Mechano- and chemoreceptor modulation of renal sympathetic nerve activity at birth in fetal sheep

JEFFREY L. SEGAR, OLIVA J. SMITH, AND AARON T. HOLLEY
Department of Pediatrics and Cardiovascular Center, University of Iowa, Iowa City, Iowa 52242

Segar, J effrey L., Oliva J. Smith, and Aaron T. Holley. Mechano- and chemoreceptor modulation of renal sympathetic nerve activity at birth in fetal sheep. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1295-R1301, 1999.—Physiological responses at birth include increases in heart rate (HR), blood pressure, sympathetic nerve activity, and circulating vasoactive peptides. The factors mediating these responses are not known. To test the hypothesis that afferent input from peripheral mechanoreceptors (arterial and cardiopulmonary baroreceptors) and chemoreceptors contribute to the sympathoexcitatory and hormonal responses at birth, we studied the effects of sinoaortic denervation (SAD) and SAD with vagotomy (Vx) on changes in HR, mean arterial blood pressure (MABP), renal sympathetic nerve activity (RSNA), and catecholamine, arginine vasopressin (AVP), and ANG II levels at birth in term sheep. One hour after delivery by cesarean section, RSNA increased by 168 ± 49 and 192 ± 32% (relative to fetal values) in SAD and SAD-Vx animals, respectively. Significant increases in HR (18 ± 5 and 20 ± 6%) and MABP (24 ± 4 and 20 ± 5%) were also observed 1 h after delivery in SAD and SAD-Vx lambs, respectively. These responses are similar to those seen in intact sheep delivered at the same gestational age. AVP levels markedly increased after birth (19.8 ± 6.7 to 136.1 ± 75.9 pg/ml) in SAD-Vx lambs, whereas SAD animals displayed no change in AVP concentrations. Plasma ANG II also did not change after birth in either group, although levels were consistently higher (P < 0.01) in SAD compared with SAD-Vx animals. In the presence of SAD, Vx resulted in significantly greater plasma levels of norepinephrine, although levels did not change after birth in either group. The epinephrine responses at birth were similar in both groups of animals. The present data suggest that afferent input from peripheral chemoreceptors and mechanoreceptors contributes little to the hemodynamic and sympathetic responses after delivery by cesarean section. On the other hand, these peripheral mechanisms appear to be involved in modulating endocrine responses at birth.

baroreceptor; blood pressure; cardiopulmonary receptor; sinoaortic denervation; vagotomy

In adults, sympathetic outflow to the heart and blood vessels is continuously modulated by an array of peripheral sensors, including arterial baroreceptors and chemoreceptors, as well as mechanoreceptors located in the heart and lungs (34). The afferent fibers from these receptors terminate primarily in the nucleus of the solitary tract, from which central neurons project to nuclei within the medulla and to higher brain centers, including several nuclei within the hypothalamus (17).

By being inserted between afferent and efferent pathways in a reflex arc, these higher centers in the brain, which also serve to integrate a variety of visceral and behavioral sensations, allow for a wide range of modulation of specific autonomic, cardiovascular, and motor responses (5).

Several of these pathways are likely involved in regulating the physiological adaptations at birth required for successful transition, including an increase in heart rate (HR), blood pressure, and peripheral vascular resistance, and a redistribution of cardiac output. Factors mediating these responses are poorly understood but include local mechanisms and circulating peptides. After delivery, there are marked increases in circulating catecholamine levels (13) and sympathoexcitatory activity (31). Previous studies by our group suggest that a number of events associated with birth, including rhythmic lung expansion, increased arterial oxygenation, and separation from the placenta, contribute little to the increase in sympathetic activity at birth (19). Studies in near-term sheep with in utero cooling demonstrated that cutaneous cooling, such as that which occurs with delivery, evokes rapid and sustained increases in HR, blood pressure, and renal sympathetic nerve activity (RSNA) similar to those seen at birth (19, 31). These findings would suggest that the autonomic responses at birth are at least in part mediated by direct stimulation of cutaneous thermoreceptors. However, in utero cutaneous cooling also elicits a sympathoexcitatory response in premature fetal sheep, at a stage of development where delivery by cesarean section is not accompanied by an increase in sympathetic nerve activity (30), implying that other factors may be involved in mediating autonomic responses at birth. It has also been suggested that hypoxemia, respiratory or metabolic acidemia, or changes in central blood flow patterns are responsible for the endocrine responses and sympathoadrenal stimulation at birth (2, 14).

