF, interactions between NO and Ang II have also been reported to be altered [14]. Liu et al. [5] reported that the blockade of Ang II receptors plus providing an exogenous source of NO

reduces RSNA below the elevated baseline levels in a pacing-induced CHF model compared with a control model.

However, the pathophysiological changes in NO and/or Ang II in the central and peripheral nervous systems have not been elucidated in salt-sensitive hypertension-induced CHF. We previously indicated that neuronal nitric oxide synthase (nNOS) neuron-mediated sympathoinhibition is up-regulated in hypertensive Dahl salt-sensitive (DSS) rats [2]. Immunohistochemical and histological studies have shown that nNOS is normally expressed in several areas of the brain and is considered to be involved in the neurogenic regulation of blood pressure [15, 16]. Ikeda et al. [17] demonstrated a reduced activity of renal nNOS activity in hypertensive DSS rats, although no differences in endothelial NOS and inducible NOS activity were observed. Hayakawa and Raij [18, 19] observed that salt-loading decreased aortic and renal constitutive NOS activity.

High-salt loading apparently suppresses the renin–angiotensin system (RAS). These findings suggest that salt-sensitive hypertension-induced CHF has a different background in the RAS and NO system compared to pacing-induced CHF. Clinically, hypertension-induced CHF is more common than tachycardia-induced CHF. Therefore, in this study we examined the effects of endogenous nNOS and Ang II on sympathetic activity in salt-sensitive hypertension-induced CHF. We elucidated the effects of Ang II on sympathetic activity when the controversial function of NO with a strong action was blocked.

Materials and methods

Animals

Salt-sensitive hypertension-induced chronic heart failure (CHF-DSS) was induced according to the methods reported by Inoko et al. [20] using five male DSS rats (CLEA Japan, Inc., Tokyo, Japan). In brief, DSS rats were fed an 8% NaCl diet for 9 weeks (from 6 to 15 weeks of age). To confirm the development of CHF, ventricular hypertrophy was estimated histologically, and left ventricular end diastolic pressure (LVEDP) was measured after the end of the experiments. Our CHF-DSS model was confirmed using another set of DSS rats: 19 high-salt-diet DSS rats and 22 regular-diet DSS rats. Five male Sprague–Dawley (SD) rats (Japan SLC, Inc., Shizuoka, Japan) were fed a high-salt chow containing 8% NaCl for 4 weeks (from 8 to 12 weeks of age) (high-salt SD), and another set of five SD rats were fed a low-salt chow containing 0.04% NaCl for 2 weeks (from 10 to 12 weeks of age) (low-salt SD). All animals were handled according to the Guidelines for Proper Conduct of Animal Experiments issued by the Science Council of Japan.

Mean arterial pressure (MAP) was higher in DSS and Dahl salt-resistant (DSR) rats than in SD rats under low-salt chow [21]. Moreover, the abundance of renal nNOS mRNA in DSS rats was similar to that of SD rats, but DSR rats exhibited approximately twice the nNOS mRNA level compared with DSS and/or SD rats under a normal-salt chow [22]. Plasma aldosterone was 2.3-fold greater in SD rats than in DSS rats under a normal-salt chow for 10 days [23]. Therefore, DSS and DSR strains have the possibility of disorders of the blood pressure regulation system and/or RAS; in this study, the SD strain was considered to be the normotensive control strain to examine the effects of endogenous Ang II.

