Arterial chemoreflex in conscious normotensive and hypertensive adult rats

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Hayward, Linda F., Alan Kim Johnson, and Robert B. Felder. Arterial chemoreflex in conscious normotensive and hypertensive adult rats. Am. J. Physiol. 276 (Hart Circ. Physiol. 45): H1215–H1222, 1999.—Evidence from human and animal studies suggests that the arterial chemoreflex may be exaggerated in essential hypertension. In the present study, cardiorespiratory responses to peripheral chemoreceptor stimulation were compared in conscious unrestrained spontaneously hypertensive (SH) and normotensive Wistar-Kyoto (WKY) and Sprague-Dawley (SD) rats (13–14 wk old). Chemoreceptors were stimulated by injections of potassium cyanide (30–125 µg/kg iv). Chemoreceptor stimulation elicited a pressor response and bradycardia. The peak change in mean arterial pressure evoked during chemoreceptor stimulation was not significantly different between SH (n = 18) and WKY (n = 18) rats but was significantly smaller in SD rats (n = 18). An evaluation of respiratory responses to chemoreceptor stimulation in conscious and anesthetized rats also demonstrated no significant difference between SH and WKY rats, but the response of the SD rats tended to be smaller. These results demonstrate that differences in the arterial chemoreflex response of SH vs. normotensive rats are not linked to hypertension but, rather, to differences between rat strains.

METHODS

All experiments were performed on age-matched (13- to 14-wk-old) adult male SH, WKY, and SD rats (250–350 g; Harlan Sprague) housed in the university animal care facility and exposed to a normal 12:12-h light (6:00 AM–6:00 PM)-dark (6:00 PM–6:00 AM) cycle. All experimental procedures were approved by the University Animal Care and Use Committee before they were carried out.

Conscious animal preparation. Two days before experimental testing the rats were anesthetized with a mixture of chloral hydrate, magnesium sulfate, and pentoxyobarbital sodium (equithesin, 3.3 ml/kg), and a PE-10 catheter connected to PE-50 tubing was inserted into the abdominal aorta through the femoral artery for direct measurement of arterial
pressure. A PE-50 catheter was inserted into the femoral vein for intravenous injection of potassium cyanide (KCN) for brief stimulation of the carotid chemoreceptors (1). Catheters were filled with heparinized saline (50 U/ml) and temporarily plugged with 23-gauge obturators. The femoral catheters were then brought under the skin to be secured between the scapulae and exited at the back of the neck through a small incision. In a small group of animals (3 of each strain) a second incision was made in the skin on the right side of the chest. Thin electromyographic (EMG) Teflon-insulated, tungsten wire electrodes (0.005, California Wire) with bare tips (0.5 cm) were inserted into the diaphragm through the abdominal wall with 27-gauge needles, brought under the skin, and exited at the back of the neck. The small incision on the right side of the chest was then sutured closed. Animals were allowed to recover from anesthesia on a warming blanket and then returned to their home cages.

Two days after the initial surgery, the animals were removed from their home cages and the arterial catheter was connected to a pressure transducer for blood pressure measurements. The venous catheter was connected to additional PE-50 tubing attached to a syringe for intravenous injections. The pressure transducer was connected to a chart recorder, which was connected to a computer data-sampling system (Cambridge Electronic Designs). In those instances where the diaphragm EMG (EMGd) was recorded, the EMG wires were connected to a preamplifier (model P511, Grass). The amplified EMGd signal was then fed to a rectifying, integrating filter (Bak Electronics, 50-ms time constant), which in turn was connected to the computer. The animals were then gently placed in testing cages with 2.5-ft-high walls located in a quiet room. Animals were allowed to acclimatize to the cages, unrestrained, for at least 30 min before arterial chemoreflex testing. All experiments were performed during daylight hours between 11:00 AM and 3:00 PM in an isolated, quiet room with normal fluorescent lighting.

