Vagal modulation of intestinal afferent sensitivity to systemic LPS in the rat


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Liu CY, Mueller MH, Grundy D, Kreis ME. Vagal modulation of intestinal afferent sensitivity to systemic LPS in the rat. Am J Physiol Gastrointest Liver Physiol 292: G1213–G1220, 2007.—The central nervous system modulates inflammation in the gastrointestinal tract via efferent vagal pathways. We hypothesized that these efferents receive synaptic input from vagal afferents, representing an autonomic feedback mechanism. The consequence of this vagovagal reflex for afferent signal generation in response to LPS was examined in the present study. Different modifications of the vagal innervation or sham procedures were performed in anesthetized rats. Extracellular mesenteric afferent nerve discharge and systemic blood pressure were recorded in vivo before and after systemic administration of LPS (6 mg/kg iv). Mesenteric afferent nerve discharge increased dramatically following LPS, which was unchanged when vagal efferent traffic was eliminated by acute vagotomy. In chronically vagotomized animals, to eliminate both vagal afferent and efferent traffic, the increase in afferent firing 3.5 min after LPS was reduced to 3.2 ± 2.5 impulses/s above baseline compared with 42.2 ± 2.0 impulses/s in controls (P < 0.001). A similar effect was observed following perivagal capsaicin, which was used to eliminate vagal afferent traffic only. LPS also caused a transient hypotension (<10 min), a partial recovery, and then persistent hypertension that was exacerbated by all three procedures. Mechanosensitivity was increased 15 min following LPS but had recovered at 30 min in all subgroups except for the chronic vagotomy group. In conclusion, discharge in capsaicin-sensitive mesenteric vagal afferents is augmented following systemic LPS. This activity, through a vagovagal pathway, helps to attenuate the effects of septic shock. The persistent hypersensitivity to mechanical stimulation after chronic vagal denervation suggests that the vagus exerts a regulatory influence on spinal afferent sensitization following LPS.

DEFENCE MECHANISMS against infectious agents entering the gastrointestinal tract are crucial to ensure the organism’s well-being and survival. The physiological response to pathogenic agents is orchestrated by an extensive network of immune cells in the gut wall. Differential cytokine release from macrophages mediates and modulates the inflammatory response and associated sickness behavior, cardiovascular responses, and paralytic ileus (5, 8, 34). The magnitude of the cytokine response must balance defense against harmful infections with maintenance of physiological function and nutrient assimilation. Thus, the regulation of the inflammatory response is of major importance following infection and depends not only on humoral factors but also on the autonomic nervous system (36).

The afferent vagus is activated following bacterial infection of the gastrointestinal tract (9, 12). One likely mechanism is that LPS, which forms part of the bacterial cell wall of gram-negative bacteria, interacts with macrophages and dendritic cells in the vicinity of afferent vagal nerve endings, triggering the release of IL-1β (13), which has the potential to stimulate vagal afferents (7, 29). Furthermore, there is recent evidence that LPS may sensitize vagal afferents directly via Toll-like receptor 4, which is expressed in the nodose ganglion (19). Subsequent central activation of vagal nuclei in the brain stem was observed following LPS exposure that was dependent on an intact vagal afferent pathway (11). Moreover, it appears from our own recent work that the afferent nerve response to LPS not only involves increased firing of intestinal afferents but also a transient hypersensitivity to mechanical stimuli that is dependent on cyclooxygenase 2 and downregulated by a mechanism involving nitric oxide (NO) (24).

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MATERIALS AND METHODS

Surgical Procedures

All procedures were performed in male Wistar rats (300–400 g) under pentobarbitone anesthesia (60 mg/kg ip). Animals were withdrawn from solid food but had free access to water for 12 h prior to surgery. Institutional guidelines for the use and care of laboratory animals were followed throughout the study.

Chronic vagotomy. To eliminate the afferent and efferent vagal innervation of the jejunum, subdiaphragmatic vagotomy was performed 1 wk before afferent recordings were made. Following general anaesthesia, animals underwent a laparotomy. The subdiaphragmatic branches of the vagal nerve were then identified at the abdominal esophagus and cut under sterile conditions. Gastric emptying was subsequently secured by a pyloroplasty. In control animals (sham operation), a pyloroplasty was also performed, and the subdiaphragmatic vagal nerve was dissected free but not cut. The time interval of 7 days between the vagotomy and afferent nerve recordings was chosen according to a previous study (23) to allow degeneration of the efferent and afferent vagal fibers innervating the jejunum after they had been cut.

