

THE PREOPTIC ANTERIOR HYPOTHALAMIC AREA MEDIATES INITIATION OF THE HYPOTENSIVE RESPONSE INDUCED BY LPS IN MALE RATS

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ABSTRACT—The mechanism responsible for the initiation of endotoxic hypotension is not fully understood, although it is often attributed to a direct effect of LPS and other vasoactive mediators on the vasculature. Alternatively, recent evidence raises the possibility that endotoxic hypotension may be initiated through a central mechanism. Previous studies have shown that LPS initiates fever, sickness behavior, and other aspects of the inflammatory response through a neural pathway that sends peripheral inflammatory signals to the preoptic anterior hypothalamic area (POA). It is also well known that the POA plays a role in the regulation of cardiovascular function, but its involvement in LPS-induced hypotension has not been examined previously. Therefore, the aim of the present paper was to investigate whether the initial abrupt fall in arterial pressure evoked by LPS in septic shock is mediated by the POA. LPS (1 mg/kg, i.v.) administration to halothane-anesthetized or conscious rats lowered arterial blood pressure by 24.8 ± 2.9 and 25.1 ± 5.8 mmHg, respectively. Bilateral lidocaine (2%; 1 μ L) injection into the POA, but not the lateral hypothalamus, prevented the hypotension evoked by LPS entirely in both anesthetized and conscious animals. Remarkably, this blockade significantly inhibited the second, delayed fall in arterial pressure induced by LPS, and simultaneously decreased TNF- α plasma levels. Together, these data indicate that the initial phase of endotoxic hypotension is mediated by the POA and suggest that the initiation of the hypotensive response induced by LPS can be essential for the development of the late fall in blood pressure.

KEYWORDS—Endotoxic shock, blood pressure, neural mechanism, lidocaine, hypothalamus

INTRODUCTION

Septic shock is a complicated medical condition that presents a challenge to both physicians and researchers. In the United States, sepsis is the 12th leading cause of death, accounting for 40,000 fatalities every year. Despite the introduction of avant-garde treatments and advances in our understanding of cellular and molecular aspects of septic shock, mortality from septic shock continues to range between 40% and 50% of cases. Recent clinical trials, targeting mediators of sepsis such as TNF- α and IL-1 β , have failed to increase the survival rate (1). Therefore, it is essential to better understand septic shock to develop new tactics for precluding its harmful effects.

The mechanism responsible for the initiation of endotoxic hypotension is not fully understood, although it is often attributed to a direct effect of LPS, a constituent of the outer wall of Gram-negative bacteria, and other vasoactive mediators such as TNF- α and NO on the vasculature (1, 2). An alternative possibility is that the initial fall in arterial pressure caused by LPS is mediated by a central mechanism. This hypothesis is supported by extensive evidence that other effects of LPS, notably fever, are mediated by the preoptic anterior hypothalamus (POA) (3). Interestingly, there is also evidence that LPS causes fever, sickness behavior, and other aspects of the inflammatory response by activating subdiaphragmatic vagal afferents (3–6). The inflammatory signal is conveyed to the nucleus of the solitary tract by vagal afferents, then to the POA via the A1/A2 noradrenergic cell groups (7, 8). Although the POA has been identified as an important site for cardiovascular regulation (9), its involvement in LPS-induced hypotension has not been examined previously.

LPS typically causes a biphasic hypotensive response in rats at doses of 1 mg/kg (i.v.) or higher. The first phase of this response starts almost immediately upon LPS administration. Arterial pressure reaches its lowest point approximately 10 min thereafter and returns toward baseline values within 30 to 40 min. The second phase of endotoxic hypotension begins approximately 1 h after LPS injection and is generally more severe and prolonged than the initial phase. The initial phase is often thought to be of little consequence and remains the least studied component of the hypotensive response during endotoxemia. Consequently, the role of the initial phase of endotoxic hypotension is uncertain, and the mechanism responsible for the biphasic nature of the response is poorly understood.

The present study examined whether endotoxic hypotension is initiated through a central mechanism. Specifically, we tested whether the POA plays an important role in the response, as it does for other effects of LPS. We found that inhibiting neuronal activity in the POA with lidocaine prevented the initial phase of LPS hypotension entirely. Moreover, lidocaine pretreatment also inhibited the second, more prolonged phase of endotoxic hypotension and, at the same time, decreased TNF- α plasma levels. These data indicate that endotoxic hypotension is initiated through a central mechanism and further suggest that the early fall in blood pressure can play an important role in the progression

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of the lethal hypotension that typifies the second phase of septic shock. On the other hand, the POA may initiate a series of events that results in late hypotension dependent or independent of the early hypotension.

