J Anesth (2006) 20:284–289
DOI 10.1007/s00540-006-0428-3

Journal of
Anesthesia

Effects of AM281, a cannabinoid antagonist, on circulatory deterioration and cytokine production in an endotoxin shock model: comparison with norepinephrine

Yuji Kadoi and Fumio Goto

Department of Anesthesiology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi 371-8511, Japan

Abstract
Purpose. The purpose of this study was to examine the comparative effects of AM281, a cannabinoid antagonist, and norepinephrine (NE) on systemic hemodynamics, and renal and mesenteric artery blood flow in an endotoxin shock model.
Methods. The study was designed to include two sets of experiments: (1) measurements of changes in systemic hemodynamics and organ artery blood flows (n = 20), and (2) measurements of biochemical variables (n = 20). For each set of experiments, male 7-week-old Wistar rats were randomly divided into four groups: group 1, controls (n = 5); group 2, receiving lipopolysaccharide (LPS: *Escherichia coli* endotoxin, 10.0 mg·kg^{-1} intravenous bolus) (n = 5); group 3, receiving intravenous LPS and NE (continuous infusion at 0.2 μg·kg·min^{-1}) (n = 5); group 4, receiving LPS and AM281 (0.1 mg·kg·min^{-1}) (n = 5). Systemic hemodynamics, regional artery blood flow changes, and biochemical variables were assessed before treatment and 1 and 3 h after treatment.
Results. Infusion of NE or AM281 prevented endotoxin-induced decreases in systemic arterial pressure, aortic blood flow, carotid artery blood flow, and renal artery blood flow. Both AM281 and NE inhibited endotoxin-induced increases in cytokine production, with significant differences observed among the three groups at 1 and 3 h after treatment. Endotoxin-induced decreases in mesenteric arterial blood flow were restored by AM281 but not by NE. AM281 improved arterial oxygenation and reduced lactate overproduction and body temperature elevation induced by endotoxin.
Conclusions. Although NE and AM281 both prevented endotoxin-induced deterioration of systemic hemodynamics, AM281 yielded better preservation of mesenteric blood flow and attenuation of cytokine production than NE.

Key words Anandamide · Inhibition · Septic shock · Mesenteric artery blood flow

Address correspondence to: Y. Kadoi
Received: October 24, 2005 / Accepted: July 4, 2006

Introduction

Septic shock induced by Gram-negative bacteria represents a major complication in critical care medicine that can lead to multiple organ failure, although the molecular and cellular events leading to the development and progression of this condition have yet to be clarified [1].

One therapeutic approach for the treatment of hyperdynamic sepsis and hypotension is the administration of catecholamines to maintain sufficient mean arterial pressure (MAP) and cardiac output [2–5]. However, no clear consensus has been reached regarding which vasopressor should be used [4,5]. Although dopamine has been recommended by an American consensus conference [5], norepinephrine (NE) was considered to the equivalent following a European consensus conference [4]. However, some researchers have shown that administration of NE leads to strong vasoconstriction in the splanchnic area, which might induce ischemia in the gastrointestinal tract [6].

Anandamide, generated by endotoxin-induced platelets and macrophages, and identified as an endogenous cannabinoid (CB) ligand, has recently been found to be expressed in abundance in the brain [7–11]. Varga et al. [8] reported that anandamide was one possible causative factor for hypotension induced by endotoxic shock. Anandamide displays vasodilatory effects and induces a state of shock via CB1 receptors [7]. Wang et al. [11] showed that removing endogenous cannabinoids by polymyxin B-selective adsorption was effective in improving hemodynamics in patients with septic shock. We have previously shown that the administration of a CB antagonist (AM281) could be effective in minimizing endotoxin-induced changes to systemic hemodynamics [12]. However, we did not examine the effects of CB antagonists such as AM281 on renal and mesenteric artery blood flow in septic shock in rats. In addition, a review by Klein et al. [13] noted that although the cannabinoid system could modulate the cytokine sys-

tem, the effects often conflict with the cytokine network. Evaluation of the inflammatory response during sepsis is important in order to understand the mechanisms underlying the development of septic shock.

