Effects of carotid and aortic chemoreceptor denervation in newborn piglets

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Serra, A., D. Brozoski, M. Hodges, S. Roethle, R. Franciosi, and H. V. Forster. Effects of carotid and aortic chemoreceptor denervation in newborn piglets. J Appl Physiol 92: 893–900, 2002. First published October 12, 2001; 10.1152/japplphysiol.00819.2001.—The objective of the present study was to test the hypothesis that in neonatal piglets there would be no hypoventilation after sham denervation or aortic denervation (AOD) alone, but there would be transient hypoventilation after carotid body denervation (CBD) and the hypoventilation would be greatest after combined carotid and aortic denervation (CBD+AOD). There was a significant (P < 0.05) hypoventilation in CBD and CBD+AOD piglets denervated at 5, 15, and 25 days of age. The hypoventilation in CBD+AOD piglets denervated at 5 days of age was greater (P < 0.05) than that of all other groups. Conversely, sham-denervated and AOD piglets did not hypoventilate after denervation. Injections of sodium cyanide showed that aortic chemoreceptors were a site of recovery of peripheral chemosensitivity after CBD. This aortic sodium cyanide response was abolished by prior injection of a serotonin 5a receptor blocker. Residual peripheral chemosensitivity after CBD+AOD was localized to the left ventricle. We conclude that 1) aortic chemoreceptors contribute to eupneic breathing in piglets that were carotid denervated at 5 days of age and 2) there are multiple sites of residual peripheral chemosensitivity after CBD.

CAROTID CHEMORECEPTORS have been viewed as essential for the control of breathing in the early postnatal period. This view has been based on studies that found hypoventilation, irregular breathing (including apneas), and significant mortality in carotid body-denervated neonatal rats, lambs, and piglets (2, 5, 6, 14). However, more recent studies using a surgical technique that minimized the trauma to the upper airways (UAW) found that there were no carotid body denervation (CBD)-related fatalities and only a mild, transient, and age-dependent hypoventilation after CBD (17, 21). Additionally, these later studies found ventilatory responses to sodium cyanide (NaCN) injections in the aorta of CBD but not sham CBD piglets, suggesting that aortic chemoreceptors may have been at least partially responsible for the paucity of effects and/or recovery after CBD (17) and that these chemoreceptors might play a significant role in the plasticity within the ventilatory control system after CBD.

Therefore, our present goal was to further investigate the role of aortic chemosensitivity in neonates, assessing the effects of aortic denervation (AOD) alone and combined aortic and carotid body denervation (CBD+AOD) in newborn piglets. We hypothesized that there would be no hypoventilation after sham denervation or AOD alone, but there would be after CBD alone and an even greater hypoventilation after CBD+AOD.

MATERIALS AND METHODS

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

Experimental Design

Carotid body and aortic denervation studies. Outbred Yorkshire pregnant sows naturally delivered in the animal facility, and the piglets were housed with the sow throughout the studies. Newborns of eight different litters (n = 87) were divided in four experimental groups: carotid body denervated (CBD), aortic denervated (AOD), combined carotid and aortic denervated (CBD+AOD), or sham denervated (sham). Surgeries were performed at three different ages: 5 (P5), 15 (P15), or 25 (P25) days of life (group 5, group 15, and group 25, respectively).

All animals were tested with full-body plethysmography from the day of birth until 21 days postsurgery. Our experimental design consisted of 1) daily assessment of weight, rectal temperature, and breathing during eupnea; 2) assessment of breathing during hypoxia (inspired O2 fraction 0.12) on postsurgery days 2 and 15; 3) assessment of breathing during three levels of hypercapnia (inspired CO2 fraction 0.03, 0.05, and 0.07) on postsurgery days 16-18; 4) assessment of peripheral chemosensitivity by injections of NaCN into a jugular vein, both carotid arteries, proximal aorta, or the left ventricle on postsurgery days 20 and 21, before and after the injection of serotonin receptor blockers; and 5) assessment of
baroreceptor responsiveness by injection of phenylephrine into a jugular vein.

After the NaCN tests, the animals were euthanized.

