Fever in Young Lambs: Carotid Denervation Alters the Febrile Response to a Small Dose of Bacterial Pyrogen

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ABSTRACT. Experiments were done on 13 young lambs to determine if carotid denervation influences the cardiovascular and metabolic responses to i.v. administration of bacterial pyrogen [*Salmonella abortus equi* (SAE) 0.3 μg]. Each lamb was anesthetized with halothane and prepared for measurements of cardiac output, arterial and mixed venous oxygen saturations, and body core temperature. No sooner than 3 d after surgery, measurements were made during a control period and at 10-min intervals for 120 min after i.v. administration of SAE in seven carotid-intact lambs and six carotid-denervated lambs. Administration of SAE produced a short-lived fever of about 1°C in the carotid-intact lambs, whereas no change in body core temperature was observed in the carotid-denervated lambs. In carotid-intact lambs, the rise in body core temperature began approximately 40 min after administration of SAE and continued for approximately 50 min. This rise in body core temperature was preceded by the onset of shivering and an increase in total body oxygen consumption. Carotid denervation produced changes in some of the cardiovascular variables during the control period (*i.e.* arterial oxygen content, cardiac index, heart rate, and pulmonary blood pressure); however, there were no additional significant changes in any of the metabolic or cardiovascular variables after administration of SAE. The mechanism of these unexpected findings remains to be determined. (*Pediatr Res* 31: 107–111, 1992)

Abbreviations

SAE, *salmonella abortus equi*
NTS, nucleus tractus solitarus

Newborn animals of a number of species, such as the guinea pig (1), rabbit (2), and sheep (3), have an attenuated or absent febrile response to bacterial pyrogen. This occurs even though these animals exhibit a thermogenic response to a decrease in ambient temperature (4, 5). Although the reason for this attenuated or absent febrile response to bacterial pyrogen is not entirely clear, recent experiments provide evidence that arginine

vasopressin, which may function as a physiologically important antipyretic substance in the brain (6), plays a role (7).

We have recently shown that carotid-intact lambs develop a fever of approximately 0.7°C in response to a small dose of bacterial pyrogen (*i.e.* 0.3 μg SAE lipopolysaccharide) by the 3rd wk of postnatal life (8). Previous experiments on adult rats have provided evidence that discrete bilateral lesions of the NTS, which disrupts afferent neural activity from the arterial baroreceptors, alter the cardiovascular and metabolic responses to thermogenic stimuli (*i.e.* a change in ambient temperature) (9). With this in mind, the present experiments have been done to determine whether carotid denervation alters the temperature and the cardiorespiratory or metabolic responses to bacterial pyrogen in young lambs.

MATERIALS AND METHODS

Thirteen lambs ranging in age from 14 to 28 d were studied. Each lamb was separated from its ewe 3 to 7 d after birth and was housed in our laboratory in a Plexiglas cage with continuous access to milk (Lamb Milk Replacer; Land O'Lakes, Inc., Fort Dodge, IA). The lambs were among other lambs, fed and slept *ad libitum*, and soon became accustomed to their surroundings and the laboratory personnel.

Surgical preparation. Each lamb underwent one operation before study. For surgery, each lamb was given atropine sulfate (0.2 mg/kg s.c.) and anesthesia was induced by having the lamb breathe 3 to 4% halothane in oxygen via a mask. The trachea was then intubated with a cuffed endotracheal tube, and anesthesia was maintained by ventilating the lamb's lungs with 0.5 to 1.0% halothane in oxygen. An electrocardiogram, end-tidal carbon dioxide levels, and rectal temperature were monitored during surgery; body temperature was kept near 39°C with a heating pad and end-tidal carbon dioxide levels were kept near 5% with a volume-cycled ventilator.

The operation was done on lambs aged between 11 and 25 d. A midline sternotomy was performed to expose the heart and great vessels. The pericardium was incised and a precalibrated electromagnetic flow transducer (SP 7515, inner diameter 9.0 or 10.0 mm; Gould-Statham, Inc., Oxnard, CA) was placed around the main pulmonary artery to measure pulmonary blood flow. Two double-lumen fiberoptic catheter oximeters (model U440 Opticath; Oximetrix, Inc., Mountain View, CA) treated with TDMAC heparin complex (Polysciences Inc., Warrington, PA) were placed to measure blood pressures and Hb oxygen saturations: one in the aorta and one in the pulmonary artery. In addition, a copper/constantan thermocouple (RET-1; Sensortek, Clifton, NJ) was inserted to the inferior vena cava via a femoral vein to measure body core temperature.

