Nishida et al., J Nephrol Ther 2013, 3:1
DOI: 10.4172/2161-0959.1000131

Journal of Nephrology & Therapeutics

Review Article Open Access

Sympathetic Activity in Dahl Salt-Sensitive Hypertension - Why is a Nitric Oxide-Induced Inhibitory System Up-Regulated in the Sympathetic Center?

Yasuhiro Nishida*, Megumi Tandai-Hiruma, Takehito Kemuriyama and Kohsuke Hagisawa

Department of Physiology, National Defense Medical College, Namiki 3-2, Tokorozawa, Saitama 359-8513, Japan

Abstract

In essential hypertension, peripheral sympathetic nerve activity is generally thought to be increased regardless of salt sensitivity or insensitivity. Recent reports suggest that the cause may be abnormal central nervous system enhancement. However, other several reports have shown that a central sympathetic inhibitory system, the neuronal nitric oxide synthase system, may be strongly enhanced in salt-sensitive hypertensive Dahl rats, an animal model of salt-sensitive hypertension. These two facts lead to questions what happens finally in peripheral sympathetic activity and what is the relationship between sympathetic nerves and hypertension. In this review, we will show evidences for enhancement of central sympathetic inhibitory system, putative cause for up-regulation of central neuronal nitric oxide synthase system, and a role of its function, then lastly we consider the relationship between hypertension and sympathetic nerves in a rat model, with a focus on salt-sensitive hypertension.

Keywords: Central nNOS neurons; Sympathetic center; Central dilemma; Endothelial abnormality; Radio-telemeter arterial pressure

Abbreviations: Acsf Icv: Intracerebroventricular Infusion Of Artificial Cerebrospinal Fluid; AP: Arterial Pressure; Baro: Arterial Baroreceptors; CNS: Central Nervous System; CPA: Caudal Pressor Area; CVLM: Caudal Ventrolateral Medulla; D: Day Time; DMH: Dorsomedial Hypothalamus; DR0.4%: Dahl Salt-Resistant Rats Fed A 0.4% Nacl Diet; DR8%: Dahl Salt-Resistant Rats Fed An 8% Nacl Diet; DS0.4%: Dahl Salt-Sensitive Rats Fed A 0.4% Nacl Diet (Regular Diet); DS8%: Dahl Salt-Sensitive Rats Fed An 8% Nacl Diet (High Salt Diet); DS8%: Nif-Dahl Salt-Sensitive Rats Fed A High Salt Diet and Oral Nifedipine, A Hypotensive Drug; ED_{50}: Half Maximal Response; E_{MAX}: Maximum Response; H: Humoral Outputs From The CNS; HR: Heart Rate; Ht: Heart; Icv: Intracerebroventricule; IML: Intermediolateral Column; LDT: Laterodorsal Tegmental Nucleus; MAP: Mean Arterial Pressure; N: Night Time; Nr: Neural Outputs From The CNS; Nnos: Neuronal Nitric Oxide Synthase; NO: Nitric Oxide; NTS: Nucleus Tractus Solitaries; Oc: Occlusion; PAG: Periaquaductal Gray Matter; PB: Parabrachial Nucleus; PSN: Peripheral Sympathetic Nerves; PVN: Paraventricular Nucleus; RSNA: Renal Sympathetic Nerve Activity; RVLM: Rostral Ventrolateral Medulla; SAP: Systolic Arterial Pressure; SD Rat: Sprague: Dawley Rat; SMTC: *S*-Methyl-L-Thiocitrulline; SON: Supraoptic Nucleus; TPR: Total Peripheral Resistance; VOL: Circulating Blood Volume

Introduction

Essential hypertension accounts for about 90% of all cases of hypertension, and both salt-sensitive and salt-insensitive cases are thought to exist [1,2]. It is unclear whether there are commonalities between these two conditions or whether they are completely different. The clear pathophysiological mechanisms of essential and/or salt-sensitive hypertension have not been elucidated and been discussed from many aspects [3-5], especially from genetics [6,7], renal abnormalities [8], central dysfunction [9], vascular endothelial dysfunction [10], hormonal dysfunction [11], immunological abnormality [12-14]. We have obtained several findings on sympathetic nerve output abnormalities in salt-sensitive hypertension, and here, we focus on the relationship between sympathetic activity and salt-sensitive hypertension animal model, and discuss the roles of sympathetic nerves in salt-sensitive hypertension.

Current thinking on the relationship between sympathetic activity and hypertension

From various research results, sympathetic nerve activity is thought to be enhanced in essential hypertension [15-17] and salt-sensitive hypertension [3,11]. Salt-sensitive hypertensive Dahl rats, well-known and long-researched animal model of salt-sensitive hypertension [14], show marked hypertension when given a high-salt diet (Figure 1). Even though no clear increase in activity was found as a result of peripheral nerve activity measurements even in this model, several reviews indicated that hypertension occurs due to sympathetic nerve enhancement from stress responses [18] and baroreceptor reflex responses [19,20].

How are hypertension and sympathetic nerve activity related? It is conceivable that peripheral vascular resistance increases when sympathetic nerve activity increases, leading to hypertension. However, this is not the only cause. Theoretically based on the fundamental physiology, sympathetic nerves also increase their release of adrenalin from the adrenal medulla [21,22], and Na^+ reabsorption is also promoted by increased renal sympathetic nerve activity [23,24]. Enhanced Na^+ accumulation leads to a negative spiral in which sympathetic nerve activity is increased and in turn promotes further Na^+ reabsorption [18]. Because a high-salt diet inhibits the volume receptor reflex in the cardiopulmonary region [25,26], Na^+ ion excretion is further inhibited by this response. However, surprisingly, Na^+ ions do not accumulate in the body of salt-sensitive hypertensive Dahl rats once they become hypertensive [27]. Once these rats become salt-sensitive hypertensive, the sensitivity of vascular contraction by sympathetic nerves becomes

***Corresponding author:** Yasuhiro Nishida, Department of Physiology, National Defense Medical College, Namiki 3-2, Tokorozawa, Saitama 359-8513, Japan, Tel: 04-2995-1483; Fax: 04-2996-5188; E-mail: ynishida@ndmc.ac.jp