MATERIALS AND METHODS

Male Sprague-Dawley rats (250–300 g; Charles River Laboratories, Wilmington, Mass) were anesthetized with 4% halothane and maintained with 1.5% halothane in 100% O₂. The left femoral artery and left jugular vein were each cannulated with PE-50 tubing filled with heparinized saline (100 U/mL) to record arterial pressure and peripherally administer drugs, respectively. The animal protocols were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The study was approved by our Institutional Animal Care and Use Committee.

At the beginning of each experiment, the arterial cannula was connected to a volumetric pressure transducer. Blood pressure and heart rate were monitored and recorded using a MicroMed BPA-200 blood pressure analyzer (MicroMed, Louisville, Ky). Anesthetized rats were mounted in a stereotaxic frame, and lidocaine (2% wt/vol, 1.0 μ L; Sigma Chemical Co., St. Louis, Mo) or saline (1.0 μ L) was injected bilaterally into the POA with a Hamilton microsyringe (model 62; Hamilton Co., Reno, Nev) lowered at a 15-degree angle to a site 3 mm lateral and 0.3 mm caudal from bregma with a depth of 8.6 mm below the dural surface according to the atlas of Paxinos and Watson (10). In control experiments, lidocaine or saline was injected bilaterally into the tuberal zone of lateral hypothalamus (LH) 1.7 mm lateral and 3.3 mm caudal from bregma to a depth of 9.0 mm below the dural surface. Lidocaine was dissolved in saline containing

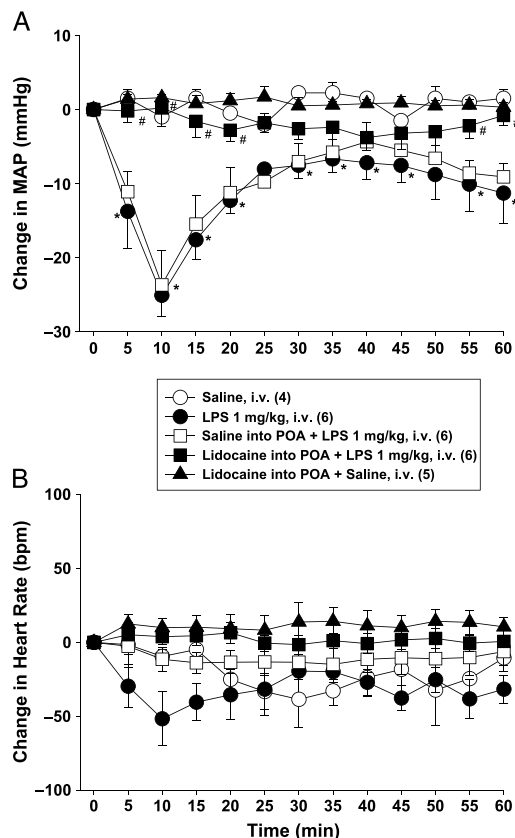


FIG. 1. Bilateral lidocaine injection into the POA inhibits the hypotension produced by i.v. LPS injection. Lidocaine (2%; 1 μ L) was injected into the POA 2 min before LPS (1 mg/kg, i.v.) injection. MAP and heart rate were monitored for 60 min. Data are presented as the mean \pm SEM change in MAP or heart rate. Baseline MAP values were saline, 108.8 \pm 3.1 mmHg; LPS, 110.1 \pm 2.2 mmHg; POA saline + LPS, 106.1 \pm 2.7 mmHg; POA lidocaine + LPS, 110.7 \pm 3.5 mmHg; POA lidocaine + saline, 109.1 \pm 2.8 mmHg. Statistical analysis was performed using two-way repeated-measures ANOVA and then Tukey post hoc test. * P < 0.05, significantly different from the i.v. saline group. # P < 0.05 significantly different from the POA saline plus LPS group.

