Cardiovascular responses to peripheral chemoreflex activation and comparison of different methods to evaluate baroreflex gain in conscious mice using telemetry

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Braga VA, Burmeister MA, Sharma RV, Davison RL. Cardiovascular responses to peripheral chemoreflex activation and comparison of different methods to evaluate baroreflex gain in conscious mice using telemetry. Am J Physiol Regul Integr Comp Physiol 295: R1168–R1174, 2008. First published July 30, 2008; doi:10.1152/ajpregu.90375.2008.—Peripheral chemoreceptors located in the carotid bodies are the primary sensors of systemic hypoxia. Although the pattern of responses elicited by peripheral chemoreceptor activation is well established in rats, lambs, and rabbits, the cardiovascular responses to peripheral chemoreflex activation in conscious mice have not been delineated. Here we report that stimulation of peripheral chemoreceptors by potassium cyanide (KCN) in conscious mice elicits a unique biphasic response in blood pressure that is characterized by an initial and robust rise followed by a decrease in blood pressure, which is accompanied by a marked reduction in heart rate. The depressor and bradycardic responses to KCN were abolished by muscarinic receptor blockade with atropine, and the pressor response was abolished by α-adrenergic receptor blockade with prazosin, suggesting that vagal and sympathetic drive to the heart and sympathetic drive to the vasculature mediate these cardiovascular responses. These studies characterized the chemoreflex in conscious mice and established the reliability of using them for studying hypoxia-related diseases such as obstructive sleep apnea. In another series of experiments, two methods for analyzing baroreflex sensitivity were compared: the classical pharmacological approach using phenylephrine and sodium nitroprusside (i.e., the Oxford technique) or the sequence method for analyzing spontaneous fluctuations in blood pressure. In pathological conditions such as hypertension and heart failure, there is impairment in the autonomic control of blood pressure, resulting in changes in the baroreflex sensitivity (9, 17, 36). For example, individuals suffering from chronic activation of the peripheral chemoreceptors during sleep apnea also often present with impaired autonomic balance and baroreflex function, which may collectively promote hypertension in these patients (11, 28, 38).

There are several methods to experimentally evaluate the baroreflex in commonly used laboratory animals, and there has been much debate about which one works best. The most frequent methods used are the classical vasoactive drug-induced activation of the baroreflex (3, 14, 39), which evaluates heart rate (HR) changes in response to pathological manipulations that increase or decrease blood pressure (i.e., the Oxford technique), and the spontaneous baroreflex analysis, which takes into consideration changes in HR produced by spontaneous fluctuations in blood pressure. In particular, the sequence method for evaluation of spontaneous baroreflex is based on the identification of sequences of four or more heart beats in which the systolic pressure and the pulse interval both progressively change in the same direction (1, 2, 23, 29).

The mouse has become the most commonly used animal for studying the genetic basis of cardiovascular and autonomic diseases, including hypertension and obstructive sleep apnea (8, 37). Furthermore, radiotelemetry for long-term recording of blood pressure in conscious, freely moving mice has proven to be a critical tool for understanding the physiology and pathophysiology of the cardiovascular system (21). Considering this, here we characterized the cardiovascular responses elicited by peripheral chemoreflex activation in conscious mice using telemetry. We hypothesized that stimulation of peripheral chemoreceptors would evoke similar cardiovascular responses in conscious mice as those seen in rats. Considering the potential clinical relevance of the interaction between both the chemoreflex and baroreflex, we also performed side-by-side compari-

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sons of the classical pharmacological method and the sequence method for analyzing baroreflex function in the same mouse model.

EXPERIMENTAL PROCEDURES

Animals. Experiments were performed on adult (10–12 wk old) C57BL/6 male mice. Mice were individually housed in a temperature-controlled room set to a 12:12-h light-dark cycle and had access to standard mouse chow (Harlan Tek-Lad Diet 7912) and water ad libitum. All procedures were approved by the Cornell University Institutional Animal Care and Use Committee.