Received April 21, 2013; **Accepted** June 17, 2013; **Published** June 24, 2013

Citation: Nishida Y, Hiruma MT, Kemuriyama T, Hagisawa K (2013) Sympathetic Activity in Dahl Salt-Sensitive Hypertension - Why is a Nitric Oxide-Induced Inhibitory System Up-Regulated in the Sympathetic Center? J Nephrol Ther 3: 131. doi:10.4172/2161-0959.1000131

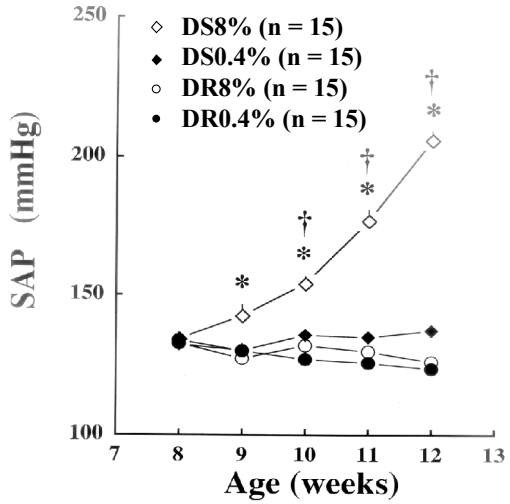

Figure 1: Development of salt-induced hypertension in Dahl rats. DS8%: Dahl salt-sensitive rats fed an 8% NaCl diet (high-salt diet); DS0.4%: Dahl salt-sensitive rats fed a 0.4% NaCl diet (regular diet); DR8%: Dahl salt-resistant rats fed an 8% NaCl diet; DR0.4%: Dahl salt-resistant rats fed a 0.4% NaCl diet; SAP: systolic arterial pressure measured with the tail cuff method in conscious rats; Age: rat age. *: $p < 0.005$ vs. DS0.4%; †: $p < 0.05$ vs. the initial (8-week) value for DS8%. The high-salt diet produced marked hypertension in Dahl salt-sensitive rats [28].

greater [28]. Moreover, various locally regulated vasoconstrictors are produced by vascular endothelial cells in peripheral vessels [29,30]. Abnormalities in local regulation in peripheral vessels also strongly contribute to hypertension.

Reasons for sympathetic nerve enhancement

What are the mechanisms that trigger this increase in sympathetic nerve activity in salt-sensitive hypertension? This question is a current focus of attention. Many studies are being conducted from the perspective of gene mutations as a causative mechanism, and reports continue to appear. Opinions on this have not yet come together, and this will not be discussed here.

Meanwhile, the mechanisms of the phenomena that explain this sympathetic nerve enhancement are also being elucidated. Na^+ ion transport abnormalities in the choroid of salt-sensitive hypertensive Dahl rats have been indicated, and elevation of the Na^+ ion concentration in cerebrospinal fluid activates the renin-angiotensin system in the brain. This is reported to cause abnormal excitement of sympathetic nerve centers [31]. Moreover, administration of antioxidants into cerebral ventricles inhibits hypothalamic reactive oxygen species, which blocks increases in sympathetic nerve activity and decreases blood pressure. Thus, abnormal production of hypothalamic reactive oxygen species is reported to enhance sympathetic nerves and lead to hypertension [32,33]. Gabor and Leenen [34,35] also have shown that a dysbalance between angiotensin II and nitiric oxide in the central nervous system including paraventriculara nucleus and rostral ventrolateral medulla leads to hypertension in Dahl salt hypertension. Even in spontaneously hypertensive rats, an animal model of essential hypertension, excessive proinflammatory substances in the medulla oblongata are reported to cause increased sympathetic nerve activity [36,37]. In all cases, abnormal excitement of central nerves has been shown.

Peripheral sympathetic nerve activity

From the above, in salt-sensitive hypertension, peripheral sympathetic nerve activity at rest is predicted to be higher than in subjects and animals with normal blood pressure. Attempts were made to measure renal sympathetic nerve activity at rest in an unanesthetized, unrestrained free movement state [38,39]. In actuality, this is not a simple thing to do. When nerve activity is expressed as a percent, no significant difference is found between normotension and hypertension (Table 1). Recently, other researchers have also reported no significant difference compared with normal blood pressure [40]. Even so, it is still difficult to say that there is no difference in nerve activity between the two. Problems exist in measurement technology and evaluations. Muscle sympathetic nerve activity in humans is evaluated and compared by the frequency of bursts only, but full nerve activity like an integrated activity cannot be shown because of differences in electric resistance of electrodes for nerve activity each by each. In animal experiments, full nerve activity is regularly evaluated to ensure accuracy, but still simple comparisons cannot be made because electrode resistance differs in each individual. Therefore, expression by percent was done as mentioned above, but because these are not absolute values, comparisons between individuals cannot be made.

From another point of views, not resting activity but the maximum activity, which is observed when baroreceptor reflex inhibition is suppressed completely, that is almost equal to an sympathetic generator activity in RVLM, may be higher in hypertensive subjects or rats than in normotensive subjects or rats, although there is still no way to confirm absolute values. From another different perspective, considering that nerve activity in hypertension might be the same level with normotension despite the high blood pressure, and/or baroreflex function may be suppressed in hypertension [19,20,41], nerve activity might be high even considering that in hypertension. Moreover, it is also true that resting nerve activity easily rises with a slight stimulus in hypertension [18,31], indicating that hypersensitivity in sympathetic response to stimuli in hypertension.