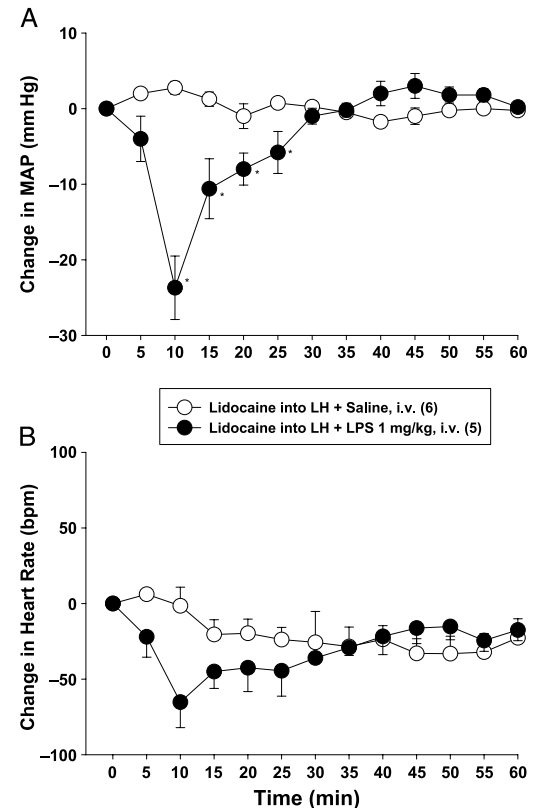


FIG. 2. Bilateral lidocaine injection into the LH does not inhibit the hypotension produced by i.v. LPS injection. Lidocaine (2%; 1 μ L) was injected into the LH 2 min before LPS (1 mg/kg, i.v.) injection. MAP and heart rate were monitored for 60 min. Data are presented as the mean \pm SEM change in MAP or heart rate. Baseline MAP values were LH lidocaine + saline, 107.1 \pm 1.3 mmHg; LH lidocaine + LPS, 108.7 \pm 2.9 mmHg. Statistical analysis was performed using two-way repeated-measures ANOVA and then Tukey post hoc test. * P < 0.05, significantly different from the LH lidocaine + saline group.

0.2% wt/vol Chicago Sky Blue dye (Sigma) to mark injection sites and was delivered at a constant rate over a 1-min period. Two minutes after lidocaine or saline injection rats were given an i.v. injection of LPS (1 mg/kg, from *Escherichia coli* O55:B5; Sigma) in a volume of 0.3 mL or saline (1 mL/kg), and arterial pressure and heart rate were recorded at 1-min intervals for 60 or 120 min.

At the end of the experiment, each rat was killed with an overdose of halothane, the brain was removed, frozen on dry ice, and sections (50 μ m) were cut with a microtome cryostat (model 505E; Microm, Waldorf, Germany). Sections were mounted on slides, stained with eosin, air-dried and coverslipped, and the location of the cannula tip within the medial POA was confirmed. Only data from confirmed preoptic placement of the cannulas were included in this report.

To assess the role anesthesia played in decreasing blood pressure, experiments were also performed in conscious rats. Under halothane anesthesia, the left common carotid artery and left jugular vein of rats were cannulated with PE-50 tubing filled with heparinized saline (100 U/mL). During the arterial cannulation procedure, the vagus nerve and the cervical sympathetic trunk were separated with care to ensure the integrity of these nerves. The catheters were exteriorized at the nape of the neck and sealed until use. For POA injections, two 26-gauge guide cannulas were implanted bilaterally above the POA at a 15-degree angle through burr holes drilled through the skull. The tips of the cannulas were positioned 3.0 mm lateral and 0.3 mm posterior to bregma and 7.6 mm below the skull surface (10). At the end of the surgical procedures, rats were placed in individual cages and allowed to recover from anesthesia for 4 to 5 h. During this period, the rats remained calm and showed no evidence of pain or distress. Arterial cannulas were then connected to the blood pressure analyzer and monitored until stable baseline blood pressure and heart rate measurements were obtained. Two 33-gauge injection cannulas were then inserted through each guide cannula to a depth of 1.0 mm below the tip of the guide cannula, and lidocaine (2% wt/vol) or saline was injected bilaterally. For conscious animals, the rest of the experiments were carried out as described above.

Blood (200 μ L) was collected 0, 10, 60, and 120 min after LPS injection for TNF- α measurements. Blood samples were centrifuged to separate serum and frozen at 50°C until analyzed. Serum TNF- α was measured with an enzyme immunometric

assay kit (TNF- α [rat] enzyme immunoassay kit no. 900-086; Assay Designs, Inc., Ann Arbor, Mich) according to the manufacturer's instructions. After samples and standards were added to wells, plates were incubated for 1 h at 37°C. Wells were washed seven times with wash solution, at which point, antibody was added to each well (except the blank) and incubated for 30 min at 4°C. After two additional wash procedures, substrate solution was added to each well, and plates were further incubated for 30 min at room temperature in the dark, at which point, stop solution was added to all wells. A UV spectrophotometer (model Ceres UV900 HDI; Bio-Tek Instruments, Inc., Winooski, Vt) was used to read plates at 450 nm.

