Periodic breathing in the mouse

FANG HAN,1 SHYAM SUBRAMANIAN,1 EDWIN R. PRICE,1 JOSEPH NADEAU,2 KINGMAN P. STROHL1
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Han, Fang, Shyam Subramanian, Edwin R. Price, Joseph Nadeau, Kingman P. Strohl. Periodic breathing in the mouse. J Appl Physiol 92: 1133–1140, 2002; 10.1152/japplphysiol.00785.2001.—The hypothesis was that unstable breathing might be triggered by a brief hypoxia challenge in C57BL/6J (B6) mice, which in contrast to A/J mice are known not to exhibit short-term potentiation; as a consequence, instability of ventilatory behavior could be inherited through genetic mechanisms. Recordings of ventilatory behavior by the plethysmography method were made when unanesthetized B6 or A/J animals were reoxygenated with 100% O2 or air after exposure to 8% O2 or 3% CO2:10% O2 gas mixtures. Second, we examined the ventilatory behavior after termination of poikilocapnic hypoxia stimuli in recombinant inbred strains derived from B6 and A/J animals. Periodic breathing (PB) was defined as clustered breathing with either waxing and waning of ventilation or recurrent end-expiratory pauses (apnea) of ≥2 average breath durations, each pattern being repeated with a cycle number ≥3. With the abrupt return to room air from 8% O2, 100% of the 10 B6 mice exhibited PB. Among them, five showed breathing oscillations with apnea, but none of the 10 A/J mice exhibited cyclic oscillations of breathing. When the animals were reoxygenated after 3% CO2:10% O2 challenge, no PB was observed in A/J mice, whereas conditions still induced PB in B6 mice. During 100% O2 reoxygenation, all 10 B6 mice had PB with apnea. Expression of PB occurred in some but not all recombinant mice and was not associated with the pattern of breathing at rest. We conclude that differences in expression of PB between these strains indicate that genetic influences strongly affect the stability of ventilation in the mouse.

A common assumption is that periodic breathing (PB; the waxing and waning of ventilation) is initiated and sustained by instability in the respiratory control system (12, 24). Short-term potentiation (STP) of ventilation, or ventilatory after-discharge, can be evoked by brief hypoxia exposure and promotes ventilatory stability and protects against dysrhythmic breathing or PB, as represented by repetitive apnea and Cheyne-Stokes respiration (15, 44). Conversely, an absence of STP would promote PB. Such proposals are supported by studies on obstructive sleep apnea (OSA) patients (18) or congestive heart failure (CHF) patients with Cheyne-Stokes respiration (1), in whom the impairment of STP occurs in the context of PB during sleep. Differences in ventilatory behavior during steady-state exposure to hypoxia or hypercapnia arise from genetic influences in the mouse (20, 37). An inherited basis for posthypoxic ventilatory and frequency (f) decline is also observed in rats (17, 34) and mice (22, 27). However, the extent to which genetic mechanisms operate in the expression of dysrhythmic breathing or PB is not known. In a previous study (21), our laboratory found that ventilation STP could be evoked by brief hypoxic exposures in unanaesthetized and unrestrained inbred A/J mice but not in C57BL/6J (B6) mice. Such a finding implies that the absence of STP in the B6 mouse removes a stabilizing mechanism and could thereby increase the propensity for dysrhythmic breathing in this strain. The hypothesis of this study was that PB could be evoked by a brief hypoxic challenge in B6 but not in A/J mice and that this ventilatory dysrhythmia is inherited through genetic mechanisms. To first address this issue, we reoxygenated B6 and A/J mice with 100% O2 or air after both poikilocapnic and CO2-enriched hypoxia exposure. Second, we examined the ventilatory behavior after termination of poikilocapnic hypoxia stimuli in inbred recombinant mice strains derived from B6 and A/J animals.

