TRPV1-mediated protection against endotoxin-induced hypotension and mortality in rats

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Am J Physiol Regul Integr Comp Physiol 294: R1517–R1523, 2008. First published March 12, 2008; doi:10.1152/ajpregu.00005.2008.—This study was designed to test the hypothesis that the transient receptor potential vanilloid type 1 (TRPV1) channel, expressed primarily in sensory nerves, and substance P (SP), released by sensory nerves, play a protective role against lipopolysaccharide (LPS)-induced hypotension. LPS (10 mg/kg iv) elicited tachycardia and hypotension in anesthetized male Wistar rats, which peaked at 10 min and gradually recovered 1 h after the injection. Blockade of TRPV1 with its selective antagonist capsazepine (CAPZ, 3 mg/kg iv) impaired recovery given that the fall in mean arterial pressure (MAP) was greater 1 h after CAPZ plus LPS injection alone (45 ± 5 vs. 25 ± 4 mmHg, P < 0.05). Blockade of the neurokinin 1 (NK1) receptor with its selective antagonist RP-67580 (5 mg/kg iv) or L-733,060 (4 mg/kg iv) prevented recovery, considering that falls in MAP were not different 1 h after injections of NK1 antagonists plus LPS from their peak decreases (66 ± 9 vs. 74 ± 5 mmHg or 60 ± 7 vs. 69 ± 3 mmHg, respectively, P > 0.05). LPS increased plasma SP, norepinephrine (NE), and epinephrine (Epi) levels compared with vehicles, and the increases in plasma SP, NE, and Epi were significantly attenuated by CAPZ or RP-67580 compared with rats treated with LPS alone (P < 0.05). Thus our results show that the TRPV1, possibly via triggering release of SP which activates the NK1 and stimulates the sympathetic axis, plays a protective role against endotoxin-induced hypotension and mortality, suggesting that TRPV1 receptors are essential in protecting vital organ perfusion and survival during the endotoxic condition.

endotoxin; transient receptor potential vanilloid type 1 channel; substance P

THE TRANSIENT RECEPTOR POTENTIAL vanilloid type 1 channel (TRPV1), also known as vanilloid receptor type 1, is a ligand-gated nonselective cation channel (4). Double immunohistochemical labeling studies have shown that, in addition to the central nervous system, TRPV1 is abundantly expressed in sensory nerves, including unmyelinated C-fibers and thinly myelinated Aδ-fibers innervating cardiovascular tissues, including the heart and blood vessels (37, 45, 48). Sensory nerves not only function as afferent fibers sending information to the central nervous system, but they also have an efferent function to release a number of sensory neurotransmitters, commonly substance P (SP) and calcitonin gene-related peptide (CGRP). The TRPV1 acts as a molecular integrator of multiple chemical and physical stimuli, including noxious heat, low pH, capsaicin, and lipid metabolites (23).

Endotoxic shock is a life-threatening cardiovascular depression with a high mortality rate (33). It is caused mainly by an exaggerated systemic response to endotoxemia induced by gram-negative bacteria and their characteristic cell wall component, lipopolysaccharide (LPS) (12). Its evolution is characterized by an increased variety of biological mediators, including cytokines, nitric oxide, and free radicals (21, 33). Excessive production of these mediators may cause hypotensive shock and multiple organ failure. Therefore, the pathogenesis of endotoxic shock is multifactorial and incompletely understood.

In this regard, an increased production of the endocannabinoid anandamide by macrophages has been reported to contribute to the endotoxin-induced hypotension (3, 40). Although it has been well documented that activation of cannabinoid receptor 1 (CB1) by endocannabinoid anandamide elicits the profound and long-lasting hypotension (24, 39), Zygmunt et al. (49) have shown that activation of TRPV1 receptors acts as a predominant mechanism for anandamide-induced relaxation in the rat mesenteric arteries, indicating that TRPV1 receptors can be activated by anandamide. The possibility is further confirmed by our in vivo studies showing that the depressor response to methanandamide, a metabolically stable analog, is attenuated by the TRPV1 antagonist capsazepine (CAPZ) (43). Therefore, the TRPV1 receptor might be important in regulating blood pressure during endotoxemia.

This study was designed to determine: 1) the potential action of TRPV1 receptors in endotoxin-induced hypotension and 2) whether TRPV1-mediated effects are attributed to activation of neurokinin 1 (NK1) receptors by SP released from sensory nerves upon TRPV1 activation.

