Transient hypercapnic stress causes exaggerated and prolonged elevation of cardiac and renal interstitial norepinephrine levels in conscious hypertensive rats

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Sobajima M, Nozawa T, Nakadate T, Shida T, Ohori T, Suzuki T, Matsuki A, Hirai T, Inoue H. Transient hypercapnic stress causes exaggerated and prolonged elevation of cardiac and renal interstitial norepinephrine (iNE) levels during and after transient hypercapnia were investigated in conscious SS rats. Dahl SS and salt-resistant (SR) 6-wk-old rats were fed a high-salt diet, and at 12 wk iNE levels in the heart and kidney were determined using microdialysis with probes inserted in the left ventricular (LV) wall and kidney. A telemetry system determined blood pressure and heart rate (HR) in separate animals. After recovery from the operation, data were collected before, during, and after exposure to normoxic 10% CO2 for 25 min under unanesthetized conditions. The plasma NE concentrations at baseline did not differ between the two strains. Both cardiac and renal iNE levels were much higher in SS rats than in SR rats at baseline as well as during hypercapnic stress. After stress, the markedly increased iNE levels of SS rats were prolonged in the LV as well as in the kidney. During hypercapnic stress, HR decreased in both SS and SR rats, while sudden increases in HR immediately after the withdrawal from stress were followed by its slower reduction in SS rats compared with SR rats. In conclusion, transient hypercapnic stress causes exaggerated and prolonged elevation of iNE levels in the heart as well as in kidneys of SS animals.

central sympathoexcitation and renal fluid retention may be involved in the development of salt-sensitive (SS) hypertension. Transient environmental or mental stress in SS animals and subjects causes a greater increase in blood pressure (BP) and renal sympathetic nerve (SN) activity and greater antinatriuresis compared with salt-resistant (SR) animals and subjects (2, 3, 9, 16). Hypertension is also accompanied by increased chemoreflex sensitivity (29, 33) and, therefore, hypoxic and/or hypercapnic stress could augment SN activity in SS hypertensive subjects complicated by sleep apnea syndrome. Thus, the enhanced SN responsiveness to stress may play a role in the high morbidity or mortality of SS hypertensive subjects. However, it remains unclear whether the augmented response of renal SN activity to transient stress occurs in parallel to the response in other organs, especially in the heart, because it is difficult to directly determine cardiac SN activity in conscious animals. Kamiya et al. (11) reported that muscle SN activity parallels the renal and cardiac SN activity in response to baroreceptor pressure changes in anesthetized rabbits. In contrast, others have reported that central or peripheral stimuli cause selective and differential influences on the SN activity of each organ in anesthetized and conscious animals (13, 36, 37).

Previous studies have shown that cardiovascular recovery from stress plays an important role in the pathogenesis of hypertension and is a predictor of overall mortality (1, 5). Sustained increases in SN activity after transient stress may accelerate cardiovascular damage. In studies of healthy volunteers, long-lasting muscle SN activation was evoked after the transient stress induced by hypoxemia (6, 38). In another study, an increase in renal vascular resistance during the handgrip exercise was exaggerated and prolonged in patients with heart failure compared with normal subjects (21), whereas earlier recovery of increased SN activity after mental stress has also been reported (20).

Accordingly, the present study was performed in conscious Dahl SS and SR rats to determine interstitial norepinephrine (iNE) levels of heart and kidney using a microdialysis method and to clarify whether the response of cardiac iNE to stress occurs in parallel to the response of renal iNE and whether responses of renal and cardiac iNE to hypercapnic stress in SS rats are exaggerated and prolonged after stress compared with SR rats.

MATERIALS AND METHODS

Animals. The present study was undertaken in accordance with the guidelines for animal experimentation at the University of Toyama, and the present experiment was approved by the Animal Experiment Committee of the University of Toyama. Dahl SS and SR rats were fed a 0.3% NaCl diet (low salt) until 6 wk of age and thereafter an 8% NaCl diet (high salt). The special diet and tap water were given ad libitum throughout the experiment.