Data are presented as mean \pm SEM and were analyzed by two-way ANOVA and then Tukey multiple comparison test using SigmaStat 3.0 (SPSS, Chicago, Ill). A two-sided P value of less than 0.05 was considered significant.

RESULTS

In the first experiment, we tested the effect of LPS (1 mg/kg, i.v.) on arterial blood pressure. As shown in Figure 1A, LPS injection reduced MAP significantly within 10 min (25.1 ± 5.7 mmHg) ($P < 0.001$) in halothane-anesthetized rats. The depressor response was transient, and arterial pressure returned approximately to baseline values within 30 min. LPS administration also lowered heart rate (from 354 ± 13.9 to 301 ± 20.3 bpm in 10 min), although the response was not statistically significant (Fig. 1B).

Subsequently, we investigated whether inhibiting neuronal activity in the POA with lidocaine would prevent LPS-induced hypotension. Bilateral lidocaine injection (1.0 μ L of

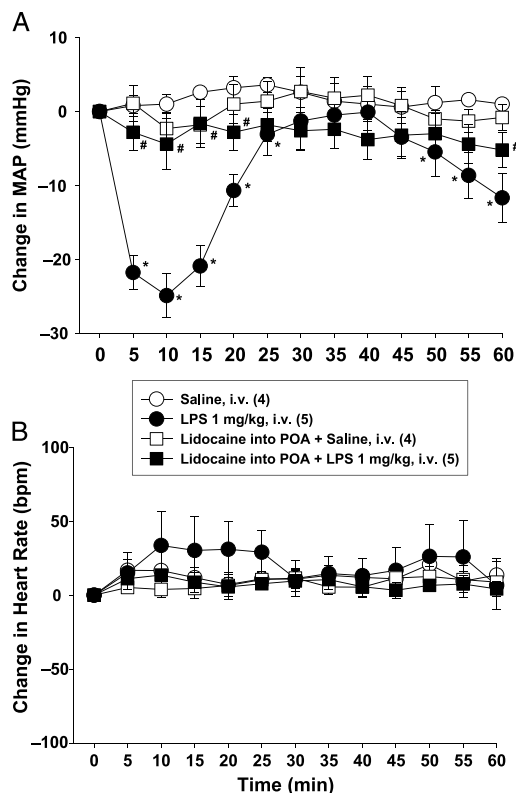


FIG. 3. Bilateral lidocaine injection into the POA inhibits the hypotension produced by i.v. LPS injection in conscious rats. Lidocaine (2%; 1 μ L) was injected into the POA 2 min before LPS (1 mg/kg, i.v.) injection. MAP and heart rate were monitored for 60 min. Data are presented as the mean \pm SEM change in MAP (A) or heart rate (B). Baseline MAP values were saline, 125.3 ± 4.4 ; LPS, 127.7 ± 5.6 mmHg; POA lidocaine + saline, 129.7 ± 5.1 ; POA lidocaine + LPS, 130.3 ± 6.5 mmHg. Statistical analysis was performed using two-way repeated-measures ANOVA and then Tukey post hoc test. * $P < 0.05$, significantly different from the saline group. # $P < 0.05$, significantly different from the LPS group.