Experimental Protocols

Surgical protocol. Femoral catheterization. The animals were preanesthetized with injections of telnetamine and zolazepam (1–2 mg/kg im). After induction, animals were connected to a breathing mask and spontaneously ventilated with continuous 2.5% isoflurane in 2 liters of 100% O2 inhalatory anesthesia throughout the procedure. Mechanical ventilation was used whenever necessary (Ohio Anesthesia, Madison, WI). Semirigid polyethylene catheters (PE50, Intramedic, Sparks, MD) were inserted into the femoral artery.

Venous drainage was performed whenever necessary (Ohio Anesthesia, Madison, WI). Semirigid polyethylene catheters (PE50, Intramedic, Sparks, MD) were inserted into the jugular vein.

Deneration. Animals of all groups were anesthetized with the same protocol described in the previous paragraph. The aortic denervation technique consisted of a thoracotomy in the left side at the fifth intercostal space, resection of all nerves originating from the aortic wall, and removal of the adventitia. Residual pneumothorax was relieved by closed-chest tube drainage. The carotid denervation technique consisted of a bilateral retromandibular incision in the neck, dissection of the carotid bifurcation, and section of the carotid sinus nerve, followed by stripping of the carotid adventitia to ensure denervation. Sham animals were subjected to the left thoracotomy and carotid dissection without denervation. After recovery, animals were returned to the sow and allowed to nurse ad libitum. During the first 48 h of the recovery period, animals received cefalexin (50 mg/kg per oral daily) for antibiotic prophylaxis and buprenorphine (0.01–0.02 mg/kg bid) for analgesia when needed.

NaCN catheterization. At the end of the physiological experiments (20th postsurgery day), animals were anesthetized, and semirigid PE50 or PE90 catheters were inserted under fluoroscopic guidance (Phillips BV-22HQ C-arm fluoroscope) into the common carotid arteries bilaterally, into the right external jugular vein, and into the proximal descending aorta. Some animals from the CBD + AOD group had the catheters inserted inadvertently into the left ventricle. Contrast arteriograms confirmed the final position of the catheters.

Physiological studies. Surviving animals from all groups were studied in an airtight barometric 100-liter plethysmograph connected to a Transducer Signal conditioner (Quintron Instrument, Milwaukee, WI), measuring breathing frequency and tidal volume to allow the calculation of minute ventilation (Ve). Data were calculated by use of the formulas of Drorbaugh and Fenn (7). Mean arterial pressure (MAP) was measured by a rectal thermometer (Omega Engineering, Stamford, CT). Ventilatory tests during eupnea, hypoxia, and hypercapnia were conducted in the plethysmograph. The animals were studied for 10 min while breathing room air, and subsequently a mixture of 12% O2 + 88% N2 (hypoxia) or 3, 5, and 7% CO2 in room air (hypercapnia) were added to the box, and data were recorded for 10 min. Arterial blood samples were drawn in the 8th minute of each study. Studies were performed only during the awake state, confirmed by visual observation of the animals. When closure of the eyes was observed, the piglets were aroused by auditory stimuli.

Peripheral chemosensitivity was tested with 3–4 injections of 6.1 mM NaCN (0.0166 ml/kg, dose 0.05 mg/kg diluted in 0.9% normal saline) into a jugular vein, both carotid arteries, the aorta, and the left ventricle. Peripheral baroreflex responses were tested with intravenous injections of the α-agonist phenylephrine (100 µg/kg). The response was compared among animals by using the interval until full MAP recovery and the maximal R-R interval. Both peripheral chemosensitivity and barosensitivity were tested before and after the intravenous injection of the serotonin receptor (5-HT3R) blockers metoclopramide (MCP; 5-HT3R blocker, 0.1 mg/kg) and methiothepin (MTN; 5-HT3R, 5aR, 6R, and 7R blocker, 0.1 mg/kg) (Sigma Chemical, St. Louis, MO).
At the end of the studies, animals were euthanized with an injection of Euthasol (3 ml iv) (Delmarva Laboratories), and their aortas were removed, washed in 0.1 M PBS, immediately frozen in liquid nitrogen, and stored at −80°C for immunohistochemistry and molecular studies not reported here.