Hemodynamic study under anesthesia. Under light anesthesia with pentobarbital sodium (20 mg/kg, ip) but spontaneous breathing, a 2-Fr micromanometer-tipped catheter was inserted in the right carotid artery and advanced into the left ventricle (LV). Heart rate (HR), LV pressure, and maximal (LV dP/dtmax) and minimal (LV dP/dtmin) rate of LV pressure change were determined at 12 wk of age. After the hemodynamic study and blood sampling (0.5 ml) for plasma NE determination, an additional dose of pentobarbital sodium (50 mg, iv) was administered. Renal and LV tissue samples were then obtained and stored at −80°C for later analysis. Plasma and tissue NE levels were measured by automated high-performance liquid chromatography (HPLC), as described previously (26).

Cardiac and renal microdialysis. Levels of iNE were determined using a microdialysis method as reported previously (23). Briefly, a
linear microdialysis probe was employed to minimize tissue damage while providing a secure implantation. The dialysis fiber, with dimensions of 7 mm length, 0.31 mm outer diameter, 0.2 mm inner diameter, and 50,000 molecular weight cutoff (PAN-130SF; Asahi Chemical, Osaka, Japan), was connected to flexible polyethylene tubes (SP8; Natsume, Tokyo, Japan) at both ends.

Rats at 12 wk of age were anesthetized with pentobarbital sodium (30 mg/kg, ip). With the animal in the lateral position, an incision was made between the fifth or sixth ribs on the left side, and the thoracic cavity was opened using a retractor. A microdialysis probe was inserted in the myocardium along the left coronary artery using an attached needle. The position of the probe in the myocardium was fixed by tissue adhesive (Aron Alpha; Konishi, Osaka, Japan) just outside the myocardial wall. Next, 23-gauge needles were connected to both ends of the probe and fixed to the back through the subcutaneous tunnel. After the chest was closed, the left kidney was exposed through a left lateral flank incision. Another microdialysis probe was inserted in the renal cortex from the surface and was fixed to the back through the subcutaneous tunnel.

The rat was allowed to recover from the surgery, and data sampling was performed 48 h after the probe implantation. The rat was held in a plastic tube under conscious conditions. The cardiac and renal probes were perfused with Ringer solution at a rate of 2 μl/min, and a baseline dialysate sample was collected after a 60-min stabilization period. Next, the rat in an enclosed cage was exposed to a gas mixture (10% CO₂-20% O₂-70% N₂) for 25 min, and a level of CO₂ in the cage was kept constant during the exposure of the gas mixture. Dialysate was sampled during the hypercapnic stress and after the withdrawal from stress. The sampling periods during and after stress were 25 min in duration. Norepinephrine in dialysate was separated and detected using a HPLC system (ECD 300; EiCOM, Kyoto, Japan) with an auto injector (EP 60; EiCOM), as described previously (23).

**Hemodynamic data using telemetry.** A telemetric radio transmitter (PhysioTel PA-C40; Data Sciences International, St. Paul, MN) was implanted to determine HR and BP under conscious and unrestrained conditions (22). SS and SR rats at 12 wk of age were anesthetized with pentobarbital sodium (30 mg/kg, ip). The catheter of the telemetric probe was inserted in the abdominal aortic lumen and advanced to the thoracic aorta. The transmitter was fixed in the peritoneal space. After surgery, the animal was allowed to recover for 48 h before data sampling. The cage was placed on a receiver plate that transferred the signals to a computer. Data were collected every minute at baseline, during 25 min exposure of hypercapnia (10% CO₂-20% O₂-70% N₂), and after the stress (25 min from the cessation of hypercapnic stress) under freely moving conditions. Hemodynamic data using a telemetric system were also obtained in separate animals held in a plastic tube under freely moving conditions. The cardiac and renal system were also obtained in separate animals held in a plastic tube under conscious conditions. The cardiac and renal tissue were also obtained in separate animals held in a plastic tube under freely moving conditions. The cardiac and renal tissue were also obtained in separate animals held in a plastic tube under conscious conditions. The cardiac and renal tissue were also obtained in separate animals held in a plastic tube under conscious conditions. The cardiac and renal tissue were also obtained in separate animals held in a plastic tube under conscious conditions.