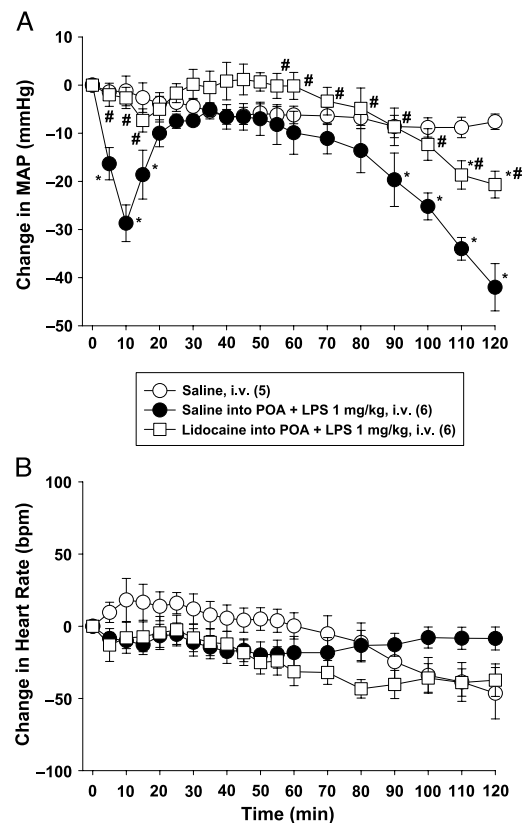


FIG. 4. Bilateral lidocaine injection into the POA attenuates the development of the second phase of LPS-evoked hypotension. Lidocaine (2%; 1 μ L) was injected into the POA 2 min before LPS (1 mg/kg, i.v.) injection. MAP and heart rate were monitored for 120 min. Data are presented as the mean \pm SEM change in MAP or heart rate. Baseline MAP values were POA saline + LPS, 110.8 ± 2.1 mmHg; POA lidocaine + LPS, 112.0 ± 3.2 mmHg. Statistical analysis was performed using two-way repeated-measures ANOVA and then Tukey post hoc test. * $P < 0.05$, significantly different from the saline group. # $P < 0.05$, significantly different from the POA saline + LPS group.

a 2% wt/vol solution) into the POA prevented the hypotension evoked by i.v. LPS (Fig. 1A). ANOVA confirmed that lidocaine inhibited LPS-induced hypotension significantly ($F_{1,7} = 17.2$; $P < 0.01$). Lidocaine administration also prevented LPS-induced bradycardia, although the effect was not significant statistically (Fig. 1B). Lidocaine did not affect arterial pressure or heart rate when microinjected into the POA of control animals that received i.v. saline (Fig. 1). These data indicated that inhibition of neuronal activity in the POA prevents LPS-induced hypotension in anesthetized animals.

As a positive control, we injected lidocaine into the tuberal region of the LH. Bilateral lidocaine injection (1.0 μ L of a 2% solution) into the LH did not prevent the fall in blood pressure induced by LPS (1 mg/kg, i.v.). Arterial pressure decreased 21.8 ± 4.2 mmHg from baseline values within 5 min after 1 mg/kg LPS injection, approximately the same as it did in controls (Fig. 2A). Heart rate was similarly unaffected (Fig. 2B). Bilateral lidocaine injection into the LH of control animals that received saline in lieu of LPS had no effect on MAP or heart rate (Fig. 2). These data indicate that LPS hypotension is mediated by the POA, but not the LH. Interestingly, postmortem histological verification of lidocaine

injection sites showed that three injections erroneously placed approximately 1 mm above the POA also failed to inhibit LPS hypotension, again suggesting that the POA is an important site for cardiovascular regulation after LPS administration.

We also investigated whether lidocaine injection into the POA was effective in conscious animals. LPS (1 mg/kg, i.v.) administration lowered MAP to approximately the same extent in conscious (24.8 ± 2.9 mmHg) (Fig. 3A) and anesthetized (25.1 ± 5.7 mmHg) (Fig. 1A) rats, although blood pressure fell more rapidly in conscious animals (Figs. 1A, 2A, and 3A). As shown in anesthetized rats, the depressor response was transient, and arterial pressure returned approximately to baseline values within 28 min. Bilateral lidocaine injection (1.0 μ L of a 2% wt/vol solution) into the POA significantly inhibited ($F_{12,108} = 7.9$; $P < 0.001$) the hypotension evoked by i.v. LPS in conscious animals (Fig. 3A), as it did in anesthetized animals (Fig. 1A). Lidocaine had no effect on arterial pressure or heart rate when microinjected into the POA of conscious animals that received saline i.v. in lieu of LPS (Fig. 3). LPS administration elevated heart rate (from 323 ± 7.8 to 356 ± 10.2 bpm in 10 min) (Fig. 3B), in contrast to the slight bradycardia evoked in anesthetized rats (Figs. 1B and 2B), although the response was not significant statistically in either conscious or anesthetized animals. These data show

