Inhibition of sympathetic responses at birth in sheep by lesion of the paraventricular nucleus

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Segar, Jeffrey L., Dan L. Ellsbury, and Oliva M. Smith. Inhibition of sympathetic responses at birth in sheep by lesion of the paraventricular nucleus. Am J Physiol Regul Integr Comp Physiol 283: R1395–R1403, 2002.—Birth is characterized by a surge in sympathetic outflow, heart rate (HR), mean arterial blood pressure (MABP) and circulating catecholamines. The paraventricular nucleus (PVN) of the hypothalamus is an important central regulatory site of sympathetic activity, but its role in the regulation of sympathoexcitation at birth is unknown. To test the hypothesis that the PVN regulates sympathetic activity at birth, experiments were performed in chronically instrumented near-term (137- to 142-day gestation, term 145 days) sheep before and after delivery by cesarean section. Stereotaxic guided electrolytic lesioning of the PVN (n = 6) or sham lesioning (n = 6) was performed 48 h before study. At 30 min after birth, renal sympathetic nerve activity (RSNA) increased 128 ± 26% above fetal values in the sham-lesioned animals (P < 0.05). In contrast, at a similar time point, RSNA decreased to 52 ± 12% of the fetal value in the PVN-lesioned animals. Lesioning of the PVN did not affect the usual postnatal increases in MABP and epinephrine levels although HR failed to rise above fetal values. ANG II but not arginine vasopressin or norepinephrine levels increased in PVN-lesioned animals after birth, whereas all three hormones increased (P < 0.05) in sham-lesioned animals. Fetal and newborn HR baroreflex responses were similar in both groups. However, the usual postnatal attenuation of baroreflex-mediated inhibition of RSNA was blunted in the PVN-lesioned group. The results of this study demonstrate that ablation of the PVN abolishes sympathoexcitation with birth at near-term gestation. The PVN may play a critical role in physiological adaptation at birth.

autonomic nervous system; fetus; newborn

ACTIVATION of the sympathoadrenal system plays a vital role in regulating many of the physiological adaptations at birth, including increases in heart rate (HR), cardiac output, arterial pressure, a redistribution of organ blood flow, and thermogenesis (32, 33). The factors mediating the increase in sympathetic outflow at birth are not known but likely involve multiple factors, including hypoxia, acidosis, head compression, and cold (29, 38). Previous studies by our group using in utero ventilation of fetal sheep suggest that rhythmic lung inflation, increased arterial oxygenation, and separation from the placental circulation contribute little to the increase in sympathetic activity at birth (29). Peripheral mechanoe- and chemoreceptor denervation also fail to attenuate the hemodynamic and sympathetic responses after delivery, suggesting afferent input from these receptors, which are known to be functional at this stage of development, is not essential for activation of the sympathetic nervous system at birth (39). Regardless of the stimuli, supramedullary centers appear to be involved in regulating sympathetic outflow, as surgical lesions through the rostral pons in fetal lambs, which do not alter resting fetal blood pressure or renal sympathetic nerve activity (RSNA), inhibit sympathoexcitation at birth as well as the normal postnatal increases in HR and blood pressure (29).

The paraventricular nucleus of the hypothalamus (PVN) is known to be an important site of central regulation of cardiovascular homeostasis (9, 45). In addition to its role in regulating the release of neurohypophyseal hormones, there is abundant evidence that the PVN is an important center for integrating autonomic function. In some species but not all, electrical and/or chemical stimulation of PVN neurons elicits increases in HR, blood pressure, and renal, splanchnic, and adrenal nerve activity (13, 25, 26, 28, 42). Lesions of the PVN attenuate the development of hypertension in spontaneously hypertensive rats and Dahl salt-sensitive rats and in one-kidney figure eight renal wrap models of hypertension as well as after sinoaortic denervation (4, 8, 47, 51). Numerous anatomic and physiological studies have demonstrated connections between the PVN and vasomotor neurons in the spinal cord and medulla, including the rostral and caudal ventrolateral medulla, sympathetic preganglionic neurons of the intermediolateral cell column, the nucleus of the solitary tract, and the area postrema (5, 7, 11, 14, 23, 43, 49, 50). Because the PVN appears important in sympathetic nervous system regulation, as well as integrating autonomic endocrine and behavioral responses, we sought to determine its contribution to the hemodynamic, humoral, and sympathetic responses at birth. More specifically, we tested the hypothesis that elec-
trolytic ablation of the PVN would attenuate the changes in RSNA, blood pressure, and arterial baroreflex function at birth.