METHODS

Animals. Experiments were performed on two strains of inbred B6 and A/J mice (Jackson Laboratory, Bar Harbor, ME) and on groups of recombinant inbred mice strains derived from B6 and A/J parental strains, all raised in the Animal Resource Center at Case Western Reserve University. All animals were housed at the Center under standard conditions of 7 AM to 7 PM light-dark cycles for at least 2 wk before testing and were provided food and water ad libitum. The study protocol was approved by the Case Western Reserve University School of Medicine Institutional Animal Care and Use Committee and was in agreement with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Experimental protocols. Measurements were made between 10:00 AM and 2:00 PM. All experiments were carried out when the animals were awake, as determined by behavioral observation. Each animal was weighed, placed in the
Fig. 1. Protocols that were used to test parental strains are presented in schematic for the presence and strength of periodic breathing occurring after hypoxic challenge.

Fig. 2. Manner in which periodic breathing was quantified for comparisons among protocols is shown in these two examples from B6 mice. M, a value describing the strength of oscillation, is calculated differently for events with obvious apneas (bottom) vs. short pauses (top). $V_{Emin}$, minimum level of instantaneous minute ventilation ($V_E$); $V_{Emax}$, maximal level of instantaneous $V_E$; $Tc$, cycle length; $Ta$, apnea length. See text for greater explanation and reference.
periodic pattern and 2) the strength of the oscillation (M), a measure of how much the ventilation changes as the oscillation goes from its point of maximum ventilation (V_{max}) to its point of minimum ventilation (V_{min}) defined by Waggoner et al. (40). For nonapneic oscillations, M was defined as the ratio of V_{max} – V_{min} divided by V_{max} + V_{min}, and for apneic oscillations, this same index was calculated as the ratio of Tc over the difference between Tc and length of apnea (43).

Data analysis. Ventilatory parameters were measured continuously throughout the testing period, and scored by computer by using a respiratory-based software program (LabView programming by I.C.E). The following variables were analyzed: inspiratory Vt (in μl), f (in breaths/min), VvE (in ml/min, Vt × f). Sighs or sniffs were excluded in the analysis. Sighs were signals that exceeded by 150% the average Vt for the past 4 s and were sometimes accompanied by a compensatory sigh. Sniffs are identified as rapid, very shallow oscillations in voltage, which, on visual examination, are temporally related to exploratory behavior which when the animal appears to be awake. During posthypoxic periods, the breathing patterns reported here could easily be seen as a regular periodicity in the strip-chart recording of voltage vs. time; the cycle time and strength of the patterns were measured directly off the strip-chart recordings and were assisted by the computer program. During 100% O2 reoxygenation tests, VvE, Vt, and f were determined when the concentration of the inspired oxygen was between 40 and 50%.

All results are expressed as means ± SE. Differences between means were tested by using a Student’s t-test (paired or unpaired as required). A point biserial correlation (Pearson correlation) was used to determine the relationship, if any, between the presence or absence of PB and ventilatory behavior among all inbred strains studied. P values of <0.05 were considered significant.

RESULTS
Reoxygenation effects on respiration after 8% O2 exposure were characterized on the first group of 10 mice of each parental strain, the average body weight being 29.8 ± 0.5 g for B6 mice and 26.5 ± 0.4 g for A/J mice (P < 0.05). Reoxygenation effects on respiration after 3% CO2-10% O2 exposure were determined on 10 other mice of each strain; in this protocol, the average weights were 29.6 ± 0.4 and 26.6 ± 0.5 g (P < 0.05), respectively. All of them were male and age matched (16–17 wk old).

Ventilatory behavior in A/J and B6 mice during baseline air breathing and during isocapnic and poikilocapnic hypoxia. At baseline, A/J mice exhibited a slower, deeper breathing pattern compared with B6 animals (Table 1). Vt and f were fairly regular; no breathing oscillation with apnea or near apnea could be visually identified in both strains of mice. Figure 3 shows a typical example of air baseline breathing of a B6 and an A/J mouse.