Acute vagotomy. This procedure was performed in acutely anesthetized animals just prior to securing the mesenteric afferent bundles for recording (see Afferent Nerve Recordings). As described above, the dorsal and ventral vagal branches were cut below the diaphragm to eliminate efferent vagal traffic from the brain to the small intestine, while afferent traffic peripheral to the section was preserved for the relatively short recording period (<2 h). The subdiaphragmatic vagus was dissected but not cut during the sham operation, which was performed in control animals.

Perivagal capsaicin. One week prior to afferent mesenteric recordings, a subgroup of animals received perivagal capsaicin treatment. For this, animals were anesthetized with pentobarbitone (60 mg/kg ip), and the left and right cervical vagal trunks were exposed. A strip of cotton wool soaked in capsaicin (1 mg/ml) was placed around the exposed nerve trunks for 30 min before the nerve trunks were thoroughly rinsed with isotonic saline. The rationale for this procedure was to defunctionalize the afferent vagus while preserving efferent vagal fibers (16, 31). In control

Table 1. Arterial blood pressure at baseline in the different subgroups

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<tr>
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<th>Acute Vagotomy</th>
<th>Chronic Vagotomy</th>
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<tbody>
<tr>
<td>Vagotomy</td>
<td>Blood pressure, mmHg</td>
<td>120.9±3.7</td>
<td>125.0±4.1</td>
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<tr>
<td>Sham</td>
<td></td>
<td>123.5±2.9</td>
<td>125.3±4.3</td>
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<tr>
<td>Vagotomy</td>
<td></td>
<td>125.0±4.1</td>
<td>125.3±4.3</td>
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<tr>
<td>Sham</td>
<td></td>
<td>120.9±3.7</td>
<td>125.0±4.1</td>
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Values are means ± SE.
animals, cervical vagi were treated with capsaicin vehicle only (10% Tween 80 in olive oil).

**Afferent Nerve Recordings**

General anesthesia was induced by an intraperitoneal injection of pentobarbitone sodium (60 mg/kg) and continued by an intravenous perfusion (0.5–1 mgkg$^{-1}$·min$^{-1}$). The trachea was intubated with a small tube (length: 1.5–2 cm) to facilitate spontaneous respiration. The right internal jugular vein was cannulated to allow the administration of anesthetic, and the left common carotid artery was cannulated to record arterial blood pressure online (transducer: DT-XX, Ohmeda; amplifier: Neurolog Pressure Amplifier NL108, Digitimer, Welwyn Garden City, UK). Body temperature was monitored with a rectal thermometer and maintained at 37°C with a heating table. Following a midline laparotomy, the abdominal wall was sutured to a steel ring with a diameter of 5 cm to form a well that was subsequently filled with prewarmed (37°C) light liquid paraffin. The cecum was then excised to increase space in the abdominal cavity. A 10-cm loop of the proximal jejunum was isolated and cannulated at both ends. The oral cannula remained open, serving as a drain to minimize potential changes in intraluminal pressure secondary to motor activity or secretion in the intestinal loop during the time-course experiments (described below). To enable mechanical distension, the oral cannula was connected to a pump-driven syringe delivering saline into the jejunal loop at the constant rate of 1 ml/min until a distending pressure of 60 cmH$_2$O was reached. The pressure was monitored by a pressure transducer connected to the distal cannula (Neurolog pressure amplifier NL 108, Digitimer).

A single mesenteric arcade 5–7 cm distal to the ligament of Treitz was placed on a black perspex platform. One of the paravascular nerve bundles was dissected from the surrounding tissue and severed 1–1.5 cm distal to the intestine to eliminate efferent nerve activity. It was then attached to one arm of a pair of platinum electrodes with a strand of connective tissue wrapped around the other to act as a differential. Electrodes were connected to a Neurolog Headstage (Neurolog NL 100). The signal was amplified (Neurolog NL 104) and filtered (Neurolog NL 125, all CED). The neurogram was displayed on a storage oscilloscope (TDS 310, Tektronix, Cologne, Germany) and relayed to a 1401 plus interface (CED) together with the signals from the arterial and intrajejunal pressure transducers. Signals were additionally recorded online by Spike 2 software (CED) running on a personal computer. Recordings were stored on the computer’s hard drive and downloaded to a CD-ROM later.