**METHODS**

Studies were performed in conscious, chronically instrumented fetal sheep at 137- to 142-day 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 (24). All surgical and experimental procedures were performed within the regulation of the Animal Welfare Act and the NIH Guide for the Care and Use of Laboratory Animals. The “Guiding Principles for Research Involving Animals and Human Beings” approved by the Council of the American Physiological Society (3) and governed by the Animal Care and Use Committee of the University of Iowa were strictly adhered to.

**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 performing a maternal abdominal flank incision, 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 cranial stereotaxic device (Kopf, Tujunga, CA). A midline incision was made in the scalp to expose the skull, 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 onto the nerve for recording of RSNA and arterial blood values (23P). In sham-lesioned animals, the electrode was lowered to approximate coordinates: AP, 24 mm; V, 27 mm; L, ±1 mm, where AP = anteroposterior, V = vertical with outer skull 0 mm, and L = lateral from midline), lesions were made in the PVN bilaterally with the use of a Radionics RFG-4A research RF lesion generator (Kopf). The tissue temperature at the tip of the electrode was set to 75°C for 30 s. This temperature and duration have previously been shown to produce approximately 3 × 3 × 2-mm lesions in the fetal sheep hypothalamus (30). In sham-lesioned animals, the electrode was lowered to the same coordinates without activation of the generator. The skull defect was filled with bone wax, and the scalp incision was closed. The fetus was returned to the uterus, and after closure of all incisions, catheters and wires were exteriorized through subcutaneous tunnels and placed in a cloth pouch on the ewe’s flank. Ampicillin sodium 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. At least 48 h were allowed for recovery from surgery before experiments were performed.

**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. Muscle paralysis was necessary to eliminate movements that interfere with nerve recording. This protocol of sedation and paralysis has previously been shown in 7-day-old and 4- to 5-week-old lambs to have no effect on systemic hemodynamics, arterial pH and blood gas values, or catecholamine levels (40). In addition, maternal sedation with diazepam and paralysis has no effect on fetal HR, arterial pressure, or plasma catecholamine, ANG II, or cortisol levels (Table 1). Diazepam was administered every 2 h while 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 of the ewe, a 1-h stabilization period was allowed before the start of the experiment.

During each experiment, fetal mean arterial blood pressure (MABP) and amniotic pressure were recorded continuously using Statham P23Db pressure transducers (Spectramed, Critical Care Division, Oxnard 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 (HIP5, Grass Instruments). The neural signal was amplified (×20,000) and filtered (low-frequency cutoff 100 Hz, high-frequency cutoff 3 kHz) using a Grass Bandpass Amplifier (P511). The output of the amplifier was visually displayed on an oscilloscope (511A, 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.

**Experimental protocol.** Fetal baseline values for HR, MABP, and RSNA were continuously recorded and averaged over 30 min. Fetal arterial blood for determination of blood gases and pH, and plasma norepinephrine, epinephrine, ANG II, and arginine vasopressin (AVP) levels were obtained.

| Table 1. Effects of maternal sedation/ventilation on fetal arterial blood values |
|----------------------------------------|------------------|------------------|
| pH                                     | Awake            | Sedation         |
|                                        | 7.38 ± 0.02      | 7.37 ± 0.02      |
| PCO₂, mmHg                             | 40 ± 2           | 39 ± 3           |
| PO₂, mmHg                              | 24 ± 2           | 23 ± 1           |
| Heart rate, beats/min                  | 152 ± 8          | 156 ± 9          |
| MABP, mmHg                             | 48 ± 2           | 48 ± 3           |
| Epinephrine, pg/ml                     | 54 ± 21          | 44 ± 18          |
| Norepinephrine, pg/ml                  | 493 ± 102        | 548 ± 94         |
| ANG II, pg/ml                          | 41 ± 9           | 49 ± 7           |
| Cortisol, µg/dl                        | 2.4 ± 0.3        | 2.6 ± 0.2        |

