Development of the ventilatory response to hypoxia in Swiss CD-1 mice

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Robinson, Dean M., Henry Kwok, Brandon M. Adams, Karen C. Peebles, and Gregory D. Funk. Development of the ventilatory response to hypoxia in Swiss CD-1 mice. J Appl Physiol 88: 1907-1914, 2000.—We examined developmental changes in breathing pattern and the ventilatory response to hypoxia (7.4% O2) in unanesthetized Swiss CD-1 mice ranging in age from postnatal day 0 to 42 (P0–P42) using head-out plethysmography. The breathing pattern of P0 mice was unstable. Apneas were frequent at P0 (occupying 29 ± 6% of total time) but rare by P3 (5 ± 2% of total time). Tidal volume increased in proportion to body mass (~10–13 ml/kg), but increases in respiratory frequency (f) (55 ± 7, 130 ± 13, and 207 ± 20 cycles/min for P0, P3, and P42, respectively) were responsible for developmental increases in minute ventilation (690 ± 90, 1,530 ± 250, and 2,170 ± 430 ml·min−1·kg−1 for P0, P3, and P42, respectively). Between P0 and P3, increases in f were mediated by reductions in apnea and inspiratory and expiratory times; beyond P3, increases were due to reductions in expiratory time. Mice of all ages showed a biphasic hypoxic ventilatory response, which differed in two respects from the response typical of most mammals. First, the initial hyperpnea, which was greatest in mature animals, decreased developmentally from a maximum, relative to control, of 2.58 ± 0.29 in P0 mice to 1.32 ± 0.09 in P42 mice. Second, whereas ventilation typically falls to or below control in neonatal mammals, ventilation remained elevated relative to control throughout the hypoxic exposure in P0 (1.73 ± 0.31), P3 (1.64 ± 0.29), and P9 (1.34 ± 0.17) mice but not in P19 or P42 mice.

METHODS

Animals. Experiments were carried out in Swiss CD-1 mice. Animals were fed water ad libitum and dry pellets, weaned at 19 days, and kept in a quiet room at 21–22°C and
50–65% relative humidity under a 12:12-h light-dark cycle. Timed mating of females was performed at ~42 days of age, and mice were tested at the following postnatal days: 0 ± 0 (P0), within 12 h of birth), 3 ± 1 (P3), 9 ± 0 (P9), 19 ± 2 (P19), and 42 ± 2 (P42). Five litters, varying in size from 6 to 10 animals, were studied. For these experiments, the selection of Swiss CD-1 mice was important because mothers tolerate disturbance in the first few hours after delivery, facilitating examination of neonates within the first few hours after birth. All procedures were performed in accordance with guidelines of the Animal Ethics Committee, University of Auckland.

Measurement of ventilation. Baseline ventilatory parameters and responses to hypoxia were measured in unanesthetized mice using continuous head-out, whole-body plethysmography modified slightly from that described elsewhere (26). The Perspex plethysmograph consisted of separate head (8 ml) and body (40 ml) chambers that were separated by a flexible latex seal (Dentsply) attached to the back of the head chamber. The head chamber consisted of threaded inner and outer cylinders. The rear edge of the inner cylinder contacted a spacer that in turn contacted the latex seal. Rotation of the inner cylinder moved it forward or backward relative to the outer cylinder, shrinking or expanding a hole in the latex seal for the animals’ heads. Animals were placed in the body chamber, and the hole in the latex seal was expanded. Animals were positioned with their heads through the hole into the head chamber, and then the edges of the latex sheet were coated with a thin layer of vacuum grease. To establish a seal without restricting respiratory airflow, the inner cylinder of the head chamber was then rotated and the diameter of the hole was gradually reduced until the body plethysmograph chamber was able to maintain constant positive pressure when air was injected into the plethysmograph chamber (after outflow through the pneumotachograph was blocked). Integrity of the seal was verified before and after each experiment. Data were excluded if the seal was not maintained throughout the trial.