Therefore, this study compared the effects of AM281 and NE on the systemic hemodynamics, renal and mesenteric artery blood flow, and inflammatory response in a model of endotoxic shock.

Materials and methods

Study protocols were in accordance with the ethical principles provided by the Experimental Animal Laboratory of Gunma University School of Medicine. Male 7-week-old Wistar rats ($n = 40$; body weight 250–350 g) were maintained at 22°C in wire-mesh cages with ad libitum access to standard laboratory feed and water, under a 12-h light/dark cycle.

Experimental protocol

The study was designed to include two sets of experiments: (1) measurements of changes in the systemic hemodynamics, and carotid, renal, and mesenteric artery flows ($n = 20$); (2) measurements of biochemical variables ($n = 20$).

Rats in the first set of experiments were randomly divided into four groups: group 1, control ($n = 5$); group 2, receiving lipopolysaccharide (LPS: *Escherichia coli* endotoxin, 10.0 mg·kg^{-1} intravenous bolus) ($n = 5$); group 3, receiving intravenous LPS and NE (continuous infusion at 0.2 μg·kg·min^{-1}) ($n = 5$); group 4, receiving LPS and AM281 (0.1 mg·kg·min^{-1}) ($n = 5$). A 10.0-mg·kg^{-1} dose of endotoxin is capable of causing 50% lethality within 6 h [14–17]. Infusion of NE or AM281 was started 30 min after LPS administration.

The most common septic shock model involves a single bolus injection of endotoxin [14,16,17], as this model is reproducible and simple to prepare. In addition, the model offers a useful tool for examining the effects of therapeutic drugs on hemodynamic changes induced by sepsis [15]. In this study, AM281 [(N-morpholin-4-yl)-5-(2,4-yl)-5-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide] was selected as a CB receptor antagonist. Gifford et al. [18] reported AM281 as a less-lipophilic analog of the CB receptor antagonist SR141716A, and displaying slightly greater potency than SR141716A in the hippocampal slice experiment.

To identify the appropriate dosage for continuous infusion of AM281 in this endotoxin shock model, we examined the effects of three dosages of AM281 (0.01, 0.05, and 0.1 mg·kg·min^{-1}) on systemic hemodynamics. As a result, 0.1 mg·kg·min^{-1} was identified as the most effective dosage to improve systemic hemodynamics induced by sepsis (data not shown).

Rats were anesthetized using intraperitoneal injection of pentobarbital (50 mg·kg^{-1}). After tracheotomy, rats were connected to an SN-480-7 volume-cycled ventilator (Shinano Manufacturing, model SN-480-7, Japan) with 30% O_2, 70% N_2, and 1% isoflurane. Rectal temperature was monitored using a temperature controller (CMA/150). A 2-ml bolus of saline solution was injected subcutaneously to maintain fluid balance. For simultaneous measurements of mean arterial pressure and heart rate (HR), the right femoral artery was cannulated using a 2-Fr high-fidelity micromanometer catheter. Drugs were administered intravenously through a polyethylene catheter (PE50) placed in the dorsal vein. The catheter in the right femoral artery was connected to a Power Lab hemodynamic monitoring system (BioRes, Nagoya, Japan). Changes in HR, mean arterial pressure (MAP), and ascending aortic, right internal carotid, renal, and mesenteric artery blood flows were measured using ultrasonic flow probes (Transonic Systems, Ithaca, NY, USA) before (baseline), and at 1 and 3 h after intravenous LPS injection. The ascending aortic, right internal carotid, renal, and mesenteric arteries were prepared and visualized. At 3 h after LPS administration, the rats were killed by injection of an overdose of pentobarbital via the dorsal vein.