At 2–3 h after chemoreflex testing a small group of animals (n = 7) was reanesthetized, and a midline incision was made on the ventral surface of the neck. The carotid arteries were exposed bilaterally, and the carotid sinus nerves were identified by their origin in the carotid bifurcation and insertion into the glossopharyngeal nerve. The carotid sinus nerves were then sectioned bilaterally near their insertion to the glossopharyngeal nerve, and the carotid body arteries were ligated. Aortic depressor nerves were left intact, since previous studies indicate that the aortic nerve in the rat contains few functional chemoreceptor afferent fibers (1, 10). After denervation the neck incision was closed and the animals were allowed to recover for 10–24 h before a second chemoreflex testing period.

Anesthetized animal preparation. In a separate group of spontaneously breathing anesthetized animals, the effect of carotid chemoreceptor stimulation on respiration was tested. Animals were anesthetized with urethane (1.3–1.4 g/kg ip), instrumented with femoral arterial and venous catheters, and intubated. After instrumentation, thin-wire EMG electrodes were inserted into the diaphragm through a small incision on the right side of the abdomen. The arterial catheter was connected to a pressure transducer and heart rate (HR) monitor (Stoelting), which was connected to the computer data-sampling system (Cambridge Electronic Designs). EMGd wires were connected to a preamplifier. The amplified signal was then rectified and integrated (Bak Electronics, 50-ms time constant). Blood gases and body temperature were monitored (Sensor Devices and Harvard Apparatus, respectively). Body temperature was kept at 37 ± 1°C with a heating blanket. Supplemental anesthesia was given when necessary, as evidenced by marked changes in blood pressure, HR, or respiration during surgery or in response to a pinch of the hindpaw. Chemoreflex testing in the anesthetized animals typically took place 2 h after the initial induction of anesthesia.

Protocol. In all animals, arterial chemoreflex responses were evoked by intravenous bolus injections of several doses of KCN. Doses were calculated by weight (30–125 μg/kg). The appropriate volume (50–125 μl) was taken from a stock solution of KCN (0.3 mg/ml) and flushed through the catheter with an additional 0.3 ml of saline. A 5-min interval separated each KCN dose, and the order in which the doses of KCN was given was randomized. An equal volume of saline was given to control for the effects of volume injection (0.3 ml). The efficacy of KCN to selectively stimulate the peripheral chemoreceptors was tested in seven conscious animals in which the cardiovascular responses to KCN injection were recorded in the conscious state before and 10–24 h after recovery from bilateral sectioning of the carotid sinus nerves and ligation of the carotid body arteries.

Data analysis. In conscious and anesthetized animals, reflex changes in respiration and blood pressure or HR typically began 1–2 s after intravenous KCN administration. In the conscious animals the peak reflex change in HR typically occurred as arterial pressure was increasing (Fig. 1). Thus the peak change in HR was calculated from the difference between the average resting HR before chemoreceptor stimulation (calculated from the average number of systolic beats during a 3-s interval immediately before chemoreceptor stimulation) and the peak HR response (calculated from the average number of systolic beats during the time arterial pressure was increasing from baseline to the 1st maximum systolic peak; see Fig. 1, right, for an example of the time period over which HR changes were calculated). In conscious animals the mean arterial pressure (MAP) response typically peaked 3–4 s after intravenous injection of KCN. Peak changes in MAP during chemoreceptor stimulation were calculated from the difference between the peak MAP response (averaged over a 500-ms interval) during chemoreceptor stimulation and the baseline MAP (averaged over a 3-s window immediately before chemoreceptor stimulation).