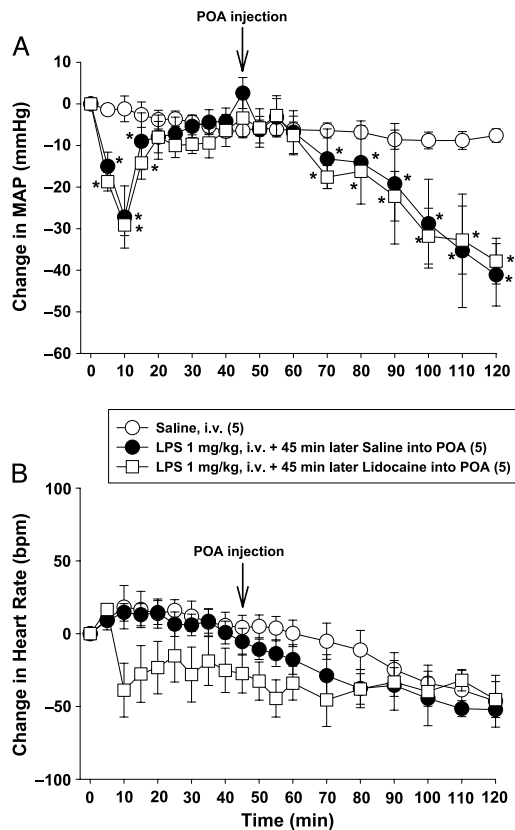


FIG. 5. Bilateral lidocaine injection into the POA 45 min after LPS injection did not block development of the second phase of hypotension. Lidocaine (2%; 1 μ L) was injected into the POA 45 min after LPS (1 mg/kg, i.v.). MAP and heart rate were monitored for 120 min. Data are presented as the mean \pm SEM change in MAP or heart rate. Baseline MAP values were POA saline + LPS, 117.8 ± 3.3 mmHg; POA lidocaine + LPS, 115.1 ± 4.2 mmHg. Statistical analysis was performed using two-way repeated-measures ANOVA and then Tukey post hoc test. * $P < 0.05$, significantly different from the saline group.

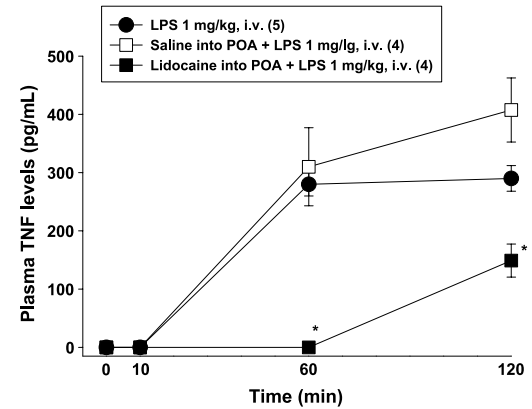


FIG. 6. Bilateral lidocaine injection into the POA attenuates the increase in plasma TNF- α concentrations induced by LPS. Lidocaine (2%; 1 μ L) was injected into the POA 2 min before LPS (1 mg/kg, i.v.) injection. Blood samples were collected at 0, 10, 60, and 120 min. TNF levels at 0 and 10 min were undetectable for all groups and at 60 min for POA lidocaine + LPS group. Data are presented as the mean \pm SEM. Statistical analysis was performed using two-way repeated-measures ANOVA and then Tukey post hoc test * $P < 0.05$, significantly different from the POA saline + LPS group.

that halothane anesthesia produces small changes in the response to LPS but demonstrate that the ability of lidocaine to prevent LPS hypotension is not an artifact of anesthesia.

We then investigated whether lidocaine pretreatment would prevent the second, late developing phase of LPS hypotension. Once again, LPS injection reduced MAP significantly within 10 min, and as before, the response was transient, and arterial pressure returned to baseline values within 30 min. Subsequently, MAP began to fall for a second time, reaching -42.2 ± 4.9 mmHg within 120 min (Fig. 4A). As shown previously, bilateral microinjection of lidocaine into the POA prevented the initial fall in blood pressure. Moreover, lidocaine pretreatment also attenuated the second hypotensive state induced by LPS significantly ($F_{1,10} = 81.3$; $P < 0.001$) (Fig. 4A). By contrast, lidocaine did not significantly affect heart rate in these experiments (Fig. 4B). These data suggest that inhibiting the initial fall in arterial pressure caused by LPS also inhibits the second phase of hypotension that otherwise ensues.