MATERIALS AND METHODS

Animals. The experiments were carried out on 7- to 8-wk-old male Wistar rats obtained from Charles River Laboratories (Wilmington, MA). The rats were housed in the animal facility for 1 wk before the experiment and were allowed free access to regular rat chow and water ad libitum. All animal procedures were in accordance with the guidelines of the National Institutes of Health and were approved by the University Animal Care and Use Committee.

Surgery. Rats were anesthetized by intraperitoneal injection of pentobarbital sodium (60 mg/kg). The trachea was cannulated and opened to room air to facilitate respiration. Catheters (PE-50) were inserted in the left carotid artery and jugular and femoral vein for the measurement of mean arterial pressure (MAP) and intravenous injection of drugs. MAP was monitored using a Statham 231D pressure

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transducer coupled to a Gould 2400s recorder (Gould Instrument Systems, Valley View, OH). Heart rate (HR) was derived from the pulse pressure via a tachograph preamplifier. The rats were placed on heating pads that maintained core temperature at 36–37°C.

Rats were allowed to stabilize for 30 min following completion of cannulation. After baseline measurements were obtained, LPS (10 mg/kg) was intravenously administered in a volume of 0.2–0.3 ml over 1 min. Blood pressure was monitored for 1 h. To explore the role of the TRPV1 or NK1 receptor in the acute hypotensive response to LPS, rats were pretreated with the TRPV1 antagonist CAPZ (3 mg/kg) or the NK1 antagonists RP-67580 (5 mg/kg) and L-733,060 (4 mg/kg) 10, 5, or 25 min, respectively, before injection of the similar dose of LPS. The doses and time frames for injection of these drugs were based on the results described previously (5, 11, 34, 44). Moreover, to determine whether CGRP contributes to the differences in MAP and HR between TRPV1 and NK1 receptor blockade during LPS injection, CGRPα,β,γ, a CGRP receptor antagonist, was intravenously administered for 2 min at the rate of 1 mg·kg⁻¹·min⁻¹ starting 10 min after LPS injection in rats pretreated with the NK1 receptor antagonist RP-67580 and continued at the rate of 0.5 mg·kg⁻¹·min⁻¹ for 48 min. The effectiveness of the dose and time frame for CGRPα,β,γ injection was verified by blockade of the hypotensive response to capsaicin (30 μg/kg), a specific TRPV1 agonist.

Survival experiment. For survival analysis, bolus injection of LPS (20 mg/kg) was intraperitoneally given in the unanesthetized rats with or without the TRPV1 antagonist CAPZ or the NK1 antagonist RP-67580. CAPZ (3 mg/kg) or RP-67580 (5 mg/kg) was intraperitoneally administered 20 min before and 6 h after injection of LPS. After injection, rats were individually housed, and the number of surviving animals was counted at 24 and 48 h after LPS treatment. Surviving animals were killed by the overdose of anesthesia.

Sample collection. Blood samples were collected via the arterial catheter 1 h after injection of LPS with or without CAPZ or RP-67580. Plasma samples were obtained by centrifugation at 1,700 g for 15 min at 4°C and stored at −80°C for measurements of plasma catecholamines, including norepinephrine (NE) and epinephrine (Epi), and SP.

Analysis of plasma catecholamines. The catecholamines in plasma were extracted using an alumina extraction procedure and eluted with acetic acid, as described previously (10, 17). The volume of plasma used was 1 ml, and the mass of activated alumina (MP Biomedicals Germany) was 10 mg. The alumina was activated before use by the procedure reported by Eisenhofer et al. (10). HPLC with coulometric detection was performed using a commercial system (ESA, Chelmsford, MA) consisting of a solvent delivery module (model 582), an autosampler (model 542) cooled to 4°C, and a CoulArray detector (model 5600A) with a high-sensitivity analytical cell (model 5011A). NE was detected at +0.3 V vs. a solid-state Palladium reference electrode. At this potential, NE was oxidized at a mass transfer limited rate. The catecholamines were separated on an HR-80 (C18, 3 μm particle size, 80 mm × 4.6 mm ID) reverse-phase column (ESA Biosciences). The mobile phase was a commercial Cat-A-Phase II (ESA Biosciences) that consisted of a proprietary mixture of acetonitrile, methanol, and phosphate buffer (pH 3.2) along with an ion pairing agent. The optimum flow rate was found to be 1.1 ml/min. The injected sample volume was 20 μl. The separation column and detection cell were maintained at 30°C.