Central inhibitory system of sympathetic nerves

The enzyme activity of neuronal nitric oxide synthase (nNOS) has been inhibited in salt-sensitive hypertensive Dahl rats to see the effect. When 7-nitroindazole, an nNOS inhibitor, was administered systemically to rats in an unanesthetized, unrestrained state, peripheral sympathetic nerve activity increased significantly [38]. Moreover, when *S*-methyl-L-thiocitrulline (SMTC), an inhibitor with high specificity, was administered intraventricularly to rats in the same unanesthetized, unrestrained state, a similar rise was seen in resting peripheral sympathetic nerve activity as well as in blood pressure [39] (Figure 2). These results suggest the following: 1) central neurons with nNOS enzyme activity comprise a central inhibitory system of blood

	MAP (mmHg)	HR (bpm)	RSNA (%)
DS8% ras (n=9)	153 ± 4*	392 ± 11	24.4 ± 3.2
DS0.4% rats (n=8)	104 ± 3	378 ± 15	28.6 ± 2.4
DR8% rats (n=8)	96 ± 3	373 ± 16	24.7 ± 2.6
DR0.4% rats (n=9)	97 ± 2	393 ± 11	25.6 ± 1.8

DS8% rats: Dahl salt-sensitive rats fed an 8% NaCl diet; DS0.4% rats: Dahl salt-sensitive rats fed a 0.4% NaCl diet; DR8% rats: Dahl salt-resistant rats fed an 8% NaCl diet; DR0.4% rats: Dahl salt-resistant rats fed a 0.4% NaCl diet. MAP: mean arterial pressure; HR: heart rate; RSNA: renal sympathetic nerve activity, expressed as a %. The maximum RSNA (100%) was obtained by release of baroreflex-mediated inhibition by caval occlusion. *: $p < 0.05$ between the S8%, S0.4%, R8%, and R0.4% rat groups. The S8% rats show marked hypertension, but the RSNA level of the group does not show any difference between the four rat groups [28].

Table 1: Resting levels of MAP, HR, and RSNA in the four rats groups.

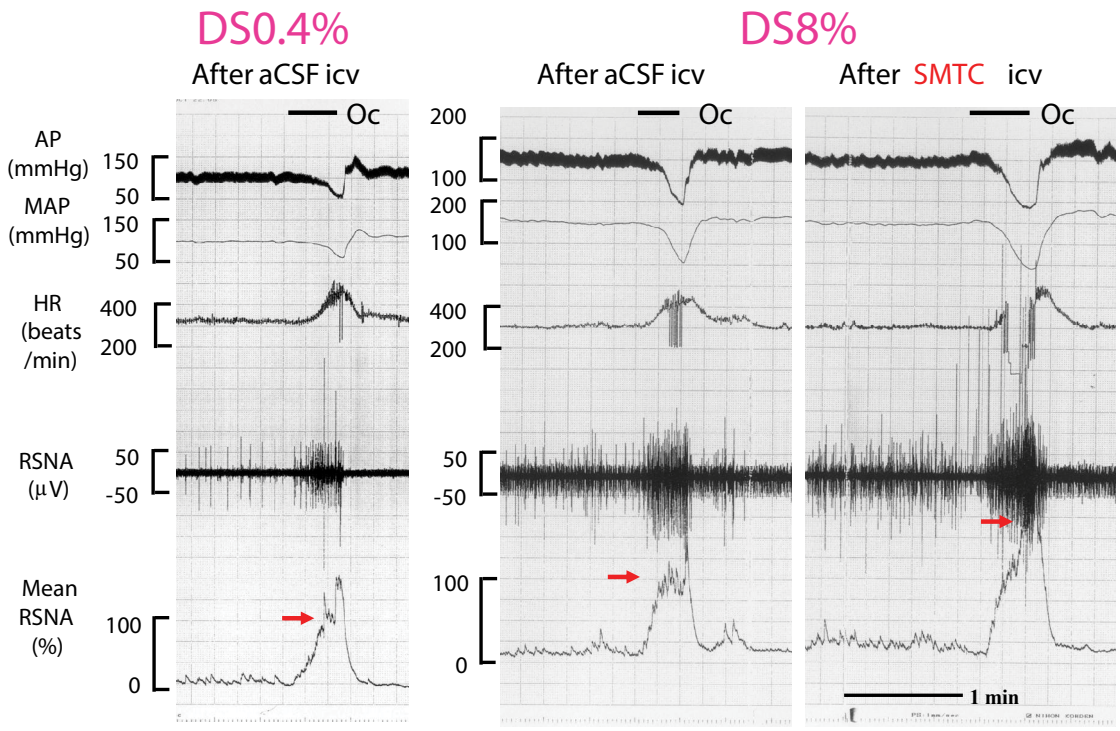

Figure 2: Effects of an nNOS inhibitor, SMTC, in the cerebrospinal of Dahl salt-sensitive rats on the maximum RSNA induced by hypotension. DS0.4%: Dahl salt-sensitive rats fed a regular diet; DS8%: Dahl salt-sensitive rats fed a high-salt diet; Oc with bar line: gradual caval occlusion in which the inferior vena cava was occluded in a ramp manner with a perivascular occluder. AP: arterial pressure; MAP: mean arterial pressure; HR: heart rate; RSNA: renal sympathetic nerve activity; mean RSNA: mean RSNA expressed as a %; aCSF icv: intracerebroventricular infusion of artificial cerebrospinal fluid (control groups); SMTC icv: intracerebroventricular infusion of 50 nmol *S*-methyl-L-thiocitrulline, an nNOS inhibitor [37]. Each arrow indicates a peak response of mean RSNA to a ramp decrease in MAP by caval occlusion. RSNA signals after these peak responses were produced by animal movements because of hypotension. Both resting RSNA and the peak response obtained by the release of baroreflex-mediated negative feedback inhibition (baroreceptor-unloaded RSNA, which indicates central sympathetic activity generated before baroreflex inhibition) were markedly increased after SMTC infusion [39].