Once the electrophysiological recording from a mesenteric afferent nerve bundle was established, the preparation was left untouched for 30 min to allow stabilization of baseline activity. Two different experimental protocols were then run in subgroups of animals undergoing previous acute vagotomy, chronic vagotomy, perivagal capsaicin treatment, or sham treatment (12 subgroups; see below).

**Time-course study.** LPS from *Escherichia coli* was given intravenously over a period of ~3 min (6 mg/kg in 1 ml). Arterial blood pressure and mesenteric afferent nerve discharge were monitored for 120 min after the injection of LPS (6 subgroups: acute vagotomy/sham-operated controls, chronic vagotomy/sham-operated controls, and perivagal capsaicin/sham-treated controls).

**Mechanosensitivity following systemic LPS.** In these experiments, LPS was administered as described for the time-course experiments. In addition, a ramp distension of the intestinal loop was performed up to 60 cmH$_2$O intraluminal pressure before LPS treatment and at 15-min intervals following its administration (6 subgroups: acute vagotomy/sham-operated controls, chronic vagotomy/sham-operated controls, and perivagal capsaicin/sham-treated controls).

**Data Analysis**

Afferent neurograms were analyzed using Spike 2 software (CED) to count the total numbers of action potentials crossing a preset threshold in sequential time bins. Mean baseline values for each of the measured variables of afferent activity (in spikes/s), intrajejunal pressure (in cmH$_2$O), and blood pressure (in mmHg) were determined over a 30-s period before any treatment. For the time course experiments, these parameters were assessed at 30 s and then in 1-min intervals until 5.5 min. Assessment was continued at 7.5 min and then at 5-min intervals from 10 to 30 min and

![Fig. 2. Time course of the blood pressure response to systemic administration of LPS (6 mg/kg) with the pretreatment of chronic vagotomy (A), acute vagotomy (B), or perivagal capsaicin (C). #P < 0.05 and ##P < 0.01 between pretreated and control groups.](http://ajpgi.physiology.org/.../V102/v102n03/V10203h01.jpg)
in 10-min intervals from 30 to 120 min after the administration of LPS. Responses to distension were determined by quantifying the firing frequency over a 3-s period at 10-cmH₂O increments of intrajejunum pressure. The baseline firing before distension was subtracted to provide values for the increase in discharge in response to distension. Data are presented as arithmetic means ± SE from 5 animals per experimental or control group. Where n values are given, they refer to the numbers of animals. Significant differences between group means were determined using one-way ANOVA followed by Dunnett’s test. A probability of P < 0.05 was considered to be indicative of a statistically significant difference.

**Chemicals**

LPS (E. coli 026:B6), Tween 80 (Roth, Karlsruhe, Germany) and capsaicin (8-methyl-N-vanillyl-monanamide) were purchased from Sigma (Munich, Germany).

**RESULTS**

**Cardiovascular Response to Systemic LPS**

**Systemic blood pressure at baseline.** The systemic blood pressure was similar in all of the experimental groups (Table 1).

**Blood pressure response to LPS.** The administration of systemic LPS (6 mg/kg iv) was followed by a decrease in arterial blood pressure with a nadir at 3.5 min after its administration and a subsequent plateau phase of reduced blood pressure compared with baseline (Fig. 1). While the biphasic pattern of this cardiovascular response was similar in all subgroups, the magnitude of the blood pressure decrease was variable. In chronically vagotomized animals, the initial drop in systemic blood pressure at 3.5 min following LPS administration was 88.5 ± 4.3 mmHg compared with 64.4 ± 6.2 mmHg in sham-operated controls (P < 0.01). After 120 min, the blood pressure had plateaued at a level 3.9 mmHg below baseline, and this was significantly greater than that in the sham-treated group, 26.0 ± 3.4 mmHg (P < 0.05; Figs. 2A and 3). In acutely vagotomized animals, the fall in systemic blood pressure compared with control animals was 16.8 ± 8.2 versus 30.3 ± 8.3 mmHg at 3.5 min (P > 0.05) and 41.5 ± 7.0 versus 20.7 ± 3.4 mmHg at 120 min (P < 0.05; Figs. 2B and 3), whereas capsaicin-pretreated animals showed an initial fall in blood pressure of 87.4 ± 10.5 mmHg compared with 50.5 ± 9.1 mmHg in sham-treated animals at 3.5 min (P < 0.05) and 38.6 ± 5.4 mmHg compared with 21.7 ± 7.6 mmHg in sham-treated animals at 120 min (P < 0.05; Figs. 2C and 3).