Radioimmunoassay. Peptides were extracted from plasma using a Strata C18-E column (Phenomenex, Torrance, CA). A rabbit anti-rat SP RIA kit (Peninsula Laboratories, San Carlos, CA) was used to determine SP. The assay was performed as recommended by the supplier. This antibody has 100% cross-reactivity with rat SP and 0.01% with rat neurokinin A. There was no cross-reactivity with rat neurokinin B.

Reagents. LPS, derived from Escherichia coli (serotype 0127:B8), was purchased from Sigma Chemicals (St. Louis, MO). CAPZ (Calbiochem, San Diego, CA), RP-67580 (Tocris Cookson, Ellisville, MO), and L-733,060 (Tocris Cookson) were dissolved in dimethyl sulfoxide (10%, vol/vol), Tween 80 (10%, vol/vol), and normal saline.

Statistical analysis. All values are expressed as means ± SE. Comparisons of MAP and HR in the different treatment groups were performed by using two-way ANOVA for repeated measurement with the Newman-Keul’s test. The differences among groups were analyzed using one-way ANOVA followed by a Bonferroni’s adjustment for multiple comparisons. Survival rate was evaluated by the Cox-Mantel test. Differences were considered statistically significant at P < 0.05.

RESULTS

There were no significant differences in the baseline MAP and HR among the groups, as presented in Table 1. As shown in Fig. 1, intravenous injection of LPS (10 mg/kg) produced a profound hypotension that lasted up to 1 h in pentobarbital-anesthetized rats. The hypotensive response was associated with tachycardia. Although blockade of TRPV1 receptors with CAPZ (3 mg/kg) did not affect the maximal hypotensive response to injection of LPS, CAPZ delayed the recovery of MAP, which remained lower than that of rats treated with LPS alone until 1 h after injection of LPS (−45 ± 5 vs. −25 ± 4 mmHg, P < 0.05). CAPZ did not affect the tachycardia response to LPS injection. Injection of CAPZ alone caused transient elevation of MAP, but it returned to the baseline level 10 min after CAPZ injection (Table 1).

To explore the role of NK1 receptors in the hypotensive response to LPS, rats were pretreated with the NK1 receptor antagonist RP-67580 (5 mg/kg) 5 min before injection of LPS. As shown in Fig. 1, the LPS-induced hypotensive response was exacerbated by RP-67580. The initial decrease in MAP (approximately −80 mmHg) was sustained in the presence of the antagonist. MAP was not different 1 h after injection of RP-67580 from the peak decrease (66 ± 9 vs. 74 ± 5 mmHg, P > 0.05). Moreover, RP-67580 significantly attenuated the LPS-induced increase in HR. The administration of RP-67580 alone had no significant effect on blood pressure but did decrease HR (Table 1).

The ability of RP-67580 to sustain the hypotensive response to LPS suggested that the NK1 receptor may contribute to the

Table 1. Effects of TRPV1 and NK1 receptor antagonists on baseline MAP and HR

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<td>Baseline</td>
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<td>MAP, mmHg</td>
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<td>HR, beats/min</td>
<td>422 ± 10</td>
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Values are means ± SE; n = 6–7 rats. CAPZ (3 mg/kg), capsazepine (transient receptor potential vanilloid type 1 receptor antagonist); RP-67580 (5 mg/kg) and L-733,060 (4 mg/kg), neurokinin 1 receptor antagonists; MAP, mean arterial pressure; HR, heart rate. *P < 0.05 vs. baseline value.
recovery of LPS-induced hypotension. To further test this possibility, the hypotensive response to LPS was tested in rats pretreated with another NK1 antagonist (L-733,060). L-733,060 (4 mg/kg) aggravated the LPS-induced hypotension, as shown in Fig. 1. During hypotension induced by LPS, L-733,060 significantly attenuated the increased HR response to LPS. L-733,060 alone did not affect the baseline MAP and HR (Table 1).