Visual interpretation of data during both hypoxia showed a relatively stable breathing pattern. No PB was observed in both strains of mice within the 5 min of hypoxia. During 8% O2 exposure, both B6 and A/J mice showed hypoxia ventilatory decline or the “roll-off” phenomenon. From the minutes 1–5, the magnitude of decrease in regard to VvE (19 ± 3 vs. 18 ± 3%, B6 vs. A/J), Vt (11 ± 3.3 vs. 10 ± 2%), and f (10 ± 2.5 vs. 9 ± 2.1%) were similar between the two strains. Measurements of ventilatory responsiveness to chemoreceptor inputs are approximated by the differences in ventilation and its components between appropriate baseline values. The two strains differ substantially in regard to f response to 3% CO2-10%O2 and 8% O2; the percentage increases in Vt during 3% CO2-10% O2 relative to room air were not different between the two strains but were significantly different during 8% O2 exposure; the relative increase in VvE with inhalation of 3% CO2-10% O2 and 8% O2 compared with resting breathing is similar in the two strains. In summary, the magnitudes of VvE changes to hypoxia between B6 and A/J animals were similar; however, the breathing pattern to achieve the same VvE change was unequivocally different between the two strains.

Posthypoxia ventilatory behavior in A/J and B6 mice. With the abrupt return to room air from 8% O2, 100% of the 10 B6 mice exhibited PB; among them, five showed breathing oscillation with apnea; but none of the 10 A/J mice exhibited a cyclic or oscillatory pattern of breathing. Figure 4 shows a representative sample of strip-chart recording of PB occurring during the posthypoxic period in a B6 mouse; changes in VvE for the same animal were directly reflected in the corresponding time-related changes in both Vt and f.

On transition from 8% O2 to 100% O2, the differences between the two strains in the posthypoxic ventilatory behavior were similar to those during air reoxygenation, except that now all 10 B6 mice showed PB with apnea. Figure 5 shows examples of the different postpoikilocapnic hypoxia ventilatory behavior in a B6 and an A/J mouse. As shown in Table 2, Tc was the same as that followed by air, but the apnea time was longer than during air reoxygenation, indicating that the magnitude of the breathing oscillations was more prominent during the 100% O2 reoxygenation. This was also demonstrated by the increased M of the oscillations during 100% O2 reoxygenation.

In protocol B, a second group of mice were studied to determine whether CO2 might affect hypoxic induced PB. When the animals were abruptly returned to room air or 100% O2 after 5 min of isocapnic hypoxia challenge, no PB was observed in all 10 A/J mice. In contrast, both of these two conditions still induced PB.

Table 1. Values for ventilatory behavior during resting breathing

<table>
<thead>
<tr>
<th>Strain</th>
<th>CS7BL/6J</th>
<th>A/J</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>f, breaths/min</td>
<td>165 ± 4</td>
<td>140 ± 6</td>
<td>0.001</td>
</tr>
<tr>
<td>Vt, μl</td>
<td>73 ± 4</td>
<td>97 ± 4.1</td>
<td>0.0002</td>
</tr>
<tr>
<td>Vt/Wt, μl/g</td>
<td>2.6 ± 0.1</td>
<td>3.9 ± 0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>VvE, ml/min</td>
<td>11.8 ± 0.7</td>
<td>12.9 ± 0.8</td>
<td>0.15</td>
</tr>
<tr>
<td>VvE/wt, ml/min^-1-g^-1</td>
<td>0.41 ± 0.02</td>
<td>0.52 ± 0.03</td>
<td>0.001</td>
</tr>
</tbody>
</table>

f, Frequency; Vt, tidal volume; VvE, minute ventilation; wt, body weight.
in all the 10 B6 mice. During air reoxygenation, 6 of them showed PB with apnea and, during 100% O\textsubscript{2} reoxygenation, all 10 mice had PB with apnea, 4 of them exhibited a breathing pattern, which was referred to as episodic breathing by Wilkinson et al. (43), consisting of periods of breathing alternating with apneas of similar duration and may be analogous to the qualitatively similar pattern known as Biot’s breath-
ing. Compared with air reoxygenation, the PB during 100% O2 reoxygenation also had the same Tc but stronger oscillation and longer apnea duration (Table 2).

Figure 6 shows examples of postisocapnic hypoxia ventilatory behavior in a B6 and an A/J mouse. Comparison of the PB between the two hypoxia gas mixtures did not disclose any difference in regard to Tc, M, and apnea time when reoxygenated with the same gas (Table 2).