Data analysis. Ventilatory data were acquired and analyzed with a CODAS/Windaqex data acquisition system (DATAQ Instruments, Akron, OH). Arterial blood samples were analyzed for arterial partial pressure of CO2 (PaCO2) with a Chiron model 248 blood-gas analyzer. Multiple-regression analysis, one-way analysis of variance (ANOVA), one-way ANOVA on ranks, 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 Dunn’s post hoc tests, accepting a confidence interval of 95%. All tests were performed with use of SigmaStat 2.3 software (SPSS, Chicago, IL).

RESULTS

Mortality

There were deaths in CBD+AOD piglets in two of the age groups (5 and 15) but none in group 25. The highest mortality was in group 15 (33%). No CBD, AOD, or sham piglet died in any age group (Fig. 1). These deaths in CBD+AOD piglets occurred in the transition from anesthesia to normal eupneic breathing, when virtually all CBD+AOD piglets had cardio-respiratory arrests. Resuscitation efforts were able to maintain the piglets alive until normal eupneic breathing was resumed, but in the four fatalities terminal apnea occurred several hours subsequent to the end of anesthesia, after the animals had been weaned from the ventilator.

Growth

There was no statistically significant difference in growth after sham denervation, CBD, AOD, and CBD+AOD in any age group (Fig. 2). Additionally, there were no apparent difficulties in feeding or swallowing.

Ventilatory Effects

Eupnea. While breathing room air (eupnea), CBD and CBD+AOD piglets of all age groups hypoventilated (Fig. 3), and the hypoventilation was greater in the CBD+AOD compared with CBD piglets (P < 0.001) in the animals denervated at 5 days of age (Fig. 3A). The hypoventilation was transient, and 2 wk after surgery there were no further statistically significant differences from sham and AOD piglets. No breathing irregularities and apneas were observed in surviving animals of all groups.

Hypoxia. Compared with other piglets, CBD+AOD piglets had a significantly smaller (P < 0.05) PaCO2 change from eupnea to hypoxia (hyperventilation) in the second day postsurgery (post day 2), in all age groups (Fig. 4). CBD animals denervated at P25 also had a significantly smaller hyperventilation compared
with sham or AOD piglets (Fig. 4A). Two weeks thereafter, on the 15th postsurgery day (post day 15), there was no difference in the hyperventilation of CBD+AOD piglets denervated at P5 or P15, but there was still a significantly smaller hyperventilation in those denervated at P25, for both CBD+AOD and CBD piglets (Fig. 4B).

**NaCN Tests**

The injection of NaCN in the jugular vein of animals in all age groups increased Vₑ in sham, CBD, CBD+AOD, and AOD piglets, and there was no statistically significant difference in the responses among the groups (P = 0.114) (Fig. 5A). NaCN injections in the carotid arteries of sham and AOD animals also increased Vₑ, whereas in CBD and CBD+AOD piglets there was no response to carotid NaCN injections, which further confirmed successful denervation of the carotid chemoreceptors. Injections of NaCN in an area of the proximal descending aorta, immediately after the bifurcation of the left subclavian artery, significantly increased Vₑ in the CBD but not in the other groups (P < 0.001), confirming successful aortic denervation in the CBD+AOD piglets. In four of four CBD+AOD animals tested, injections of NaCN into the left ventricle/coronary arteries increased Vₑ, suggesting another site of peripheral chemoreception (Fig. 5B). In these same animals, the withdrawal of the catheter into the ascending aorta and further injection of NaCN yielded no Vₑ responses, confirming that the responses were indeed originating in the heart or coronary arteries (Fig. 5C).

The aortic ventilatory responses to NaCN were dependent on 5-HT₃R (Fig. 6). The injection of the 5-HT₃R-blocker MCP did not significantly alter the Vₑ response to NaCN in any group. The injection of the 5-HT₁₇, 5₅₂R, 6R, and 7R blockers MTN abolished the response to NaCN in the aorta of CBD piglets (P < 0.05). Additionally, AOD+CD piglets tended to have a decrease in the venous response after MTN. Continuous ventilatory monitoring of the animals for 30 min showed no changes in Vₑ after the administration of the drugs and before the injection of NaCN (data not shown). MCP and MTN were randomly injected, and the order of these injections did not alter the outcome.

**CO₂ Sensitivity**

There was no statistically significant difference in CO₂ sensitivity (∆Vₑ/ΔPaCO₂) between groups 5, 15, and 25 wk after denervation (P = 0.167, 0.538, and 0.571, respectively) (Fig. 7).