Electrodes for the following recordings were also implanted: electrocorticogram (recorded from electrodes placed through

burr holes to lie over the parietal cortex), electro-oculogram (recorded from electrodes placed at the inner and outer canthus of the right eye), nuchal electromyogram (recorded from electrodes placed in the dorsal cervical musculature), and diaphragm electromyogram (recorded from electrodes placed transabdominally into muscle fibers adjacent to the lateral margin of the central tendon of the right hemidiaphragm). A reference wire was sutured into the s.c. tissue of the scalp. The electrodes were made in our laboratory and were paired, Teflon-coated, multistranded, stainless steel wires (AS 633; Cooner Wire Co., Chatsworth, CA); approximately 3 mm of the tip of each was bared for implantation. The proximal end of each wire was bared and soldered to the appropriate pin of an 18-pin electrical plug, which was interfaced with four differential high impedance probes (7HIP5G; Grass Medical Instruments, Quincy, MA) during a study.

Carotid denervation was performed in six of the 13 lambs as follows. The carotid body and carotid sinus were approached as described by Appleton and Waites (10) and denervated as described by Bureau et al. (11). Briefly, the denervation procedure consisted of: *1*) cutting the sinus nerve, *2*) stripping the adventitia from the wall of the carotid artery from the origin of the lingual artery to 0.5 cm below the origin of the occipital artery, *3*) removing all fibroadipose nodular tissue from around the occipital-carotid artery junction, *4*) sectioning all minute vessels arising in the area of the carotid and occipital artery bifurcation, *5*) stripping the adventitia from the wall of the occipital artery for 1 cm from its origin from the carotid artery, and, lastly, *6*) painting the walls of the stripped vessels with 7% phenol.

The lambs were allowed to recover from surgery in a Shor-Line intensive care unit for small animals (Schroer Manufacturing Company, Kansas City, MO) and were then returned to their Plexiglas study cage in our sleep laboratory but were not studied before the 3rd postoperative day. Each lamb received antibiotics daily (penicillin G and dihydrostreptomycin), beginning on the day of surgery.

Conditions of observations. Our sleep laboratory consists of a large room that contains two sound-attenuating chambers. Temperature, sound, and lighting can be precisely controlled in each chamber. The lambs in this series of experiments were raised in an environmental temperature of 25 ± 1°C. Each chamber also has a one-way viewing mirror as well as a closed-circuit video system to observe the lambs. Our recording equipment was kept in the room adjacent to the chamber. Before a study, a partition was placed in the cage to prevent the animal from turning around once the catheters, electrodes, and cables were connected. However, the lamb could still lay down, stand up, and feed *ad libitum.*

For an experiment, the optical sensors were connected to the optical modules of the oximeter processors and the vascular catheters were connected to strain gauge manometers (Gould P23ID; Gould, Inc., Oxnard, CA) using rigid pressure-monitoring tubes; the strain gauge manometers were placed at the approximate level of the heart when the animal was lying down. The flow transducer cable was connected to a Gould SP2202 Blood Flowmeter (Gould, Inc.) and the thermocouple was connected to an Iso-Thermix Unit (Columbus Instruments International Corp., Columbus, OH) that was interfaced with a Zenith Lap-Top Computer (model ZA-180-21). The 18-pin electrical plug was connected to the differential high-impedance probes; a heavy duty cable connected the differential high-impedance probes to A.C. preamplifiers (model 7P5 Wide Band A.C. EEG Pre-amplifier; Grass Medical Instruments) in the adjacent room. The electrophysiologic signals were filtered as follows: electrocorticogram 1–35 Hz, electro-oculogram 0.3–35 Hz, and electromyograms 3–35 Hz.