**Interstitial NE levels in conscious animals.** At baseline, cardiac iNE levels were significantly higher in SS rats than in SR rats, despite the reduced cardiac tissue NE contents of SS rats. This was also true for renal iNE levels. During hypercapnic stress, cardiac iNE levels increased in both SS and SR rats, but the levels were much higher in SS rats than in SR rats. After the withdrawal from stress, the cardiac iNE levels returned to the baseline value in SS rats, whereas the stress-induced increases in cardiac iNE were maintained after stress, and the iNE levels were still significantly higher after the stress than at baseline in SS rats. Similarly, the iNE responses of the kidney to hypercapnic stress in SS rats were exaggerated during the stress and prolonged after the stress compared with SR rats (Fig. 2).

**Responses of BP and HR to hypercapnic stress under unrestrained conditions.** Hypercapnic stress significantly increased respiratory rate in both SS and SR rats, and these increases in respiratory rate were not different between the two strains (Table 2). HR and BP responses to hypercapnic stress under conscious and unrestrained conditions are shown in Fig. 3. Hypercapnic stress modestly increased mean BP in both SS and SR rats, but the stress-induced increases in BP did not differ between the two strains (Table 2). In animals treated with atropine, hypercapnic stress-induced decreases in HR were attenuated, and HR during stress was not significantly different from HR at baseline in both SS and SR rats (Table 3 and Fig. 4). After the withdrawal from stress, HR in SS rats tended to be high compared with SR rats, but the difference did not reach statistical significance.

**Hemodynamic responses to stress determined under conscious but restrained conditions in a plastic tube were similar to...**
those under freely moving conditions. That is, average HR at baseline, during, and after hypercapnic stress was 413/60, 301/22, and 446/19 beats/min ($P < 0.01$), respectively, in SS rats ($n = 5$) and was 408/42, 282/19, and 417/38 beats/min ($P < 0.01$), respectively, in SR rats ($n = 5$). Mean BP at baseline, during, and after hypercapnic stress was 131/18, 127/15, and 127/18 mmHg (not significant), respectively, in SS rats and was 110/6, 106/19, and 108/6 mmHg (not significant), respectively, in SR rats.

**DISCUSSION**

The major findings of the present study are as follows. First, cardiac and renal iNE levels at baseline were increased compared with SR rats, suggestive of selective increases in cardiac and renal SN activity in SS rats. Second, transient hypercapnic stress increased iNE levels of the heart and kidney in both strains. However, the stress-induced increases in renal iNE were greater in SS rats than in SR rats, and this augmented response to the stress was also observed in the hearts of the SS rats. Finally, stress-induced increases in iNE levels were maintained after the stress in both the heart and kidney of SS rats, whereas their iNE levels rapidly returned to the basal level in SR rats. This was also true for HR responses; that is, an increase in HR just after the cessation of stress was followed by a slow reduction in SS rats in contrast to a rapid reduction in SR rats. Thus, transient hypercapnic stress produced an exaggerated and prolonged elevation of adrenergic activity in the heart and kidneys of SS rats.

Cardiac and renal iNE levels at rest. Microdialysis has been used to sample the extracellular compartment of the heart and kidneys in anesthetized and conscious animals (4, 8, 40). The present methods of cardiac and renal microdialysis under conscious conditions might determine the extracellular NE levels of each organ [see the Supplemental Data (Supplemental data for this article may be found on the *American Journal of Physiology: Heart and Circulatory Physiology* website.)]. The levels of iNE are most likely influenced by various factors, including the magnitude of SN drive to each organ, the amount of NE release from the nerve terminals, and the neuronal function at each nerve terminal, including NE uptake function. Circulating NE in plasma may also affect iNE levels (14). In our previous study (26), cardiac NE uptake function, deter-

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**Fig. 1.** Comparisons of plasma norepinephrine (NE) concentrations and cardiac and renal tissue NE contents between Dhal salt-resistant (SR, open bars) and salt-sensitive (SS, filled bars) rats. Plasma NE was determined in 5 SR and 5 SS rats, tissue NE in 5 SR rats and 6 SS rats. **$P < 0.01$ vs. SR rats.