**Afferent Nerve Response to Systemic LPS**

**Afferent discharge at baseline.** Baseline afferent nerve discharge did not differ in the different subgroups investigated (Table 2).

**Mesenteric afferent nerve response to systemic LPS.** Mesenteric afferent discharge increased within 10 min following systemic administration of LPS and continued to rise until the end of the 2-h observation period. In chronically vagotomized animals, the afferent nerve discharge initially increased by 3.2 ± 2.5 impulses/s compared with 42.2 ± 2.0 impulses/s in sham-operated controls at 3.5 min following LPS (P < 0.001), whereas this rise in afferent traffic was 18.9 ± 4.8 impulses/s compared with 46.5 ± 6.5 impulses/s in sham-operated controls at 120 min (P < 0.01; Fig. 4A). In the acute vagotomy group, the increase in afferent nerve discharge at 3.5 min following LPS was 4.3 ± 4.2 compared with 11.2 ± 5.9 impulses/s in controls (P > 0.05). At 120 min following LPS, the rise was 61.9 ± 5.3 compared with 57.7 ± 7.2 impulses/s in controls (P > 0.05; Fig. 4B). Animals having undergone perivagal capsaicin treatment had a rise in afferent impulse traffic of 7.5 ± 2.9 impulses/s compared with 18.3 ± 2.7 impulses/s in sham-treated animals at 3.5 min following LPS (P < 0.05); the increase compared with baseline at 120 min was 8.6 ± 1.7 and 47.0 ± 4.9 impulses/s, respectively (P < 0.001; Fig. 4C).

**Mechanosensitivity**

**Mechanosensitivity before LPS.** Mechanical distension of the intestinal loop to 60 cmH₂O triggered a pressure-dependent increase in intestinal afferent nerve discharge. The peak magnitude of this response was unchanged in acutely vagotomized animals compared with their controls. However, in chronically vagotomized animals and in animals treated with perivagal

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<tr>
<td>Afferent discharge, impulses/s</td>
<td>21.1±0.2</td>
<td>22.6±1.0</td>
<td>22.5±0.8</td>
</tr>
<tr>
<td></td>
<td>19.1±2.2</td>
<td>21.2±0.9</td>
<td>21.9±0.7</td>
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Values are means ± SE.
Mechanosensitivity after LPS. Fifteen minutes following LPS, the afferent nerve response to mechanical distension (60 cmH₂O) in control animals was increased but had returned to baseline 15 min later. After chronic vagotomy, afferent sensitization to mechanical distension of the intestinal loop was also observed following LPS administration but persisted until the end of the observation period at 120 min (Fig. 5). In contrast, acute vagotomy and perivagal capsaicin did not influence the transient nature of the LPS-induced mechanical sensitization.