Radiotelemetry surgery. Mice were anesthetized (ketamine, 117 mg/kg ip in combination with xylazine, 17 mg/kg ip) and instrumented with TA11PA-C10 radio telemetry probes (Data Sciences International, Arden Hills, MN) as previously described (3, 7, 10, 23, 41). Briefly, the catheter of the telemeter was implanted in the thoracic aorta via the left common carotid artery, and the body of the probe was placed in a subcutaneous pocket created in the right flank. The wound was closed and sutured, and body temperature was maintained at 37°C using a heating pad until sternal recumbency had been recovered. Mice remained undisturbed in their home cages for 7 days before undergoing any subsequent experimentation so as to allow for full recovery of normal circadian rhythm and cardiovascular parameters (7).

Jugular vein catheterization. Following telemetry surgery (1 wk), mice were anesthetized (ketamine, 117 mg/kg ip in combination with xylazine, 17 mg/kg ip) and instrumented with jugular catheters for intravenous vehicle/drug administration. With the aid of a dissecting stereomicroscope (Olympus, SZ61), sterile heparinized saline-filled (50 U/ml) catheters (Microrenathane 0.1 cm OD × 0.06 cm ID; Braintree Scientific) were inserted in the jugular vein and fixed to the surrounding tissue with Vetbond veterinary adhesive. The free ends of the catheters were plugged, tunneled subcutaneously, and exteriorized and sutured at the dorsal surface of the neck. The catheters were flushed daily with heparinized saline to maintain patency.

Blood pressure recordings and drug administration. After a 5-day recovery period following implantation of the jugular catheters, telemetry probes were activated for continuous measurement of baseline arterial pressure (sampling frequency = 2,000 Hz). Mean arterial pressure (MAP) and HR were derived offline from the blood pressure tracing. Following baseline sampling, an intravenous injector was securely attached to each animal’s indwelling jugular catheter; the intravenous injector consisted of microrenathane tubing connected to a syringe for injection of vehicle/drug. Animals were then returned to their home cages. The microrenathane tubing was extended outside of the cages so as to keep disturbance to the animals to a minimum. After stabilization and additional baseline sampling, drug or isotonic saline vehicle (30 μl) was delivered intravenously via the syringe/injector assembly. MAP and HR were analyzed before and after drug/vehicle administration.

Drugs and protocols. The peripheral chemoreflex in conscious mice was activated by administering KCN (Sigma, St Louis, MO) intravenously at a dose of 26 μg/g, as previously established for anesthetized mice (32). The peripheral chemoreflex was first activated before (control response) and after muscarinic receptor blockade with atropine (1 μg/g ip; Sigma). Following 40 min, the chemoreflex was activated again in the same animal after α-adrenergic receptor blockade with prazosin (1 μg/g ip atropine + prazosin; Sigma). One final KCN injection was performed 2 h after treatment with atropine and prazosin to verify the reversibility of these compounds’ antagonistic effects. In additional studies, the chemoreflex was activated following α-adrenergic receptor blockade with prazosin alone (1 μg/g ip). Each drug was administered as an intravenous bolus in a volume of 30 μl, with isotonic saline as vehicle.

The baroreflex was evaluated in another series of experiments. Changes in blood pressure were evoked by intravenous bolus injection of phenylephrine (PE, 4 μg/kg; Sigma) and sodium nitroprusside (SNP, 10 μg/kg; Sigma); these doses were previously established in studies by Bissonnette et al. (3). After 40 min of baseline blood pressure recording, SNP was injected. After blood pressure returned to baseline levels, PE was injected before (control response) and after the muscarinic receptor antagonist atropine (1 μg/g; ip; Sigma). After 2 h, PE was injected again before and after β-adrenergic receptor blockade with propranolol (1 μg/kg; ip; Sigma). Similar to the chemoreflex studies, each drug was administered an intravenous bolus in a volume of 30 μl, with isotonic saline as vehicle.

The ambient air temperature of the room in which all studies were conducted was ~72°F (22°C). All studies were performed between the daytime hours of 1000 and 1400.