**Fig. 2.** Levels of interstitial norepinephrine (iNE) at baseline, during hypercapnic stress, and after stress (poststress) in SR (open bars, $n = 5$) and SS (filled bars, $n = 5$) rats. *$P < 0.05$ and **$P < 0.01$ vs. baseline. #*$P < 0.05$ and ##*$P < 0.01$ vs. the corresponding SR rats.
mined using radiolabeled metaiodobenzylguanidine, was well preserved in both Dahl SS and SR rats at 12 wk of age. Taken together, increased cardiac iNE levels in 12-wk-old SS rats appear to reflect augmented cardiac SN activity. Excessive cardiac SN activity may be related to cardiac hypertrophy and arrhythmias, whereas elevated renal SN activity may increase renal tubular sodium reabsorption, decrease renal blood flow, and activate the rennin-angiotensin system; these alterations in the kidneys may aggravate hypertension (7).

Response to hypercapnic stress. The peripheral chemoreceptors respond primarily to hypoxic stimulation, while the central chemoreceptors respond to hypercapnia. These relations are not absolute, and hypercapnia can also activate the peripheral chemoreceptors (12). The sympathetic response to hypoxia is greater in hypertensives and heart failure animals than in controls (29, 32), whereas the central chemoreflex response to hypercapnia is also enhanced in patients with heart failure (25, 39). Thus, chemoreflex sensitivity is exaggerated in patients with hypertension as well as those with heart failure. In the present study, hypercapnic stress increased cardiac and renal iNE levels in both Dahl SS and SR rats, but the magnitude was greater in SS rats than in SR rats. However, the mechanism by which exaggerated sympathoexitation occurs in SS rats in response to hypercapnic stress remains unclear, but enhanced cardiovascular and renal responsiveness to stimuli has been reported in SS subjects. SS subjects showed greater increases

| Table 2. Responses of heart rate, blood pressure, and respiratory rate to stress in unrestrained rats |
|-------------------------------------------------|-------------------|-------------------|-------------------|-------------------|
| Heart rate, beats/min                           | 1–5 min           | Stress            | 1–25 min          | Poststress        |
| SS (n = 5)                                       | 368 ± 7           | 343 ± 13          | 336 ± 12†         | 479 ± 24††        |
| SR (n = 5)                                       | 341 ± 4           | 314 ± 12††        | 310 ± 10††        | 389 ± 24††        |
| Mean BP, mmHg                                   |                   |                   |                   |                   |
| SS (n = 5)                                       | 135 ± 2           | 144 ± 3††         | 142 ± 3†          | 142 ± 5††         |
| SR (n = 5)                                       | 102 ± 1##         | 107 ± 2††, ##     | 103 ± 1###        | 101 ± 2##         |
| RR, breaths/min                                 |                   |                   |                   |                   |
| SS (n = 5)                                       | 123 ± 3           | 145 ± 3††         | 122 ± 4           |                   |
| SR (n = 5)                                       | 120 ± 4††         | 144 ± 3††         | 124 ± 7           |                   |

Values are means ± SD; n, no. of rats. BP, blood pressure; RR, respiratory rate. Nos. in parentheses indicate % changes from each baseline value. †P < 0.05 and ††P < 0.01 vs. baseline. #P < 0.05 and ##P < 0.01 vs. the corresponding SS rats.

Fig. 3. Heart rate (HR) and averaged mean blood pressure (mBP) at baseline, during hypercapnic stress, and after stress (poststress) in SS (filled circle, n = 5) and SR (open square, n = 5) rats. HR significantly decreased during stress and rapidly increased after the cessation of stress in both SS and SR rats. Thereafter, HR decreased rapidly with time in the SR rats, but the time course of HR reduction was relatively slower in SS rats.
in HR and BP in response to mental stress due to enhanced central nervous responsiveness compared with SR subjects (2, 3). Air jet stress increased renal SN activity in Dahl SS rats on a high-sodium diet, but it had no effect in rats on a low-sodium diet. Dietary salt and genetic factors may contribute to enhanced renal SN activity, antinatriuresis, and pressor responses to the environmental stress (9, 16). An intracerebroventricular infusion of sodium-rich cerebrospinal fluid causes greater responses of BP, HR, and renal SN activity to air jet stress in Dahl SS rats than in SR rats (10). High-salt intake may increase sodium concentration in the cerebrospinal fluid only in Dahl SS rats (24). These results may suggest that an elevated sodium level in cerebrospinal fluid by high-sodium diet causes enhanced responses of renal and cardiac SN activity to various stress, including mental, air jet, and hypercapnic stress, in SS animals.