The following electrophysiologic criteria were used to define sleep state. During wakefulness, the electrocorticogram showed a fast wave-low voltage pattern; there were occasional eye movements and there was tonic activity on the nuchal electromyogram. During quiet sleep, the electrocorticogram showed a slow

wave-high voltage pattern; there were no eye movements and there was tonic activity on the nuchal electromyogram. During active sleep, the electrocorticogram showed a fast wave-low voltage pattern; there were rapid eye movements on the electro-oculogram; there was no activity on the nuchal electromyogram; and there were occasional twitches of the ear, face, and limbs.

Experimental protocol. The lambs were studied in an environmental temperature of 25 ± 1°C. During an experiment, systemic and pulmonary arterial blood pressures, Hb oxygen saturations, pulmonary blood flow, and the electrophysiologic signals were recorded on a Grass model 7 polygraph (Grass Medical Instruments) and were digitized at 128 Hz (Zenith AT, Data Translation 2801A A/D, DATAQ WFS-200 Hardware Scroller, and Asystant+ Data Acquisition Software) for "off-line" analysis. Both environmental and lamb core temperatures were recorded using an Iso-Thermix Unit (Columbus Instruments, Dayton, OH). The following calculations were made from the measured variables: arterial oxygen content (CaO_2) [Hb concentration (g/dL) × Hb O_2 binding capacity (1.36 mL O_2/g Hb) × SaO_2, where SaO_2 is arterial blood oxygen saturation], mixed-venous oxygen content (CvO_2) [Hb concentration (g/dL) × Hb O_2 binding capacity (1.36 mL O_2/g Hb) × SvO_2, where SvO_2 is venous blood oxygen saturation, systemic oxygen transport (SOT) (Qp × CaO_2, where Qp is pulmonary blood flow), total body oxygen consumption (VO_2) Qp × (CaO_2 − CvO_2)], and total body oxygen extraction [(VO_2/SOT) × 100]. Hb concentration was measured using an IL282 Co-oximeter after calibration of the instrument with whole blood. The Hb of the whole blood used for instrument calibration was determined using the cyanmethemoglobin technique.

Measurements were made during a 1-min control period and during 1-min experimental periods at 10-min intervals for 120 min after i.v. administration of 0.3 μg of bacterial pyrogen in seven carotid-intact lambs and six carotid-denervated lambs. Control measurements were made when the lambs were in quiet sleep. The bacterial pyrogen used was a lipopolysaccharide extracted from SAE (Difco Laboratories, Detroit, MI). In lambs, 0.3 μg of SAE has been shown to produce a monophasic fever of about 0.7°C during this age range (8). Experiments began between 0800 and 1000 h each day to obviate possible superimposed effects of circadian rhythms.

Statistical analysis. For every animal, we determined an average value for each variable during each data collection period; these values were used for statistical analysis. We performed a two-factor analysis of variance for repeated measures of the same variable followed by a Duncan's multiple comparison test to determine if administration of bacterial pyrogen (control *versus* 10 min, 20 min, 30 min, etc.) or carotid denervation (carotid-intact *versus* carotid denervation) affected cardiac index, heart rate, stroke volume, systemic arterial blood pressure, systemic vascular resistance, pulmonary arterial blood pressure, arterial oxygen content, mixed-venous oxygen content, systemic oxygen transport, total body oxygen consumption, total body oxygen extraction, or body core temperature (12).

RESULTS

Intravenous administration of 0.3 μg of SAE produced a short-lived monophasic fever of about 1°C in the carotid-intact lambs (Fig. 1). In contrast, a febrile response was not observed after i.v. administration of SAE in the carotid-denervated lambs.

