Mortality after carotid body denervation in rats

A. SERRA,1 D. BROZOSKI,1 N. HEDIN,2 R. FRANCIOSI,2 AND H. V. FORSTER1

Departments of 1Physiology and 2Pathology, Medical College of Wisconsin and Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin 53226-0509

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Serra, A., D. Brozoski, N. Hedin, R. Franciosi, and H. V. Forster. Mortality after carotid body denervation in rats. J Appl Physiol 91: 1298–1306, 2001.—Carotid body denervation (CBD) in neonatal goats and piglets results in minimal irregular breathing and no fatalities. Redundancy and/or plasticity of peripheral chemosensitivity and a relatively mature ventilatory control system at birth may contribute to the paucity of CBD effects in these species. In the present study, we tested the hypothesis that CBD mortality would be greater in neonates of a less mature species such as the rat. We found that the mortality in rats denervated at 2–3 and 7–8 days of age was significantly higher (P < 0.05) than in sham-CBD rats. In all surviving rats, pulmonary ventilation during hypoxia was lower in CBD than in sham operated rats 2 days after denervation. In surviving rats denervated during the 7th and 8th postnatal days, there was also reduced weight gain and pulmonary ventilation during eupnea, including apneas up to 20 s in duration. However, the effects of CBD were compensated within 3 wk after denervation. Local injections of NaCN indicated that aortic chemoreceptors might have been one of the sites of recovery of peripheral chemosensitivity. We concluded that CBD has higher mortality in newborn rats than in other mammals, possibly because of the relative immaturity of these animals at birth. Nonetheless, in survivors there was enough redundancy and plasticity in the control of breathing to eventually compensate for the consequences of CBD.

Peripheral chemosensitivity; critical window; neonates; control of breathing; plasticity

Initial studies on the effects of carotid body denervation (CBD) found that CBD in neonatal rats, lambs, and piglets resulted in hypoventilation, irregular breathing including apneas, and significant mortality (3–5, 14). These effects seemed to be age dependent, and the conclusions were that carotid chemoreceptors were essential for the control of breathing in specific periods (the “critical windows”) of newborn life. This conclusion was challenged by later studies on the effects of CBD in newborn goats and piglets (19, 20). In these studies, there were no CBD-related fatalities, and CBD produced only a transient, age-dependent, mild hypoventilation. A possible cause of the difference in findings between earlier and more recent studies was the surgical approach employed, because in initial studies the denervation was performed through a midline access for bilateral carotid dissection, which potentially resulted in considerable upper airway (UAW) trauma that may have had an impact on breathing. In more recent studies, the surgical technique was switched to a potentially less traumatic lateral neck incision. The conclusion of these more recent CBD studies was that the carotid chemoreceptors have an important, but not essential, role in the control of breathing in newborns (19, 20, 22).

Goats and piglets are relatively mature at birth, and this maturity may have been one of the causes of the paucity of CBD effects. We reasoned that in these species other components of the ventilatory control system were sufficiently mature to minimize the consequences of the loss of carotid input. Therefore, our present goal was to investigate the effects of CBD in newborns of a less mature species such as rats. We hypothesized that CBD in rats would result in greater mortality than in piglets and goats. Additionally, we hypothesized that in the CBD survivors, the plasticity/redundancy within the ventilatory control system would compensate for effects of CBD on breathing.

In these studies, we found that the effects of CBD were age dependent; thus we conducted a separate study in additional litters of unoperated newborn rats, investigating the maturation of the control of breathing by testing the ventilatory responses to hypoxia and hypercapnia. We also evaluated the impact of potential stress factors such as the environmental temperature and the transition from a dependent life in the litter nest to an independent life.

Materials and Methods

All experiments and animal procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health), and all the protocols were approved by the Medical College of Wisconsin Animal Care and Use Committee.

Experimental Design

Carotid body denervation studies. Outbred Sprague-Dawley pregnant dams were obtained from Charles River Laboratories (Wilmington, MA). Rat pups were naturally delivered in our animal facility and housed with the rat dam. Weight and rectal temperature (measured by use of a 30-
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gauge thermocouple) were monitored daily. At the 21st day of
life (P21), animals were weaned and housed separately for the
remainder of the study. Newborns of 13 different litters (n = 135)
divided in two experimental groups: carotid body denervated (CBD)
or sham carotid body denervated (sham). Surgeries were performed at different ages: group 2–3 (denervated between 2 and 3 days of life), group 7–8, group 12–15, group 20–21, and group 90. Rats of seven litters (n = 69) were studied acutely for 5 days postsurgery and killed (for histological purposes not reported here). Rats from six litters (n = 66) were studied chronically for 26 days postsurgery and killed.