However, nonuniform SN responses to stimuli have been reported. An intravenous infusion of hypertonic saline elevates BP and lumbar SN discharge but reduces renal SN discharge (37). It is difficult to directly determine cardiac SN activity under conscious conditions in diseased animals. In a conscious, healthy sheep, intracerebroventricular infusion of angiotensin II had differential actions on sympathetic outflows, causing a prolonged increase in cardiac SN activity and a pronounced decrease in renal SN activity (36). In the present study, however, hypercapnic stress resulted in increasing iNE levels in kidneys as well as in a heart. As discussed above, it seems most likely that increases in cardiac iNE in response to hypercapnia

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<th>Table 3. Responses of heart rate, blood pressure, and respiratory rate to stress in rats treated with atropine</th>
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Values are means ± SD; n, no. of rats. Nos. in parentheses indicate %changes from each baseline value. †P < 0.05 vs. baseline. #P < 0.05 vs. the corresponding SS rats.

Fig. 4. HR and averaged mBP at baseline, during hypercapnic stress, and after stress (poststress) in SS (filled circle, n = 4) and SR (open square, n = 5) rats treated with atropine. HR decreased during stress, but the reduction was not significant in either SS or SR rats.

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might result from the augmentation of cardiac SN activity. Cardiac tissue NE contents, which almost exclusively represent the amount of NE within the sympathetic neurons (28), were lower in SS rats than in SR rats, but the response of cardiac iNE to hypercapnia was augmented in SS rats. This finding may indicate that cardiac SN in hypertrophic hearts can release a considerable amount of NE from the nerve terminals in response to stimuli, despite a reduction in the amount of neuronal NE contents.

Hypercapnic stress decreased HR in both SS and SR rats despite stress-induced increases in iNE levels of LV. A decrease in HR during hypercapnic stress may result partially from arterial baroreflex activation and sympatheoinhibitory influences of hyperventilation (27, 31) and was attenuated in rats treated with atropine in the present study. That is, hypercapnic stress caused reflex-mediated vagal activation as well as SN activation in the heart. Somers et al. (30) showed that baroreceptor activation did not abolish the SN activation response to hypercapnia, a finding consistent with the present results. However, atropine did not completely abolish hypercapnia-induced decreases in HR in the present study. The present dose of atropine (1 mg/kg) may not completely intercept the vagal activation, but mechanisms other than baroreflex activation during hypercapnia might also contribute to a reduction in HR. Hypercapnia or acidosis may directly decrease HR (19, 34).

Cholinergic innervation in LV is sparse, but the dense cholinergic innervation exists in the conducting system, and the sinus node has the highest cholinergic innervation (18). Therefore, variations in autonomic innervation in a heart could cause different responses between HR and iNE levels of LV when sympathetic and parasympathetic activities are increased simultaneously. Moreover, negative chronotropic and inotropic effects of vagal activity depend on the background level of the sympathetic activity (18). During hypercapnic stress in animals treated with atropine, HR did not increase but rather decrease. This may result from combined effects of a relatively low sympathetic drive to the sinus node compared with the parasympathetic drive, the incomplete inhibition of vagal activity by the present dose of atropine, and factors other than parasympathetic drive.

None of BP, HR, or respiratory rate responses to hypercapnic stress were different between the two strains despite significantly greater increases in cardiac and renal iNE levels of SS rats. Although the possibility that reflex-mediated vagal activation during stress modified responses of HR and BP to hypercapnia-induced SN activation cannot be ruled out, these results may suggest that the electrophysiological and vascular responses to stress in rats on high-salt intake are not due to widespread and nonselective augmentation of responses mediated by the SN system (17). Changes in acid-base status induced by hypercapnia should also be considered, but the modulation of vasotone by intracellular pH depends on the type of blood vessel as well as on the pattern of regulatory input signals (35).