Surgery

For caval occlusion, a balloon catheter (Fogarty-2F, Edwards Lifesciences, Irvine, CA) was inserted into the inferior vena cava from the right femoral vein or a perivascular occluder was put around the inferior vena cava in open-chest surgery under sterile conditions as described elsewhere [1]. Two weeks after this occluder surgery, electrodes (Teflon-coated stainless steel wires: AS633 Cooner Wire, Chatsworth, CA) for recording RSNA or electrocardiogram (ECG), and vascular catheters (Polyurethane tube: MRE-033, Braintree Scientific Inc., Braintree, MA) were implanted as described elsewhere [1]. Briefly, rats were anesthetized with pentobarbital (50 mg/kg, i.p.), and the left renal nerve was exposed through a left flank incision and dissected free from surrounding tissue under a dissecting microscope. Stainless steel bipolar electrodes were put under the nerve. The nerve and electrodes were covered and stabilized with a silicone rubber gel (Semicosil 932A and 932B, Wacker Chemie, Burghausen, Germany). The ECG electrodes were implanted under the skin at midchest. Heparin-filled catheters were inserted into the abdominal aorta from the left femoral artery to measure arterial pressure (AP) and MAP, and into the superior vena cava from the right jugular vein for the administration of phenylephrine (PE) or other drugs. All of the electrodes, catheters, and the occluder catheter were routed subcutaneously to exit at the nape of the neck and attached to a slip ring connected to a flexible wire, which allowed the rats to move freely. After each surgery, rats were treated with ampicillin (6.0 mg/kg) and pentazocine (1.0 mg/kg).

Experimental procedures

More than 48 h after the last surgery, experiments were performed on conscious and unrestricted rats that were chronically instrumented in their home cages. After a brief

stabilization period, resting AP, heart rate (HR), and RSNA were recorded for 20 min, and then baroreceptor (baro)-unloaded RSNA was measured. To obtain baro-unloaded RSNA, AP was decreased to produce maximal RSNA by caval occlusion. To obtain the noise level, AP was increased by the infusion of PE (10–15 μg/kg). Next, a selective nNOS inhibitor, *S*-methyl-L-thiocitrulline (SMTC, 10 mg/kg, Sigma Chemical Co., Tokyo), was administered intravenously (i.v.). At 40 min after the infusion of SMTC, resting AP, HR, RSNA, and baro-unloaded RSNA were recorded. Lastly, an Ang II type 1 (AT1) receptor blocker, losartan (10 mg/kg, kindly provided by Merck & Co., Inc., Whitehouse Station, NJ), was administered i.v. 60 min after the infusion of SMTC. At 60 min after the infusion of losartan (120 min after the infusion of SMTC), resting AP, HR, RSNA, and baro-unloaded RSNA were recorded. Based on the finding that with the SMTC (10 mg/kg, i.v.) doses used the attenuation of the NO response remained unaltered up to 3 h after drug administration [24], the blood pressure-lowering effects of losartan (10 mg/kg, i.v.) were sustained for at least 2 h [25]. Hence, nNOS and AT1 receptor were inhibited even 60 min after the infusion of losartan following SMTC administration.

Recordings

RSNA, AP, MAP, and HR were recorded by methods described elsewhere [1, 2]. RSNA was expressed as a percentage of the maximum RSNA obtained by decreasing AP in the control phase. To determine whether RSNA reached the maximum value, RSNA data were recorded while AP was decreased in a ramp fashion and were plotted against MAP data. A plateau in the sigmoid curve was confirmed on a computer with sigmoid curve-fitting [26]. The maximum RSNA in the control phase was considered to be 100%. All digitized values were displayed with a Macintosh microcomputer (Power Mac G4, Apple, CA, USA) and saved on a disk.

nNOS activities

After the end of the confirmation experiment using the other set of CHF-DSS and control rats, some of the animals were killed by decapitation to measure brain-tissue nNOS activity. The brainstem ($n = 16$) and diencephalon ($n = 12$) were immediately excised, rinsed with saline, frozen, and stored at −80°C until use. The activity of brain-tissue nNOS was measured as described elsewhere [2].

Statistical analysis

Values are expressed as the mean ± standard error (SE), and n is the number of animals. The significance of differences among the three groups (control, SMTC, and SMTC+Losartan; low-salt SD, high-salt SD, and CHF-DSS) were analyzed with one-way analysis of variance (ANOVA) and then compared to control values by Fisher's protected least-significant difference test (Fisher's PLSD). The significance of differences between two groups was analyzed with Student's unpaired t test. Statistical significance was defined as $P < 0.05$.