DISCUSSION

There is a growing body of evidence suggesting that LPS has the potential to sensitize abdominal vagal afferents (11, 19) and that sensory information is relayed to vagal nuclei in the brain stem that may give rise to efferent vagal modulation of the LPS-induced immune response and cardiovascular consequences (2, 20, 28). Considering this background, we specifically investigated the vagal afferent innervation of the proximal jejunum in regard to its sensitivity to LPS, its role in hypersensitivity to mechanical stimuli, and its involvement in the systemic cardiovascular response that characterizes septic shock. We found that capsaicin-sensitive vagal afferents contribute to the mesenteric afferent nerve response to LPS since afferent discharge was reduced following elimination of vagal afferents in the mesenteric bundles by chronic subdiaphragmatic vagotomy or perivagal capsaicin. Afferent sensitivity was unchanged following acute subdiaphragmatic vagotomy, which may not be surprising since this procedure leaves the vagal afferents within the mesenteric bundles intact. We had predicted that the acute elimination of efferent input to the gastrointestinal tract would have augmented inflammatory events triggered by LPS (as described previously in Ref. 2) and that this would have a secondary influence on afferent sensitivity, resulting in an increase in the afferent response to LPS. This, however, was not observed, but the previously reported (24) biphasic fall in arterial blood was more pronounced after acute vagotomy. This suggests a complex interplay between inflammatory mediators, cardiovascular responses, and the sensitivity of afferents supplying the gastrointestinal tract.

The biphasic fall in arterial blood pressure observed in the present study represents an early effect of LPS, a subsequent partial recovery, and a later response that is likely to be secondary to the macrophage-driven cytokine cascade triggered via Toll-like receptors (1, 20). A similar biphasic response was observed in regard to the increase in afferent nerve firing following systemic LPS, confirming the ability of mesenteric afferents to signal the presence of LPS to the central nervous system. These observations in the present study were consistent with our previous observations and those made by...
VAGAL MODULATION OF INTESTINAL SENSITIVITY TO LPS

Fig. 5. A–C: afferent nerve responses to distension at 60 cmH₂O in animals that had undergone acute vagotomy (A), chronic vagotomy (B), or perivagal capsaicin treatment (C) at 15, 30, and 90 min compared with their appropriate control groups. For details, see MATERIALS AND METHODS in the text. Data are normalized to the control response before LPS (~5 min). Note that a transient increase in afferent discharge was noted in vagotomized animals (###P < 0.01; ##P < 0.05).

A

B

C

other groups (24, 25). One difference between this and our earlier studies was the dramatic and often fatal cardiovascular consequence of LPS administration in animals following prior surgical intervention. This necessitated using a lower dose of LPS administered over a longer time course (1–2 min) than that used previously (24). Even so, the dose of LPS was relatively high to ensure a robust alteration of intestinal afferent nerve discharges and cardiovascular responses. This was advantageous as this protocol provided a sound basis to investigate alterations following vagal manipulation. However, high systemic doses of LPS will not only affect peripheral vagal afferents to relay their signals to the brain stem but may also give rise to humoral signals that affect the central nervous system directly (10, 11). Circulating IL-1β may directly activate central neurons, especially in regions where the blood-brain barrier is deficient (4). Moreover, blood-borne IL-1β appears to stimulate prostaglandin E₂ in cerebral vessels, which, in turn, may diffuse into the brain parenchyma to activate neurons in the central nervous system (6).

The release of inflammatory cytokines following LPS exposure is likely to contribute to the dramatic fall in arterial blood pressure, as described previously (24, 25). In previous work, we have shown that the initial fall in blood pressure is likely to be inducible NO synthase (iNOS) dependent, whereas the later phase of hypotension persists after treatment with aminoguanidine (24). In the present study, the hypotensive response to systemic LPS was more pronounced following acute and chronic vagotomy than after perivagal capsaicin treatment. It appears, therefore, that an intact abdominal vagal afferent pathway helps to ameliorate the cardiovascular response to LPS. The mechanisms underlying this protective effect are unknown but may be a protective mechanism related to the vagovagal anti-inflammatory reflex. Tracey et al. showed that the extent of cytokine release following LPS is influenced by the vagus nerve (2, 30). This is generally considered an action of the efferent vagus. However, the present observation, that chronic vagotomy and perivagal capsaicin have similar effects, would suggest that vagal afferents may contribute to these by providing a sensory input to the brain stem vagovagal circuitry that determines vagal efferent outflow.