In carotid-intact lambs, the rise in body core temperature began approximately 40 min after administration of SAE and continued for approximately 50 min. This rise in body core temperature was preceded by the onset of shivering and an increase in total body oxygen consumption. The increase in total body oxygen consumption was met by an increase in total body oxygen extraction as systemic oxygen transport did not change (Table 1). Heart rate increased and stroke volume decreased between 40 and 70 min after administration of SAE; however
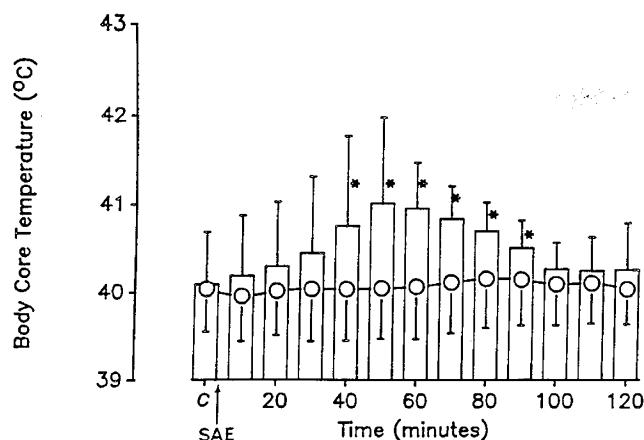
Fig. 1. Influence of bacterial endotoxin on body core temperature in carotid-intact ($n = 7$; open bars) and carotid-denervated ($n = 6$; open circles) lambs. Data are means ± 1 SD. *, Significant difference from control value within a group.

cardiac output did not change significantly (Table 2). Pulmonary arterial blood pressure increased after administration of SAE.

Carotid denervation produced changes in some of the cardiovascular variables during the control period (i.e. arterial oxygen content, cardiac index, heart rate, and pulmonary blood pressure). However, there were no additional significant changes in any of the metabolic or cardiovascular variables after administration of SAE.

Hypercapneic hypoxemia was observed in carotid-denervated

lambs compared to carotid-intact lambs (Table 3). Because hypoxemia was observed in the carotid-denervated lambs and hypoxemia has been shown to diminish the thermogenic response to pyrogen in carotid-intact rats (13), guinea pigs (14), and lambs (15), experiments were repeated on three of the lambs when they were breathing an oxygen-enriched gas mixture that increased their arterial oxygen pressure to approximately 300 torr. A febrile response was still not observed after the administration of SAE in these lambs.

DISCUSSION

Our experiments provided new information about factors that influence the febrile response to a small dose of bacterial pyrogen in young lambs. Carotid denervation eliminated the febrile, metabolic, and cardiovascular responses as compared with those observed in carotid-intact lambs. Thus, intact carotid baroreceptors and/or chemoreceptors are important for the thermoregulatory response to a small dose of bacterial pyrogen in young lambs.

Intravenous administration of 0.3 μg of SAE produced a short-lived fever of approximately 1°C in the carotid-intact lambs (Fig. 1). The increase in body core temperature was preceded by shivering—and most likely nonshivering—thermogenesis (16–18) and a resulting increase in total body oxygen consumption. Neither an increase in body core temperature, total body oxygen consumption, nor shivering were observed after the administration of bacterial pyrogen in the carotid-denervated lambs.

It is important to point out that our carotid-denervation procedure not only eliminated afferents from the carotid baroreceptors but also eliminated afferents from the carotid chemo-

Table 1. Effect of i.v. administration of 0.3 μg of SAE on systemic oxygen transport and systemic oxygen utilization in carotid-intact (CI) and carotid-denervated (CD) young lambs*