Results

Nine weeks of salt-loading generated ventricular enlargement and hypertrophy compared with a control rat (Fig. 1a), and an increase in mean LVEDP in CHF-DSS rats (Fig. 1b). LVEDV was 12.1 ± 1.8 mmHg in five CHF-DSS rats and 3.6 ± 1.0 mmHg in five SD rats that had been fed regular chow containing 0.4% NaCl ($P < 0.05$). Nine-week high-salt DSS rats ($n = 19$) and 9-week regular-salt DSS rats ($n = 22$) showed significant differences in body weight (308 ± 8 g vs. 396 ± 5 g, $P < 0.001$), heart weight per body weight (5.7 ± 0.15 mg/g vs. 3.2 ± 0.05 mg/g, $P < 0.001$), and left ventricle weight per body weight (3.8 ± 0.1 mg/g vs. 2.2 ± 0.04 mg/g, $P < 0.001$).

Table 1 shows MAP and HR in the low-Salt SD, high-Salt SD, and CHF-DSS rats before and after administration of the two inhibitors. MAP in CHF-DSS rats was significantly higher than those in low-salt and high-salt SD rats ($P < 0.001$). No significant difference was found in control HR among the three groups. The blockade of nNOS significantly increased MAP in CHF-DSS rats ($P < 0.05$), but not in low-salt SD or high-salt SD rats. Such blockade did not significantly change HR in any of the three groups. The successive blockade of AT1 receptors following SMTC

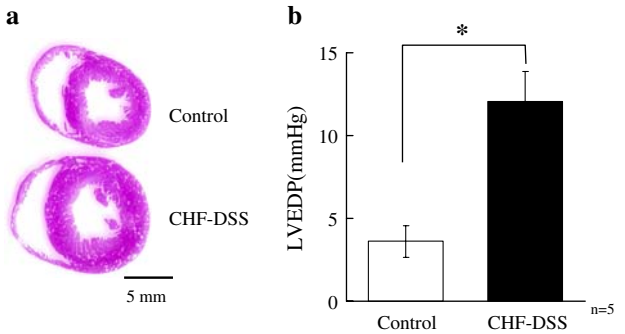

Fig. 1 **a** Representative cross-sectional tissue slices of the left ventricle from a high-salt-loaded Dahl salt-sensitive (CHF-DSS) rat and a regular-salt-diet Dahl salt-sensitive (control) rat. Tissues were stained by hematoxylin-eosin. **b** Left ventricular end diastolic pressure (LVEDP) from five CHF-DSS rats and five regular-salt-diet Sprague–Dawley rats (control). Values are expressed as mean ± SE. *$P < 0.05$ versus control

Table 1 Mean arterial pressure (MAP) and heart rate (HR)

	MAP (mmHg)	HR (beats/min)
Low-salt SD		
Control	89 ± 5	364 ± 22
SMTC	85 ± 6	373 ± 19
SMTC+losartan	69 ± 5*	445 ± 26*
High-salt SD		
Control	101 ± 4	391 ± 15
SMTC	109 ± 3	384 ± 11
SMTC+losartan	102 ± 6	387 ± 14
CHF-DSS		
Control	172 ± 8†,††	378 ± 20
SMTC	198 ± 8*	345 ± 18
SMTC+losartan	157 ± 10	416 ± 12

Control: before injection of drugs, SMTC: 40 min after a bolus injection of SMTC (10 mg/kg), SMTC+losartan: 60 min after subsequent injection of losartan (10 mg/kg) following SMTC

Low-salt SD: five Sprague–Dawley (SD) rats fed a low-salt chow, high-salt SD: five SD rats fed a high-salt chow, CHF-DSS: five Dahl salt-sensitive rats with hypertensive heart failure induced by high-salt loading

* Fisher's PLSD $P < 0.05$ versus Control

† Fisher's PLSD $P < 0.001$ versus high-salt SD

†† Fisher's PLSD $P < 0.001$ versus low-salt SD

decreased MAP and increased HR, which resulted in a return to control levels in CHF-DSS rats, but significantly deceased MAP ($P < 0.05$) and increased HR ($P < 0.05$) from the control level in low-salt SD rats, or had no effects on MAP or HR in high-salt SD rats.