It is particularly interesting to note that in all animals undergoing prior surgical procedures, the sensitivity to LPS was dramatically augmented, although more so following chronic vagotomy and perivagal capsaicin than in their corresponding sham groups. The reason for this enhanced cardiovascular sensitivity is unlikely to be related to exposure and handling of the gut since it was similar after abdominal and cervical surgery. However, pentobarbitone anesthesia was used for both groups 7 days prior to the experiments, and it has been shown that pentobarbitone triggers the expression of inducible NO (17, 27). Therefore, one possible mechanism is that NO production following LPS was increased in previously anesthetized animals. The enhanced NO release would then exacerbate the acute hypotension following systemic LPS. Alternatively, the stress associated with any surgical procedure could alter both autonomic outflow via vagal and sympathetic pathways and the hypothalamic-pituitary-adrenal axis, both of which could have a marked influence on cardiovascular sensitivity and immune responsiveness. Certainly, stress has been shown to alter intestinal permeability (32), and, as such, the system may have been primed to respond aggressively upon exposure to LPS.

The early component of the mesenteric afferent response depends to a certain extent on the magnitude of the fall in arterial pressure, particularly the dramatic hypotensive response in surgically treated animals. Certainly, mesenteric afferents are sensitive to ischemia with an early response in predominantly vagal afferents and a later response from the spinal afferent population (3). This is consistent with the current data showing that the initial increase in afferent firing
that is associated with the initial hypotensive response is absent in animals that have undergone perivagal capsacin or chronic vagotomy. However, since the afferent response in these animals remained blunted even after recovery from this initial transient hypotensive response, this suggests that other mechanisms contribute to the LPS-mediated sensitivity of mesenteric afferent bundles. These mechanisms may involve both direct and indirect activation of vagal afferents by LPS. Indeed, there is evidence for Toll-like receptor 4 in the rat nodose ganglion, so this receptor may be present on vagal afferents, allowing LPS binding with subsequent afferent activation (19). Alternatively, indirect activation of vagal afferents may occur subsequent to the local release of the sensitizing inflammatory mediators such as IL-1β (13).

Mesenteric afferent sensitivity to LPS persists, albeit to a lesser extent, after elimination of vagal afferents within mesenteric bundles. Thus, spinal afferents and intestinofugal fibers, in addition to vagal afferents, may also share sensitivity to LPS. Spinal afferents, in particular, may be involved since sensitivity to capsaicin persists after chronic vagotomy and the sensitivity to high distending pressures is consistent with the properties of the spinal afferent innervation described by others (33). The mechanism underlying spinal afferent sensitization remains to be determined, although prostanooids remain a good candidate since prostaglandin E2 sensitizes mesenteric afferents (15) and, in addition, the afferent nerve response to prostaglandin E2 is dramatically increased in the presence of IL-1β (22). It is therefore possible that maintained sensitization to mechanical stimulation seen after chronic vagotomy, but not acute vagotomy or perivagal capsacin, represents enhanced sensitivity of spinal afferents following an exaggerated response to local or circulating cytokines triggered by LPS.

A number of studies have demonstrated that a close association exists between vagal afferent nerve endings and immune cells in the intestinal mucosa, and this is a basis for neuroimmune interactions (21, 37). Interestingly, the density of these cells in the intestinal mucosa depends on an intact vagal innervation and changes occur following chronic vagotomy i.e., mucosal mast cells decrease and numbers of plasma cells become elevated (14). One might speculate that after chronic vagotomy, the loss of efferent innervation leads to altered neuroimmune signaling in the gut. Under control conditions, these mechanisms serve to limit hypersensitivity by restoring mechanosensitivity to control levels within 30 min of activation. However, this mechanism of downregulation appears to be lost after chronic vagotomy, leading to maintained mechanical hypersensitivity. We have previously shown that the inhibition of iNOS by aminoguanidine prevents the downregulation of hypersensitivity (24). Such plasticity may take time to develop and so may not occur after acute vagotomy. Thus, one potential mechanism to explain the absence of downregulation after chronic vagotomy may be that NO released during the immune activation that normally occurs after LPS (18) is missing after chronic vagotomy. The precise mechanism underlying this, however, remains to be determined.

We conclude that LPS has the potential to sensitize vagal afferent nerve fibers. The intact afferent vagal innervation prevents an exacerbated cardiovascular response following LPS as the afferent vagus may form part of a protective autonomic neural reflex mechanism. Vagal afferents do not appear to form the substrate of hypersensitivity to mechanical stimuli following LPS, although the vagus seems to exert a regulatory influence on this phenomenon.

GRANTS
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REFERENCES