Normoxic and hypoxic gases (see below) were pulled through the head chamber at 250 ml/min to a Datex O2/CO2 gas analyzer. The body chamber was connected to the atmosphere through a pneumotachograph high-resistance head (Fleisch) with an MP 45-1 pressure transducer (Validyne Engineering), the output of which was passed through a CD15 carrier demodulator (Validyne Engineering). The output voltages of both the CD15 carrier demodulator and the gas analyzer were digitized by a MacLab analog-to-digital converter and recorded at 40 Hz using Chart 3.3.8 (AD Instruments) running on a Power PC Macintosh 7300/180 under Mac OS 8.0 (Apple Computer). Volume calibration was performed at the beginning and end of each experiment by injection of air into the chamber from 10-, 50-, and 100-μl Hamilton syringes. The frequency independence of the measurement system was established in a preliminary set of experiments in which volumes ranging from 10 to 100 μl were injected at frequencies ranging from 20 to 250 cycles/min.

Zero flow was defined at the beginning of each experiment by opening the low-resistance calibration port, which resulted in zero flow being registered at the pneumotachograph. Zero flow was confirmed throughout the experiment when flow fell to, and remained at, zero during extended end-expiratory pauses (or apneas). Baseline did not drift during the protocol (see Fig. 2).

Chamber temperature was maintained in thermoneutral ranges (43, 46) by connecting a chamber temperature probe to a Bat-12 digital thermometer, TCAT-1 temperature controller (Physitemp), and infrared lamp. Chamber temperature was maintained 35–36°C for P0–P9 animals and at 32–33°C for P19 and P42 animals.

Inspired gas mixtures. Normoxic gas (medical air, 21% O2) was obtained commercially. Hypoxic gas (7.4% O2) was mixed by diluting medical air with oxygen-free nitrogen using a Wösthoff pump. This level of hypoxia was selected on the basis of preliminary experiments, where it produced consistent, robust hypoxic ventilatory responses in animals of all ages, including neonates. Gases were stored in 100-liter Douglas bags and humidified before delivery. Composition of the gas leaving the head chamber was continuously monitored by a Datex O2/CO2 gas analyzer and recorded on computer and was stable throughout experiments.

Experimental protocol. Once the mice were resting quietly, recording was started. Control data were acquired for 5 min. Inspired gas was then switched from normoxia to hypoxia via a three-way valve. Changeover of inspired gases within the head chamber was complete within 5–10 s (see Fig. 2B). Preliminary experiments on P0 and P9 animals indicated that, in contrast to neonates of most other species (27), ventilation remained significantly greater than control after 5 min of hypoxia. The period of hypoxic exposure was therefore extended to 12 min to ensure that sufficient time was allowed for the hypoxic depression of ventilation to develop. After 12 min of hypoxia, inspired gas was returned to normoxia and recovery data were collected for 10 min.

Data analysis. Chart 3.3.8 records were saved as text files and converted to binary files by a custom-written Qbasic program running under DOS on a Power Macintosh 386. The data files, representing flow, were then digitally integrated to generate volume information.

Values of Vt, tidal volume (Vt), respiratory frequency (f), average instantaneous breathing frequency (breathing frequency excluding periods of apnea), inspiratory (TI) and expiratory time (TE), frequency of apnea, and percentage of total time spent apneic for quiet breathing were averaged for each 30-s period of the 27-min protocol. To measure TE, the analysis program defined the flow reversal associated with the change from inspiration to expiration, and TE was defined as the interval extending from this point (end inspiration) to the beginning of the next inspiration. The minimum duration of zero flow greater than 3 s in duration were defined as apnea (18). Although this had the potential to overestimate TE in the P9 and P19 age groups, it minimized the risk of overestimating the frequency of apnea in the young animals. The degree of hypoxic depression was determined by comparing peak levels of ventilation (relative to control) observed between minutes 1 and 3 of hypoxia (phase one) with levels observed between minutes 9 and 11 of hypoxia (phase two). Data are reported in absolute terms and relative to normoxic control values.

Most pups had periods of quiet breathing intermittently disturbed by short bursts of activity. Active periods were apparent as pressure changes many times larger than those associated with respiratory airflow. Thus, to obtain values of respiratory parameters for quiet breathing, the custom analysis software (Qbasic) was designed to scan the entire experimental run for pressure changes greater than three standard deviations of the mean. These periods were then visually inspected and excluded from analysis if their irregularity was consistent with movement artifact.

To obtain the best possible picture of “quiet” breathing pattern in mice during development, all experimental runs having excessive movement artifact (occupying >5% of the total time) or evidence of a seal rupture during the course of the experiment were rejected. Six to seven animals were studied per litter at each age group. Given the difficulty of
The increase in $f$ between P0 and P3 was primarily due to a developmental reduction in the frequency of apneas, which therefore the amount of time spent apneic. P0 to a developmental reduction in the frequency of apneas, was replaced by the stable pattern of breathing pattern typical of P0 mice, punctuated with frequent apneas, was replaced by the stable pattern of breathing pattern in small mammals, we did not assess arousal state.