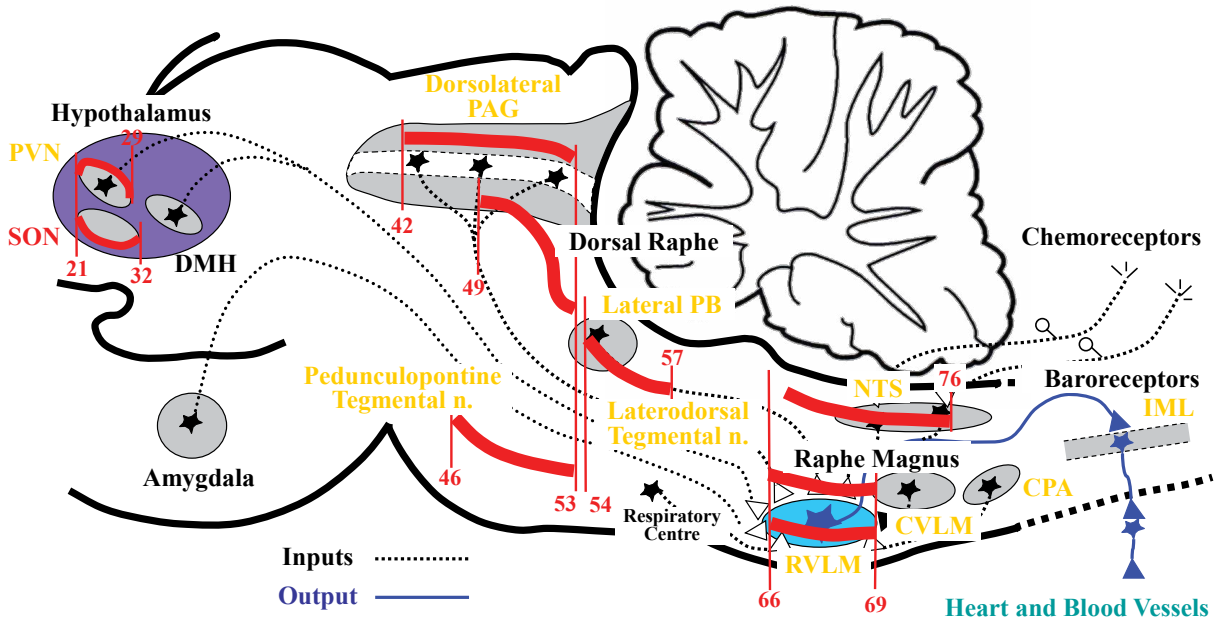

Figure 3: Distribution of nNOS neurons in rat brain [43]. Red bands indicate areas with higher numbers of nNOS neurons in Dahl salt-sensitive hypertensive rats compared with salt-sensitive normotensive rats. Yellow text indicates parts of the sympathetic center. Numbers indicate the plate number in the book by George Paxison [44]. PVN: paraventricular nucleus; SON: supraoptic nucleus; DMH: dorsomedial hypothalamus; PAG: periaquaductal gray matter; PB: parabrachial nucleus; NTS: nucleus tractus solitarius; RVLM: rostral ventrolateral medulla; CVLM: caudal ventrolateral medulla; CPA: caudal pressor area; IML: intermediolateral column.

pressure agonistic sympathetic nerve centers; 2) when inhibition is blocked, the activity of the rostral ventrolateral medulla (generator neurons of sympathetic nerve centers [39,42]) increases; and 3) the central inhibitory system is upregulated in salt-sensitive hypertensive Dahl rats.

Central nNOS neurons

Brainstem-tissue nNOS activity and nNOS protein amount were compared between 4 rats groups (salt-sensitive normotensive Dahl rats, salt-sensitive hypertensive Dahl rats, salt-resistant Dahl rats fed regular diet, salt-resistant Dahl rats fed high-salt diet) [39]. Both of brainstem nNOS activity and nNOS protein amount were significantly higher in the DS8% hypertensive group than in the other 3 normotensive rat-groups, and no significant difference was found in both of activity and protein amount between the 3 normotensive rat-groups (salt-sensitive normotensive Dahl rats, salt-resistant Dahl rats fed regular diet, salt-resistant Dahl rats fed high-salt diet) [39].

Immunostaining of nNOS enzymes in the brains of salt-sensitive hypertensive rats has been used to compare the distribution and number of nNOS neurons in the brain with normotensive groups [39,43]. The distribution of nNOS neurons in the brain is the same in salt-sensitive hypertensive Dahl rats (DS8%), salt-sensitive normotensive Dahl rats (DS0.4%), salt-resistant Dahl rats (DR0.4% and DR8%), and Sprague-Dawley (SD) rats on which they are based. This distribution is shown in Figure 3. nNOS neurons are distributed widely in nerve nuclei from the hypothalamus to the medulla, and many of the distributed nerve nuclei that contain these neurons correspond to blood pressure agonistic sympathetic nerve centers.

The number of nNOS neurons was counted for each brain nucleus and compared in hypertensive and normotensive rats [39,43,44] (Table 2). In hypertension, the number of nNOS neurons was significantly increased in seven of the ten different nuclei in which nNOS neurons were present. The number of all nNOS neurons was also significantly increased. Each of these seven nuclei is important as a sympathetic nerve center. These results demonstrate that nNOS neurons, which form a sympathetic nerve center inhibitory system, are upregulated in salt-sensitive hypertensive rats.

What is the cause of this upregulation of nNOS neurons? There are three possibilities: high salt, elevated blood pressure, and gene mutation. When hypertension was caused by a high-salt diet, blood pressure was decreased to a normal level with oral administration of nifedipine (Figure 4). When the number of nNOS neurons in the brain of salt-sensitive hypertensive rats with not-high blood pressure was compared (Table 2), the number of nNOS neurons had returned to the same number as in normotension in four of the seven nuclei in which the nNOS neuron number had increased [45]. The number in the pedunculopontine tegmental nucleus did not return enough to the same number as in salt-sensitive normotensive Dahl rats, but significantly decreased from the number in salt-sensitive hypertensive Dahl rats. In other words, the cause of the nNOS neuron up-regulation in these five nuclei was mostly hypertension per se.

In a comparison of nNOS neuron number in the brains of salt-sensitive hypertensive and normotensive Dahl rats and SD rats, the number of neurons was smaller in both salt-sensitive and resistant Dahl rats. Hence, the cause of the nNOS neuron activation in both nuclei of the supraoptic nucleus (SON) and the laterodorsal tegmental nucleus (LDT) that increased with salt-sensitive hypertension and that did not respond to hypertension treatment was thought to be high salt rather than gene mutations.