Biochemical measurements

To exclude the influence of blood sampling on hemodynamic variables flow, hemodynamic and biochemical parameters were also measured in another 20 animals divided into the same four groups. To extrapolate data from these to the experimental set of animals in which hemodynamic variables were evaluated, the rats were exposed to identical experimental conditions for systemic measurements. Plasma concentrations of lactate, glucose, tumor necrosis factor (TNF)α, interleukin (IL)-1β, and partial pressures of arterial blood gases were measured before (baseline), and 1 and 3 h after LPS injection using 2.0 ml blood collected from the femoral artery. Partial pressures of arterial blood gases were analyzed using an ABL3 acid–base laboratory machine (Radiometer, Copenhagen, Denmark). Plasma TNFα activity was quantified by measuring cytotoxicity against L929 cells in rabbit serum. IL-1β levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (IL-1; R&D Systems, Tokyo, Japan). After the measurements of hemodynamic and biochemical parameters, the rats were killed by pentobarbital overdose.

Statistical analysis

All data are presented as arithmetic means ± standard deviation. After confirming equal variance among groups using the Bartlett test, analysis of variance (ANOVA) for multiple comparisons were performed. Scheffe's method was used to compare means. Values of $P < 0.05$ were considered to be statistically significant. All statistical analyses were performed using StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA).

Results

Table 1 shows the time-courses of variables in the 4 groups, as studied in the first set of animals. No variables in group 1 changed significantly during the study. In group 2, MAP was decreased at 1 and 3 h after LPS administration, while the decrease in MAP induced by LPS was ameliorated in groups 3 and 4. No significant changes in Pa_{O_2}, Pa_{CO_2}, or hematocrit were noted in groups 1 and 4 during the study. Pa_{O_2} was significantly decreased at 3 h after LPS administration in both groups 2 and 3 compared with the baseline and the other two groups. Plasma glucose levels were significantly decreased at 3 h after LPS administration in both groups 2 and 3 compared with the baseline and the other two groups. Plasma lactate levels were significantly increased at 1 and 3 h after LPS administration. The values of TNFα and IL-1β in group 1, did not appear to change throughout the study, but were significantly increased in groups 2–4 at 1 and 3 h after LPS.

Figures 1–s4 show time courses of changes in the ascending aortic, carotid, mesenteric, and renal artery blood flows in the four groups, as measured using ultrasonic flow probes. These blood flows remained fairly constant in group 1, compared with baseline values. LPS administration significantly decreased these blood flows. Infusion of NE or AM281 returned ascending aortic, carotid, and renal artery blood flows to baseline values (Figs. 1, 2, and 4).

Infusion of AM281 returned mesenteric artery blood flow to the baseline value. In contrast, infusion of NE did not return mesenteric artery blood flow to the baseline value (Fig. 3).

Discussion

Continuous infusion of NE or AM281 could prevent endotoxin-induced deterioration in systemic hemodynamics, but these agents exerted substantially different effects on mesenteric blood flow in the endotoxin shock model.

This study found that NE and AM281 both improved the decreases in renal blood flow seen following LPS