Baro-unloaded RSNA was measured when AP was decreased by caval occlusion enough to obtain the maximum RSNA, as described elsewhere [1, 2]. Figure 2 shows typical recordings of baro-unloaded RSNA in the control, SMTC, and SMTC+Losartan phases in a CHF-DSS rat. The maximum level was confirmed by plotting a RSNA-MAP graph on a computer, indicated by arrows in Fig. 2. The average data of low-salt SD, high-salt SD, and CHF-DSS rats are shown in Fig. 3. In CHF-DSS rats, the blockade of nNOS did not significantly change resting RSNA even when it increased MAP, and the subsequent blockade of AT1 receptors did not significantly increase resting RSNA (Fig. 3c). In low-salt SD rats, the blockade of nNOS did not significantly change resting RSNA, but the subsequent blockade of AT1 receptors greatly increased resting RSNA (from the control of 42.9 ± 11.5% to 85.6 ± 10.9%; $P < 0.05$) with a decrease in MAP (Fig. 3a). Simultaneous blockade of nNOS and AT1 receptor did not appear to have any significant effect on resting RSNA and did not change MAP in high-salt SD rats (Fig. 3b).

In CHF-DSS rats, SMTC significantly decreased baro-unloaded RSNA (from 102.4 ± 1.7% to 76.0 ± 9.9%; $P < 0.05$), and subsequent losartan significantly recovered baro-unloaded RSNA to the control levels (from the control of 102.4 ± 1.7% to 105.0 ± 5.3%) (Fig. 3c). In low-salt SD rats, simultaneous blockade of nNOS and AT1 receptor did not appear to have any significant effect on baro-unloaded RSNA (Fig. 3a). In high-salt SD rats, while the blockade of nNOS did not significantly change baro-unloaded RSNA, the successive blockade of AT1 receptor significantly increased baro-unloaded RSNA (from the control of 97.8 ± 1.1% to 133.5 ± 11.8%; $P < 0.05$) (Fig. 3b).

Figure 4 shows brain-tissue nNOS activities in the brainstem ($n = 16$) and diencephalon ($n = 12$) of CHF-DSS rats compared to those in control rats. No significant difference was found in the brainstem nNOS activity of CHF-DSS rats compared to control rats (Fig. 4a). However, a significant difference was found in the diencephalon nNOS activity of CHF-DSS rats (8,361 ± 370 cpm/min/μg) compared to control rats (11,307 ± 276 cpm/min/μg) ($P < 0.001$; Fig. 4b).

Discussion

In this study, we examined the effects of intravenous losartan with SMTC on resting and baro-unloaded renal sympathetic activity in conscious and unrestrictive rats with salt-sensitive hypertension-induced CHF. There were two major findings: first, systemic inhibition of AT1-receptor concomitant with nNOS inhibition had no effect on baro-unloaded RSNA in CHF-DSS rats; second, the blockade of nNOS significantly decreased baro-unloaded RSNA in CHF-DSS rats.

Systemic administration of SMTC and/or losartan significantly changed MAP and RSNA. However, these changes were the product of baroreflexive negative feedback regulation, since, AP affected RSNA at ordinary times. To estimate the primary effect of SMTC and/or losartan on RSNA, we need to reduce the baroreflexive perturbation. Baro-unloaded sympathetic activity, which was obtained when AP was decreased enough to give the maximum level of RSNA, indicates that sympathetic activity was generated before baro-mediated inhibition and was little affected by AP. Therefore, baro-unloaded sympathetic activity was reflection of tonic sympathetic activity. Our previous studies [7, 26] suggested that sympathetic activity is raised at any given level of AP when baro-unloaded sympathetic activity is elevated. This means that an increase in baro-unloaded sympathetic activity may reflect an increase in tonic sympathetic activity. The administration of SMTC plus losartan did not change