**Segregation of PB with ventilatory behavior.** Table 3 shows the presence or absence of PB in strains of parental and selected recombinant inbred strains, contrasting the presence or absence of PB to ranking of strains in regard to f, relative VT, and Ve. We conclude that the presence or absence of PB with reoxygenation after 8% hypoxia is not a function of the pattern of breathing or Ve at rest. Although the location of the genetic elements is not yet known through this experimental approach, it is clear that ventilatory behavior and PB segregate as genetically independent traits.

**DISCUSSION**

This study describes significant strain differences in posthypoxic ventilatory behavior in the mouse. First, during resting air breathing, no PB could be visually identified in B6 and A/J mice. Second, after 5 min of poikilocapnic or isocapnic hypoxia challenge, 100% of the behaviorally awake adult B6 mice exhibited PB on reoxygenation with both air and 100% oxygen; in contrast, none of the A/J mice showed discernible oscillations in ventilatory patterns during the same series of environmental gas exposures. The occurrence of PB was independent of sleep, degree of the previous hypoxia and added CO2 during hypoxia, or O2 level of the

![Fig. 5. Tracings show the differences between A/J and B6 animals in regard to ventilatory behavior ~30 s after reoxygenation with either air or 100% oxygen after a 5-min exposure to 8% oxygen.](image1)

![Fig. 6. Tracings show the differences between A/J and B6 animals in regard to ventilatory behavior ~30 s after reoxygenation with either air or 100% oxygen after a 5-min exposure to 3% CO2-10% oxygen.](image2)

**Table 2. Indexes for periodic behavior during post-challenge in the B6 strain**

<table>
<thead>
<tr>
<th>Strain</th>
<th>n</th>
<th>Challenge Gases</th>
<th>CL, s</th>
<th>M*</th>
<th>Apnea Time, s</th>
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<tr>
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<tr>
<td>C57BL/6J</td>
<td>10</td>
<td>8% O2-air</td>
<td>4.6 ± 1.0</td>
<td>1.7 ± 0.4</td>
<td>0.93 ± 0.28</td>
</tr>
<tr>
<td>C57BL/6J</td>
<td>10</td>
<td>8% O2-100% O2</td>
<td>2.8 ± 0.5</td>
<td>5.5 ± 0.7</td>
<td>2.0 ± 0.27</td>
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<td>Study 2</td>
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<tr>
<td>C57BL/6J</td>
<td>10</td>
<td>3% CO2-10% O2-air</td>
<td>3.5 ± 0.5</td>
<td>2.0 ± 0.4</td>
<td>0.90 ± 0.41</td>
</tr>
<tr>
<td>C57BL/6J</td>
<td>10</td>
<td>3% CO2-10% O2-100% O2</td>
<td>2.5 ± 0.3</td>
<td>5.5 ± 0.9</td>
<td>2.2 ± 0.29</td>
</tr>
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</table>

Values are means ± SE (n = 10 mice for each group). CL, cycle length; M, strength of oscillation. *Dimensionless number for M. For CL, no significant difference was observed between studies. After reoxygenation with 100% O2, M was significantly greater than when reoxygenated with air for each group.
Table 3. Presence or absence of PB in mouse strains according to relative ranking in trait values for ventilatory behavior at rest