Variable	Control	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min	100 min	110 min	120 min
Total body oxygen consumption (mL/kg/min)													
CI	11.8	11.7	12.8	14.7†	14.9†	13.6	13.1	12.5	10.9	11.8	11.9	11.4	11.7
	± 3.0	± 3.5	± 3.7	± 5.8	± 5.1	± 2.6	± 2.3	± 1.0	± 3.3	± 2.7	± 2.7	± 2.8	± 2.7
CD	10.9	12.0	11.5	11.9	12.2	12.1	11.5	11.0	13.0	12.4	12.6	13.2	12.7
	± 2.6	± 2.8	± 2.3	± 2.4	± 2.0	± 2.0	± 3.2	± 3.8	± 4.4	± 3.7	±3.1	± 4.0	± 3.3
Systemic oxygen transport (mL/kg/min)													
CI	25.3	24.7	25.3	25.6	24.2	25.0	26.4	25.7	24.1	24.9	24.4	24.3	25.4
	± 6.5	± 6.7	± 6.8	± 8.5	±6.7	± 4.5	± 4.5	± 4.1	± 4.6	± 5.4	± 5.0	± 5.8	± 7.1
CD	23.6	22.9	24.2	25.2	23.0	23.6	22.3	22.1	24.3	24.2	23.4	24.8	25.6
	± 5.7	± 6.3	± 5.8	± 5.1	± 5.7	± 5.9	± 7.7	± 7.0	± 8.1	± 7.1	± 7.6	± 6.9	± 8.0
Total body oxygen extraction (%)													
CI	47.1	47.3	50.2	57.2†	60.8†	53.8	49.9	49.7	46.0	48.3	49.4	47.1	46.9
	± 5.3	± 5.5	± 5.1	± 9.8	± 9.9	± 2.4	± 5.2	± 9.9	±13.8	± 9.8	± 8.9	± 7.2	± 5.8
CD	45.4	50.6	49.6	48.0	52.8	50.0	49.1	47.0	48.7	48.4	50.5	49.3	45.1
	± 4.5	± 4.6	± 7.7	± 6.9	±11.0	± 9.0	± 8.0	± 5.5	± 6.7	± 6.8	± 7.2	± 5.9	± 5.0
Arterial oxygen content (mL/dL)													
CI	12.2‡	12.1	11.9	11.7	11.7	12.0	12.2	12.3	12.0	12.1	12.0	12.1	12.2
	± 1.4	± 1.4	± 1.6	± 1.7	± 1.6	± 1.4	± 1.4	± 1.3	± 2.0	± 1.4	± 1.6	± 1.5	± 1.4
CD	9.9‡	9.8	10.0	10.1	10.0	9.7	10.0	10.2	10.2	10.3	10.4	10.5	10.6
	± 2.9	± 2.9	± 2.6	± 2.6	± 2.7	± 2.8	± 2.6	± 2.6	± 2.7	± 2.6	± 2.6	± 2.3	± 2.3
Mixed venous oxygen content (mL/dL)													
CI	6.4	6.4	. 5.9	5.0†	4.6†	5.6	6.1	6.1	6.3	6.2	6.0	6.4	6.5
	± 0.5	± 0.6	± 0.9	± 1.5	± 1.5	± 0.8	± 0.5	± 1.0	± 1.0	± 1.1	± 1.1	± 1.1	± 0.9
CD	5.4	4.9	5.2	5.3	4.9	5.0	5.2	5.5	5.3	5.4	5.2	5.4	5.9
	± 1.6	± 1.9	± 1.8	± 2.0	± 2.4	± 2.3	± 2.1	± 1.8	± 1.9	± 1.9	± 2.0	± 1.8	± 1.7

* Values are means ± 1 SD.
† $p < 0.05$ for control vs time within a group.
‡ $p < 0.05$ for CI control vs CD control.

Table 2. *Effect of i.v. administration of 0.3 µg of SAE on cardiovascular variables in carotid-intact (CI) and carotid-denervated (CD) young lambs*