However, the contribution of peripheral chemoreceptors and mechanoreceptors to autonomic adjustments at birth is not known. The present studies were therefore designed to test the hypothesis that afferent input from peripheral chemoreceptors and mechanoreceptors contributes to the sympathoexcitatory and hormonal responses at birth in near-term fetal sheep. More specifically, we examined the effects of sinoaortic denervation (SAD) with and without vagotomy (Vx) on birth-related changes in systemic hemodynamics, RSNA, circulating arginine vasopressin (AVP), ANG II, and catecholamine levels. We compared our results with those previously published in intact fetal and newborn sheep. In addition, we sought to determine the effect of acute SAD-Vx on fetal HR, blood pressure, and RSNA.
METHODS

Studies were performed in conscious, chronically instrumented fetal sheep at 135–140 days gestational age (term 145 days). Pregnant ewes of Dorset and Suffolk mixed breeding were obtained from a local source; gestational ages were based on the induced ovulation technique as previously described (12). All surgical and experimental procedures were performed within the regulation of the Animal Welfare Act and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. We strictly adhered to the Guiding Principles in the Care and Use of Animals, approved by the Council of the American Physiological Society and governed by the Animal Care and Use Committee of the University of Iowa. At least 24 h were allowed for recovery from surgery before experiments were performed.

Surgical preparations. After induction with 12 mg/kg of thiopental sodium (Abbott Laboratories, North Chicago, IL), anesthesia was maintained using a mixture of halothane (1%), oxygen (33%), and nitrous oxide (66%). After a maternal abdominal flank incision was performed, the uterus was partially externalized and opened over the fetal hindlimbs. Polyethylene catheters were placed into the fetal femoral arteries and veins bilaterally. A catheter for recording amniotic pressure was also secured to the fetal skin. The left kidney, renal artery, and renal nerves were exposed through a flank incision, and a plastic-coated copper wire, used as a ground wire, was secured in the paravertebral muscle. After a branch of the left renal nerve bundle was isolated, platinum electrodes were secured on the nerve for recording of RSNA as described previously (33). Function of the renal nerve was tested by audible monitoring of pulse-synchronous bursts of neural activity and by examining oscilloscope tracings during bolus phenylephrine infusion. When function was demonstrated, electrodes were secured using a silicon gel (Sil-Gel 604A and 604B; Wacker-Chemie, Munich, Germany), and the flank incision was closed in separate layers. After closure of the uterine incision, a second uterine incision was made near the fetal head. A midline neck incision was made, and SAD was accomplished as previously described (11, 20), including 1 bilateral stripping of the nervous and connective tissue rostral and caudal to the origin of the occipital and lingual arteries, respectively; 2 applying 10% phenol to the bifurcation of the carotid arteries; and 3) sectioning bilaterally the aortic depressor and superior laryngeal nerves at their junction with the nodose ganglion. In a subgroup of animals, bilateral midcervical vagotomy was also performed. completeness of SAD was confirmed at the time of surgery and before each experiment by observing the absence of changes in RSNA when arterial pressure was increased by a bolus infusion of phenylephrine (2 µg/kg). In preliminary studies, we also confirmed that this technique of SAD abolished HR and sympathetic responses to injection of NaCN (50–200 µg).

After closure of incisions, catheters and wires were exteriorized through subcutaneous tunnels and placed in cloth pouches on the ewe’s flank. Ampicillin sodium (Wyeth Laboratories) was administered to the ewe intramuscularly before surgery (2 g) and infused into the amniotic cavity after surgery (2 g). After surgery, pregnant ewes were returned to individual pens and allowed free access to food and water.