Our experimental design consisted of 1) testing during eupnea for 10 min daily; 2) testing during hypoxia [inspired O2 fraction (FiO2) 0.12] for 5 min on the second postsurgery day (all rats) and on the 22nd and 23rd postsurgery days (chronic rats); 3) testing during hypercapnia (FiCO2 0.07) for 5 min on the 24th postsurgery day (chronic rats); and 4) testing with localized (venous, carotid, aortic) injections of sodium cyanide (NaCN) the 25th postsurgery day (chronic rats).

Hypoxia-hypercapnia-temperature studies. Additional litters of outbred Sprague-Dawley pregnant dams were obtained from the same vendor and housed as described above. In the hypoxia-hypercapnia-temperature protocol, unoperated newborn rats from three separate litters (n = 26) were studied daily from P0 until P21 during eupnea by using full-body plethysmography. Animals were tested during hypoxia (FiO2: 0.12) or hypercapnia (FiCO2: 0.07) every other day. For the temperature studies, unoperated newborn rat pups were divided in two groups, one exposed to an environmental temperature of ~24°C (room temperature) and the other to ~34°C (average litter nest temperature). These animals were tested daily during eupnea for 10 min from P0 to P15, with measurement of rectal temperature and ventilation.

Experimental Protocols

Surgical protocol. For denervation, animals of groups 2–3 and 7–8 were anesthetized with ice (hypothermia), whereas animals from groups 12–15, 20–21, and 90 were anesthetized with intramuscular injections of ketamine (40 mg/kg), xylazine (2.5 mg/kg), and acepromazine (0.6 mg/kg) (Phoenix Laboratories, St. Joseph, MO). CBD consisted of a lateral incision in the neck bilaterally and dissection under microscope of the carotid bifurcation. After identification, the carotid sinus nerve was sectioned, and the adventitia of the internal carotid artery and/or carotid body was stripped to ensure denervation. Sham animals had similar dissection of the internal carotid artery and/or carotid body was stripped to ensure denervation. Sham animals had similar dissection but no removal of the carotid sinus nerve or carotid adventitia. After recovery, animals were returned to the dam and their behavior was monitored continuously for 24 h.

For catheterization, animals in the 21st postsurgery day were anesthetized with intramuscular injections of the ketamine-xylazine-acepromazine solution, and semirigid polyethylene catheters (PE10, PE 50, and PE 90, Intramedic, Sparks, MD) were inserted into the femoral artery and femoral vein. In selected animals, additional catheters were inserted during the same procedure in the carotid arteries and in the proximal descending aorta for NaCN testing.

Physiological studies. All physiological studies were conducted solely on surviving rats. The animals were studied in an airtight barometric 1-liter (from P0 to P10) or 10-liter (after P10) plethysmograph connected to a transducer signal conditioner (Quintron Instrument, Milwaukee, WI), measuring breathing frequency and tidal volume and allowing the calculation of minute ventilation (Ve). The data were calculated using the formulas of Drorbaugh and Fenn (6). Rectal temperature was measured by using a 30-gauge thermocouple (Omega Engineering, Stamford, CT). Ventilatory tests during hypoxia and hypercapnia were conducted in the same plethysmograph. In each run, the animals were studied for 5 min while breathing room air, and subsequently a mixture of 12% O2 + 88% N2 (hypoxia) or 7% CO2 in room air (hypercapnia) was added to the box and data recorded for 5 min. Temperature studies were conducted in the same plethysmograph that was kept at room temperature (~24°C) or heated to the average litter nest temperature (~34°C) with a heating lamp, before animals were inserted and studied.

Arterial blood sampling was possible through the indwelling femoral catheters. Peripheral chemosensitivity was tested with three to four injections of 6.1 mM NaCN in 0.9% normal saline (0.0166 ml/kg, dose: 0.05 mg/kg) in the femoral vein, carotid arteries, or aorta.

At the end of the studies, animals were killed with an intravenous injection of 2 ml of Euthasol (Delmarva Laboratories).