	DS04%	DS8%	DS8%-nif
Supraoptic nucleus	4355 ± 55	4886 ± 15*	4855 ± 53*
Paraventricular nucleus	2625 ± 59	2700 ± 41	2634 ± 72
Dorsolateral periaqueductal gray	1562 ± 41	2133 ± 38*	1545 ± 55†
Pedunculopontine tegmental nucleus	1590 ± 42	1921 ± 56*	1718 ± 60*†
Dorsal raphe nucleus	275 ± 36	322 ± 18	333 ± 17
Lateral parabrachial nucleus	1341 ± 32	1670 ± 27*	1424 ± 47†
Laterodorsal tegmental nucleus	2687 ± 166	3548 ± 134*	3443 ± 38*
Raphe magnus	420 ± 16	420 ± 12	420 ± 10
Rostral ventrolateral medulla	1751 ± 73	2432 ± 61*	1742 ± 56†
Nucleus tractus solitarius	788 ± 39	1072 ± 23*	698 ± 37†
Total	17394 ± 189	21106 ± 213*	19012 ± 198*†

DS0.4%: Dahl salt-sensitive normotensive rats (n=6); DS8%: Dahl salt-sensitive hypertensive rats (n=6); DS8%-nif: Dahl salt-sensitive rats fed a high-salt diet (n=6), in addition, their arterial pressure was normalized with the hypotensive drug, nifedipine (calcium antagonist, 50-62.5 mg/day *p.o.*). All nNOS-positive neurons were counted in every slice of each brain nucleus. Data are the mean ± SEM (n=6). *: $p < 0.05$ vs. the S0.4% group; †: $p < 0.05$ vs. the S8% group. (Modified from Ref. 45) The number of nNOS neurons is increased in most nNOS neuron-containing brain nuclei in salt-induced hypertensive rats. Treatment of hypertension abolishes the up-regulation of nNOS neuronal activity in most nNOS neuron-increased nuclei except for the supraoptic nucleus and the laterodorsal tegmental nucleus, in salt-induced hypertension.

Table 2: The number of nNOS neurons in the Dahl salt-sensitive rat brain.

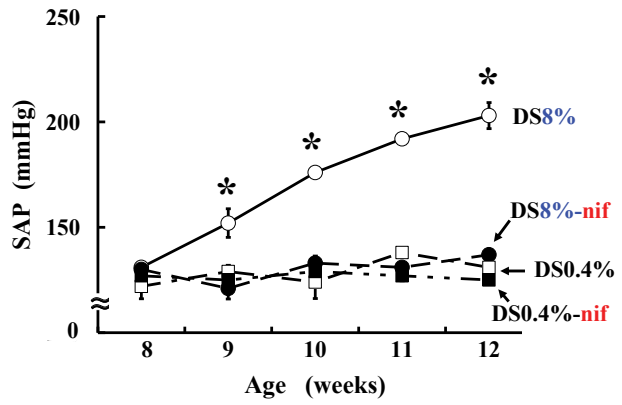

Figure 4: Arterial pressure was normalized with nifedipine in salt-induced hypertensive rats. DS 8%: Dahl salt-sensitive rats fed a high-salt diet only; DS 8%-nif: Dahl salt-sensitive rats fed a high-salt diet concomitant with nifedipine (50-62.5 mg/day); DS 0.4%-nif: Dahl salt-sensitive rats fed a regular salt diet concomitant with nifedipine (50-62.5 mg/day). SAP: systolic arterial pressure measured with the tail cuff method in conscious rats (n = 5); Age: rat age. *: $p < 0.05$ vs. DS-0.4%. Oral nifedipine, a hypotensive drug that acts via calcium antagonism, normalized arterial pressure in salt-induced hypertension [30].

Roles of central nNOS neurons

One may ask whether these upregulated nNOS neurons really inhibit sympathetic nerve activity that lowers blood pressure. When very small doses of SMTC were intraventricularly administered continuously for 2 weeks in unanesthetized, unrestrained salt-sensitive hypertensive rats, arterial pressure that had been hypertensive was found to rise even further [45] (Figure 5). Because nNOS neurons have been shown to inhibit sympathetic nerves from the acute infusion experiments of SMTC [38,39] and from the chronic infusion experiments of SMTC (Figure 5, [45]), activated nNOS neurons in the

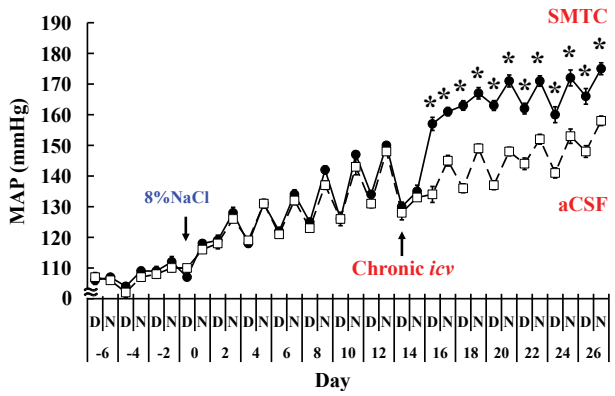

Figure 5: Changes in 24-hr arterial pressure measured with telemetry in Dahl salt-sensitive hypertensive rats fed a regular diet for 6 days followed by a high-salt diet (8% NaCl diet) for 26 days. After 14 days, an icv catheter and an osmotic minipump were implanted aseptically, and then an nNOS inhibitor, SMTC (7 μg/hr, SMTC group), or vehicle (0.5 μl/hr, aCSF group) was infused icv over 12 days in salt-induced hypertensive rats. aCSF: artificial cerebrospinal fluid; MAP: mean arterial pressure. The MAP value in each day or night phase (D or N) of the day is the average of 1440 sampled values obtained with radiotelemetry over 12 hr for each group. Data are the mean ± SE (n = 5 for each group). *: $p < 0.05$ compared with the corresponding phase on Day 12 in the SMTC group, or compared with the corresponding day in the aCSF group. icv SMTC significantly amplified hypertension in salt-induced hypertension and worsened hypertension compared to the saline icv group [45].

brain were demonstrated to inhibit hypertension through sympathetic nerve inhibition.