Table 1. Changes in variables over time for the four groups

	Baseline				1 h				3 h			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Heart rate (beats/min)	322 ± 34	341 ± 31	311 ± 29	309 ± 26	329 ± 26	389 ± 34[a]	333 ± 39	359 ± 30[a]	311 ± 28	388 ± 41[a]	329 ± 35	379 ± 34[a]
MAP (mmHg)	101 ± 5	105 ± 5	97 ± 5	102 ± 5	96 ± 5	76 ± 10[ab]	98 ± 11	99 ± 12	96 ± 6	54 ± 14[ab]	94 ± 10	102 ± 11
Pa_{O_2} (mmHg)	166 ± 13	157 ± 12	166 ± 15	164 ± 15	161 ± 11	150 ± 18	149 ± 17	160 ± 19	153 ± 15	118 ± 22[ab]	131 ± 21[a]	157 ± 18
Pa_{CO_2} (mmHg)	38 ± 5	39 ± 4	38 ± 4	39 ± 5	40 ± 5	39 ± 7	40 ± 5	41 ± 6	39 ± 4	40 ± 6	39 ± 5	39 ± 6
Ht (%)	35 ± 4	36 ± 5	36 ± 5	35 ± 3	35 ± 4	35 ± 4	35 ± 4	36 ± 5	35 ± 5	35 ± 4	34 ± 7	35 ± 5
Glucose (mg/dl)	199 ± 24	188 ± 27	180 ± 20	177 ± 29	188 ± 27	247 ± 38[a]	211 ± 33	202 ± 25	180 ± 19	311 ± 39[ab]	234 ± 33[a]	218 ± 29
Lactate (mM)	0.6 ± 0.2	0.6 ± 0.3	0.6 ± 0.4	0.5 ± 0.3	0.5 ± 0.3	3.9 ± 1.1[ab]	1.9 ± 1.3[a]	1.3 ± 1.1[a]	0.5 ± 0.3	9.4 ± 2.9[ab]	3.1 ± 2.2[ac]	1.9 ± 1.1[a]
RT (°C)	37.3 ± 0.3	37.5 ± 0.4	37.3 ± 0.4	37.5 ± 0.3	37.2 ± 0.2	37.7 ± 0.5	37.6 ± 0.6	37.5 ± 0.6	37.3 ± 0.3	38.3 ± 0.5[ab]	37.3 ± 0.6	37.4 ± 0.9
TNFα (ng/ml)	nd	nd	nd	nd	nd	5.0 ± 1.9[ab]	2.5 ± 1.8[a]	1.4 ± 1.1[a]	nd	3.4 ± 2.2[ab]	2.4 ± 1.9[ac]	1.9 ± 1.1[a]
IL-1β (ng/ml)	nd	nd	nd	nd	nd	0.9 ± 0.2[ab]	0.6 ± 0.2[a]	0.3 ± 0.1[a]	nd	2.5 ± 1.1[ab]	0.9 ± 0.4[ac]	0.2 ± 0.1[a]

All data are expressed as mean ± SD

[a] $P < 0.05$ compared with baseline; [b] $P < 0.05$ compared with the other three groups; [c] $P < 0.05$ compared with group 4

HT, hematocrit; RT, rectal temperature; IL, interleukin; TNF, tumor necrosis factor; nd, not detectable; MAP, mean arterical pressure; NE, norepinephrine

Group 1 ($n = 5$); control; group 2 ($n = 5$), receiving lipopolysaccharide (LPS: *Escherichia coli* endotoxin, 10.0 mg·kg^{-1} intravenous bolus); group 3 ($n = 5$), receiving intravenous LPS and NE (continuous infusion at 0.2 μg·kg·min^{-1}); group 4 ($n = 5$), receiving LPS and AM 281 (0.1 mg·kg·min^{-1})