In those animals in which respiration was monitored, changes in respiration typically preceded cardiovascular changes. The earliest change in respiration observed in the conscious rat occurred ~750 ms after the injection of KCN. The peak respiratory response typically occurred 1 s later and preceded the peak change in MAP by ~1 s. In conscious and anesthetized animals the respiratory parameters measured included EMGd burst duration, interburst interval, and respiratory frequency (calculated from the interval from the start of one burst to the start of the next burst). All respiratory parameters were calculated from the rectified and integrated signal. EMGd burst duration was measured from the onset of an increase in EMGd activity above baseline to the offset. EMGd interburst interval was measured from the offset of one EMGd burst to the onset of the next EMGd burst. All respiratory parameters were averaged over 5-s intervals. Peak changes in respiratory parameters were calculated by subtracting the preceding 5-s baseline value from the peak 5-s reflex response.

Statistical comparisons between the effect of chemoreceptor stimulation in SH rats and those of WKY and SD rats were made with a two-way ANOVA; the two factors were KCN dose and rat strain. When significant differences were identified, a one-way ANOVA followed by Scheffé’s F test was used to identify differences between rat strains. In addition, a one-way ANOVA was used to identify significant differences
RESULTS

Conscious animals. Eighteen animals of each strain were tested for their cardiovascular responses to increasing doses of KCN. The average weight of the SH and WKY rats was similar but significantly lower than that of the SD rats (Table 1). The conscious resting MAP of the SH rats was significantly higher than the resting MAP of the WKY and SD rats. The resting HR of WKY rats was significantly lower than that of the SH and SD rats (Table 1).

Figure 1 shows an example of the conscious chemoreflex responses from the three different strains of rats tested. The lower dose of KCN (12 µg) tended to produce a small pressor response in the SH and WKY rats, which was accompanied by only a slight change in HR. There was little or no cardiovascular response by the SD rats at the lowest KCN dose. As the dose of KCN increased, the amplitude of the pressor response increased in all strains and was greatest in the SH and WKY rats. The magnitude of the bradycardia also increased with increasing doses of KCN across all strains of rats.

Figure 2 illustrates the dose-response relationships for MAP and HR of all SD, SH, and WKY rats to intravenous KCN, with dose expressed as a function of the average body weight of each strain. For MAP the overall dose-response relationships of the SH and WKY rats were significantly different (P < 0.001), with the SH rats having a higher baseline blood pressure. However, there was no difference in the magnitude of the increase in MAP elicited by chemoreceptor stimulation in SH and WKY rats (i.e., at 114–125 µg/kg KCN the peak increase in MAP was 72 ± 4 and 68 ± 3 mmHg in SH and WKY rats, respectively). The WKY and SD rats were similar in baseline MAP and MAP dose-response relationships. However, the magnitude of the increase in MAP was significantly smaller in the SD rats than in the SH and WKY rats (i.e., at 114–125 µg/kg KCN the peak MAP increase for SD rats was 54 ± 5 mmHg). There was a significant difference between the SH and WKY rats in the HR dose-response relationship, with the baseline HR significantly lower in the WKY rats. In contrast, the baseline HR and the HR dose-response relationship were quite similar for SD and SH rats. However, the magnitude of the reduction in HR elicited by KCN was similar across rat strains (P ≥ 0.07).

The effects of chemoreceptor stimulation on respiration were tested in a separate set of experiments (n = 3 for SH, WKY, and SD). In these studies there was no significant difference in the resting respiratory rate of SH and WKY rats (Table 2). There was also no significant difference in baseline respiratory rate between SH