Thus, in salt-sensitive hypertensive rats, Na^+ transport abnormalities in the choroid in the brain [31] and overproduction of reactive oxygen species in the hypothalamus [32] increase sympathetic nerve activity centrally. However, nNOS neurons, which comprise the central sympathetic nerve inhibitory system, are upregulated by elevated blood pressure and block increases in peripheral sympathetic nerve activity. Peripheral nerve activity is thought not to increase much as a result, so that the marked difference with normotension is no longer found, at least in the periphery.

Causes of continuing hypertension

Because evaluations of sympathetic nerve activity in the hypertension formation process are not necessarily accurate, the role of sympathetic nerve activity in this process is not well understood. However, looking at hypertension that already exists, resting sympathetic nerve activity is relatively stabilized [38,39], which suggests that sympathetic activity may not be a powerful factor in maintaining hypertension.

Osborn et al. reported that hypertension induced by a high-salt diet is normalized by renal denervation [46]. This may also involve blood pressure normalization from elimination of Na^+ ion reabsorption by the renal nerves and stimulation of renin secretion, and the possibility has been suggested that information from afferent nerves from the kidneys also contributes in some way [47]. Moreover, the contractility of peripheral vessels is known to be increased (Figure 6), and local dysregulation due to vascular endothelial cells continues to be shown [28,30].

Considering the above observations together, the primary causes of continuing hypertension may be peripheral control problems, such as local dysregulation [29,48,49] in peripheral vessels or renal dysfunction [14,50-52], rather than a problem in central control.

Conclusion

In Dahl hypertensive rats, the sympathetic center becomes pathophysiologically hyper-reactive, concomitant with compensatory upregulated activity in nNOS neuron-mediated inhibitory systems of the central sympathetic center, which results in almost same activity in resting peripheral sympathetic nerve of hypertensive Dahl rats as that of normotensive Dahl rats. The enhancement of the central inhibitory system caused by high blood pressure *per se* produces reduction in arterial pressure, indicating that the sympathetic control system seems to be operated in order to counter-attack hypertension, although the other part of the sympathetic center becomes pathophysiologically enhanced. This is a kind of dilemma in the sympathetic center: one inhibited and the other excited. Peripheral sympathetic activity in hypertensive Dahl rats is not so high as to explain hypertension, but the target organs have enough damage to explain hypertension. The kidney functions abnormally, and the peripheral vascular system shows hypertrophy and abnormally functioning endothelium, as shown in Figure 7.

Hypertension is a cause of nNOS neuron upregulation, meaning that signals from the periphery where hypertension is sensed induce enhancement of the inhibitory system. Information from baroreceptors may be involved. Peripheral information that tries to block central abnormalities and enhancement of the inhibitory system occur in addition to local dysregulation of peripheral tissue, and ultimately, development of hypertension will occur when all of these factors contribute.

The functions necessary for an organism to live are divided and specialized, and the life of an individual comes from the integration of all these various functions. This integration is achieved through circulation, and blood pressure is the driving force of that circulation. Therefore, the essential mission of the long-term blood pressure regulatory mechanism [53] cannot be fulfilled with only one-way instructions from either peripheral tissues or central nerves. Even if central or peripheral abnormalities exist, hypertension may form when a steady state is reached as a result of compromise between the demands of both.

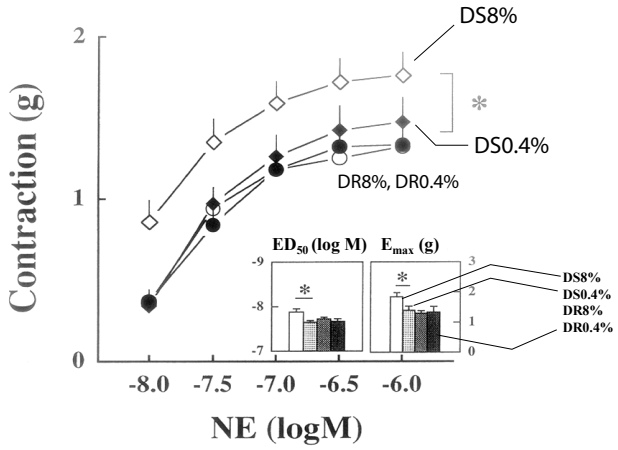

Figure 6: Contractive activities evoked by norepinephrine (NE, 10^{-8} to 10^{-6} mol/l) in aortic rings of rats in the four groups. ◇, □: Dahl salt-sensitive rats fed 8% NaCl (n = 10); ◆, lightly dotted bars: Dahl salt-sensitive rats fed 0.4% NaCl (n = 12); ○, heavily dotted bars: Dahl salt-resistant rats fed 8% NaCl (n = 12); ●, ■: Dahl salt-resistant rats fed 0.4% NaCl (n = 10). ED_{50}: a logarithm of agonist concentration at half maximal response; E_{max}: maximum response. *: $p < 0.05$ between high-salt and low-salt Dahl salt-sensitive rat groups [28].