Data Analysis

Ventilatory data were acquired and analyzed with a CO-DAS/Windaex data acquisition system (DATAQ Instruments, Akron, OH). Arterial blood samples were analyzed for arterial PO2 (PaCO2) with a Chiron model 248 blood gas analyzer. Fischer exact tests, χ2 analysis, and one-way or two-way ANOVA for repeated measures were used for comparison of the variables among the different groups and experimental conditions. ANOVA results were further analyzed with Bonferroni or Tukey's post hoc tests accepting a confidence interval of 95%. All tests were performed using SigmaStat 2.03 software (SPSS, Chicago, IL).

RESULTS

Mortality

There were deaths after CBD in all age groups. Fatalities in these rats happened almost exclusively during the transition from anesthesia to eupneic breathing, when the rats would slowly start waking up but never regain a normal, regular breathing pattern. Instead, there were progressively prolonged apneas until death. The mortality ranged from 25% in groups...
20–21 and 90 and up to 42% in group 7–8 (Fig. 1). There was a significantly (P ≤ 0.05) greater mortality in CBD rats compared with sham in groups 2–3 and 7–8 but not in the older age groups. The deaths in sham rats were solely caused by surgical-anesthetic complications (ruptured arteries and exsanguination, abrupt cessation of breathing). Therefore, if we consider the mortality from respiratory causes only, CBD caused more fatalities in all age groups (P < 0.05, Fisher’s exact test). Additionally, there was no statistically significant difference in CBD deaths among the different age groups (P = 0.906, χ² analysis).

Growth and Development

In the animals from group 7–8 that survived CBD, there were delayed opening of the eyes and development of the fur coat (Fig. 2) and there was reduced weight gain (P < 0.05) (Fig. 3). There were no significant differences in weight gain between CBD and sham animals in group 2–3 (P = 0.855), group 12–15 (P = 0.307), group 20–21 (P = 0.821), or group 90 (P = 0.340) (Fig. 3).

Ventilatory Effects

All V̇E data are normalized for animal weight because of the differences in weight gain described above. There was a transient, statistically significant decrease in V̇E after CBD in rats of groups 7–8 and 12–15, but 3 wk after denervation the V̇E of CBD rats was significantly lower than sham rats (P ≤ 0.05).

Fig. 2. The effects of CBD on growth in rats denervated at postnatal days 7–8 (P7–P8). The two siblings in the picture were denervated at P7 and shown a week later (P14). The sham animal is adequately developed. In contrast, the CBD animal is smaller and has an irregular fur cover, closed eyes, and mild cyanosis.

Fig. 3. Weight gain in unoperated rats (A) and in rats before and after CBD or sham CBD at 2–3 or 7–8 days of age (B and C, respectively). Vertical lines in B and C indicate day of surgery. P values represent statistical comparison of CBD and sham animals. Note that there is little variability in weight gain in intact animals (A). Note also that only in group 7–8 was there a significant effect of CBD on weight gain.

Fig. 4. Pulmonary ventilation (V̇E; in ml·min⁻¹·g⁻¹) while breathing room air of rats before and after CBD or sham CBD at 2–3, 7–8, and 12–15 days of age (A, B, and C, respectively). Dashed lines represent day of surgery. P values refer to comparison between CBD and sham CBD. Note the significant decrease in V̇E in CBD rats in the early postsurgery days in groups 7–8 and 12–15 and the subsequent recovery.
confirmed that the effects of CBD on eupneic breathing were age dependent and transient. There was no significant difference in eupneic PaCO2 between CBD and sham rats in groups 2–3, 7–8, 12–15, and 20–21 3 wk after surgery. Additionally, there was no difference between either CBD or sham and age-matched unoperated animals. Only in the CBD rats from group 90 was there a small but significant hypoventilation compared with sham (P < 0.001) and unoperated rats (P = 0.006).

Hypoxia

There was a statistically significant (P < 0.05) lower V̇E during hypoxia in CBD animals in all age groups on the second postdenervation day (Fig. 7), confirming successful CBD. However, on the 22nd postdenervation day there was no statistically significant difference between the V̇E response during hypoxia in CBD vs. sham or unoperated rats.