Blockade of the TRPV1 or NK1 receptors with CAPZ or RP-67580 delayed the recovery of MAP and HR. The delay was significantly greater in rats pretreated with RP-67580 than in rats treated with CAPZ (Fig. 1). As shown in Fig. 2, the difference in MAP and HR between rats treated with RP-67580 and CAPZ was prevented by blockade of the CGRP receptor by its antagonist CGRP8-37. CGRP8-37 infusion alone led to very brief increases in MAP and HR that reached the peak 60–90 s after its administration and vanished (MAP and HR returned to the baseline levels) 150–180 s after CGRP8-37 injection.

To investigate the role of the sympathetic nervous system in LPS-induced hypotension, we determined the plasma catecholamine levels using HPLC. As shown in Fig. 3, the plasma NE and Epi levels significantly increased 1 h after injection of LPS compared with vehicle \( (P < 0.05) \). The increased plasma NE and Epi levels were significantly attenuated by pretreatment with the TRPV1 receptor antagonist CAPZ or the NK1 receptor antagonist RP-67580. Injection of CAPZ or RP-67580 alone did not affect the plasma NE and Epi levels compared with the vehicle (data not shown).

In addition, we found that intravenous injection of LPS (10 mg/kg) significantly increased the plasma SP levels compared with vehicle \( (P < 0.05) \), as presented in Fig. 4. The enhanced plasma SP level was prevented by pretreatment with CAPZ. However, pretreatment with the NK1 receptor antagonist RP-67580 did not affect LPS-induced increases in the plasma SP.

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Fig. 1. Lipopolysaccharide (LPS)-induced changes in mean arterial pressure (A) and heart rate (B) in anesthetized rats with or without the transient receptor potential vanilloid type 1 (TRPV1) receptor antagonist capsazepine (CAPZ) or the neurokinin 1 (NK1) receptor antagonists RP-67580 and L-733,060. LPS (10 mg/kg) was injected iv at 0 min. CAPZ (3 mg/kg iv), RP-67580 (5 mg/kg iv), or L-733,060 (4 mg/kg iv) was injected 10, 5, or 25 min before administration of LPS. Values are means ± SE \( (n = 6–7 \text{ animals/group}) \). * \( P < 0.05 \) vs. LPS group.

Fig. 2. Changes in mean arterial pressure (A) and heart rate (B) 60 min after injection of LPS in anesthetized rats pretreated with the TRPV1 receptor antagonist CAPZ or the NK1 receptor antagonist RP-67580 with or without the calcitonin gene-related peptide (CGRP) receptor antagonist CGRP8-37 (C8-37). CAPZ (3 mg/kg iv) or RP-67580 (5 mg/kg iv) was injected 10 or 5 min before injection of LPS (10 mg/kg iv). The dose and time frame for C8-37 were stated in MATERIALS AND METHODS. Values are means ± SE \( (n = 5–7) \). * \( P < 0.05 \) vs. CAPZ + LPS group (*) and vs. RP-67580 + LPS group (#).
level. In addition, injection of CAPZ or RP-67580 alone did not affect the plasma SP levels compared with the vehicle (data not shown).

Because the TRPV1 and NK1 receptors were likely to be involved in LPS-induced hypotension, we investigated their effects on the survival in the model of LPS-induced septic shock. The survival rates among groups are presented in Fig. 5. Pretreatment with CAPZ or RP-67580 significantly decreased the survival rate at 24 or 48 h after injection of LPS (20 mg/kg) compared with injection of LPS alone. Injection of CAPZ or RP-67580 without LPS had no effect on animal survival or mortality (data not shown).

**DISCUSSION**

Our current study investigated the effects of the TRPV1 receptor on LPS-induced changes in blood pressure. This study provides evidence showing that pretreatment with CAPZ, a selective TRPV1 receptor antagonist, exaggerated LPS-induced hypotension, suggesting that TRPV1 predominately expressed in sensory nerves participates in the regulation of blood pressure during septic shock. The results are consistent with recent studies by Clark et al. (7) demonstrating a new role of TRPV1 in conferring resistance to hypotension in endotoxemia. Additionally, we further demonstrated that SP released by sensory nerves appeared to be involved, since radioimmunoassay studies revealed increased plasma SP levels during septic shock, and the NK1 receptor antagonists sustained the depressor response induced by LPS. Moreover, the increased plasma catecholamine levels during septic shock were attenuated by the TRPV1 and NK1 receptor antagonists. These observations support the notion that the effects of TRPV1 receptors mainly expressed in sensory nerves on blood pressure during endotoxemia may be attributed to the activation of NK1 receptor.
receptors by increasing SP release, leading to activation of the sympathetic axis.