**Blood Pressure and Baroreflexes**

There were no statistically significant changes in MAP before and after surgery in groups 5 and 15 (P = 0.146 and 0.430, respectively). CBD animals from group 25 had a persistent, significantly higher MAP by 10.22 ± 0.33.6 on August 29, 2017 http://jap.physiology.org/ Downloaded from

![Fig. 5. Ventilatory response to jugular venous, carotid, aortic, and cardiac sodium cyanide (NaCN) injections in CBD, AOD, CBD+AOD and sham denervated piglets (A). Data were obtained on average 21 days postsurgery. NaCN ratio is calculated by dividing the minute ventilation (Vₑ) after the injection of NaCN by the Vₑ immediately before the injection. A ratio of 1.0 denotes no ventilatory response. There was no significant difference in the ventilatory response of CBD, AOD, CBD+/H11001 and AOD animals. There were responses to aortic NaCN injections only in the CBD piglets. In four CBD+AOD animals. There were responses to aortic NaCN injections only in the CBD piglets. In four CBD+AOD animals, there were Vₑ responses after NaCN injections in the left ventricle. B and C: plethysmograph recordings of breathing and of arterial blood pressure before, during, and after injection (as marked) of NaCN into the left ventricle (B) and aorta (C). Blood pressure recording confirms the site at which the catheter was located. Note the increase in breathing after the injection of NaCN into the left ventricle (B) and the absence of a response after injection into the aorta. This absence of a response to the aortic injection confirms successful carotid and aortic denervation and the cardiac origin of the response in B.

![Fig. 6. Ventilatory response to NaCN injections in CBD, AOD, CBD+AOD, and sham-denervated piglets before (control) and after the intravenous administration of the serotonin receptor blockers metoclopramide (MCP) and methiothepin (MTN). Injections of NaCN were made in the site of primary peripheral chemosensitivity (carotid arteries in sham and AOD piglets, aorta in CBD piglets, and jugular vein in CBD+AOD piglets). A ratio of 1.0 denotes no ventilatory response. Note that there was no significant difference in the ventilatory response of CBD, AOD, CBD+AOD, and sham piglets to injections of NaCN after MCP compared with control. However, MTN abolished the response to NaCN in the aorta of CBD piglets (P < 0.05). Additionally, in AOD+CD piglets there was a tendency of a decrease in the venous response after MTN.

J Appl Physiol • VOL 92 • MARCH 2002 • www.jap.org
compared with sham animals ($P = 0.030$) (Fig. 8).
There were no statistically significant changes in the time for recovery of MAP (Fig. 9A) or the R-R interval (Fig. 9B) after venous injections of the α-agonist phenylephrine, suggesting that baroreflexes were normal 2 wk after carotid and/or aortic denervation.

**DISCUSSION**

The major findings of the present study were that aortic chemoreceptors contributed minimally to eucapnic breathing in piglets at all ages and only partially after CBD at <5 days of age. Aortic chemosensitivity was developed after CBD in piglets of all ages, which may have been dependent on serotonergic mechanisms. Additionally, residual peripheral chemosensitivity was found after combined carotid and aortic denervation.

**Hypoventilation After CBD and CBD+AOI**

The increase in $\text{Pa}_\text{CO}_2$ after CBD in all age groups confirms that the carotid chemoreceptors have an important role in the control of breathing in the early neonatal period. In a previous work by Lowry et al. (17), there was a small but insignificant hypoventilation after CBD in 5-day-old piglets and mild but significant hypoventilation in those denervated at 15 and 25 days of life. Lowry et al. also found that carotid intact piglets had a ventilatory response to NaCN injection in the aortic arch up to the 8th day of life. They have therefore concluded that aortic chemoreceptors were functional for a few days after birth and that these aortic chemoreceptors minimized the effects of CBD in younger piglets. The present observation of greater hypoventilation in CBD+AOI compared with
CBD piglets denervated at 5 days of life suggests that indeed aortic chemoreceptors may contribute to eupneic breathing after birth. In older piglets, there were no differences in $P_aCO_2$ between CBD and CBD + AOD piglets; thus, in these piglets, aortic chemoreceptors probably do not contribute to eupneic breathing. The lack of effects on breathing after aortic denervation alone is consistent with previous findings and with the concept that these chemoreceptors normally contribute minimally to the control of breathing. Furthermore, the small increase in absolute $P_aCO_2$ (albeit statistically significant) after CBD and CBD + AOD indicates that the ventilatory control system is designed to minimize changes in breathing after loss of these chemoreceptors.