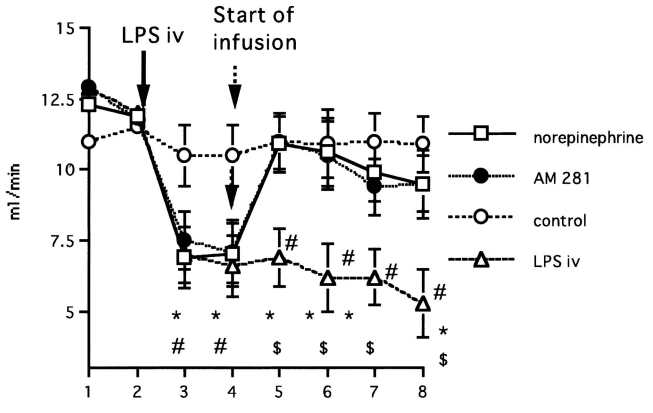

Fig. 1. Time courses of changes in ascending aortic blood flow in the 4 groups. *1*, before administration of lipopolysaccharide (*LPS*); *2*, at time of *LPS* administration; *3*, 15 min after *LPS* administration; *4*, 30 min after *LPS* administration (start of continuous infusion of norepinephrine (NE) or AM281); *5*, 30 min after start of continuous infusion of NE or AM281; *6*, 1 h after start of continuous infusion of NE or AM281; *7*, 2 h after the start of continuous infusion of NE or AM281; *8*, 3 h after start of continuous infusion of NE or AM281. $^{*}P < 0.05$ compared with before *LPS* administration within each group; $^{\#}P < 0.05$ compared with control group at each time point; $^{\$}P < 0.05$ compared with the other three groups at each time point. Group 1, control; group 2, intravenous *LPS*; group 3, intravenous *LPS* + NE; group 4, intravenous *LPS* + AM281

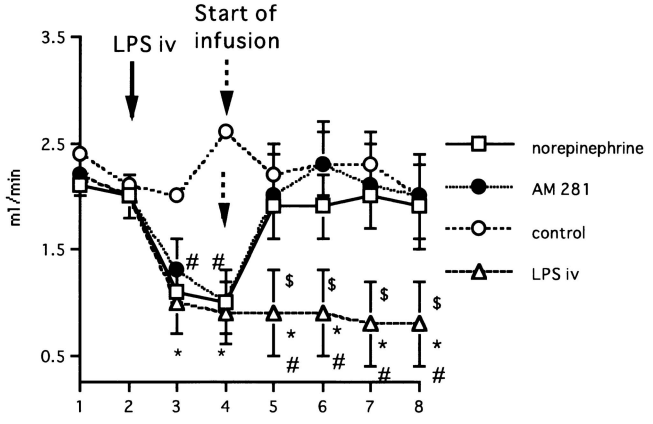

Fig. 2. Time courses of changes in carotid artery blood flow in the four groups

administration. Whether NE restores renal blood flow which decreased during septic shock remains controversial [19,20]. In contrast to controversial reports regarding the effects of NE on renal blood flow, no reports have examined the effects of cannabinoid antagonists on renal blood flow and function. Continuous infusion of AM281 can plausibly act to restore renal blood flow decreased by LPS, as cannabinoid agonists such as anandamide and 2-AG display vasodilatory effects via peripheral CB1 receptors [7]. This study suggests that infusion of AM281 facilitates the maintenance of renal blood flow during endotoxic shock.

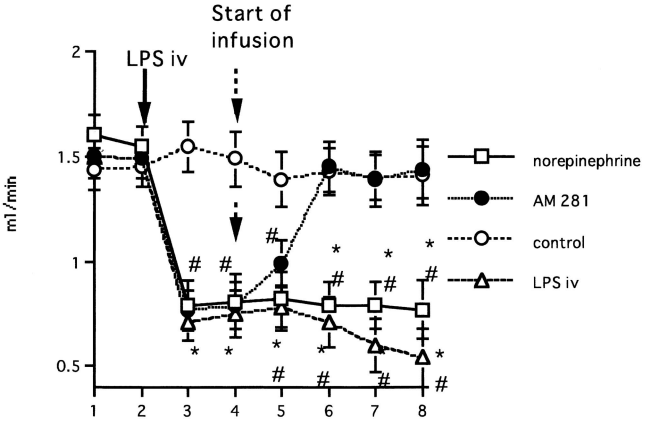

Fig. 3. Time courses of changes in mesenteric artery blood flow in the four groups