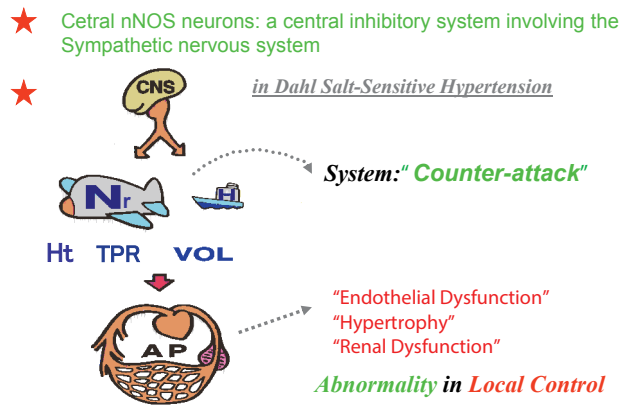

Figure 7: Putative characteristics of the blood pressure control system and the target organs in Dahl salt-sensitive hypertension [53]. Baro: Arterial Baroreceptors; CNS: Central Nervous System; Nr Inside An Airplane: Neural Outputs From The CNS; H Inside A Ship: Humoral Outputs From The CNS; Ht: Heart; TPR: Total Peripheral Resistance; VOL: Circulating Blood Volume; AP: Arterial Pressure; PSN: Peripheral Sympathetic Nerves [53]. In Dahl hypertensive rats, the sympathetic center becomes pathophysiologically hyper-reactive, concomitant with compensatory upregulated activity in nNOS neuron-mediated inhibitory systems of the central sympathetic center, which is a dilemma in the sympathetic center, resulting in almost same activity in resting peripheral sympathetic nerve in hypertensive Dahl rats as that in normotensive Dahl rats. Once the NO-mediated inhibitory system is suppressed due to some stimuli, hypertensive Dahl rats produce hyper-reactivity in peripheral sympathetic activity. On the other side of the target organs, the kidney functions abnormally, and the peripheral vascular system shows hypertrophy and abnormally functioning endothelium.

Acknowledgments

The authors thank Associate Professor Kouichi Fukuda and the staff of the Center for Laboratory Animal Science, National Defense Medical College for their cooperation for this research. This study was conducted with research funds from the Salt Science Research Foundation (#0338, #0435, #0535), a 2007-2009 Special Research Grant from the National Defense Medical College, and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (C 11009567). We are grateful for this support.

References

1. Ando K, Fujita T (2005) Salt-sensitive hypertension. Nihon Rinsho 63 Suppl 3: 125-131.
2. Fujita T, Henry WL, Bartter FC, Lake CR, Delea CS (1980) Factors influencing blood pressure in salt-sensitive patients with hypertension. Am J Med 69: 334-344.
3. Ando K, Fujita T (2012) Pathophysiology of salt sensitivity hypertension. Ann Med 44 Suppl 1: S119-126.
4. Rodriguez-Iturbe B, Romero F, Johnson RJ (2007) Pathophysiological mechanisms of salt-dependent hypertension. Am J Kidney Dis 50: 655-672.
5. Johnson RJ, Feig DI, Nakagawa T, Sanchez-Lozada LG, Rodriguez-Iturbe B (2008) Pathogenesis of essential hypertension: historical paradigms and modern insights. J Hypertens 26: 381-391.
6. Sanada H, Jones JE, Jose PA (2011) Genetics of salt-sensitive hypertension. Curr Hypertens Rep 13: 55-66.
7. Armani C, Botto N, Andreassi MG (2011) Susceptibility genes in hypertension. Curr Pharm Des 17: 2973-2986.
8. Trepiccione F, Zacchia M, Capasso G (2012) The role of the kidney in salt-sensitive hypertension. Clin Exp Nephrol 16: 68-72.
9. Takahashi H, Yoshika M, Komiyama Y, Nishimura M (2011) The central mechanism underlying hypertension: a review of the roles of sodium ions, epithelial sodium channels, the renin-angiotensin-aldosterone system, oxidative stress and endogenous digitalis in the brain. Hypertens Res 34: 1147-1160.
10. Michell DL, Andrews KL, Chin-Dusting JP (2011) Endothelial dysfunction in hypertension: the role of arginase. Front Biosci (Schol Ed) 3: 946-960.
11. Osborn JW, Fink GD, Kuroki MT (2011) Neural mechanisms of angiotensin II-salt hypertension: implications for therapies targeting neural control of the splanchnic circulation. Curr Hypertens Rep 13: 221-228.
12. Rodríguez-Iturbe B, Franco M, Tapia E, Quiroz Y, Johnson RJ (2012) Renal inflammation, autoimmunity and salt-sensitive hypertension. Clin Exp Pharmacol Physiol 39: 96-103.
13. Schiffrin EL (2010) T lymphocytes: a role in hypertension? Curr Opin Nephrol Hypertens 19: 181-186.
14. Zicha J, Dobešová Z, Vokurková M, Rauchová H, Hojná S, et al. (2012) Age-dependent salt hypertension in Dahl rats: fifty years of research. Physiol Res 61: S35-87.
15. Grassi G (2010) Sympathetic neural activity in hypertension and related diseases. Am J Hypertens 23: 1052-1060.
16. Wallin BG, Delius W, Hagbarth KE (1973) Comparison of sympathetic nerve activity in normotensive and hypertensive subjects. Circ Res 33: 9-21.
17. Yamada Y, Miyajima E, Tochikubo O, Matsukawa T, Ishii M (1989) Age-related changes in muscle sympathetic nerve activity in essential hypertension. Hypertension 13: 870-877.
18. Mark AL (1991) Sympathetic neural contribution to salt-induced hypertension in Dahl rats. Hypertension 17: I86-90.
19. Gordon FJ, Mark AL (1984) Mechanism of impaired baroreflex control in prehypertensive Dahl salt-sensitive rats. Circ Res 54: 378-387.
20. Ferrari AU, Gordon FJ, Mark AL (1984) Primary impairment of cardiopulmonary baroreflexes in Dahl salt-sensitive rats. J Hypertens Suppl 2: S401-403.
21. Abd-Allah NM, Hassan FH, Esmat AY, Hammad SA (2004) Age dependence of the levels of plasma norepinephrine, aldosterone, renin activity and urinary vanillylmandelic acid in normal and essential hypertensives. Biol Res 37: 95-106.
22. de Champlain J, Farley L, Cousineau D, van Ameringen MR (1976) Circulating catecholamine levels in human and experimental hypertension. Circ Res 38: 109-114.
23. DiBona GF (1978) Neural control of renal tubular sodium reabsorption of the dog. Fed Proc 37: 1214-1217.
24. DiBona GF (1992) Sympathetic neural control of the kidney in hypertension. Hypertens 19: 128-135.
25. Mark AL, Victor RG, Ferrari A, Morgan DA, Thorén P (1987) Cardiac sensory receptors in Dahl salt-resistant and salt-sensitive rats. Circulation 75: I137-140.
26. Thornton RM, Wyss JM, Oparil S (1989) Impaired reflex response to volume expansion in NaCl-sensitive spontaneously hypertensive rats. Hypertension 14: 518-523.
27. Tsunooka K, Morita H (1997) Effect of a chronic high-salt diet on whole-body and organ sodium contents of Dahl rats. J Hypertens 15: 851-856.
28. Nishida Y, Ding J, Zhou MS, Chen QH, Murakami H, et al. (1998) Role of nitric oxide in vascular hyper-responsiveness to norepinephrine in hypertensive Dahl rats. J Hypertens 16: 1611-1618.
29. Barton M, d'Uscio LV, Shaw S, Meyer P, Moreau P, et al. (1998) ET(A) receptor blockade prevents increased tissue endothelin-1, vascular hypertrophy, and endothelial dysfunction in salt-sensitive hypertension. Hypertension 31: 499-504.
30. Zhou MS, Nishida Y, Chen QH, Murakami H, Hosomi H, et al. (1998) Is a hypertensinogenic factor present in the kidney of hypertensive dahl rats? Clin Exp Pharmacol Physiol 25: 800-804.
31. Huang BS, Leenen FH (2011) Mineralocorticoid actions in the brain and hypertension. Curr Hypertens Rep 13: 214-220.
32. Ando K, Fujita M (2012) Reactive oxygen species and the central nervous system in salt-sensitive hypertension: possible relationship with obesity-induced hypertension. Clin Exp Pharmacol Physiol 39: 111-116.
33. Fujita M, Ando K, Kawarazaki H, Kawarasaki C, Muraoka K, et al. (2012) Sympathoexcitation by brain oxidative stress mediates arterial pressure elevation in salt-induced chronic kidney disease. Hypertension 59: 105-112.
34. Gabor A, Leenen FH (2012) Central neuromodulatory pathways regulating sympathetic activity in hypertension. J Appl Physiol 113: 1294-1303.