Recovery from transient stress. In the present study, during hypercapnia, changes in HR, BP, and respiratory rate from baseline in SS rats were not different from those of SR rats. Marked increases in HR at the initial several minutes after the cessation of stress might result partially from the withdrawal of vagal activation and sympathoinhibition due to baroreflex in both SS and SR rats, since the administration of atropine attenuated the increases after stress (Table 3 and Fig. 4). Higher and prolonged increases in HR after stress in SS rats (Table 2) might be because of prolonged elevation of cardiac iNE levels after stress. However, a sudden increase in HR after the cessation of stress was also observed in animals treated with atropine. Therefore, factors other than parasympathetic drive might considerably affect changes in HR during and after stress.

Recovery from stress may play a role in the pathogenesis of cardiovascular diseases, and slow recovery may be a predictor of overall mortality (1, 5). Middlekauff et al. (21) reported that renal vasoconstriction during the handgrip exercise was exaggerated, and recovery of vasoconstriction from the exercise was sustained in patients with heart failure. However, at recovery after mental stress, muscle SN activity returned promptly to baseline levels while HR remained elevated in heart failure patients compared with control subjects in whom muscle SN activity remained elevated and HR returned promptly to baseline (20). In a study of healthy volunteers, hypoxic stress produced long-lasting SN activation after the withdrawal from the stress, but hypercapnic stress did not produce a sustained elevation of SN activity (6, 38). In the present study, however, hypercapnia caused a prolonged elevation of cardiac and renal iNE levels in SS rats in association with a slower reduction in HR after stress; both returned rapidly to baseline after the stress in SR rats. Thus, the recovery course of HR or SN activity from stress might be heterogeneous and affected by various factors, including differences in species, pathophysiological conditions, or types of stress. Thus, it remains unknown whether exaggerated and prolonged responses to hypercapnic stress in SS animals might be simply extrapolated to those to other stress. However, the present results may indicate that SS subjects complicated by sleep apnea syndrome are at risk for arrhythmias or aggravating hypertension.

Limitations. There are several limitations in interpreting the present results. First, the responses to hypercapnic stress were studied in SS and SR rats on a high-salt diet but not on a low-salt diet. Huang et al. (10) showed that chronic intracerebrospinal fluid infusion containing high sodium enhanced responses of renal SN activity and BP to air-jet stress greater in Dahl SS rats than in SR rats, but these responses were not different between the two strains when the infusion with non-high-sodium fluid was performed. Koepke et al. (16) also reported that air stress did not increase renal SN activity in either Dahl SS or SR rats on a low-sodium diet but increased it greater in SS rats than in SR rats on a high-salt diet. Taken together, exaggerated responses of iNE to hypercapnic stress in SS rats compared with SR rats might at least in part result from a high-salt diet. However, a further study will be required to find out whether iNE responses to stress are enhanced in SS rats on a low- or normal salt diet. Second, data sampling of iNE was performed under unanesthetized conditions but not under freely moving conditions. Rats were held in a plastic tube during data sampling and therefore may have been under some stress even at baseline, which may have affected the present results. However, hemodynamic responses to hypercapnic stress using a telemetric system showed the similar trend between rats under freely moving conditions and under restrained conditions in a plastic tube. Surgical influences might also have affected the present results to some extent. However,
these influences were most likely similar between the SS and SR rats. Finally, we did not determine iNE levels in animals treated with atropine. However, it is shown that the cardiac vagal afferent activation reduced cardiac iNE levels, but the efferent vagal activation did not affect the iNE levels, using a similar microdialysis method to the present study (15). Therefore, treatment with atropine might little affect iNE levels of LV.

In conclusion, despite the reduced cardiac tissue contents of NE in SS rats, iNE levels in response to transient hypercapnic stress were exaggerated in the kidneys as well as in the heart of SS rats. Exaggerated and prolonged increases in cardiac and renal iNE levels in response to transient stress may contribute to the deterioration of hypertensive hearts.

DISCLOSURES

None.

REFERENCES