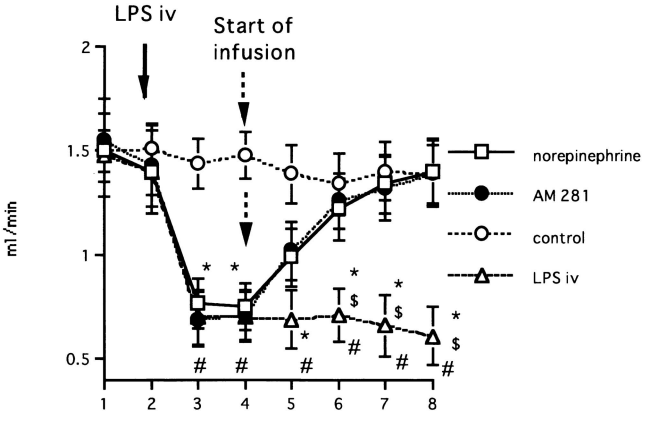

Fig. 4. Time courses of changes in renal artery blood flow in the four groups

Numerous reports have noted that administration of NE could improve systemic hemodynamics, but whether administration of NE can improve intestinal perfusion during septic shock remains controversial [21–27]. Agents such as phenylephrine and NE that display α-adrenergic effects have been considered to cause intestinal ischemia by decreasing intestinal perfusion during septic shock [21]. Our findings are consistent with previous reports that NE induces global mesenteric vasoconstriction [6]. Guzman et al. [19] also reported that continuous infusion of NE at 0.2 μg·kg·min^{-1} could not improve portal or mucosal blood flow as measured by ultrasonographic probe during septic shock. In contrast, Di Giantomasso et al. [27] found no affects on mesenteric blood flow after NE infusion at 0.4 μg·kg·min^{-1} [27]. These effects were also observed by Revelly et al. [26] and Backer et al. [21] Such discrepancies might be attributable to differences in species, fluid resuscitation, and anesthesia [22].

We found that although NE had no effect, AM281 did act to restore mesenteric blood flow during endotoxic

shock. No previous reports have examined the effects of cannabinoid antagonists on mesenteric blood flow. This result suggests that infusion of AM281 is beneficial to maintain intestinal perfusion during septic shock. Although the underlying mechanism is unclear, several causes should be considered. Amelioration of mesenteric artery blood flow induced by AM281 is thought to be attributable to improvements in intestinal microcirculation. This improvement may induce a decrease in endotoxin translocation from gut to systemic circulation, potentially preventing the overexpression of endotoxin and cytokines during sepsis [1,16]. Proinflammatory cytokines are known to deteriorate the micro- and macrocirculation [1]. This preventable effect of cytokine production by AM281 might thus also be attributable to the restoration of intestinal perfusion, resulting in prevention of impairments to arterial oxygenation and increases in lactate production, blood glucose, and body temperature.

The observed preventive effect of AM281 may be due to antagonistic effects on the CB-1 receptor. This is supported by the results of Varga et al. [8], who found that pretreatment of animals with CB-1 antagonist prevented LPS-induced hypotension. These findings provide insight into the pathogenesis of septic shock, and may lead to new therapeutic options in the management of this condition.

This study showed that administration of AM281 decreased plasma cytokine levels. However, the effects of cannabinoid ligands on the cytokine system during sepsis remain controversial [13]. Molina-Holgado et al. [28] reported that anandamide inhibits LPS-induced production of TNFα by astrocyte cultures. Other cannabinoid ligands, such as HU-211 and 9-tetrahydrocannabinoid (THC), have also been shown to display similar inhibitory effects on TNFα production. That report suggested that administration of AM281 should induce increases in plasma cytokine levels, which is inconsistent with the present findings [28]. Klein et al. [13] reviewed the effects of the cannabinoid system on the cytokine network, and noted that cannabinoids have a potentially wide-ranging role to play in immunomodulation. The possibility that AM281 improves the hemodynamic deterioration induced by sepsis via cytokine modulation cannot be ruled out.

The mechanisms underlying the hypotensive effects of endocannabinoids induced by endotoxin on arterial blood pressure remain unclear. Mendizabal et al. [29] reported that the vascular effects of endocannabinoids in a modelof hypertension caused long-term suppression of nitric oxide synthesis in rat isolated mesenteric beds. Zygmunt et al. [30] showed that anandamide induces vasodilation by activating vanilloid receptors on perivasucular sensory nerves and causing release of calcitonin-gene-related peptide. In contrast, Pacher et al. [31] indicated that mice lacking vanilloid receptors display a normal cardiovascular profile, and the predominant cardiovascular depressor response to anandamide is mediated through CB1 receptors. Further investigation is thus necessary to clarify the role of endocannabinoids during sepsis.