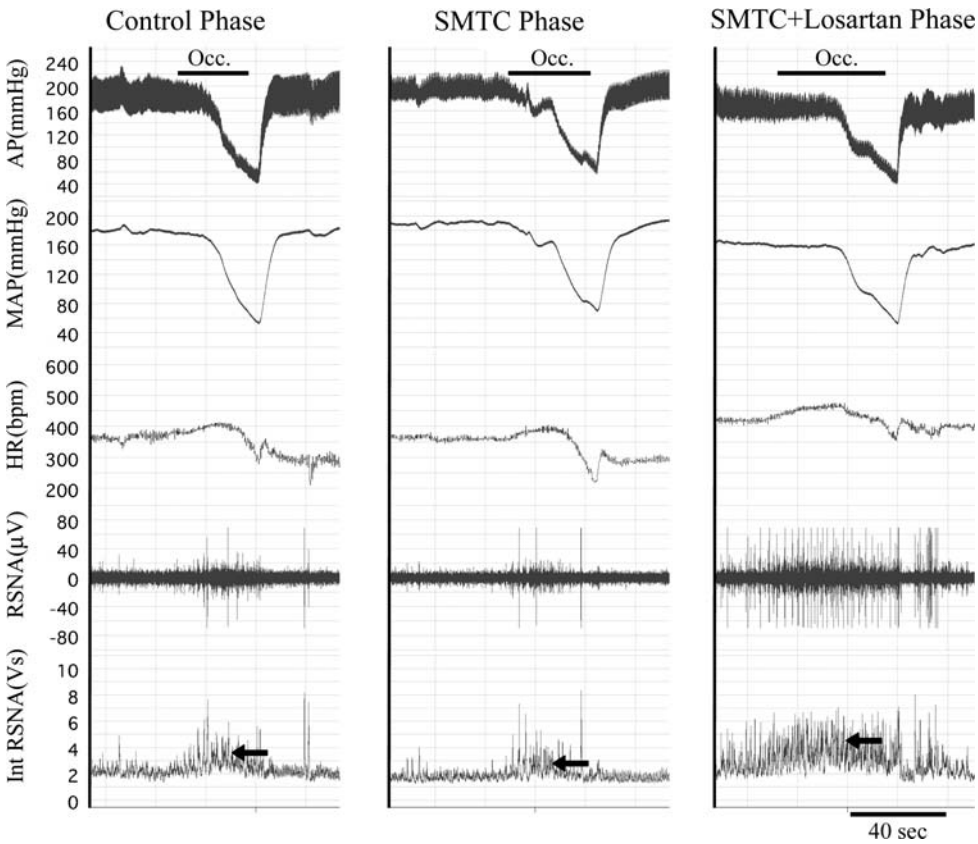

Fig. 2 Recordings obtained from a CHF-DSS rat in the control, SMTC, and SMTC+losartan phases. Control: before any drugs; SMTC: 40 min after intravenous *S*-methyl-L-thiocitrulline (SMTC, 10 mg/kg); SMTC+losartan: 60 min after intravenous losartan (10 mg/kg) following intravenous SMTC. *Occ*: caval occlusion to decrease arterial pressure at a rate of 3–5 mmHg/s. *AP* arterial pressure, *MAP* mean arterial pressure, *HR* heart rate, *RSNA* renal sympathetic nerve activity, *Int RSNA* integrated RSNA. Each *arrow* indicates a peak response of mean RSNA to a ramp decrease in AP by caval occlusion