Physiological studies. Before the start of the experiments, the ewe was transferred to the laboratory in a small cart that was placed in a Faraday cage. The pregnant ewe was then sedated with diazepam (0.3 mg/kg), given an intravenous bolus infusion of vecuronium bromide (0.1 mg/kg), intubated, and ventilated to maintain venous blood gas values similar to those obtained during spontaneous respiration. Sedation with diazepam and paralysis has previously been shown to have no effect on HR, arterial pressure, or plasma catecholamine concentrations in lambs (32). Diazepam (0.1 mg/kg estimated wt) and vecuronium (0.1 mg/kg estimated wt) were also administered to the fetus. Muscle paralysis was necessary to eliminate movements that interfere with nerve recording. Additional doses of vecuronium (0.1 mg/kg) were administered when movement was detected. During the experiments a constant infusion of a solution of 5% dextrose and 0.2% sodium chloride was administered to the ewe at a rate of 125 ml/h and to the fetus at 100 ml·kg⁻¹·day⁻¹. After intubation, a 1-h stabilization period was allowed before the start of the experiment.

During each experiment, fetal MABP and amniotic pressure were recorded continuously using Statham P23Db pressure transducers (Spectramed, Critical Care Division, Oxford, CA) and a Grass 7–24P chart recorder (Grass Instruments, Quincy, MA). Fetal MABP was corrected relative to concomitant amniotic pressure. HR was monitored with a cardiotachometer triggered from the arterial pressure pulse waves. The renal nerve electrodes and ground wire were attached to a high-impedance probe (HP15; Grass Instruments). The neural signal was amplified (×20,000) and filtered (low-frequency cutoff 100 Hz, high-frequency cutoff 3 kHz) using a Grass band-pass amplifier (P511). The output of the amplifier was visually displayed on an oscilloscope (S11A, Tektronix, Beaverton, OR) routed to a Grass AM8 audio monitor. The neural signal was integrated over 1 s using a Grass voltage integrator. The integrated voltage and neurogram signals were displayed on the recorder and simultaneously recorded online to a personal computer using Labtech Notebook (version 7.2; Laboratory Technologies, Wilmington, MA).

Experimental protocol. The first series of studies was designed to determine the effects of SAD (n = 6) and SAD-Vx (n = 7) on the hemodynamic, sympathetic, and hormonal responses at birth in near-term fetal sheep. After a 1-h equilibration period, fetal values for HR, MABP, and RSNA were obtained by recording and averaging those values over a 30-min period. Arterial blood for determination of blood gases, pH, and plasma norepinephrine, epinephrine, AVP, and ANG II levels was then obtained. During the experiments the volume of blood sampled from the fetus was replaced immediately with an equivalent volume of maternal blood to avoid any hemodynamic effects of sampling. The amount of background noise in the nerve signal was then assessed by inhibiting nerve activity using an intravenous infusion of the ganglionic blocking agent tetraethylammonium bromide (10 mg/kg).

After the fetal studies were completed, the ewes were returned to the surgical area and mechanical ventilation was continued. Low spinal anesthesia (1% lidocaine, 10 ml) was administered to the ewe, after which the lamb was delivered by cesarean section. Tracheal intubation of the lamb was performed before cutting the umbilical cord. Lambs were placed on an infant warmer bed, dried, manually ventilated, and returned to the laboratory. Lambs were then transferred to a sling-frame assembly to maintain them in an upright position and mechanically ventilated with a time-cycled, pressure-limited infant ventilator. Initial ventilator settings included fractional inspired O₂ concentration of 1.0, a respiratory rate of 40 breaths/min, an inspiratory time of 0.5 s, and a peak expiratory pressure of 4 cmH₂O, and peak inspiratory pressure of 26 cmH₂O. Arterial blood gases were obtained no less often than every 20 min, and ventilator settings were adjusted to maintain arterial Pₐ O₂ at 75–150 Torr and Pₐ CO₂ at 35–45 Torr. Newborn core temperature was maintained between 38.5 and 39.0°C by use of a heating pad.
and warming lamp. Diazepam and vecuronium were administered to the lambs in doses previously noted. At 30, 60, and 120 min after delivery, HR, MABP, and RSNA were again recorded for 10 min. Blood for determination of plasma norepinephrine, epinephrine, AVP, and ANG II were obtained immediately after these recording periods, and an equivalent volume of maternal blood was returned. At the completion of the study, background noise in the nerve signal was again assessed as described above.