One alternative explanation for this finding is that both the first and second phase of LPS hypotension are mediated by the POA. To test this possibility, we injected lidocaine into the POA 45 min after LPS, just before the second phase of LPS hypotension normally begins. We found that when lidocaine was administered 45 min after LPS, it had no effect at all on the second, late phase of hypotension (Fig. 5A). Heart rate was similarly unaffected (Fig. 5B).

Finally, we measured TNF- α concentrations to determine whether there was a temporal correlation between plasma TNF- α and arterial blood pressure. TNF- α was undetectable in plasma from control animals (detection limit, 20 pg/mL) and remained less than the detection limit of the assay 10 min after LPS (1 mg/kg, i.v.) administration. Plasma TNF- α concentrations increased to approximately 300 to 400 pg/mL 60 min after LPS administration and remained at approximately the same level at the 120-min time point. Lidocaine injection into the POA immediately before LPS administration prevented the LPS-induced rise in plasma TNF- α levels

completely at the 60-min time point. Plasma TNF- α increased during the second hour after LPS treatment in lidocaine-pretreated rats but remained significantly less than plasma levels of saline-treated control animals (Fig. 6).

DISCUSSION

The results of the present study show that inhibition of neuronal activity in the POA with lidocaine completely blocked the initial fall in arterial pressure evoked by LPS in both conscious and halothane-anesthetized rats. Interestingly, this blockade also attenuated development of the second, lethal fall in arterial pressure induced by LPS and inhibited the rise in plasma TNF- α levels. Taken together, these data indicate that the initial phase of endotoxic hypotension is mediated by a neural mechanism that involves the POA. Notably, the data also show that the initial phase of LPS hypotensive is an essential prelude for development of the later, second fall in blood pressure evoked. Nevertheless, the second phase of LPS-induced hypotension does not seem to be mediated directly by the POA. This conclusion is based on the finding that microinjection of lidocaine into the POA 45 min after LPS administration failed to prevent development of the second hypotensive response. Alternatively, the POA may initiate a signaling cascade that results in the second phase of hypotension independent of the initial hypotension caused by LPS. In either case, these findings show that the POA plays a pivotal role in the profound hypotension that leads to septic shock.

The POA is an important site for coordination of the inflammatory response, although its involvement in LPS-induced hypotension has not been examined previously. It has been known for some time that electrical or chemical stimulation of the POA lowers arterial pressure and heart rate and facilitates the baroreflex response in anesthetized animals (11–13). The finding that lidocaine inhibited LPS hypotension without affecting arterial pressure or heart rate in control animals indicates that the POA participates in septic shock but may not be critical for the normal regulation of cardiovascular homeostasis. Anatomical tract tracing studies support a role for the POA in cardiovascular regulation, showing that POA neurons innervate the nucleus tractus solitarius, parabrachial nucleus, midbrain periaqueductal gray (PAG), and other brain regions that regulate cardiovascular function (14). The POA projection to the PAG seems to be particularly important. Selective destruction of neuronal cell bodies in the ventrolateral column of the PAG (vlPAG) with kainic acid (13) or inhibition of neuronal activity in the vlPAG with lidocaine (11) prevents the fall in arterial pressure evoked by POA stimulation. Destruction of neurons in the nucleus raphe magnus is also effective (13), consistent with evidence that the vlPAG can influence cardiovascular function through a descending pathway that involves the midline raphe nuclei and ventrolateral medulla (15). In either case, experiments in which POA neurons are activated chemically or electrically tell us nothing about the physiological stimuli that normally activate the POA. Hence, the present results are important to the extent that they provide evidence for a physiological role for the POA in cardiovascular regulation during septic shock.

One caveat to this conclusion is that these experiments were conducted under halothane anesthesia, which may have influenced the experimental outcome. We examined this possibility by conducting parallel experiments in conscious animals. We found that LPS lowered arterial pressure to approximately the same extent in both conscious and anesthetized rats. Moreover, bilateral lidocaine injection into the POA inhibited LPS-induced hypotension in conscious rats, much as it did in halothane-anesthetized animals. Thus, inhibition of neuronal activity in the POA inhibits LPS hypotension in both conscious and anesthetized animals.