Chemoreflex and baroreflex analyses. Peripheral chemoreflex responses were analyzed as the peak of the increase and/or decrease in blood pressure and the peak of the decrease in HR following KCN injection during control and after pretreatment with either atropine or prazosin. Baroreflex responses were analyzed as the gain of the baroreflex sequence. This was calculated as the ratio of the mean mean arterial pressure and the following R-R interval either both increased or decreased. Conversely, a nonbaroreflex relationship was defined by sequences of at least four consecutive heart beats in which both systolic blood pressure and the following R-R interval either both increased or decreased.

Statistical analysis. Results are expressed as means ± SE. The magnitude of the changes in cardiovascular parameters in response to reflex activation was compared before and after treatments by “one-way” repeated-measures ANOVA with subsequent Tukey posttest. Statistical significance was defined as P < 0.05.

RESULTS

Cardiovascular responses to peripheral chemoreceptor activation. The typical tracings shown in Fig. 1A illustrate changes in blood pressure and HR following peripheral chemoreflex activation in a conscious mouse before and after autonomic blockade with atropine and/or prazosin. Summary data from six mice presented in Fig. 1B show that activation of peripheral chemoreceptors with KCN produced a rapid yet transient increase in blood pressure (+25 ± 3 mmHg, P < 0.05) that lasted for 5–8 s followed by a comparatively
prolonged decrease in blood pressure (-31 ± 5 mmHg, P < 0.05) that lasted for ~25 s. In addition to the changes in blood pressure, chemoreflex activation elicited a pronounced bradycardia (-218 ± 30 beats/min, P < 0.05). Overall, these responses were transient, since both blood pressure and HR had returned to baseline within 20–40 s following KCN injection. Moreover, 20-min pretreatment with the muscarinic receptor antagonist atropine (1 μg/g, ip) prevented the bradycardia produced by KCN (+20 ± 35 vs. -218 ± 30 beats/min, P < 0.05), demonstrating that this response is mediated by an increase in the parasympathetic drive to the heart. Interestingly, the decrease in blood pressure in response to chemoreflex activation after atropine was also virtually abolished (-4 ± 1 vs. -31 ± 5 mmHg, P < 0.05), suggesting that it was, at least...
Table 1. Changes in of MAP and HR evoked by drug-induced activation of the baroreflex

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>SNP</th>
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<th>PE</th>
<th>Baseline</th>
<th>PE + Atropine</th>
<th>Baseline</th>
<th>PE + Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg (n = 5)</td>
<td>124±4</td>
<td>67±2*</td>
<td>112±5</td>
<td>147±5*</td>
<td>119±4</td>
<td>165±5*</td>
<td>111±4</td>
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<tr>
<td>HR, beats/min (n = 5)</td>
<td>622±18</td>
<td>765±15*</td>
<td>605±27</td>
<td>420±26*</td>
<td>733±14</td>
<td>629±18*</td>
<td>723±14</td>
<td>109±9*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of mice. SNP, sodium nitroprusside; PE, phenylephrine; MAP, mean arterial pressure; HR, heart rate. *P < 0.05 vs. respective baseline.

in part, dependent on the bradycardia. Furthermore, 20 min pretreatment with the adrenergic receptor antagonist prazosin (1 μg/g, ip) in the same animal (i.e., prazosin + atropine) prevented both the increase in blood pressure and the bradycardia in response to chemoreflex activation (MAP, +3 ± 1 vs. +25 ± 3 mmHg, HR, −16 ± 11 vs. −218 ± 30 beats/min, P < 0.05). In additional experiments, prazosin alone prevented the increase in blood pressure without affecting the bradycardia and the fall in blood pressure elicited by KCN (increase in MAP, +4 ± 2 vs. +25 ± 3 mmHg, P < 0.05), indicating that the pressor component of the response is mediated by an increase in the sympathetic drive to the vasculature. The biphasic response in blood pressure and the bradycardia were recovered 2 h after treatment with the antagonists, as indicated by the cardiovascular responses to a repeat intravenous bolus injection of KCN. Saline, which was used as vehicle control, produced negligible changes in blood pressure (+5 ± 1 mmHg) and HR (9 ± 8 beats/min).

