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

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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: 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); DSNF: Nif-Dahl Salt-Sensitive Rats Fed A High Salt Diet and Oral Nifedipine, A Hypotensive Drug; ED50: Half Maximal Response; EMAX: Maximum Response; H: Humoral Outputs From The CNS; HR: Heart Rate; Ht: Heart; Icv: Intracerebroventricle; IML: Intermediolateral Column; LDT: Lateraldorsal 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; RVL: Rostral Ventrolateral Medulla; SAP: Systolic Arterial Pressure; SD Rat: Sprague: Dawley Rat; SMT: 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 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...
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 the medulla oblongata is reported to enhance sympathetic nerves and lead to hypertension in Dahl salt-sensitive rats [28]. 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 yet it is considered that abnormalities in the central nervous system are involved. For example, abnormal excitement of central nerves has been shown. Thus, abnormal production of hypothalamic reactive oxygen species (ROS) 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 of angiotensin II and nitric oxide in the central nervous system including paraventricular 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 a 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 NOS inhibitor, was administered systemically to rats in an unanesthetized, unrestrained state, peripheral sympathetic nerve activity increased significantly [38]. Moreover, when S-methyl-L-thiocitrulline (SMT), 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 pressure in Dahl salt-sensitive hypertensive rats, and 2) 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.

| MAP (mmHg) | HR (bpm) | RSNA (%) |
|------------|----------|----------|
| DS8% (n=9) | 153 ± 4† | 392 ± 11 | 24.4 ± 3.2 |
| D0.4% rats (n=6) | 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; D0.4% 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 caudal occlusion. †: p < 0.05 between the S8% and D0.4% rats. From another point of view, not resting activity but the maximum activity, which is observed when baroreceptor reflex inhibition is suppressed completely, that is almost equal to a 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.

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Figure 2: Effects of an nNOS inhibitor, SMTC, in the cerebrospinal fluid 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: periaqueductal 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 in seven of the ten different nuclei in which nNOS neurons were present. The number of nNOS neurons in the 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 lateral dorsal tegmental nucleus, in salt-induced hypertension.

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 (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.

| Nucleus                  | DS0.4%     | DS8%      | DS8%-nif |
|--------------------------|------------|-----------|----------|
| Supraoptic nucleus       | 4355 ± 55  | 4886 ± 15 | 4865 ± 53|
| Paraventricular nucleus  | 2625 ± 59  | 2700 ± 41 | 2634 ± 72|
| Dorsolateral periaqueductal gray nucleus | 1562 ± 41 | 2133 ± 36 | 1549 ± 58 |
| 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|

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

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.

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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 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].

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

| Age (weeks) | 0 | 8 | 9 | 10 | 11 | 12 |
|-------------|---|---|---|----|----|----|
| SAP (mmHg)  | 250 | 200 | 150 | * | * | * |
| DS8%        | * | * | * | * | * | * |
| DS8%-nif    | * | * | * | * | * | * |
| DS0.4%      | * | * | * | * | * | * |
| DS0.4%-nif  | * | * | * | * | * | * |

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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.
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