This study focused on the comparative effects of NE or anandamide antagonist on organ blood flow, and did not examine the effects of AM281 on mortality in endotoxin shock. However, previous studies have shown that AM281 could improve mortality rates in a rat model of endotoxic shock.

Since changes in ascending aortic blood flow and internal carotid arterial blood flow are thought to parallel changes in cardiac output and cerebral blood flow, the decreases in ascending aortic blood flow and internal carotid arterial blood flow seen in this study are indicative of cardiac output and cerebral blood flow [12,16].

In conclusion, continuous infusion of AM281 restored decreases in MAP and organ blood flow and ameliorated increases in cytokine production in a model of endotoxic shock. These findings might have significant therapeutic implications in the treatment of septic shock.

Acknowledgments. The authors wish to thank Forte (Tokyo, Japan) for assistance with manuscript preparation in English. This study was supported by grants (to Dr. Kadoi, no. 155919914, and to the Center of Excellence Program at Gunma University) from the Japanese Ministry of Science, Education and Culture.

References

1. Ghosh S, Latimer RD, Gray BM, Harwood RJ, Oduro A (1993) Endotoxin-induced organ injury. Crit Care Med 21:S19–24
2. Parratt JR (1973) Myocardial and circulatory effects of *E. coli* endotoxin: modification of responses to catecholamines. Br J Pharmacol 47:12–18
3. Chernow B, Roth BL (1986) Pharmacologic manipulation of the peripheral vasculature in shock: clinical and experimental approaches. Cir Shock 18:141–155
4. Sprung CL, Bernard GR, Dellinger RP (2001) Guidelines for the management of severe sepsis and septic shock. Int Care Med 27(Suppl):S128–134
5. Task Force of the American Collage of Critical Care Medicine, Society of Critical Care Medicine (1999) Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. Crit Care Med 27:639–660
6. Meier-Hellman A, Reinhart K (1995) Effects of catecholamines on regional perfusion and oxygenation in critically ill patients. Acta Anaesthesiol Scand 39(Suppl 107):239–248
7. Wagner JA, Karoly V, Ellis EF, Rzigalinski BA, Martin BR, Kunos G (1997) Activation of peripheral CB1 cannabinoid receptors in hemodynamic shock. Nature 390:518–521
8. Varga K, Wahner JA, Bridgen T, Kunos G (1998) Platelet- and macrophage-derived endogenous cannabinoids are involved in endotoxin-induced hypotension. FASEB J 12:1035–1044
9. Sarker KP, Obara S, Nakata M, Kitajima I, Maruyama I (2000) Anandamide induces apoptosis of PC-12 cells: involvement of superoxide and caspase-3. FEBS Lett 472:39–44