Values are means ± SE; n = 4 fetuses. Values were obtained with ewe awake and 30–45 min after maternal sedation, intubation, and paralysis. MABP, mean arterial blood pressure.
at the completion of the baseline period. 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. Baroreflex function in the fetus was then determined by producing ramp changes in MABP with a continuous intravenous infusion of progressive doses of phenylephrine or nitroprusside (1–30 μg·kg⁻¹·min⁻¹) over a 5- to 7-min period using a Harvard infusion pump while simultaneously recording HR and RSNA. A 40- to 60-min recovery period was allowed for MABP, HR, and RSNA to return to baseline values before the alternative drug was administered. At the completion of the baroreflex studies, the amount of background noise in the fetal nerve signal was 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 ewe was returned to the surgical area and mechanical ventilation 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 initially placed on an infant warmer bed, dried, and manually ventilated. The animals were then transferred to the laboratory in 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 of 1.0, a rate of 40 breaths/min, an inspiratory time of 0.4 s, positive end-expiratory pressure of 4 cmH₂O, and peak inspiratory pressure of 20–26 cmH₂O. Arterial blood gases were obtained no less often than every 20 min, and ventilator settings were adjusted to maintain arterial Po₂ 75–150 mmHg and arterial PCO₂ 35–45 mmHg. Newborn core temperature was maintained between 38.5 and 39.0°C by use of a heating pad and warming lamp. Diazepam was administered to the lambs in doses previously noted. Continuous recording of HR, MABP, and RSNA began 10–15 min after delivery. Blood for determination of plasma norepinephrine, epinephrine, AVP, and ANG II was obtained immediately after the recording period at 60 min, and an equivalent volume of maternal blood was returned. Newborn baroreflex function was then tested using the protocol as described for the fetus. Hemodynamic and RSNA recordings were continued for 2 h after delivery. At the completion of the study, background noise in the nerve signal was again assessed using tetraethylammonium bromide.

**Analytical 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 plasma AVP and ANG II were determined by radioimmunoassay (University of Wisconsin School of Veterinary Medicine Radioimmunoassay Laboratory, Dr. M. Brownfield, Director). Plasma norepinephrine and epinephrine levels were determined by radioimmunoassay in our laboratory according to the manufacturer’s specifications (Katcombi RIA RE29291, KMI Diagnostics, Minneapolis, MN).

**Computation and data analysis.** RSNA was integrated and 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; the amount of activity measured during the initial fetal baseline period was defined as 100%. Baroreflex sensitivity was determined by calculating the slope of the linear regression relating the absolute change in MABP to percent decrease in HR. Statistical analyses of differences in HR, MABP, RSNA, slope of baroreflex, plasma hormone concentrations, and arterial blood gas values during the described study periods were performed using 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. Data exhibiting a lack of homogeneity of variances among groups were analyzed nonparametrically using the Kruskal-Wallis test. Differences were considered significant when P < 0.05. All results are expressed as means ± SE.

**RESULTS**

Two fetuses (1 PVN lesioned, 1 sham lesioned) did not survive the perioperative period. Data obtained from fetuses with lesions outside the PVN (1 animal with a unilateral miss, 2 animals missed bilaterally) were excluded. All three of these animals displayed postnatal hemodynamic and RSNA values similar to those in control animals, although the RSNA at birth in the lamb with a unilateral PVN lesion was somewhat attenuated (RSNA at 30 min after delivery was 65% greater than the fetal value). In lesioned animals, the lesioned area included all of the PVN bilaterally as well other areas of the dorsomedial hypothalamus and the walls of the third ventricle. Figure 1 illustrates the extent of the lesions produced by electrolytic ablation in all six fetuses in which the PVN was involved bilaterally. Damage of the fornix was generally observed while the lesion on occasion involved the periventricular nucleus, suprachiasmatic nucleus, and medial preoptic nucleus.

**Effects of PVN ablation on baseline hemodynamics and RSNA.** Fetal MABP and HR were similar in PVN-lesioned and sham-lesioned animals (Fig. 2). Thirty minutes after delivery by cesarean section, HR in the sham-lesioned animals was significantly increased above the fetal value (P < 0.05) and remained elevated at 120 min. In contrast, HR did not increase after birth in PVN-lesioned animals and was significantly less than that seen in sham-lesioned animals at 30 and 120 min. MABP values were significantly increased from fetal values in both groups of animals 30 and 120 min after delivery. No differences in resting MABP were detected between groups at any time point. Because we used intact, whole nerve recording techniques, comparison of resting RSNA between animals is not possible and the effect of PVN lesion on resting fetal RSNA cannot be determined. Fetal baseline RSNA is therefore defined as 100% in both groups of animals. At 30 min after birth, RSNA increased 128 ± 26% above fetal values in the sham-lesioned animals (P < 0.05) and remained elevated at 120 min (Fig. 3). However, in PVN-lesioned lambs, RSNA decreased after delivery. RSNA at 30 and 120 min after birth in the PVN-lesioned animals was significantly less than the fetal value and the values at similar time points in sham-lesioned lambs.