Statistical analysis. Statistical analysis was conducted using SAS 6.1 (SAS Institute). Raw data were tested for normality using the Shapiro-Wilk statistics and, where appropriate, subjected to a two-way ANOVA. To restrict inflation of Type I error rate, comparisons between age groups were restricted to the control period, minutes 1–3 and 9–11 of hypoxia, and minutes 1, 5, and 10 of recovery. Differences among interventions were sought (at the 95% level of confidence, $P < 0.05$) using mutually orthogonal contrast coefficients to partition the treatment sum of squares.

Nonnormal and nonparametric data were subjected to the Kruskal-Wallis test; differences between groups were sought using Wilcoxon’s signed rank tests with Bonferroni-adjusted $P$ values. Data are presented as means ± SE. Data for some age groups were omitted for clarity.

RESULTS

Developmental changes in breathing pattern. Baseline measurements of weight-corrected respiratory parameters averaged for 5 min before hypoxic exposure are presented in Table 1. Flow traces from individual mice of different ages illustrate how the unstable breathing pattern typical of P0 mice, punctuated with frequent apneas, was replaced by the stable pattern of adult mice (Fig. 1).

The most profound changes in breathing pattern occurred in the period between P0 and P3. $V\dot{E}$ more than doubled, due largely to an increase in average $f$, since weight-corrected $Vt$ was constant between P0 and P42. The increase in $f$ between P0 and P3 was primarily due to a developmental reduction in the frequency of apneas and therefore the amount of time spent apneic. P0 animals were apneic 29 ± 6% of the time. By P3, this had decreased to 5.1 ± 2.4%, and apneas were not commonly observed after P3. Increases in instantaneous $f$, from 94 ± 7 to 146 ± 11 breaths/min between P0 and P3, also contributed to the increase in average $f$ over this developmental window. Thus greater values of $Tt$ contributed to the lower $f$ in P0 animals. Elevations in $Te$ are also likely to have contributed to the lower $f$ in young animals. However, higher values of $Te$ in animals showing significant apnea (P0 and P3 animals) must be viewed with caution as these high values may reflect inclusion of apneas shorter than the arbitrary cutoff of 3 s.

Beyond P3, when apneas are virtually absent and instantaneous $f$ corresponds to average $f$, the most obvious change in pattern was a continued increase in $f$, due to a reduction in $Te$, and an increase in $V\dot{E}$, such that at P19 and P42 $V\dot{E}$ was significantly greater than at P3 and P9.

Hypoxic ventilatory response. All age groups responded to hypoxia (7.4% $O_2$) with a rapid increase in ventilation. In the long time-scale recordings of airflow, the ventilatory response is most obvious in P0 animals as a reduction in the frequency and duration of apneas (Fig. 2).

In P0 and P19 animals (also observed in P3 and P42 animals, data not shown), elevations in flow rate were obvious at the transition from normoxia to hypoxia. Note that there was some variability in the time to the peak of the hypoxic ventilatory response. It occurred within the first 3 min of hypoxia in most animals (27/34) but after minute 3 in two of nine P0, two of seven P3, and one of six P9, P19, and P42 animals. Between control and phase one, $V\dot{E}$ increased from 690 ± 90 to 1,650 ± 170, 1,530 ± 250 to 2,570 ± 280, 1,600 ± 160 to 2,810 ± 420, 2,460 ± 210 to 3,380 ± 330, and 2,170 ± 430 to 2,750 ± 510 ml·min$^{-1}$·kg$^{-1}$ in P0, P3, P9, P19, and P42 mice, respectively (Fig. 3).