Because SAD and/or Vx could alter baseline fetal RSNA, which would then influence the calculated changes in RSNA after birth, we performed a separate series of studies (n = 3) to determine the acute effects of SAD-Vx on RSNA. Fetuses were surgically prepared as described above with the following exceptions. After completing the first stage of the surgery (catheters and electrodes), low spinal anesthesia (1% lidocaine, 10 ml) was administered to the ewe, and inhalation anesthetics were stopped. After 1 h, fetal HR, MABP, and RSNA were continuously monitored for 15 min. Inhalation anesthetics were then readministered, fetal SAD-Vx was performed, and the surgical procedures were completed. At the end of surgery, spinal anesthesia was again administered, inhalation anesthetics were discontinued, and fetal HR, MABP, and RSNA were recorded after allowing a 1-h recovery period.

Analytic procedures. Arterial blood for pH, PCO₂, and PO₂ was collected anaerobically in heparinized syringes, and measurements were immediately determined using a BGM 1302 pH/blood gas analyzer (Instrumentation Laboratory, Lexington, MA). All blood gas values were corrected for fetal temperature. Measurements of AVP, ANG II, and catecholamines were performed by RIA as previously established in our laboratory (Univ. of Iowa Cardiovascular Center RIA Core Facility, Donna B. Farley, Director).

Computation and data analysis. Integrated RSNA was corrected by subtracting the background noise level obtained in the presence of ganglionic blockade. RSNA was normalized for each animal and expressed as the percentage of activity observed in the fetus. Statistical analyses of differences in HR, MABP, RSNA, plasma hormone concentrations, and arterial blood gas values during the described study periods were performed with a two-way repeated-measures ANOVA, factoring for treatment group and time. If the F statistic was found to be significant (P < 0.05), comparison among means was performed by the Bonferroni t-test for multiple comparisons (8). For data exhibiting a lack of homogeneity of variances among groups (test of normality), nonparametric analysis was applied using the Kruskal-Wallis test. Differences were considered significant when P < 0.05. All results are expressed as means ± SE.

RESULTS

Effect of delivery on arterial blood gas values. Fetal and newborn arterial blood values before and after delivery are summarized in Table 1. No differences in fetal arterial PO₂, PCO₂, or pH were seen in the SAD and SAD-Vx animals. Arterial pH and PCO₂ were similar before and after birth, whereas PO₂ increased after birth as expected. The measured values are similar to those seen in intact near-term fetuses and newborn lambs delivered by cesarean section (31).

Effect of SAD and Vx on systemic hemodynamics and RSNA at birth. The changes in HR, MABP, and RSNA occurring with delivery in SAD and SAD-Vx animals are shown in Fig. 1. Data for intact sheep were previously published by our group (31) and are presented for comparison with values obtained in denervated animals. Fetal HR values were similar between SAD and SAD-Vx animals. Significant increases in HR were seen in fetal SAD and SAD-Vx animals, although these values are significantly higher than those previously reported in intact fetuses of similar gestational age (31). Within 30 min after delivery, MABP increased

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<tr>
<th>pH</th>
<th>Fetus</th>
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<tr>
<td>SAD</td>
<td>7.36 ± 0.03</td>
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<td>SAD + Vx</td>
<td>7.36 ± 0.02</td>
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<td>PCO₂, mmHg</td>
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<td>SAD</td>
<td>46 ± 2</td>
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<td>SAD + Vx</td>
<td>49 ± 4</td>
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<td>PO₂, mmHg</td>
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<tr>
<td>SAD</td>
<td>23 ± 1*</td>
<td>80 ± 12</td>
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<tr>
<td>SAD + Vx</td>
<td>24 ± 1*</td>
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Values are means ± SE; n = 6 animals with sinoaortic denervation (SAD) and 7 animals with SAD and vagotomy (SAD + Vx). *P < 0.05 vs. newborn values.