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<th>Parameter</th>
<th>SH</th>
<th>WKY</th>
<th>SD</th>
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<tr>
<td>MAP, mmHg</td>
<td>164 ± 4*†</td>
<td>126 ± 4</td>
<td>123 ± 4</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>432 ± 9</td>
<td>395 ± 9†</td>
<td>439 ± 8</td>
</tr>
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<td>Mean body wt, g</td>
<td>266 ± 6†</td>
<td>258 ± 5†</td>
<td>321 ± 5</td>
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<tr>
<td>MAP, mmHg</td>
<td>135 ± 5*†</td>
<td>91 ± 3</td>
<td>105 ± 4</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>316 ± 2</td>
<td>299 ± 43</td>
<td>352 ± 14</td>
</tr>
<tr>
<td>Mean body wt, g</td>
<td>285 ± 8†</td>
<td>264 ± 15†</td>
<td>342 ± 12</td>
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Values are means ± SE. SH, spontaneously hypertensive; WKY, Wistar-Kyoto; SD, Sprague-Dawley; MAP, mean arterial pressure; HR, heart rate. *Significant difference between SH and WKY; †significant difference between SH and SD; ‡significant difference between WKY and SD.
and SD rats, although respiratory rate was significantly higher in the WKY than in the SD rats (P < 0.001). Similarly, resting EMG\textsubscript{di} burst duration was not significantly different between SH and WKY rats but was significantly longer in the SD rats than in the WKY and SH rats (Table 2). There was no significant difference in the duration of the interburst interval across strains.

Figure 3 illustrates the effects of KCN on these respiratory parameters. In all three rat strains the respiratory rate increased in response to increasing doses of KCN. The increases in respiratory rate were accompanied by the expected decreases in EMG\textsubscript{di} burst duration and interburst interval. Statistical comparisons between rat strains demonstrated no significant differences in overall dose-response relationships or magnitude of change for any of the respiratory parameters measured. There was, however, a notable trend for the respiratory responses to be greater in the WKY and SH rats than in the SD rats, similar to the trend observed in the cardiorespiratory response.

Interestingly, respiratory rate also increased in response to the control injection of saline (0.3 ml volume), as illustrated in Fig. 4. The increase in respiratory rate during saline injection was significantly higher in the SH rats than in the WKY and SD rats. Thus some of the respiratory responses to KCN administration in the conscious animal may have been due to the intravenous injection alone or environmental cues (i.e., this was a novel experience for the rats), with the SH rats demonstrating the greatest sensitivity. Unlike the KCN injections, however, saline injections elicited small decreases in blood pressure (−5 ± 1.3 mmHg, n = 9).

To demonstrate that the cardiovascular effects of KCN resulted from peripheral chemoreceptor activation, the effect of increasing doses of KCN on MAP and HR was tested in a group of SD rats (n = 5) before and 12–24 h after bilateral sectioning of the carotid sinus nerve and ligation of the carotid body arteries. Bilateral denervation of the carotid sinus nerves produced a small but significant decrease in baseline MAP (−10 ± 4 mmHg, P < 0.05), but there was no change in baseline HR (P > 0.4). After denervation all blood pressure and HR responses to chemoreceptor stimulation were abolished (Fig. 5); MAP and HR responses to KCN were not significantly different from baseline (P > 0.6). The cardiovascular responses to KCN were also completely eliminated in the one SH rat and the one WKY rat tested after bilateral carotid sinus denervation (data not shown).

Urethan-anesthetized animals. The cardiorespiratory responses to KCN were examined in five anesthetized SH, WKY, and SD rats. Similar to the conscious animals, the mean body weight of the SH and WKY rats was significantly lower than that of the age-matched SD rats (Table 1). The average resting MAP was also significantly higher in the SH rats than in the WKY and SD rats (P < 0.02). There was no significant difference in baseline HR across rat strains, although similar to the conscious animals there was a trend for the baseline HR of the WKY rats to be the lowest.

Cardiovascular responses to chemoreceptor stimulation are known to be blunted by anesthesia. As expected, KCN administration in the anesthetized rat produced only small decreases in MAP. At the highest dose of KCN (75 µg/kg) the mean decrease in MAP was −6 ± 4, −2 ± 4, and −7 ± 6 mmHg for the SH, WKY, and SD rats, respectively. The mean decrease in HR at the highest dose of KCN was −55 ± 8, −40 ± 10, and −47 ± 13 beats/min for the SH, WKY, and SD rats, respectively. There was no significant difference in MAP and HR responses across rat strains.