Table 1. Developmental analysis of respiratory variables measured under normoxic conditions in mice

<table>
<thead>
<tr>
<th>Age, days</th>
<th>n</th>
<th>Mass, g</th>
<th>$V_t$, ml/kg</th>
<th>$T_t$, s</th>
<th>$T_e$, s</th>
<th>$V\dot{E}$, ml·min$^{-1}$·kg$^{-1}$</th>
<th>Frequency, events/min</th>
<th>Respiratory Apnea</th>
<th>$T_a$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0±0</td>
<td>9</td>
<td>1.6±0.1</td>
<td>12.7±1.3</td>
<td>0.28±0.04</td>
<td>0.48±0.06</td>
<td>690±90</td>
<td>55±7</td>
<td>6.7±0.7</td>
<td>29±6</td>
</tr>
<tr>
<td>3±1</td>
<td>7</td>
<td>2.9±0.1</td>
<td>11.2±0.9</td>
<td>0.12±0.01</td>
<td>0.33±0.03</td>
<td>1,530±250*</td>
<td>130±13*</td>
<td>2.2±0.7*</td>
<td>5.1±2.4*</td>
</tr>
<tr>
<td>9±0</td>
<td>6</td>
<td>6.0±0.4</td>
<td>9.9±1.3</td>
<td>0.13±0.01</td>
<td>0.25±0.04</td>
<td>1,600±160</td>
<td>169±21*</td>
<td>0.3±0.1*</td>
<td>0.1±0.1*</td>
</tr>
<tr>
<td>19±1</td>
<td>6</td>
<td>9.4±0.5</td>
<td>12.6±1.3</td>
<td>0.14±0.01</td>
<td>0.19±0.02</td>
<td>2,460±210*</td>
<td>182±12*</td>
<td>0.1±0.1</td>
<td>0.0±0.0</td>
</tr>
<tr>
<td>42±1</td>
<td>6</td>
<td>25.8±1.3</td>
<td>11.0±1.9</td>
<td>0.13±0.02</td>
<td>0.16±0.02</td>
<td>2,170±430</td>
<td>207±20*</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of mice. $V_t$, tidal volume; $T_t$, inspiratory time; $T_e$, expiratory time; $V\dot{E}$, minute ventilation; $T_a$, percentage of total time spent apneic. *Significantly ($P < 0.05$) different from younger age groups.
Fig. 2. A: long time-scale recordings of respiratory airflow from P_0, P_9, and P_19 mice showing entire hypoxic test protocols comprising 5 min of air breathing followed by 12 min of breathing 7.4% O_2 and 10 min of recovery (only 5 min of recovery are shown). B: short time-scale recording of airflow (top trace) from a P_9 mouse illustrating the rapid change in breathing pattern that occurs immediately after the transition from normoxia to hypoxia. Artifact in the airflow trace is associated with valve motion and indicates point of transition from normoxia to hypoxia. Bottom trace is a recording of inspired O_2 fraction (FIO_2) in the gas flowing through the head chamber showing that the concentration of O_2 dropped from 21 to 7.4% within 3 s of switching the valve.

Although the absolute magnitude of the increase in \( V_E \) was similar across age groups, the increase in \( V_E \) relative to control was significantly greater for P_0 and P_3 age groups due to the high incidence of apnea and low resting levels of \( V_E \) in these age groups. Relative to control, the peak \( V_E \) in phase one (first 3 min of hypoxia) was 2.58 ± 0.29, 1.86 ± 0.24, 1.74 ± 0.14, 1.39 ± 0.14, and 1.32 ± 0.09 of control for P_0, P_3, P_9, P_19, and P_42 mice, respectively. P_9 animals, respectively. P_9 animals were the only exception in which ventilation fell to, but not below, control levels. \( V_E \) remained depressed below control levels in P_0 animals for the entire 10-min recovery period due primarily to a sustained increase in the frequency of apnea over control (prehypoxia) levels (Fig. 5). In P_3 animals, \( V_E \) gradually returned to control after the posthypoxic depression. In P_9, P_19, and P_42 animals, the posthypoxic reduction in \( V_E \) was followed by a rebound increase to levels greater than control levels, which gradually returned to control in P_9 animals but remained elevated throughout the 10-min recovery period in the P_19 (Fig. 3) and P_42 age groups.

**DISCUSSION**

Developmental changes in breathing pattern. The most striking developmental change in breathing pattern was the prevalence of apnea in newborn (P_0) mice and its sixfold reduction by P_3. Reductions in apnea were associated with increases in \( f \) between P_0 and P_3 (Table 1 and Ref. 18). However, these increases in \( f \) resulted not only from a decreased incidence of apnea but also from increases in instantaneous \( f \).

Unstable breathing patterns are commonly observed in newborns of many species (26). The breathing pattern of P_0 mice, however, has rarely been quantified. Previous analyses typically excluded P_0 animals or grouped observations on P_0 mice with data from P_1–3 animals and did not report the degree of apnea (26, 29, 30). Our separate analysis of P_0 and P_3 mice was motivated by evidence that respiratory networks, neurons, and modulatory systems change considerably even over this relatively short developmental window (13, 17, 42).