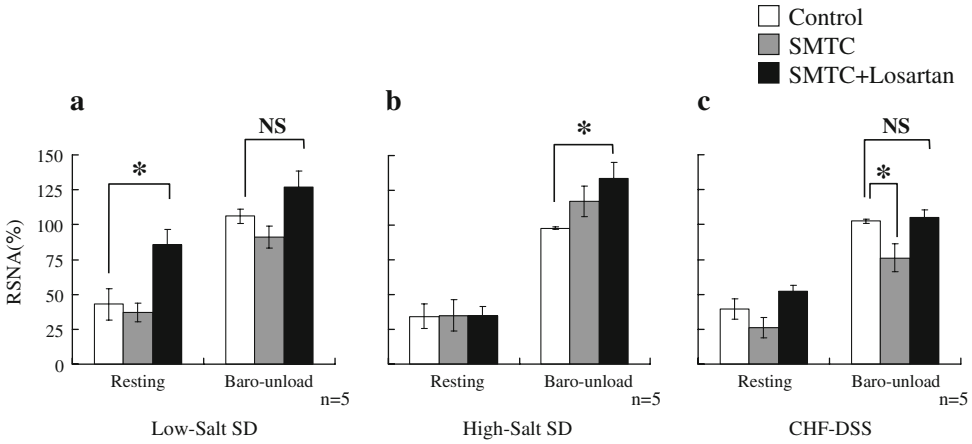

Fig. 3 Responses of resting and baroreceptor-unloaded (baro-unload) RSNAs to SMTC and SMTC+Losartan in low-salt SD, high-salt SD, and CHF-DSS rats. Low-salt SD: Sprague–Dawley rats fed a low-salt diet; high-salt SD: Sprague–Dawley rats fed a high-salt diet; CHF-DSS: Dahl salt-sensitive rats fed a high-salt diet with heart failure. RSNA was expressed as a percentage of the maximum RSNA in the control phase. Values are expressed as mean ± SE. $*P < 0.05$ versus the control phase. *NS* not significant

baro-unloaded RSNA, indicating that endogenous Ang II, independent of the effects of nNOS, has no effect on tonic sympathetic activity, which reflects central sympathetic activity generated before baro-mediated inhibition, in salt-sensitive hypertension-induced heart failure. This result is inconsistent with Zucker's observation, which will be discussed below.

Salt-sensitive hypertension-induced heart failure in this study was developed according to the method described by Inoko et al. [20]. Nine weeks of salt-loading produced hypertension (Table 1), ventricular hypertrophy, and increased LVEDP (Fig. 1). Another set of DSS rats, which received the same salt load, showed a decrease in body weight and an increase in heart weight and left ventricle

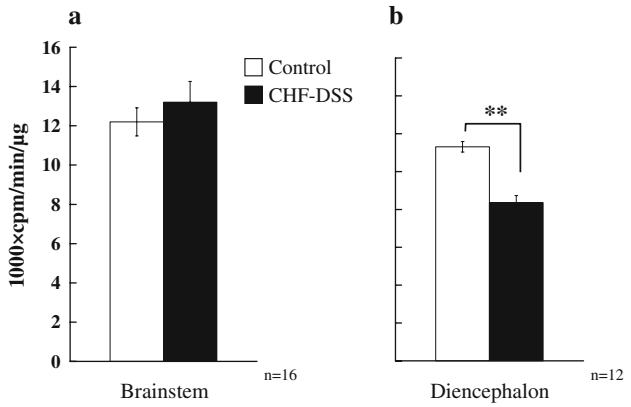

Fig. 4 Brain-tissue activity of neuronal nitric oxide synthase (nNOS) in the brainstem (**a**) and diencephalon (**b**) of high-salt-loaded Dahl rats (CHF-DSS) and regular-salt-diet Dahl rats (control). Enzyme activity was expressed as 1,000 cpm/min/μg of enzyme protein. Values are expressed as mean ± SE. $^{**}P < 0.001$ versus control

weight, which indicated cardiac cachexia and cardiac hypertrophy. Considering all of our findings, we believe that 9 weeks of salt-loading in DSS rats could induce heart failure, i.e., salt-sensitive hypertension-induced CHF.