Cardiovascular responses to classical drug-induced baroreflex activation vs. spontaneous baroreflex analysis. Alterations in baroreflex gain assessed by classical vasoactive drug-evoked activation of the baroreflex vs. the sequence method analysis of spontaneous baroreflex were compared in the same animal in all studies. In Table 1, baseline blood pressure and HR values are shown, along with the cardiovascular changes evoked by drug-induced activation of the baroreflex. Representative tracings of the changes in blood pressure and HR produced by intravenous bolus injection of PE or SNP are shown in Fig. 2, A and B. Summary data from five mice presented in Fig. 3 show that intravenous bolus injection of PE produced an increase in MAP (+35 ± 2 mmHg, P < 0.05) with a significant reflex bradycardia (−185 ± 17 beats/min, P < 0.05), translating into a baroreflex gain of −5.2 ± 0.5 beats·min⁻¹·mmHg⁻¹. This was comparable to the value of the baroreflex gain measured using the sequence method, whereby the gain of baseline “up” sequences (i.e., sequences in which both MAP and the following R-R interval increased) was examined (−3.5 ± 0.3 beats·min⁻¹·mmHg⁻¹). In addition, SNP (iv) produced a decrease in MAP (−57 ± 4 mmHg, P < 0.05) with a reflex tachycardia (+143 ± 14 beats/min, P < 0.05), resulting in a baroreflex gain of −2.6 ± 0.3 beats·min⁻¹·mmHg⁻¹. This was comparable to the value of the baroreflex gain measured using the sequence method, whereby the baroreflex gain of baseline “down” sequences (i.e., sequences in which both MAP and the following R-R interval decreased) was examined (−2.5 ± 0.7 beats·min⁻¹·mmHg⁻¹).

As shown in Fig. 4A, the reflex bradycardia evoked by the increase in blood pressure produced by PE (+46 ± 2 mmHg, P < 0.05) was reduced significantly (−94 ± 14 beats/min, P < 0.05) by 20-min pretreatment with atropine, indicating that there was an attenuation of the baroreflex gain by cholinergic receptor blockade (−2.6 ± 0.4 beats·min⁻¹·mmHg⁻¹, P < 0.05). Alternatively, the bradycardia evoked by the increase in blood pressure produced by PE (+48 ± 3 mmHg, P < 0.05) was significantly potentiated (−514 ± 20 beats/min, P < 0.05) by 20-min pretreatment with propranolol, demonstrating a significant increase in the baroreflex gain by β-adrenergic receptor blockade (−10.8 ± 0.5 beats·min⁻¹·mmHg⁻¹, P < 0.05). Using the sequence method, the baroreflex gain of baseline up sequences was similarly inhibited by intraperitoneal treatment with atropine (−1.7 ± 0.4 beats·min⁻¹·mmHg⁻¹, P <
The peripheral chemoreflex is an important mechanism in oxygen sensing during hypoxic states such as obstructive sleep apnea (34, 37) and sudden infant death syndrome (15). Although this reflex is not well understood in mice, it has been well characterized in other species (5, 16, 18, 19). Here our results demonstrate that peripheral chemoreflex activation evokes a biphasic response in blood pressure and bradycardia in mice. The first response to KCN-induced activation of peripheral chemoreceptors was a rapid rise in blood pressure. This was attributable to an increase in sympathetic drive to the vasculature since pretreatment with the α-adrenergic receptor antagonist prazosin prevented this component of the response; similar findings have been previously observed in rats (18) and fetal lambs (19). This rapid elevation in blood pressure was immediately followed by a significant hypotension, which appeared to be, at least in part, dependent on the bradycardia since pretreatment with the muscarinic receptor antagonist atropine attenuated both of these responses. In addition, we cannot rule out the effects of cyanide acting directly in vasculature producing additional hypotension and the activation of the baroreflex during the increase in blood pressure resulting in a transient sympathoinhibition. Moreover, although not examined in the present study, it is likely that the observed biphasic...
blood pressure response to carotid chemoreceptor activation is strongly influenced by changes in ventilation as previously described in experiments by Rutherford and Vatner (35). In these studies, carotid chemoreceptor stimulation in conscious dogs with spontaneous respiration resulted in a biphasic vascular response, whereby pulmonary inflation reflexes attenuated the initial vasoconstrictor response to carotid chemoreceptor stimulation and were responsible for a later period of vasodilation.