The possibility that the high incidence of apnea in P_0 animals reflects obstruction of the airway by the latex seal separating body and head chambers can be excluded. First, the plethysmograph was designed to allow fine control of the tension in the latex seal (see METHODS). Second, whole body plethysmography and video analysis of unrestrained animals revealed levels of apnea (Funk and Kwok, unpublished observations) similar to those recorded with head-out plethysmography. Third, pattern analysis of an inbred mouse strain, although having lower values overall, showed a similar five- to sixfold reduction between P_0 and P_1–3 in the amount of time spent apneic (18).
Beyond P₃, the major developmental change in respiratory pattern was an increase in f and Vₑ. Consistent with values reported separately for neonate (P₀–₃) (26, 29, 30) and adult mice (33, 44), changes in Vₑ (weight corrected), Tₑ, or the ratio of Tₑ to total cycle duration are minimal. Similar observations have been made in rats. Vₑ remains constant relative to body weight throughout development, whereas f and Vₑ increase over the first 2–3 postnatal wk (1, 6, 14, 15) before decreasing to adult levels (1, 14).

Despite these generalities, an important feature of breathing pattern data is their variability. In neonatal mice for example, values of f range from 110 to 210 breaths/min (8, 18, 26, 29, 30), whereas values for adult mice range from 110–385 breaths/min (4, 33, 44, 45). Although methodological differences will account for some of the variability, genetic differences between strains will also contribute (44). Thus, although analysis of Swiss CD-1 mice is an important first step in characterizing the ontogeny of breathing pattern in mice, similar analyses in a variety of mouse strains are necessary to establish the generality of the profile recorded in Swiss CD-1 mice. Increased interest in understanding respiratory deficits of transgenic mice (8) and the role of these deficits in the inability of many transgenic animals to survive beyond P₁–₂ (11, 18) are likely to result in a more complete description of how the pattern of breathing changes, not only in the later developmental stages but also in embryonic and the earliest postnatal periods.

Ontogeny of the hypoxic ventilatory response. The ventilatory response to hypoxia is biphasic in virtually all mammals examined, regardless of the magnitude of the hypoxia or the age of the animal (reviewed in Ref. 27). Ventilation increases rapidly following a stepwise reduction in inspired O₂ (the hypoxic hyperpnea) before gradually decreasing over several minutes to lower, steady levels. Variability in the magnitude of the initial
hyperpnea, the secondary depression (roll-off), and time course of the response is extremely large, even within the same species, due to a variety of experimental and biological factors (reviewed in Ref. 27). There is also considerable variability in the ontogeny of the hypoxic ventilatory response between species and studies. The “generalized” response in neonatal mammals including rats (6, 9), rabbit pups (16), kittens (41), piglets (7), lambs (3, 31), and human infants (24, 39; also see Ref. 29) comprises an initial increase in ventilation of variable magnitude that is followed by a secondary roll-off to levels ranging from above to below control. In adult mammals, the hypoxic hyperpnea is generally greater than in neonates, and ventilation falls more slowly during the second phase of the response and remains greater than control (reviewed in Ref. 27).

The hypoxic ventilatory response described here for developing mice, and described elsewhere for neonatal (26–29) and adult (J. M. Bissonnette and S. J. Knopp, personal communication) mice, is similar to the “generalized” response in that both neonates and adults show biphasic responses. The ontogeny of the response in mice is also similar to the “generalized” response in that the relative magnitude of the roll-off is greatest in the newborn. However, it differs from the typical response in that the increase in V̇E is substantially greater in neonatal mice than in neonates of other species (29) and in fact is larger (in relative terms) than the hypoxic hyperpnea of juvenile and adult Swiss CD-1 and C57BL/6 mice (Bissonnette and Knopp, personal communication). Thus, despite the large secondary depression of V̇E in Swiss CD-1 mice (but not C57BL/6 mice; Bissonnette and Knopp, personal communication), ventilation remains elevated significantly above control for prolonged periods in neonatal mice. In fact, comparison with neonates of 18 different species revealed that neonatal mice maintain a higher level of V̇E than all but one other species (29). The sustained increase in V̇E is even more remarkable in light of the fact that, in most altricial species like mice that deliver relatively immature young (reviewed in Refs. 19 and 29), ventilation tends to fall to control or below control. The response of mice is more typical of species that deliver precocial young in which ventilation remains above control.