The present study showed that the systemic inhibition of AT1-receptor concomitant with nNOS had no effect on baro-unloaded RSNA in CHF-DSS rats, although the successive injection of losartan following SMTC may be effective enough to block both nNOS and Ang II. This finding suggests that endogenous Ang II may not have any modulating effect on tonic sympathetic activity in the absence of perturbation by nNOS in salt-sensitive hypertension-induced CHF. However, Liu et al. [5] reported that the blockade of Ang II receptors plus providing exogenous NO reduces RSNA below elevated baseline levels in pacing-induced CHF. They stated that endogenous Ang II contributes to sympathoexcitation and both a loss of NO and an increase in Ang II are important for sustained increases in sympathetic activity in the CHF state [5, 13]. This is inconsistent with our results, and there are at least two possible explanations for this discrepancy. The first is the difference in activity in the RAS: high RAS activity in pacing-induced CHF versus lower RAS activity in salt-sensitive hypertension-induced CHF, which will be discussed below. The second is a methodological difference in the order of inhibitor administration (AT1 receptors are blocked first vs. second), or exogenous NO providing versus nNOS inhibition.

It is well accepted that plasma renin and/or Ang II level is elevated in CHF due to rapid pacing [27], cardiac infarction [28, 29], mitral valvular diseases [30], or human congestive heart failure [31]. On the other hand, Iwanaga et al. [32] reported that the plasma Ang II level was within a normal range in salt-sensitive hypertension-induced heart failure, which indicates that salt-induced heart failure may not have high RAS activity.

We compared the effect of losartan independent of the effects of nNOS activity on resting or baro-unloaded RSNA between the high RAS and low RAS states in normal SD rats. Low-salt loading may induce higher RAS activity because of marked decreases in AP after losartan. Wang et al. [33] demonstrated that low-salt intake causes higher plasma renin activity. Otherwise, high-salt loading may induce low RSA activity because of the lower decrease in AP after losartan. In fact, Sechi et al. [34] demonstrated that high-salt loading suppressed the plasma renin concentration and renal and hepatic tissue-angiotensinogen levels, indicating that salt-loading induces a low RAS state. There was a significant difference in the effects of losartan on tonic RSNA between the high and low RAS states (Fig. 3). These results might partly explain the effect of endogenous Ang II on RSNA between pacing-induced CHF and salt-induced CHF.

Our results showed that the systemic administration of SMTC significantly decreased baro-unloaded RSNA in CHF-DSS rats, suggesting that endogenous nNOS may enhance tonic sympathetic activity in salt-sensitive hypertension-induced CHF. This result is inconsistent with the finding that the systemic or intracerebroventricular administration of nNOS blockers markedly increases baro-unloaded RSNA in hypertensive DSS rats, suggesting that nNOS neuron-mediated sympathoinhibition is up-regulated in salt-sensitive hypertension [1, 2]. No clear explanation for this discrepancy has been elucidated.

We compared brain-tissue nNOS activity of the brainstem or diencephalon between control and CHF-DSS rats. While there was no significant difference in the activity of the brainstem between them, nNOS activity in the diencephalon was significantly lower in CHF-DSS rats than in control rats (Fig. 4). We have previously reported that there was no significant difference in the activity of the diencephalon between hypertensive DSS rats and regular-salt-diet DSS rats [2]. Heart failure significantly suppressed diencephalon nNOS activity, which was significantly different from the results in salt-sensitive hypertension without heart failure. This result partly supports our speculation on the fluctuating interaction between the endogenous nNOS and Ang II systems. No other report can explain the discrepancy described above.

The effects of NO or Ang II on sympathetic activity are still controversial. While some studies have indicated that NO has sympathoexcitatory effects [6], others have noted sympathoinhibitory effects [3]. Likewise, while some have demonstrated that Ang II shows sympathoexcitatory actions [4, 5], others have reported sympathoinhibitory actions [7, 8]. Further studies are needed from the perspective of reactive oxidant stresses or other mechanisms

associated with sympathetic generators and endogenous nNOS or Ang II systems.

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