**Effects of PVN ablation on arterial blood values.** Fetal and newborn arterial blood gas values are shown in Fig. 4. No differences in fetal and newborn arterial
pH, $P_{CO_2}$, and $P_{O_2}$ were present between the two groups at any time point. As expected, arterial $P_{O_2}$ increased significantly after birth in both groups. Arterial $P_{CO_2}$ was decreased at 120 min compared with the fetal value; the extent of the decrease was similar in both groups.

Fetal plasma norepinephrine and epinephrine levels in PVN-lesioned animals were approximately twice the values seen in sham-lesioned fetuses (both $P < 0.05$) although all values were within the range we have previously seen in intact fetuses at this stage of development (Fig. 5) (29, 38, 39). Thirty minutes after birth, norepinephrine levels had increased over threefold ($P < 0.05$) in sham-lesioned lambs and remained significantly elevated at 120 min. On the other hand, plasma norepinephrine values failed to increase after delivery in PVN-lesioned lambs, although the values were not significantly different from those seen in sham-lesioned animals. Plasma epinephrine levels increased after birth in both groups of animals to a similar extent at 30 and 120 min.

Circulating levels of ANG II increased after birth in both groups and were similar between groups at each fetal and postnatal time point (Fig. 6). Fetal AVP levels were similar in both groups, increasing within 30 min of birth in the sham-lesioned group and remaining elevated at 120 min ($P < 0.05$). In contrast to the
sham-lesioned animals, AVP levels did not increase after delivery in lambs with bilateral PVN lesions. In this group of animals, vasopressin levels at 30 and 120 min after birth remained similar to those seen in the fetus and significantly less than the values seen in sham-lesioned lambs.

Effects of PVN ablation on baroreflex control of HR and RSNA. The pressor and depressor limbs of the arterial baroreflex were evaluated separately by recording the change in HR resulting from increases in MABP produced by infusion of phenylephrine or decreases in MABP produced by infusion of nitroprusside. Using linear regression analysis, we found the slope (gain) of the relationship between fetal MABP and HR was similar between groups for both the depressor limb (AVP lesioned vs. sham lesioned, respectively) and pressor limb (AVP lesioned vs. sham lesioned, respectively) of the reflex. After birth, the slope of the HR baroreflex response to increases in MABP was greater (P < 0.05) in sham-lesioned (−4.3 ± 0.5 vs. −3.9 ± 0.5%/mmHg, PVN lesioned vs. sham lesioned, respectively) and pressor limb (−3.3 ± 0.4 vs. −3.2 ± 0.4%/mmHg, PVN lesioned vs. sham lesioned, respectively) of the reflex. After birth, the slope of the HR baroreflex response to increases in MABP was greater (P < 0.05) in sham-lesioned (−4.4 ± 0.8%/mmHg) compared with PVN-lesioned lambs (−2.7 ± 0.4%/mmHg). This was related to the fact that the resting HR was greater in sham-lesioned compared with PVN-lesioned lambs. The maximal induced reflex bradycardia, in terms of absolute HR, was similar in both groups (−100 beats/min). The depressor limb of the baroreflex was similar after birth in both groups with no reproducible increase in HR present in response to a decrease in blood pressure.

The maximum and minimum fetal RSNA values achieved during unloading of baroreceptors with nitroprusside and loading of baroreceptors with phenylephrine, respectively, were similar in both groups (Fig. 7). In both sham-lesioned and PVN-lesioned newborns, RSNA could not be significantly increased above newborn baseline levels by nitroprusside-induced hypotension. Although the maximal inhibition of RSNA with phenylephrine-induced hypertension after birth was significantly attenuated compared with fetal values, consistent with our previous studies (38), the extent of this baroreflex-mediated inhibition of RSNA differed between groups. In sham-lesioned newborns, RSNA could be inhibited by ~34% from baseline ([baseline RSNA − minimum RSNA]/baseline RSNA; (228% − 151%)/228%), whereas RSNA in PVN-lesioned animals could be inhibited by 69%. When analyzed in this manner for all animals the attenuation of RSNA by baroreceptor stimulation was significantly greater in PVN-lesioned compared with sham-lesioned lambs (P < 0.05).

DISCUSSION

The results of these studies demonstrate that electrolytic ablation of the PVN does not alter resting fetal hemodynamics, baroreflex function, or most circulating vasoactive hormone levels. However, lesion of this area...
of the hypothalamus abolishes the postnatal increase in HR and RSNA that typically occurs in near-term sheep delivered by cesarean section while not altering the increase in MABP. The studies have also shown that lesions of the PVN prevent the postnatal increase in AVP secretion but not circulating ANG II or epinephrine levels.