Additionally, there was no significant difference in the hyperventilation during hypoxia among CBD, sham, and unoperated rats in any age group (Fig. 8) 3 wk after denervation.
**NaCN Tests**

The injection of NaCN in the femoral vein of animals in all age groups increased $V_\dot{E}$ in CBD, sham, and unoperated rats. Moreover, the responses were not significantly different among the three groups ($P = 0.339$) (Fig. 9A). The injection of NaCN in the carotid arteries of sham and unoperated animals also increased $V_\dot{E}$, whereas in the CBD rats there was no response to carotid NaCN injections, which further confirmed successful CBD (Fig. 9B). Injections of NaCN in an area of the proximal descending aorta, immediately after the bifurcation of the left subclavian artery, increased $V_\dot{E}$ in the CBD but not in the sham or unoperated animals (Fig. 9C).

**Hypercapnia and CO2 Sensitivity**

Unoperated newborn rats at 1–3 days of age had a significant ($P = 0.025$) increase in $V_\dot{E}$ while breathing 7% inspired CO$_2$, but the same rats at P6–7 had no significant increase in ventilation during hypercapnia ($P = 0.130$) (Fig. 10). A gradual return of the response ensued, and after P12–P13 there was again a significant increase in $V_\dot{E}$ in response to CO$_2$.

There was no significant ($P > 0.10$) difference in the ventilatory response to CO$_2$ in CBD rats compared with sham rats. There was a tendency for reduced CO$_2$ sensitivity ($\Delta V_\dot{E}/\Delta P_{aCO_2}$) in CBD rats of group 90 (Fig. 11), although the limited number of successful experiments precluded statistical conclusions.

**Temperature Studies**

The rectal temperature of P2 rats exposed to an environment of ~24°C for 10 min decreased significantly ($P < 0.05$) compared with that of same-age rats at ~34°C (Fig. 12A). This rectal temperature difference was progressively reduced as animals aged, and by P9 there was a smaller difference between the two groups in the end rectal temperature (Fig. 12B).
the initial, particularly at P9 (Fig. 12). Rats at ~24°C increased their V̇E whereas rats at ~34°C decreased V̇E during the 10-min duration of the trial, but there was no significant difference between the two groups at P2 (Fig. 12C). However, there was a significant decrease in V̇E in rats at ~34°C at P9 (Fig. 12D).

DISCUSSION

The major finding of this study is that CBD in rats resulted in significant mortality, but in surviving rats there was enough plasticity and redundancy to allow an adequate recovery from other CBD effects.

Mortality after CBD

The reduced V̇E during hypoxia 2 days after CBD and the subsequent absence of a V̇E increase when NaCN was injected directly into the carotid artery confirm successful CBD in the rats that survived. We have no comparable objective data to verify CBD in those animals that died, because they never regained normal breathing after the denervation of the carotid bodies. We are confident, though, that CBD was the cause of death because, as already described, the nature of death was clearly different than in those that died after sham CBD surgery. In addition, the high rate of successful CBD in survivors suggests that those that died were indeed denervated.

The mortality after CBD in the present paper ranged from 25 to 42% with a higher number of deaths in rats denervated at P7–P8 than in those denervated at the other ages. This mortality after CBD in rats contrasts with previous data from Lowry et al. (19, 20), in which CBD in goats and piglets caused no fatalities. The lack of deaths in goats and piglets was attributed to ample and efficient mechanisms of plasticity and redundancy in peripheral chemosensitivity, which were present and functional at birth (19, 20). We hypothesize that the same mechanisms may not be as efficient in compensating for the loss of carotid chemoreceptors in rats due to the relative immaturity of the rat at birth. If one of the excitatory sources such as the carotid bodies is lost, not enough excitatory afferent input reaches the brain stem respiratory neurons, thus creating a potentially lethal situation.

The number of fatalities in our rat series was smaller than in previous studies on rats, in which CBD caused a high and age-dependent mortality. In a study by Hofer (14), the mortality after CBD in rats ranged from 0 (rats denervated after P20) to 70% (in rats denervated at P1–P3). Likewise, CBD and aortic denervation resulted in a mortality of 0 (P8–P9) to 59% (P1–P3) in a study by Shair and Myers (24). The timing and circumstances of deaths also differ in our study compared with previous data (14, 24). In the latter, most deaths occurred within 48–72 h after the denervation and were associated with apneas and gasps. In our animals, all deaths occurred in the transition from anesthesia to eupneic breathing, with progressively
prolonged apneas until death, and all animals that recovered from anesthesia remained alive.