<table>
<thead>
<tr>
<th>Mean value, breaths/min PB</th>
<th>Strain</th>
<th>Mean value, μl PB</th>
<th>Strain</th>
<th>Mean value, ml/min PB</th>
<th>Strain</th>
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<tr>
<td><strong>f vs. PB</strong></td>
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<tr>
<td>107</td>
<td>+</td>
<td>BXA-14</td>
<td></td>
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<tr>
<td>123</td>
<td>–</td>
<td>AXB-5</td>
<td></td>
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<tr>
<td>127</td>
<td>–</td>
<td>AXB-15</td>
<td></td>
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<tr>
<td>138</td>
<td>–</td>
<td>A/J</td>
<td></td>
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<tr>
<td>160</td>
<td>+</td>
<td>AXB-22</td>
<td></td>
<td></td>
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<tr>
<td>164</td>
<td>+</td>
<td>B6</td>
<td></td>
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<tr>
<td>172</td>
<td>+</td>
<td>AXB-1</td>
<td></td>
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<tr>
<td>185</td>
<td>–</td>
<td>BXA-24*</td>
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<tr>
<td><strong>V̇e vs. PB</strong></td>
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<tr>
<td>73</td>
<td>+</td>
<td>B6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>83</td>
<td>–</td>
<td>BXA-24</td>
<td></td>
<td></td>
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<tr>
<td>95</td>
<td>–</td>
<td>AXB-5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>–</td>
<td>A/J</td>
<td></td>
<td></td>
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<tr>
<td>101</td>
<td>+</td>
<td>AXB-22</td>
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<td></td>
<td></td>
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<tr>
<td>136</td>
<td>+</td>
<td>AXB-1</td>
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<tr>
<td>138</td>
<td>+</td>
<td>BXA-14</td>
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<tr>
<td>150</td>
<td>–</td>
<td>AXB-15</td>
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Strains listed from lowest to highest value. Periodic breathing (PB) is as defined in the text. +, Presence of PB; –, absence of PB.

*Breathing appeared regularly irregular but did not meet criteria for PB.

re-oxygenation gases. The strain differences of PB in B6 and A/J as well as in the recombinant strains indicate a genetic influence on the stability of the posthypoxic ventilation in mice.

Hypoxia, imposed through either inhalation of low O₂ mixtures or ascent to altitude, is well known to induce PB in animals and humans (5, 8, 10, 19, 42). Sleep, increased gain, increased time delay, and decreased damping of the system are all known to promote respiratory instability (23). However, a major finding in this study is that re-oxygenation can induce PB in awake B6 mice but not in awake A/J mice. PB has also been observed in awake patients with chronic heart failure (30), and awake normal adults can develop irregular and PB during induction of mild hypoxia produced by nasal administration of nitrogen (10). In awake newborn lambs, it is possible to produce PB on demand when appropriate settings of blood gases are reached to drive the chemoreceptors (9). These reports indicate that sleep was not obligatory in eliciting PB. In the present study, we did not monitor the electroencephalogram and did not have a rigorous measurement of how wakeful or alert animals were during the protocol, although we took care to observe animals and did not observe behaviors indicating sleep during the induction of PB.

A commonly proposed mechanism for PB involves hypoxia-induced increased gain of the carotid chemoreceptors. Mathematical models and studies on humans have demonstrated strong statistical correlations between the incidence of PB and hypoxic sensitivities (2, 28, 42). Posthypoxic PB during sleep occurs more frequently in individuals with higher peripheral chemosensitivity (19, 42). The finding that PB could occur in B6 mice during hypoxia-air re-oxygenation is consistent with the evidence for a critical role of peripheral chemoreceptors in the genesis of PB. However, the breathing periodicity during 100% O₂ re-oxygenation cannot be mediated by the peripheral chemoreceptors only because it occurs against a background of arterial hyperoxia, which is sufficient to minimize O₂-sensitive ventilatory drive. Further evidence supports that PB is mediated by mechanisms other than peripheral chemoreceptors, namely the studies on cats and ponies; in both species, hypoxia-induced PB continued after carotid body denervation (7, 41). As proposed by Wilkinson et al. (43), the observation of episodic breathing in some B6 mice during 100% O₂ re-oxygenation in this study also suggests that this pattern of breathing is mediated via the central chemoreceptor. As reported before (21) and shown in this study, the magnitudes of V̇e change, to both poikilocapnic and isocapnic hypoxia and hypercapnia (5% CO₂) between B6 and A/J animals, were the same.

Thus the strain difference in posthypoxic PB cannot be attributed solely to the different chemoresponsiveness.