Our present results showed that LPS-induced hypotension was exaggerated by the TRPV1 receptor antagonist CAPZ, suggesting that TRPV1 may be an important target for LPS. It has been well established that the TRPV1 can be activated by multiple stimuli, including low pH and prostanoids (23). In addition, Zygmunt et al. (49) demonstrated that, in rat mesenteric arterial preparation in vitro, anandamide-induced relaxation was almost completely blocked by a selective TRPV1 receptor antagonist, CAPZ, but not by a selective CB1 receptor antagonist, SR-141716A. Considering that endotoxia may be associated with tissue acidification and increased production of several eicosanoids, including anandamide and arachidonic acid metabolites (30, 40, 46), it is likely that TRPV1 receptors are activated during endotoxia, leading to CGRP and SP release. However, the seemingly opposite effect of TRPV1 on preventing LPS-induced hypotension indicates that different sequences of events or pathways mediate distinct effects of TRPV1 in vitro and in vivo, which is discussed below.

It is known that the death in septic shock is attributed to refractory hypotension or progressive multiple organ failures. The hallmark of septic shock is marked peripheral arteriolar vasodilatation, which results in low systemic vascular resistance, high cardiac output, severe hypotension, and inadequate tissue perfusion (3, 33). The important compensatory response to hypotension includes an immediate baroreceptor sensing of the hypotension that initiates an autonomic response, i.e., sympathetic outflow to both heart and peripheral vessels is increased and serves to restore blood pressure to normal. Experimental models of septic shock indicate that the baroreflex, which regulates peripheral sympathetic nerve activity, is increased (2, 26). Moreover, human studies have provided convincing evidence showing that septic shock is characterized by an increased sympathetic nerve activity (13, 25). In agreement with these studies, we found that plasma catecholamine levels were increased during LPS-induced hypotension, suggesting that an increased sympathetic tone occurred in the pathological condition.

In addition, LPS initiates the release of nitric oxide, free radicals, and cytokines such as interleukin-1 and tumor necrosis factor-α (33, 41, 47), which contribute to LPS-induced vasodilation and/or decreased cardiac contractility (33, 41). Thus the net effect of LPS on vascular tone and cardiac contractility depends on the balance between sympathetically mediated vasoconstriction and positive inotropy and the opposing vasodilatory and negative inotropy actions of local and circulating vasoactive mediators. Based on the fact that blockade of the TRPV1 inhibits the rise of plasma catecholamine levels and exaggerates LPS-induced hypotension, we proposed that removal of enhanced sympathetic nerve activity by blockade of the TRPV1 would leave vasodilatory and negative inotropy actions of local and circulating vasoactive factors unopposed, leading to exaggeration of LPS-induced hypotension.

SP is an important member of the family of structurally related peptides named tachykinins. Tachykinin receptors are G protein-coupled receptors, termed NK1, NK2, and NK3. Although SP may activate all three tachykinin receptors, its potency is greatest when binding to the NK1 receptor subtype (18, 27). The nucleus tractus solitarius (NTS) plays a crucial role in the control of cardiovascular function via baroreflex. High densities of NK1 receptors have been identified in the NTS areas, which are involved in the transmission of cardiovascular reflexes (19, 29). Several lines of evidence show that microinjections of SP or neurokinin receptor agonists in the NTS increase blood pressure and baroreflex sensitivity (1, 14, 31), although the opposite response has also been reported (19). These functional studies confirm anatomical evidence that suggests that NK1 receptors modulate baroreflex control.

In addition, SP has a direct action on postganglionic sympathetic nerve activity. Immunohistochemical and receptor autoradiographic studies indicate that SP-positive sensory nerves and postganglionic sympathetic neurons may constitute a peripheral reflex mechanism (8, 22, 28). Moreover, several studies have shown that sympathetic ganglia stimulated by SP in situ increase renal sympathetic nerve activity, blood pressure, and HR (15, 16). The increases in these parameters can be attenuated by the selective NK1 receptor antagonist GR-82334, indicating that SP increases postganglionic sympathetic nerve activity via activation of NK1 receptors (35). On the other hand, SP has a direct action on endothelial NK1 receptors to cause vasodilation by release of endothelium-derived relaxant factor (42). Thus the actions of SP on blood pressure are determined by the balance between vasodilation and increased sympathetic nerve activity stimulated by SP. We found that the NK1 receptor antagonists RP-67580 or L-733,060 aggravated LPS-induced hypotension in the present study, suggesting that the increased sympathetic nerve activity stimulated by SP activation of NK1 is intense enough to override the vasodilator action.