The lower mortality in our series may be due to the surgical approach used for CBD. Lowry and co-workers (10, 20) observed some fatalities, irregular breathing, apneas, severe hypoventilation, and signs of laryngopharyngeal dysfunction and feeding abnormalities when CBD in piglets was performed through a midline incision previously described. In the subsequent series by Lowry et al., the surgical technique was switched to a lateral neck incision that allowed access to the carotid arteries without requiring extensive dissection, and there were no fatalities or UAW dysfunction. All previous studies on rats also employed the same midline dissection, potentially causing trauma and increasing the morbidity and mortality from CBD, whereas we used the seemingly less traumatic lateral approach. Finally, other factors cited as possible causes of death were “excessive manipulation and instrumentation of the rat pups in the postoperative period, long separation from the rat dam and cannibalism of the rat pups” (24). In our experiments, the manipulation of the animals was minimal and the pups did not stay longer than 15 min away from the litter nest.

Acute and Chronic Effects of CBD in Survivors

In CBD survivors, there were acute and chronic consequences for breathing and for other physiological functions. In past studies, CBD in rats has produced severe irregular breathing with apneas and high-amplitude gasps, UAW occlusion, cyanosis, inability to feed, and weight loss (14, 24). These effects were age dependent, and invariably the younger the animal when CBD was performed, the more severe the effects, particularly during the first week of life. CBD caused few if any effects in newborn rats denervated after the second week of life. Therefore, the early neonatal period and particularly the first week of life were considered a critical period for the loss of the carotid chemoreceptors.

In the present study there were few effects in animals denervated at P2–P3, P20–P21, or P90. We found a significant but transient decrease in VE after CBD in groups 7–8 and 12–15 and a significant hypoventilation during eupnea in the adult rats. Rats denervated at P7–P8 had a multitude of acute effects after CBD besides the ventilation decrease, especially decreased weight gain and delayed development. The failure to thrive was not due to UAW damage, because continuous 24-h monitoring of the animals afterward showed that there were no difficulties in swallowing, but a lethargic behavior that prevented the CBD rats from competing with siblings and nursing properly. This lethargy, which lasted for several days, could be a consequence of hypoxia, because it was accompanied by a high incidence of apneas and moderate cyanosis. Because of the size of animals, there are no Pao2 data to confirm this hypothesis.

This “critical period” at the end of the first week of life may be associated with the profound changes that newborn rats experience during this epoch. Our data on unoperated rats show a significant increase in VE during hypercapnia at P1–P3 and after P12–P13, but there is no significant increase during hypercapnia in rats at P6–P7. The decreased CO2 sensitivity in 7-day-old rats has also been recently observed by Stunden et al. (26). Other data suggest that there may also be a maturation period in central mechanisms. Wang and Richerson (27) have shown an increase in the number of neurons excited and a decrease in those inhibited by CO2 after the 12th day of life in rat medullary slices. Recent data from Liu and Wong-Riley (18) showed a decrease in cytochrome oxidase (CO) activity in several respiratory nuclei in the brain stem of newborn rats, particularly at P3–P4. According to these authors, “if the changes in CO activity reflect synaptic readjustment or reorganization, this may represent a period when the system is less responsive to changing respiratory demands and, therefore, more vulnerable to perturbations and insults” (18). This conclusion further emphasizes the concept of a vulnerable period for the control of breathing in newborns. The recording of afferent activity of the carotid bodies during hypoxia by Kholwadwala and Donnelly (15) suggested that the maturation of chemoreceptor sensitivity occurs between the first and the second week of life in rats. If this age-dependent increase in central and peripheral chemosensitivity correlates with the maturation of the control of breathing, rats would be vulnerable in the transition point, about the end of the first week of life (15, 18, 27).

In addition, the influence of the environment in rats at P7–P9 further emphasizes the vulnerability at this age. When P9 unoperated rats were exposed to an environment of ~34°C (the average litter nest temperature), there was a significant decrease in VE compared with rats kept at room temperature, possibly as a result of a decrease in metabolism attempting thermoregulation. This observation suggests that 34°C may represent a thermal challenge for rats at P7–P10, the age at which they begin developing a fur cover and the litter nest starts to disassemble. Given the inability to adequately compensate for the additional environmental stress, other physiological functions such as the control of breathing can be affected. Consequently, if the animals lose an important source of excitatory input such as the carotid bodies in this sensitive period of changes and maturation, the consequences are far more damaging than in younger or older animals. These findings may be relevant to neonatal breathing disorders such as sudden infant death syndrome (SIDS), which is the predominant cause of death in human newborns between the first week and first year of age (17). Environmental stressors coupled with an immature and poorly adapting control of breathing may be intimately associated with the etiology of SIDS.