![Fig. 1. Changes in mean arterial blood pressure (MABP), heart rate, and renal sympathetic nerve activity (RSNA) at birth in sinoaortic-denervated (SAD) and SAD and vagotomized (SAD-Vx) term lambs delivered by cesarean section. Data for intact fetuses are from Segar et al. (31). bpm, Beats per minute. *P < 0.05 compared with SAD and SAD-Vx at similar time.](http://ajpregu.physiology.org/)
above fetal values by 26 and 30% in the SAD and SAD-Vx groups, respectively, and remained significantly above fetal MABP at 1 h (24 and 20%, respectively) and 2 h (28 and 17%, respectively). These initial increases in MABP 1 h after birth were significantly more than the 12% increase we have previously observed in intact newborns of similar gestational age (31). Delivery also produced rapid and sustained increases in RSNA in both groups of animals. The increases were present by 30 min of postnatal life, whereas no further increases were seen with increasing postnatal age. The increases in RSNA at 1 h of life in both SAD (168 ± 49%) and SAD-Vx (192 ± 32%) animals were similar to that seen in intact lambs (228 ± 53%) (31).

Effect of SAD and Vx on endocrine responses at birth. No differences were detected in fetal AVP values between SAD and SAD-Vx animals (Fig. 2). Within 30 min after birth, AVP significantly increased in the SAD-Vx group, with the maximum value occurring at 2 h. On the other hand, no birth-related changes in plasma AVP levels were seen in the SAD animals. No changes in ANG II levels were detected after birth within each group (Fig. 2). However, fetal and newborn ANG II levels were consistently greater in the SAD compared with SAD-Vx animals (P < 0.01, 2-factor ANOVA).

Plasma epinephrine levels were similar in fetuses in both groups and significantly increased after delivery (Fig. 3). No differences in levels were present between SAD and SAD-Vx newborn lambs at any time point. The increase in epinephrine 1 h after birth was similar to that seen in intact lambs. In contrast to epinephrine values, a large discrepancy in norepinephrine levels existed between SAD or SAD-Vx animals and intact lambs. In contrast to intact lambs, which display a large increase in norepinephrine levels after birth, neither the SAD nor the SAD-Vx animals exhibited significant increases in norepinephrine levels after birth. However, norepinephrine levels at 30 min, 1 h, and 2 h after delivery were significantly higher in the SAD-Vx lambs compared with SAD lambs. Although the mean value for norepinephrine concentration in SAD-Vx fetuses was over twice that seen in SAD fetuses, the difference did not reach statistical significance because of the large variability within the SAD-Vx group.

Effect of acute SAD and VX on fetal hemodynamics and RSNA. To determine the effect of baroreceptor and chemoreceptor denervation on basal RSNA, studies were performed in acutely denervated fetuses. Because quantitation of RSNA after birth is most accurately performed by comparing an individual animal to itself and because the quality of the nerve signal may change over prolonged periods of time, we elected to perform these studies in acutely prepared animals (n = 3). In this series of studies, no differences in HR were detected between intact (195 ± 6 beats/min) and denervated (189 ± 7 beats/min) periods. As expected, there was a significant increase in MABP after denervation from 48 ± 2 to 55 ± 3 mmHg. There was a slight increase in RSNA in all three fetuses after denervation, although this change (43 ± 31%) did not reach statistical significance (P < 0.1).
DISCUSSION

The results from these studies demonstrate that afferent input from peripheral chemoreceptors and mechanoreceptors contributes little to the systemic hemodynamic and sympathetic responses after term delivery by cesarean section. Furthermore, birth-related increases in circulating norepinephrine but not epinephrine appear dependent on afferent input from the carotid sinus or aortic depressor nerves, which carry both chemo- and baroreceptor afferents from the carotid sinus and aortic arch, respectively. Finally, we observed that vagal afferent activity regulates basal fetal plasma ANG II levels and exerts a tonic inhibitory effect on AVP release after birth.

Both peripheral chemoreceptors and baroreceptors have been shown to be functional during fetal life. The fetal cardiovascular response to acute hypoxemia is well described, consisting of a decrease in heart rate and increase in peripheral vascular resistance (7). Carotid denervation abolishes these responses to hypoxemia and NaCN, a chemical stimulant of chemoreceptors (2). Sinoaortic denervation also produces marked fluctuations in arterial pressure and HR in fetal sheep (10, 41), suggesting a role for arterial baroreceptors in maintaining cardiovascular homeostasis. A number of investigators have shown in fetal animals that carotid sinus nerve activity is phasic and pulse synchronous and that the rate of discharge increases with a rise in arterial or carotid sinus pressure (3, 23). Finally, baroreceptor stimulation elicits marked inhibition of HR and efferent RSNA, whereas unloading of the baroreceptor results in tachycardia and an increase in sympathetic activity (29). Taken together, the results support a role for peripheral baro- and chemoreceptors in regulating fetal cardiovascular function.