The recent development of selective, nonpeptide NK1 receptor antagonists has enabled investigation of the role of tachykinin. RP-67580 and L-733,060, both nonpeptide antagonists, are generally more potent, selective, and stable than the previous peptide tachykinin NK1 receptor antagonist (11, 36). Our results, obtained with the use of these two antagonists, point to a protective role of NK1 receptors in LPS-induced hypotension. L-733,060 readily crosses the blood-brain barrier to interact with central NK1 receptors after systemic administration (9, 34). In contrast, RP-67580 has poor brain penetration in rats (20). Based on the effects of RP-67580 and L-733,060 on the LPS-induced hypotension in the present study, we speculate that peripheral NK1 receptors may primarily contribute to the recovery of LPS-induced hypotension. However, further studies are required to discriminate between the central and peripheral effects mediated by tachykinin NK1 receptor on the LPS-induced hypotension.

In patients with severe septic shock, profoundly low peripheral vascular resistance often persists in the presence of high levels of circulating endogenous catecholamines (13, 25). Hypotension that ensues is frequently resistant to high doses of α-adrenergic agonists and may lead to inadequate perfusion of vital organs and death (6). Nevertheless, it is possible that removal of TRPV1 or its neuropeptide-mediated sympathetic vasoconstriction would further compromise tissue perfusion. This notion was supported by the fact that TRPV1 or tachykinin NK1 antagonist exaggerated LPS-induced hypotension. Furthermore, our findings showed that pretreatment with antagonists of TRPV1 or tachykinin NK1 lowers the survival rate of endotoxemic rats.
Taken together, these data point to the conclusion that SP released from sensory nerve terminals upon TRPV1 activation plays a protective role against LPS-induced hypotension and mortality via action of the NK1 receptors. It appears that, however, the changes in blood pressure and HR by blockade of TRPV1 and NK1 during LPS administration were not fully the same, as shown in Fig. 1 in which blockade of NK1 prevented recovery of both blood pressure and HR, whereas HR but not blood pressure recovered in the case of TRPV1 blockade. Indeed, in addition to SP, CGRP is a common neuropeptide released from sensory nerves when TRPV1 is activated. CGRP is a potent vasodilator and has been shown to inhibit sympathetic nerve activity (32, 38). It is likely that the apparent discrepancies between blockade of TRPV1 and NK1 were that, when TRPV1 was blocked, both SP-induced stimulation and CGRP-induced inhibition of the sympathetic nervous system were removed, whereas, in the case of NK1 blockade, CGRP-mediated action was left unopposed, leading to lower blood pressure and HR than that of TRPV1 blockade, as shown in Fig. 1. This notion is supported by the findings showing that the differences in MAP and HR between TRPV1 and NK1 during LPS administration were not fully the same, as shown in Fig. 1 in which blockade of NK1 prevented recovery of both blood pressure and HR, whereas HR but not same, as shown in Fig. 1 in which blockade of NK1 prevented recovery of both blood pressure and HR, whereas HR but not

**Perspectives and Significance**

On the basis of results of the present study, it appears that TRPV1 and SP play a protective role against endotoxin-induced hypotension and mortality. These findings may have broader perspective and significance. Although the pathophysiological changes of septic shock have been studied extensively and for decades, the mortality rate is still unacceptably high, and effective treatment strategies are yet to be developed. The traditional treatment approaches and available therapeutic means have been focused on altering the activity of the sympathetic nervous systems. The data presented in the present study indicate that TRPV1 expressed in the sensory nerves and TRPV1-mediated sensory neuropeptide release are involved in the septic shock process and regulate sympathetic nervous activity. It is conceivable that modulation of TRPV1 function may serve as an effective means and may be beneficial in treating hypotension as well as in reducing the complications and mortality resulting from septic shock.

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