Variable	Control	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min	100 min	110 min	120 min
Cardiac index (mL/kg/min)													
CI	212‡	207	217	224	212	213	220	213	206	207	206	205	211
	± 69	± 67	± 69	± 79	± 79	± 54	± 51	± 49	± 50	± 47	± 48	± 61	± 66
CD	254‡	254	257	264	245	266	239	235	258	250	246	254	261
	± 61	± 60	± 63	± 69	± 52	± 68	± 65	± 58	± 68	± 56	± 62	± 60	± 61
Heart rate (bpm)													
CI	166	164	182	185	189†	195†	201†	192†	171	168	169	166	164
	± 49	± 37	± 41	± 44	± 52	± 38	± 39	± 39	± 33	± 37	± 40	± 36	± 36
CD	191	189	194	190	187	190	177	179	181	186	188	184	189
	± 42	± 37	± 37	± 40	± 34	± 38	± 39	± 40	± 43	± 42	± 47	± 41	± 40
Stroke volume (mL/kg)													
CI	1.33	1.26	1.23	1.21	1.14†	1.13†	1.11†	1.11†	1.23	1.27	1.26	1.29	1.31
	± 0.40	± 0.36	± 0.31	± 0.30	± 0.29	± 0.30	± 0.34	± 0.25	± 0.35	± 0.35	± 0.36	± 0.41	± 0.38
CD	1.33	1.35	1.32	1.35	1.35	1.42	1.35	1.35	1.45	1.33	1.33	1.38	1.40
	± 0.29	± 0.23	± 0.23	± 0.24	± 0.23	± 0.21	± 0.24	± 0.26	± 0.15	± 0.14	± 0.18	± 0.17	± 0.11
Systemic arterial pressure (mm Hg)													
CI	72	75	79	77	73	71	72	70	75	81	81	80	80
	± 5	± 10	± 7	± 10	± 9	± 10	± 11	± 8	± 6	± 8	± 11	± 11	± 11
CD	78	80	78	81	79	81	80	81	80	80	79	81	81
	± 7	± 6	± 8	± 6	± 6	± 5	± 7	± 9	± 10	± 10	± 10	± 11	± 8
Systemic vascular resistance (mm Hg/mL/kg/min)													
CI	0.383	0.411	0.417	0.404	0.403	0.374	0.371	0.366	0.389	0.414	0.407	0.426	0.413
	± 0.125	± 0.154	± 0.139	± 0.148	± 0.137	± 0.124	± 0.122	± 0.119	± 0.111	± 0.115	± 0.089	± 0.117	± 0.138
CD	0.322	0.332	0.323	0.325	0.333	0.333	0.358	0.362	0.338	0.350	0.350	0.348	0.340
	± 0.079	± 0.086	± 0.099	± 0.085	± 0.078	± 0.071	± 0.069	± 0.095	± 0.111	± 0.083	± 0.082	± 0.093	± 0.091
Pulmonic arterial blood pressure (mm Hg)													
CI	18‡	18	27†	32†	30†	26†	25†	22	19	25†	26†	27†	22
	± 4	± 6	± 15	± 16	± 19	± 13	± 12	± 11	± 8	± 11	± 8	± 13	± 11
CD	26‡	30	27	31	29	30	31	30	30	29	29	29	27
	± 10	± 13	± 15	± 15	± 6	± 8	± 9	± 12	± 12	± 9	± 14	± 13	± 14

* Values are means ± 1 SD.
† $p < 0.05$ for control vs time within a group.
‡ $p < 0.05$ for CI control vs CD control.

Table 3. *Influence of bacterial pyrogen and fraction of inspired oxygen on arterial blood gases and pH in carotid-intact and carotid-denervated lambs*

	Control	30 min	60 min	90 min	120 min
Carotid-intact (FIO_2 0.21; $n = 7$)					
pHa	7.41 ± 0.03	7.39 ± 0.04	7.41 ± 0.03	7.41 ± 0.04	7.40 ± 0.03
Pao_2	73 ± 6	62 ± 12	72 ± 9	74 ± 10	72 ± 11
$Paco_2$	37 ± 3	37 ± 6	37 ± 4	35 ± 4	38 ± 5
Carotid-denervated (FIO_2 0.21; $n = 6$)					
pHa	7.36 ± 0.02	7.37 ± 0.02	7.36 ± 0.01	7.37 ± 0.02	7.38 ± 0.02
Pao_2	57 ± 13	49 ± 7	55 ± 4	58 ± 8	50 ± 15
$Paco_2$	50 ± 3	54 ± 6	48 ± 9	51 ± 3	52 ± 9
Carotid-denervated (FIO_2 0.60; $n = 3$)					
pHa	7.36 ± 0.04	7.39 ± 0.07	7.41 ± 0.05	7.41 ± 0.04	7.40 ± 0.07
Pao_2	293 ± 16	311 ± 11	311 ± 27	313 ± 22	334 ± 20
$Paco_2$	41 ± 0	41 ± 2	41 ± 7	37 ± 1	41 ± 1

* Data are means ± 1 SD. FIO_2, fraction of inspired oxygen; pHa, arterial pH; Pao_2, arterial O_2 tension; and $Paco_2$ arterial CO_2 tension.

receptors. The effectiveness of our carotid-denervation procedure is proved by the following evidence. First, hypoventilation and hypoxemia were observed during resting conditions (Table 3) as compared with carotid-intact animals. Second, this procedure eliminated the early respiratory frequency response to rapidly developing hypoxemia as compared with intact animals (19).