SAD removes peripheral arterial baroreceptor as well as chemoreceptor afferent input to the central nervous system, whereas vagal denervation interrupts mechanoreceptor afferent fibers from the cardiac atria, ventricles, and lungs. Our results would suggest that peripheral chemoreceptors and arterial baroreceptors, the afferent fibers of which travel within the carotid sinus and aortic depressor nerves, have little importance in regulating the increases in blood pressure, HR, and RSNA after birth. We recognize that in our model, mechanical ventilation and sedation of the lamb after birth may alter the neural and endocrine responses compared with spontaneously breathing animals and that different results may be obtained in animals delivered vaginally rather than by cesarean section. Nonetheless, these limitations do not detract from the findings of this study, in which all animals underwent similar postnatal management. Not unexpectedly, fetal SAD results in significantly higher baseline MABP compared with normal fetal lambs; this effect was seen both acutely and 24 h after surgery. Other investigators have also found that, in fetal lambs of similar gestational age (2, 41) studied 1–3 days postoperatively and in newborn lambs (9), SAD results in increased blood pressure. This effect is likely related to loss of baroreceptor afferent activity, which exerts a tonic inhibitory effect on efferent sympathetic innervation of vascular smooth muscle. Our finding of a slight but consistent increase in renal sympathetic activity after acute SAD is consistent with this explanation.

In the present study, peripheral denervation had several profound effects on endocrine responses at birth. Notably, serum AVP levels, which increase in newborn infants and animals after vaginal delivery and, to a far lesser extent, after cesarean section without labor (15, 21, 22), were markedly different after birth between SAD and SAD-Vx animals. Several investigators (15, 21) demonstrated in sheep that serum AVP is increased two- to threefold above fetal values after cesarean section. In the present study, we were unable to demonstrate a significant increase in AVP levels in SAD animals after birth. However, in this group of animals, fetal values were already elevated to levels previously reported in newborn lambs, a finding likely related to postoperative stress, inasmuch as measurements were taken ~24–30 h after completing surgery. On the other hand, AVP levels significantly increased after birth SAD-Vx lambs, despite having similar fetal values compared with SAD animals. A number of studies have investigated the role of afferent input on AVP responses during fetal life. SAD and Vx have no effect of fetal baseline AVP values (36, 40), suggesting that either mechanoreceptors and chemoreceptors exert no tonic inhibition of AVP in fetal lambs or that neurohumoral adaptation occurs after the loss of afferent input. However, in response to hypoxia, Vx attenuates the increase in AVP (36), whereas SAD has no effect on plasma AVP (6, 25). In contrast to that demonstrated in adult animals, in which AVP secretion in response to hemorrhage is mediated by cardiac receptors (24), SAD but not Vx alters the release of AVP in response to hypotension in fetuses (38–40). Our findings of increased AVP levels after birth in Vx lambs suggest that vagal afferent activity at birth exerts a tonic inhibitory effect on AVP release. Anderson et al. (1) demonstrated in adult dogs that stimulation of left heart baroreceptors inhibits release of AVP even in the face of systemic hypotension. At birth there is normally an increase in left-sided pressure related to increased pulmonary blood flow with increased left atrial filling, as well as an increase in systemic pressures and increased left ventricular pressures related to the loss of the umbilical circulation. Stimulation of left-sided cardiac receptors from these changes in central circulatory patterns would then attenuate an increase in AVP secretion, potentially mediated by a central chemosensitive area controlling AVP release (39). The absence of central afferent input, resulting from vagotomy, would serve as a signal for hypotension and/or decreased intravascular volume. This in turn stimulates AVP release, resulting in vasoconstriction and fluid reten-