Analysis of resting respiratory parameters demonstrated that under anesthesia the baseline respiratory frequency was significantly lower and EMG\textsubscript{di} burst duration was significantly longer in the SH rats than in the WKY rats, which more closely resembled the SD

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**Table 2. Baseline characteristics of respiration for conscious and anesthetized SH, WKY, and SD rats**

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<tr>
<th>Parameter</th>
<th>SH</th>
<th>WKY</th>
<th>SD</th>
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<tr>
<td>Respiratory rate, breaths/min</td>
<td>145 ± 36</td>
<td>163 ± 22</td>
<td>128 ± 29</td>
</tr>
<tr>
<td>Burst duration, ms</td>
<td>159 ± 40</td>
<td>156 ± 20</td>
<td>200 ± 40</td>
</tr>
<tr>
<td>Interburst interval, ms</td>
<td>291 ± 70</td>
<td>230 ± 40</td>
<td>310 ± 130</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>72 ± 13†</td>
<td>115 ± 19</td>
<td>100 ± 11</td>
</tr>
<tr>
<td>Burst duration, ms</td>
<td>448 ± 36†</td>
<td>297 ± 52</td>
<td>282 ± 70</td>
</tr>
<tr>
<td>Interburst interval, ms</td>
<td>412 ± 56</td>
<td>249 ± 46</td>
<td>309 ± 34</td>
</tr>
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Values are means ± SE. See Table 1 footnote for definition of abbreviations. *Significant difference between SH and WKY; †significant difference between SH and SD; ‡significant difference between WKY and SD.
rats (Table 2). There was no significant difference in any of the baseline respiratory parameters between SD and WKY rats. Comparison of the respiratory rates in the anesthetized vs. the unanesthetized rats suggests that anesthesia had a more pronounced effect on the baseline respiration in the WKY and SH rats than in the SD rats.

Unlike the conscious animals, the anesthetized rats demonstrated no significant change from baseline respiratory rate, EMGdi burst duration, or EMGdi interburst interval during control injections of saline (0.3 ml volume; Fig. 4). Yet the respiratory responses to chemoreceptor stimulation with KCN were similar to those recorded in the conscious animal (Fig. 6). There were no significant differences between the SH and WKY rats in the overall dose-response relationships for respiratory rate, EMGdi burst duration, or interburst interval. The overall dose-response relationship for respiratory rate was significantly less robust in the SD rats than in the WKY rats, and the interburst interval dose-response relationship was less in SD rats than in SH and WKY rats. The magnitude of the increase in respiratory rate was similar in the SH and WKY rats, but the magnitude of the increase in respiratory rate of the SD rats was significantly smaller than in the SH and WKY rats. The shortening in EMGdi burst duration in response to KCN was significantly different between all strains, with the greatest change observed in the SH rats (i.e., the change in EMGdi burst duration at 50 µg/kg KCN was -240 ± 43, -91 ± 7, and -47 ± 20 ms in SH, WKY, and SD rats, respectively, P < 0.05). Finally, there was no significant difference across rat strains in magnitude of the reduction in interburst interval during chemoreceptor stimulation.

DISCUSSION

An exaggerated chemoreflex in the SH rat was first suggested in the late 1970s, when the blood gases of young SH and normotensive Wistar rats were compared and it was found that young SH rats had increased arterial PO2 and pH and decreased arterial PCO2 (8). It was hypothesized that these blood gas changes in the SH rat reflected hyperventilation, possibly resulting from a hyperactivity of the chemoreflex. In agreement with this hypothesis, recordings from the carotid sinus nerve in the adult rat have demonstrated that the sensitivity of arterial chemoreceptors to hypoxia is increased in the adult SH rat compared with normotensive controls (WKY and Wistar rats) (2). In addition, several studies have confirmed that the resting minute ventilation of the adult, anesthetized SH rat is significantly higher than the resting ventilation rate of the normotensive Wistar rat (7, 9). The changes in chemoreceptor sensitivity in the SH rat have been attributed to a decrease in the lumen of the carotid body arteries, perhaps resulting from arteriosclerosis of the carotid artery (5). It was suggested that these morphological changes may reduce blood flow to the carotid body in these animals, making the region of the carotid body ischemic and resulting in a tonic increase in chemoreceptor drive.