Recovery from CBD

Within 3 wk of denervation, surviving rats recovered adequately from most of the effects of CBD in all age
groups. The significantly higher inhibition of $V_{\dot{E}}$ during acute hypoxia seen at 2 days after denervation was not present 22 days postoperatively, when there was no difference in the $V_{\dot{E}}$ response and in the hyperventilation of CBD and sham rats. Moreover, both groups at this age had a response similar to that of age-matched unoperated newborn rats (8, 9, 11). Comparable results were described by Martin-Body et al. (21), in which the respiratory depression during hypoxia 3 days after CBD in adult rats disappeared by the 10th postoperative day and was followed by a return of the ventilatory response by the 17th postoperative day. Nonetheless, at the end of the study some effects of CBD were not fully compensated. $CO_2$ sensitivity remained slightly attenuated, and there was a persistent modest hypoventilation 3 wk after CBD in the adult rats. This slower recovery in group 90 suggests that some plasticity/redundancy is lost as animals mature and/or the compensatory mechanisms take longer to offset the effects of CBD effectively.

Many authors have attempted to establish the site of residual chemosensitivity in rats after CBD, but there are no conclusive data. Likely candidates are other peripheral chemoreceptors such as aortic and subclavian bodies, central chemoreceptors, or a combination of both. Roux et al. (23) investigated the recovery of the hypoxic ventilatory response in rats after CBD and found that there was a profound reorganization of the central $O_2$ chemoreflex pathway, including changes in ventilatory pattern and medullary catecholaminergic activity. The input from different peripheral afferents such as the aortic chemoreceptors could play a significant role in this rearrangement, although the existence and activity of aortic chemoreceptors in rats remain controversial. Brophy et al. (2) recorded increased firing in the aortic nerve during hypercapnic hypoxia and after NaCN injections in carotid-intact rats. This observation contrasts with recent data on recordings of the aortic depressor nerve in anesthetized rats, which have shown no increase in firing rate during hypoxia or hypercapnia in carotid-intact animals and no suppression of the physiological responses to hypoxia after aortic denervation (16). It is possible that the lack of responses was due to the anesthesia, alternative afferent pathways, or insufficient stimulation. Other authors have described chemoreceptors or glomus tissue in the aortic arch, in the aortocapillary membrane, or in aortic branches such as the subclavian arteries or the caudal common carotid arteries (8, 12, 13). However, functional data in rats showing the normal role of these chemoreceptors and particularly after CBD have been sparse.

Data in other mammals suggest a role for the aortic chemoreceptors in the recovery from CBD. The loss of residual responses to hypoxia in CBD cats and ponies after vagal denervation is indirect evidence that aortic chemoreceptors may be the site of recovery (1, 25). In piglets, Lowry and co-workers (10, 20) have shown that there was an increase in $V_{\dot{E}}$ after NaCN injections in specific areas of the descending aorta of CBD piglets but not in sham animals. In the present study, we have also obtained ventilatory responses after NaCN injections in similar areas of the aorta solely in CBD rats, which strongly suggests that the aortic chemoreceptors are indeed involved at least partially in the recovery from CBD effects.

It remains unclear whether the aortic chemoreceptors played a role in the ventilatory responses to hypoxia in the sham and unoperated rats. NaCN elicited no ventilatory responses when injected in the aorta of sham denervated or unoperated rats 25 days postsurgery, suggesting that the aortic bodies were not functional at those ages. However, Lowry et al. (20) have shown that in carotid-intact piglets there were ventilatory responses to NaCN injection in the aortic arch up to the eighth day of life. It is possible that a similar mechanism is present in rats in the early neonatal period, although we do not have data to corroborate this supposition.

In conclusion, CBD in newborn rats caused higher mortality than in other mammals. However, the redundancy and plasticity within the system controlling breathing eventually compensated the acute and chronic effects. The predominant effect at P7–P8 suggests a critical window for the maturation of respiratory control mechanisms in this species. The relative immaturity of newborn rats at birth may be responsible for the differences between this species and other mammals.

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