The hypoxic ventilatory response of juvenile and adult Swiss CD-1 mice also differs from the generalized response. The magnitude of the initial hypoxic hyperpnea for adult Swiss CD-1 mice fits within the range reported for a variety of inbred mouse strains (44). However, in contrast to most species but consistent with preliminary data on C57BL/6 mice (Bissonnette and Knopp, personal communication), the hypoxic hyperpnea is small in juvenile and/or adult mice relative to newborns. Given the strain-specific variability in the magnitude of this initial hypopnea (0–120%, Ref. 44), evaluation of developmental changes in the hypoxic ventilatory response is required in other strains to...
establish the generality of developmental decreases in the magnitude of the hypoxic hyperpnea.

The hypoxic ventilatory response of juvenile and adult Swiss CD-1 mice and C57BL/6 (Bissonnette and Knopp, personal communication) mice is also unique in that ventilation does not remain elevated relative to control during sustained hypoxia. Comparable data from other strains of mice are not available.

Breathing pattern changes mediating the hypoxic ventilatory response. Comparison of pattern changes that underlie the hypoxic ventilatory response is complicated by variation in hypoxic sensitivity and the fact that changes in respiratory pattern depend on the degree of hypoxia (29). For example, a rapid shallow breathing pattern in kittens (29) and neonatal rats (6) during mild hypoxia (10–15% O₂) changes abruptly to slower deeper breathing with further reductions in O₂. Thus species with higher hypoxic sensitivity may respond to the same degree and duration of hypoxia with slower deeper breathing.

Despite these potential sources of variability, changes in breathing pattern that underlie the biphasic hypoxic ventilatory response are qualitatively similar across development and in different species. As seen for Swiss CD-1 mice, the hyperpnea in most mammals, including eight strains of inbred mice (44), rats (6), piglets/pigs (7), kittens/cats (23, 25, 41, 47), rabbits (16), lambs (3), and humans (5), neonates and adults alike, is mediated primarily by increases in respiratory frequency (for more complete list, see Ref. 29). In contrast, the hypoxic depression is primarily mediated by reductions in VT (3, 5–7, 23, 25, 41, 47). However, as seen here for Swiss CD-1 mice of all ages except P₀, and for human infants (24, 39), reductions in f can also contribute (3, 14).

Mechanisms. The biphasic hypoxic ventilatory response is largely attributed to an interaction between the excitatory actions on central respiratory networks of peripheral chemoreceptors and possibly rostral brain areas and the depressive effects of hypoxia on the central nervous system (9, 40, 41) and metabolism (28). Biphasic responses in rhythmically active in vitro preparations from which peripheral chemoreceptors are removed (37, 38, 48) suggest that central neurons (21, 48) also contribute to the initial hyperpnea. Developmental changes in the response may therefore represent a shift in the balance of these components where central inhibitory processes dominate in the fetus, peripheral stimulation dominates in the adult, and neonates represent an intermediate stage (6, 9) in which responses are further confounded by hypoxia-induced reductions in metabolism (28, 29).

Given the complex interplay of multiple mechanisms mediating the hypoxic ventilatory response, each with potentially different ontogenies, interspecific differences in the development of the hypoxic ventilatory response are expected. The sustained increase of Ve in neonatal mice relative to other species may therefore reflect early development of chemoreceptive pathways and reduced susceptibility to hypoxia-induced reductions in metabolic rate. A relatively mature chemoreflex in neonatal mice is supported by their large hypoxic ventilatory response relative to neonates of other species (29). Resistance to metabolic depression is also apparent. In contrast to other rodents, which show an ~50% decrease, the metabolic rate in neonatal mice falls <10% during 10% O₂ breathing (29). Although metabolic depression is not essential for expression of the biphasic response (2, 22, 39), the degree of metabolic depression has a significant influence on the magnitude of the ventilatory roll-off (reviewed in Ref. 28).

In summary, the mechanisms underlying the hypoxic depression are of considerable interest, due to their potential role in conditions such as sudden infant death syndrome, but remain unclear in many species. Here, we have described the ontogeny of the hypoxic ventilatory response in developing mice on the basis that the mouse model, because of its potential in genetic manipulation and because we can use it to study functioning respiratory networks throughout development in vivo and in vitro, may offer insight into the mechanisms underlying the biphasic hypoxic ventilatory response.

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