35. Gabor A, Leenen FH (2013) Central mineralocorticoid receptors and the role of angiotensin II and glutamate in the paraventricular nucleus of rats with angiotensin II-induced hypertension. Hypertension 61: 1083-1090.

36. Waki H, Gouraud SS, Maeda M, Paton JF (2008) Specific inflammatory condition in nucleus tractus solitarii of the SHR: novel insight for neurogenic hypertension? Auton Neurosci 142: 25-31.

37. Waki H, Hendy EB, Hindmarch CC, Gouraud S, Toward M, et al. (2013) Excessive leukotriene B4 in nucleus tractus solitarii is prohypertensive in spontaneously hypertensive rats. Hypertension 61: 194-201.

38. Nishida Y, Chen QH, Tandai-Hiruma M, Terada S, Horiuchi J (2001) Neuronal nitric oxide strongly suppresses sympathetic outflow in high-salt Dahl rats. J Hypertens 19: 627-634.

39. Tandai-Hiruma M, Horiuchi J, Sakamoto H, Kemuriyama T, Hirakawa H, et al. (2005) Brain neuronal nitric oxide synthase neuron-mediated sympathoinhibition is enhanced in hypertensive Dahl rats. J Hypertens 23: 825-834.

40. Yoshimoto M, Onishi Y, Mineyma N, Shirai M, Miki K (2012) Renal and lumbar sympathetic nerve activity during the development of hypertension in Dahl-salt sensitive rats. Experimental Biology 2012 Program.

41. Brunner MJ, Kligman MD (1992) Rapid resetting of baroreflexes in hypertensive dogs. Am J Physiol 262: H1508-H1514.

42. Nishida Y, Bishop VS (1992) Vasopressin-induced suppression of renal sympathetic outflow depends on the number of baroafferent inputs in rabbits. Am J Physiol 263: R1187-1194.

43. Nishida Y, Tandai-Hiruma M, Kemuriyama T, Sato Y, Tsukada S, et al. (2007) Central nNOS neuron-mediated sympathetic regulation in salt-sensitive hypertension. In: Central Mechanisms of Cardiovascular Regulation, edited by Kubo T, Kuwaki T. Transworld Research Network, Kerala, India, pp. 45-56.

44. Paxinos G, Watson C (1998) The Rat Brain in Stereotaxic Coordinates. (5thedn), San Diego, CA: Academic Press 21-76.

45. Tandai-Hiruma M, Kato K, Kemuriyama T, Ohta H, Tashiro A, et al. (2013) High blood pressure enhances brain stem neuronal nitric oxide synthase activity in Dahl salt-sensitive rats. Clin Exp Pharmacol Physiol 40: 197-204.

46. Osborn JW (2005) Hypothesis: set-points and long-term control of arterial pressure. A theoretical argument for a long-term arterial pressure control system in the brain rather than the kidney. Clin Exp Pharmacol Physiol 32: 384-393.

47. Jacob F, Ariza P, Osborn JW (2003) Renal denervation chronically lowers arterial pressure independent of dietary sodium intake in normal rats. Am J Physiol Heart Circ Physiol 284: H2302-2310.

48. Schulman IH, Zhou MS, Raij L (2006) Interaction between nitric oxide and angiotensin II in the endothelium: role in atherosclerosis and hypertension. J Hypertens Suppl 24: S45-50.

49. Lukaszewicz KM, Lombard JH (2013) Role of the CYP4A/20-HETE pathway in vascular dysfunction of the Dahl salt-sensitive rat. Clin Sci (Lond) 124: 695-700.

50. Wadei HM, Textor SC (2012) The role of the kidney in regulating arterial blood pressure. Nat Rev Nephrol 8: 602-609.

51. Schulz A, Kreutz R (2012) Mapping genetic determinants of kidney damage in rat models. Hypertens Res 35: 675-694.

52. Liu J, Kennedy DJ, Yan Y, Shapiro JI (2012) Reactive Oxygen Species Modulation of Na/K-ATPase Regulates Fibrosis and Renal Proximal Tubular Sodium Handling. Int J Nephrol 2012: 381320.

53. Nishida Y, Tandai-Hiruma M, Kemuriyama T, Hagisawa K (2012) Long-term blood pressure control: is there a set-point in the brain? J Physiol Sci 62: 147-161.