As far as we are aware, there are no other reports in the literature regarding the influence of carotid baroreceptors and/ or chemoreceptors on the febrile response to bacterial pyrogen.

However, Gautier *et al.* (20) have shown that carotid denervation does not alter the shivering thermogenic response to cold in adult unanesthetized cats. Similarly, Blatteis (4) showed that carotid sinus nerve section does not prevent either the metabolic response to cold of neonatal rabbits or its depression by hypoxia. Furthermore, Wilson and Fyda (9) have shown that discrete bilateral lesions of the NTS influence the coregulation of nutritive and heat conserving/dissipating functions of the circulation in response to changes in the ambient temperature in rats. Although

NTS lesion has a negligible effect on the animals' ability to regulate rectal temperature over the short term, the effector mechanisms used to thermoregulate are altered. In response to a mild cold challenge (e.g. 19, 15, or 11°C), which should activate similar effector mechanisms as bacterial pyrogen, the NTS-lesioned animals show an accentuated pressor response but an attenuated metabolic response compared to sham-operated animals.

Although this study was not designed to determine the mechanism of the altered febrile response in carotid-denervated lambs, our findings allow us to rule out certain possibilities and to speculate upon the mechanism. There are at least four possibilities: the first is that arterial hypoxemia after carotid denervation diminishes the thermogenic response to bacterial pyrogen as we have previously observed in carotid-intact lambs (15); the second is that carotid denervation alters the formation of endogenous pyrogen (e.g. IL-1, tumor necrosis factor) after injection of exogenous pyrogen; the third is that carotid denervation alters the CNS response to endogenous pyrogen; and the fourth is that carotid-denervation alters the coregulation of nutritive and heat conserving/dissipating functions of the circulation such that effector mechanisms are not capable of increasing body temperature.

We believe that it is unlikely that the degree of hypoxemia observed in our animals after carotid denervation attenuated the thermogenic response to bacterial pyrogen because a fever was still not observed when three of the lambs were retested while breathing an oxygen-enriched gas mixture. Furthermore, we are unaware of any data that suggest that carotid denervation alters the formation of endogenous pyrogen after injection of exogenous pyrogen and think that it is highly unlikely to be responsible for our results. Lastly, we did not observe a change in systemic arterial blood pressure or systemic vascular resistance after injection of bacterial pyrogen in either group and thus do not think that an ineffective shift in effector mechanisms (e.g. decreased metabolic response and increased heat conserving response) is responsible for the lack of a response.

It is possible that carotid denervation alters the CNS response to endogenous pyrogen. Numerous investigations have provided evidence that both the carotid (21, 22) and aortic (23) baroreceptors reflexly affect plasma concentrations of arginine vasopressin. Furthermore, recent evidence has been provided that chronic sinoaortic denervation produces time-related, region-specific changes in brain arginine vasopressin in adult rats (24). This information, taken with the evidence that arginine vasopressin may function as an antipyretic substance in the brain (6), allows one to formulate the hypothesis that the lack of a febrile response may be due to a regional specific increase in brain arginine vasopressin concentration after chronic carotid denervation. However, this hypothesis remains to be tested. Kasting et al. (25) have provided evidence that mild hemorrhage, which results in an increased concentration of arginine vasopressin in plasma, attenuates the febrile response to bacterial endotoxin in sheep.

Pulmonary arterial blood pressure increased significantly after the administration of bacterial pyrogen in the carotid-intact lambs but not in the carotid-denervated lambs. An increase in pulmonary arterial pressure and pulmonary vascular resistance has been observed by a number of investigators after experimental sepsis (26) or after the administration of endotoxin (27, 28). Although the mechanism of the pulmonary vasoconstriction is not perfectly clear, recent data provide evidence that thromboxane A_2 plays a major role (29, 30). The most likely reason for the lack of a pulmonary vascular response after administration of bacterial pyrogen in the carotid-denervated lambs is that their pulmonary vascular bed was preconstricted by the arterial hypoxemia that followed carotid denervation.

In summary, we have shown that carotid denervation eliminates the febrile, metabolic, and cardiovascular responses to a small dose of bacterial pyrogen in young lambs. The mechanism for the altered response remains to be determined.

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