Notably, the present results show that lidocaine injection into the POA attenuates the late fall in arterial blood pressure and prevents the rise in plasma TNF- α concentrations normally produced by LPS. TNF- α is an essential mediator of endotoxemia, which initiates a series of biochemical and immunological responses that culminate in lethal hypotensive shock (2). TNF- α lowers blood pressure primarily by activating inducible NO synthase that causes vasodilation by generating NO (16, 17). The finding that plasma TNF- α concentrations were elevated within 60, but not 10 min, after LPS administration is consistent with our earlier finding that a substantially lower dose of LPS (2 $\mu\text{g}/\text{kg}$, i.v.) elevated plasma TNF- α slightly 30 min and maximally 60 min after injection (18). In contrast to the present data, however, plasma TNF- α levels returned toward baseline values within 90 min after 2 $\mu\text{g}/\text{kg}$ LPS administration (18). Hence, TNF- α release is correlated with the late, sustained (i.e., after ~ 30 min) hypotension that occurs during endotoxemia, but it does not adequately explain the initial fall in arterial pressure that occurs within minutes of LPS administration.

The finding that inhibition of neuronal activity in the POA with lidocaine attenuates the rise in plasma TNF- α evoked by LPS is consistent with earlier reports that central administration of α -melanocyte-stimulating hormone (19) or nonsteroidal anti-inflammatory drugs (20) inhibits cytokine-induced cutaneous inflammation, presumably, by activating sympathetic neurons (21, 22). Activation of vagus nerve efferents also inhibits systemic inflammation. Electrical stimulation of the vagus nerve or central administration of the anti-inflammatory drug CNI-1493 attenuates LPS-induced TNF- α release and prevents the development of endotoxin-induced septic shock (23, 24). It is therefore plausible to hypothesize that the POA can play an important role in controlling the efferent mechanisms that mediate the release of TNF- α during endotoxic shock.

It remains to be determined exactly how LPS activates neurons in the POA. One possibility is that LPS stimulates release of TNF- α or other cytokines, and the vagus nerve conveys the immunological message to the brain. This idea is supported by evidence that subdiaphragmatic vagotomy inhibits other centrally mediated effects of LPS and other immune modulators, including sickness behavior, fever, and adrenocorticotrophic hormone release (4, 5, 8). Moreover, Mailman (25) reported that LPS-induced hypotension can be attenuated by applying lidocaine or resiniferatoxin (which inhibits afferent, but not efferent, impulse flow) to the abdominal vagus nerve. These findings are consistent with

the hypothesis that LPS lowers arterial pressure by activating vagus nerve afferents, although it is difficult to envision the precise mechanism whereby LPS might activate the vagus. The response can be mediated by TNF- α , but, as discussed previously, LPS lowers arterial pressure within minutes of injection, far too soon to be simply explained by the appearance of TNF- α in the general circulation, which is not detectable until at least 30 min later. Nevertheless, it is conceivable that LPS induces TNF- α release locally, and that high TNF- α concentrations in the vicinity of the vagus nerve stimulate cognate receptors on vagus nerve afferents that rapidly convey their messages to the POA well before TNF- α is detectable in the general circulation.

The role of the POA in the thermoregulation has been studied extensively. LPS administration to laboratory animals produces fever at low doses, mild hypothermia and then fever at intermediate doses, and pronounced hypothermia at higher doses, including those capable of lowering arterial blood pressure (1, 26). LPS is thought to produce fever by stimulating cytokine release from macrophages and other immune cells that influence thermosensitive neurons in the POA. Traditionally, cytokines were thought to act directly on or near the POA, although more recent data indicate that cytokines may also influence POA neurons indirectly by activating vagus nerve afferents (27). Considerably less is known about the mechanism responsible for the hypothermia caused by high-dose LPS. Based on the present data, it is tempting to speculate that the effects of LPS on body temperature and arterial blood pressure are mediated by the POA, perhaps through the same or a similar mechanism. This speculation is consistent with a report that inhibiting neuronal activity in the POA prevents the hypothermia associated with hemorrhage, for example (28). However, recent data indicate that bilateral electrolytic lesions of the POA fail to prevent LPS-induced hypothermia and suggest instead that the effect is mediated by the dorsomedial nucleus of the hypothalamus (26). Hence, the role of the POA in coordinating the thermoregulatory and cardiovascular effects of LPS, if any, remains to be fully elucidated.

In conclusion, the present study shows that the initial phase of endotoxic hypotension is mediated by a central mechanism that includes the POA. The data further suggest that the initial transient phase of LPS hypotensive is essential for the development of the later, more severe, fall in arterial blood pressure, although, alternatively, the POA can also produce the late phase of hypotension by initiating a signaling cascade independent of the early hypotension. These novel findings may help to better understand the mechanisms of endotoxic hypotension.

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