Differences in plasma ANG II levels were also seen between SAD and SAD-Vx lambs, although neither group demonstrated an increase in plasma ANG II.
levels after birth. Again, the fact that fetuses were delivered by cesarean section before the onset of labor likely explains the absence of significant increases in plasma ANG II concentrations such as have been seen after vaginal delivery (4, 18). Analysis of the AVP data by two-way ANOVA revealed a significant effect of group, which was higher in the SAD animals, but not of time. The ANG II levels seen in the SAD-Vx group are similar to those we have previously reported in near-term fetuses that underwent similar anesthesia and surgical procedures (31) except for denervation. Therefore, the Vx animals appear to have decreased ANG II levels both before and after birth. Reasons for these differences are not clear but cannot be attributed to differences in arterial blood pressure, because this was the same in both groups of animals. Stein et al. (36) also reported that SAD-Vx fetuses had similar ANG II levels compared with intact fetuses. Although the effects of Vx on ANG II levels are not known, Vx does not alter basal fetal plasma renin activity (PRA) or the PRA response to hemorrhage (40). It is plausible that the decreased fetal ANG II value in the SAD-Vx group was related to increased ANG II clearance, which occurs primarily in the placental vascular bed (28). However, SAD has no significant effect of umbilicoplacental blood flow (10), whereas the effect of Vx on umbilicoplacental blood flow is not known.

The fetal values and increases in epinephrine 1 h after birth in both groups of animals were similar to those previously reported in intact lambs (31). However, SAD and SAD-Vx lambs failed to show significant increases in plasma norepinephrine levels after birth, demonstrating that increases in norepinephrine are dependent on afferent input from the carotid or aortic depressor nerves. Interestingly, despite 1) the lack of increase in norepinephrine after birth and 2) the differences in plasma norepinephrine values between the SAD and SAD-Vx animals, no differences were seen in pre- or postnatal HR or blood pressure between groups, and both groups experienced large increases in HR and blood pressure after birth. The finding that sympathoexcitation, reflected in the increase in RSNA, was not accompanied by an increase in norepinephrine is not surprising given that circulating norepinephrine levels are not an accurate indicator of overall sympathetic activity during stress (16, 26). Stein et al. (35) have also shown that the increase in circulating catecholamine levels at birth is related to alterations in plasma clearance rather than production. It is also possible that the RSNA is not reflective of generalized postsynaptic sympathetic activity (37).

Perspectives

In view of the fact that peripheral mechano- and chemodenervation did not alter the increase in RSNA at birth, the question arises as to what the mechanisms stimulating sympathoexcitation are. As a number of investigators have suggested, the autonomic and cardiovascular adaptations at birth are similar to those described as part of the defense reaction, or the “fight or flight” response (14, 31). It is likely that multiple factors, including hypoxia and acidosis (perhaps detected by central chemoreceptors), head compression, and cold, produce a stress that in turn triggers efferent sympathetic activity. Clearly, supramedullary centers are involved, inasmuch as surgical lesions through the rostral pons in fetal lambs inhibit sympathoexcitation at birth as well as the normal increases in HR and blood pressure (19). The mechanism also appears to be developmentally regulated and inducible, inasmuch as antenatal corticosteroid administration accentuates the sympathetic response in prematurely delivered lambs at a developmental stage when sympathoexcitation at birth is otherwise absent (30). Preterm lambs exposed to in utero cooling 1–2 h before delivery also have augmented cardiovascular and sympathetic responses at birth (30). At the cellular level, neuronal excitation may be triggered by increased expression of any number of neuromodulators or immediate early genes, such as c-fos, which is known to be increased in birth (27). Interestingly, studies in newborn rats have shown that c-fos mRNA expression is maximal 30 min after cesarean section and is not altered by exposure to hypoxia and hypothermia (27). Thus the transition from the intra- to extrauterine environment provides an as yet poorly identified stimulus (or more likely multiple stimuli), which, when perceived by the central nervous system, increases sympathetic outflow, particularly to target organs vital to successful physiological adaptation to birth.

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Address for reprint requests and other correspondence: J. L. Segar, Dept. of Pediatrics, Children's Hospital of Iowa, 200 Hawkins Drive, Iowa City, IA 52242 (E-mail: jeffrey-segar@uiowa.edu).

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