The finding that MABP increased to a similar extent in PVN and sham-lesioned animals was not unexpected. In the present study, epinephrine and ANG II levels increased after delivery to a similar extent in both groups of animals. Postnatal changes in blood pressure, cardiac output, and system vascular resistance are similar in intact and chemically sympathectomized newborn lambs, emphasizing the importance of circulating vasoactive hormones, particularly ANG II, and adrenal epinephrine secretion to physiological adaptation at birth (12, 32). The importance of activation of the sympathetic nervous system should not, however, be underestimated or dismissed on the basis of these findings. Prolonged sympathetic inhibition, as occurs with sympathectomy, allows for compensatory mechanisms to be initiated. For example, lambs sympathectomized in utero display increased sensitivity to the pressor effects of norepinephrine and phenylephrine (27). o-Adrenergic receptor blockade also causes a significant decrease in blood pressure in intact but not sympathectomized lambs, suggesting an important role for resting sympathetic tone in these animals (27). Ganglionic blockade in newborn lambs (1 day old) results in a reduction in cardiac function, manifested by a decrease in HR, cardiac output, and arterial pressure (31).

Sympathetic innervation and function are also important for the initiation of nonshivering thermogenesis, a process essential for successful neonatal adaptation. In lambs, chemical sympathectomy impairs the metabolic response at birth by an amount approximated by the thermogenic potential of brown fat (2). The initiation of lipolysis that is signaled for by cutaneous cooling appears dependent on direct innervation and neurally mediated sympathetic stimulation of brown adipose tissue and not a rise in circulating catecholamine levels (20). Neuroanatomic studies also demonstrate that the central nervous system origins of the sympathetic innervation of brown adipose tissue include the PVN as well as other sites in the hypothalamus and brain stem (6).

Large increases in a number of vasoactive hormones, including epinephrine, norepinephrine, ANG II, and AVP, have been shown to occur at birth. Fetal chemical sympathectomy abolishes the large surge in norepinephrine but not epinephrine levels after birth, suggesting the majority of circulating norepinephrine seen at birth arises from postganglionic sympathetic nerves, so-called neuronal spillover (1, 44). The lack of increase in plasma norepinephrine at birth in PVN-lesioned animals before and 30 and 120 min after delivery by cesarean section. *P < 0.05 compared with fetus in same group. †P < 0.05 compared with sham lesion group at similar time point.
animals is therefore consistent with the lack of increase in sympathetic outflow. The higher baseline values for fetal norepinephrine seen in the PVN-lesioned fetuses may have resulted from increased basal sympathetic activity, greater adrenal release of norepinephrine, or altered norepinephrine clearance.

The mechanism(s) by which electrolytic lesion of the PVN attenuated the normally occurring surge in RSNA at birth was not addressed in this study. We recognize that the lesioned area included all or parts of hypothalamic nuclei other than the PVN, as well as fibers of passage. Afferent fibers to the PVN, in particular those originating from the subfornical organ (SFO), have previously been shown to participate in regulating sympathetic outflow (16, 21, 37). The SFO, like other circumventricular organs, lacks a blood-brain barrier, allowing the central nervous system to "sample" the chemical or hormonal status of the blood by allowing large-molecular-weight substances to pass from the plasma to underlying neural tissue. We speculate that the PVN functions as an important center for integrating the hormonal and autonomic responses at birth.

We have previously shown that delivery of the near-term fetus elicits near-maximum stimulation of renal sympathetic outflow and HR (38). Namely, unloading of the arterial baroreceptors soon after birth failed to further increase RSNA or HR. This was also seen in our sham-lesioned and PVN-lesioned animals in the current study, although the maximum RSNA and HR were significantly less in the PVN-lesioned animals. On the other hand, lesion of the PVN had a marked effect on the RSNA reflex response to baroreceptor loading. In this group of newborn lambs, baroreflex-mediated inhibition of RSNA was far less attenuated than seen in intact or sham-lesioned lambs. This finding suggests that the PVN is not only important in sympathoexcitation but also in the "overriding" of the baroreflex that occurs at birth. A role of the PVN in mediating baroreflex function has previously been demonstrated. Activation of baroreceptor afferent fibers alters the discharge of neurons in the PVN (9). PVN neurons also project to baroreceptor-sensitive neurons in the caudal ventrolateral medulla, where they likely influence sympathetic tone (49). Stimulation of the PVN modulates activity of neurons in the nucleus of the solitary tract and area postrema (14, 43). Results reported by Yang and Coote (50) also suggest that activation of select PVN neurons may attenuate transmission of the baroreflex. In rabbits, blockade of PVN neurons with lidocaine had no effect on resting hemodynamics or lumbar sympathetic activity but augmented baroreceptor-mediated inhibition of nerve activity. It therefore appears that the PVN mediates not only sympathoexcitation at birth but also the attenuation of the baroreflex. Whether these responses are mediated by the same or separate groups of PVN neurons will require further investigation.