Age-dependent effects of CBD were also recently observed in newborn rats, where animals denervated before P10 had increased mortality, severe apneas, and decreased $V_E$ compared with those denervated after P10 (24). The severity of these effects at the earlier age was attributed to the relative immaturity of animals at birth. Because piglets are more mature at birth than rats, the effects of CBD were less severe and there were age-related differences only when an additional component of the ventilatory control system was removed (i.e., aortic chemoreceptors). Nonetheless, CBD and CBD + AOD piglets recovered within 3 wk of denervation in all age groups, as indicated by the absence of hypoventilation during eupnea and similar $CO_2$ and hypoxia sensitivity in CBD and CBD + AOD piglets, compared with sham and AOD animals.

In contrast to past data, in which CBD survivors had severe breathing abnormalities (apneas) and laryngopharyngeal dysfunction (5, 6, 12), surviving animals in our series did not show any irregular breathing or signs of UAW dysfunction. A possible explanation for this difference is the surgical approach presently employed for carotid denervation, which minimized the damage to the UAW. This approach was also recently employed in rats (24), in which again the effects of CBD were less severe compared with previous data (14).

**Mortality**

The mortality after CBD + AOD in piglets further suggests that there may be a role for aortic chemoreceptors in eupneic breathing only at the earlier ages. Lowry and co-workers (17, 21) found no deaths after CBD in goats and piglets, and there were no fatalities after CBD at all ages in the present series. However, there were four fatalities after CBD + AOD, and these deaths could not be attributed to surgical complications. The terminal apneas observed in these piglets were very similar to those observed after CBD in rats (24), in which all deaths also occurred in the transition from anesthesia to eupneic breathing. Accordingly, it appears that, during a period when overall ventilatory drive is reduced, as it would be during the transition from anesthesia to wakefulness, breathing is highly dependent on chemoreceptor excitatory inputs to the respiratory rhythm generator. It also appears that piglets can withstand loss of carotid excitatory inputs but not loss of both carotid and aortic inputs. On the other hand, rats do not tolerate well even loss of carotid inputs, conceivably because other inputs are less well developed in this more immature species at birth.

The majority of deaths after CBD + AOD occurred in the group denervated at 15 days of life. A similar “critical period” has been observed in rats at the end of the first week of life. In rats, this critical period is associated with decreased $CO_2$ sensitivity (26, 27) and a decrease in cytochrome oxidase activity (which correlates to neuronal activity) in several respiratory nuclei (16). Certainly, there are other possible factors related to maturation of ventilatory control mechanisms, which potentially contribute to the critical period. The present findings may relate to neonatal breathing disorders such as sudden infant death syndrome (SIDS). The present triple-risk model for the etiology of SIDS hypothesizes a susceptible infant exposed to a harmful environment (such as hypoxia, hypercapnia, or recovery from anesthesia) during a critical period when the infant is not able to develop an adequate respiratory response, thus leading to terminal apnea. Similarly, the simultaneous denervation of aortic and carotid chemoreceptors in 15-day-old piglets may have created a scenario of vulnerability in the control of breathing, in which there were insufficient excitatory stimuli and plasticity in the system to overcome the harmful environment (anesthesia), resulting in death.

**Site, Extent, and Mechanism of Plasticity in Arterial Chemoreception**

The hyperventilation during hypoxia was significantly less in CBD and CBD + AOD piglets 2 days after denervation but was comparable 15 days after surgery among CBD, CBD + AOD, sham, and AOD piglets denervated at P5 and P15. Similarly, Martin-Body et al. (18) found a respiratory depression during hypoxia 3 days after CBD in rats but not at the 10th day post-denervation, and by the 17th day the ventilatory response to hypoxia had returned. Nonetheless, at the end of the study some effects of CBD were not fully compensated, because CBD and CBD + AOD piglets denervated at P25 still had a significantly lesser hyperventilation during hypoxia. The delayed recovery in piglets denervated at P25 suggests that the plasticity/redundancy of ventilatory control systems is reduced as animals mature and/or the compensatory mechanisms take longer to effectively offset the effects of denervation. Adult rats showed a similar delayed recovery of hyperventilation during hypoxia after CBD (24).