More recent studies, however, have questioned whether the chemoreflex response of the adult SH rat is actually enhanced. For example, in 1995, Grisk and colleagues (4) found no differences in ventilatory responses to hypoxia in unanesthetized neonatal SH and WKY rats. These investigators also found no differences in respiratory responses to hypoxia between anesthetized adult SH rats and WKY and Wistar rats. Their results demonstrated that the resting respiratory rate was higher in the WKY rats than in the SH and Wistar rats and that the increase in the respiratory rate during hypoxia was smaller in the WKY rats than in the other two strains (4). However, the reflex increase in minute ventilation during 1 min of hypoxia in SH rats was not significantly different from the response of the Wistar rat. These results suggest that the respiratory component of the arterial chemoreflex may...
be different between rat strains, with no relation to the presence of hypertension.

Observations concerning chemoreflex function in the SH rat have potentially important implications for our understanding of cardiovascular regulation. Because the arterial chemoreflex has cardiovascular and respiratory components and changes in respiration can strongly influence cardiovascular reflex responses, it is conceivable that an enhanced chemoreceptor responsiveness might be causally related to hypertension in the SH rat. Our data in the adult SH rat provide no support for that hypothesis. On the contrary, in our small sample of conscious animals, normotensive WKY rats had a slightly higher baseline respiratory rate and a greater response to KCN than the SH rats, although these trends did not reach statistical significance. In our anesthetized rats the baseline respiratory rate for the WKY rats also tended to be highest, and the change in respiratory rate during chemoreceptor stimulation was not different between the SH and WKY rats. Whether conscious or anesthetized, the SD rats had smaller respiratory responses to KCN, consistent with data published by others (1). In summary, in the conscious and anesthetized adult rats we found no evidence for a link between hypertension and the respiratory responses to chemoreceptor activation.

In that context, it is notable that we also found no evidence for an exaggerated cardiovascular component of the chemoreflex in conscious adult SH rats. Although the peak MAP achieved by the SH rats during chemoreceptor stimulation was significantly higher than that achieved by the WKY rats (primarily because of a significant difference in resting MAP), the change in MAP during chemoreceptor stimulation was not significantly different between the SH and WKY rats. Likewise, the peak change in HR during chemoreceptor stimulation was not significantly different. We also examined the cardiovascular response to chemoreceptor stimulation of another normotensive strain of rat commonly used in cardiovascular research, the SD rat. Our results demonstrated that the peak increase in MAP elicited during peripheral chemoreceptor stimulation was significantly lower in SD rats than in SH and WKY rats, although the HR response was similar to both groups. All cardiovascular responses to KCN administration were abolished by bilateral carotid sinus nerve section. Together these data demonstrate that the magnitude of the cardiovascular response to peripheral chemoreceptor stimulation in the adult rat may differ depending on the rat strain and that hypertension in the SH rat does not result from an exaggerated chemoreflex response. These studies also suggest that use of two normotensive controls may be important when trying to identify differences in the SH rat that are associated with hypertension rather than with strain differences.

Our study differs from all previous studies comparing cardiovascular responses to chemoreflex activation in SH and normotensive control rats, in that we used adult animals. The cardiovascular response to chemoreceptor stimulation in the adult rat may differ depending on the rat strain and that hypertension in the SH rat does not result from an exaggerated chemoreflex response. These studies also suggest that use of two normotensive controls may be important when trying to identify differences in the SH rat that are associated with hypertension rather than with strain differences.