Regarding the cardiovascular responses, the pattern of changes in HR in mice is variable among different studies. A previous report by Pearson et al. (30) showed that acute changes in HR in mice is variable among different studies. A vasodilation.

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these studies, carotid chemoreceptor stimulation in conscious blood pressure response to carotid chemoreceptor activation is strongly influenced by changes in ventilation as previously obtained in experiments by PE and KCN. When PE was administered, a significant decrease in HR was observed, whereas KCN produced no changes in HR. In our experiments, we show that acute activation of the peripheral chemoreflex with KCN produced significant bradycardia as seen in other species (5, 6, 18, 19). This difference might be related to the different stimuli used to activate peripheral chemoreceptors. Of note, peripheral chemoreflex activation triggered by apnea in humans elicits hypertension and bradycardia known as the diving reflex (38). In addition to the direction of the response (i.e., increase or decrease in HR), there is also a difference in the magnitude of this response among species. For example, Peotta et al. (32) observed a much more reduced bradycardia using the same dose of KCN in anesthetized mice when compared with our findings. This blunted bradycardia could be explained by the depressive effect of anesthesia on cardiovascular reflexes. The biphasic blood pressure response observed in conscious mice in the present studies was different from that observed in conscious rats, fetal lambs, and anesthetized rabbits in which there is only an increase in blood pressure associated with intense bradycardia (5, 6, 16, 18, 19).

Regarding the baroreflex, in the present study, we compared two methods of assessing baroreflex gain in the same conscious mouse using telemetry. First, baroreceptor reflex control of HR was quantified by classic vasoactive drug administration, which serves to either raise or lower systemic arterial pressure (3, 33, 39). Second, high-frequency blood pressure recordings (2,000 Hz) attained by telemetry were analyzed using the spontaneous baroreflex method, which involves computer-based analysis to locate sequences of four or more heart beats in which blood pressure spontaneously increases or decreases with parallel changes in pulse interval (1, 23, 29, 40). We observed comparable values with both methods except for a higher baroreflex gain in PE-treated animals compared with the up sequences examined during spontaneous fluctuations in blood pressure, which could be explained by the fact that PE may have activated nerve fibers related to the cardiopulmonary reflex, which, in turn, could have contributed to the greater baroreflex gain observed (4). Of note, although the values obtained by us regarding the gain of the baroreflex in the drug-induced method were somewhat lower than those reported by others (25–27), they were close to the values obtained during the spontaneous baroreflex analysis. This discrepancy could be attributed to different mathematical approaches to estimate baroreflex sensitivity.

The pros and cons of classical methods for baroreflex assessment have been reviewed elsewhere (22). Unfortunately, neither classic drug-induced baroreflex assessment nor the spontaneous baroreflex method take into account input variables such as diastolic pressure, pulse pressure, stroke volume, and dP/dT, all of which are involved in baroreflex regulation of R-R interval, but instead only consider systolic and MAP. Thus, it is difficult to control all of these variables with either of the described methods. It could be presumed that the cardiac baroreflex provides a buffer solely against short-term disturbances in blood pressure and only under resting conditions when stress levels are low. In contrast, it can be overridden or reset to higher pressures during rapid rises in HR in response to a variety of stimuli such as exercise, the defense reaction, or during chronic pathological conditions such as hypertension (12, 20, 24, 31). As a result, we suggest that these two methods of analyzing baroreflex sensitivity be implemented complimentarily to each other.

Perspectives and Significance

Chronic intermittent activation of peripheral chemoreceptors in patients suffering from sleep obstructive apnea results in impaired autonomic control and affects baroreflex function, which could facilitate hypertension (11, 28, 38). Considering the potential clinical relevance of the interaction between both the chemoreflex and baroreflex, we have assessed both of these reflexes in the same animal model. In addition, we have evaluated two different methods commonly used to analyze the sensitivity of the baroreflex. The use of telemetry for studying these cardiovascular reflexes in an anesthetized- and stress-free environment will undoubtedly contribute to a better understanding of some of the pathological conditions that adversely affect the functioning of these reflexes such as obstructive sleep apnea and hypertension.

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