10. Smith PB, Compton DR, Welch SP, Razdan RK, Mechoulam R, Martin BR (1994) The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice. J Pharm Exper Ther 270:219–227
11. Wang Y, Liu Y, Ito Y, Hashiguchi T, Kitajima I, Yamakuchi M, Shimizu H, Matsuo S, Imaizumi H, Maruyama I (2001) Simultaneous measurements of anandamide and 2-arachidonylglycerol by polymyxin B-selective adsorption and subsequent high-performance liquid chromatography analysis: increase in endogenous cannabinoids in the sera of patients with endotoxic shock. Anal Biochem 294:73–82
12. Kadoi Y, Hinohara H, Kunimoto F, Kuwano H, Saito S, Goto G (2005) Effects of AM281, a cannabinoid antagonist, on systemic hemodynamics, internal carotid artery blood flow and mortality rate in septic shock in rats. Br J Anesth 94:563–568
13. Klein TW, Lane B, Newton CA, Friedman H (2000) The cannabinoid system and cytokine network. Exp Biol Med 225:1–8
14. Kadoi Y, Saito S (1996) An alteration in the γ-aminobutyric acid receptor system in experimentally induced septic shock in rats. Crit Care Med 24:298–305
15. Kadoi Y, Saito S, Kunimoto F, Imai T, Fujita T (1996) Impairment of the brain beta-adrenergic system during experimental endotoxemia. J Surg Res 61:496–502
16. Kadoi Y, Goto F (2004) Selective inducible nitric oxide inhibition can restore hemodynamics, but does not improve neurological dysfunction in experimentally induced septic shock in rats. Anesth Analg 99:212–220
17. Kadoi Y, Saito S, Kawahara F, Nishihara F, Goto F (2002) G-protein-coupled receptor kinase 2 is altered during septic shock in rats. J Surg Res 108:69–76
18. Gifford AN, Bruneus M, Gatley SJ, Lan R, Makriyannis A, Volkow ND (1999) Large receptor reserve for cannabinoid actions in the central nervous system. J Pharm Exp Ther 288:478–483
19. Guzman JA, Rosado AE, Kruse JA (2003) Vasopressin vs. norepinephrine in endotoxic shock: systemic, renal, and splanchnic hemodynamic and oxygen transport effects. J Appl Physiol 95:803–809
20. Schrier R, Wang W (2004) Acute renal failure and sepsis. New Engl J Med 351:159–169
21. Treggiari MM, Romand JA, Burgener D, Suter PM, Aneman A (2002) Effect of increasing norepinephrine dosage on regional blood flow in a porcine model of endotoxin shock. Crit Care Med 30:1334–1339
22. De Backer D, Creteur J, Silva E, Vincent JL (2003) Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med 31:1659–1667
23. Sautner T, Wessely C, Riegler M, Sedivy R, Gotzinger P, Losert U, et al. (1998) Early effects of catecholamine therapy on mucosal integrity, intestinal blood flow, and oxygen metabolism in porcine endotoxin shock. Ann Surg 228:239–248
24. Meier-Hellmann A, Specht M, Hannemann L, Hassel H, Bredle DL, Reinhart K (1996) Splanchnic blood flow is greater in septic shock treated with norepinephrine than in severe sepsis. Intensive Care Med 22:1354–1359
25. Chrusch C, Bands C, Bose D, Li X, Jacobs H, Duke K, Bautista E, Eschun G, Light RB, Mink SN (2000) Impaired hepatic extraction and increased splanchnic production contribute to lactic acidosis in canine sepsis. Am J Respir Crit Care Med 161:517–526
26. Revelly JP, Liaudet L, Frascarolo P, Joseph JM, Martinet O, Markert M (2000) Effects of norepinephrine on the distribution of intestinal blood flow and tissue adenosine triphosphate content in endotoxic shock. Crit Care Med 28:2500–2506
27. Di Giantomaso D, May CN, Bellomo R (2003) Norepinephrine and vital organ blood flow during experimental hyperdynamic sepsis. Intensive Care Med 29:1774–1781
28. Molina-Holgado F, Lledo A, Guaza C (1997) Anandamide suppresses nitric oxide and TBF-alpha responses to Theiler's virus or endotoxin in astrocytes. Neuroreport 8:1929–1933
29. Mendizabal VE, Orliac ML, Graschinsky EA (2001) Long-term inhibition of nitric oxide synthase potentiates effects of anandamide in the rat mesenteric bed. Eur J Pharm 427:251–262
30. Zygmunt PM, Petersson J, Andersson DA, Chuang HH, Sorgard M, Di Marzo V, Julius D, Hoquestatt ED (1999) Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 400:452–457
31. Pacher P, Batkai S, Kunos G (2004) Hemodynamic profile and responsiveness to anandamide of TRPV1 receptor knock-out mice. J Physiol 558:647–657