Fig. 4. Respiratory response elicited during intravenous saline injection in conscious vs. anesthetized normotensive and hypertensive rats. Average increase in respiratory rate (breaths/min) in response to intravenous bolus injection of saline (0.3 ml) in conscious (left, n = 3 each strain) and urethan-anesthetized (right, n = 5 each strain) SH, WKY, and SD rats is shown. Values are means ± SE. * Significantly different from WKY and SD rats.

Fig. 5. Effect of bilateral carotid sinus nerve denervation on cardiovascular response of conscious, unrestrained SD rats to peripheral chemoreceptor stimulation. Average increases in MAP and HR elicited by increasing intravenous doses of KCN before (●) and 10–24 h after bilateral carotid sinus denervation (○; n = 5) are shown. Values are means ± SE. *Significant difference in dose-response relationship after denervation.
sinus denervation (7), suggesting that the depressor response in the anesthetized state is not mediated through activation of reflex pathways but may reflect an effect of hypoxia on central receptors or on vasculature. With respect to the cardiovascular responses, data from conscious animals clearly provide a more realistic assessment of chemoreceptor responsiveness. However, as our study demonstrates, the potential influence of environmental stimuli, e.g., respiratory response to intravenous injection, must be recognized.

In our anesthetized animals, respiratory responses to KCN were altered but still present. The baseline respiratory rate in the WKY rats tended to be higher, but the increase in respiratory rate was similar for the SH and WKY rats, whereas the SD rats had a significantly less robust response. These results are slightly different from those reported by Grisk and colleagues (4). In their study a significant difference in the change in breathing rate during activation of the chemoreflex was observed between the SH and WKY rats, but not between the SH and Wistar rat. Some of the differences in results may reflect differences in methodology (the use of hypoxia vs. KCN to stimulate arterial chemoreceptors), differences in rat strains, in anesthesia (i.e., in their study animals were anesthetized with chloralose-urethan). Our finding that the baseline respiratory parameters were more profoundly influenced by anesthesia in the SH and WKY rats than in the SD rats suggests that the differences observed under anesthesia between SH and WKY rats may be related to the effects of anesthesia.

As expected, the cardiovascular responses to chemoreceptor stimulation were substantially altered by anesthesia. The increase in blood pressure was abolished in all three groups, and the HR responses were blunted. Under these conditions, there were no discernible differences in the cardiovascular responses to KCN, but the data must be considered in light of altered chemoreflex sensitivity.

In summary, the present study evaluated for the first time the cardiorespiratory response of conscious unrestrained hypertensive and normotensive rats to brief periods of chemoreceptor stimulation. Our results did not show a significant difference in the peak MAP or HR response between SH rats and the normotensive WKY rat. We did, however, observe an attenuation of the peak MAP response of the SD rats compared with the SH and WKY rats. A similar trend was observed for the respiratory component of the chemoreflex when examined in the conscious and anesthetized state. The respiratory responses of SH and WKY rats were not significantly different, but both appeared to be significantly larger than the response of the SD rats. Thus the results of the present study suggest that a difference in chemoreflex sensitivity may be associated with the common genetic background of the WKY and SH rats but does not appear to be linked specifically to the expression of hypertension in the SH rat. It has, however, been reported that baseline chemoreceptor afferent input is increased in SH rats (2) compared with WKY rats. Thus the role of tonic increases in chemoreceptor afferent input in the SH rat in the development of hypertension remains to be determined. In addition, if the afferent input from chemoreceptors is indeed increased in the adult SH rat, as suggested by Fukuda and colleagues (2), but the reflex output in the SH rat is not significantly different from that of the WKY rat, there may be a central resetting of the chemoreflex response in the SH rat similar to resetting of the arterial baroreflex, which has already been described in adult SH rats (3, 6). In that case, differences in cardiovascular and respiratory components of the chemoreflex might be masked. This hypothesis remains to be tested.

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