While the postnatal increase in blood pressure was similar in the two groups, AVP failed to increase after birth in the PVN-lesioned animals. This finding suggests that the normal rise in circulating AVP occurring at birth is not vital to the normal increase in blood pressure. That the postnatal increase in circulating AVP was completely blocked by lesion of the PVN was not surprising given the known role of magnocellular neurosecretory neurons in the PVN as well as the supraoptic nucleus in the release of AVP into the circulation. AVP-containing neurons are present in both of these nuclei in fetal and newborn sheep (15). We speculate that in the lesioned animals, vasopressin release, although still present due to an intact supraoptic nucleus, is impaired secondary to the loss of AVP-secreting neurons in the PVN. Rossi and Chen (36) also recently demonstrated in rats that PVN lesions prevent an increase in vasopressin in response to lateral ventricle injection of endothelin-1.

The cardiovascular component of the defense reaction, characterized by tachycardia, increased cardiac contractility, increased skeletal muscle blood flow, hyperton, and baroreceptor reflex inhibition mimics many of the physiological changes that occur at birth (10, 22, 35). The coordinated increases in cardiovascular function and release of adrenal catecholamines are believed to be regulated by activation of central command neurons that provide input to the heart, vascular beds, and the adrenal medulla. While a detailed discussion of the autonomic control and pathways of the defense reaction is not appropriate, the response is readily evoked from stimulation of other hypothalamic areas, such as the perifornical region, or the midbrain periaqueductal gray (17, 22). There are also reasons to believe the PVN may participate in the response, likely in coordination with other central nervous system regions mediating the defense reaction. Chemical or electrical stimulation of the PVN elicits the stereotypical pattern of cardiovascular responses seen in the defense reaction (28, 34). As noted earlier, stimulation of PVN neurons inhibits the activity of barosensitive neurons of the nucleus of the solitary tract and caudal ventrolateral medulla, thus attenuating the baroreceptor reflex (14, 50). This suppression of the baroreflex is a key component of the defense reaction. Finally, using a double-virus transneuronal labeling technique and injecting separate labeling viruses into the stellate ganglion (sympathetic ganglion innervating heart) and the adrenal gland, Loey and colleagues (23) identified several central nervous system regions of double-labeled neurons, including the PVN (23). The majority of the PVN neurons did not co-label with oxytocin but appear capable of regulating both the cardiac and adrenal, and presumably other sympathetic, outflow responses.

**Perspectives**

Little is known regarding central control of cardiovascular function early in life. Williams et al. (48) identified sites in the fetal sheep hypothalamus from which electrical stimulation elicited tachycardic and pressor responses. The pressor response was abolished by prior administration of the α-adrenergic blocker phentolamine. In neonatal pigs, Gootman (19) showed...
posterior hypothalamic stimulation produced increases in blood pressure and HR.

The transition from the intra- to extraterine environment provides a number of stimuli, including stimulation of thermoreceptors and chemoreceptors, which when perceived by the central nervous system may increase sympathetic outflow and initiate a variety of physiological responses. Activation of neurons within the PVN appears critical for the increase in sympathetic activity at birth, although the central mechanisms and neuromodulator(s) regulating the response are not known. Almost 20 years ago, over 30 putative biologically active peptide and neurotransmitters had been identified within the PVN and certainly more exist (46).

McDonald and Nathanielsz (30) previously demonstrated in fetal sheep that PVN lesion prevented the normal predelivery increase in fetal plasma ACTH and cortisol and resulted in prolonged gestation. Given its importance in initiating the onset of parturition, it is intriguing to speculate that the PVN acts as a central integrator of neuroendocrine and autonomic function, signaling parturition only when a certain degree of physiological maturity, including autonomic function, has been achieved. Further investigation is required to establish the nature and interaction of the afferent signals, central integration, and efferent responses that are vital for successful adaptation of the newborn to its new environment.

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