Apart from the carotid chemoreceptor excitation, hypoxia is also reported to depress ventilatory activity via direct effects on the central nervous system (39) or via central accumulation and/or release of inhibitory neurotransmitters on respiratory neurons (31). Hypoxia was considered a “primary event” inducing PB via its central depressant effect in the neonatal period (32). Prolonged or more severe hypoxia had an important central inhibitory influence on the mechanisms of STP and would predict that ventilatory instabilities, such as PB, would be more likely to occur (14, 29). In this study, we identified the roll-off phenomenon during the 5-min hypoxic exposure in both strains of mice, indicating the existence of hypoxic depression. However, there is no evidence suggesting an influence of hypoxic depression on the occurrence of PB in B6 mice. First, as reported in Table 2, we found no qualitative or quantitative differences about the effect of hypoxic severity (8 vs. 10%) on PB, despite the presumably higher level of central tissue hypoxia when 8% O₂ was added. Second, we observed PB in 4 of the 10 B6 mice that showed PB when re-oxygenated with 100% O₂ after air breathing, i.e., without prior hypoxic exposure (Fig. 7). This is consistent with findings in awake neonatal lambs that there is no effect on posthypoxic PB of central tissue hypoxia by carbon monoxide inhalation (carboxyhemoglobin = 30%) (9). Furthermore, there was no difference in regard to the degree of ventilatory decline during hypoxia between the two strains. This suggests that strain differences in posthypoxic PB are not related to the preceding hypoxic depression.
Human and animal studies have provided evidence supporting the importance of hypocapnia in the genesis of hypoxia-induced PB (11, 38). In the awake goat (16) and sleeping human (4), STP was largely eliminated and PB develops, if posthypoxic hypocapnia is permitted. However, in the present study, the presence or absence of PB in B6 and A/J mice occurred independent of the hypoxic hypocapnia. Therefore, the difference in posthypoxic ventilatory behavior between the two strains cannot be easily attributed to a difference in arterial partial pressure of CO2.

Oxygen administration seems to have a paradoxical effect on breathing stability. First, according to the predicted model, inhalation of oxygen would depress the carotid body activity and, therefore, should stabilize breathing and eliminate or attenuate PB. This is supported by most experimental and clinical studies (3, 13). Second, some researchers reported the persistence of PB despite O2 administration. Wilkinson et al. (43) could induce PB just by switching inspired gas from air to hyperoxia in lambs but could not produce PB during air breathing after passive hyperventilation. This demonstration supports the idea that inhalation of hyperoxia against a background of hypoxia promotes instability in the respiratory controller. In the present study, the difference of M in B6 mice between air and hyperoxia reoxygenation, and the posthypoxic breathing change in A/J mice during different reoxygenation procedures, clearly indicates that the oxygen level of reoxygenation gas had a significant influence on posthypoxic ventilatory behavior in both strains. However, 100% O2 reoxygenation neither made PB in B6 mice, which did so during air reoxygenation disappear, nor provoked PB in A/J mice, which had no PB during air reoxygenation. Thus the occurrence of strain-related posthypoxic PB may not depend on the oxygen level of the reoxygenation gas.

Increased time delay and decrease in damping lung volume may also be involved in the genesis of PB, but these mechanisms are unlikely to play major roles in mice because hypoxia increases cardiac output and shortens circulation time, and end-expiratory lung volume may increase with hypoxia (6).

From the present findings, inheritance is a mechanism that might produce a difference in neural networks, which act to influence ventilatory stability and produce PB. It is known that there are significant intrastrain differences in hypoxic responsiveness in mice (36), and a limited number of genes may influence the level of ventilation on hypoxia (35). Proof of the principle of genetic transmission of posthypoxia ventilatory behavior is also supported by observations by Kline et al. (25), who reported respiratory depression in response to brief hyperoxia was pronounced in wildtype mice but nearly absent in nitric oxide synthase (NOS) III mutant mice. A second study (26) indicated that NOS I might also be involved in an unstable breathing pattern during hypoxia, again in mice. Jacobs and Thach (22) reported that, in a spontaneous recovery from hypoxic apnea, prolonged but ineffective gasping was more often seen in SWR mice, whereas gasping was absent in SW mice. The present study used inbred B6 and offspring (B6 × A/J) inbred recombinant mice to confirm an inherited basis for PB in the adult mouse.

Thus genetic influences act to influence the expression of PB in mice. The questions of relative strength of the genetic components and the identification of the genes, proteins, and systems that produce ventilatory dysrhythmia in the B6 warrant further investigation.
REFERENCES