Past attempts to establish residual chemosensitive sites after CBD in rats showed that other peripheral chemoreceptors such as aortic and subclavian bodies, central chemoreceptors, or a combination of both may be involved. Roux et al. (23) suggested that aortic chemoreceptors might have a role in the reorganization of central $O_2$ chemoreflex pathway after CBD, and
Brophy et al. (3) showed increased firing in the aortic nerve during hypercapnic hypoxia and after NaCN injections in carotid intact rats. Functional chemoreceptors or glomus tissue were also found in the aortic arch, in the aortico-pulmonary tissue, or in aortic branches such as the subclavian arteries or the proximal common carotid arteries of rats and dogs (4, 8, 11, 13, 15).

Previous data in other mammals already suggested that aortic chemoreceptors were important in the recovery from CBD, such as the loss of residual responses to hypoxia in CBD cats and ponies after vagal denervation (1, 25) and the Ve response to hypoxia in cats 5 yr after CBD (9). In piglets, Lowry and co-workers (10, 17) showed an increase in Ve after NaCN injections in specific areas of the descending aorta of CBD piglets but not in sham animals. In CBD rats, there were also positive Ve responses in the aorta after injections of NaCN (24). In the present study, there were ventilatory responses after NaCN injections in similar areas of the aorta only in CBD piglets, confirming that aortic chemoreceptors were functional in these animals. Of particular interest were the findings of Ve responses after NaCN injections in the hearts of CBD+AOD piglets, which showed that peripheral chemosensitivity includes sites other than the carotid arteries and the aorta. Noteworthy is a report of functional chemoreceptor fibers in the right atrium and in the root of the aorta, adjacent to the branching of the coronary arteries (20).

Additionally, if baroreceptors were concomitantly denervated with chemoreceptors, there was enough plasticity and/or redundancy in the blood pressure control mechanisms to overcome any consequences of the denervation, because there were no striking effects on MAP and baroreflexes were preserved.

The response to NaCN in the aortas of CBD piglets may depend on functional 5-HT₃R, as evidenced by the complete absence of aortic response after animals were given intravenous injections of the 5-HT blocker MTN. Preliminary data from our laboratory using immunohistochemistry and other molecular techniques showed that the receptors predominantly expressed in the proximal descending aorta are the 5-HT₃R and the 5-HT₅aR. Wang et al. (28) found that 5HT₅aR are expressed in the glomus cells of the rat carotid bodies and petrosal ganglion, suggesting that these receptors may be involved in the chemosensitivity of the carotid bodies. Others have also suggested that 5-HT may be important for the function of the carotid bodies (19, 29). Because MCP, a specific 5-HT₃R blocker, did not affect the Ve response to NaCN, it was assumed that the 5-HT₅aR, which have a high and specific binding affinity for MTN (22), were involved in aortic chemosensitivity. MTN does cross the blood-brain barrier, and receptors with a high affinity for MTN are found in the brain; thus the effects of MTN on the aortic NaCN response could have been in the central nervous system. However, the lack of inhibition of carotid Ve responses to NaCN in sham and AOD piglets speaks against a central effect of the blocker. Additionally, the lack of Ve changes in the 30 min after the injection of the blockers and before NaCN testing also suggests that the effect was not central. No changes in baroreflexes after injections of the 5-HT₃R blockers were observed (data not shown), suggesting that the effect of MTN was specific for the aortic chemosensitivity.

In conclusion, we found that there was no hyperventilation in piglets after aortic denervation alone, but there was a transient hyperventilation after CBD and an age-dependent, greater hyperventilation after CBD+AOD. CBD+AOD also caused increased mortality compared with CBD alone. However, the redundancy and plasticity within the system controlling breathing allowed these piglets to recover from the effects of denervation. The plasticity in peripheral chemosensitivity extended beyond carotid and aortic chemoreceptors, possibly including cardiac chemoreceptors. Finally, the chemosensitivity in the aorta after CBD may be dependent on serotoninergic pathways, more specifically on 5-HT₅aR.

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